

The safety and efficacy of oral Arborium plus, a herbal liquid formulation in the treatment of diabetic foot syndrome: an open label study

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ABSTRACT

Background: Diabetic foot ulcers are the most universal cause of non-traumatic amputations of the foot in developing countries. One of the treatment modalities is to improve the peripheral blood supply to the area of ulcer. To this purpose the study was done to evaluate the safety and efficacy of oral Arborium plus (herbal liquid formulation) in the wound closure of diabetic foot patients.

Methods: 50 patients were randomly assigned to either of the groups (each group 25 patients) to receive either the test drug (Arborium plus) at tertiary care teaching hospital, it was an open label prospective and interventional parallel group study to evaluate the efficacy and safety of Arborium plus in diabetic foot syndrome. The study participants were randomized into control and intervention groups. Base line measurements of vascular flow was ankle- brachial pressure index (ABPI) and wound size measurement.

Results: The baseline characteristics of the patients age in years test and control group 68±12.3 and 67±13.4 respectively. Male/female in both groups was 21/4 and 22/3 respectively. Duration of diabetes in years 8.65±8.3 and 8.5±7.6 respectively. BMI was 25.11±4.15 and 24.75±0.85, duration of smoking (years) 17.3±9.5 and 19.5±10.5 respectively in both groups. Among the test group who received the proprietary formulation of Arborium plus, there was a significant reduction in the wound size.

Conclusions: Wound healing and ABPI improvements were observed with usage of Arborium plus suggest an improvement in peripheral vascular flow in diabetic foot subjects.

Keywords: Oral Arborium plus, Diabetic foot ulcer, Type-2 diabetes, Herbal formulation

INTRODUCTION

Diabetic foot is a leading reason for hospitalization among all possible complications of type 2 diabetes mellitus. Its prevalence is estimated to be 4% to 15%. The lifetime risk for developing foot ulceration is 25% among diabetics of which most of the affected patients

will need amputation within four years of initial diagnosis.¹⁻⁵

Epidemiological data reveals that the risk of developing neuropathy alone is about 50%, peripheral arterial occlusive disease is about 15% in cases of diabetic foot syndrome. In 35% foot ulcerations, both neuropathy and

angiopathy occur. Autonomic neuropathy accompanies peripheral neuropathy in 30% to 50% of diabetic cases. Peripheral autonomic neuropathy leads to vasomotor paresis, sudomotor paresis, changes in the microvasculature, resulting in arteriovenous shunting and impaired vasoreactivity. In patients with type 2 diabetes, these changes lead to capillary hypoperfusion, probably further impairing wound healing.⁶⁻¹⁰ As a result, foot skin dries out, reducing protective skin function & there is an increased risk of injury.

Diabetic foot ulcers are found at typical predisposed locations (areas of high pressure - head of first metatarsal bone) and are of circular shape with hyperkeratotic borders. Diabetic foot lesions cause complex dysfunction of wound healing at the cellular level.

Establishing a good supply of blood flow inside the wound bed is the basic principle behind all conservative and operative approaches.

The present oral herbal liquid formulation is extracted from *Rhododendron arboreum*. Different parts of this plant have various medicinal properties like anti-oxidant, anti-diarrhoeal, anti-inflammatory, anti-diabetic, hepatoprotective activity and cardioprotective activity with low side effects.¹⁰⁻¹⁴ The three biologically active components, i.e., quercetin, rutin and coumaric acid, have been extracted from the flowers of *R. arboreum* using high-performance thin-layer chromatography.¹⁵ These components have shown to exert vasodilation and myocardial protection in the preclinical studies. So the present study aims to measure the improvement in the vascular flow of *R. arboreum* in diabetic foot syndrome and its effect on the wound healing property. The primary objective of the study was to measure the efficacy of Arborium plus on the wound closure in patients with a diabetic foot. Secondary objectives of the study were to measure the efficacy of Arborium plus on the improvement of peripheral vascular flow in patients with diabetic foot and to measure the safety and tolerability of Arborium plus in patients with diabetic foot.

METHODS

An open-label prospective and interventional parallel-group study to evaluate the efficacy and safety of Arborium plus in diabetic foot syndrome. The study population is patients with diabetic foot who are on standard treatment for diabetic foot ulcer (surgical debridement followed by wound care), randomized into two groups, one group receiving test drug and the second group without test drug. A total of 50 patients are randomly assigned to either of the groups (each group 25 patients) to receive either the test drug (Arbrium plus) or control (without test drug). The study conducted in Sri Padmavathi Medical College for Women Hospital, SVIMS, Tirupati and duration is 90 days (01 April 2019 to 01 June 2019).

Inclusion criteria

Inclusion criteria were patients with type-2 diabetes mellitus of aged 18 years old or more having peripheral vascular disease (ABI lower than 1.3 or ankle systolic pressure more than 70 mmHg); peripheral neuropathy assessed by biothesiometer, foot ulcer extending through epidermis and dermis but not involving bone, tendons, ligaments or muscles (grade 1 A as defined by University of Texas Diabetic Wound classification), well controlled infection or cellulitis (systemic -antibiotic therapy as per culture and sensitivity report) and patients who are willing to give signed informed consent.¹⁶⁻¹⁹

Exclusion criteria

Patients with hepatic disease, renal dysfunction, ulcers of other cause like electrical, chemical, radiation burns, bedsores, venous ulcer, osteomyelitis affecting the area of target ulcer, poorly controlled diabetes mellitus, HbA1c more than 12%, known connective tissue disease or malignancy, concomitant treatment with corticosteroids, immunosuppressive areas, anti-cancer chemotherapy and pregnant and lactating mothers were excluded in this study.

The study participants are randomized into control and intervention groups. Baseline measurements of vascular flow: ankle-brachial index (ABI), wound size measurement. Patients visited at an interval of two weeks.²⁰ ABI and wound size measured at each visit. Any adverse effects also asked the patients during the study period. Instruments are used in this study are sphygmomanometer, measuring tape.

Confidentiality maintained, before starting the study, informed consent taken from all the patients. The investigators of the study were confided patients' identity and details according to statutory guidelines of IEC, SVIMS. A total of 66 patients was screened for the study. Out of 66 patients, 50 patients who satisfied both the inclusion and exclusion criteria were recruited into the study. Patients were randomized into a test group and control group who received arbrium plus formulation and multivitamin syrup respectively, 25 patients in each group.

Out of 25 patients in the test group, 24 patients have completed the study and one was lost to follow up. Out of 25 patients in the control group, 23 patients have completed the study and two are lost to follow up. Results are analyzed statistically using Student's T-test for a total of 47 patients who completed the study.

RESULTS

Table 1 shows the baseline characteristics of the patients age in years test and control group 68 ± 12.3 and 67 ± 13.4 respectively. Male/female in both groups was 21/4 and 22/3 respectively. Duration of diabetes was 8.65 ± 8.3

years and 8.5±7.6 years respectively in both the groups. BMI was found to be 25.11±4.15 and 24.75±.85 in both groups respectively. Duration of smoking in test was 17.3±9.5 years and in control was 19.5±10.5 years.

Table 1: Baseline characteristics of the patients.

| Characteristics | Test (Mean±SD) | Control (Mean±SD) |
|-----------------------------|----------------|-------------------|
| Age | 68±12.3 | 67±13.4 |
| Male/female | 21/4 | 22/3 |
| Duration of diabetes | 8.65±8.3 | 8.5±7.6 |
| BMI | 25.11±4.15 | 24.75±.85 |
| Duration of smoking (years) | 17.3±9.5 | 19.5±10.5 |

Table 2 shows comparison of wound size within test control group: control group baseline mean was 52.8. Second week it was 50.92 mean and percentage (%) reduction is 2%, fourth week it was 47.44 mean and 10.22% reduction. Sixth week it was 45.24 mean and 14.31% reduction, week eight it had shown 40.24 mean and 23.70% reduction.

Table 2: Comparison of wound size within test control group.

| Control group | Baseline | Week 2 | Week 4 | Week 6 | Week 8 |
|---------------|----------|--------|--------|--------|--------|
| Mean | 52.8 | 50.92 | 47.44 | 45.24 | 40.24 |
| Reduction (%) | - | 2 | 10.22 | 14.31 | 23.70 |

Table 3: Comparison of wound size within test group.

| Test group | Baseline | Week 2 | Week 4 | Week 6 | Week 8 |
|---------------|----------|--------|--------|--------|--------|
| Mean | 54.76 | 44.16 | 33.72 | 14.8 | 7.24 |
| Reduction (%) | - | 19.30 | 38.70 | 72.60 | 86.40 |

Table 4: Comparison of wound size between test and control groups.

| | Baseline | Week 2 | Week 4 | Week 6 | Week 8 |
|---------|-----------|-----------|----------|----------|-----------|
| Control | 52.8±4.8 | 50.92±4.8 | 47.4±4.6 | 45.2±4.5 | 40.24±4.3 |
| Test | 54.76±4.5 | 44.16±3.8 | 33.7±3.5 | 14.8±1.4 | 7.24±1.01 |

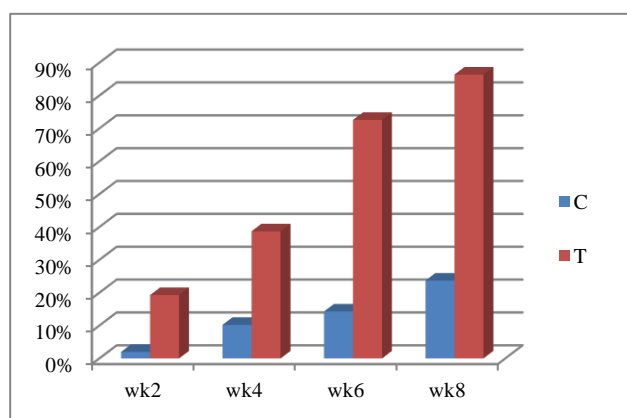


Figure 1: Percent reduction of wound size among test and control groups.

Table 3 shows comparison of wound size within test group: Test group baseline mean was 54.76. Second week it was 44.16 mean and percentage (%) reduction is 19.30%, fourth week it was 33.72 mean and 38.70% reduction. Sixth week had shown 14.8 mean and 72.60% reduction, and week eight showed 7.24 mean and 86.40% reduction.

Among the test group who received the proprietary formulation of Arborium plus, a significant reduction in the wound size was seen. The percentage reduction in mean of wound size among the test group is 19.3% at week 2, and 38.7% at week 4. At week 6 it was 72.6% and 86.4% at week 8.

Table 4 shows at the baseline visit, there was no statistically significant difference in the wound size between the two groups. At week 2, there was no statistically significant difference in the wound size reduction between the two groups (p>0.05). There was a statistically significant difference in the wound size reduction at week 4, week 6, and week 8 (p<0.05).

Figure 1 shows the percentage (%) reduction in control and test. Second week showed 2% and 19.30%, fourth week showed 10.22% and 38.70%. On sixth week it was 14.31% and 72.60%, and on eight week it was 23.70% and 86.40%.

Table 5: Comparison of ABPI among two groups before treatment.

| No. of patients | ABPI<1 | ABPI>1 |
|-----------------|--------|--------|
| Test | 8 | 17 |
| Control | 9 | 16 |

Table 5 shows comparison of the ankle- brachial pressure index (ABPI) among two groups, at the beginning of the study, 8 patients among the test and 9 patients among the control group had ABPI <1. At 8 weeks, 17 patients

among the test group were found to have ABPI >1. Among the control group, only 16 patients had ABPI >1 at 8 weeks.

Table 6: Comparison of ABPI among two groups at 8 weeks after treatment.

| No. of patients | ABPI<1 | ABPI>1 |
|-----------------|--------|--------|
| Test | 2 | 22 |
| Control | 8 | 15 |

Table 6 shows the comparison of the ABPI among two groups, At the 8 weeks after treatment, 2 patients among the test and 8 patients among the control group had ABPI <1. At 8 weeks, 22 patients among the test group were found to have ABPI >1. Among the control group, only 15 patients had ABPI >1 at 8 wks.



Figure 2: (A) Wound size at the end of 8 weeks in test group, (B) wound size at screening visit in test group.

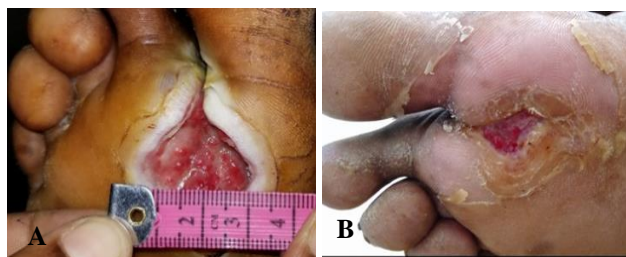


Figure 3: (A) Wound size at screening visit in the test group, (B) wound size at the end of 8 weeks in the test group.

Safety and tolerability

Out of 24 subjects in the test group, four patients complained of nausea in the first visit, increased bowel frequency at 4 weeks. At 8 weeks, patients have noted a decrease in nausea as well as bowel frequency.

Out of 23 subjects in the control group, four patients complained of nausea at 2 weeks and 4 weeks. There was a reduction in nausea at 8 weeks.

DISCUSSION

Peripheral arterial occlusive disease is one of the most important causes of diabetic foot ulcers. The other reason

being a combination of autonomous neuropathy and vasculopathy. It is well known that long-standing diabetes leads to macrovascular as well as microvascular complications. *Rhododendron arboreum*, the active component of Arborium plus, has a cardioprotective effect as well as a lipid-lowering effect.^{21,22}

The present study aims to study the efficacy and tolerability of Arborium plus in diabetic foot ulcer.

There was a significant improvement in the ulcer size in the test group (subjects who received Arborium plus) as compared to the test group at all the study visits. Also noted that the patients who received the study drug showed faster healing rates, such as the development of granulation tissue and health wound margins.

Further, there was an improvement in the ABPI in 20% of patients who received the study drug. This suggests that the drug is effective in improving vascular flow in the peripheral circulation.

The study drug was found to be tolerated well by 96% of patients as compared to the control group, where the compliance was 92%. Nausea and increased bowel movements were seen in the study group, which have decreased after six weeks of use.

Thus *R. arboreum* facilitates helps in improving peripheral flow as well as healing ulcers in diabetic foot and may reduce the need for surgical intervention.

The present study supported by Murthy et al, study revealed the hypolipidemic property of Arborium plus (*Hippophae ramnoides* L. fruit juices and *R. arboreum* Linn flower juice in a 1:4 ratio).²³

Thangaraj et al reported hypolipidemic activity of *R. arboreum* flower juice.²⁴ The efficacy of *R. arboreum* flower juice was studied on atherogenic index, high sensitivity C- reactive protein (hs CRP) triglycerides, low-density lipoprotein, total cholesterol, and high-density lipoprotein. The flower juice was given orally and results demonstrate that *R. arboreum* flower juice is very efficient in reducing cholesterol and hs CRP and significantly enhance high density lipoprotein levels.

Sonar et al reported the antimicrobial activity of aqueous and ethanolic extract of flower of *R. arboretum* against *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans*, *Pseudomonas aeruginosa*, *Agrobacterium tumefaciens*, *Bacillus subtilis* and *Aspergillus niger*.²⁵

CONCLUSION

Wound healing was significantly better in subjects with herbal formulation Arborium plus when compared to the subjects with multivitamin supplements. The present herbal formulation Arborium plus was observed to have near/equal tolerability when compared to multivitamin

syrup. Wound healing and ABPI improvements were seen with the usage of Arborium plus suggest an improvement in peripheral vascular flow in diabetic foot subjects.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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