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Review Article

Systemic enzyme therapy in chronic venous disease: a review

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ABSTRACT

Chronic venous disease (CVD), a sequel of venous insufficiency, has great medical and socioeconomic impact. Varicose veins and venous ulcer are amongst its commonest manifestations. In CVD, incompetent valves, weakened vascular walls, venous hypertension and increased permeability of venous walls lead to the release of proinflammatory mediators like tumor necrosis factor (TNF)-α, interleukin (IL)-1β, reactive oxygen species (R.O.S.), and reactive nitrogen species (R.N.S.) in the venous milieu. Pharmacotherapy with nonsteroidal anti-inflammatory drugs (NSAIDs) is often used to relieve pain caused by venous disease. However, there is a need for therapies that target the microcirculatory disorders and act on chronic inflammatory processes. Systemic enzyme therapy (SET), with orally administered combination of proteolytic enzymes- trypsin, bromelain, and flavonoid rutoside, has been used since decades for their anti-inflammatory, analgesic, anti-edematous, antithrombotic and antioxidant properties. This review discusses the various relevant pharmacodynamic properties demonstrated by the ingredients, followed by clinical studies of SET, which have demonstrated benefit in both subjective and objective parameters. These studies indicate that SET has good efficacy, tolerability and holds great promise to improve the quality of life of a patient with CVD.

Keywords: Chronic venous disease, Systemic enzyme therapy, Venous ulcer, Varicose veins

INTRODUCTION

Chronic venous disease (CVD) represents the sequelae of a general venous insufficiency, mostly of the lower extremities.[1] CVD are vascular pathologies of great medical and socioeconomic impact because of an impaired ability to engage in social and occupational activities, reducing the quality of life and imposing financial constraints. This is always overlooked due to incomplete recognition of the various presenting manifestations of primary and secondary venous disorders. Lack of preventive practice is a major reason for higher prevalence of CVD.[1-3] CVD affect a large part of the population (around 60%) worldwide, according to the Vein Consult Program in which, more than 91000 subjects in various geographic regions were evaluated for clinically significant CVD. Prevalence of CVD is more in females (73%) than males (56%).[1,3] Incidence of early stages of venous reflux occur in as many as 25% of women and 15% of men while later stages may occur in 5% of the population.[4] Some important symptoms of CVD are prominent dark blue blood vessels, aching pain or tenderness along the course of a vein, tired legs with heaviness, numbness, swelling, itching, burning sensation in legs, night cramps, pigmentation and bulging, rope-like bluish veins.[2] The important risk factors for developing CVD include advanced age, sex, obesity, a positive family history, pregnancy, phlebitis, and previous leg injury. Prolonged standing and perhaps a sitting posture at work also increases the risk for CVD.[3,5] Being a common pathologic condition, CVD spans a wide spectrum of clinical manifestations including telangiectases, reticular

veins, varicose veins, pain, edema, skin changes, hyperpigmentation, venous eczema, lipodermatosclerosis, atrophie blanche, and healed or active venous ulcers.[1,3]

Amongst various manifestations of CVD, varicose veins and venous ulcer are commonest. According to research articles in vascular disease, 15-20% of the population in India is suffering from varicose veins.[3] In the adult population, with a female: male predominance of 3:1, varicose veins have an estimated prevalence between 5% and 30%. The prevalence of venous ulcer, the more serious consequence of CVD is approximately 0.3%. Approximately 1.0% of adult population show active or healed ulcers.[3] Varicose veins is a pathologic condition of the peripheral vessels of lower extremities leading to the development of venous ulcer in some cases.[6] Varicose veins are twisted, enlarged veins near the surface of the skin and they mostly develop in the legs and ankles. When sitting or standing for a long time, the blood in the veins of the legs can pool and the pressure in the veins can increase and cause stretching. Stretching of veins can sometimes weaken the walls of the veins and damage the vein valves resulting in varicose vein.[2] Varicose veins are often primary (affecting only the superficial veins), and often result from a congenital or familial predisposition, that leads to the loss of elasticity of the vein wall. Secondary varicosities occur when trauma, obstruction, or inflammation causes damage to the valves (which affect the deep veins). The pursuant changes in subcutaneous tissues like hyperpigmentation, lipodermatosclerosis, atrophe blanche and varicose eczema, edema, skin fragility leads to the risk of leg ulceration and delayed healing. This affects the quality of life.[7]

This article explains pathophysiology, treatment modalities of CVD and various mechanisms of action of systemic enzyme therapy (SET) along with clinical evidences of its application in CVD. Systemic enzyme therapy (SET) is a combination of proteolytic enzymes trypsin, bromelain and flavonoid rutoside (rutin) having oral route of administration. Empirically SET has been used since decades, but better understanding of the mechanisms by which SET exerts the desired effects are being uncovered with the help of advances in the fields of immunology, biochemistry and molecular biology in the last few decades. These enzymes have high intestinal absorption rate and, hence, can be available in active form at the site of action in body. Having many therapeutic properties such as anti-inflammatory, analgesic, anti-edematous, antioxidant, antithrombotic effects, SET has been used in the management of sports injuries, arthritis, burns, post-surgical inflammation, pelvic inflammatory diseases, etc. Studies have also shown effectiveness of SET in the treatment of CVD.

PATHOPHYSIOLOGY

Body's veins are provided with valves, which ensure flow of blood back to the heart and prevent retrograde flow of blood. Dysfunction or incompetence of venous valves leads to the condition called 'reflux'.[3] Pathophysiology of CVD can be explained as incompetent valves, weakened vascular walls, and venous hypertension.[5] Microcirculation and microangiopathic changes are the manifestations of the elevated ambulatory pressure in the peripheral venous system of CVD patients. This impaired microcirculation is responsible for remodeling of the vein walls and valves, venous hypertension, formation of varicosities, edema, and leg ulceration.[1,8] Whereas, worsening of clinical symptoms like diminished vascular reserve, drop in the oxygen content of the skin, elevated subcutaneous flow and changes in capillary, like increased permeability, morphological changes and decreased number of capillaries, are observed with the microangiopathic changes.[8] Epidermis of dilated vessel wall leaks fibrinogen leading to the formation of fibrin cuff which is responsible for trapping of growth factors and matrix. Formation of fibrin cuff in blood vessels also acts as a barrier to diffusion of oxygen and nutrition to the tissue resulting in ulceration.[9,10]

The venous hypertension induces enhanced production, secretion and activation of enzymes like matrix metalloproteinases (MMPs). These MMPs destroy the protective layer of glycocalyx from the surface of endothelial cells. This may result in chemokine mobilization, modulating leukocyte adhesion, a vital process in inflammation. Under these conditions of high hydrostatic reflux pressure, the inflammatory burden is concentrated at the post- capillary venules of the microcirculation. When this gets transferred to larger vessels, the infiltration of leukocytes in peri-venous microenvironment occurs, which is responsible for the release of Intercellular adhesion molecules (ICAM – 1), vascular cell adhesion molecule-1 (VCAM – 1), P and L selectins. The increased permeability and the passage of different types of leukocytes from the circulatory system to the extra-cellular matrix are the inflammatory responses of the venous wall which in turn release pro inflammatory mediators like tumour necrosis factor (TNF)-α, interleukin (IL)-1β, reactive oxygen species (R.O.S.), reactive nitrogen species (R.N.S.) in venous milieu.[1,10] The increased capillary filtration rate, leukocyte adhesion, degranulation, and release of cytoplasmic granules from neutrophils, macrophages, mastocytes, endothelial cells, and platelets are the biological processes which activate inflammatory and proteolytic cascades in the vascular microenvironment and impaired micro and macro-circulatory flow.[1,11]

MANAGEMENT

The standard treatments for CVD include conservative, interventional and surgical treatments. The main aim of each treatment is symptom improvement, prevention of further complications and sequelae of CVD, and promotion of ulcer healing.[3,5] First conservative treatment consists of compression therapy, pharmacologic therapy and exercise therapy. Amongst these compression therapy is easy to use and counteracts the primary

pathophysiological mechanism – venous reflux and hypertension by opposing hydrostatic forces. Exercise therapy based on the rehabilitation of calf muscle pump helps in improving the symptoms. Interventional management of CVD include sclerotherapy, endovenous ablative therapy and endovenous deep system therapy. The patients with persistent discomfort, disability and non-healing venous ulcers may be treated with surgical management of CVD. This treatment is complementary to compression therapy. Surgery for truncal vein or venous tributaries, perforator vein surgery and valve reconstruction are some types of surgical management of CVD.[5,3,2] Nonsteroidal anti-inflammatory drugs (NSAIDs) with compression can help to relieve pain caused by venous disease and is used in the treatment of superficial thrombophlebitis.[12] Other pharmacologic therapies like horse chestnut seed extracts, flavonoids include quercetin derivatives, micronized purified flavonoid fraction, natural pine bark extract, coumarin derivatives, calcium dobesilate, and pentoxifylline are also used to improve venous tone and capillary permeability.[11] Pentoxifylline is a haemorheological agent and is believed to increase red and white cell filterability, and decrease whole blood viscosity, platelet aggregation, and fibrinogen levels. It shows influence on microcirculatory blood flow and oxygenation of ischemic tissues.[13]

Venous ulcer is a serious complication in CVD. The persistence and non- responsiveness of venous ulcer to conservative therapy and higher relapse rates after surgery show less effectiveness of these treatments. There is a need for further treatment modalities which can treat microcirculatory disorders and act on chronic inflammation in the ulcer, constant leukocyte infiltration and changes in the metabolism of endothelial cells.[6] This microcirculatory dysfunction can be treated by pharmacologic intervention or compression therapy or using a combination of both. This combination may show some additive effects in the treatment of CVD.[11] To treat CVD, flavonoid drugs are also used since many years. Some recent studies have been carried out to assess their effects on the microcirculation.[14]

SYSTEMIC ENZYME THERAPY (SET)

SET, the enzyme-flavonoid combination with oral route of administration, have shown interesting results in the management of CVD with respect to efficacy and tolerability. As per available treatment modalities in CVD, sometimes compression as well as other management show less efficacy in CVD.[6] In such cases SET may act as an effective individual therapy or adjuvant to compression therapy. Particularly in older patients, non-compliance with compression therapy is common. In such conditions oral SET may be used as adjunctive therapy to compression and other effective treatment modalities.[15]

Combinations of the enzymes trypsin and bromelain, along with the bioflavonoid Rutoside, is available for use as SET in many countries, since many decades. In India, this combination is available in different formulations – dispersible (example- Disperzyme), enteric-coated (example- Phlogam), and strengths. Orally administered trypsin, exists in blood in bound form to alpha-1 antitrypsin and has more affinity to it than plasmin, allows more plasmin to be available for fibrinolysis.[16] Fibrinogen breakdown leads to the improvement of macro and micro-circulation, removal of inflammatory products and adequate supply of oxygen and nutrients.[17] T cell activation is increased by trypsin with the help of selective cleavage of accessory molecules on antigen presenting cells.[18,19] The levels of proinflammatory cytokines (such as TNF-α, IL-1, IFN-γ) can be lowered by trypsin.[20] A growing family of G-protein-coupled protease-activated receptors (PARs), which play a major role in healing can be cleaved and activated by trypsin.[21] Trypsin having proteolytic activity, potentiate the differentiation of human monocytes to fibrocytes in cell culture and promote healing.[22] Alteration of macrophage surface marker expression and the macrophage secretion profile towards an M2a phenotype is the action of trypsin through G-protein-coupled protease-activated receptors (PARs), specifically PAR1 and PAR2 receptors. Wound healing and fibrosis involve M2a macrophages.[23]

Bromelain blocks the activation of extracellular regulated kinase-2 (ERK-2) in T Cells proteolytically, and inhibits T cell signaling and cytokine production.[24] By proteolytic removal of the CD128 chemokine receptor, bromelain effectively decreases IL-8-induced neutrophil migration to sites of acute inflammation both in vitro and in vivo. It also inhibits leukocyte migration as anti-inflammatory effect.[25] By influencing prostaglandin (PGE2, PGF2) and thromboxane (B2) synthesis, bromelain shows anti-inflammatory action.[26,27] Bromelain has demonstrated, in various in vitro and in vivo studies, fibrinolytic, antiedematous, antithrombotic, and anti-inflammatory activities.[26] In a rat model of intra-abdominal adhesions, bromelain treatment led to reduction in inflammation, fibrosis and neo-vascularization scores.[28] Bromelain also inhibits thrombus formation, by inhibiting platelet aggregation.[29]

Rutoside shows various effects as anti-oxidant, anti-inflammatory, and organ-protective activities.[30,31] Inhibition of inflammation-related gene expression and the release of nitric oxide, TNF-α, IL-1, and IL-6 has been demonstrated, when rutoside was added to activated human macrophages.[30] In silico molecular docking analysis rutoside shows anti-inflammatory activity by forming 6 hydrogen bond interaction with TNF-α.[32] Rutoside also complements bromelain in aggregation of human platelets by inhibiting intracellular Calcium [Ca2+] mobilization in platelets (which is required for platelet activation).[33] Reductions in production of superoxide ion, hydroxyl radicals and lipid peroxy radicals, as well as iNOS-mediated nitric oxide (NO) demonstrates the antioxidant action of rutoside.[34] The vascular permeability increase due to histamine, bradykinin and fibrin degradation products has been attenuated by rutoside.[35]

Table 1: Beneficial actions of systemic enzyme-flavonoid agents on the pathology of CVD.

Pathology in CVD	Action of systemic enzyme-flavonoid
Vasodilation and increased vascular permeability, mediated by histamine, bradykinin and fibrin degradation products	• Bromelain reduces vascular permeability by depleting kininogen, which is required for producing bradykinin. • Rutoside helps to reduce vascular permeability by inhibiting nitric oxide (NO) production through attenuation of iNOS gene expression.
Dilatation of vessels, followed by leakage of fibrinogen from capillaries, which coagulates and hardens to form a fibrin cuff	• Trypsin displaces 'bound' plasmin from plasma proteins and the free plasmin mediates fibrinolysis. • Bromelain helps fibrinolysis by proteolytically converting plasminogen to active plasmin.
Stasis of blood and damage of vessel wall predisposes fibrin formation and platelet aggregation, leading to thrombosis	• Bromelain inhibits platelet aggregation by inhibition of adhesion molecules on the platelet surface. • Rutoside prevents platelet activation by inhibiting intracellular Calcium [Ca^{2+}] mobilization in platelets (which is required for platelet activation).
Increased leukocyte migration to the site of inflammation	• Bromelain alters the cell surface molecules that are involved in leucocyte cellular adhesion to prevent leukocyte migration. • Rutoside inhibits the transcription of genes encoding for chemotactic factors.
Increased production of proinflammatory cytokines such as TNF-α, IL-1β	• Bromelain reduces cytokine production by altering the cell surface molecules that are involved in leucocyte activation. • Rutoside inhibits the transcription of genes encoding for proinflammatory cytokines.
Release of reactive oxygen species and nitrogen species causing tissue damage	• Rutoside inhibits production of superoxide ion, hydroxyl radicals and lipid peroxy radicals, as well as iNOS-mediated nitric oxide (NO).
Continued inflammatory changes and venous stasis results in chronic/non-healing ulcers	• Trypsin, by activation of PAR1 and PAR2 receptors on macrophages, promotes the differentiation of macrophages to a more healing/repairing profile (M2), rather than inflammatory profile (M1).

Hydroxyethylrutoside is rutoside derivative which acts on the microvascular endothelium to reduce hyperpermeability and edema. It also improves microvascular perfusion and microcirculation, and reduces erythrocyte aggregation. Having a protective effect on the vascular endothelium, rutoside derivative therapy helps to improve signs and symptoms of CVD.[31] The beneficial effects of systemic enzyme-flavonoid combination on the pathology of CVD has been summarized in Table 1.

CLINICAL STUDIES WITH SET

There are several clinical studies and few meta-analyses in literature evaluating the utility of SET with trypsin, bromelain and rutoside in combination or as individual ingredients in various manifestations of CVD. These include studies in varicose veins, venous ulcer, thrombophlebitis and pregnancy related venous insufficiency.

Efficacy of SET with trypsin-bromelain-rutoside combination was evaluated against conservative treatment (wound dressings, compression and phlebotropic drug therapy) in patients with varicose veins of lower extremities and venous trophic ulcers. SET was administered to 20 patients, while 18 patients receiving conservative treatment comprised the control group. Treatment was given for the duration of one month. Quantitative assessment of symptoms ("heavy legs", pain, swelling, cramps) and the analysis of the wound healing dynamics (healing of the ulcer and the condition of the surrounding tissues) were performed using Venous Clinical Severity Score (VCSS) and the ulcer and skin condition score. Discomfort in daily activities was assessed using Visual Analogue Scale (VAS). Bacteriological analysis of ulcer discharge was also performed. Lymphocyte counts and surface receptors were evaluated before and after treatment. Total ulcer epithelization in SET group was observed in 40% patients by week 3 and at the end of the treatment in 90% patients, compared to 22% and 50%, respectively in the control group. Patients in the SET group also reported more significant pain relief and reduction of discomfort around the ulcer during treatment compared to the control group. Results of immunoassays showed reduction of regulatory T cells and increased level of memory cells in SET treated group. The study, thus, demonstrated beneficial effects of SET on the regenerative processes in damaged tissues and on the function of T-cell mediated immunity in patients with varicose veins. It led to the regression of clinical symptoms and accelerated the healing process of venous trophic ulcers.[6]

Efficacy and safety of SET, in acute thrombophlebitis, was evaluated in a double-blind placebo-controlled trial of 100 patients, treated over 14 days. The patients had moderate to severe pain as monitored on a visual analog scale, pain under pressure, and presence of at least three of the following symptoms: skin redness, hyperthermia, phlebitic cords, feeling of heaviness and tenseness. Patients were investigated on day 0 (baseline) as well as on days 4, 7 and 14. Pain at rest was evaluated on a 10 cm VAS, and patients with a value ≤ 1 were defined as "responders". Pain under pressure was assessed using Meyer's pressure points at the lateral side of the tibia and Krieger's pressure point in the popliteal space. All other symptom severity was assessed by the physician or the patient by assigning a score of 0 to 3. Primary efficacy endpoints were the mean difference of rest pain between day 0 and 7 and the number of responders on day 7. A 94% reduction in average resting pain, from baseline, was reported in SET group compared to 71% in the placebo group. No patient in the SET group still had pain exceeding 2 cm on the VAS on day 14, compared to one-third of patients in the placebo group. The proportion of responders was 84% in SET group compared to only 20% in the placebo group. Reduction in pain under pressure occurred faster in SET treated group (96% reduction from baseline at day 14). At no time after the start of treatment were any of the symptoms more severe in the SET group than the placebo group. Overall, symptom relief was significantly better in the SET group compared to placebo, as demonstrated in the "sum score" of all five symptoms under study. Efficacy was assessed as "very good" by 78% of physicians and 76% of patients in the SET group, as opposed to 0% and 2%, respectively, in the placebo group. Only 12% patients developed adverse events in SET-treated group compared to 26% in the placebo group. All AEs were mild to moderate; in the SET group, most common events were diarrhea and loose stool, while stomach pain was the most frequent event in placebo group. This study demonstrated that SET is an effective and safe treatment option to alleviate pain and symptoms of acute thrombophlebitis. treatment.[36]

A few other studies in similar indication have been published, which have been briefly discussed further. In a placebo controlled trial, the efficacy of systemic enzyme therapy was studied in 119 patients suffering from acute thrombophlebitis of superficial veins in lower extremities and in 66 patients with post thrombophlebitic disease of the lower extremities. Overall result of this study shows that SET is an effective treatment in acute thrombophlebitis.[37] Efficacy of SET in thrombophlebitis and post-thrombophlebitic syndrome was evaluated in some studies. In a study, total 150 patients admitted to clinic of vascular and microsurgery were treated with SET. Amongst these 83 patients with venous system disease like acute thrombophlebitis and post-thrombophlebitic syndrome, showed decrease of pain, reduction of edema and trophic ulcers after treatment with SET. In 42 patients suffering with traumas of the hand, treatment with SET led to improvement in microcirculation of the injured site, reduction of edema and pain. Same treatment given to other 25 patients with arterial pathology improved with positive clinical outcomes. In another study, comparison between SET therapy and conventional therapy of lower limb post phlebitis syndrome for the duration of 3 months was done. Results of SET were more significant with respect to changes in hemostasis and blood rheological parameters, increased blood fibrinolytic activity and inhibited platelet function. Based on these parameters, SET showed more effectiveness as compared to conventional therapy. In one study, 46 patients with deep venous thrombosis were treated with SET for the duration of one year. This resulted in omission of anticoagulant treatment in 20 patients, reduction of leg edema in another 26 patient and better quality of patient's life.[38]

A combination of bromelain with oligomeric procyanidins (OPC) and coumarine was investigated in a large prospective, multicenter study of CVD patients. Amongst total 648 enrolled patients 165 patients were treated with compression stockings, 252 received compression stockings plus bromelain-OPC-coumarin combination and 231 patients received only bromelain-OPC-coumarin combination treatment. Significant reduction in malleolus circumference of both limbs was reported in all groups, but more evident in bromelain-OPC-coumarin plus compression stocking and monotherapy of bromelain-OPC-coumarin combination groups compared to the group which received only compression stocking.[39]

Rutoside, alone, has also been studied extensively, for the treatment of venous insufficiency associated conditions. In a double-blind, randomized, placebo-controlled study, 40 patients with venous insufficiency were treated with hydroxyethyl rutoside (rutoside) and 20 received placebo for 4 weeks. Overall symptoms reduced more effectively in rutoside treated group than placebo controlled group, with good tolerability and without side effects.[40] Signs and symptoms of venous insufficiency associated with pregnancy and lymphedema and CVD also showed improvement in placebo-controlled studies of duration up to 6 months. Rutoside was found effective and well-tolerated.[31] Another multicentre, double-blind, randomised, placebo-controlled trial in patients over 65 years of age with venous insufficiency or varicose veins was carried out to study efficacy and tolerability of rutoside. Amongst 104 patients, tolerability in 102 patients and efficacy in 86 patients were analysed. A 6-month treatment was given with monthly examinations. Five symptoms were studied, out of which, leg cramps, heavy legs and restless legs showed significant improvement in rutoside treated group than in placebo control group. Aching pain and paraesthesia, however, did not improve significantly. Ankle and calf circumferences, pitting edema of the leg and eczema of the leg also reduced significantly in rutoside treated group as compared with control group.[41]

Two independent studies were carried out to investigate differences in efficacy between rutoside and D+H (500 mg, diosmin+hesperidin) in patients with CVD. Both

studies have similar study format and total 212 patients were randomized to rutoside or D+H groups, who received either oral rutoside (2 g/day, 8 weeks) or D + H (1.5 g/day for 8 weeks). In the first study, skin flux at rest (RF), strain-gauge-derived rate of ankle swelling (RAS), and analogue symptoms score (ASLS) were main targets of evaluation. Whereas in second study venous-related quality of life was evaluated by using a specific questionnaire. Both studies showed higher improvement in all parameters in rutoside treated group than D+ H treated group. From both these studies it was concluded that rutoside as compared to D+H was more effective on microcirculatory parameters, on signs/symptoms of CVD and on the associated quality of life.[42,43]

The efficacy of rutoside at different dose concentrations was also evaluated in some trials. One of such trials is a randomized double-blind study against placebo with 30 female patients. Antiedematous effect of four different concentrations of rutoside drinking solutions with 600, 900, 1200 and 1500 mg active substance was tested. The symptoms like "tired and heavy legs", "tenseness" and "tingling sensation" were reduced. There was also a significant decrease in leg volume, which related to decrease in oedema.[44] The different dose concentrations of rutoside with different treatment modalities were evaluated in studies of 5 years of duration. One registry evaluation conducted in post-thrombotic syndrome (PTS) patients (with a minimum five-year follow up). Percent increase in circumference measured at the PTS limb was observed in five year follow up. Three different treatment regimens evaluated – First was compression, second was compression with rutoside (1 g/day) and third was compression with rutoside (2 g/day). Occurrence of deep venous thrombosis, lipodermatosclerosis, ulcerations, edema score, ankle circumference and need for surgery were reduced more significantly in rutoside treated group and also showed significantly better reduction in higher dose group in comparison with the other groups. Thus, rutoside was found to be more effective and tolerable when used alone or in combination with compression.[45] Another is the prospective controlled trial for the evaluation of efficacy of rutoside in patients having a severe degree of CVD and venous microangiopathy, in preventing complications such as venous ulcerations and edema over 5 years of administration. Capillary filtration rate (CFR) was also evaluated in association with a clinical score scale. Patients were divided into four different groups – patients with CVD without diabetes mellitus and treated with 1500 mg/d of rutoside, patients with CVD and diabetes mellitus and treated with 2 g/d of rutoside, control group without any treatment, patients received compression treatment only. CFR decreased significantly in rutoside treated group, but more significant decrease in CFR was observed with higher concentrations of rutoside. No adverse events were observed. It was observed in this trial that rutoside is effective in the prevention of ulcerations, deterioration of distal venous system and for the treatment of venous edema. Both these studies show significant long-term efficacy and tolerability of rutoside in the treatment and prevention of complications of CVD.[46]

Studies were also conducted to evaluate efficacy of rutoside in pregnancy related venous insufficiency. In a double-blind trial involving 69 patients to investigate the efficacy of rutoside in pregnancy related varicosities. In this study, one group of patients was treated with rutoside and second group was given placebo for 8 weeks. Significantly greater number of patients in the rutoside group reported subjective improvement; this was associated with significant decrease in leg circumference. Rutoside showed minimal side effects and had no adverse impact on the delivered babies, indicating its safety in pregnancy.[47] In another study 51 pregnant women divided into three groups – first group with physical therapy of cold foot baths, second group treated with rutoside and third group left untreated. Significant reduction of all parameters such as leg circumference and diameters of vein was observed in rutoside treated group.[48]

A meta-analysis of trials with rutoside against placebo was carried out in patients with CVD. Total 15 trials involving 1643 participants were included in this meta-analysis. The data showed significant reduction in symptoms of pain, heavy leg and cramps in rutoside group than control group. Tolerability was also evidenced as there was no adverse event reported with rutoside group.[49] Another meta-analysis of randomized trials of rutoside Was carried out. Pain of the legs, nocturnal cramps, tired legs, swelling sensations and restless legs were the parameters for analysis. Average rutoside dose was 1000 mg/day administered for at least 4 weeks. Total 1973 patients from 15 trials were analysed. This analysis showed superior result of rutoside therapy in the treatment of symptoms related to CVD.[50]

CONCLUSION

The term CVD covers various conditions of venous diseases according to the severity and manifestation of insufficiency which affect quality of life. Some conventional treatment modalities like compression, ablation, sclerotherapy, surgery, anti-inflammatory drugs, pharmacologic therapies, coumarins, plant extracts are used to treat CVD. But still, there is a need of a therapy which acts on the pathophysiology at a biochemical and molecular level. The enzyme-flavonoid combination of trypsin-bromelain-rutoside has demonstrated the potential to act on the numerous pathways involved in CVD pathophysiology. This is further supported by multiple clinical studies that have shown impressive efficacy and tolerability with SET. SET with trypsin-bromelain-rutoside has great potential to bolster the pharmacologic armamentarium for anti-CVD.

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