Chapter 44

Effective Role of Herbal Medicines in Sepsis Treatment

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ABSTRACT

Throughout the world, herbal medicines are considered as a significant part of healthcare. Plant based medicines have been used extensively for many years. Plants have been used for the treatment of various health conditions including allergy, arthritis, skin infections, respiratory problems, gastrointestinal problems and others. Different herbal medicines possess anti-oxidative, anti-inflammatory, antibacterial, antiviral as well as antifungal characteristics. In sepsis, there is uncontrollable and excessive innate immune system response as a result of the invading infectious microorganisms. Despite the presence of modern antibiotics and technologies, the treatment of sepsis is a challenge as it is life threatening. Different Chinese Herbal Medicines can be helpful in sepsis treatment. However, in several countries, herbal products are not regulated as widely as compared to conventional drug treatment. In recent times, there is a need of conducting more research that evaluates the utilization of herbal drugs. Apart from the benefits of using herbal medicines, there are some concerns such as possibility of contamination of product, or adulterations, toxicity associated with the herb, and possibility of unknown and known drug and herb interactions. Herbal experts or clinicians should be aware of the potential interactions and potential toxicity.

KEYWORDS
Herbal medicine, Sepsis, Treatment, Herbs, Inflammatory

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INTRODUCTION

Herbal medicines are of natural origin and derived from plants that can be used for the treatment of different illnesses. These products are considered as complex mixtures of organic chemicals. These products may be obtained from any processed or raw part of a plant. Herbal medicine, also termed as herbalism is a medical system which depends on the utilization of plant extracts or plants that can be either applied to the skin or eaten (Sam, 2019). Herbal medicines are thought to be the most commonly used and oldest medical system throughout the world. In present years, plant derived products are used either alone or in combination with other drugs by several people for healing purpose and to promote health care. In the developing and developed countries, many people depend on the utilization of herbal medicines for their health maintenance. The World Health Organization (WHO) reported that herbal medicines meet the medical needs of 80% of people living in advanced countries (Mirzaeian et al., 2021).

Sepsis can be defined as a systemic infectious inflammatory response syndrome which can result in tissue hypo-perfusion, dysfunctioning of the organ and even irreversible persistent hypotension (termed as septic shock) and mortality rate to the extent of 80%. Sepsis is usually seen in ICU (intensive care unit). It is a frequent complication of severe infection, trauma, surgery and severe burn. The body is occupied by pathogens and endotoxins resulting in the release of large amount of inflammatory mediators, increasing the expression of inflammatory factors of serum [interleukin-6 (IL-6), interleukin-2 (IL-2), tumor necrosis factors- α (TNF- α) and C-reactive protein (CRP)]. The immune system as well as the anti-inflammatory system will be disturbed with deregulation of the intestinal flora. Coagulation disorders will occur and there will be damage to the organ function. The typical causes of sepsis include decrease in the autoimmunity, surgery, use of cytotoxic drugs, chronic disease and invasive examination. For the treatment of the disease, infection control and mechanical ventilation adjuvant therapy are considered. However, the conventional therapy doesn't have the ability to instantly control the serum inflammatory response and regulate the immune system of the body. Therefore, Traditional Chinese Medicine (TCM) has been helpful for the treatment of sepsis. The components of Traditional Chinese Herbal Medicine possess the characteristics to clear away toxic substances and heat

as well as to destroy bacteria, regulate immunity, and promote the restoration of the neuro-endocrine network system (Wen et al., 2021).

Significance of Herbs

It has been estimated that almost 25% of the drugs which have been prescribed throughout the world are driven from plant sources. Out of the 252 drugs, according to the list of essential medicines provided by the World Health Organization (WHO), 11% of the drugs are from plant source. As a matter of fact, the first pharmacological compound, morphine, was processed almost about 200 years ago from opium which was extracted from the poppy flower's seed pods. From that times, different scientists have been investigating plants to form different pharmaceutical drugs that are known to us at present. Nowadays, plants are being utilized to treat many health conditions including arthritis, allergies, skin infection, migraines, fatigue, burns, wound, gastrointestinal problems, and even though for the treatment of cancer. This has truly proven that food is medicine. These herbal medicines seem to be safer for treatment purposes and less costly than the conventional treatment drugs. This is the reason that many people are now choosing the idea of using traditional medicines (Sam, 2019).

Herbal Medicine in the Treatment of Different Diseases

Herbal medicines which are derived from plant extracts have been increasingly used to treat different clinical diseases (Ghosh et al., 2011). Since the origination of human civilization, herbs have been a fundamental part of the society. Their medicinal as well as culinary properties are responsible for their utilization. In the manufacturing of commercial drug products known today, herbal medicine has contributed largely. This includes salicin (source of aspirin) from *Salix alba*, reserpine from *Rauwolfia serpentina*, digitoxin from *Digitalis purpurea* and ephedrine from *Ephedra sinica*. Plants based medicines have been used for different cardiovascular conditions such as in systolic hypertension, congestive heart failure, atherosclerosis, arrhythmia, venous insufficiency, and angina pectoris (Rastogi et al., 2016).

Plants based medicines have been commonly used since centuries for the treatment of liver diseases due to the lower toxicity factor. Through clinical evaluations, the hepato-protective ability of different herbs has been assessed (Ghosh et al., 2011). Herbal products seem to be a favorable alternative medicine for the treatment of Alzheimer's patients. Experiments have been carried out to test herbal medicines in animal models as well as in cell models of Alzheimer disease. Also herbal drugs have been tested to a less extent in clinical trials (Anekonda and Reddy, 2005). Phenolic compounds from natural sources have an important role to prevent and treat cancer. Phenolic compounds (from dietary plants and medicinal herbs) involve flavonoids, phenolic acids, tannins, curcuminoids, lignans, coumarins, quinones and some others (Huang et al., 2009). In many Asian countries including China, Traditional Chinese Herbal Medicines (TCHMs) and western pharmacotherapy are often used in combination to treat chronic kidney diseases (CKD) (Zhong et al., 2013). Various herbs have been traditionally recommended to treat diabetes. In addition to this, many researchers have outlined the anti-diabetic effects of a number of plants (Ghorbani, 2013). A while ago, publications have reported the antiviral properties of *Chaihu*, *Prunella vulgaris* and *Herba patriniae* against Coxsackie B virus, Herpes simplex virus, and Respiratory syncytial virus, respectively (Wang et al., 2009).

SEPSIS

Sepsis can be defined as an organ dysfunction which is life threatening and caused by dysregulated host response to infection. A latest report of Global Burden of Diseases highlighted that sepsis is prevalent with almost 50 million cases of sepsis globally on annual basis. This can affect people of all ages (van der Poll et al., 2021). The pathophysiology of sepsis is complex. The occurrence of sepsis is gradually rising. The mortality rate ranges between 30% and 50% throughout the world (Cheng and Yu, 2021). Sepsis may be caused by bacteria, viruses or fungi. Among hospitalized patients in the intensive care unit (ICU), it is of the most frequent cause of death. Due to its high mortality and morbidity rate, sepsis stands as a considerable health problem. To enhance the probability of survival, identification and early treatment are very important (Rello et al., 2017).

Pathophysiology

In sepsis, there is uncontrollable and excessive innate immune system response as a result of the invading infectious microorganisms. It is characterized by excessive production of pro-inflammatory mediators, for examples, tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), interleukin-1β, and high mobility group box 1 (HMGB1). In case of severe sepsis, the massive formation of pro-inflammatory cytokines together with reactive oxygen species may affect the function of organ and contribute to the initiation of abnormal apoptosis in various organs, following multiple organ dysfunction syndrome and death. Therefore, drugs which have the potential to weaken the inflammatory response may be helpful as therapeutic agents for sepsis (Alikiaii et al., 2021).

Causes of Sepsis

The causes for sepsis can be divided in to infectious and non-infectious. Systemic inflammatory response syndrome (SIRS) occurs as a result of non-infectious agents. Sepsis features can be seen without any identifiable infection. Surgical injuries, trauma, drug reactions, tissue ischemia, pancreatitis, autoimmune diseases and neoplastic diseases can be the

examples and can be progressed to shock and different organ failure. Infectious sepsis can be caused by gram positive bacteria, gram negative bacteria, parasites and fungi. These infectious agents include vancomycin resistant enterococcus (VRE), methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin sensitive enterococcus (VSE), *Streptococcus pneumoniae*, *Staphylococcus epidermis*, Klebsiella spp., *Escherichia coli*, Acinetobacter spp., Pseudomonas spp., Candida spp., and Aspergillus spp. (Alikiaii et al., 2021).

Role of Herbs in the Treatment of Sepsis

Despite the presence of numerous modern antibiotics together with the intensive care technologies, the treatment for septic shock persists to be challenging. Dependence on antibiotics along with other methods which target the modulation of the systemic inflammatory response including cytokine antagonists, steroids and hemofiltration have not resulted in reliable successful therapy for inflammation and infection related septic shock. Resistance of bacteria to different drugs is one factor leading to the lack of success to the therapy (Wang et al., 2009).

The diagnosis and treatment of sepsis have been a focal point for infectious disease studies, emergency medicine and critical medicine. This is because of the massive incidence and mortality rate of sepsis. From the time of 1992, experts have suggested diagnoses and several plans for the treatment. Considering the treatment of sepsis, Chinese Herbal Medicines appear to have therapeutic properties. Basic scientific experimentation on these herbal medicines is expanding. Chinese Herbal Medicines (CHMs) have the potential to restrain aggregation of platelet, regulate inflammation as well as immune response, and also refine microcirculation, thus preventing sepsis progression and improving sepsis prognosis in patients. Such medicines are single Chinese herbs, Chinese herbal prescriptions and Chinese patent medicines (Cheng and Yu, 2021).

For thousands of years, herbal medicines have been used as therapeutics for shock and infections globally. The active compounds of these natural products generally possess one or more of the below mentioned properties:

1) Directly attack or suppress the bacterial pathogen
2) Modulate the immune system of host which results in inflammation suppression and repression of excessive production of inflammatory mediators
3) Neutralization of toxic free-radicals (Wang et al., 2009).

Immunomodulators are well known for modulation of the immune response and improve diseased conditions thus playing an important role in inflammatory conditions. These can either exist naturally from plant sources or can be synthetically produced from parent compound. Natural modulators acquired from raw vegetables and fruits involve plant sterols and sterolins. Various plants parts and their extracts have been acknowledged as effective natural immuno-modulators. For example, juice of Aloe vera leaf, oil of *Nigella sativa*, ginseng root, root of Ashwagandha, *Syzygium jambolanum* extract, extract of mushroom, Rhubarb extract, chamomile tea, *Isodon serra* extract, juice and extract of leaves of *Carica papaya*. The outcome of an earlier study suggested that *Jatropha cureas* methanolic extract has immuno-modulatory results by enhancing the level of lymphocytes and macrophages in blood along with an increase in antibody titers. Manifestations from former studies recommended that a number of herbal medicines yield certain antioxidants which can help in the control of oxidative stress during inflammation. In patients with severe sepsis, modifications in hematologic system are generally observed with an evidence of surge in mortality. Anyhow, survival rate may be improved by timely diagnosis and therapy of disturbed hematologic system. A study indicated that platelet /neutrophil complexes become greater in initial phase of sepsis and decreased in severe sepsis as there is thrombocytopenia associated with sepsis. A research evaluated that the leaves of *Carica papaya* escalates the production of platelet count. Constituents of plants like Genistein, Epigallocatechin-3-gallate (EGCG), and Baicalein remarkably reduce high blood pressure, therefore, serve a potential role of hypotensive drug in septic rats (Usmani et al., 2021).

Salvia miltiorrhiza, *Astragalus membranaceus*, and *Angelica sinensis* which are Traditional Chinese medicines (TCM) have immune-modulatory or anti-inflammatory effects thus helping in the regulation and improvement of immune system. Different types of Traditional Chinese Medicines have been researched deeply. For examples, several researches reported vasorelaxant property, antioxidant potential, and antiplatelet aggregation activity of the rhubarb along with detailed mechanisms. Apart from this, certain other effects have been discovered, for example, prevention of over secretion of tumor necrosis factor- α (TNF- α), promotion of gastrointestinal electric activity and also intestinal peristalsis, endotoxin reduction, reduction of bacterial translocation and improved microcirculation. Several compounds of *Salvia miltiorrhiza* (a commonly used Chinese medicine) were extracted. It has been reported that these compounds possess particular activity against platelet aggregation, leukocyte adhesion, endothelial cell injury and release of oxygen radicals. Two proteins isolated from *Salvia miltiorrhiza* have antifungal activity. This Chinese medicine also plays efficient role in reducing over production of prostaglandins (PGs), neutrophil degranulation, and nitric oxide synthase induction (Liang et al., 2015).

In Malaysia, different plants have been utilized for therapeutic reasons based on various practices and culture. Here are some Malaysian herbal plants with their active components and potential therapeutic applications in sepsis.

Andrographis paniculata

A. paniculata is also known as King of Biters. It is a bushy therapeutic plant. It is widely distributed in Southern Asia and Southeast Asia. This plant is known as "*pokok cerita*" or "*hempedu bumi*" in Malaysia. The scientifically proved effects of this pant involve anti-inflammatory, antibacterial, anti-diabetic and antioxidant actions.

Zingiber officinale

Z. officinale is also known by the name of ginger. Among Indian and Chinese communities, its rhizome has been historically used for medicinal purpose. The ginger has a variety of advantages which include its anti-inflammatory, antioxidant and anti-carcinogenic effects along with prohibition of cardiovascular diseases.

Curcuma longa

In general, C. longa is called as turmeric. For so many years, turmeric has been utilized for culinary purpose and also in the Ayruvdeic tradition. Its rhizome appears to have numerous medicinal activities including antibacterial, antifungal, antiviral, anti-inflammatory, anti-diabetic, as well as antioxidant effects. A main compound present in its rhizome is curcumin which has been widely studied due to its antisepsis ability.

Piper nigrum

Investigations have reported that *Piper nigrum* holds hepatoprotective, antioxidant, antimicrobial, and anticancer characteristics. (Liew et al., 2020).

Some other Traditional Chinese Medicines (TCMs) include:

Rhubarb

Rhubarb contains organic acids, glycosides, anthracene derivatives, volatile acids and certain other active components. So it is used in Traditional Chinese Medicine. It has the ability to improve kidney function, digestive system, inhibits lung disease, and prevents antioxidant stress. In addition to this, it shows antiviral, antibacterial, anti-inflammatory and antitumor actions.

Berberine

One of the major effective constituents of *C. chinensis* is berberine. It is an alkaloid which is acquired from *C. chinensis*. This component demonstrates an inhibitory action when there is acute and chronic inflammation. C. chinensis and berberine can increase the phagocytosis of white blood cells in vitro and in vivo and partially stops the inflammatory reaction mechanism. Furthermore, berberine is helpful to prevent and treat sepsis induced multiple organ dysfunction syndrome (MODS).

Safflower Yellow

Toxins and heat cause blood stasis which have a remarkable role in the manifestation and development of sepsis. Removal of blood stasis and activation of blood circulation are aided by safflower. Safflower yellow (recognized effective constituent of safflower) possesses antioxidant, anti-inflammatory and immune function boosting qualities.

Ginseng

Ginseng holds chemical ingredients like ginseng polysaccharides, amino acids, volatile oils and ginsenosides. These components have pharmacological potential, for example, anti-oxidative, anti-fatigue and immunity boosting effects. A number of studies have been performed to investigate the actions of ginsenoside to prevent and treat MODS in sepsis, along with sepsis associated encephalopathy, lung damage, liver damage as well as myocardial injury (Zhang et al., 2023).

***Angelica sinensis* (Oliv). Diels**

The low molecular weight fraction of aqueous extract of *Angelica sinensis* (a Chinese herb) is beneficial against lethal experimental sepsis and endotoxemia in a dose dependent manner.

***Salvia miltiorrhiza* Bunge**

Salvia miltiorrhiza, a natural remedy which has been experimentally proved to interact with HMGB1. It was used traditionally for the treatment of cardiovascular diseases. It was reported to be defensive against lethal LPS-induced endotoxemia and sepsis by reducing HMGB1 proportion in vivo in a murine model.

***Glycyrrhiza Glabra* L. (Licorice)**

Rhizomes and roots are the principle therapeutic parts of licorice. Various studies have revealed that licorice has antiviral property against hepatitis C virus. Moreover, anti-inflammatory, antimicrobial and anti-oncogenic characteristics have been reported. Glycyrrhetinic acid (GTA) and glycyrrhizic acid (GA) are the compounds which may be isolated from licorice plant.

***Perilla Frutescens* (L.) Britton**

Rosmarinic acid (RA) can be extracted from *Perilla frutescens*. It has the potential to inhibit the release of HMGB1 and down regulate HMGB1-dependent inflammatory responses in endothelial cells of humans (Wyganowska-Swiatkowska et al., 2020).

A flavonoid which is apigenin is found in ample amount in plenty of vegetables and fruits. This flavonoid has demonstrated excellent effectiveness for the control of inflammatory response. Salidroside is obtained majorly from the root and rhizome tissues of *Rhodiola rosea* (rose). Several investigations mentioned that it possesses antibacterial, anti-inflammatory and anti-oxidative effects. Another flavonoid, baicalein is gained from the roots of *Scutellaria baicalensis georgi* (a Chinese herb). The anti-oxidative and anti-inflammatory properties of baicalein have been shown through different experiments. A non-flavonoid polyphenol, resveratrol has anti-oxidative quality. This component is present in fruits skin like berries and grapes. Pretreatment with resveratrol guarded mice against CLP-induced ALI (Song et al., 2023).

An exemplary therapeutic drug would weaken excessive harmful responses, help out in the clearance of microbes, and guard tissues, consequently assisting in organ preservation and function of system with increasing survival. Based on the preclinical studies, it can be proposed that polyphenols (PPLs) which is a group of chemicals found in abundance in plant based beverages and food, achieves the above mentioned criteria and carries the ability to manage sepsis. The largest group of phytochemicals is polyphenols (PPLs). Greater than 8000 are thought to occur and present in different amounts in majority plant derived foods (such as fruits, vegetables, spices along with legumes). Some examples include olive oil, green tea, soybeans, turmeric and red wine which have high content of polyphenols which contribute to their health benefits (Shapiro et al., 2009).

Classification and subclassification			Polyphenols	Source
Phytochemicals	Polyphenols	Flavonoids	Genistein	Tofu, soya
			Quercetin	Apple
			Naringenin, hesperidin	Citrus fruits
			Anthocyanins, cyanidin	Berries
			Glabridin	Licorice (*Glycyrrhiza glabra*)
		Nonflavonoids	CAPE	Propolis
			Oleuropein	Olive oil
			Curcumin	Turmeric

Classification and Sources of Polyphenols with Curative Ability for Sepsis (Shapiro et al., 2009).

Research in Herbal Medicines

To determine the safety and effectiveness of Traditional Herbal Medicines, there are limited clinical trials. The lack of research does not hinder many of the people from using them, given that these remedies are usually grounded in long cultural traditions. Ethical analysis of global herbal medicine research was published recently. They give rise to a number of scientific queries that enlighten the problems of performing research with herbal medicines globally. To find suitable ways to perform this kind of research is an existent challenge (Rivera et al., 2013).

Potential Risks Related to Herbal Medicines

It is believed by the public and some professionals of health care regarding herbal medicine that they are natural so they are comparatively safe. In spite of the fact that very little data is present in the support of this presumption. Studies have also highlighted serious consequences as a result of the side effects of particular herbal drugs. From the utilization of herbal medicine, numerous harmful and deadly complications have been disclosed. Majority of this data has been collected from health care centers and emergency rooms. These bad consequences of herbal products may happen by means of different mechanisms such as direct harmful effect of the herb, effects due to contamination, as well as interaction with some other herbs or drugs. Complications may occur due to contamination of heavy metals (such as arsenic, mercury, or lead). Besides this, contamination may be due to the undeclared pharmaceutical products which are illegally and purposefully added to the herb to attain a desirable effect (Rodriguez-Fragoso et al., 2008).

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