

## Plant tannins: A novel approach to the treatment of ulcerative colitis

By Catherine Clinton, ND

### Introduction

Ulcerative colitis (UC) is a common inflammatory bowel disease with a prevalence in the United States in children younger than 20 years of 28 (95% CI, 26-30) per 100,000 and a prevalence in adults of 238 (95% CI, 234-241) per 100,000.<sup>1</sup> UC is more common in women and Caucasians. The disease is characterized by lesions in the colon that are a nonspecific inflammatory response limited to the colonic mucosa and submucosa. Symptoms include bouts of diarrhea, low-grade fever, right lower-quadrant pain, intestinal cramping, weight loss, flatulence, malaise, and bloody stools. Common extraintestinal manifestations include peripheral arthritis, skin complications, ankylosing spondylitis, liver disease, sacroiliitis, uveitis, erythema nodosum, episcleritis, and primary sclerosing cholangitis. UC has no cure and requires a lifetime of treatment, making accurate diagnosis imperative.

The etiology of UC is multifaceted. Prostaglandins are dramatically increased in the mucosa, serum and stools of UC patients. Research indicates that an imbalance of the gastrointestinal (GI) mucosal immune system of UC patients causes an overproduction of inflammatory cytokines and leukocytes into the colon.<sup>2</sup> This increase in inflammatory molecules creates a state of uncontrolled intestinal inflammation. The intestinal mucosa in UC displays a pro-inflammatory pattern with molecules like tumor necrosis factor, interferon-gamma, interleukin-1, IL-6, and IL-12 tipping the scales toward inflammation.

In addition to prostaglandin production, the mucosal immune system regulates several other factors involved in the pathophysiology of UC. Mucins are high molecular-weight glycoproteins responsible for the viscous characteristics of secreted mucus in the colon. Mucin offers protection against inflammatory and oxidized molecules. Mucin defects are seen in patients with UC<sup>3</sup> and increase mucosal thickening, proliferation and superficial erosions thereby increasing overall intestinal inflammation.<sup>4</sup> Without the protective function of mucin, inflammation in the GI tract is dramatically increased.

Altered intestinal microflora is another factor that greatly affects GI mucosal immunity. UC patients demonstrate increased colonic pathogenic bacteria and a decrease of lactobacilli and bifidobacteria.<sup>5</sup> UC is believed to be partly induced by bacterial metabolic products that increase inflammatory cytokines, which induce epithelial injury by blocking epithelial metabolism or overwhelming the genetically susceptible host's ability to degrade reactive oxygen species.<sup>6</sup>

Matrix metalloproteinases (MMPs) are also a major player in the GI mucosal immune system. MMPs are zinc-dependent endopeptidases that are responsible for the degradation and remodeling of the extracellular matrix and basement membrane proteins during both normal physiologic activity and disease. MMPs may also play a role in the pathogenesis of UC by inducing mucosal breakdown in response to an increase in inflammatory cytokines. MMPs have been exhibited at increased levels in patients with UC.<sup>7</sup>

Another factor influencing GI mucosal immunity is the integrity of the lining of the GI tract, namely the tight junctions that inhibit intes-

tinal permeability. Patients with UC display defects in the intestinal epithelial barrier function.<sup>8</sup> These defects in the integrity of the intestinal barrier increase inflammation.

Lastly, the interaction of food and the GI mucosal immune system is an important factor in intestinal inflammation. Patients with UC demonstrate increased mucosal eosinophils and IgE in relation to certain foods.<sup>9 10</sup> Although defects in mucin production, alteration in GI flora, increased MMP activity, increased intestinal permeability, and food allergies play a clear role in the pathogenesis of UC, the question remains of how to effectively treat these factors.

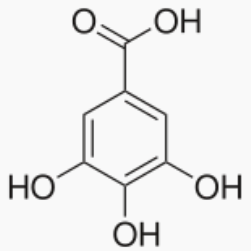
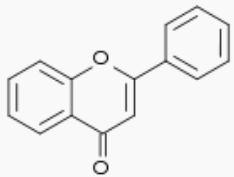
Plant tannins provide a novel therapeutic option for the major factors in the induction of UC. Plant tannins are a large, diverse group of polyphenolic compounds found throughout several species in the plant kingdom. Tannins have a protective function in the bark of the roots and stems, or any outer layers of plants. They are astringent in nature due to their high polyphenol content. This attribute confers the ability to form strong complexes with proteins, starches and other macromolecules.

In the following discussion we explore how the five aforementioned issues that contribute to the progression of UC all deal with an increase in inflammatory molecules, which tannins have the ability to bind or downregulate. We discuss how tannins can modulate inflammation caused by food allergens and pathogenic microflora in the GI tract. We explore how the increased inflammatory molecules incite an increase in MMPs in the GI tract and how tannins can affect this process. We also investigate how tannins help decrease the inflammatory molecules that are problematic for UC patients who have a defect in mucin or an increase in intestinal permeability.

### Structures of Plant Tannins

Tannins are classified into two categories: condensed tannins and hydrolyzed tannins (Figure 1).

Figure 1. Molecular structures of tannins

<b>Base Unit:</b>	 Gallic Acid	 Flavone
<b>Class:</b>	Hydrolyzed Tannins	Condensed Tannins

Hydrolyzed tannins are compounds formed from gallic acid or epigallocatechin gallate units condensed to a central sugar molecule. When hydrolyzed, these tannins produce gallic or epigallocatechin gallate and sugar. Hydrolyzed tannins have a very low bioavailability following oral ingestion, due both to their poor lipid solubility and their ability to form strong complexes with proteins. Hydrolysis of tannins occurs mostly in the large bowel at neutral to alkaline pHs.

Hydrolyzed tannins inhibit the absorption of iron, which may, if prolonged, lead to anemia.<sup>11</sup> Tannins are metal ion chelators, which render the iron unavailable to the body. Tannins only reduce the bioavailability of plant sources of iron; animal sources of iron are left available for absorption. Tannic acid does not affect absorption of other trace minerals such as zinc, copper, and manganese in rats.<sup>12</sup> Condensed tannins do not interfere with iron absorption.<sup>13</sup> They are preferable for human consumption and therapeutic treatment, so this paper focuses on the benefits of condensed tannins for patients with UC.

Condensed tannins are dimers or oligomers of catechin, epicatechin, or similar units. These units are polymers of 2 to 50 or more flavonoid units that are joined by carbon-carbon bonds, which are not susceptible to being cleaved by hydrolysis. Mixtures of these oligomers are powerful antioxidants known as oligomeric proanthocyanidins. Oligomeric proanthocyanidins have powerful antioxidant properties that combat the inflammation seen in the five contributing factors of UC. Examples of condensed tannins include Rhatany root (*Krameria triandra*), wine grape seed (*Vitis vinifera*), and Scotch pine bark (*Pinus sylvestris*). Condensed tannins can be found in commonly used foods (Figure 2). The higher the proanthocyanidin content the more powerful the food's ability to combat inflammation.

**Figure 2.** Concentration of Proanthocyanidins (PAs) in common foods<sup>14</sup>

No.	Food	Total PAs	Type
10c	Grape seed (dry)	3532.3 ± 105.8	PC
11a	Apple, red delicious, with peel	125.8 ± 6.8	PC
31	Pecans	494.1 ± 86.2	PC, PD
38	Red wine	313 ± 5	PC, PD
2b	Cranberry juice cocktail	231 ± 2	A, PC
10d	Grape juice	524 ± 2	PC, PD
40	Cinnamon, ground	8108.2 ± 424.2	A, PP, PC

(The PP, PC, and PD are propylgallates, procyanidins, and prodelphinidins, respectively. "A" indicates the existence of A-type PAs.)

## Therapeutic Use of Condensed Tannins

Condensed tannins can help decrease the inflammation of UC patients who have been left vulnerable from a defect in GI mucin. The production of mucin by the intestinal goblet cells, the structural component of the colonic mucus layer, is found at lower levels in inflammatory bowel disease.<sup>15</sup> When rats with and without the mucin defect were given the colitis-inducing agent, dextran sulfate sodium, the rats with the defect in mucin showed an increase in inflammation of the colon.<sup>16</sup> Studies conducted in mice with mutations in mucin production developed mild distal intestinal inflammation and chronic diarrhea.<sup>17</sup> Mice without the normal mucin production showed less stored mucin in goblet cells, a diminished mucus barrier, increased susceptibility to colitis induced by a luminal toxin, increased local production of IL-1beta, TNF-alpha, and IFN-gamma in the distal colon, and increased intestinal permeability.<sup>18</sup> It stands to reason that the lower

levels of mucin found in UC leave a patient vulnerable to the increase in inflammatory molecules in the GI tract. Whether that increase in inflammatory molecules comes from food allergens or pathogenic bacteria, its increase incites an increase in MMPs and their subsequent mucosal damage.

The defect in mucin production can also be linked to the increase in intestinal permeability that we see in the GI tracts of patients with UC. Patients with UC don't have the protective benefit of normal mucin production, which can also leave them vulnerable to oxidized molecules and the damage they provoke in the GI tract. These oxidized products are believed to increase the inflammation and mucosal injury seen in UC.<sup>19</sup> The tannins appear to exert a protective effect against oxidative stress-induced cell death.<sup>20</sup> The procyanidins in condensed tannins interact with the plasma membrane of intestinal cells and inhibit the binding of TNFalpha to its receptor and the subsequent NF-kappaB activation.<sup>21</sup> To compensate for the lack of protection from mucin, tannins can help tip the delicate scales of inflammation away from the pro-inflammatory cytokines of UC.

Condensed tannins can also help return the GI flora to a state of balance. Patients with UC have GI flora that favors pathogenic bacteria.<sup>22-23</sup> Mucosal gamma delta T cells stimulate the mucosal tissue immune system to respond to pathogenic bacteria and cancers as well as induce epithelium repair. Tannins support these functions by inducing gamma delta T cell expansion within the GI cells.<sup>24</sup> Tannins have shown antibacterial activities against *Kocuria rhizophila*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Pseudomonas aeruginosa*.<sup>25</sup> Research clearly points to several different mechanisms by which tannins effectively alter the GI flora away from pathogenic bacteria.

Condensed tannins can also mitigate the damage that MMPs inflict on the GI mucosa in UC. IgG plasma cells from patients with UC express large amounts of MMP-3 that remain in circulation for long amounts of time, accounting for the damage they incite in the GI tract.<sup>26</sup> Research also indicates that UC patients show increased levels of MMP-9, which contributes to the intestinal inflammation seen clinically.<sup>27</sup> Condensed tannins have been shown to suppress the secretion of MMP-2 and MMP-9 in Caco-2 cells.<sup>28</sup> The Caco-2 cell line is a line of heterogeneous human epithelial colorectal adenocarcinoma cells, developed by the Sloan-Kettering Institute for Cancer Research, for *in vitro* studies on absorption rates of compounds across the intestinal epithelial cell barrier. In research conducted with condensed tannins isolated from cranberries, MMP production and catalytic activity were both inhibited.<sup>29</sup> The tannins appeared to reduce the phosphorylation of critical intracellular kinases and inhibited NF-kappaB p65 activity, which can account for the decrease in MMP production and in their catalytic activity. It stands to reason that several classes of MMPs are responsible for the colonic damage in UC, and the use of condensed tannins can help reduce their presence and inflammatory effects in the GI tract.

Intestinal permeability is another factor in the colonic inflammation of UC that can be treated with condensed tannins. Procyanidins isolated from cocoa tannins display the ability to inhibit the loss of integrity in Caco-2 cell permeability induced by oxidants.<sup>30</sup> An increase in oxidized molecules and oxidative damage is seen consistently in patients with UC. As described previously, condensed tannins can decrease intestinal permeability by mitigating GI inflammation caused by oxidative molecules, making them a good therapeutic option for UC.

Lastly, condensed tannins can decrease the effect that food allergens have on GI inflammation in UC. Patients with UC display GI increased by the presence of higher levels of mucosal eosinophils and IgE in relation to certain foods. Data suggest an association between UC, tissue eosinophilia, and type-I allergy.<sup>31</sup> Research with ova-sensitized rats given apple-derived condensed tannins demonstrates tannins' ability to inhibit the development of the oral sensitization; that inhibition could correlate with the rise in the population of gamma delta T cells in the

intestinal intraepithelial cells.<sup>32</sup> Not only do tannins increase gamma-delta T cells, but they dramatically inhibit serum OVA-specific immunoglobulin E, immunoglobulin G1 titers, and histamine.<sup>33</sup> This inhibition decreases the tissue eosinophilia and type-I allergy seen in UC. The research highlights the role tannins could play in the treatment of UC and warrants more clinical studies with tannins and patients with UC.

## Contraindications and Interactions

Although controversy still surrounds the use of hydrolyzed tannins at large doses or for prolonged periods because they can bind essential minerals in the human diet, condensed tannins have a relatively safe profile. While research on condensed tannins is limited, people have been consuming condensed them for centuries without reported adverse effects. Research conducted with tannins derived from grape-seed and -skin extracts demonstrates high-dose tannins administered for a three-month period to rats displayed no histological changes upon full necropsy of all tissues.<sup>34</sup> Administration of a form of condensed tannin extracted from lychee fruit to rats displayed no adverse effects in food consumption, body weight, mortality, clinical chemistry, hematology, gross pathology, or histopathology, supporting the safety of another tannin.<sup>35</sup>

Oral consumption of condensed tannins can be assumed to be safe in humans, but it would stand to reason that due to the proanthocyanidins' ability to bind metals and proteins, they would be most effective and beneficial to ingest separately from food and other medications. A diet rich in tannin-containing foods might aid in the prevention of UC progression and help maintain remission in patients with UC. Several commercial products exist with high tannin content, and these should be further investigated in the treatment of UC.

## Summary

UC is an emergent health problem that exacts not only a physical toll, but also an economic and social cost on patients and their families. The GI inflammation that is characteristic of UC has several contributing factors. These factors include the lack of protection from inflammation due to a defect in mucin production, an alteration in GI flora, an increase in MMPs, an increase GI intestinal permeability, and the effect of food allergens. The increase in inflammatory molecules seen with food allergens can incite MMPs and increase mucosal damage in UC. The modulation of inflammatory molecules by tannins can decrease the damage produced by MMPs. The intestinal permeability and the defect in mucin can leave patients with UC vulnerable to increased inflammation. Tannins can modulate this increase, as well as the pathogenic bacteria associated with UC and the increase in inflammatory molecules. Current research with flavonoids and UC demonstrate a protective effect in mice treated with the colitis-inducing agent, dextran sulfate sodium, so as to prevent the occurrence of colitis.<sup>36</sup> Green tea polyphenols have shown similar benefits in mice by attenuating colonic injury induced by experimental colitis.<sup>37</sup> The research highlights how condensed plant tannins could be an effective treatment option to address each of these contributing factors in the GI inflammation of UC and should be investigated further in clinical trials.

## About The Author

Catherine Clinton, ND, is a board certified naturopathic physician. She graduated from the National College of Natural Medicine with her doctorate in naturopathic medicine. Dr. Clinton currently practices at the Clinic of Natural Medicine in Eugene, Oregon, with a focus on gastroenterology, autoimmune conditions and chronic fatigue syndrome. She is a member of the Ontario Association of Naturopathic Physicians and the American Association of Naturopathic Physicians.



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