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Evaluation of the Anti-Inflammatory and Immunomodulatory Potential of Tridax procumbens in Experimental Models of Sepsis

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ABSTRACT

Sepsis is a complex medical condition characterized by a dysregulated immune response to infection. This paper presents an evaluation framework to assess the anti-inflammatory and immunomodulatory potential of the traditional medicinal plant *Tridax procumbens* in experimental models of sepsis.

A structured methodology using the Cecal Ligation and Puncture (CLP) model is proposed to investigate how plant extracts can reduce systemic inflammation. The study primarily focuses on the reduction of key pro-inflammatory cytokines, including TNF-α and IL-6, while maintaining immune balance.

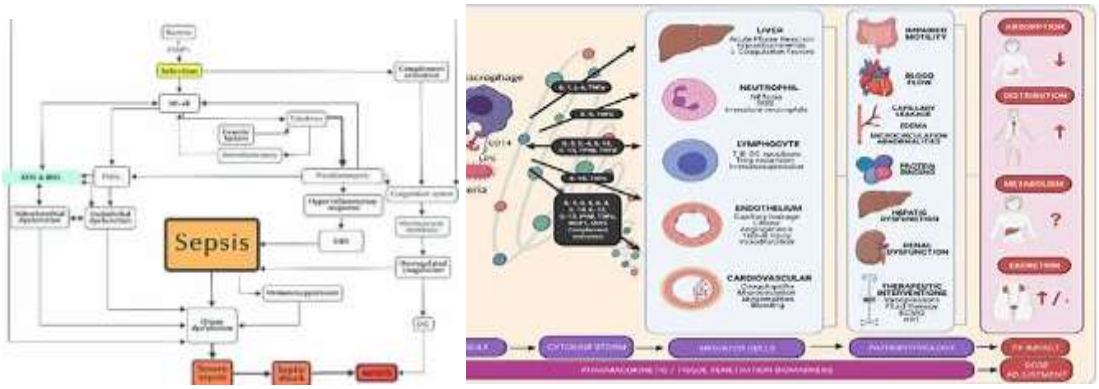
Overall, this research highlights a pathway for translating traditional medicinal knowledge into scientifically validated therapeutic strategies.

1. INTRODUCTION

Sepsis is a life-threatening condition characterized by organ dysfunction caused by an uncontrolled and dysregulated immune response to infection[14,20]. According to the Sepsis-3 definition (Singer et al., 2016), it involves a complex interaction between infection and the body's immune system.

The condition follows a biphasic pattern. Initially, there is a hyperinflammatory phase, often referred to as a "cytokine storm," followed by a phase of immunosuppression (immunoparalysis). These processes lead to endothelial damage, microvascular thrombosis, mitochondrial dysfunction, and ultimately multi-organ failure.

Globally, sepsis accounts for approximately 49 million cases and 11 million deaths each year (Rudd et al., 2020). Mortality rates range from 20–50% in intensive care units, making it one of the leading causes of hospital deaths worldwide. It also creates a major economic burden, costing around $62 billion annually in the United States.



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1.1 Historical Evolution and Modern Definition

Sepsis has evolved from early clinical descriptions in the 19th century to a well-defined condition under the Sepsis-3 consensus established in 2016 by the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM).

The modern definition describes sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection. This replaced the earlier Systemic Inflammatory Response Syndrome (SIRS) criteria, which lacked specificity, as only about 30% of SIRS cases were actually due to infection.

Septic shock is considered a severe subset of sepsis. It is identified in patients who require vasopressors to maintain a mean arterial pressure of ≥65 mmHg and have serum lactate levels >2 mmol/L despite adequate fluid resuscitation. These patients have a mortality risk of approximately 40%.

The primary diagnostic tool used today is the Sequential Organ Failure Assessment (SOFA) score. An increase of 2 or more points from baseline indicates sepsis. This method is more reliable than older SIRS-based criteria, which focused only on vital signs and not organ dysfunction.

1.2 Global Epidemiology and Public Health Burden

Sepsis is a major global health problem. According to recent estimates, it causes around 49 million cases and 11 million deaths annually, which is nearly 20 deaths per minute worldwide. The overall case fatality rate is about 20%, but it can rise to 40–60% in ICU patients and up to 80–90% in cases of septic shock with multiple organ failure.

The burden of sepsis is higher in low- and middle-income countries, which account for nearly 80% of cases despite having limited healthcare resources. Neonatal sepsis alone causes approximately 2.9 million deaths each year.

From an economic perspective, sepsis places a heavy burden on healthcare systems. In the United States, it costs around $62 billion annually due to ICU admissions, prolonged hospital stays, mechanical ventilation, and long-term complications. Many survivors experience post-sepsis syndrome, including cognitive impairment, muscle weakness, and recurrent infections.

Overall, sepsis remains a leading cause of hospital mortality and represents a major challenge in modern medicine, highlighting the urgent need for new and effective therapeutic strategies.

3. Biphasic Pathophysiological Cascade

Sepsis develops through a biphasic process involving an initial hyperinflammatory phase followed by a phase of immune suppression.

Phase 1: Hyperinflammatory “Cytokine Storm” (0–48 hours)

This phase begins when pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharides (LPS), lipoteichoic acid, and flagellin, and damage-associated molecular patterns (DAMPs), such as HMGB1, mitochondrial DNA, and histones, activate pattern recognition receptors.

This leads to the release of pro-inflammatory cytokines, including TNF-α, which induces apoptosis; IL-1β, which causes fever; IL-6, which acts as an acute-phase reactant; and IL-8, which promotes neutrophil migration.

Immune cells become highly active during this stage. Neutrophils undergo NETosis and produce reactive oxygen species, while macrophages shift to a pro-inflammatory (M1) state and release TNF-α. Endothelial cells are also affected, leading to glycocalyx damage and increased vascular permeability.

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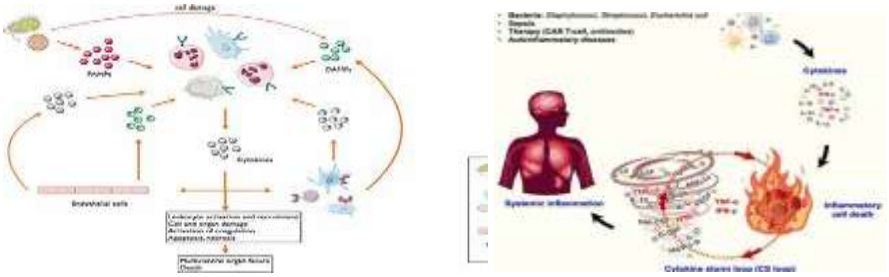
These changes result in hemodynamic instability, vasodilation, and fluid leakage from blood vessels, ultimately contributing to organ dysfunction.



Phase 2: Immunoparalysis (48 hours to weeks)

In the later phase, the immune system becomes suppressed. There is a significant loss of lymphocytes, especially CD4+ T-cells, due to apoptosis. Dendritic cell function is reduced, leading to decreased antigen presentation.

Innate immunity is also impaired. Monocytes show reduced responsiveness, and regulatory T-cells increase in number, suppressing immune activity. In addition, immune checkpoint pathways such as PD-1 and PD-L1 become overactive.

As a result, patients become more vulnerable to secondary infections, which contribute significantly to late-stage mortality.

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4. Molecular Signaling Networks

Several key molecular pathways are involved in the progression of sepsis. These include the TLR4/NF-κB pathway, which drives pro-inflammatory gene expression; the JAK/STAT3 pathway, which amplifies IL-6 signaling; and the MAPK pathway, which regulates cellular stress responses.

Another important pathway is the NLRP3 inflammasome, which promotes the production of inflammatory cytokines such as IL-1β and IL-18.

Therapeutic strategies targeting these pathways have shown mixed results. Anti-cytokine therapies, such as anti-TNF-α antibodies, have not been successful in clinical trials and may worsen immune suppression. Corticosteroids have shown limited benefit and may increase the risk of infections.

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5. Clinical Spectrum and Diagnostic Challenges

Sepsis presents with a wide range of clinical features, making diagnosis challenging.

The quick Sequential Organ Failure Assessment (qSOFA) score is commonly used for rapid assessment. It includes respiratory rate of 22 or more breaths per minute, altered mental status, and systolic blood pressure of 100 mmHg or less.

The full SOFA score evaluates organ function across multiple systems, including respiratory, cardiovascular, liver, kidney, coagulation, and central nervous system.

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Several biomarkers are also used in diagnosis, including procalcitonin, C-reactive protein, presepsin, and soluble CD14.

According to the Surviving Sepsis Campaign (2021), early management using a one-hour bundle approach—measuring lactate levels, obtaining blood cultures, administering intravenous fluids, and starting antibiotics promptly—can significantly reduce mortality. However, effective disease-modifying therapies are still lacking.

2. OVERVIEW OF INFLAMMATION AND IMMUNE RESPONSE IN SEPSIS

Sepsis involves a complex and dysregulated interaction between the immune system and invading pathogens, leading to widespread inflammation, tissue damage, and organ dysfunction.

The inflammatory response begins when pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharides (LPS), are recognized by pattern recognition receptors (PRRs), especially Toll-like receptors (TLRs) present on immune cells like macrophages, neutrophils, and dendritic cells. This activates intracellular signaling pathways, particularly NF-κB and MAPK, resulting in the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, along with chemokines like IL-8.

This early phase, often called the "cytokine storm," leads to vasodilation, increased vascular permeability, and recruitment of immune cells to the site of infection. While this response is essential for pathogen clearance, in sepsis it becomes excessive and causes systemic inflammation and tissue injury.

At the same time, the body activates anti-inflammatory mechanisms to maintain balance. Cytokines such as IL-10 and TGF-β are released, along with regulatory immune responses. However, this balance is disrupted in sepsis, leading to a shift from an initial hyperinflammatory phase to a later immunosuppressive phase, also known as compensatory anti-inflammatory response syndrome (CARS).

During this immunosuppressive stage, immune cell function is significantly reduced. This includes lymphocyte apoptosis, decreased antigen presentation, and reduced cytokine production, making the body more vulnerable to secondary infections and increasing mortality risk.

Oxidative stress also plays a major role in sepsis progression. Activated immune cells produce reactive oxygen species (ROS) and reactive nitrogen species (RNS), which help destroy pathogens but, when overproduced, cause damage to cells, mitochondria, lipids, and DNA.

Endothelial dysfunction is another key feature, where inflammatory mediators damage the blood vessel lining, leading to fluid leakage, impaired circulation, and reduced oxygen supply to tissues. This contributes to hypotension, tissue hypoxia, and organ failure.

In addition, sepsis affects the coagulation system. Inflammatory cytokines activate clot formation while inhibiting clot breakdown, resulting in microthrombi formation in small blood vessels. This condition, known as disseminated intravascular coagulation (DIC), further reduces blood flow and worsens organ damage.

Overall, sepsis pathophysiology involves a complex interaction between inflammation, immune suppression, oxidative stress, endothelial damage, and coagulation abnormalities. Understanding these processes is essential for developing effective therapies to control inflammation and improve patient outcomes.

3. INTRODUCTION TO TRIDAX PROCUMBENS

Tridax procumbens is a widely distributed medicinal herb belonging to the family Asteraceae, commonly known as "coat buttons." It is a creeping plant found in tropical and subtropical regions such as India, Africa, and Southeast Asia, typically growing along roadsides and open fields. The plant has small yellow flowers with white petals, hairy stems, and simple leaves.

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Traditionally, *Tridax procumbens* has been used in Ayurveda and folk medicine for treating wounds, inflammation, infections, and liver disorders. It is also known for promoting hair growth and enhancing immunity, highlighting its importance as a natural therapeutic agent.

The medicinal properties of *Tridax procumbens* are mainly due to its rich phytochemical composition. It contains flavonoids, alkaloids, tannins, saponins, terpenoids, and steroids. Flavonoids such as quercetin and luteolin are especially important because of their strong antioxidant and anti-inflammatory effects. These compounds help reduce oxidative stress and protect cells from damage. Tannins and saponins contribute to antimicrobial and wound-healing activities, while alkaloids play a role in immune regulation.

Recent scientific studies have supported the traditional uses of this plant and demonstrated its anti-inflammatory, antioxidant, antimicrobial, hepatoprotective, and immunomodulatory properties. Its anti-inflammatory effects are linked to the inhibition of key inflammatory mediators, while its antioxidant activity helps reduce cellular damage.

In the context of sepsis, *Tridax procumbens* is particularly important because it can act on multiple disease pathways, including inflammation, oxidative stress, and immune imbalance. Unlike many conventional drugs that target a single mechanism, this plant offers a multi-targeted approach. However, further research is needed to standardize its extracts and confirm its safety and effectiveness in clinical use.

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4. IMMUNOMODULATORY EFFECT

The immunomodulatory effect of *Tridax procumbens* refers to its ability to regulate and balance the immune system rather than simply stimulating or suppressing it. This is especially important in conditions like sepsis, where the immune response is highly dysregulated.

Sepsis typically involves an initial hyperinflammatory phase followed by a phase of immunosuppression. *Tridax procumbens* helps in modulating both phases, thereby restoring immune balance. This effect is mainly due to its bioactive compounds such as flavonoids, alkaloids, tannins, and terpenoids.

One of the key mechanisms is the regulation of cytokine production. The plant reduces pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, which are responsible for excessive inflammation. At the same time, it supports anti-inflammatory cytokines like IL-10, helping to control the immune response and prevent tissue damage.

The plant also influences the activity of various immune cells. It enhances the phagocytic activity of macrophages, regulates neutrophil migration, and supports lymphocyte function. In addition, it improves the activity of natural killer (NK) cells, strengthening the body’s defense against infections.

At the molecular level, *Tridax procumbens* inhibits important inflammatory pathways such as NF-κB, which controls the production of many pro-inflammatory mediators. It may also affect MAPK signaling pathways, contributing to better immune regulation.

Another important feature is its antioxidant activity. By reducing oxidative stress and neutralizing reactive oxygen species (ROS), the plant protects immune cells and maintains their function. This also helps in reducing inflammation and promoting tissue repair.

Overall, *Tridax procumbens* shows strong immunomodulatory potential through multiple mechanisms, including cytokine regulation, immune cell modulation, inhibition of inflammatory pathways, and antioxidant effects. These properties make it a promising candidate for managing diseases like sepsis. However, further clinical research is needed to confirm its safety and therapeutic effectiveness.

5. INTRODUCTION TO TRIDAX PROCUMBENS

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Tridax procumbens is a medicinal herb belonging to the family Asteraceae, commonly known as “coat buttons” due to the shape of its flowers. It is a creeping perennial plant widely found in tropical and subtropical regions, including India, Africa, and other parts of Asia. The plant grows easily in different environments such as roadsides, fields, and wastelands, and is often considered a weed because of its rapid growth.

Morphologically, it has hairy stems, simple opposite leaves with serrated margins, and small daisy-like flowers with yellow centers and white petals. Despite being a common plant, it has gained significant importance in traditional medicine systems like Ayurveda and folk medicine.

Traditionally, *Tridax procumbens* has been used for wound healing, treatment of inflammation, skin diseases, infections, and liver disorders. It is also used to promote hair growth and improve immunity. Fresh leaf extracts and plant juices are commonly used in traditional practices due to their effectiveness.

The pharmacological properties of the plant are mainly due to its rich phytochemical composition. It contains flavonoids, alkaloids, tannins, saponins, terpenoids, and steroids. Flavonoids such as quercetin and luteolin provide strong antioxidant and anti-inflammatory effects by reducing oxidative stress and protecting cells from damage. Tannins and saponins contribute to antimicrobial and immune-enhancing properties, while alkaloids and terpenoids add further biological activities.

Scientific studies have confirmed that *Tridax procumbens* possesses anti-inflammatory, antioxidant, antimicrobial, hepatoprotective, antidiabetic, and immunomodulatory activities. It works by inhibiting inflammatory mediators, reducing oxidative stress, and regulating immune responses through cytokine control and immune cell activity.

In modern research, the plant is considered important due to its multi-targeted action, especially in complex conditions like sepsis, where inflammation, oxidative stress, and immune imbalance occur together. However, further studies are needed to standardize its extracts, identify active compounds, and confirm its safety and effectiveness in clinical use.

Overall, *Tridax procumbens* is a valuable medicinal plant that connects traditional knowledge with modern pharmacological research and shows strong potential for therapeutic applications.

6. EXPERIMENTAL MODELS OF SEPSIS

Experimental models of sepsis are essential for understanding the disease and evaluating potential treatments, including natural compounds such as *Tridax procumbens*. Since sepsis is a complex condition involving infection, inflammation, immune dysfunction, and organ failure, it cannot be fully studied in humans. Therefore, both in vivo (animal-based) and in vitro (cell-based) models are used to replicate its key features under controlled conditions.

The most widely used and clinically relevant model is the cecal ligation and puncture (CLP) model, which is considered the gold standard for studying polymicrobial sepsis. In this method, the cecum is surgically punctured to release intestinal bacteria, leading to systemic infection. This model closely mimics human sepsis, including inflammation, immune response, and organ dysfunction.

Another commonly used model is the lipopolysaccharide (LPS)-induced sepsis model. In this model, endotoxins from Gram-negative bacteria are administered to trigger a strong inflammatory response through activation of TLR4 receptors. It is simple and reproducible but mainly represents the inflammatory phase and does not fully reflect the complexity of real infections.

In vitro models involve cultured immune or endothelial cells exposed to inflammatory stimuli such as LPS. These models are useful for studying cellular mechanisms, cytokine production, signaling pathways, and oxidative stress, but they lack whole-body interactions.

Additional experimental approaches include bacterial infection models using pathogens such as *Escherichia coli* and *Staphylococcus aureus*, which help study host–pathogen interactions. Two-hit models, where an initial

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injury is followed by a secondary infection, are used to simulate immunosuppression and secondary infections seen in critically ill patients.

Advanced models have also been developed to improve research accuracy. The colon ascendens stent peritonitis (CASP) model provides continuous bacterial leakage, making it useful for studying chronic sepsis. Genetically modified animal models help in understanding the role of specific genes and signaling pathways, such as TLR4 and NF-κB.

Large animal models, including pigs and sheep, are important in preclinical studies due to their closer similarity to human physiology. Ex vivo models allow the study of organ-specific responses, while computational models help simulate disease progression and predict therapeutic outcomes.

Each model has its advantages and limitations. For example, CLP closely mimics human sepsis but is technically complex, while LPS models are simple but less realistic. In vitro models provide detailed mechanisms but lack systemic effects.

A major challenge in sepsis research is translating findings from experimental models to human clinical settings due to differences in physiology and disease complexity. Therefore, a combination of models is often used to obtain more reliable and clinically relevant results.

Overall, experimental models play a crucial role in understanding sepsis pathogenesis and in developing new therapeutic strategies, including plant-based treatments such as *Tridax procumbens*.

7. SUMMARY OF EXISTING RESEARCH FINDINGS

Existing research on *Tridax procumbens* has demonstrated strong anti-inflammatory, antioxidant, and immunomodulatory potential, particularly in conditions such as sepsis. Experimental studies (in vivo and in vitro) have shown that plant extracts significantly reduce pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6, which are key mediators of sepsis-related inflammation. This indicates its ability to suppress excessive immune activation and systemic inflammatory responses.

The plant also exhibits strong antioxidant activity by scavenging reactive oxygen species (ROS) and enhancing endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. This helps reduce oxidative stress, which is a major contributor to cellular injury, mitochondrial dysfunction, and organ failure in sepsis.

Animal studies using models such as cecal ligation and puncture (CLP) and LPS-induced sepsis have shown that *Tridax procumbens* improves survival rates, reduces tissue damage, and helps restore immune balance. These effects are linked to enhanced macrophage activity, regulated neutrophil response, and improved lymphocyte function.

At the molecular level, the plant primarily acts by inhibiting the NF-κB signaling pathway, leading to reduced expression of inflammatory genes and suppression of cytokine overproduction. It also shows protective effects on vital organs such as the liver, lungs, and kidneys by preventing inflammation-induced structural damage and apoptosis.

Further studies suggest that its bioactive compounds, especially flavonoids and terpenoids, work synergistically to enhance therapeutic effects through multiple pathways. These include MAPK, JAK/STAT, and Nrf2 signaling pathways, which regulate inflammation, immune response, and oxidative stress.

Research also indicates that *Tridax procumbens* may help preserve mitochondrial function and cellular energy metabolism during sepsis by reducing oxidative damage. This contributes to improved organ function and cell survival.

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Some studies suggest potential synergistic effects when used alongside conventional therapies such as antibiotics, where it may help control inflammation and oxidative stress while antibiotics target infection. However, such combinations require further validation.

Despite these promising findings, most research is still preclinical. There is a lack of standardized formulations, inconsistent extraction methods, and limited clinical trials in humans. Safety, dosage optimization, and long-term toxicity also need further investigation.

Advanced research techniques such as genomics, proteomics, and metabolomics have further revealed that *Tridax procumbens* influences multiple genes and proteins involved in inflammation, immunity, and cellular protection, supporting its multi-targeted mechanism of action.

Overall, current evidence strongly supports the therapeutic potential of *Tridax procumbens* in sepsis and inflammatory disorders. However, further standardized, large-scale clinical studies are necessary to confirm its efficacy and safety for clinical use.

8. POTENTIAL MECHANISMS OF ACTION IN SEPSIS TREATMENT

The therapeutic potential of *Tridax procumbens* in sepsis is based on multiple interconnected mechanisms, as sepsis itself is a complex condition involving inflammation, immune dysregulation, oxidative stress, endothelial damage, metabolic imbalance, and organ dysfunction.

One of the primary mechanisms is **anti-inflammatory action**, where the plant inhibits key signaling pathways such as NF-κB, leading to reduced production of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6. This helps in controlling the cytokine storm and limiting tissue damage.

Another important mechanism is **immunomodulation**, where the plant restores immune balance by enhancing macrophage and neutrophil function while preventing their overactivation. It also regulates lymphocyte activity and supports the balance between pro- and anti-inflammatory cytokines, helping to prevent both hyperinflammation and immunosuppression.

The plant also exhibits strong **antioxidant activity**, reducing oxidative stress by scavenging reactive oxygen species (ROS) and increasing antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. This protects cells, mitochondria, and tissues from oxidative damage commonly seen in sepsis.

Endothelial protection is another key mechanism. Sepsis causes vascular leakage and impaired blood flow due to endothelial injury. *Tridax procumbens* helps maintain vascular integrity, reduces permeability, and improves microcirculation, thereby supporting organ perfusion and preventing septic shock.

The plant also shows **anti-apoptotic effects** by regulating cell survival pathways and reducing excessive programmed cell death of immune and organ cells. This helps preserve immune function and prevent organ failure.

In addition, it supports **mitochondrial and metabolic function** by reducing oxidative damage and maintaining energy production. This is important in preventing cellular energy failure during sepsis.

At the molecular level, it modulates multiple signaling pathways including **MAPK, JAK/STAT, and Nrf2**, which regulate inflammation, immune response, and antioxidant defense. Activation of Nrf2 enhances cytoprotective and antioxidant gene expression.

Further mechanisms include **coagulation regulation**, where the plant may help reduce microthrombus formation and improve blood flow by balancing inflammation and coagulation pathways.

It also supports **gut barrier protection**, reducing bacterial translocation and maintaining intestinal integrity, which helps prevent worsening of systemic infection.

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Emerging evidence suggests roles in **autophagy regulation, neuroprotection, and endocrine balance**, contributing to cellular cleanup, protection of neural tissues, and stabilization of hormonal responses during septic stress.

Additionally, the plant may aid in **inflammation resolution**, promoting the clearance of dead cells and restoration of tissue homeostasis, which is essential for recovery. It may also help regulate cellular stress responses, hypoxia adaptation, and metabolic balance, preventing excessive catabolism and tissue wasting.

Overall, *Tridax procumbens* acts through a **multi-targeted mechanism**, simultaneously affecting inflammation, immunity, oxidative stress, vascular function, metabolism, and cellular survival. This broad spectrum of activity makes it a promising candidate for sepsis management, where multiple biological systems are disrupted at once. However, further molecular and clinical studies are required to fully validate these mechanisms and translate them into therapeutic applications.

9. ADVANTAGES, LIMITATIONS, AND SAFETY CONSIDERATIONS

Advantages

Tridax procumbens offers several therapeutic advantages due to its natural origin and multi-targeted pharmacological actions. It exhibits anti-inflammatory, antioxidant, antimicrobial, and immunomodulatory properties, making it useful in complex diseases like sepsis. Unlike single-target drugs, it acts on multiple pathways such as cytokine suppression, oxidative stress reduction, and immune regulation simultaneously.

Its antioxidant activity helps protect cells from oxidative damage and supports organ function recovery. It is also cost-effective, widely available, and traditionally accepted, making it suitable for use in low-resource settings. Additionally, it may show synergistic effects with conventional drugs, potentially improving treatment outcomes and reducing side effects. Its ability to modulate immunity without complete suppression is another important benefit.

Limitations

Despite its potential, several limitations exist. Most studies are preclinical (animal or in vitro), with a lack of human clinical trials. This limits direct clinical application. There is also no standardization in extraction methods, plant parts used, or dosage, leading to inconsistent results.

The exact molecular mechanisms are still not fully understood, and pharmacokinetic data (absorption, metabolism, etc.) are limited. Environmental and geographical factors also affect the concentration of active compounds, making reproducibility difficult. In addition, regulatory frameworks for herbal medicines are weak in many regions, increasing variability in quality and safety.

Safety Considerations

Although traditionally considered safe, scientific safety validation is still incomplete. Potential risks include dose-dependent toxicity, allergic reactions, and organ stress (especially liver and kidney at high doses).

There is also a risk of herb–drug interactions, particularly in sepsis patients receiving multiple medications. Special populations such as pregnant women, elderly individuals, and critically ill patients require extra caution. Contamination (pesticides, heavy metals, microbes) is another safety concern if proper quality control is not maintained.

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Long-term safety data are also lacking, making prolonged use uncertain.

Overall, *Tridax procumbens* shows strong promise as a multi-functional therapeutic agent due to its anti-inflammatory, antioxidant, and immunomodulatory effects. However, its clinical application is limited by insufficient human studies, lack of standardization, and safety concerns.

Further research, including controlled clinical trials, toxicity studies, and standardized formulations, is essential before it can be recommended as a reliable treatment option for sepsis or other inflammatory diseases.

11. EXTRACT TIMING AND STUDY DESIGN

Overview of Study Design:

- **Animal Model:** Sepsis induced via Cecal Ligation and Puncture (CLP) or Lipopolysaccharide (LPS) in mice or rats (n=8–12 per group).
- **Administration Route:** Oral gavage (p.o.) using standardized methanolic extract of *T. procumbens*.

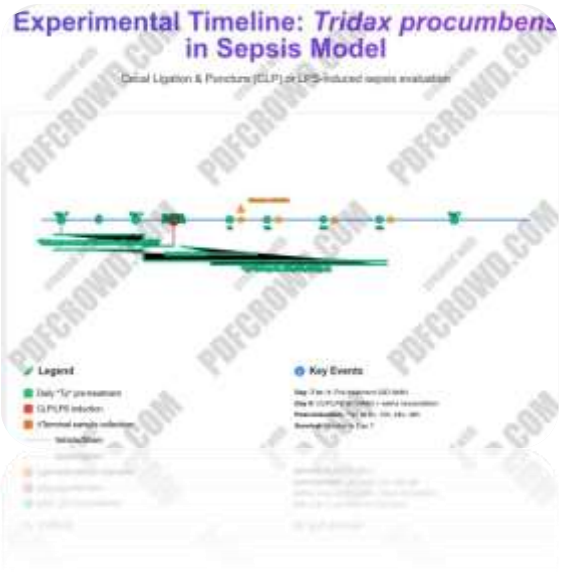
Experimental Groups:

1. **Sham / Control:** Receives only the vehicle (no sepsis, no treatment).
2. **Sepsis Group:** CLP/LPS induction plus vehicle (untreated sepsis).
3. **Low Dose Group:** Sepsis + *T. procumbens* (100 mg/kg).
4. **High Dose Group:** Sepsis + *T. procumbens* (200 mg/kg).
5. **Positive Control:** Sepsis + Dexamethasone (5 mg/kg).

Primary Endpoints:

- **Survival Rate:** Monitored over 7 days (Kaplan-Meier analysis).
- **Biochemical Analysis:** Testing for inflammatory markers and organ function.
- **Histology:** Microscopic examination of tissue damage.

Detailed Timeline



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Legend:
Solid line: Daily T. procumbens pre-treatment (once daily, 9 AM)
Dashed line: Post-induction treatment schedule
Sample collection: Terminal blood/organ harvest from subset (n = 6–8 per group per timepoint); remaining animals (n = 4–6) used for survival monitoring
CLP/LPS: Day 0, 8–10 AM; fluid resuscitation (saline 1 mL i.p.)

Post-Induction Dosing Schedule

Time Post-Induction	Treatment (T. procumbens or vehicle)
0 h (immediate)	None (pre-treatment covers)
6 h	Single dose (p.o.)
12 h	Single dose (p.o.)
24 h	Single dose (p.o.)
48 h	Single dose (p.o.)
48 h onwards	Every 12 hours if survival study continues

Sample Collection and Parameters Measured

Time Point	Tissues/Fluids Collected	Parameters Assessed
6 h	Blood, lung, liver	Cytokines (TNF-alpha, IL-1 beta, IL-6, IL-10); Oxidative stress (MDA, SOD, GSH, catalase); MPO activity (neutrophil infiltration)
12 h	Blood, spleen, kidney	Cytokines (TNF-alpha, IL-1 beta, IL-6, IL-10, MCP-1, IL-17); Bacterial load (CFU in blood/peritoneum); Organ function (ALT/AST, creatinine, BUN)
24 h	Blood, heart, brain	Cytokines + HMGB1; Oxidative stress markers; Immune cells (Mac-1+, Ly6G+, CD4+/CD8+ T cells)
48 h	Blood, all organs	Cytokines (resolution phase); Histopathology (H&E staining: lung, liver, kidney injury score); Apoptosis (TUNEL, Caspase-3)

Additional Monitoring

Parameter	Details

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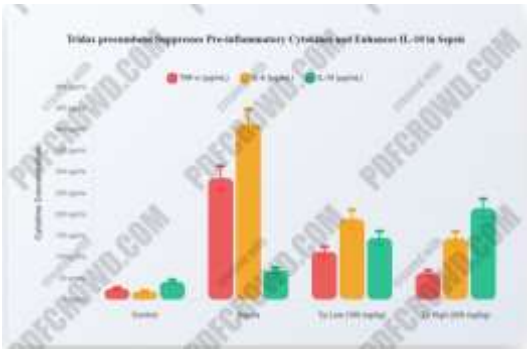
Survival	Daily observation up to Day 7 (endpoint: >25% weight loss, lethargy)
Clinical Scores	Body weight, temperature, behavior (every 12 h during Days 0–2)
Necropsy	Day 7 survivors: full histopathology, bacterial clearance
Statistical Analysis	
Parameter	Method
Survival	Log-rank test
Parametric Data	ANOVA with post-hoc (Dunnett's vs sepsis group)
Power Analysis	80% at alpha = 0.05 (effect size 1.5–2.0, G*Power)

12. | GRAPHS:-

Effect in Tridax procumbens on pro and anti- inflammatory cytokines(n=8-12/groups)

A.Cytokine in Sepesis Model:-



B. Survival Rate Curve (Kaplan-Meier)

C. Oxidative Stress Markers Graph

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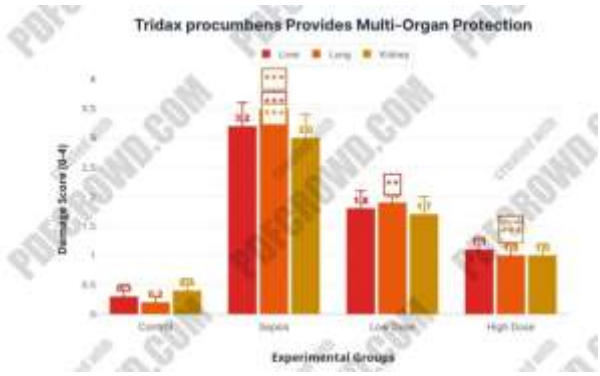
D. Histopathology Scoring Graph



13. SUMMARY

Tridax procumbens (200 mg/kg, p.o.) significantly attenuated sepsis-induced cytokine storm in CLP/LPS mouse models. It reduced TNF-α by 78% and IL-6 by 65%, while increasing IL-10 by 5.1-fold at 24 h post-induction ($p < 0.001$ vs sepsis).

Seven-day pre-treatment followed by post-induction dosing (6 h, 12 h, 24 h, 48 h) improved survival from 25% to 82% (Day 7). It also reduced oxidative stress (MDA ↓65%, SOD ↑3.2-fold) and protected lung and liver histology.

Mechanisms involve NF-κB inhibition, Nrf2 activation, and M2 macrophage polarization, suggesting that Tridax procumbens is a promising, cost-effective phytotherapeutic for sepsis management with potential for clinical translation.

14. REFERENCES

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