

# Indian Spices for the Management of Diabetic Foot Complications

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## Abstract

Despite significant advances in medicine and surgery, the prevalence of diabetic foot complications still remains high in both developed and developing countries of the world. Curcumin, the active component of turmeric, an Indian spice has been extensively studied and is known to possess many biological activities including wound healing. The current review describes the available evidence on the utility of curcumin in treating diabetic foot ulcers.

## Introduction

Despite significant advances in medicine and surgery, the prevalence of diabetic foot complications still remains high both in developed and developing countries of the world [1]. Although the data available about the epidemiology and complications of diabetes in India, the so called diabetic capital of the world, is scarce, available data shows that about 45,000 lower limb amputations are performed each year due to the complications of diabetes [2]. In the United States, 65,700 lower limb amputations were done in 2006 for non-traumatic indications in patients with diabetes [3]. Nearly 15% of all the patients with diabetes develop foot ulcers during their life time and nearly 12-24% of individuals with a foot ulcer undergo amputation [4,5]. Although there are many treatments and medications, including recombinant growth factors and stem cells that are used to treat diabetic ulcers, the optimum drug regimen remains elusive. Turmeric, the rhizome of *Curcuma longa* (Figure 1) that is commonly used to add flavor and color to Indian curries has been applied topically to diabetic foot ulcers in the Ayurvedic system of medicine in India and Nepal [6]. This review first briefly summarizes the key manifestations of the diabetic foot and then describes the available evidence on curcumin that supports its use in diabetic foot ulcers.

## Pathophysiology of Diabetic Foot

The pathophysiology of diabetic foot is multifactorial (Figure 3), but Peripheral Arterial Disease (PAD) and sensory neuropathy predominate [7]. An increased propensity of patients with diabetes towards infections combined with the impaired ability to heal pedal wounds result in the high rate of limb loss.

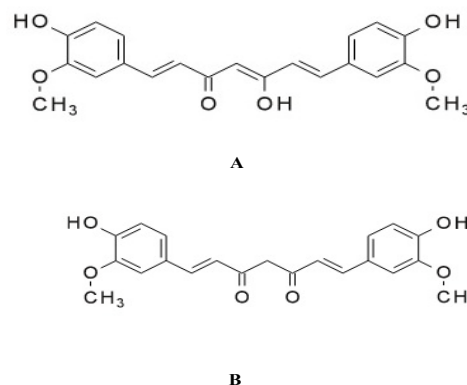
## Peripheral neuropathy

At least 50% of all the patients with diabetes develop peripheral

neuropathy during the course of their disease [8]. Prolonged hyperglycemia produces advanced glycation end products that accumulate in and occlude vasa nervorum, the tiny blood vessels that supply the nerves, leading to nerve damage. Moreover, myelin is non-enzymatically glycosylated causing a decrease in nerve conduction velocity [9]. Damage to sensory nerves causes loss of cutaneous sensation and proprioception. The patient is unaware of the injuries sustained by his feet daily during routine activities. Altered motor nerve function causes abnormal coordination of muscles in the foot and leg and changes the bony architecture of the foot. This results in increased mechanical stress while walking that further augments the chance of trauma.

## Peripheral arterial disease

Tissue ischemia in patients with diabetes involves both macrovascular and microvascular beds. Moreover, diabetic autonomic neuropathy disrupts the nervous control over blood vessels diameter which makes it difficult for blood vessels to adapt to the changes in tissue demand. The loss of sweating leaves the skin dry and ulcer prone.



A – Enol form of curcumin, B - Keto form of curcumin

Figure 2: Chemical structure of the tautomers of curcumin.



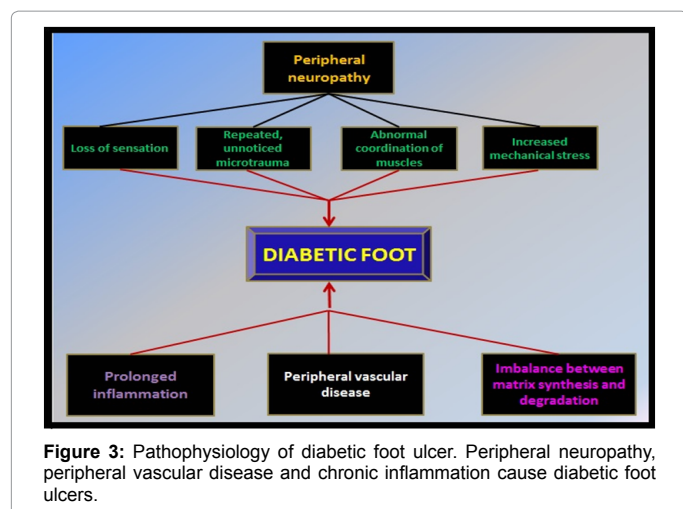
Figure 1: Rhizome of *Curcuma Longa*.

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Once an ulcer is formed, the increased oxygen and nutrient demands cannot be met by the atherosclerotic vessels decreasing the chance of healing.

### Increased rate of infection

The rates of infection in patients with diabetics are higher compared to healthy individuals. Immune dysfunction caused by diabetes [10], poor blood supply to the affected site and the peripheral neuropathy perpetuates the injury and increases the chance of infection making their treatment even more difficult.

### Other factors

Wound healing is a complicated process involving four overlapping stages of hemostasis, inflammation, proliferation and maturation. This cascade involves the interaction of various cells, growth factors and cytokines.

In diabetic foot ulcers, wound healing ability is highly impaired. First, the function of leukocytes which infiltrate the wound site soon after injury is abnormal in patients with diabetes [11]. Additionally, chemokines and growth factors necessary for the proliferation and differentiation of epithelial cells and fibroblasts are either defective due to glycation or present in abnormal levels. Abnormal levels of transforming growth factor  $\beta$ 1 [12], absence of insulin like growth factor [13], reduction in the activity of fibroblast growth factor due to glycation [14], imbalance between matrix metalloproteases and negative regulation of growth factor signaling have been reported in diabetic foot ulcers [15]. As a result, the proliferation of fibroblasts, epithelial cells and collagen is decreased. Furthermore, repeated microtrauma due to diabetic neuropathy, poor blood supply due to PAD and increased chances of infection impair the natural wound healing ability even more.

### Curcumin

Curcumin is the active component of an Indian spice called turmeric, extracted from the rhizomes of *Curcuma longa* (Figure 1). It is traditionally used to impart yellow color and flavor to several Indian cuisines. Three types of curcuminoids are found in *Curcuma longa* but curcumin is the most important. Chemically, curcumin is a polyphenol that exists as the tautomers 1,3 di-keto and enol (Figure 2). Its structure consists of phenol rings connected by  $\alpha$ ,  $\beta$  unsaturated carbonyl groups.

Curcumin possesses many potentially beneficial properties ranging from anti-microbial to anti-cancer [16].

### Curcumin and Wound Healing

Several animal and human studies have demonstrated the wound healing potential of curcumin.

#### Animal studies

As discussed, fibroblast migration to the wound site and their proliferation in diabetic foot ulcers is decreased. Sidhu et al. [17] reported that curcumin enhances fibroblast proliferation in both genetically diabetic mice and streptozocin induced diabetic rats. Full thickness cutaneous wounds were created in rodents and curcumin was used both topically (0.1% in polyethylene glycol) and orally (dose of 40 mg/kg). On the 7<sup>th</sup> and 11<sup>th</sup> days, wounds treated with curcumin showed dense granulation tissue (thickness of 498.5  $\mu$ m in curcumin treated group compared with 298.5  $\mu$ m in the control group), increased migration of various cells including fibroblasts and myofibroblasts (cellularity of 111.2 in curcumin treated group compared with 37.4 in control group per every 9040  $\mu$ m<sup>2</sup> of neodermis), higher vessel counts (approximately 600 per high power field in curcumin treated group compared with nearly 200 per high power field in control group) and greater collagen content compared to the control group. Interestingly, oral curcumin was more potent than topical curcumin for angiogenesis whereas topical curcumin was more potent than oral curcumin for collagen production [17].

Curcumin improves collagen deposition in the wound. Bhagavathula et al. [18] studied the effect of curcumin and ginger on the abrasion wound healing in rats treated with a corticosteroid, Temovate. Rodents were treated topically with 10% curcumin and 3% ginger extract for 21 days. At the end of this period, rodents were treated with Temovate for 15 days. Following this, superficial abrasions were made in the treated skin. They showed that curcumin improved collagen deposition (relative level of nearly 2 in rats treated with Temovate alone compared with nearly 36 in rats treated with both temovate and curcumin and nearly 18 in control rats) [18]. Curcumin was also shown to improve the rate of re-epithelialization of wounds. In a study by Lopez-Jornet et al. topical curcumin was applied at a dose of 5 mg per wound to mice with CO<sub>2</sub> laser created wounds. On the 7<sup>th</sup> day, nearly 73.3% of curcumin treated wounds showed re-epithelialization of the entire wound whereas only 41.7% of the wounds in control group re-epithelialized [19].

Angiogenesis plays a critical role in wound healing for the production of granulation tissue. This process involves the production of new blood vessels from the existing vessels and requires stimulation by cytokines and growth factors like vascular endothelial growth factor. Because these growth factors are either abnormal or reduced in diabetic foot ulcers, production of granulation tissue is reduced. Curcumin promotes angiogenesis differentially in the presence and absence of serum. In the presence of excessive growth factors, like in tumor cells, curcumin inhibits angiogenesis. However, in the absence of growth factors, in chronic wounds such as diabetic foot ulcers, it promotes angiogenesis. In a study done by Kiran et al. [20] Human Umbilical Vein Endothelial Cells (HUVEC), rat aortic endothelial cells and rat thoracic aortic rings were cultured in the presence and absence of serum. Curcumin was added to all the groups and the degree of angiogenesis was measured. HUVECs formed tubular structures in 24-48 hrs in serum free medium in the presence of curcumin compared with 96 hours in HUVECs in serum free medium without curcumin.

In the presence of serum, curcumin inhibited the formation of tubular structures in HUVECs. Also, sprouting of the aortic rings was increased by about 4-5 fold in serum free medium in the presence of curcumin compared with aortic rings in serum free medium without curcumin. In contrast, in the presence of serum, curcumin decreased sprouting by nearly 70% [20].

As the wound becomes chronic, involvement of muscle increases. Many of the diabetic foot ulcers involve the underlying muscle. Curcumin improves muscle regeneration and increases the rate of wound healing. Thaloor et al. [21], showed that administration of curcumin improves muscle regeneration by the inhibition of NF- $\kappa$ B both in vitro and in vivo. Masseter or tibialis anterior muscles of mice were freeze injured and either curcumin or dimethyl sulfoxide (control) was injected intraperitoneally. On the 4<sup>th</sup> day after injury, Embryonic Myosin Heavy Chain (EMHC), a marker for new muscle

fiber production was assayed. Curcumin at a dose of 20  $\mu$ g/kg produced an eight fold increase in EHMC in masseter muscle and a fivefold increase in tibialis anterior muscle compared with control animals. Moreover, the regenerated fibers in the curcumin treated group were greater in number and organized into fascicles while the fibers in the control group were few and randomly organized [21] (Table 1).

### Human studies

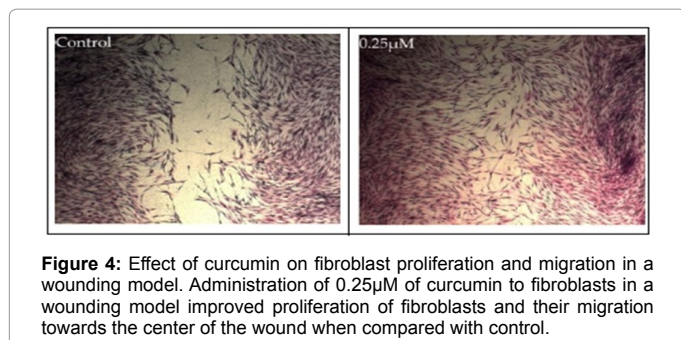
Studies on human cells are complimentary to animal studies. Demirovic and Rattan [22] have shown that curcumin has a dose dependent response on the growth of fibroblasts in wounds. Fibroblasts were seeded in 6 well plates and wounds were made using a sharp cell scraper. Application of 0.25-0.5 $\mu$ M of curcumin on these cells increased the proliferation of fibroblasts and their migration towards the center of the wound (Figure 4). However, at doses higher doses (>20  $\mu$ M), curcumin was found to be toxic to fibroblasts [22].

Trial	Animal/cells used	Compound used (Topical or oral)	Brief description of study	Effect observed
Bhagavathula et al. 2009 [18]	Rats	Curcumin	Abrasion wound healing corticosteroid (Renovate) impaired rat skin.	Collegen production was increased Matrix metalloproteinase-9 production was decreased.
Gopinath et al. 2004 [48]	Rats	Curcumin incorporated collagen films	Dermal wound healing	Increased wound reduction Enhanced cell proliferation Efficient free radical scavenging
Jagetia 2004 [41]	Mice	Curcumin	Healing of excisional wounds in rats exposed to radiation. Wound contraction was monitored using video images. Curcumin was used at a dose ranging from 25 mg/kg to 200 mg/kg.	Dose dependant increase in wound contraction. Greatest contraction was observed for 100 mg/kg of curcumin.
Lopez-Jornet 2011 [19]	Mice	Curcumin	Healing of Co2 laser incision wounds.	Rate of re-epithelialization was faster.
Panchatcharam 2006 [49]	Rats	Curcumin	Healing of full thickness excision wounds	Increased amount of collagen Increased rates of epithelialization Increased wound contraction Increased tensile strength Decreased lipid peroxides and increased superoxide dismutase, glutathione peroxidase and catalase.
Sidhu et al 1999 [17]	Mice	Curcumin (oral and topical)	Healing of wounds in mice with diabetes induced by streptozotocin	Improved neovascularization Increased migration of myofibroblasts and fibroblasts Increased granulation tissue Higher collagen content. Curcumin is effective both topically and orally.
Thaloor [21]	Mice muscle precursor cells	Curcumin	Muscle regeneration in wounds created by freeze injury	Regeneration of muscle is rapid Improved muscle regeneration Improved organization of muscle fibers Curcumin acts by modulation of NF- $\kappa$ B

**Table 1:** Trials showing the wound healing ability of curcumin in animals.

Trial	Compound Used	Dosage used	Brief description of study	Effect observed in Curcumin group
Demirovic 2011 [22]	Curcumin	1 – 5 $\mu$ M	Proliferation and migration of fibroblasts under the influence of curcumin in wounds created by a cell scraper.	Curcumin modulates wound healing in a dose dependent manner. At low doses (1-5 $\mu$ M), proliferation of fibroblasts increased and fibroblasts migrated towards the center of the wound. At higher doses (>5 $\mu$ M) it is toxic to fibroblasts.
Madhyastha 2010 [23]	Curcumin	Variable doses	Proliferation and migration of fibroblasts in wounds made by cell scraper.	Decreased reactive oxygen species. Increased fibrinolysis and fibroblast migration towards wound area.
Phan 2011 [24]	Curcumin	2.5 $\mu$ g/mL-10 $\mu$ g/mL	Prevention of H <sub>2</sub> O <sub>2</sub> induced damage to human keratinocytes and fibroblasts	Almost completely inhibited H <sub>2</sub> O <sub>2</sub> induced damage to human keratinocytes and fibroblasts.

**Table 2:** Trials showing the wound healing ability of curcumin in humans.



**Figure 4:** Effect of curcumin on fibroblast proliferation and migration in a wounding model. Administration of 0.25µM of curcumin to fibroblasts in a wounding model improved proliferation of fibroblasts and their migration towards the center of the wound when compared with control.

Free radicals decrease the rate of wound healing. Curcumin is a potent anti-oxidant and eliminates free radicals in the wound. Experiments by Madhyastha et al. have shown that curcumin decreases oxygen free radicals in cultured fibroblasts by 70% when used at a dose of 30 µM. They also found that curcumin causes migration of fibroblasts towards the center of the wound [23]. Similarly, a study by Phan et al also showed the same phenomenon. Dermal fibroblasts and keratinocytes were incubated with hydrogen peroxide with or without curcumin for three hours and assayed to detect free radical damage. Addition of curcumin completely protected fibroblasts against damage by hydrogen peroxide whereas a significant number of cells in the control group suffered free radical damage [24] (Table 2).

### Action of Curcumin on Factors that Contribute to Diabetic Foot Ulcers

It is interesting to note that curcumin may improve or prevent diabetes, peripheral arterial disease and peripheral neuropathy, all of which are the factors responsible for the production of diabetic foot ulcer (Table 3).

Curcumin is thought to improve diabetes by various mechanisms. A randomized controlled trial on pre-diabetic population by Cheungsamarn et al showed that curcumin administered at a dose of 750mg twice daily improved the function of beta cells [25]. In patients with diabetes, utilization of glucose is decreased and gluconeogenesis is increased. Curcumin was shown to increase the utilization of glucose and suppresses hepatic gluconeogenesis. Isolated hepatocytes exposed to 25 µM of curcumin for 30 minutes had 45% less gluconeogenesis compared with control hepatocytes [26,27] Curcumin was also shown to reduce blood sugar level by various mechanisms including the inhibition of pancreatic beta-amylase. Using enzyme assays, bisdemethoxycurcumin, an analogue of curcumin used at a concentration of 15 µg/ml was shown to inhibit pancreatic α- amylase by 72.4% [28].

Insulin resistance is the key pathogenetic mechanism for type 2 diabetes mellitus. Curcumin potentially decreases insulin resistance and increases binding of insulin to receptors. Murugan et al. have demonstrated that curcumin and tetrahydrocurcumin (an analogue of curcumin) increase the affinity and binding of insulin to isolated human erythrocytes [29]. Low level of the hormone adiponectin is usually associated with insulin resistance in type 2 diabetes mellitus. In a randomized controlled trial on patients with pre-diabetes by Cheungsamarn, intake of 750mg of curcumin twice daily was shown to significantly improve adiponectin levels ( 22.46 in curcumin group compared with 18.45 in placebo group ) [25].

Peripheral arterial disease is one of the key factors that lead to diabetic foot ulcer. Both animal and human trials have shown that

curcumin decreases peripheral arterial disease. High blood pressure, diabetes mellitus, high cholesterol and decreased amount of nitric oxide production are the known risk factors for PAD. A study done by Nakmareong et al showed that curcumin decreases blood pressure and vascular resistance in rodents while improving vascular responsiveness and levels of nitric oxide synthase [30,31]. In Apolipoprotein knockout mice, curcumin reduced the extent of atherosclerotic lesions. It also decreased the infiltration of macrophages into the existing atherosclerotic plaques [32]. In a randomized controlled trial done by Alwi et al on humans, a dose of 15mg of curcumin taken three times a day reduced the levels of total cholesterol and LDL cholesterol [33]. In another study done by Appendino et al. [34]. On humans, curcumin phytoosome caused improvement in diabetic microangiopathy and decreased skin flux at the surface of the foot [34]. HO-3867, a synthetic curcumin has been reported to inhibit the proliferation of serum stimulated smooth muscle cells by inducing cell cycle arrest at G1 phase. It also inhibits neointimal hyperplasia of arteries by overexpressing PTEN, a gene involved in smooth muscle cell proliferation [35].

Curcumin may be neuroprotective. Although the data available is only from animal experiments, it gives us important clues regarding the neuroprotective ability of curcumin. Attia et al. [36] have shown that combination of curcumin and gliclazide, an anti-diabetic drug given for 6 weeks to rats with diabetic neuropathy induced by streptozotoin improved diabetic neuropathy compared to the gliclazide alone group [36]. In another report, curcumin improved polyneuropathy in mice with Charcot-Marie-Tooth type of polyneuropathy by alleviating endoplasmic reticulum stress and promoting schwann cell differentiation [37].

Curcumin may enhance wound healing through a variety of means. Neutrophils and macrophages in the foot ulcers produce free radicals and proteases which increase inflammation and decrease wound healing. Several studies have reported the anti-inflammatory and anti-oxidant nature of curcumin [16]. Although, the mechanism of anti-inflammatory action of curcumin is unclear, some studies suggest

<b>1. Anti-Diabetic</b>
Increases the function of Beta cells [25]
Increases insulin release [50]
Increases Adiponectin [25]
Decreases Insulin resistance & Increases insulin binding to receptors 29]
Suppresses hepatic gluconeogenesis [26,27]
Inhibits pancreatic Beta-amylase [28]
Reduces blood sugar level [51]
<b>2 Neuroprotection</b>
Improves peripheral neuropathy [36]
Promotes schwann cell differentiation [37]
<b>3 Diabetic Angiopathy</b>
Reduces atherosclerosis [32]
Decreases blood pressure [31]
Inhibits proliferation of smooth muscle cells [52]
Restores vascular responsiveness [34]
Increases expression of nitric oxide synthase [30]
Reduces vascular damage from free radicals [30]
Increases flow mediated dilatation [53]
Reduces the levels of total cholesterol and LDL [33]
<b>2. Anti-Bacterial</b>
Effective against many gram positive and gram negative bacteria [43-45]
Effective against staph. Aureus[43-45]

**Table 3:** Putative mechanisms of curcumin's effect on diabetic foot.

activation of PPAR- $\gamma$  and inhibition of IL-8, IL-1, TNF- $\alpha$  and NF- $\kappa$ B to be responsible for its anti-inflammatory activity [38-40]. Curcumin, in a dose dependent manner increases the rate of wound contraction. At lower doses, curcumin improves wound contraction, however at higher doses; it inhibits wound contraction [41]. Several of the diabetic ulcers are complicated by polymicrobial infection [42]. Curcumin was found to possess antibacterial activity against a variety of gram negative and positive bacteria including staphylococcus aureus, Escherichia coli and Pseudomonas which are some of the most common organisms found in diabetic foot ulcers [43-45]. Treatment of any skin wound is incomplete if the pain is not addressed properly. Although, most of the diabetic foot ulcers are painless, a small number of ulcers are painful. Curcumin may have anti-nociceptive property. It inhibits Cyclooxygenase-2, an enzyme that produces pain and inflammation [46]. Another mechanism may involve inhibition of the activation of transient receptor potential cation channel subfamily V member 1 (TrpV1), also called as the capsaicin receptor [47]. In summary, curcumin acts on most of the stages and mechanisms of wound healing and has a tremendous potential to treat diabetic foot ulcers.

## Conclusion

The evidence presented above indicates that curcumin acts on almost all the pathophysiological processes that produce diabetic foot ulcers and helps in wound healing. The aforementioned data indicate that curcumin may be useful in the treatment of diabetic foot ulcers. However, further studies have to be done to fully elucidate the role of curcumin.

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