Herbs for Optimizing Tissue Repair and Regeneration

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Kerry Bone is the co-founder and innovation driver at MediHerb, where he serves as Director of Research and Development. In 2016 MediHerb was awarded the American Botanical Council’s (ABC’s) Varro E. Tyler Award for excellence in Phytomedicinal Research.

As part of his educational role, Kerry is Principal of the Australian College of Phytotherapy and also Adjunct Professor at New York Chiropractic College, providing input into their postgraduate applied nutrition program.

Kerry is co-author of more than 30 scientific papers on herbal research. He has also written and co-written six popular textbooks on herbal medicine, including his latest, the second edition of *Principles and Practice of Phytotherapy* which was awarded the 2013 James A. Duke Excellence in Botanical Literature Award by the ABC.

Kerry maintains a busy herbal and naturopathic practice in Toowoomba, Queensland, where he has been in continuous service for more than 30 years.

In 2015, Kerry’s lifelong contribution to the field of herbal medicine was recognized with his receiving the prestigious Lady Cilento award from the complementary medicine industry in Australia.
Introduction

- As a profession we place great emphasis on assisting the body to heal itself
- But herbs that promote tissue healing (other than by topical application) are scarce in our materia medica
- One stand-out exception is the humble weed Gotu Kola (*Centella asiatica*)
Topics

- The healing process
- Gotu Kola the healer: a promoter of connective tissue regeneration and regulation
- Gotu Kola and circulation: veins, microcirculation and arteries
Topics

- Gotu Kola and the CNS: neuroprotective and neuroregenerative?
- Combining Gotu Kola with other herbs to support healing
Phases of Tissue Healing

The healing process is divided into three overlapping phases:

- Inflammatory phase
- Proliferative phase
- Remodeling or maturational phase

Porth CM. *Pathophysiology* 7th Ed. Lippincott Williams and Wilkins, Philadelphia, 2005
Inflammatory Phase

- Begins at time of injury
- Results in vascular response leading to fluid exudate $\rightarrow$ edema
- This facilitates a cellular response characterized by infiltration of white blood cells

Image: By Red_White_Blood_cells.jpg: Electron Microscopy Facility at The National Cancer Institute at Frederick (NCI-Frederick) derivative work: WhatamIdoing (Red_White_Blood_cells.jpg) [Public domain], via Wikimedia Commons

Porth CM. *Pathophysiology 7th Ed.* Lippincott Williams and Wilkins, Philadelphia, 2005
**Proliferation Phase**

- Begins several days after injury
- Involves generation of repair cells, most important are the fibroblasts
- Fibroblasts: connective tissue cells that synthesize and secrete collagen

*Image credit: CC BY SA 3.0, Heiti Paves, 23 Oct 2012*

Porth CM. *Pathophysiology 7th Ed.* Lippincott Williams and Wilkins, Philadelphia, 2005
Proliferation Phase

- Angiogenesis: essential in the production of collagen as it:
  - ↑ local blood flow and thus
  - ↑ oxygen availability
  - → enabling the fibroblasts\(^1\)

- Myofibroblasts (derived from fibroblasts) ⇒ for wound contraction and early strength of repair\(^2\)

Remodeling Phase

- Begins approximately 3 weeks after injury and can continue for 6 months or longer
- Continued remodeling of scar tissue by the simultaneous synthesis of collagen and lysis by collagenase enzymes
- Resulting in changes in the architecture of the repair to ↑ tensile strength

Porth CM. *Pathophysiology 7th Ed.* Lippincott Williams and Wilkins, Philadelphia, 2005
The Healing Process

1. Clotting
2. Vascular response
3. Inflammation
4. Scar formation
5. Epithelial healing
6. Contraction
7. Scar Remodeling
Factors that Inhibit Healing

- Malnutrition and micronutrient deficiency
- Poor blood supply, including microcirculation issues
- Sustained inflammation; eg infection, trauma etc
- Prescribed drugs
Gotu Kola and TTFCA

- TTFCA ⇒ total triterpenic fraction of *Centella asiatica* (Gotu Kola)
- Contains mainly asiaticoside, asiatic acid and madecassic acid
- Many key pharmacological and clinical studies
- Can extrapolate data to whole herb extracts ⇒ provided herbal dose contains around 120 to 180 mg/day of TTFCA
Gotu Kola and Connective Tissue

- Earlier experimental studies ⇒ oral administration of either Gotu Kola extract or TTFCA improved collagen synthesis and maturation of collagen ⇒ improved strength of scar tissue in dermal wounds$^{1,2}$
- Later *in vivo* studies ⇒ burn healing ↑$^{3}$ and cartilage protective activity$^{4}$

Gotu Kola: The Healer

Early European Research

- Research in the 1980s ⇒ benefit in healing gastric and duodenal ulcers\(^1\)
- Early French and Italian clinical research (1960s and 1970s) ⇒ good healing rates in refractory cases of:
  - skin and leg ulcers\(^2\)
  - episiotomies\(^3\)


Gotu Kola: The Healer

Early European Research

- corneal wounds\(^1\)
- surgical wounds\(^2\)

- Beneficial effects were also noted in 20 children with scleroderma in Spanish research\(^3\) and also in adults\(^4,5\)

5. Guseva NG, Starovoitova MN, Mach ES. *Ter Arkh* 1998; 70(5): 58-61. PMID: 9644746
Gotu Kola: The Healer

Early Indian and Egyptian Research

- Indian research ⇒ improved healing in leprosy\(^1,2\)
- Egyptian research ⇒ benefits in:
  - liver fibrosis\(^3\)
  - cataract surgery\(^4\)

Gotu Kola and Keloid Scarring

- Oral TTFCA for elevated scars and keloids, including post burn keloids
- 139 patients, dose 60-90 mg/day ⇒ 82% benefited from the extract after 2-18 months, either relief of symptoms or disappearance of inflammation

Gotu Kola and Veins

- A 4-week, dose-finding study: normal volunteers (180 mg/day) and patients with chronic venous insufficiency (CVI, doses 0, 90 and 180 mg/day)
- Changes in capillary flow and ankle edema
- Dose-response effect observed, (no change in the placebo group and normal volunteers)
- Objective changes ⇒ correlated with symptom improvements (next slide)

# Gotu Kola and CVI

Average score obtained by considering four major symptoms*

<table>
<thead>
<tr>
<th>Groups</th>
<th>Before</th>
<th>After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>7.7 ± 1.5</td>
<td>4.6 ± 1.1†</td>
</tr>
<tr>
<td>B</td>
<td>7.8 ± 6.2</td>
<td>6.2 ± 1.7†</td>
</tr>
<tr>
<td>C</td>
<td>7.7 ± 1.2</td>
<td>7.6 ± 1.3 ns</td>
</tr>
</tbody>
</table>

A = 180 mg/day, B = 90 mg/day, C = placebo

* (1) swelling sensation, (2) restless lower extremities, (3) pain and cramps and (4) tiredness. The analog scale ranged from 1 to 10

† p<0.05

ns: not significant

Why Veins?

- Varicose veins and CVI long regarded as disorders of valvular incompetence
- Recent evidence: changes in the vein wall precede incompetence
- Varicosities often observed below competent valves and occur before valvular incompetence
- Defects in extracellular matrix (ECM) and collagen composition in vein wall thought to be part of this process

Veins and TTFCA

Review of Gotu Kola actives:

- Act on fibroblasts in the vein wall; improve the synthesis of collagen and stimulate collagen remodeling
- May decrease endothelial cell damage
- Improve microcirculation, decrease edema and improve lymphatic drainage

Microcirculation and Health

Compromised microcirculation ⇒

- Heart attack, stroke, CVI
- Insulin resistance
- Liver and kidney disease
- Neurological disorders
- Osteoarthritis
- Retinal diseases
- Poor healing/tissue damage

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Smoking and Microcirculation

- Passive smoking\(^1\)
- Smoking affects healing capacity\(^2\)
- Carbon monoxide is thought to play role\(^3\)

Anesthesia and Wound Repair in Aging

- Surgical wound repair in elderly
- Surgery disrupts microvasculature of aged skin
- Most anesthetics affect microcirculation

Bentov I, Reed MJ. *Anesthesiology* 2014; 120(3): 760-772. PMID: 24195972
Gotu Kola and Microcirculation

- Two controlled trials investigated the activity of TTFCA in patients with microvascular damage due to diabetes
- Largest trial: 100 patients with or without neuropathy; extract versus placebo over 12 months and also in 40 healthy controls
- Extract significantly more effective at improving microcirculatory measures and edema

Gotu Kola and Microcirculation

- Smaller trial: 50 patients compared TTFCA to placebo or no treatment for 6 months
- Significant improvements in measures linked to microscopic vascular damage, including capillary permeability

Stages of Arterial Plaque Development

- Endothelial and microcirculatory (vasa vasorum damage)
- Inflammation
- Lipid accumulation and calcification
- Unstable plaque formation/resolution

Image: CC BY 3.0, Bruce Blaus, 28 May 2014
Vulnerable Plaque

- Unstable or vulnerable plaque: atherosclerotic plaque at a high short-term risk of rupture
- Rupture can result in a massive aggregation of platelets (known as a thrombus): can block the artery
Vulnerable Plaque

- Only plaque with very thin fibrous cap at risk of rupture
- Are essentially unstable because of a deficiency of connective tissue
- Also referred to now as thin-cap fibroatheroma (TCFA) or high-risk plaque

Plaque is a Wound

- Arterial plaque is a wound on the blood vessel wall
- Vulnerable plaque: not healing appropriately, like an ulcer or abscess
- Even in presence of widespread arterial disease, rarely more than a few plaques appear to be at risk of rupture at any given moment\(^1\)

Stabilizing Plaque

- If vulnerable plaque is a wound that has not healed properly, promoting healing should help.
- In two early placebo-controlled clinical trials, Gotu Kola (Centella) actives stabilized low-density carotid\(^1\) and femoral plaques\(^2\)

Stabilizing Plaque

- The dose used in both trials was 180 mg/day of Gout Kola (Centella) triterpenoids for 12 months.
- Clinical outcome was assessed by significant and marked increases in the echogenicity of plaques compared to placebo.
Gotu Kola: 2015 Trial

- 391 low risk, asymptomatic people followed over 4 years
- Carotid and femoral plaques assessed
- Group 1 (controls): education, exercise and diet
- Group 2: pine bark OPCs (100 mg/day)
- Group 3: pine bark OPCs (100 mg/day) and Gotu Kola (100 mg/day)
Gotu Kola: 2015 Trial

- Plaque characteristics assessed by ultrasound
- Plaques became more dense in both treatment groups (2 and 3)
- Anginal events < 3% in treatment groups (2 and 3) versus 6.25% in control (1)
- Other ischemic events lower in treatment groups

Gotu Kola and the Brain

- Thai clinical research: Gotu Kola improved memory and accuracy in both short-term (1 hour) and long-term (60 days) studies
- Long-term use also lifted reaction times and recognition skills
- Gotu Kola also boosted calmness and mood
- Doses used were 250 to 750 mg/day of an extract containing 5% triterpenes

Gotu Kola and the Brain

Neuroprotective and Neuroregenerative?

- Gotu Kola extract accelerated nerve regeneration after oral doses in rats (300–330 mg/kg/day) and contained multiple active fractions that increased neurite elongation in vitro\(^1\)
- Anticonvulsant activity in vivo (200 mg extract/kg/day)\(^2\) and a neuroprotective effect in a model of parkinsonism (300 mg extract/kg/day)\(^3\)

Gotu Kola and Anti-aging Effects

- Gotu Kola extract: 250, 500 and 750 mg/day significantly improved physical strength and fitness measured by the 30-second chair stand test in 80 healthy older volunteers (average age around 65 years)
- Two higher doses also improved the physical subscale of a quality of life scale (SF-36)
- Was a placebo-controlled, randomized, double blind trial

Ginkgo: Role in Tissue Healing

Activities associated with Ginkgo that support tissue healing:

- Anti-PAF, as platelet activating factor (PAF) is associated with inflammation
- Improved circulation in arteries, veins and capillaries, especially the microcirculation
- Nrf2 based antioxidant: ↓ oxidative stress associated with damaged tissues

Grape Seed

- Grape Seed extract from the seeds of red or white grapes
- Contains a range of polyphenols, mostly oligomeric procyanidins (OPCs)
- OPCs have a number of key actions related to tissue healing

Grape Seed and Collagen

*In vitro* and *in vivo* studies demonstrate that Grape Seed extract:

- Supports connective tissue, by protecting collagen and elastin within the microvessel wall\(^1\)
- Stabilizes connective tissue by facilitating the formation of collagen microfibrils and collagen crosslinking\(^2\)
- Protects vascular endothelium during ischemia\(^2\)

Grape Seed and Microcirculation

- Several clinical trials using doses 100-150 mg/day OPCs have demonstrated benefits for capillary resistance and capillary permeability
- For example, 100 mg/day OPCs to elderly patients with capillary fragility
- Very good results were achieved in 67%, good in 17% and moderate in 13%
- Treatment with 150 mg/day of OPCs stabilized retinopathic lesions in 80% of patients

Morgan M, Andrews C. *Nutritional Perspective* 2007; **26**: 1-3
Grape Seed and CVI

Various clinical trials on patients with CVI and/or oxidative stress: Grape Seed extract (100-150 mg/day):
- ↓ edema
- repaired capillary damage
- increased peripheral circulation

Morgan M, Andrews C. *Nutritional Perspective* 2007; **26**: 1-3
Grape Seed and CVI

- 80% of patients with CVI had a significant ↓ in lower limb swelling after 10 days of OPC treatment (100 mg/day)¹
- Compared to placebo and diosmin (a flavonoid),
- 150 mg/day OPCs ↓ the functional problems associated with impaired venous back flow²

Healing involves development of new circulation followed by laying down of new connective tissue and endothelium.

- Ginkgo will support microvascular development and circulation, as will Grape Seed extract.
- Grape Seed extract has also been shown to support and strengthen connective tissue.
- Gotu Kola stimulates connective tissue production.

Morgan M. A Phytotherapist’s Perspective No. 52 April 2007. Available via www.mediherb.com
Vein Health

Key Herbs

- Horsechestnut
- Butcher’s Broom
- Gotu Kola
- Ginkgo
- Grape Seed
- Bilberry
- 5-Point Microcirculation Phytonutrient Protocol
Eye Vascular Health

Key Herbs

- Bilberry
- Gotu Kola
- Ginkgo
- Grape Seed
- 5-Point Microcirculation Phytonutrient Protocol
Arterial Health

Key Herbs
- Ginkgo
- Gotu Kola
- Grape Seed
- Turmeric
  and other Nrf2 herbs
- 5-Point
  Microcirculation
  Phytonutrient Protocol
Joint Tissue Health

- Boswellia
- Turmeric
- Gotu Kola
- Ginkgo
- Grape Seed
- 5-Point Microcirculation Phytonutrient Protocol

Image: [Link](http://www.gnu.org/copyleft/fdl.html), JM Garg, 02 Feb 1910
Post-Surgery

- Milk Thistle
- Echinacea root
- Gotu Kola
- Ginkgo
- Grape Seed
- 5-Point Microcirculation Phytonutrient Protocol
Nourishing Tissue

- **Microvascular integrity** - Grape Seed extract, Bilberry, Gotu Kola
- **Microvascular flow** - Ginkgo, beets, Ginger, Garlic
- **Endothelial function** - Green Tea, cocoa, Garlic,
- **Blood quality** - Ginger, Turmeric, Garlic, omega-3 fatty acids
The 5-Point Microcirculation Phytonutrient Protocol

1. Boost dietary nitrate - beets
2. Increase cocoa intake
3. Increase berry anthocyanin intake
4. Raw crushed garlic: ½ to 1 clove/day
5. Increase herbs and spices: green tea, turmeric and ginger
Thank You and Questions