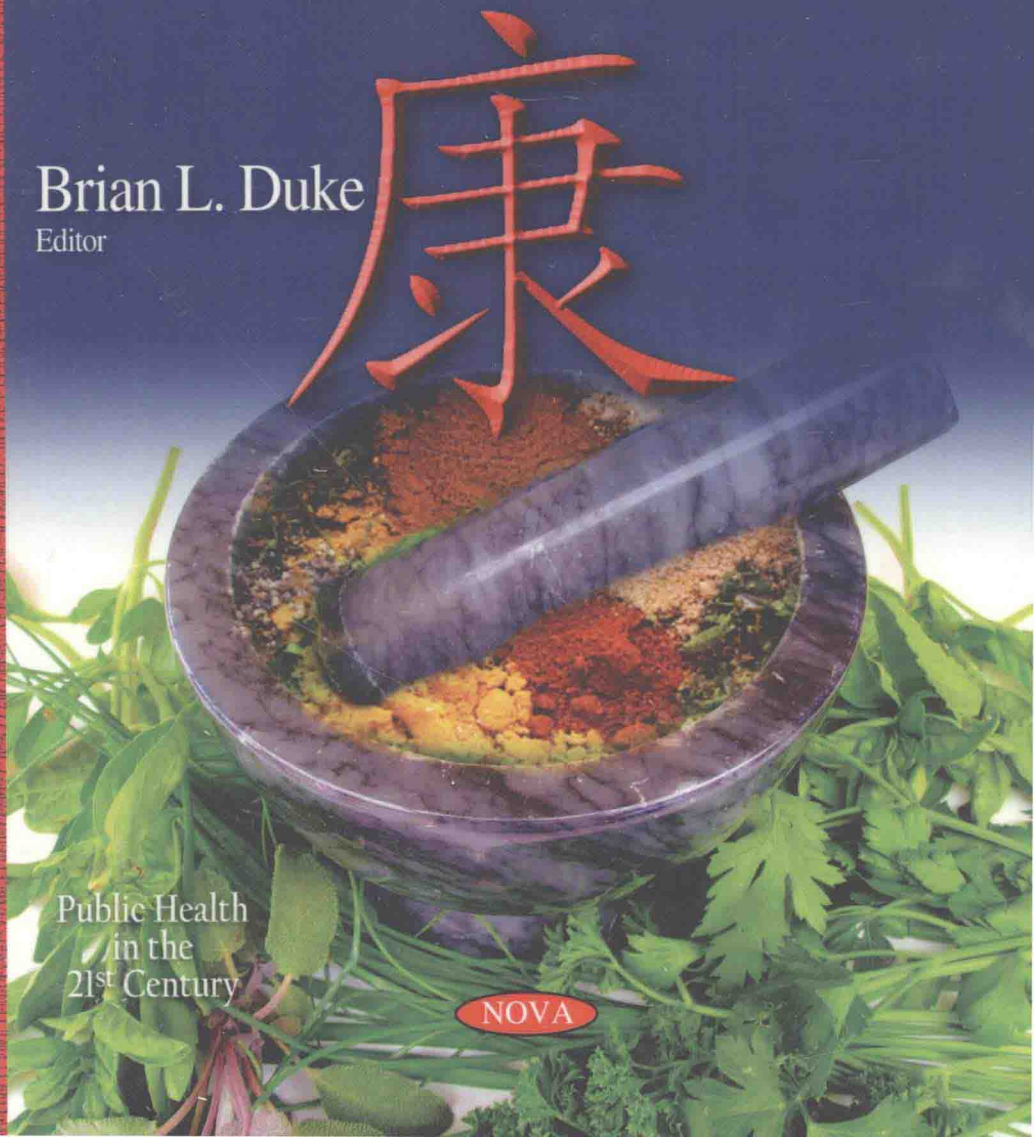
Chinese Herbs and Herbal Medicine

Essential Components, Clinical Applications and Health Benefits

Brian L. Duke
Editor



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Preface

Radix Bupleuri (Chai Hu) is one of the most commonly used herbs in the Chinese medicine clinical practice. In Chinese medicine, it is believed that Radix Bupleuri is acrid, cool and bitter and enters liver and gallbladder meridians. This book discusses the use of Chinese herbs, such as Chai Hu, and other different herbal medicines for diseases and illnesses such as atopic dermatitis, and for cutaneous wound healing. It discusses the essential components, clinical applications and health benefits of herbal medicine.

Chapter I – A cutaneous wound is a break in the skin integrity as a result of physical, thermal or chemical injuries. There are many types of wounds, such as incisions, lacerations, contusions and burns. After hemostasis occurs at the moment of injury, the wound healing process proceeds to subsequent yet overlapping stages, namely inflammatory, proliferative and remodeling phases. The inflammatory phase consists of phagocytosis and microvascular changes induced by chemical mediators. The proliferative phase mainly involves angiogenesis, granulation tissue formation, wound contraction and re-epithelialization. In the remodeling phase, new collagen formation occurs to strengthen the wound. In general, the strategy for wound care management is to prevent infection and to promote healing. Currently, herbal medicine has increasingly become a field of interest for wound care. A number of investigations into its therapeutic roles in wound management have been conducted in human and animal models. The well-recognized and most studied medicinal plants include *Aloe vera*, *Centella asiatica* and *Curcuma longa*. These herbs have been used for centuries in traditional Chinese medicine and Ayurveda. Based on the existing scientific evidence, the above-mentioned herbal medicines can accelerate cutaneous wound healing and repair by suppressing inflammation, promoting angiogenesis, inducing cellular growth and proliferation, reducing oxidative stress in the wound, controlling

infection, and improving wound remodeling. This chapter will provide insight into the mechanisms underlying various stages of cutaneous wound healing. To establish a foundation of basic knowledge, the first part of the chapter provides an overview of wound healing mechanisms, wound management strategies, and experimental approaches to wound healing, including research models for wounding and the evaluation of critical events during each phase of the wound healing process. Also, a wound microcirculation study using a dorsal skinfold chamber preparation and an intravital microscopic technique to demonstrate cutaneous microvascular changes *in vivo* will be described.

Chapter II – Radix Bupleuri (Chai Hu) is one of the most commonly used herbs in the Chinese medicine clinical practice. In Chinese medicine, it is believed that Radix Bupleuri (Chai Hu) is acrid, cool and bitter and enters Liver and Gallbladder meridians. It is used to reduce fever, release the stagnation of Liver Qi and raise clear Yang. Details of its actions, indications, contraindications, dosage and control are discussed from Chinese medicine perspective. In Western medicine, the clinical and experimental studies have shown that Radix Bupleuri (Chai Hu) has anti-inflammatory, antimicrobial, antiviral, immune-regulatory and anti-tumour effects. Radix Bupleuri (Chai Hu) also has effects on central nervous system, cardiovascular system, digestive system and metabolism. This monograph presents details of its pharmacodynamics, pharmacokinetics and mechanism, toxicology and interactions as well as side effects with evidence from comprehensive literature search. Guidelines for its use and regulatory control in different countries are also reviewed.

Chapter III – Atopic dermatitis (AD) is a common chronic inflammatory skin disease in children that could adversely affect their quality of life, and its prevalence is increasing in the last few decades. As definitive cure is lacking, there has been a considerable interest on using traditional Chinese Herbal Medicines (CHM) as an alternative treatment for AD. However, no data are available to provide an overview of the use of CHM for AD. In this chapter, we explored all the available relevant literatures on the clinical applications of CHM for AD, including its indications, contraindications, individual medicines, formulae, regimes, effectiveness, efficacy, safety, adverse effects and toxicity. The main objective is to review the available clinical studies on CHM for its therapeutic use in AD patients and the potential adverse outcomes. Over 140 literatures were identified, including the observational designed studies (exploratory studies, descriptive studies and analytical studies as case series, cohort studies, case-control studies, cross-sectional studies), the experimental studies (quasi- and randomized controlled trials) and the

qualitative studies. Based on the principles and workflows from Centre for Evidence-Based Medicine of Oxford University and Cochrane Review, only few studies were selected for the systematic review and further meta-analysis. The result showed that compared with modern medicine groups, combined use of CHMs and modern medicines was significantly effective as a treatment option for atopic dermatitis. However there was insufficient proof on its safety although no specific safety problem was reported in the clinical trials. More scientific evidences through comprehensive studies on the efficacy and safety of CHM for AD are still necessary for its wider application.

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Chapter I

Herbal Medicine and Mechanisms for Cutaneous Wound Healing

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Abstract

A cutaneous wound is a break in the skin integrity as a result of physical, thermal or chemical injuries. There are many types of wounds, such as incisions, lacerations, contusions and burns. After hemostasis occurs at the moment of injury, the wound healing process proceeds to subsequent yet overlapping stages, namely inflammatory, proliferative and remodeling phases. The inflammatory phase consists of phagocytosis and microvascular changes induced by chemical mediators. The proliferative phase mainly involves angiogenesis, granulation tissue formation, wound contraction and re-epithelialization. In the remodeling phase, new collagen formation occurs to strengthen the wound. In general, the strategy for wound care management is to prevent infection and to promote healing. Currently, herbal medicine has increasingly become a field of interest for wound care. A number of investigations into its therapeutic roles in wound management have been conducted in human and animal models. The well-recognized and most studied medicinal plants include *Aloe vera*, *Centella asiatica* and *Curcuma longa*.

These herbs have been used for centuries in traditional Chinese medicine and Ayurveda.

Based on the existing scientific evidence, the above-mentioned herbal medicines can accelerate cutaneous wound healing and repair by suppressing inflammation, promoting angiogenesis, inducing cellular growth and proliferation, reducing oxidative stress in the wound, controlling infection, and improving wound remodeling. This chapter will provide insight into the mechanisms underlying various stages of cutaneous wound healing. To establish a foundation of basic knowledge, the first part of the chapter provides an overview of wound healing mechanisms, wound management strategies, and experimental approaches to wound healing, including research models for wounding and the evaluation of critical events during each phase of the wound healing process. Also, a wound microcirculation study using a dorsal skinfold chamber preparation and an intravital microscopic technique to demonstrate cutaneous microvascular changes *in vivo* will be described.

Introduction

A cutaneous wound is a disruption of the normal continuity of the skin caused by a physical, thermal or chemical injury. Cutaneous wounds can be classified into several types according to the character and cause of the injury: incisions, lacerations, contusions and burns.

An incised wound is a wound that is inflicted by a cutting instrument and that involves minimal tissue damage. A lacerated wound is one in which the tissues are torn or mangled by a dull or blunt instrument.

Another injury that results from blunt trauma is called a contusion, in which the skin is unbroken, but the underlying tissues and blood vessels are damaged. Abrasions are associated with a loss of the superficial layer of the skin. Burns can be caused by thermal (heat), electrical, radioactive, or chemical injuries that destroy cellular proteins and cause cell death.

In response to tissue injury, the body restores the continuity and function of the disrupted skin by undergoing wound healing processes that consist of successive albeit overlapping stages. Any alterations during each healing stage can give rise to delayed- or non-healing wounds. Successful healing thus requires a proper treatment regimen, which involves systemic support and local wound care. Since ancient times, herbal medicine has been implicated in the treatment and management of wounds, particularly in the primary healthcare systems of many countries. The role of herbal medicine in wound healing has also gained increasing attention in research.

The objective of this chapter is to provide insight into the mechanisms of action of herbal medicines in wound healing.

The first part of this chapter provides a general consideration of wound healing, and it is intended to describe the basic concepts of wound healing physiology, as well as influential factors, strategies for wound care management, and a brief outline of the associated experimental approaches, including research models and techniques used to evaluate the process of wound healing with an emphasis on the wound microcirculation studies. The aforementioned knowledge is fundamental to provide the scientific evidence needed to clarify the therapeutic efficacy and underlying mechanisms of herbal medicines in wound healing. To achieve this goal, the last part of this chapter provides a compilation of the scientific evidence regarding the therapeutic roles and mechanisms of action of the three most commonly studied medicinal herbs in wound management: *Aloe vera, Centella asiatica,* and *Curcuma longa.*

Part I: General Considerations of Wound Healing Physiology of Wound Healing

Wound healing is a process of the restoration of integrity to injured tissue as the body attempts to cure itself. Tissue injury generally has two outcomes -- regeneration and repair --- depending on the extent and continuity of the injury, as well as the regenerative potential of the affected tissue.

Regeneration is the replacement of the injured tissue by parenchymal cells of the same cell type without significant scar formation, as in moderate sunburn. Repair is replacement with connective tissue, resulting in scarring and fibrosis, as in abscess formation. An understanding of the physiology of wound healing and the factors that affect healing will provide the basis for proper wound care and management.

A number of interrelated physiological mechanisms are implicated in wound healing. After hemostasis occurs at the moment of injury, wound healing generally proceeds to three subsequent yet overlapping stages, namely the inflammatory, proliferative and remodeling phases. After being triggered by tissue injury, these processes involve a complex series of events that are regulated by many cell types and by the mediators produced (Table 1).

Following skin injury, vascular damage is often present that allows the blood to extravasate into the wound.

The body immediately responds to stop the bleeding and to prevent further blood loss via a process called hemostasis. This brief hemostatic period consists of three key events: 1) vasoconstriction; 2) platelet activation and aggregation; and 3) coagulation or clot formation. The first response of the blood vessels to direct injury is vascular smooth muscle constriction, which helps to control bleeding. In endothelial injuries, exposed collagen fibrils underlying the endothelial layer stimulate platelets to adhere to the damaged site. The activated platelets release cytoplasmic granules containing serotonin, which is a vasoconstrictor, and adenosine diphosphate and thromboxane A_2 (TXA2), which trigger platelet aggregation and thus the formation of a temporary platelet plug. The final hemostatic mechanism, i.e., the coagulation or clotting cascade, is initiated by factors that are released from the damaged tissue and activated platelets. This process leads to the conversion of prothrombin into thrombin and, subsequently, fibrinogen into fibrin, which combines with von Willebrand factor and platelets to form a mesh, giving rise to a blood clot [1].

In addition to playing a central role in hemostasis, platelets produce several growth factors and cytokines that regulate the ensuing healing cascade by modulating the functions of leukocytes, endothelial cells and fibroblasts. These platelet-derived molecules include platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1), epidermal growth factor (EGF), transforming growth factor-beta (TGF-beta), and platelet factor-IV [1-3].

Inflammatory Phase

The inflammatory phase occurs during days 1 to 3 after wound infliction. This phase consists mainly of two components: microvascular changes; and leukocyte recruitment and activation to kill microorganisms via phagocytosis.

These inflammatory reactions are responsible for the characteristic manifestations of inflammation, which are warmth, erythema (redness), edema (swelling), and pain. Inflammation that occurs during this phase is intended to protect against wound infection and to initiate the repair process [2].

Microvascular Changes

Microvascular changes during inflammation include vasodilatation and increased vascular permeability. After temporary vasoconstriction as an immediate response during hemostasis, vasodilatation occurs within seconds to a few minutes.

This process is caused by a vasoconstriction-mediated reduction of blood flow, creating tissue hypoxia, which stimulates the production of vasodilator substances, such as nitric oxide, adenosine, and vasoactive metabolites.

Mast cells also release histamine and other active amines, which cause vasodilatation and increased vascular permeability. Moreover, there is an activation of vasoactive substances, such as serotonin, bradykinin and prostaglandins. Vasodilatation leads to increased blood flow, resulting in erythema and warmth. Increasing vascular permeability results in the leakage of plasma and proteins, producing exudate and edema.

These vascular reactions help to deliver leukocytes and plasma proteins to the injured site. It is worth noting that a proper amount of exudate aids the healing process by cleansing the wound, maintaining a moist environment and facilitating epithelialization [2].

Leukocyte Recruitment and Activation

During leukocyte recruitment and activation, leukocytes are recruited from the circulation to the wound site. Subsequently, they are activated to eliminate microbes and dead tissues.

The mechanisms underlying leukocyte recruitment from the blood vessels to the extravascular space at the focus of the injury involve four steps: 1) margination and rolling along the vessel wall; 2) adhesion of leukocytes to the endothelial surface; 3) transmigration through the endothelium, or diapedesis; and 4) movement toward the site (also called chemotaxis).

These steps are mediated by different molecules: selectins in rolling, such as E-selectin, P-selectin and L-selectin; integrins in adhesion, such as intercellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), together with integrin activation by chemokines, such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-1 (IL-1); platelet endothelial cell adhesion molecule (PECAM-1; also known as CD31) in transmigration; and chemotactic molecules in chemotaxis, such as chemokines and leukotrienes. Early cellular infiltrates consist predominantly of polymorphonuclear leukocytes or neutrophils within the first 24 to 48 hours. Later, within 48 to 72 hours, circulating monocytes, attracted by molecules derived from platelets and damaged cells, constitute the next cell type to enter the wound and differentiate into tissue macrophages [2].

When recruited to the wound site, leukocytes are activated by several mediators. During the early inflammatory phase, the activated neutrophils ingest bacteria and tissue debris via a process called phagocytosis, and they kill and degrade these microorganisms by releasing lysosomal enzymes, nitric

oxide and reactive oxygen species as a result of the oxidative burst that occurs during robust neutrophil activity. In addition, neutrophils can destroy microbes and dead tissues extracellularly by producing these substances, as well as "traps". Therefore, the main function of neutrophils is to prevent infection [2].

During the late phase of the inflammatory process, prior to the proliferative phase, acute inflammation must be terminated, and leukocytes produce anti-inflammatory mediators to limit the reaction. This process is followed by resolution and then initiation of the subsequent repair process. Once activated, macrophages phagocytose any remaining bacteria or debris, and they release proteolytic enzymes to clear the wound site. They also initiate and regulate the subsequent repair process by producing many growth factors that are essential for the proliferation of fibroblasts, smooth muscle cells and endothelial cells. Thus, alterations in macrophage function can lead to impaired healing [2].

Proliferative Phase

Following the cessation of inflammation, the proliferative phase begins approximately by day 3, and it lasts until week 2 to 4 post-wounding, depending on the size of the wound. This phase mainly involves angiogenesis, granulation tissue formation, wound contraction and re-epithelialization.

As such, the mechanisms underlying healing during this stage are designed to restore the vascularization of the wounded area, repair the tissue defect, decrease the wound size and cover the wound surface.

Angiogenesis

The establishment of a vascular supply to the wounded skin, called angiogenesis or neovascularization, is critical for healing. It is the process of new blood vessel development.

Endothelial cells are the key cells in this process, which is stimulated by tissue hypoxia and by a number of growth factors. As mentioned previously, the wounded area is hypoxic, inducing macrophages to release angiogenic growth factors, the most important of which are vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF or so called FGF-2). New capillary buds or sprouts are then formed from the intact vessels, and they further develop the capillary loop into the wound.