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Clinical Outcomes of Diabetic Foot Management with Circulat

J. A. Olalde, M. Magarici, F. Amendola, O. del Castillo*, S. Gonzalez and A. Muhammad
Adaptogenic Medical Center, Caracas 1080, Venezuela

Major and minor lower-extremity amputation is a common complication among diabetics. Various sources indicate diabetic foot ulcer prevalence at between 2.2% and 15% in diabetics. This study evaluates the efficacy and tolerance of a standardized plant extract combination, Circulat, developed for the prevention and treatment of severe manifestations of type 2 diabetes, such as necrotic damage of the foot. Thus, a retrospective cohort study was carried out in 174 patients treated with Circulat with diabetic foot grades D1–D3, according to The University of Texas Wound Classification System, in 50 medical centers, from 2004 to 2007. Circulat obtained 50.57% complete cure of diabetic foot, significant improvement in 37.9% and prevented amputation in 88.5% of the study's total population. The treatment was well tolerated. Four patients (2.3%) had slight gastrointestinal unrest which did not warrant suspension of treatment. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: diabetes; diabetic foot amputation; adaptogens; systemic.

INTRODUCTION

The World Health Organization (WHO, 2006) estimates that more than 180 million people worldwide have diabetes. This number is likely to more than double by 2030. Diabetic foot ulcers are one of the most frequent complications of this disease. The prevalence of diabetic foot ulcers has been estimated at 2.2% to 15% (Abbot *et al.*, 2002; Gulam-Abbas *et al.*, 2002). The difference being attributed to the diversity of risk factors, ethnicity, age, sex, level of education, quality of health service and others (Table 1). Diabetic foot ulcers represent a large emotional and economic burden on patients and caregivers as well. Foot complications are caused by diabetic neuropathy or peripheral ischemic vessel disease or a combination of both (Ratzmann *et al.*, 1994) and are the most frequent reason for hospitalization in patients with diabetes. Diabetic foot complications are the most common cause of non-traumatic lower extremity amputations in the industrialized world. The risk of lower extremity amputation is 15–46 times higher in diabetics than in persons who do not have diabetes mellitus (Nabuura-Franssen *et al.*, 2005; Armstrong *et al.*, 1997). Approximately 40–60% of all lower extremity amputations are performed in patients with diabetes. More than 85% of these amputations are precipitated by a foot ulcer deteriorating to deep infection or gangrene (Apelqvist and Larsson, 2000). In people with healed diabetic foot ulcers, the 5 year cumulative rate of ulcer recurrence is 66% and of amputation is 12% (Apelqvist *et al.*, 1993). The high amputation incidence and healing failure after lower extremity amputation for the treatment of diabetic foot ulcer (Malay *et al.*, 2006) is a distinct signal that the efficiency of conventional medical treatments used is less than optimal. This substantiates the need to search for effective therapeutic alternatives and to diminish the suffering and high economic and social costs caused by this common diabetic patient complication. Various medicinal plants have been used traditionally for the treatment of circulatory obstructive diseases. In the last couple of decades many of their active principles and action mechanisms have been discovered. Also, traditional healing know-how has been proven to be effective in many cases. This raises the possibility of using herbal therapeutic protocols to complement conventional treatments for complications in diabetes. In particular, there is mounting evidence which demonstrates that medicinal plants contain synergistic and/or side-effect neutralizing combinations (Thyagarajan *et al.*, 2007; Gilani and Rahman, 2005). In contrast to synthetic pharmaceuticals based upon single chemicals, many phytomedicines exert their beneficial effects through the additive or synergistic action of their multitude of constituents acting at single or multiple target sites (Dalby-Brown *et al.*, 2005); because of their primary and secondary metabolite roles (Greenspan *et al.*, 1994) and the adjuvant substances which enhance the activity of components actually responsible for the effect (Gilbert and Alves, 2003; Stermitz *et al.*, 2000). In order to take maximum advantage of the therapeutic properties as well as benefits of the synergistic action of the active principles in medicinal plants, it is necessary to use herbal combinations. Herbal formulations have been used for hundreds of years, however, little is known of the methodology to combine plants and obtain effective compositions.

The Systemic Theory provided the fundamentals which allowed the formulation of an effective herbal composition, Circulat, patent application number 11/271,940, for treating diabetic foot (Olalde, 2005a, b and c; Olalde *et al.*, 2005). Circulat is a systemic standardized plant extract combination consisting of (1) Energy plants (E) associated with ATP synthesis (such as tricarboxylic

* Correspondence to: O. del Castillo, Adaptogenic Medical Center, Calle Luis de Camoens c/c Del Arenal, La Trinidad, Caracas 1080, Venezuela. E-mail: corpgov2004@yahoo.com

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Table 1. Examples of diabetic foot ulcer prevalence by country and reference

Prevalence of diabetic foot ulcers (%)	Country	Reference
2.2	UK	Abbot *et al.*, 2002
3–8	Sweden	Apelqvist and Larsson, 2000
4.6	Kenya	Nyamu *et al.*, 2003
5.3–5.6	Finland	Lehto *et al.*, 1996
5.4–7.3	USA	Moss *et al.*, 1996
10.2	Sri Lanka	Fernando, 1996
15	Tanzania	Gulam-Abbas *et al.*, 2002

acid cycle, oxidative phosphorylation, etc) which boost the system's energy-work capacity: *Eleutherococcus senticosus*, *Leuzea carthamoides*, *Panax ginseng*, *Panax quinquefolius*, *Pfaffia paniculata* and *Rhodiola rosea*, (2) Bio-Intelligence plants (I) which modulate the neuroendocrine and immunological systems and cellular processes enhancing the system's informational potential intelligence (specifically in this formulation they increase insulin production, insulin receptor sensitivity, improve intracellular glucose uptake, contribute anti-microbial properties, reduce inflammation and improve humoral and cellular immunity): *Echinacea angustifolia*, *Echinacea purpurea*, *Ganoderma lucidum*, *Grifola frondosa*, *Hydrastis canadensis*, *Petiveria alliacea*, *Sutherlandia frutescens*, and *Uncaria tomentosa* and finally (3) Organizational plants (O) which enhance the structure and functional organization of specific organs supporting overall health (in Circulat's case, among others, promoting vasodilatation, tissular perfusion improvement, regeneration and skin scarring): *Angelica sinensis*, *Crataegus oxyacantha*, *Croton lechleri*, *Ginkgo biloba*, *Hydrocotyle asiatica*, *Ruscus aculeatus*, *Vaccinium myrthillus* and *Tabebuia avellanedae*. Table 2 describes Circulat's plants action mechanisms according to E, I and O. It must be noted that although some of these plants act predominantly over one of the factors that influence the overall individual's health (E, I and O), some of them act over more than one of these factors (examples: *Panax ginseng* and *Ganoderma lucidum*) (Table 2). Recently, some of this study's authors and other collaborators participated in a study that identified significant changes in the expression levels of 187 genes, with Circulat treatment, and demonstrated the synergistic molecular–genetic action of this herbal combination. The modulation included four genes (IL6, HMGA1, SLC19A2 and C4A) that have been previously implicated in the development of diabetes, as well as a large proportion of genes known to be involved in energy metabolism, protein synthesis, glucose metabolism and signaling pathways. 'Results of our experiments provide molecular foundation for the clinically-observed effectiveness of Circulat components . . . in treating severe manifestations of type 2 diabetes, such as the necrotic damages of the plantar foot, and demonstrate the potential of this preparation for normalization of gene expression altered in type 2 diabetic' (Antoshechkin *et al.*, 2007).

OBJECTIVE

To evaluate the clinical efficacy of Circulat in healing diabetic foot, to measure the amputation rate and to determine patient's tolerance to the treatment.

RESEARCH DESIGN AND METHODS

A retrospective, cohort, study of patients with type 2 diabetes and foot ulcerations from 50 medical centers, from 2004 to 2007. The patients were classified in accordance with The University of Texas Health Science Center Diabetic Wound Classification System (Lavery *et al.*, 1997). Patients were administered ten Circulat 900 mg capsules twice per day, on an outpatient basis, during a period of 2–4 months. Each case was followed-up during a period of 6 months, after the end of the treatment. A patient was considered to attain clinical improvement if the lesion visibly decreased in size and depth, or closure or scarring of the wound was attained. All patients received conventional treatment for metabolism correction, local topic cures and systemic antibiotics.

Inclusion criteria: Patients of any age and gender diagnosed with diabetes mellitus type 2, grades D1, D2 and D3 (University of Texas Diabetic Wound classification).

RESULTS

The total number of patients completing the treatment according to the study's inclusion criteria was 174. The mean was 61.3 years of age. The gender classification was 101 male (58.1%) and 73 female (41.9%). The clinical results are reflected in Table 3. To be noted, amputations were prevented in 88.55% ($p < 0.001$, 99.999%) of all 174 patients in the D1–D3 categorization. The treatment was well tolerated; only four patients (2.3%) had minor gastrointestinal unrest which did not warrant treatment suspension.

DISCUSSION

Conventional diabetic foot treatments, based on risk factors control, affected area's functional relaxation, metabolism correction, topical cures, antibiotics, rheology improving agents, prostanoid vasoactive therapy, platelet aggregation inhibitors, thrombolytic agents, tricyclic antidepressants or benzodiazepines for neuropathies and invasive treatments, such as endovascular, endarterectomy, by-pass or sympathectomy surgeries, do not manage to prevent small and large amputations which occur in 1.86–5.9 per 1000 diabetics per year (Bilenko *et al.*, 2006; Winell *et al.*, 2006; Rayman *et al.*, 2004; Lavery *et al.*, 2003; Trautner *et al.*, 2001; Lavery *et al.*, 1997). Circulat- in combination with conventional therapy-prevents more amputations than many conventional treatments reported (Fig. 1).

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Table 2. Circulat components action mechanisms

Energy plants	
Panax ginseng and *Panax quinquefolius*	Increases ATP synthesis by stimulating activities of enzymes related to tricarboxylic acid cycle and oxidative-phosphorylation, such as succinate dehydrogenase, malate dehydrogenase, citrate synthetase, cytochrome oxidase and phosphorylase (Wang *et al.*, 2003)
Eleutherococcus senticosus	Increases ATP synthesis by stimulating activities of enzymes related to tricarboxylic acid cycle, such as succinate dehydrogenase and malate dehydrogenase (Sugimura *et al.*, 1989). In ATP deficient tissues, improves the formation of glucose-6-phosphate, producing substrates for the biosynthesis of nucleic acids and proteins (Farnsworth *et al.*, 1985)
Leuzea carthamoides and *Pfaffia paniculata*	Increase ATP synthesis, stimulates activities of enzymes related to tricarboxylic acid cycle, such as succinate dehydrogenase. Also, normalize NADH dehydrogenase activity, enzyme related to the oxidative phosphorylation processes, contributing to buildup the electrochemical potential used to produce ATP (Tashmukhamedova *et al.*, 1986)
Rhodiola rosea	Activates the synthesis or resynthesis of ATP in mitochondria and stimulates reparative energy processes (Abidov *et al.*, 2003)
Antiinflammatory-immunostimulant plants (Immune Intelligence)	
Tabebuia avellanedae	Inhibits NO, iNOS, COX-2 and PGE(2) release. Attenuates expression of mRNA and pro-inflammatory cytokines proteins, such as interleukin (IL)-1beta, IL-6 and tumor necrosis factor (TNF)-alpha. Suppresses NF-kappa B activation by blocking IkappaBalpha degradation and downregulating ERK, p38 mitogen-activated protein kinase (MAPK) and Akt pathway (Moon *et al.*, 2007)
Echinacea angustifolia and *Echinacea purpurea*	Antiinflammatory due to: (a) reduction of IL-2 production (Sasagawa *et al.*, 2006); and (b) down-regulation of COX-2 expression (Groom *et al.*, 2007)
	Immunostimulant due to: (a) macrophage phagocytosis stimulation (Raso *et al.*, 2002); (b) cellular immunity and neutrophils' phagocytosis stimulation. Increases the number of leucocytes and lymphocytes, especially T lymphocytes (Jurkstiene *et al.*, 2004); (c) Significant enhancement of IgM specific antibody forming cell response (Freier *et al.*, 2003); (d) complement properdin increases (Kim *et al.*, 2002)
Ganoderma lucidum	Promotes phagocytosis and cytotoxicity of macrophages (Zhu *et al.*, 2007).
Grifola frondosa	Antiinflammatory: because it inhibits cyclooxygenase (COX) enzyme (Zhang *et al.*, 2002)
	Immunostimulant because it increases IL-10, NO and IFN-gamma. Enhances both the innate and adaptive arms of the immune response (Kodama *et al.*, 2004)
Hydrastis canadensis	Antiinflammatory due to a prostaglandin E2 production reduction as a result of AP-1 binding inhibition (Kuo *et al.*, 2004).
Sutherlandia frutescens	Antiinflammatory because it inhibits COX-2 and through activation of activator protein-1 (AP-1) (Kundu *et al.*, 2005)
Uncaria tomentosa	Antiinflammatory achieved by a TNFalpha and PGE2 production inhibition (Piscoya *et al.*, 2001)
	Immunostimulant because it stimulates macrophage phagocytosis (Groom *et al.*, 2007)
Panax ginseng and *Panax quinquefolius*	Antiinflammatory: It inhibits iNOS and COX-2 protein expression, and activates the transcription factor, NF-kappaB (Park *et al.*, 2004).
	Immunomodulator: Increases neutrophiles and macrophages phagocytosis, stimulates humoral and cell immune factors and induces important regulating cytokines–interferon gamma and tumor necrosis factor (Smolina *et al.*, 2001)
Eleutherococcus senticosus	Immunostimulant: Activates B cells and macrophages (Han *et al.*, 2003)
Pfaffia paniculata	Increases macrophage activity (Pinello *et al.*, 2006)
Angelica sinensis	Immunomodulatory activity by regulating expression of Th1 and Th2 related cytokines (Yang *et al.*, 2006)
Hypoglycemic plants (Biochemical Intelligence)	
Panax ginseng	Reduces blood glucose levels (Reay *et al.*, 2005). -Inhibits the formation of glycated hemoglobin (Bae and Lee, 2004)
Panax quinquefolius	Decreases postprandial glycemia (Vuksan *et al.*, 2000)
Eleutherococcus senticosus	Lowers circulating glucose and lipids, and enhances insulin action (Park *et al.*, 2006)
	Improves insulin sensitivity (Liu *et al.*, 2005)
Ganoderma lucidum	Stimulates glucose uptake, stimulating the activity of phosphatidylinositol 3-kinase, Protein kinase B, AMP-activated protein kinase which are regulatory molecules in the glucose uptake pathway (Jung *et al.*, 2006). -Lowers glucose levels through insulin-releasing activity due to facilitation of Ca^{2+} inflow to pancreatic beta cells (Zhang and Lin, 2004)
Grifola frondosa	Decreases fasting plasma glucose levels and increases insulin sensitivity (Hong *et al.*, 2007)
Hydrastis canadensis	Stimulates glucose uptake via: (a) increasing GLUT1 activity and adenosine monophosphate-activated protein kinase and acetyl-coenzyme A carboxylase phosphorylation (Zhou *et al.*, 2007); and (b) through the AMP-AMPK-p38 MAPK pathway (Cheng *et al.*, 2006). -Inhibitor of aldose reductase (Feng *et al.*, 2005)

Table 2. (*Continued*)

Petiveria alliacea	Decreases: (a) blood glucose levels (Lores and Cires Puyol, 1990); and (b) fasting glucose, post-prandial glucose levels, and hemoglobin A1c in type 2 diabetic patients, by acting downstream in the insulin signaling pathway (Kim *et al.*, 2007)
Sutherlandia frutescens	Normalizes insulin levels and increases glucose uptake (Chadwick *et al.*, 2007)
	Decreases fasting glucose, post-prandial glucose levels, and hemoglobin A1c in type 2 diabetic patients, by acting downstream in the insulin signaling pathway (Kim *et al.*, 2007)
Antimicrobial and Skin Scarring plants (Organization)	
Tabebuia avellanedae	Antibacterial activity against methicillin-resistant *S. aureus*, *S. epidermidis* and *S. haemolyticus* strains, the last two being hetero-resistant to vancomycin (Pereira *et al.*, 2006)
Petiveria alliacea	Broad spectrum of antimicrobial activity (Kim *et al.*, 2006)
Hydrastis canadensis	Broad spectrum of antimicrobial activity (Scazzocchio *et al.*, 2001)
Sutherlandia frutescens	Antibacterial against against *S. aureus*, *E. faecalis* and *E. coli* (Katerere and Elfo, 2005)
Uncaria tomentosa	Antimicrobial activity on Enterobacteriaceae, *S. mutans* and *Staphylococcus* spp. (Ccahuana-Vasquez *et al.*, 2007)
Croton lechleri	Potent antibacterial activity (Chen *et al.*, 1994)
	Cicatrizant effect because it increases the migration of skin fibroblasts (Vaisberg *et al.*, 1989)
Hydrocotyle asiatica	Promotes fibroblast proliferation and extracellular matrix synthesis in wound healing because it upregulates 54 genes with known functions for cell proliferation, cell-cycle progression and synthesis of the extracellular matrix (Lu *et al.*, 2004)
Vasodilating and Circulatory plants (Organization)	
Eleutherococcus senticosus	Vasorelaxant effect endothelium-dependent and mediated by nitric oxide and/or endothelium-derived hyperpolarizing factor (Kwan *et al.*, 2004)
Leuzea carthamoides	Reduces viscosity of the whole blood and plasma (Plotnikov *et al.*, 2001). -Reduces the coagulation potential (Azizov, 1997)
Panax ginseng and *Panax quinquefolius*	Relaxes vessels as a consequence of endothelium-derived nitric oxide production and release, to which iNOS induction contributes (Kim *et al.*, 2003)
Rhodiola rosea	Inhibits angiotensin I-converting enzyme (ACE) (Kwon *et al.*, 2006)
	Induces biosynthesis and increases level of endogenous opioid peptides which, as it is known, act on opioid receptors at the central and peripheral level, regulating vascular status (Lishmanov *et al.*, 1997)
Ganoderma lucidum	Vasodilation due to its central inhibition of sympathetic nerve activity (Lee and Rhee, 1990)
	Can inhibit angiotensin I-converting enzyme (Morigiwa *et al.*, 1986)
Grifola frondosa	Vasodilation due to modulation of the renin-angiotensin system (Talpur *et al.*, 2002)
Hydrastis canadensis	Inhibits angiotensin I-converting enzyme (Kang *et al.*, 2002). -Endothelium-dependent nitric oxide mediated vasorelaxant effect (Ko *et al.*, 2000). -Central sympatholytic effect (Liu *et al.*, 1999)
	Alpha-adrenoceptor antagonistic action (Olmez and Ilhan, 1992)
Angelica sinensis	Inhibits the formation of TXA2 and increases the formation of PGI2 (Wang *et al.*, 1993). -Increases formation of nitric oxide which contributes to endothelium-mediated vasorelaxation, while inhibits the calcium influx producing vascular smooth muscle relaxation (Rhyu *et al.*, 2005). -Induces vasodilatation by inhibiting the dependent calcium channel and receptor-operated calcium channel, and receptor-mediated Ca(2+) influx and release (Cao *et al.*, 2006)
Crataegus oxyacantha	Causes endothelium-dependent NO-mediated vasorelaxation associated with cyclic GMP production (Kim *et al.*, 2000)
	Can inhibit angiotensin I-converting enzyme (Lacaille *et al.*, 2001)
	Inhibits biosynthesis of vasoconstrictors such as thromboxane A2 (Vibes *et al.*, 1994)
Ginkgo biloba	Increases endothelial nitric oxide synthase (eNOS) promoter activity and eNOS expression, increasing endothelial nitric oxide production. (Koltermann *et al.*, 2007). -Vasorelaxation due to the inhibition of Ca(2+) influx through the Ca(2+) channel. Might be in part due to the inhibition of Ca(2+)-activated K(+) current and PGI(2) release (Nishida and Satoh, 2003)
Hydrocotyle asiatica	Improves microcirculation and decreases capillary permeability (Cesarone *et al.*, 2001)
Ruscus aculeatus	Protective effects on capillaries, endothelium, and smooth muscle. Strengthens blood vessels, reduces capillary fragility, and improves circulation (Redman, 2000)
Vaccinium myrtillus	Endothelium-dependent arterial relaxation (Bell and Gochenaur, 2006)

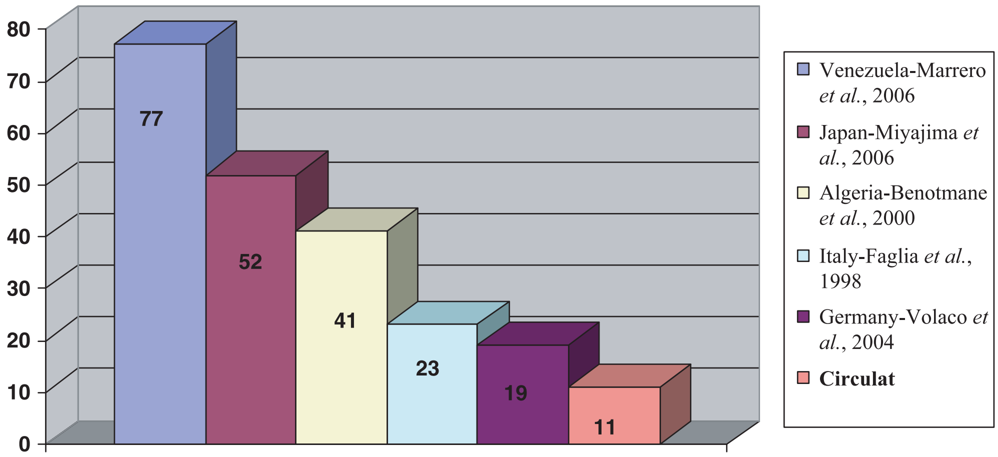

Figure 1. Examples of amputation rates (%) of diabetic foot patients.

Table 3. Results of Circulat treatment in diabetic foot

University of Texas Diabetic Wound Classification Grade	N	Total scarring	Improvement	Total scarring + Improvement	Amputation
D1: Infected ischemic superficial wounds, no tendon, capsule, or bone	88	52 (59.09%)	36 (40.9%)	88/88 (100%)	–
D2: Infected ischemic wounds, penetrating to tendon or capsule	80	32 (40%)	30 (37.5%)	62/80 (77.5%)	18/80 (22.5%)
D3: Infected ischemic wounds, penetrating to bone or joint	6	4 (66.6%)	–	4/6 (66.6%)	2/6 (33.3%)
Total	174	88 (50.57%)	66 (37.9%)	154/174 (88.5%)	20/174 (11.5%)

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