ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Review Article

Centella asiatica in the Conservative Treatment of Anal Fissure and Hemorrhoids in Comparison with Flavonoids

Massimo Chiaretti[1]*, Annalisa Italia Chiaretti[1] and Giovanna Angela Carru[2]

[1]Department of General Surgery, Surgical Specialties and Organ Transplantation 'Paride Stefanini', University of Rome "La Sapienza", Italy

[2]Health Department University Hospital, Policlinico Umberto I, Rome, Italy

***Corresponding Author:** Massimo Chiaretti, Department of General Surgery, Surgical Specialties and Organ Transplantation 'Paride Stefanini', University of Rome "La Sapienza", Italy.

Received: September 03, 2021; **Published:** October 12, 2021

Abstract

Background: In this review, we report about therapeutic effects of *Centella asiatica* (Ca) in comparison with Flavonoids (Fs) to find out which of them best deals with some items such as bleeding and pain healing time in the treatment of outpatients with chronic Anal Fissure (AF) on one hand. On the other hand, we report about the same parameters in outpatients treated for hemorrhoidal disease (HD).

Methodology: Ninety-eight outpatients who complained of AF were randomly assigned to the treated group (either Fs or Ca) and control group [1]. The control group (group C, n = 32) underwent standard treatment. Patients assigned the treated group were divided into subgroups that were treated, additionally, either with Fs (group A, n = 30) or Ca (group B, n = 36) and observed over 8 weeks. In another study on 130 outpatients (who underwent hemorrhoidectomy and operated for hemorrhoidal thrombosis) bleeding and pain were studied [2]. The treated group (both conservative and surgical) was randomized into two subgroups: the one treated with Fs (group A), the other with Ca (group B). Sixty patients (the control group C, both conservative and surgical) received the standard treatment. Time-to-stop bleeding was checked at the start (day 0) up to day 42 (end of the 6th week).

Results: Outpatients complained of AF, the median time-to-stop bleeding in group A resulted in 1 week, in 3 weeks group B, and 4 weeks in group C respectively. Among groups, for the time-to-end-bleeding (A vs B: p-value = 0.022; A vs C: p-value < 0.001; B vs C: p-value = 0.070) significant differences were observed. As for the pain score, from day 0 up to the end of the 2nd week, on the one hand among groups A and B, and on the other hand among groups A vs C, and B vs C significant differences respectively were observed (A vs C: p-value = 0.004; B vs C: p-value 0.035). All patients healed within the end of 8th week [1].

The paper about patients with HD showed "time-to-stop bleeding of 2 weeks for groups A and B; 3 weeks for group C" [2]. As for the VAS score (irritation) comparison among groups (A vs C: p = 0.007; B vs C: p = 0.041; and A vs B: p = 0.782) respectively resulted [2]. The patients underwent hemorrhoidectomy, "the time-to-stop bleeding was 3 and 4 weeks in groups A and B and 5 in group C", respectively [2]. "Histopathology showed a tight association between flavonoids and piles' fibrosis (p = 0.008)" [2].

Discussion: "The outpatients with AF treated with either Fs or Ca experienced an earlier healing and disappearance of pain in comparison with patients underwent to the traditional treatment" [1]. Fs showed the most efficacy for bleeding. Ca showed the most efficacy for edemas. Fs and Ca did not show side effects.

Conclusion: The outpatients with AF as well as those with HD treated either with Fs or Ca (phlebotonics) experienced early pain disappearance in comparison with the standard treatment group respectively. In the treatment of HD as well as after anal surgery, Fs and Ca showed significant beneficial effects. Fs among phlebotonics are the most effective against bleeding and anal irritation in HD. As for the Ca, among phlebotonics, seems the most effective for tissues' edema.

Keywords: *Centella asiatica; Anal Fissure; Hemorrhoids; Flavonoids*

Introduction

"Primary AF is benign ulceration of the anal mucosa of elliptical shape and a few millimeters in length, usually located between the pectinate line and the anal verge of the rectal canal back wall. The posterior wall is more fragile because of sphincter fibers decussation. Primary fissures are likely to be related to repetitive injury by hard stools, prolonged diarrhea, penetration [1]". An acute mucosa lesion that fails to heal in 6 - 8 weeks [3] progresses into a chronic AF. "HD has a general population prevalence ranging from 13% to 36%" [4] "with an estimated incidence of approximately 50% between 45 and 65 aged" [5]. "HD appears with symptoms and signs of soiling, itching, pain, prolapse and defecation bleeding that are commonly associated with enlarged hemorrhoidal cushions" [2]. "It may also be symptomatic of other diseases [2,6,7]". Anal irritation in the anorectal region can be due to fissure, anal itching, diabetes skin tags, yeast infection, acquired immunodeficiency disease syndrome, herpetic infection [8], allergic or irritant dermatitis, and fungal infections on the anus skin [2,9]. Etiology seems related to predisposition grounds and triggering factors. Up to 80% of "women develop piles during menstrual period and pregnancy [2,9,10]". The hormones and the oral contraceptive pills intake seem to facilitate HD and acute hemorrhoidal crisis [6,7,10]. Moreover, age, poverty-related factors, and low-in-water and low-in-vegetable-fibers diets promote constipation [11-14], which is related to the start of HD [4-7]. The conservative management (phlebotonics, diet rich in water and fibers, and hygienic cares) is a possible HD treatment from I to III grade in Golligher's classification [2,4-7,11-13].

Flavonoids

The name Flavonoid derives from the Latin word "flavus" (yellow) because flavonoids are yellow pigments in citrus fruits, fruits, and in most angiosperms. The distribution involves flowers, fruits, and leaves. They are grouped under the name of vitamin P, are classified among the semi-essential nutrients, and constitute a class of about eight hundred compounds. "The coloring they give to plant tissues depends on the pH and the bonds with metal ions" [2]. Blue pigments are formed by chelation with ferric ion or aluminum ion. Anthocyanins are pigments red, and blue, and violet and color flowers, and fruits. They are a group of flavonoids, with an important role in pollination. To the flavonoids belong Hesperidin, troxerutin, quercetin, and diosmin. Research abroad [14-18] and La Torre [19-22] have shown that flavonoids can play a role in the treatment and prevention of diseases of proctological interest.

Chemistry

Flavonoids are a polyphenolic class of compounds, secondary metabolites of higher plants, water-soluble, usually found as glycosides. "More than 4000 flavonoid glycosides and more than 1800 aglycones belonging to this class are currently known" [2].

Pharmacological effects

Flavonoids (Fs) have a modulatory effect on the body's response to allergens, viruses, and some carcinogens [18,20,23]. This ability is demonstrated by their anti-inflammatory, antiallergic, antiviral [24], and antineoplastic [18,24,25] properties. They optimize the intestinal absorption of iron and dietary calcium, assisting the therapy of osteoporosis. Fs act as antioxidants; provide greater protection than vitamins C, E, selenium, and zinc, against damage from oxygen free radicals [24]. Hesperidin, troxerutin, and diosmin exert a therapeutic effect on osteoporosis and enhance the immune reaction against Herpes labialis [14]. The Fs also act on capillary permeability, and blood circulation, and favoring collagen biosynthesis. Quercetin slows fibroblastic proliferation and stimulates the release of metal-proteinases (MMP-1) playing an important role in reducing the formation of scar keloids [14]. The Fs influence collagen metabolism by strengthening molecular cross-links, as well as inhibiting the enzymatic hydrolysis of collagen. Moreover, Fs reduce enzymes secreted by leukocytes during inflammation. "Fs prevent the release and biosynthesis of inflammation molecules and reduce the hyperergic response such as histamine, serine-protease, prostaglandins, and leukotrienes" [2].

Rutin

Synonyms are rutoside, vitamin P, quercetin-3-rutinoside, soforin. Rutin (Figure 1), is extracted from the fruits of the Fava D'Anta tree (*Dimorphandra gardneriana*), a northeastern Brazil typical plant [27]. Rutin is a solid compound that crystallizes with three water molecules, it is a flavonoic glycoside, of the genus Citrus plants, in the leaves and petals of genus Rheum plants, in buckwheat, in red wine, in peppermint, and eucalyptus. "The glycoside is formed from the flavonol quercetin (aglycones) linked to the disaccharide rutinose" [2]. Rutin has the greatest antioxidant capacity among seven compared flavonoids: rutin, quercetin, morin, acacetin, hispidulin, hesperidin, and naringin [15,27]. Rutin prevents the formation of the bond with hydrogen peroxide (binding divalent iron) that is produced in cytoplasmic metabolism and therefore prevents the formation of free radicals that can damage the cytoplasmic organelles [15]. "Rutin and its glycosidic derivatives also have the property of strengthening the capillary wall, reducing bleeding" [2] as in the case of hematomas or bleeding hemorrhoids. Clinical rutin is used to provide relief from symptoms due to lymphatic stasis and slowing of venous circulation in the lower limbs [28] as well as in our experience.

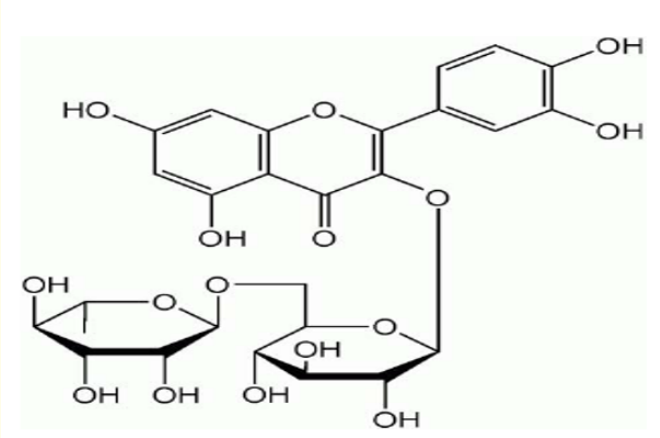

Figure 1: *Molecular formula of rutin.*

Rutin reduces LDL and cholesterol oxidation-related effects. Moreover, Rutin decreases cardiac ischemia risk [29] and exhibits antihistamine activity. Finally, in the past, in Latin America, chewed and ingested tea or rutin leaves were used as oral contraceptives, to induce abortion and in emergency contraception [30].

Diosmin

It has a protective action on capillary microcirculation thanks to its anti-inflammatory properties; in fact, it manages to block cyclooxygenase by inhibiting the formation of prostaglandins and thromboxanes. By reducing endothelial adhesion molecules, diosmin (Figure 2) reduces chemotaxis, the activation of leukocytes and macrophages. The anti-edema effect of diosmin is expressed by increasing the lymphatic flow and oncotic pressure. Diosmin has anti-oxidant properties, induces an increase in glutathione-peroxidase levels, in diabetic patients, determines the reduction of glycated hemoglobin levels [15], reduces vascular resistance with a therapeutic effect against blood stasis [19,20]. There have been no documented cases of adverse drug interactions with other drugs except metronidazole, used in abdominal surgery and peritonitis [17].

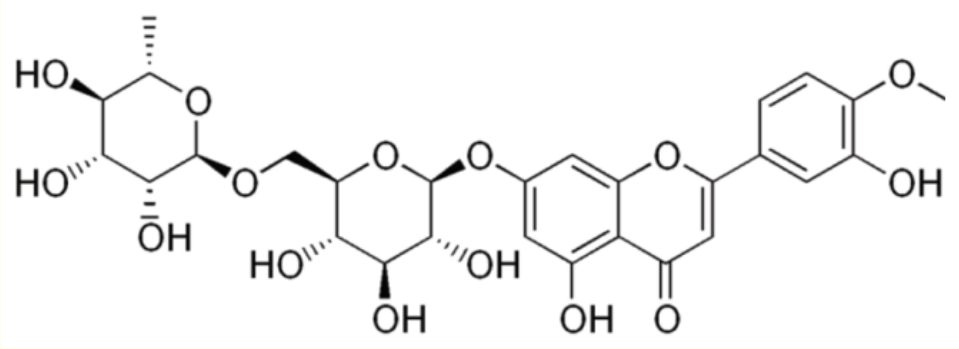

Figure 2: *Molecular formula of diosmin.*

Centella asiatica

Hydrocotyle asiatica (Gotu Kola), synonymous with Ca is a plant native to the tropical belt between the Tropic of Cancer and the Tropic of Capricorn and includes Africa, Madagascar, North and South America, the northern belt of the southern continent, and Southeast Asia. It belongs to the Apiaceae and Umbrelliferous family and grows spontaneously in humid, marshy places and some authors believe that the etymology of its name "*Centella*" derives from "sip, sip" continuously the water in the wetlands in which it lives. The pharmacological activity of triterpene esters characterizes the extract of this medicinal plant (Asian and madecassic acid) and the glycoside derivatives (asiaticoside, madecassoside) (Figure 3). Triterpenes have an affinity for microcirculation and for the connective tissue on which they are believed to carry out a physiological support activity (trophodermic action). The *Centella* phyto-complex is rich in polyphenols. *Centella asiatica* extract is used in cosmetology for the treatment of cellulite. The phyto-complex contains molecules that stimulate the synthesis of type [1] collagen, the production, and accumulation of a new extracellular matrix, improve vascular-connective tissue tropism, accelerates the repair processes of tissue damage, reduces lymphedema [31,32]. One of the first studies showed that asiaticoside can accelerate the healing of numerous types of wound, also thanks to the selective stimulation of the activity of the reticuloendothelial system [33]. Pre-clinical studies have highlighted the efficacy of the triterpene fraction of *Centella asiatica* in the induction of collagen synthesis by human fibroblasts grown in the laboratory, as well as in the increase of fibronectin, a structural protein important for the sealing of the venous vessel wall [34,37]. Numerous studies have also shown that the triterpene fraction is effective in the treatment of venous insufficiency thanks to its ability to regularize the structure of the connective tissue of the perivascular sheath, reduce sclerosis and improve blood flow in the affected limbs [37]. As for the clinical aspects, *Centella* a. has proved effective in various disorders related to chronic venous insufficiencies, such as venous hypertension and diabetic micro-angiopathy [34,37]. In all clinical studies, the triterpene fraction, administered orally, generally at a daily dose of 120 mg increase in transcutaneous oxygen saturation, a decrease in transcutaneous CO_2 saturation, a decrease in neck-foot edema, and a decrease in the capillarity effect [36,38]. A meta-analysis evaluated various herbal medicines in patients with chronic venous insufficiency. The natural substances included in the evaluation were horse chestnut, flavonoids, extracts of seeds and skins of red grapes, procyanidins, and triterpene fraction of Ca. The study concludes that all the substances evaluated can determine a significant improvement of the venous microcirculation, with reduction of the capillary filtration fraction, of transcutaneous CO_2 saturation, and increase of transcutaneous O_2 saturation with an improvement of subjective and objective symptoms [39].

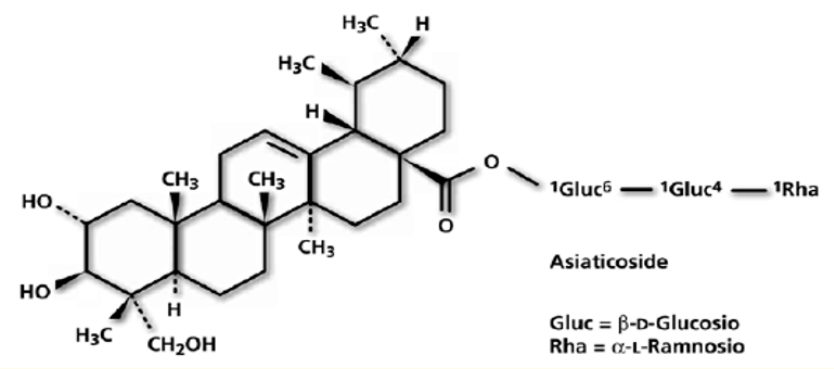

Figure 3: *Molecular formula of asiaticoside, triterpene glycoside of Centella asiatica.*

Hamamelis virginiana

It is a bushy shrub, originally from North America, used as an ornamental and medicinal plant due to the high content of tannins with antioxidant power.

Aesculus hippocastanum

It is an arboreal plant native of Eastern Europe, its fruits are rich in active ingredients but not edible for humans. The extract is used to improve microcirculation and favoring interstitial fluids reabsorption.

Risk profile

In none of the studies of Arpaia [36], Cesarone [37], Incandela [38], serious adverse events were detected, however, *Centella asiatica* can enhance the pharmacological effect of thyroid hormones and can interact with anticonvulsants, antidepressants, anticholinergics, antihistamines, statins, and oral hypoglycemic agents, although these interactions have not yet been well defined [34,39]. In recent studies both Fs and Ca did not show side effects [1,2].

Discussion

"Sanei, *et al.* referred that in their randomized clinical trial in the comparison of GTN with DTZ, 33.3% and 45.1% of their patients respectively, underwent sphincterotomy" [1,5]. Brady., *et al.* evaluated the characteristics and outcomes of patients who received either Botulinum toxin, (BT) or lateral internal sphincterotomy (LIS) comparing anal fissure treated with temporary chemical denervation (BT) instead of sphincterotomy (LIS) due to concerns for long-term incontinence as measured with Cleveland Clinic Fecal Incontinence (CCFI) score [1,40]. Fissure recurrence was significantly higher for BT than LIS patients. Both LIS and BT patients had some durable changes in continence raising the question of whether there is a safe technique [1,40]. Chiaretti *et al.* [1] report mucosal fissure complete closure. Moreover, the stop-of-bleeding and disappearance of defecation pain in all patients were obtained, earlier in groups treated with studied phlebotonics (Fs and Ca) in comparison to the control group C. No patients with chronic anal fissure [1] needed sphincterotomy and no patient complained of incontinence [4,5,9,40]. Bhardwaj showed GTN [6] to be as effective as diltiazem hydrochloride in producing a temporary chemical sphincterotomy with healing rates that Sajid indicates as ranging from 30 - 46% [8] to 83 - 86% [5,7]. On the other hand 80% of patients treated with GTN experienced headaches during the treatment and DTZ showed fewer side effects [5]. DTZ, GTN, and botulinum toxin showed temporary incontinence of flatus of 18% and temporary incontinence of stools of 5% respectively [1,5,10,41]. The treatment of AF requires first of all overcoming constipation or diarrhea with a specific diet, that gives the patients an appropriate

provision of fibers and cellulose [11,41,42,47], without contents irritating the mucosa [42], aimed to obtain a stable modification of the patient's eating behavior [1,6,9,10,11,41,43]. The group A median time-to-stop-bleeding was 1 week. As for pain treatment, on one hand, statistical differences among groups A and B (treated with phlebotonics from baseline to the 2nd week) and group C were observed. On the other hand, also changes in the VAS score were observed. "These results highlight that both Fs and Ca are effective on pain treatment" [1]. "Group A shows a nearly complete disappearance of bleeding already by the end of 1st week" [1]. Phlebotonics seem to reduce bleeding and pain healing times in comparison to the traditional treatment.

Chiaretti *et al.* [1] significant differences on weight sensation and tenesmus sensation detected neither with Fs nor with Ca.

"Boyle attributes to Rutin the property of strengthening the wall of capillaries as well as observed, reducing bleeding and lymphedema and inflammation. As for effectiveness in terms of healing and safety, on one hand, all patients healed, within the end of 1st week (group A), 3rd week (group B), and 4th week (group C), an improved result compared to other Authors. On the other hand no adverse reactions were observed in patients treated with Fs [12-15] nor in patients treated with Ca, probably thanks to the great attention paid to exclusion criteria" [1].

"Cho [14] documented that Fs [12-15] and Ca [36] stimulate the synthesis of collagen type 1, the production and accumulation of new extracellular matrix improving vascular-connective tissue deposition, accelerating the repair processes of the tissue damage, reducing vascular ectasia and lymphedema. Last but not least both Fs and Ca are effective on microbial and leucocytes enzymatic hydrolysis inhibition that occurs during infection and inflammation respectively, shielding the collagen" [1].

"In the experience on 130 with HD bleeding at baseline, the median time-to-stop bleeding was 2 weeks in group A, 3 weeks in groups B and C with significant differences between the groups (A vs B, $p = 0.007$; A vs C, $p < 0.001$; B vs C, $p = 0.152$). As for anal irritation, after the first week, groups A and B showed a similar improvement better than group C". The results are similar to La Torre outcomes for symptoms (anal irritation = pruritus and bleeding) [45]. Along with medical checkups, grade IV and III HD resulted understated respectively to III and II grade. The upper section of table 4 reports on grade III HD patients' sensitivity. It shows statistically significant differences among groups of treatment. Twenty out of 22 patients of group A, 11 out of 17 patients of group B, and 2 of 14 patients of group C showed a clinical understaging (A vs C, $p < 0.001$; B vs C $p < 0.001$). As for 31 cases with bleeding grade III-IV HD underwent hemorrhoidectomy, the histomorphometry revealed that the type of administered therapy influences the volume of anal cushion, vessels' number, and ectatic vessels number for microscopic field with a strong association to flavonoids ($p = 0.008$) [2].

Conclusion

As for bleeding, patients with AF treated with Fs "bleeding stops after the 1st week of treatment". Combined therapy with dilators, diet, and hygienic protocol showed useful on bleeding and pain, especially with the adjunctive either Fs or Ca. As for VAS score and pain, from baseline to the 2nd week, statistical differences between groups A and B compared to the Control group were detected. Fs and Ca resulted equally effective on pain" [1]. No risks for continence were revealed with this combined therapy. "As for weight sensation and tenesmus, no significant difference was found" [1].

In our opinion is advisable to avoid capsaicin alkaloids and alcoholic beverages. That is true that some authors consider these spices harmless, but some subjects are more sensitive than others. As for HD groups A and B had better trends than group C. As for pain in operated patients, statistical difference was detected in VAS scores. Phlebotonics showed no significant differences even if healing occurred in both groups A and B within the second week. Group C's patients healed at the end of the fourth week. VAS scores of groups A and B decreased significantly faster than group C. Phlebotonics in HD, as well as after surgery, showed evident beneficial effects" [2]. Phlebotonics are particularly effective, so they should no longer be considered dietary supplements, but receive the same attention as medications. The

histopathology results show a clear action that could also affect other anatomical districts. Therefore, a careful prescription of phlebotonics is recommended.

Bibliography

1. Chiaretti M., *et al*. "Comparison of Flavonoids and Centella asiatica for the treatment of chronic anal fissure. A randomized clinical trial". *Annali Italiani Chirurgia* (2018): 7.

2. Chiaretti M., *et al*. "Comparison of *Centella* with Flavonoids for Treatment of Symptoms in Hemorrhoidal Disease and After Surgical Intervention: A Randomized Clinical Trial". *Scientific Reports* 10 (2020): 8009.

3. Everhart JE. "The burden of digestive diseases in the United States". In: US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Everhart, J, E., ed. US Government Printing Office, Washington, DC US:NIH Publication (2008): 65-68.

4. Hiltunen KM and Matikaiven M. "Anal manometric in anal fissure. Effect of anal dilatation and lateral subcutaneous sphincterotomy". *Acta Chirurgica Scandinavica* 152.1 (1985): 65-68.

5. Sanei B., *et al*. "Comparison of topical glyceryl trinitrate with diltiazem ointment for treatment of chronic anal fissure. A randomized clinical trial". *Annali Italiani di Chirurgia* 80 (2009): 379-383.

6. Bhardwaj R and Parker MC. "Modern perspectives in the treatment of chronic anal fissures". *Annals of the Royal College of Surgeons of England* 89.5 (2007): 472-478.

7. Knight JS., *et al*. "Topical Diltiazem ointment in the treatment of chronic anal fissure". *British Journal of Surgery* (2001): 553-556.

8. Sajid MS., *et al*. "The efficacy of diltiazem and glyceryl trinitrate for the medical management of chronic anal fissure: a meta-analysis". *The International Journal of Colorectal Disease* 23.1 (2008): 1-6.

9. Walker WA., *et al*. "Morbidity of internal sphincterotomy for anal fissure and stenosis". *Diseases of the Colon and Rectum* (1985): 832-835.

10. Schlichtemeier S and Engel A. "Anal fissure". *Australian Prescriber* 39.1 (2016): 14-17.

11. Nelson RL., *et al*. "Non-surgical therapy for anal fissure". *Cochrane Database of Systematic Reviews* 2 (2012): CD003431.

12. Monograph Diosmin. *Alternative Medicine Review* 9.3 (2004): 178-211.

13. Kim HP., *et al*. "Anti-inflammatory Plant Flavonoids and Cellular Action Mechanisms". *Journal of Pharmacological Sciences* 96 (2004): 229-245.

14. Cho JW., *et al*. "Onion extract and quercetin induce matrix metalloproteinase-1 in vitro and in vivo". *International Journal of Molecular Medicine* 25.3 (2010): 347-352.

15. Asgary S., *et al*. "Anti-oxidant effect of flavonoids on hemoglobin glycosylation". *Pharmaceutica Acta Helvetiae* 73.5 (1999): 223-226.

16. Khafagy W El Nakeeb A., *et al*. "Conventional hemorrhoidectomy, stapled hemorrhoidectomy, Doppler guided hemorrhoidectomy artery ligation; post-operative pain and anorectal manometric assessment". *Hepatogastroenterology* 56.93 (2009): 1010-1015.

17. Monograph –Diosmin. *Alternative Medicine Review* 9.3 (2004).

18. Jiag ZM and Cao JD. "The impact of micronized purified flavonoid fraction on the treatment of acute haemorrhoidal episodes". *Current Medical Research and Opinion* 22.6 (2006): 1141-1147.

19. La Torre F., *et al*. "Malattia emorroidaria e trattamento conservativo. Revisione della letteratura sull'impiego di Diosmina ed Esperidina micronizzate". *Minerva Chirurgica* 54.12 (1999): 909-916.

20. La Torre F and Nicolai AP. "Clinical Use of Micronized Purified Flavonoid Fraction for Treatment of Symptoms after Hemorrhoidectomy: Results of a Randomized, Controlled Clinical Trial Dis Colon Rectum (2004).

21. Altomare DF., *et al*. "Red Hot Chili Pepper and Hemorrhoids: The Explosion of a Myth: Results of a Prospective, Randomized, Placebo-Controlled, Crossover Trial". *Diseases of the Colon and Rectum* 49 (2006): 1018-1023.

22. Donato F Altomare., *et al*. "Red Hot Chili Pepper and Hemorrhoids: The Explosion of a Myth: Results of a Prospective, Randomized, Placebo-Controlled, Crossover Trial". *Diseases of the Colon and Rectum* 49 (2006): 1018-1023.

23. Chobotova K., *et al*. "Bromelain's activity and potential as an anti-cancer agent: Current evidence and perspectives". *Cancer Letters* 290.2 (2010): 148-156.

24. Bhui K., *et al*. "Bromelain inhibits COX-2 expression by blocking the activation of MAPK regulate NF-kappa B against skin tumor-initiation triggering mithocondrial death pathway". *Cancer Letters* 282.2 (2009): 167-176.

25. Shin DY., *et al*. "Induction of apoptosis in human colon cancer HCT-116 cells by anthocyanins through suppression of Akt and activation of p38-MAPK". *International Journal of Oncology* 35.6 (2009): 1499-1504.

26. Lyu SY., *et al*. "Antiherpetic activities of flavonoids against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) in vitro". *Archives of Pharmacal Research* 28.11 (2005): 1293-1301.

27. Montano HG., *et al*. "Phytoplasma in "fava d'anta" tree (Dimorphandra gardneriana) in Brazil". *Bulletin of Insectology* 60.2 (2007): 147-148.

28. Boyle SP., *et al*. "Bioavailability and efficiency of rutin as an antioxidant: a human supplementation study". *European Journal of Clinical Nutrition* 24 (2000): 774-782.

29. Iacobellis O., *et al*. "Influence of excess fat on cardiac morphology and function: study in uncomplicated obesity". *Obesity Research* 10.8 (2002): 767-773.

30. Cataldi A., *et al*. "Effectiveness of the combination of alphatocopherol, rutin, melilotus, and centella asiatica in the treatment of patients with chronic venous insufficiency". *Minerva Cardiology and Angiology - Journals* 49.2 (2001): 159-163.

31. Weed S. Wise woman Herbal for the Chilbearing Year.

32. Cesarone MR., *et al*. "Evaluation of treatment of diabetic microangiopathy with total triterpenic fraction of Centella asiatica: a clinical prospective randomized trial with a microcirculatory model". *Angiology* 52.2 (2001): S49-54.

33. Vannacci A., *et al*. "Herbal medicine in the management of venous insufficiency and lymphedema". G.I.O.T. 35 (2009): 23-33.

34. Della Loggia R. Atlante di Fitoterapia, UTET (2006).

35. Lu L., *et al*. "Asiaticoside induction for cell-cycle progression, proliferation and collagen synthesis in human dermal fibroblasts". *International Journal of Dermatology* 43 (2004): 801-807.

36. Arpaia MR., *et al*. "Effects of Centella asiatica extract on mucopolysaccharide metabolism in subjects with varicose veins". *International Journal of Pharmacology Research* 10 (1990): 229-233.

37. Cesarone MR., *et al*. "Microcirculatory effects of total triterpenic fraction of Centella asiatica in chronic venous hypertension: measurement by laser Doppler, TcPO2-CO2, and leg volumetry". *Angiology* 52.2 (1992): S45-48.

38. Incandela L., *et al*. "Total triterpenic fraction of Centella asiatica in chronic venous insufficiency and in high-perfusion microangiopathy". *Angiology* 52 (2001): 9-13.

39. Wollina U., *et al*. "A review of the microcirculation in skin in patients with chronic venous insufficiency: the problem and the evidence available for therapeutic options". *The International Journal of Lower Extremity Wounds* 5 (2006): 169-180.

40. Brady JT., *et al*. "Treatment for anal fissure: Is there a safe option?". *The American Journal of Surgery* 214 (2017): 623-628.

41. Potgieter M., *et al*. "The gut microbiota and host health: a new clinical frontier". *FEMS Microbiology Reviews* 39.4 (2015): 567-591.

42. The enteric microbiota in the pathogenesis and management of constipation". *Best Practice and Research Clinical Gastroenterology* 25.1 (2011): 119-126.

43. LARN. "Livelli di Assunzione di Riferimento di Nutrienti ed energia per la popolazione italiana". *Revisione* (2012).

44. Casley-Smith JR., *et al*. "Fine structural aspects of lymphoedema in various tissues and the effects of treatment with coumarin and troxerutin". *British Journal of Experimental Pathology* 55 (1974): 88-93.

45. La Torre F and Nicolai AP. "Clinical use of micronized purified flavonoid fraction for treatment of symptoms after hemorrhoidectomy: results of a randomized, controlled, clinical trial". *Diseases of the Colon and Rectum* 47 (2004): 704-710.

Volume 8 Issue 11 November 2021