

## Review Article

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

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In this review we report effects Centella asiatica (Ca) in comparison with Flavonoids (Fs) to find out which best deals with healing time, bleeding and pain in the treatment of outpatients with chronic Anal Fissure (AF) on one hand. On the other hand, we report also the time-to-stop bleeding, and the anal irritation in patients who complained of Hemorrhoidal Disease (HD).

Ninety-eight outpatients with AF were divided randomly into treated (either Fs or Ca) and control group. The control group (Group C, n=32) received the traditional treatment along with the other two subgroups which were treated, additionally, with Fs (Group A, n=30) or Ca (Group B, n=36). Patients were observed once weekly over 8 consecutive weeks. In another study, 130 patients with HD were studied for bleeding and pain after hemorrhoidectomy (31 patients) and hemorrhoidal thrombosis (34 patients) in the short time (II). The treated group (both conservative and surgical) was divided into two subgroups: one treated with Fs (Group A, n = 73), the other with Ca (Group B, n = 66). Sixty patients were randomized to receive the routine treatment (both conservative and surgical) (control Group C). Time-to-stop bleeding was checked at baseline and checkups (0 up to day 42).

**Results:** The outpatients with AF the median time to stop bleeding in the group A was 1 week, in the Group B was 3 weeks and in the group C was 4 weeks. Significant differences between Groups in terms of 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) were observed. Pain score from baseline to the 2<sup>nd</sup> week was statistically different between A and B Groups on the one hand and Group C on the other hand (A vs. C: p-value=0.004; B vs. C: p-value 0.035). All patients healed within 8<sup>th</sup> week.

The study on patients with HD showed time-to-stop bleeding of 2 weeks for Groups A and B; 3 weeks for Group C. As for VAS scores comparison among Groups (irritation): A vs. C, p = 0.007; B vs. C, p = 0.041; and A vs. B, p = 0.782 respectively. The patient underwent to hemorrhoidectomy, the time-to-stop bleeding was 3 and 4 weeks in Groups A and B and 5 in Group C. Histopathology showed an association between flavonoids and piles' fibrosis (p = 0.008).

**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. Fs showed the most efficacy for bleeding. Fs and Ca did not show side effects.

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

**Keywords:** Centella asiatica; Flavonoids; Hemorrhoidal disease

## Introduction

“Primary AF is a 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 [2,3] 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. It may also be symptomatic

of other diseases [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. Etiology seems to relate to triggering factors and the predisposition grounds. Up to 80% of women develop piles during menstrual period and pregnancy [9,10]. The hormones and the oral contraceptive pill's 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], that 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 [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 on the bonds with metal ions. Blue pigments are formed by chelation with ferric or aluminum ions. A specific group of flavonoids, anthocyanins, pigments flowers, and fruit in red, blue, and violet 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.

## 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 on blood circulation, and favoring collagen biosynthesis. Quercetin slows fibroblastic proliferation and stimulates the release of metalloproteinases (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 [26]. 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 [13].

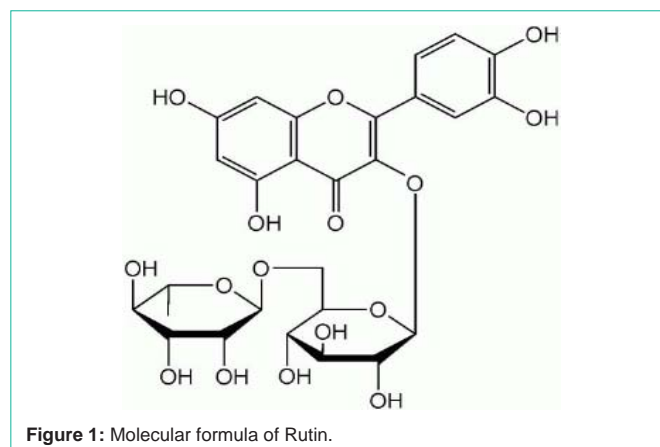


Figure 1: Molecular formula of Rutin.

## 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 in eucalyptus. The glycoside is formed from the flavonol quercetin (aglycone) linked to the disaccharide rutinose. 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 [25]. Rutin and its glycosidic derivatives also have the property of strengthening the capillary wall, reducing bleeding 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.

Rutin could reduce the effects related to the oxidation of LDL cholesterol and decrease the risk of cardiac ischemia [29] and possesses 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 the 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 it 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].

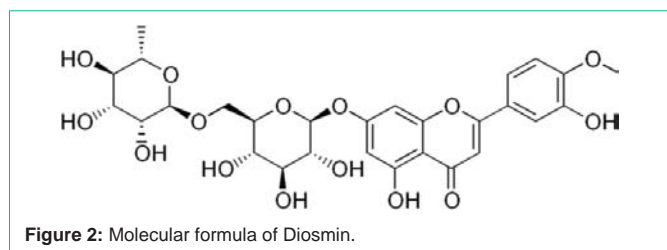


Figure 2: Molecular formula of Diosmin.

## Centella Asiatica

*Hydrocotyle asiatica* (Gotu Kola), synonymous of 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, improves vascular-connective tissue tropism, accelerates the repair processes of tissue damage, reduces lymphedema [31,32]. One of the first studies showed that asiaticoside is able to accelerate the healing of numerous types of wound, also thanks to the selective stimulation of the activity of the reticuloendothelial system [33]. Preclinical 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.* it has proved effective in various disorders related to chronic venous insufficiency, such as venous

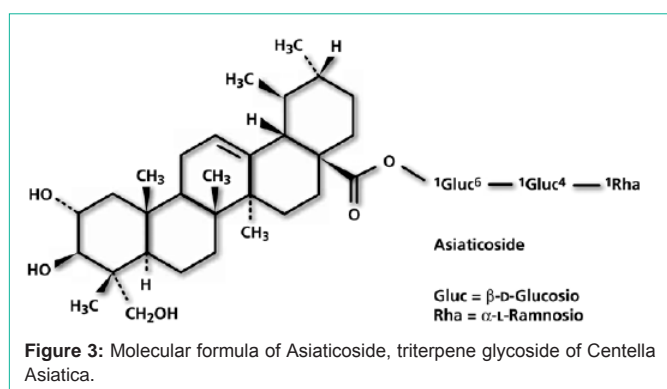


Figure 3: Molecular formula of Asiaticoside, triterpene glycoside of *Centella Asiatica*.

hypertension and diabetic micro-angiopathy [34,37]. In all clinical studies, the triterpene fraction, administered orally, generally at a daily dose of 120mg, resulted in an increase in transcutaneous oxygen saturation, a decrease in transcutaneous CO<sub>2</sub> saturation, a decrease in neck-foot edema and a decrease in capillary [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, triterpene fraction of Ca. The study concludes that all the substances evaluated are able to determine a significant improvement of the venous microcirculation, with reduction of the capillary filtration fraction, of transcutaneous CO<sub>2</sub> saturation and increase of transcutaneous O<sub>2</sub> saturation with improvement of subjective and objective symptoms [39].

## 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

Arboreal plant native to Eastern Europe whose fruit is not edible for humans but rich in active ingredients, useful in improving the microcirculation, favoring the reabsorption of interstitial fluids.

## 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 [5]. Brady et al. evaluated the characteristics and outcomes of patients who received either Botulinum Toxin (BT) or lateral internal sphincterotomy (LIS) [40] 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. 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. In our own randomized clinical trial complete mucosal closure over the fissure, the stop of bleeding, and disappearance of defecation pain in all patients were obtained, earlier in Groups treated with Fs and Ca compared to the control group C. No patients required sphincterotomy [4,5,9,40] and incontinence was not. 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 headache 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 [5,10,40]. 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], without contents irritating the mucosa [42], aimed to obtain stable modification of the patient's eating behavior [6,9-11,41,43]. The median time to bleeding cessation in the Group A was 1 week. Fs seemed to be the most effective treatment on AF bleeding [30]. As for pain, we observed statistical differences between Group A and Group B (from baseline to the 2<sup>nd</sup> week) on one hand, and the Group C on the other hand in terms of changes of VAS score. These results highlight that both Fs and Ca are effective on pain treatment. Group A [11-13,30,34,37,41,44] shows a nearly complete disappearance of bleeding already by the end of 1<sup>st</sup> week. Group B A [11-13,30,34,37,41,44] showed a significant difference in comparison with traditional treatment but lower than Group A. Fs and Ca seem to reduce bleeding and pain healing times compared to traditional treatment. We did not detect significant differences on weight sensation and tenesmus sensation with either Fs or Ca. Boyle attributes to Rutin the property of strengthening the wall of capillaries as well as observed, reducing bleeding and lymphedema and inflammation [30]. As for effectiveness in terms of healing and safety, on one hand all patients healed, within the end of 1<sup>st</sup> week (Group A), 3<sup>rd</sup> week (Group B) and 4<sup>th</sup> week (Group C), an improved result compared to other Authors [5,8,10,43]. On the other hand, no adverse reactions were observed in patients treated with Fs [12-15] nor in patients treated with Ca [34], probably thanks to the great attention paid to exclusion criteria. Cho [14] documented that Fs [12-15] and Ca [34] 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 [9,10]. "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 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 statistical significant differences among Groups of treatment. In fact, 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].

## Conclusions

As for bleeding in patients affected by AF treated with Fs bleeding stops after the 1<sup>st</sup> week of treatment. A 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 2<sup>nd</sup> week, statistical differences between Groups A and B compared to the Control group were detected. Fs and Ca resulted equally effective on pain.

As for weight sensation and tenesmus no significant difference were found.

In our opinion, avoiding capsaicin alkaloids, as well as alcoholic drinks is advisable.

"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 among Groups A and C ( $p = 0.045$ ). 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 (A vs. B,  $p < 0.001$ ; A vs. C,  $p < 0.001$ ; B vs. C,  $p < 0.001$ ). Phlebotonics in HD, as well as after surgery, showed significant beneficial effects [1].

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