

3 NATURAL STRATEGIES FOR CROHN'S AND ULCERATIVE COLITIS

BY DR. SEAN GOLDEN

PART 3

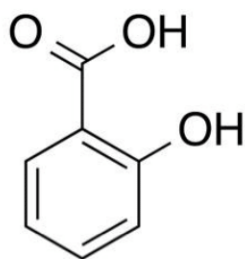
WHITE WILLOW BARK

White Willow Bark is Literally Nature's Aspirin, but Better

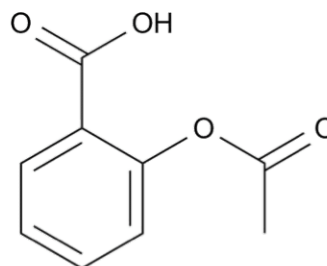
(Note: Just like mesalamine, sulfasalazine, and other 5-ASAs, white willow may work a little better for UC than for Crohn's.)

White willow bark has been used for centuries now for pain and inflammation. White willow naturally contains salicin, which converts to salicylic acid in the colon. Over 100 years ago, we created synthetic aspirin by attaching an "acetyl" group onto the natural salicylic acid molecule found abundantly in nature. The acetyl group is essentially the acid that is in vinegar, which is why an old bottle of aspirin can develop a vinegar-like smell to it.

Thus, we turned *salicylic acid* into *acetyl-salicylic acid*.



Salicylic acid



Acetyl-salicylic acid (AKA aspirin)

(Don't worry if you're a little rusty with your chemistry, you won't need to memorize any of these structures!)

Attaching that acetyl group onto salicylic acid changes its properties. The biggest change is that **aspirin inhibits the COX enzymes** that can create inflammatory prostaglandins (similar to other anti-inflammatory medication like ibuprofen), while the natural **salicylic acid does not**.

COX enzymes --> prostaglandins --> inflammation AND repair

This is what makes aspirin so damaging to the stomach lining. This is also why aspirin is usually **contraindicated** in Crohn's and UC.

One of the prostaglandins, PGE2, is needed for mucus production of the stomach and for proper blood flow to the lining of the stomach.¹ Since aspirin inhibits PGE2 production, it inhibits the ability for the stomach to secrete enough protective mucus and repair itself

from small ulcers.

Natural salicylic acid, on the other hand, does not inhibit COX enzyme functioning. Actually, **salicylic acid has been shown to be protective** against stomach mucosal damage from other irritants and anti-inflammatory drugs.²

Most of the typical anti-inflammatory medications such as aspirin and ibuprofen inhibit inflammation by inhibiting the COX enzymes, which is also where many of their side effects come from. However, if salicylic acid doesn't inhibit the COX enzymes, then how does it lower inflammation?

Salicylic Acid Inhibits the “Master of All Inflammation”

One important concept to understand is while some prostaglandins can promote inflammation, others can be very anti-inflammatory and even help to “resolve” existing inflammation.

When you block the COX enzymes with anti-inflammatory medications, you inhibit BOTH the pro- and anti-inflammatory prostaglandins. Thus, while they can sometimes help with the current inflammation you are having at the moment, they don't really do anything to solve the problem.

It turns out, one of that major ways that salicylic acid blocks inflammation is through down-regulating NF-kB, the “master regulator of inflammation”.^{3,4} NF-kB plays a central role in the response to inflammatory stimuli.

NF-kB has been found to be dysregulated in Crohn's and U.C., and this dysregulation increases both acute and chronic inflammation in these conditions.⁵

By targeting NF-kB, salicylic acid from white willow bark can powerfully block the heart of inflammation without the ulcer and bleed risk that comes with aspirin!

Pharmaceutical Companies Already Figured This Out!

Pharmaceutical companies saw the potential in aspirin to powerfully block inflammation in the colon from Crohn's or U.C., but they also saw the GI side effects of aspirin as a big downside.

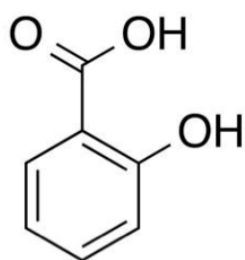
However, since salicylic acid didn't have the GI side effects of aspirin but still inhibited NF-kB, what if they could come up with a modified version of aspirin that didn't inhibit the

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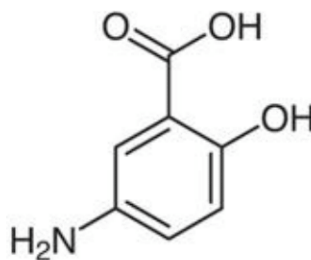
COX enzymes but still inhibited NF-kB like salicylic acid. Even better, what if they could patent it?

This is exactly what they did: **enter the 5-amino-salicylates**

They ended up attaching an “amino” group on to salicylic acid instead of an “acetyl” group, like in aspirin. The structures are below:



Salicylic Acid



5-amino-salicylic acid
(AKA mesalamine, Lialda, Delzicol, etc.)

The Rise of the 5-amino-salicylates

After the companies realized this, prescribing 5-amino-salicylates became one of the first line treatments. They found that these, like salicylic acid and aspirin, also inhibited NF-kB.⁷

Brands such as Canasa, Delzicol, Asacol HD, Pentasa, Apriso, Lialda, and sfRowasa are all examples of 5-amino-salicylates (aka Mesalamine).

Since their inception, they have largely replaced sulfur-based salicylates (which have more side effects), and are used as a first-line of treatment.^{6,16}

While they have a high response rate (40-70%) and remission rate (15-20%), their main drawback is their cost.⁶

5-amino-salicylates are targeted to the colon... but so is white willow

Unlike aspirin, the body doesn't absorb the active molecule right away with white willow bark.

The molecule that starts off in white willow bark is actually salicin, which is mostly

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inactive. Once salicin makes its way down to the colon, **the bacteria** there convert salicin into salicylic acid.⁸

Thus, not only does the active molecule bypass the stomach, but this essentially ensures that salicylic acid will actually be in the colon to do its anti-inflammatory work, just like 5-amino-salicylates!

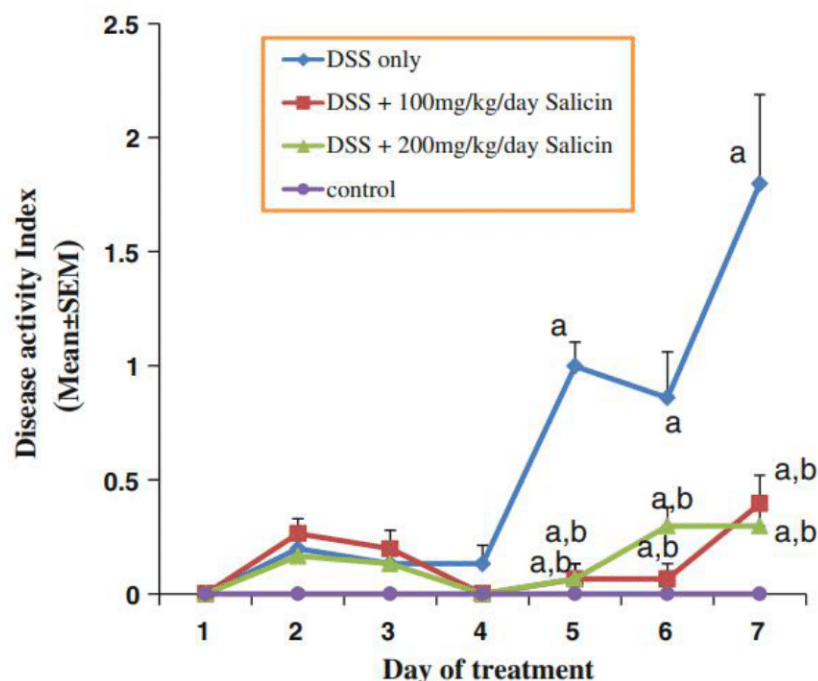
Rodent Studies with White Willow / Salicin

There is evidence that salicin from white willow bark has strong anti-inflammatory effects in the colon.

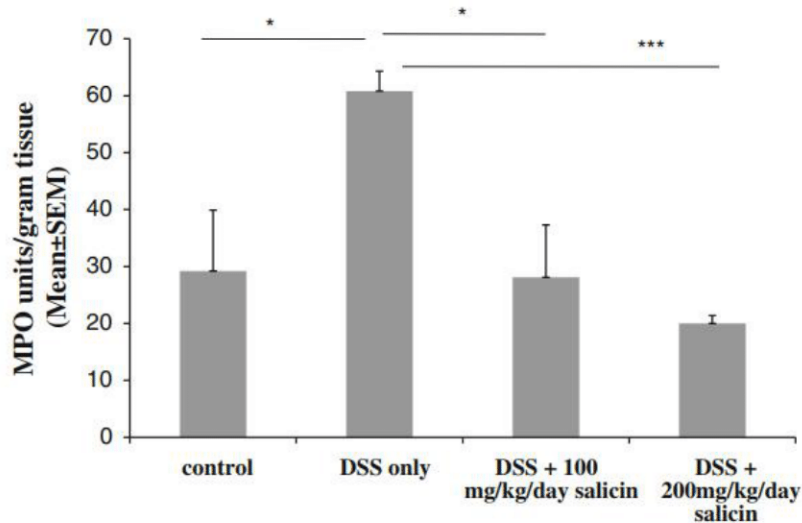
In 2014, researchers induced colitis in mice and broke the mice into groups. During this time, the researchers put one group on low dose salicin, another group on high dose salicin, and the last group was a control group.²⁰

After a week, the salicin significantly protected the mice from the effects of colitis:

(Top image shows the “Disease Activity” and the second image shows myeloperoxidase, a marker of inflammation for colitis.)



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As you can see, salicin significantly protected these mice against the symptoms and inflammation of the colon.

The dose used in this study corresponds to a human dose of around 500mg per day for the “low dose” and 1,000mg per day for the “high dose” for a 150lbs person.

White Willow Bark is More Than Just Salicylic Acid

Besides the salicin / salicylic acid from white willow bark, it also contains an abundance of polyphenols, flavonoids, and proanthocyanidins.^{9,10}

These compounds have been shown to also have powerful anti-inflammatory activity throughout the intestinal tract and are very likely responsible for some of the favorable response to white willow bark.^{10,11} In fact, **proanthocyanidins on their own** achieve powerful effects in the rodent models of Ulcerative Colitis.¹¹

Therefore, with white willow bark you are really getting the best of both worlds: A delivery of salicin / salicylic acid to the colon, as well as a multitude of other beneficial plant anti-inflammatory compounds!

White Willow Bark and Cancer

Both the compounds in white willow bark and the extract itself have been found to have broad-spectrum anti-cancer effects and inhibit the survival of colon cancer cells.^{17,18,19}

While we can't say it will prevent colon cancer (there are many different risk factors to consider), this certainly isn't a bad "side effect" to have!

How to take White Willow Bark

White willow bark can easily be found in capsules in most health food stores and online. The kind standardized for 15% salicin is good, and the brand "NOW" makes a good product at an affordable price.

Usually the pills are 800 mg for 2 pills, or 400 mg for 1 pill. The standard dosage to start with is 3-4 pills a day, though you can test just one pill to make sure you don't have an allergy. Due to a good safety profile, you can discuss with your treating physician about doses higher than 4 pills.

The main side effect to look out for is ototoxicity, which can give you tinnitus or "ringing in the ears". This is very rare with white willow bark compared to aspirin, but theoretically any salicylate-based supplement or medication can cause this. If you start to notice any high pitched ringing in the ears, discontinue the supplement right away, and it should fade. After it fades, you can try a lower dose or skip this supplement altogether. **If you already have tinnitus, any salicylate-based drug / supplement, including white willow bark, can make it worse.** If you notice any worsening, stop the supplement immediately and it should revert. Again, tinnitus is a very rare side effect that the vast majority of the patients never get, and is temporary if you stop / reduce the dose, but I just want you to be aware of this possibility in case it comes up.

To put this in context with aspirin, 4 pills of 15% salicin white willow bark contain 240 mg of salicin, less than 1 tablet of aspirin (325 mg acetyl-salicylic acid). Also, not all of that 240 mg of salicin will convert to salicylic acid; some of it ends up just going right through you.⁸

If you want to try to mimic the dose used in the study above, 4 pills twice a day (8 pills a day) of 15% salicin would give you 480mg of salicin, similar to the "low dose" used in the study above. If you take only 1-2 pills a day, do not expect much.

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Make sure to discuss with your treating physician before making any changes or adding any new supplement to your regimen. This information is for educational purposes only and is not medical advise in any way!

Sincerely,

Dr. Sean Golden DC

References:

1. Takeuchi K, Amagase K. Roles of Cyclooxygenase, Prostaglandin E2 and EP Receptors in Mucosal Protection and Ulcer Healing in the Gastrointestinal Tract. *Curr Pharm Des.* 2018;24(18):2002-2011. doi:10.2174/1381612824666180629111227
2. Ota S, Razandi M, Sekhon S, et al. Salicylate effects on a monolayer culture of gastric mucous cells from adult rats. *Gut.* 1988;29(12):1705-1714. doi:10.1136/gut.29.12.1705
3. Yin MJ, Yamamoto Y, Gaynor RB. The anti-inflammatory agents aspirin and salicylate inhibit the activity of I(kappa)B kinase-beta. *Nature.* 1998;396(6706):77-80. doi:10.1038/23948
4. Kopp E, Ghosh S. Inhibition of NF-kappa B by sodium salicylate and aspirin. *Science.* 1994;265(5174):956-959. doi:10.1126/science.8052854
5. McDaniel DK, Eden K, Ringel VM, Allen IC. Emerging Roles for Noncanonical NF-κB Signaling in the Modulation of Inflammatory Bowel Disease Pathobiology. *Inflamm Bowel Dis.* 2016;22(9):2265-2279. doi:10.1097/MIB.0000000000000858
6. Karagozian R, Burakoff R. The role of mesalamine in the treatment of ulcerative colitis. *Ther Clin Risk Manag.* 2007;3(5):893-903.
7. Bantel H, Berg C, Vieth M, Stolte M, Kruis W, Schulze-Osthoff K. Mesalazine inhibits activation of transcription factor NF-kappaB in inflamed mucosa of patients with ulcerative colitis. *Am J Gastroenterol.* 2000;95(12):3452-3457. doi:10.1111/j.1572-0241.2000.03360.x
8. Akao T, Yoshino T, Kobashi K, Hattori M. Evaluation of salicin as an antipyretic prodrug that does not cause gastric injury. *Planta Med.* 2002;68(8):714-718. doi:10.1055/s-2002-33792
9. Untergehrer M, Kiermaier J, Reintjes S, Heilmann J, Jürgenliemk G. Identification of phase-II metabolites from human serum samples after oral intake of a willow bark extract. *Phytomedicine.* 2019;57:396-402. doi:10.1016/j.phymed.2018.11.003
10. Hostanska K, Jürgenliemk G, Abel G, Nahrstedt A, Saller R. Willow bark extract (BNO1455) and its fractions suppress growth and induce apoptosis in human colon and lung cancer cells. *Cancer Detect Prev.* 2007;31(2):129-139. doi:10.1016/j.cdp.2007.03.001

11. Głabska D, Guzek D, Gałązka K, Lech G. Therapeutic Potential of Proanthocyanidins in Ulcerative Colitis in Remission. *J Clin Med*. 2020;9(3):771. Published 2020 Mar 12. doi:10.3390/jcm9030771

12. Patel DK, Ogunbona A, Notarianni LJ, Bennett PN. Depletion of plasma glycine and effect of glycine by mouth on salicylate metabolism during aspirin overdose. *Hum Exp Toxicol*. 1990;9(6):389-395. doi:10.1177/096032719000900606

13. Patel DK, Hesse A, Ogunbona A, Notarianni LJ, Bennett PN. Metabolism of aspirin after therapeutic and toxic doses. *Hum Exp Toxicol*. 1990;9(3):131-136. doi:10.1177/096032719000900302

14. Gunther, T & Rebentisch, E & Vormann, Jürgen. (1989). Enhanced ototoxicity of salicylate by magnesium deficiency.. *Magnesium-Bulletin*. 11. 15-18.

15. Mahmoudian-Sani, Mohammad & Hashemzadeh-Chaleshtori, Morteza & Asadi-Samani, Majid & Yang, Qian. (2017). Ginkgo biloba in the treatment of tinnitus: An updated literature review. *The International Tinnitus Journal*. 21. 10.5935/0946-5448.20170011.

16. Hanauer SB, Krawitt EL, Robinson M, Rick GG, Safdi MA. Long-term management of Crohn's disease with mesalamine capsules (Pentasa). *Pentasa Crohn's Disease Compassionate Use Study Group. Am J Gastroenterol*. 1993 Sep;88(9):1343-51. PMID: 8362827.

17. Hostanska K, Jürgenliemk G, Abel G, Nahrstedt A, Saller R. Willow bark extract (BNO1455) and its fractions suppress growth and induce apoptosis in human colon and lung cancer cells. *Cancer Detect Prev*. 2007;31(2):129-39. doi: 10.1016/j.cdp.2007.03.001. Epub 2007 Apr 6. PMID: 17418981.

18. Bonaterra GA, Kelber O, Weiser D, Metz J, Kinscherf R. In vitro anti-proliferative effects of the willow bark extract STW 33-I. *Arzneimittelforschung*. 2010;60(6):330-5. doi: 10.1055/s-0031-1296296. PMID: 20648923.

19. Islam, Muhammad & Dantas, Rafael. (2017). Anticancer prospection of salicin, a historical origin of aspirin. *International Journal of Medicine*. 5. 264-265. 10.14419/ijm.v5i2.8533

20. Verma N, Verma R, Kumari R, Ranjha R, Paul J. Effect of salicin on gut inflammation and on selected groups of gut microbiota in dextran sodium sulfate induced mouse model of colitis. *Inflamm Res*. 2014 Feb;63(2):161-9. doi: 10.1007/s00011-013-0685-1. Epub 2013 Nov 17. PMID: 24240229.