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Medicinal plants and polymicrobial sepsis: A review

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Abstract
Sepsis is a metabolic and systemic inflammatory response to infection. Morbidity and mortality of septic patients has not been changed with conventional therapy. In addition, clinical trials in sepsis have failed. Natural medicine is an important source on developing of new anti-inflammatory agents for infectious diseases. We performed a search from 2005 to 2017 on Medline-PubMed database. We selected studies that evaluated the therapeutic potential of medicinal plants or herbal mix in polymicrobial sepsis by cecal ligation and puncture (CLP). We identified 19 medicinal plants and herbal mix used to treat animals in polymicrobial sepsis model. Medicinal plant administration promotes immunomodulatory actions through receptors, cytokines, biomarkers of injury tissue, leukocyte migration and apoptosis of lymphocytes. In addition, survival rate was improved after medicinal plants treatment. New approaches using medicinal plants in polymicrobial sepsis could improve healthcare conditions in many countries because natural products are promising candidate against infectious diseases.

Keywords: polymicrobial sepsis, CLP, medicinal plants, alternative medicine

Introduction
Sepsis is a systemic inflammatory response to the bacteria, fungi or virus infections. Long-term sepsis morbidity and mortality remains a clinical problem in the health centers [1]. Nowadays, the alternative treatments associated to the antibiotic administration and managements of septic patients has not been satisfactory in clinical trials. Thus, health systems require the high administrative costs in the critical care medicine, resulting in a significant economic and social impact [2].
New possibilities of immune intervention during sepsis correlate with its physiopathology. Some patients need immune-stimulatory response to improve host immunity against infection, while others benefit from therapies which suppress immunity [3, 4]. Natural, synthetic and recombinant products are important sources on developing of new anti-inflammatory agents for infections based on the insufficient response of the immune system [5, 6].
Medicinal plants are used as an alternative therapy in developing countries, due its accessibility, low cost and popular culture [7]. Therefore, scientists use their expertise with phytotherapy to investigate its protection in the inflammatory models because phytomedication could be improve healthcare conditions in many countries. This review aimed to analyze the publications involving polymicrobial sepsis and treatment with medicinal plants in the last years.

Methods
We performed a review of articles in Medline-PubMed database up to March, 2017. All studies were selected by means of different combination of terms or keywords such as polymicrobial sepsis, CLP, treatment, medicinal plants, extract and essential oil. We read and analyzed only original articles available in English, published between 2005 and 2017. We selected studies that evaluated the therapeutic potential of medicinal plants or herbal mix in polymicrobial sepsis by cecal ligation and puncture (CLP). The experimental model induces cardiovascular, metabolic and immunological changes such as the clinical course of human sepsis [8]. The articles that analyzed isolated compounds from medicinal plants were excluded in this review. The inclusion and exclusion criteria were applied and we selected 24 articles for a full text review.

Results

First, we identified 19 medicinal plants and herbal mix used to treat animals in polymicrobial sepsis model. We verified that administration of medicinal plants was oral administration or intravenous or intraperitoneal injection previous and/or after surgery. Also, the articles performed CLP in mice or rats.

Next, we verified the sepsis biomarkers. Pro- and anti-inflammatory cytokines have an important role to determine the degree of sepsis progression. Excessive systemic activity of pro-inflammatory cytokines can lead to a detrimental systemic response and organ failure [9, 10]. In this review, many articles showed modulation of IL-1b, TNF-a, IL-6, IL-17A, IL-10, IL-2, IL-12 and IFN-g cytokines levels in blood, liver, lung, *bronchoalveolar lavage* fluid (BAL) and/or fluid peritoneal cavity in septic animal with medicinal plants administration (table 1).

High-mobility group box 1 (HMGB1) is a potent proinflammatory cytokine involved in the maintenance of nucleosome structure and regulation of gene transcription. Extracellular HMGB1 is detectable in the circulation after of lethal endotoxemia and CLP sepsis model [11]. In the last years, many studies have been investigated the activity of medicinal plants in the modulation of HMGB1 levels in polymicrobial sepsis. They showed that the treatment with aqueous extract of roots from *Angelica sinensis* [12] or *ethanolic extract of* roots from *Inula helenium* L [13] attenuated HMGB1 blood levels. We found that *alcoholic extract of flowers from Prunella vulgaris* var. *lilacina* [14] and plants mix named Xuebijing [15] reduced HMGB1 serum and expression in lung.

Inflammation systemic can cause organ dysfunction, failure, and necrotic cell death. Many tissue damage markers have been associated to organ failure. Nitric oxide is an inflammatory mediator involved in the failure of neutrophil migration at the site of infection [16] and tissue injury. We found that alcoholic extract of *Alpinia katsumadai* [17], hydroalcoholic extract of fresh leaves of *Syzygyum jambolanum* [18] and *Eugenia uniflora* [19] reduced serum NO levels and/or iNOS expression. Moreover, some studies related that phytotherapy with *Carum carvi* [20], ethanolic extract of seeds from *Nigella sativa* [21], *Melilotus suaveolens* [22] increased the activity of the antioxidants enzymes such as glutathione (GSH) and superoxide dismutase (SOD).

Activated neutrophils release myeloperoxidase (MPO) with strong oxidative activity during inflammation and its can cause tissue damage. In addition, enzymatic activity measurements of MPO is a biomarker of the inflammatory responses in patients with SIRS and sepsis [23, 24]. Administration of *Alpinia katsumadai* [17], Xuebijing herbal mix [15, 25], *Astragalus membranaceus* [26], *Carum carvi* [20], *Eugenia uniflora* [19], *Melilotus suaveolens* [27], *Nigella sativa* [21] reduced MPO serum and lung levels after CLP. Moreover, malondialdehyde (MDA), a stress oxidative marker highly elevated in sepsis was attenuated in animals treated with *Nigella sativa* [21].

Blood urea nitrogen (BUN) and creatinine reduction are important to inhibit or alleviate dysfunction renal. Anti-inflammatory properties of alcoholic extract of flowers buds from *Lonicera japonica* [28], alcoholic extract of roots from *Inula helenium* [13], *Aloe vera* gel [29] and hydroalcoholic extract or essential oils caraway from *Carum carvi* [30] ameliorated kidney function by attenuated release of these biomarkers.

Elevated serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels indicate acute liver injury. The liver failure is associated with mortality in patients with bacterial sepsis [31]. Administration of *Aloe vera* [29], *Alpinia katsumadai* [17], *Astragalus membranaceus* [26], essential oils from *Carum carvi* [30], Huang-Lian-Jie-Du-Tang herbal mix [32], *Lonicera japonica* [28] decreased AST and ALT levels in this experimental model. The literature has been showed that *Eugenia uniflora* [19] attenuated cyclooxygenase-2 (COX-2) expression in ileum of the septic animals.

Apoptosis is other factor that contributes to multiple organ dysfunction syndrome and immunosuppression in sepsis. In addition, the apoptotic processes may play a determining role in the outcome to sepsis syndromes. Thymus, spleen, lung and gut of mice has widespread apoptosis when challenged to cecal ligation and puncture model. We found that therapy with *Rhodiola rosea* [33] inhibited CD4+ and CD8+ T cell death in spleen. Also, *Lonicera japonica* [34] decreased T cells apoptosis and CD3+, CD4+, CD4+/CD8+ ratio increased in thymus.

Many studies related that medicinal plant therapy played an important role in the control of inflammation by suppresses TLR4 pathway and NF-kB activation. The alcoholic extract of flowers buds from *Lonicera japonica* [28], Melilotus extract [22] and Xuebijing herbal mix [25] downregulated TLR4 expression. In addition, NF-kB inactivation is crucial to protect mice from lethality in murine sepsis. Xuebijing [25], *Lonicera japonica* [28] and *Melilotus suaveolens* [22, 27] suppressed NF-kB expression in polymicrobial sepsis model.

The articles showed that medicinal plants treatment increase survival rate of animals subjected to surgery. Also, the protective effect of the medicinal plants against sepsis mortality is due antibacterial activity demonstrated in many studies [17, 28, 29, 35]. However, *Carum carvi* [20, 30] and *Chenopodium ambrosioides* [35] studies did not show data about mortality. YANG *et al*. [36] related that *Toona sinensis* administration improves survival of septic animals, but they did not report which inflammatory parameters are involved with treatment. Also, we identified that leukocyte migration to the site of infection was necessary for the control of sepsis and for the prevention of bacterial dissemination [17, 18]. In addition, inhibition of neutrophil migration into the organs can attenuate injury tissue [13, 15, 20, 25]. We also verified that phytotherapy can modulate migration of cells into the lymph node of septic animals [35, 37]. We also identified that temperature [38] and arterial pressure [17] can be stabilized with medicinal plants administration after CLP. The article that only administered Bai-Hu-Tang [39] showed that treatment reduced IL-6 and IL-10 cytokines levels in septic animals.

Table 1. Medicinal plants used to treatment of septic animals in the polymicrobial sepsis model

N.	plant specie	part used	immunomodulatory activities	Reference
1	*Aloe vera*	lyophilized gel	↓ IL-1b, IL-6, TNF-a, AST, ALT, LDH, BUN and creatinine serum levels	[29]
2	*Alpinia katsumadai*	Seeds	↓ IL-1b, TNF-a, AST, ALT and NO serum levels ↓ MPO liver and lung levels ↑ leukocyte migration into the peritoneal cavity ↑ arterial pressure with treatment.	[17]

3	*Angelica sinensis*	Roots	↓ HMGB serum levels	[12]
4	*Angelicae sinensis Radix, Carthami flos, Chuanxiong Rhizoma Paeoniae Radix Rubra,Salviae miltiorrhizae* (Xuebijing)	herbal mix	↓ IL-1b, IL-6, TNF-a serum levels ↓ anal temperature with treatment	[38]
			This study analyzed the immunomodulatory treatment in the lungs: ↓ IL-1b, IL-6, TNF-a levels in the BAL fluid ↓ NF-kB65 and TLR4 protein expression ↓ neutrophil infiltration and MPO levels	[25]
			↓ IL-1b, IL-6, TNF-a levels in the BAL fluid ↓ neutrophil infiltration and MPO levels ↓ HMGB1 protein expression in the lung ↓ HMGB1 serum levels	[15]
5	*Astragalus membranaceus*	Roots	↓ AST, ALT, LDH, MPO and NO serum levels ↓ IL-1b, iNOS mRNA expression in livers	[26]
6	*Attalea speciosa* syn *Orbignya phalerata* Mart.	Fruits	↓ IL-6 and TNF-a serum levels ↑ mesenteric lymph node cells	[37]
7	*Carum carvi*	seeds	↓ creatinine and urea plasma levels	[30]
			↓ AST, ALT, MPO and ↑ GSH plasma levels ↓ cell infiltration in liver	[20]
8	*Chenopodium ambrosioides*	leaves	↑ leukocyte migration until the peritoneal cavity ↓ IL-1b, IL-6, TNF-a and IL-10 serum levels ↓ lymph node cells	[35]
9	*Cortex Phellodendri Fructus Gardeniae Rhizoma Coptidis, Radix scutellariae, (Huang-Lian-Jie-Du-Tang)*	herbal mix	↓ IL-1b, IL-6, TNF-a, IL-17A, AST and ALT blood levels ↓ IL-17A, IL-4 and ↑ IFN-g mRNA expression in spleens	[32]
10	*Eugenia uniflora*	leaves	↓ IL-1b and TNF-a serum and MPO lung levels ↓ iNOS and COX-2 expression in ileum	[19]
11	*Gypsum Fibrosum,* nonglutinous Rice Radix Glycyrrhizae Preparata, R*hizoma Anemarrhenae* (Bai-Hu-Tang)	herbal mix	↓ IL-6 and IL-10 plasma levels	[39]
12	*Inula helenium.*	roots	↓ AST, ALT, BUN, creatinine and HMGB1 blood levels ↓ cell infiltration in liver	[13]
13	*Lonicera japonica*	flower buds	↓ IL-1b, IL-6, TNF-a, MCP-1, HMGB-1, ALT, LDH, BUN and creatinine serum levels ↓ TLR4 and NF-kB mRNA expression levels in liver and lung	[28]
			This study analyzed the immunomodulatory treatment in the spleen: ↓ $CD4^+$ and $CD8^+$ T cells splenocyte apoptosis ↓ TNF-a, IL-2 and IL-17A levels	[34]
14	*Melilotus suaveolens*	plant dried	↓ IL-6, TNF-a, IL-12 and ↑ IL-2 and IL-10 plasma levels ↓ inflammatory cells in BAL fluid and MPO lung levels ↓ NF-kB mRNA expression in mononuclear cells	[27]
			↓ IL-1b, IL-6 and TNF-a levels in BAL fluid ↓ TLR4 and NF-kB mRNA expression levels ↑ SOD levels in lung	[22]
15	*Nigella sativa*	seeds	↓ MPO, MDA and ↑ SOD, GSH lung levels	[21]
16	*Prunella vulgaris* var. *lilacina*	flowers	↓ HMGB1 serum and lung levels	[14]
17	*Rhodiola rosea*	root	↑ IL-2, IL-12 and IFN-g plasma levels ↓ $CD3^+$, $CD4^+$, $CD8^+$ T apoptotic cells in the thymus	[33]
18	*Toona sinensis*	leaves	↑ survival rate with treatment	[36]
19	*Syzygium jambolanum*	leaves	↓ TNF-a and nitrite serum levels ↑ neutrophil migration into the peritoneal cavity	[18]

Conclusion

This review can contribute to other research centers that search alternative therapeutics against sepsis. These studies showed that the improvement of host defense in the initial focus can inhibits bacterial dissemination and pro-inflammatory response in other tissues. We verified that medicinal plants can have immunomodulating actions through receptors, cytokines, and biomarkers of injury tissue, leukocyte migration and apoptosis of lymphocytes. Furthermore, there is evidence that administration of medicinal plants improve survival in septic animals. We suggest new approaches about medicinal plants treatment in polymicrobial sepsis as promising candidate against infectious diseases.

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