

# Determining the Effect of Hydroalcoholic Extract of Anvilia Garcini on Ulcerative Colitis

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**Abstract— Introduction:** Ulcerative colitis is a chronic inflammatory disease of the colon and rectum, which is associated with symptoms such as rectal bleeding, diarrhea, and sometimes abdominal pain. Anvilia Garcini is a flavonoid that has anti-inflammatory and antioxidant properties. This research was designed to evaluate the effects of Anvilia Garcini for the treatment and control of inflammation in an animal model of ulcerative colitis. **Materials and methods:** In this experimental study, after inducing colitis with acetic acid, male rats were divided into 6 groups of 5 (negative control group, enema treatment with Asacol, oral treatment with mesalazine 10 mg.kg, oral treatment with Anvilia dose 250 and 500 ml gram, enema was divided with Anvilia 250 mg.kg). All rats were examined in terms of body weight changes, tissue changes and biochemical indicators of MPO, MDA. **Results:** The largest weight gain was the Asacol enema group, Anvilia enema (250 mg.kg), Mesalamine oral treatment, Anvilia oral treatment (500 mg.kg), Anvilia oral treatment (250 mg.kg) and finally the control group. It was negative. The negative control group was significantly different from the treatment groups in terms of wound and inflammatory cell secretion and reduction of mucous cells. **Conclusion:** Treatment with Anvilia Garcini improved the reactions which were confirmed by changes in oxidative stress markers, improved disease severity index, and reduction of tissue scars. Therefore, Anvilia Garcini reduces the symptoms of ulcerative colitis. As a result, the use of Anvilia Garcini as a substance of plant origin with much less side effects can be used as a new method for the treatment of ulcerative colitis.

**Keywords—** Ulcerative colitis, Anvilia garcini, acetic acid.

## I. INTRODUCTION

Ulcerative Colitis (UC) is an inflammatory bowel disease characterized by chronic and uncontrollable inflammation of the intestinal mucosa (1). This disease affects the colon from the anorectal area to the higher areas. UC is a debilitating disease that severely affects quality of life. The prevalence of UC has increased in the past decades in North America and Europe and is increasing in other parts of the world (2). Inflammatory bowel diseases can occur at any age, but usually begin between 15 and 30 years of age. The prevalence of this disease is slightly higher in men (3). This disease can cause bloody diarrhea, abdominal pain and malnutrition. Also, the risk of anemia, nutritional deficiencies, hepatobiliary diseases, kidney stones, osteoporosis, and colon cancer is higher in patients with UC. The cause of this disease is unknown, but various factors such as genetic environmental factors, microbial factors of the immune system and autonomic nerves are known to be involved in the development of this disease (4-6).

Inflammatory mediators and oxidative stress also play an important role in causing this disease (7). Overexpression of pro-inflammatory immune products -IL-1beta, TNF-a, IL-6 and IL-13 in UC has been well demonstrated in studies. In UC, neutrophils and macrophages are secreted into the intestinal mucosa, active neutrophils. In the intestinal mucosa, they produce and secrete reactive oxygen species such as hydroxyl radicals, hydrogen peroxide and superoxide ions. These factors

cause the peroxidation of lipids, increase the permeability of mucus and blood vessels, and as a result increase the entry of neutrophils into the mucous tissue and the development of inflammation. Reactive oxygen species also increase the transcription of cytokine genes and enzymes involved in the inflammatory response by activating the NF-KB transcription factor (8-10). The release of inflammatory mediators and enzymes causes the destruction of the intestinal wall, causing bleeding ulcers and diarrhea. Therefore, control of inflammation can play an important role in improving ulcerative colitis (11).

Garcinii belongs to the Asteraceae family, which is a shrub with yellow flowers and includes four species distributed in areas from North Africa to Iran, including a number of Middle Eastern countries, including Egypt, Palestine, and Saudi Arabia (12). *Avillea garcinii* with the Persian name Sandani is widely used by local people for its medicinal properties and is traditionally used to treat dysentery diseases, digestive problems, hepatitis, lung diseases, colds, digestive problems, digestion and lung complications, and liver diseases. In addition, research in the past, the anti-inflammatory, analgesic and antioxidant effects of anvil plant have been shown (13). Flavonoids and sescolactones are the major class of secondary metabolites obtained by phytochemical studies on *A. garcinii*. Previous researches of this plant showed the presence of lactones of the most muscular types of guaianolide and germacranolide, the corresponding amino acid compounds, as

well as some flavonoid glycosides (14-16). Anvillea sesculinary lactone by derivatives with parthenolide skeleton, germanolides that have significant biological activities in cancer and inflammation as well as in metabolic disorders (17). Previous review of aerial parts of *Agarcinii*. showed several members of the parthenolide class such as -9alpha and 9beta-hydroxy parthenolide and 9-alpha and 9-beta hydroxy-10alpha-\1betaepoxy parthenolide\parthenolide-9-one and their cis isomers. In addition, guaianolide-type sesquiterpenoids constitute a class of phytochemicals with a wide range of activities, including anti-protozoal cytotoxicity and outstanding anti-inflammatory potential. Leucodin and zaluzanin C and their derivatives as well as garcinamine E and other guaianes are among these compounds (18).

Reviews of articles and bibliography showed that many evaluations have been done on the *Anvilia Garcini* plant and since the most important drug treatment for UC is the use of synthetic drugs that have anti-inflammatory effects, but most of these drugs have severe side effects. are. It seems that *Anvilia Garcini*, due to being rich in secondary metabolites and having compounds with strong antioxidant properties, can create effects that play a significant role in the healing process of ulcerative colitis. (19-21).

Today, in medical challenges, we are looking for more complete treatments with less side effects. Due to the side effects of the existing drugs for the treatment of ulcerative colitis in humans, we are looking for new treatment solutions. Yes, the existing drugs need to be replaced, because according to the articles published in 2021, only 40% of people with the disease respond to the existing drugs (21-23).

Considering the importance of the issue and the high prevalence of ulcerative colitis in Iran, there is still a need for more studies in this field. Therefore, in the following study, we tried to determine the effect of the hydroalcoholic extract of *Anvilia Garcini* on some biochemical indicators and histopathological changes in ulcerative colitis in rats.

## II. METHOD AND MATERIALS

### - Preparation of herbal extract

For hydroalcoholic extraction, after drying, the plant is powdered using a grinder and 24 grams of the prepared powder is poured into the percolator, and 70% ethanol will be added to it three times the volume of the plant after 72 hours. By opening the lower valve of the percolator device, 70% ethanol is poured from the top of the device by the separating funnel with the decanter. Add the solution and this process will continue for a while. that the solution removed from the device becomes colorless, and in order to separate the ethanol, the solution obtained from the percolator device was transferred to the tank of the rotary device, and after removing the solvent, the extract was prepared.

### - Ulcerative colitis induction method

First, the animals are kept in NPO (OFF FEED) mode for 36 hours. Then the animal is anesthetized with ketamine (100 mg/kg) and xylazine (10 mg/kg) and a soft tube with a thickness of two mm and a length of 10 cm is inserted into The animal's rectum is inserted and one ml of acetic acid is injected into the

rectum. The animals are hung vertically in the air for 40 seconds and then they are returned to their cages At the end of the 8th day, the rats are euthanized using the rapid COP method in the induction chamber. The colon tissues are collected in 4% formalin for evaluation The pathological samples were transferred to the laboratory.

30 adult serrats in 6 groups of 5 are studied as follows.

1. The control group was a 5 serrat negative control after developing ulcerative colitis without treatment during the study for 8 days.
2. The control group of two positive controls of 5 serrats received 10 mg.kg orally mesalamine daily during the study for 8 days after developing ulcerative colitis.
3. The control group of three positive controls of 5 serrats received Asacol by enema daily during the study for 8 days after developing ulcerative colitis to the extent of ICC.
4. Test group 1: Five rats received 250 mg/kg of the extract orally daily during the study for 8 days after developing ulcerative colitis.
5. The test group received 500 mg.kg of the extract orally daily during the study for 8 days after developing ulcerative colitis.
6. Test group two 5 serrats received 250 mg.kg of the extract as an enema daily during the study for 8 days after developing ulcerative colitis.

Biological investigation of the effects of frankincense essential oil

### *Malondialdehyde (MDA) level evaluation*

Malondialdehyde (MDA) is the main end product of the oxidation of unsaturated fatty acids, so its average concentration (nmol.g) in wet tissue shows the amount of lipid peroxidation. In this regard. The reaction of lipid peroxide with thiobarbituric acid (TBA) produces thiobarbituric acid (TBARS), which are determined by spectrophotometric methods.

### *Evaluation of colonic myeloperoxide (MPO) levels.*

The part to be evaluated is weighed, piece by piece in 10 ml of 50 mmol potassium phosphate buffer. (pH 6) containing 0.5 HETAB and 10 mmol EDTA Krawisz, are homogenized. The homogenous solution was centrifuged for 20 minutes at 2000 rpm and the amount of MPO in the supernatant was evaluated with ELISA kits.

### Data Analysis:

The statistical methods used to compare the groups in terms of primary and secondary outcomes and the methods used in additional analyzes such as subgroup analysis and adjusted analyzes should be described.

Statistical analysis was performed using SPSS statistical software version (19.0). Results are expressed as mean and standard error of the mean (SEM). Kolmogorov-Smirnov test was used to evaluate normality. Analysis of variance (ANOVA) followed by post hoc test (Bonferroni test) and Kruskal-Wallis test was used to analyze the data. P values less than 05.0 were considered statistically significant.

### III. RESULTS

The highest weight gain was in the Asacol enema group, Anvilia enema (250 mg.kg), Mesalamine oral treatment, Anvilia oral treatment (500 mg.kg), Anvilia oral treatment (250 mg.kg) and finally the negative control group.

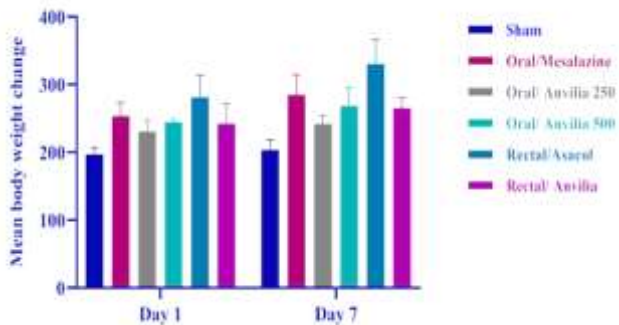


Figure 1: Weight comparison of 6 groups on the first and seventh day

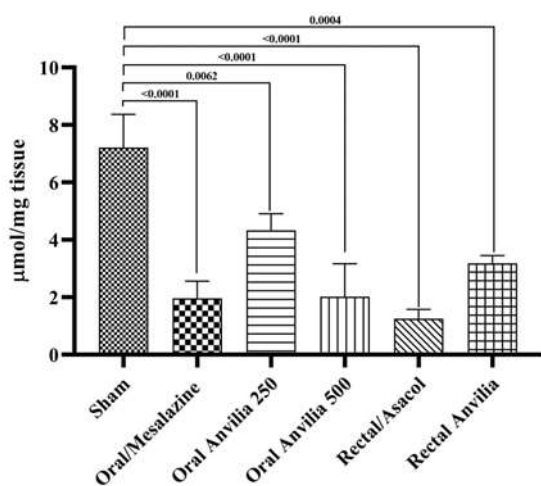


Figure 2: Comparison of MDA activity in intestinal tissue homogenate in different groups

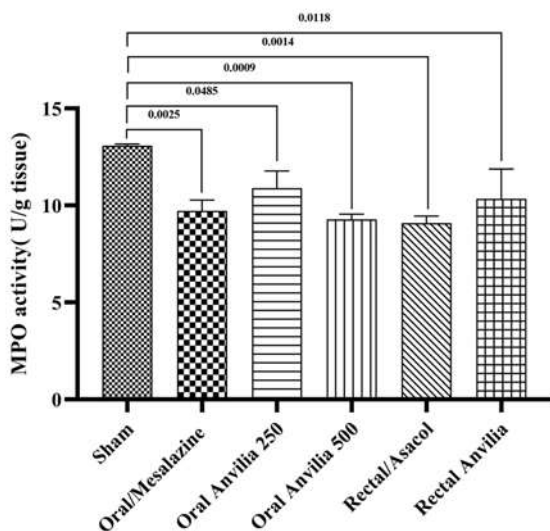


Figure 3: Comparison of MPO activity in intestinal tissue homogenate in different groups

The highest level of MDA activity in the negative control group was Anvilia oral treatment (250 mg.kg), Anvilia enema (250 mg.kg), Anvilia oral treatment (500 mg.kg), Mesalamine oral treatment, and the lowest amount in the Asacol enema group, which All 5 groups had a significant decrease compared to the negative control group.

The highest level of MPO activity in the negative control group was Anvilia oral treatment (250 mg.kg), Anvilia enema (250 mg.kg), Mesalamine oral treatment, Anvilia oral treatment (500 mg.kg) and the lowest amount was in the Asacol enema group, which in each 5 groups had a significant decrease compared to the negative control group.

### IV. DISCUSSION

Although there have been many advances in the understanding of the pathogenesis of UC, its mechanism is still unknown. The latest researches have emphasized that the onset and progression of UC is influenced by various factors, including genetic susceptibility, environmental factors, and the body's immune system. Ulcerative colitis is a chronic inflammatory disease of the large intestine and rectum, which is accompanied by symptoms such as bleeding from the rectum, diarrhea, constipation and sometimes abdominal pain. The peak incidence of this disease varies between the ages of 15 and 45 (23-25). On the other hand, the exact cause of this disease has remained unanswered until now, but during the last decade, it has been determined that this disease is caused by an out-of-regulation immune response in the intestinal area, which is caused by a set of interactions between the host's genotype and the microflora inside the lumen or other factors. which are potentially pathogenic. The treatment of this disease is with common drugs such as aminosalicylates, steroids, antibiotics, immunomodulators and serratiopeptidase (anti-TNF treatment), which have some side effects (26-28).

Acidic colitis is one of the most common animal models of inflammatory bowel disease, and the similarities of the inflammation mechanism including arachidonic acid metabolism in this model and in humans make it possible to use it in screening the potential therapeutic effects of medicinal substances. On the other hand, anvilia plant is traditionally used to treat weak immunity. Therefore, in the present research, we have investigated the therapeutic effect of this plant on colitis induced by acidotic in rats. During the duration of this study, all rats were examined in terms of changes in body weight, MDA, MPO levels and the amount of tissue damage.

Histologically, intestinal inflammation is characterized by the infiltration of polymorphonuclear leukocytes, monocytes and macrophages. Crohn's disease and ulcerative colitis are two main forms, genetic factors, infectious and immunological factors, tobacco, drugs and some pathological factors play a role in pathophysiology (29,30). Oxidative stress also plays an important role in the pathogenesis of intestinal damage. A significant imbalance in antioxidant activity was observed in colonic mucosal sampling, resulting in increased oxidative stress and weakening of antioxidant defenses. If the amount of free radicals is high or antioxidant protection is low, a state of oxidative stress occurs, which may cause chronic or permanent damage to cells (30-33). One of the markers of oxidative stress

is the increase of lipid peroxidation in cells, which is determined by measuring the amount of reactive substances with thiobarbituric acid. Previous studies have shown the presence of oxidative stress in biological fluids such as saliva and plasma in patients with the effectiveness of various therapeutic methods in treatment may be attributed to their antioxidant function. Compounds such as sulfasalazine and its metabolites, 5-aminosalicylic acid, which are used in treatment, are very effective removers of active oxygen compounds. Neutrophils play a major role in inflammatory and immune reactions (34,35). Myeloperoxidase enzyme is able to form a large number of oxidant substances, so that it catalyzes the oxidation of electron donating compounds (such as halides) by hydrogen peroxide. It has also been determined that the level of activity, which is mostly found in neutrophil granules and which characterizes the number of neutrophils, increases in the experimental model induced by acetic acid. Acetic acid-induced colitis is a facile model to establish the similarity profile of inflammatory mediators, showing that the inflammatory phase has similarities with intestinal inflammation in humans (36-38).

The expression of COX2 enzyme is increased as one of the key steps in gastrointestinal inflammation, including IBD, which leads to the synthesis of PGD2, PGF2a, and PGE. So, recent clinical studies have widely shown the role of non-steroidal anti-inflammatory drugs and selective COX2 inhibitors in the treatment of IBD (39).

During inflammation and inflammatory processes (IBD), the expression of inflammatory cytokines, such as IL1, IL6, and TNF-alpha, increases with the disruption of the mucosal balance at the molecular level (40,41).

Luteolin is one of the flavonoids present in the aerial branches of *Garcinia* plant and has many therapeutic effects including anti-inflammatory activity. In addition, it has antioxidant and anti-allergic properties as well as anti-tumor effects. Luteolin exerts some of its anti-inflammatory effects by inhibiting alpha-TNF and COX2 enzyme. Luteolin induces apoptosis of all types of cancer cells and weakens all types of stimuli caused by the expression of pro-inflammatory genes and skin, colon and breast carcinogens. Luteolin inhibits the expression of inflammatory mediators by blocking the NFkB/Akt pathway (42,43). In macrophages, luteolin effectively inhibits the expression of pro-inflammatory cytokines induced by lipopolysaccharide LPS in Gram-negative bacteria and the production of nitric oxide. Luteolin satisfactorily reduces PMN activity, production of superoxide anions and secretion, migration and chemotoxic effect of leukotriene 4B. A recent research has shown that luteolin acts against PMN activity through mitogen-activating protein kinase and extracellular signals PI3K/Akt, MEK/ERK (44,45).

Reactive oxygen species such as superoxide, hydrogen peroxide, and hydroxyl radicals play a role as inflammatory mediators in experimental animal models as well as human IBD, and MPO activity and TBARS concentration are indicators of oxidative stress in colitis. Studies show that flavonoid compounds act as an important class of natural antioxidant compounds due to the presence of numerous OH factors in their structure and the ability to neutralize free

radicals, thus inhibiting the wound and by inhibiting lipolysis and the ability to inhibit the peroxidation of lipids from penetration. The necrotic agent prevents mucus (40, 46, 47).

One of the most important destructive effects of free radicals is the initiation of lipid peroxidation, which leads to the destruction of cell membranes. In this process, free radicals pull electrons from the unsaturated hydrocarbon chain of lipids, causing lipid degradation and production of active compounds. After the destruction of carbon bonds, these active compounds produce a wide range of substances such as ketones and aldehydes. The main aldehyde produced during these reactions is malondialdehyde. Malondialdehyde caused by lipid peroxidation can react with other cellular components such as proteins of the genomic structure and create various lesions and finally may cause apoptosis with extensive disease symptoms (48,49).

Malondialdehyde is produced from the peroxidation of lipids, and its production rate is proportional to the breakdown and excretion of unsaturated fatty acids. Therefore, measuring MDA is a suitable indicator for lipid peroxidation (50). The results of this study showed that the level of MDA in rats with colitis shows a significant and significant increase compared to healthy rats. The production of free radicals and reactive oxygen species is one of the unavoidable issues in the metabolism process. In recent years, due to the properties of antioxidants in preventing the effects of free radicals in causing disease, the role and effect of antioxidants has been the focus of researchers. The sum of the body's non-enzymatic antioxidants (uric acid, vitamin E, ascorbic acid, reduced glutathione, bilirubin and beta-carotene) that can be measured as a whole is called total antioxidant capacity. An antioxidant is a substance that can prevent or delay oxidative damage to a target molecule. Antioxidants play an important role in neutralizing free radicals (51-53).

However, the antioxidant and anti-inflammatory properties of this plant extract have been proven. According to the studies that have been done, in one of the researches, the effects of the hydroalcoholic extract of this plant on the activity of myeloperoxidase enzyme MPO in colitis induced by acetic acid were investigated, after that, severe inflammatory reactions occur, which indicate macroscopic and microscopic changes in myeloperoxidase enzyme (54,50). It is an enzyme that plays a role in the function of germicide and causes the conversion of hydrogen peroxide to (HOCl) and finally, the anti-inflammatory peptide of *Anvilia Garcini* causes the activity of myeloperoxidase enzyme to increase in such a way that this plant increases the activity of the enzyme to the normal level before the disease. brings (46,47).

Reviewing the results section again shows that *Anvilia* extract has been able to significantly reduce the amount of changes in some colon microscopic factors (ulcerosis and inflammatory factors and mucous cells) and enzyme factors involved in colitis (MPO activity and MDA level). As a result, the use of *Anvilia Garcini* as a substance of plant origin with much less side effects can be used as a new method for the treatment of ulcerative colitis. According to the research conducted in this study and the results of biochemical factors and macroscopic examinations of the colon tissue, *Anvilia*

Garcini probably reduces the symptoms of the disease by inhibiting phosphodiesterases and blocking adenosine receptors.

## V. CONCLUSION

The results of the present study showed that using acetic acid inside the colon causes adverse effects on the colon. The treatment with Anvilia Garcini improved the reactions which were confirmed by the changes in oxidative stress markers, the improvement of the disease severity index, and the reduction of tissue wounds. Therefore, Anvilia Garcini reduces the symptoms of ulcerative colitis. As a result, the use of Anvilia Garcini as a substance of plant origin with much less side effects can be used as a new method for the treatment of ulcerative colitis.

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