(PDPN). PDPN can be a significant strain on an individual's quality of life (QOL), with the burden arising as a result of physical pain, sleep disturbance, limitation of activity, polypharmacy, and depression. Glycemic control is currently the only option for the prevention of diabetic neuropathy, with therapeutic options for PDPN limited to symptomatic treatments, including antidepressants, anticonvulsants, and topical agents for pain management.

Bitter apple, *Citrullus colocynthis* L., is a plant found in Africa and Asia that has been used for a variety of medicinal purposes, including pain relief and as a topical treatment on the feet of diabetic patients. The aim of the present study was to examine the efficacy and safety of a topical formulation of *C. colocynthis* in patients with PDPN in a randomized, double-blind placebo-controlled clinical trial.

Study subjects were recruited from patients attending diabetic clinics associated with an Iranian university. Patients with a clinical diagnosis of PDPN of the lower extremities for a period of three months or more were eligible for inclusion. Subjects were required to have controlled diabetes in the three months prior and be over 18 years age. Exclusion criteria included lower extremity pain caused by other diseases, history of allergic dermatitis, diabetic foot ulcers, and current use of other medications for diabetic neuropathy. *Citrullus colocynthis* was bought from a local market in Iran, with the fruit ground and decocted in water before being boiled in an oily vehicle (sesame oil) to create the topical formulation. Sesame oil was used as the placebo control. Patients were required to apply 2mL of the bitter apple oil formulation or sesame oil control twice daily for three months to the plantar and dorsal surface of affected feet. Patients were evaluated before and after three months of treatment, with assessment including a neuropathic pain scale, a QOL assessment with scores in physical, psychological, social and environmental domains, and nerve conduction studies of lower extremities.

Of the 73 patients assessed for eligibility, 60 were recruited and randomized for treatment on a 1:1 basis. At the completion of the study, results were available for 28 patients in the *C. colocynthis* group and 27 for the placebo group. Baseline characteristics for the groups were similar except for a significant difference in the prevalence of risk factors for neuropathy, with the *C. colocynthis* group having more risk factors.

After three months of treatment, a significant decrease in subjective neuropathic pain score was observed in both groups, but the mean change in score was significantly greater in the *C. colocynthis* arm. Mean changes in nerve conduction velocity of the tibial nerve, distal latency of the superficial peroneal nerve and sural nerve, and sensory amplitude of the sural nerve were significantly higher in the *C. colocynthis* arm than placebo, favouring treatment. No significant differences were observed in the other nerve conduction studies. In the QOL assessment, a significant improvement in the physical domain was observed for the treatment group, with no significant differences in the other domains. Treatments were generally well tolerated, with one patient from the *C. colocynthis* experiencing what was considered to be a local allergic reaction. A number of complaints from both study arms were made about the oily formulation.

The study presents preliminary support for a potential role in decreasing pain in patients with PDPN, and improvement in some areas of QOL. The study is strengthened by its objective evaluation of nerve function through nerve conduction studies in addition to the subjective pain and QOL scores. Whilst this is the first study evaulating bitter apple as a treatment for PDPN, previous studies have identified analgesic and anesthetic actions of *C. colocynthis.* The precise mechanism for these effects is unknown. Authors note that the control and vehicle for the *C. colocynthis* extract was not inert, with sesame having been demonstrated to exhibit anesthetic and anti-oxidant activity. The combination of both ingredients may have contributed to its significant effect and evaluation of bitter apple without an active vehicle may further support a potential role in management of PDPN.

Cinnamon compared to Ibuprofen in Primary Dysmenorrhoea

Jaafarpour M, Hatefi M, Khani A, Khajavikhan J. 2015. Comparative effect of cinnamon and Ibuprofen for treatment of primary dysmenorrhea: A randomised double-blind clinical trial. *J Clin Diagn Res* 9(4): 4-7.

Primary dysmenorrhea is one of the most common gynaecological complaints, affecting more than half of menstruating women at some stage in their lives. It is caused by an increase in synthesis and release of prostaglandins, particularly PGF2 from the uterine endometrium, resulting in contraction of smooth muscles in adjacent tissues leading to colicky pains, spasmodic pain in lower abdomen and lower back pain. Significant impact on quality of life can occur. Primary dysmenorrhea is also a common cause of absenteeism from work, with data from the USA associating dysmenorrhea with an annual economic loss of 600 million work hours and $US2billion. Non-steroidal anti-inflammatory drugs (NSAIDs) are often used to relieve symptoms, but there is concern about side effects, particularly with long-term administration.

Cinnamomum zeylanicum (syn. *C. Verum*), cinnamon, also called Ceylon cinnamon or true cinnamon, has previously demonstrated a number of different therapeutic actions including astringent, antimicrobial, anti-inflammatory, antioxidant, analgesic and antispasmodic properties. With a lack of comprehensive research for cinnamon in the management of dysmenorrhoea, the authors of the present study aimed to compare the effect

of cinnamon and Ibuprofen for treatment of primary dysmenorrhoea in a sample of Iranian female college students.

The trial was randomised, double-blind and placebo-controlled, with subjects allocated to receive Ibuprofen capsule containing 400mg three times daily (TDS), *Cinnamomum zeylanicum* capsule containing 420mg cinnamon as dried powder TDS, or a placebo capsule containing starch TDS, for 24 hours. In total, 114 female college students were recruited for the trial, with 38 subjects in each study arm. Inclusion criteria included: being aged 18-30 years; regular menstrual cycles; moderate dysmenorrhea;, lack of chronic diseases; not having symptoms such as burning, itching or abnormal vaginal discharge; lack of pelvic inflammatory disease, tumour, or fibroma; lack of recent stressors; and within defined body mass index range of 19-26 kg/m^2. Exclusion factors included: oral contraceptive pill use; medicine or plant allergy; and mild dysmenorrhea. Pain intensity and duration of pain were monitored for subjects in the first 72 hours of cycle. To determine the severity of pain a Visual Analogue Scale (VAS) was employed, and the Cox Menstrual Scale was used to determine the duration of pain.

Baseline characteristics between groups were similar, with similar pain scores reported before treatment. After treatment, the mean pain severity score reported for Ibuprofen was significantly less that the placebo group from the first time interval of 1hr post treatment, and at each subsequent interval til 72hrs. For the cinnamon group, no statistically significant difference in pain severity score was observed for the first four hours compared to placebo. After the next time interval of 8hr post intervention, however, a statistically significant reduction in pain severity was observed in the cinnamon group compared to placebo that continued til the end of observation at 72hrs. Duration of pain in the Ibuprofen and cinnamon groups were reported to be significantly less than placebo at reported time intervals after intervention. The effect of cinnamon was lower than that observed with Ibuprofen.

The study and the interpretation of its findings are limited by a lack of clarity around the plant and timing of interventions. The authors do not report on the part of plant used nor describe the preparation of plant material. Furthermore, it is unclear from the study when the intervention was initiated, i.e. at onset of menstruation, at onset of pain or another set time point, whether the intervention timing was standardised amongst study subjects, and whether the results were time after the initial or final dose of the intervention. Some discrepancy in tables provided also limit interpretation of the data.

The study provides some evidence for the use of *Cinnamomum zeylanicum* in dysmenorrhoea, demonstrating that compared to placebo, cinnamon intervention significantly reduced the severity and duration of pain during menstruation, albeit to a lesser extent that Ibuprofen. For women looking for non-pharmaceutical management of dysmenorrhoea, cinnamon may provide some benefit. Whilst the study seems to be a reasonably well-designed trial, it is unfortunate that presentation of data and unclear definitions of the therapy limit the interpretation and ability to apply the findings more broadly. Future studies that address some of these limitations, and with greater numbers of subjects, will further understanding.

Berberis integerrima compared to sildenafil in pulmonary hypertension

Mahdavi N, Joukar S, Najafipour H, Asadi-Shekaari M. 2015. The promising effect of barberry (Zereshk) extract against experimental pulmonary microvascular remodelling and hypertension: A comparison with sildenafil. *Pharm Biol*. In press. DOI: 10.3109/13880209.2015.1050676.

Pulmonary arterial hypertension (PAH) is described as a mean pulmonary artery pressure ≥ 25 mmHg at rest or ≥ 30 mmHg with exercise and a normal pulmonary capillary wedge pressure. PAH may be primary or idiopathic, or associated with other diseases including HIV infection, connective tissue disease, portal hypertension, and congenital heart disease. Untreated, the survival time for idiopathic PAH has been reported to be three years, with the prognosis of secondary PAH influenced by the underlying disease. Three main classes of drugs are currently used for treatment of PAH including prostanoids, enothelin-1 receptor antagonists, and phophodiesterase-type 5 (PDE5) inhibitors. While these medications can attenuate clinical symptoms and slow PAH development, they are not cures for the disease and accordingly interest remains for potential new therapies.

The major chemical constituents of the fruits of *Berberis integerrima* (barberry), of the Berberidaceae family, include coumarin, ascorbic acid, berberine, caffeic acid, β-carotene, flavonoids, malic acid, palmatine, carbohydrates, tannin, and ursolic acid. Whilst related to another barberry species, *Berberis vulgaris*, comparisons between the two species report differences in chemical make-up such as higher total phenolic and anthocyanin content in the fresh fruits of *B. integerrima*. Traditionally used for treatment of heart conditions including hypertension and arrhythmia, pharmacological studies on barberry and its key constituent berberine have demonstrated effect on decreasing systemic hypertension. Following from this, authors conducted the present study to examine the effect of a water extract of barberry (*B. intergerrima*) fruit on a monocrotaline-induced PAH rat model and compare its effect with sildenafil, a PDE5 inhibitor.

Seventy-two male Wistar rats were divided into nine groups as follows: the control group, the monocrotaline (M) group, the barberry (B) groups with doses of 50, 100,