

Worms, Stool, and Alternative Therapies for IBD- Hype or Hope?

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Education Symposium**

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Definition of Complementary and Alternative Therapies

- Good place to start is National Center for Complementary and Alternative Medicine (NCCAM)
 - <http://nccam.nih.gov/health/whatiscam>
- Complementary: using non-mainstream approach together with conventional medicine
- Alternative: using non-mainstream approach in place of conventional medicine
- Perhaps what we want is integrative medicine or integrative health care

2 main subgroups of “CAM”

- Natural products (often sold as dietary supplements)
 - Herbs (botanicals)
 - Vitamins
 - Minerals
 - Probiotics
- Mind and body practices
 - Acupuncture
 - Massage therapy
 - Meditation
 - Movement therapies
 - Relaxation techniques
 - Yoga
 - Tai chi, qi gong
 - Hypnotherapy

Today

- Herbals
 - Aloe Vera
 - Wheat grass
 - Andrographis paniculata
 - Wormwood
 - Curcumin
- Brief review FMT (refer to talk earlier today)
- Worms
- Low Dose Naltrexone
- Cannabis

Aloe Vera Gel

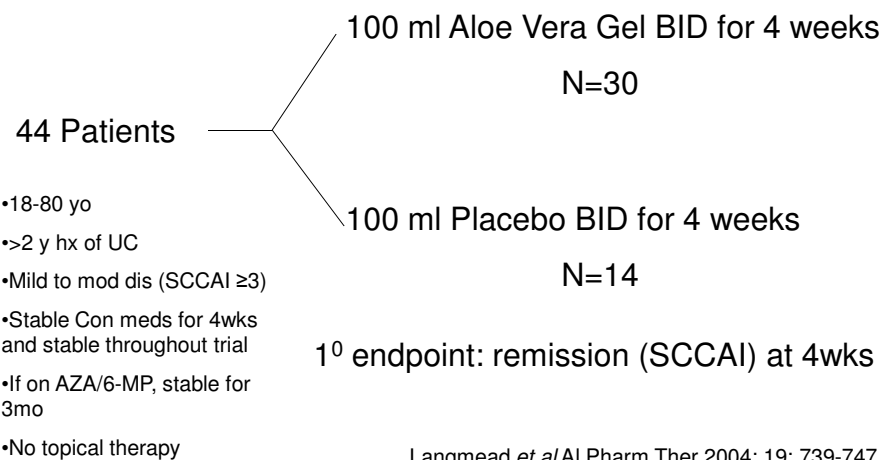
- Has been used as a medicinal ingredient for over 5000 years
- Primarily used for skin conditions
- Purported to have a number of biologically active compounds
- One of the most commonly used natural remedies by patients with IBD
- Aloin is a compound found in some species, a strong laxative taken off market in 2002



Aloe Vera Gel

Single-center single blind randomized controlled trial

Active Ulcerative Colitis

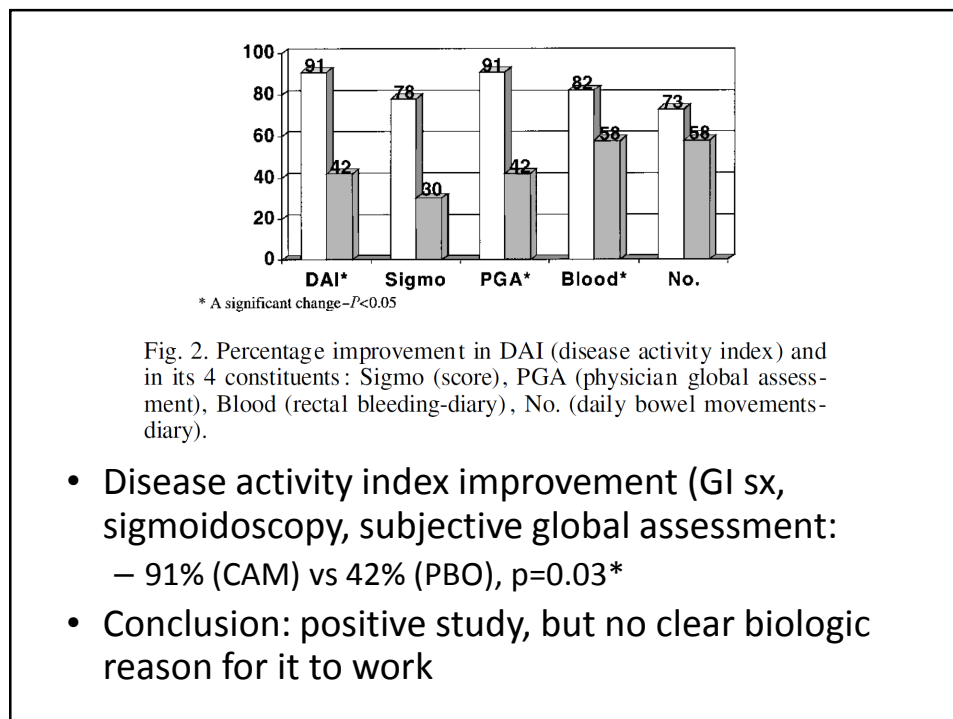
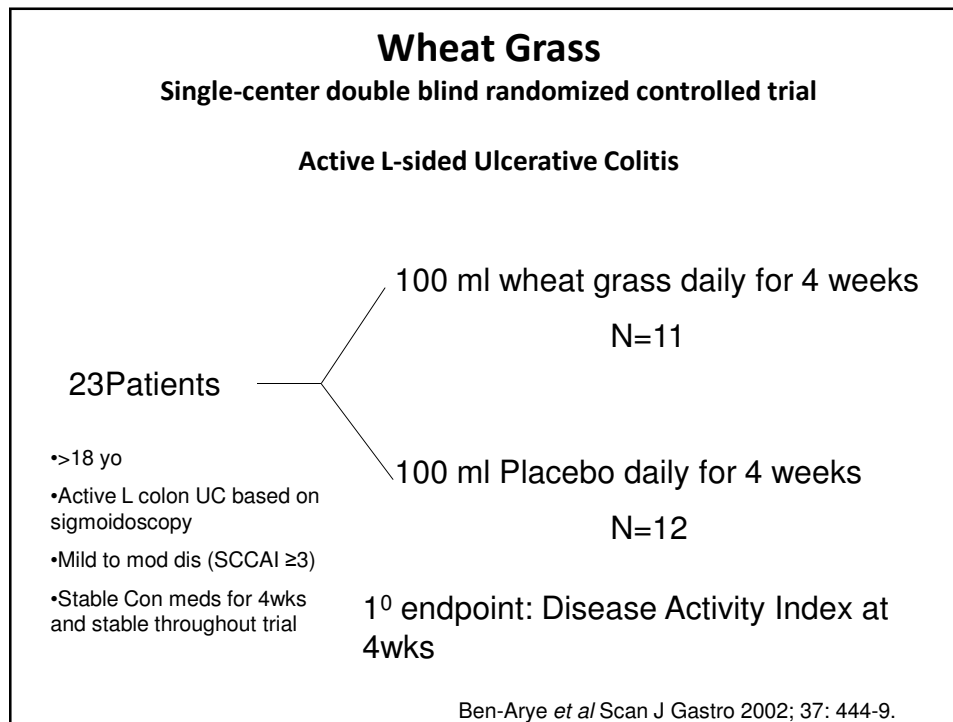


Results

- Clinical remission: 30% vs 7% ($p=0.09$)
- Clinical response: 47% vs 14% ($p<0.05$)
- Histological scores improved with aloe vera but not placebo ($p=0.03$)
- Sigmoidoscopy scores no different
- Conclusion: mixed results but promising. Needs more study

Wheat grass juice

- Extract squeezed from mature sprouts of wheat seeds (*Triticum aestivum*)
- Sold as juice or powder concentrate, thought to have therapeutic qualities when fresh
- Good source fiber, vitamins A, C, E, K, thiamin, niacin, riboflavin, zinc, Cu, Selenium, manganese
- No clear logic why should help in UC, but trial patient anecdotes led to this trial



Andrographis paniculata extract

- Herbal remedy used in China, India, Thailand, other Asian countries
- Extract inhibits inflammatory molecules such as TNF-alpha
- Pilot study showed similarly efficacy to mesalamine

Data for Andrographis paniculata

- Author/Study/Yr: Sandborn, 5 countries USA/Europe, 2013
- Population: Active UC
- Patients: 224
- CAM: 1800 mg daily
- Comparator: PBO
- Duration: 8 weeks
- Remission/Response:
 - 38% (CAM) vs 25% (PBO), $p=0.1$
 - 60% (CAM) vs 40% (PBO), $p=0.02^*$
- Promising: Phase III clinical trial currently enrolling patients with UC on mesalamine

Wormwood

Contains a number of active ingredients

Absinthin

Anabsin

Anabsinthin

Known anti-HSV, VZV, EBV, HHV, CMV properties

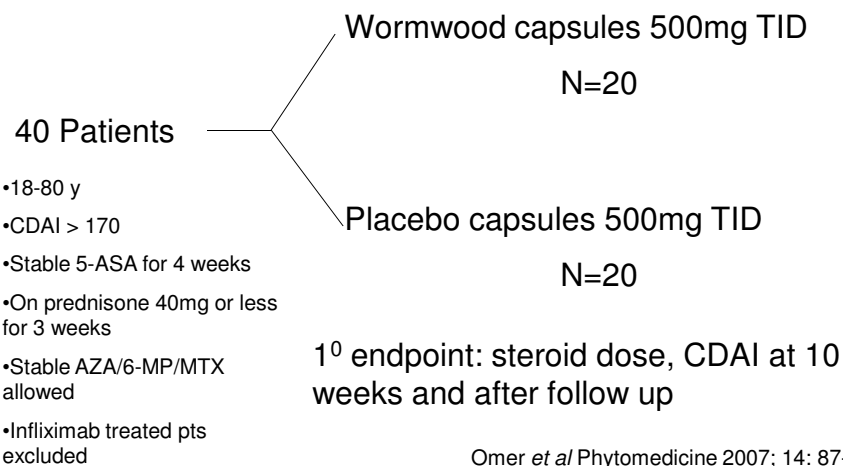
Induces production of interferon¹

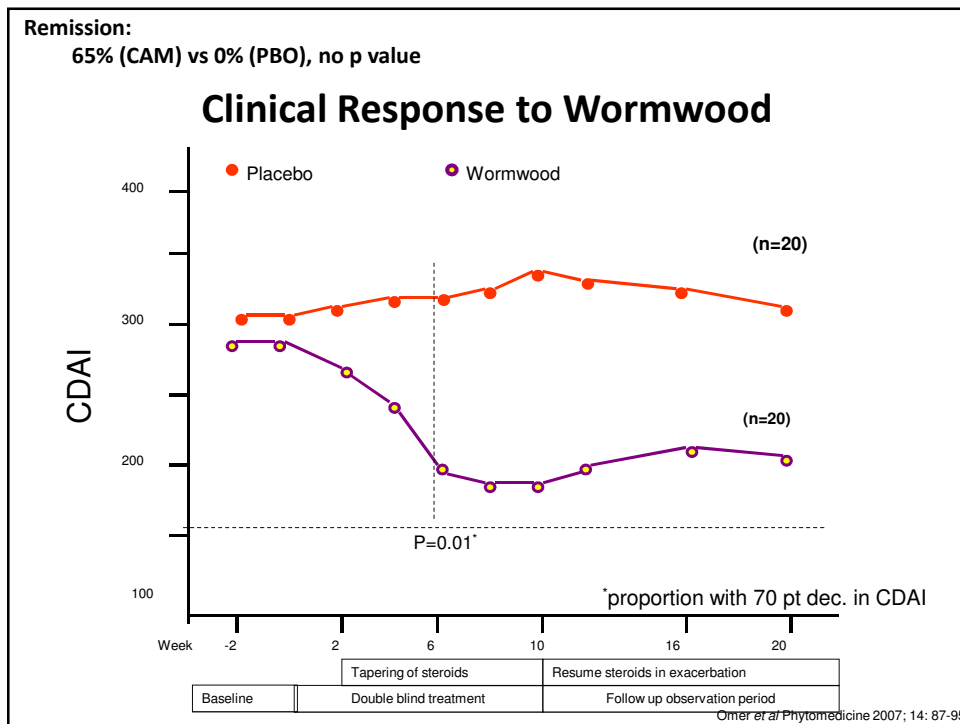


Artemisia absinthium

Wormwood for Steroid Sparing in Crohn's Disease

Multi-center double blind randomized placebo controlled trial





Data for Wormwood 2

- Author/Study/Yr: Krebs, Germany, 2010
- Population: Crohn's in remission
- Patients: 20
- CAM:
- Comparator: PBO
- Duration: 6 weeks
- Remission:
 - 80% (CAM) vs 20% (PBO), no p value

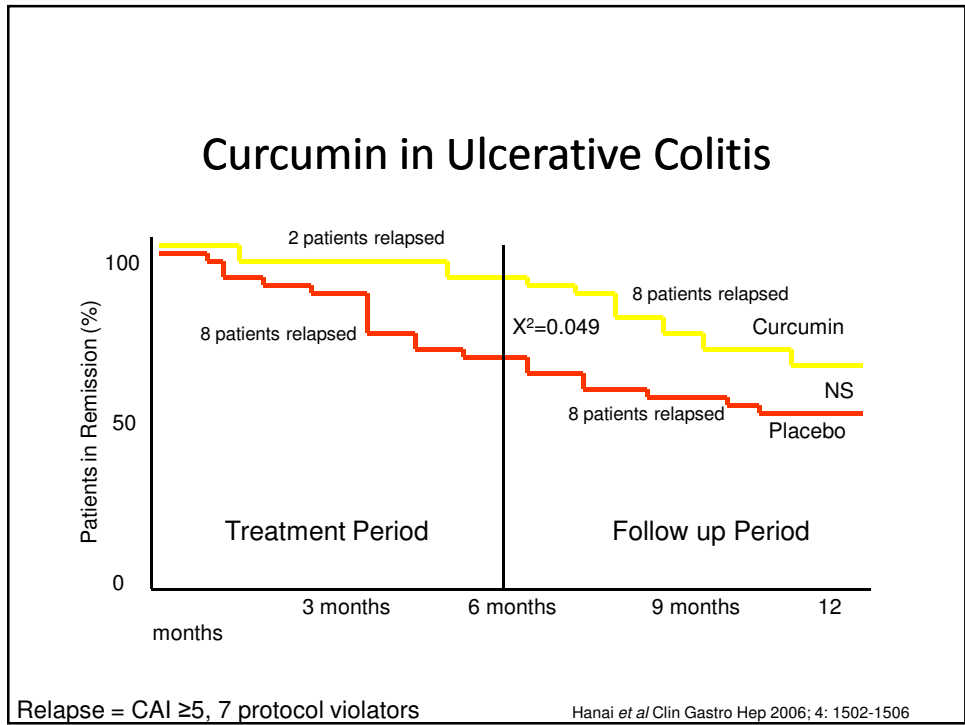
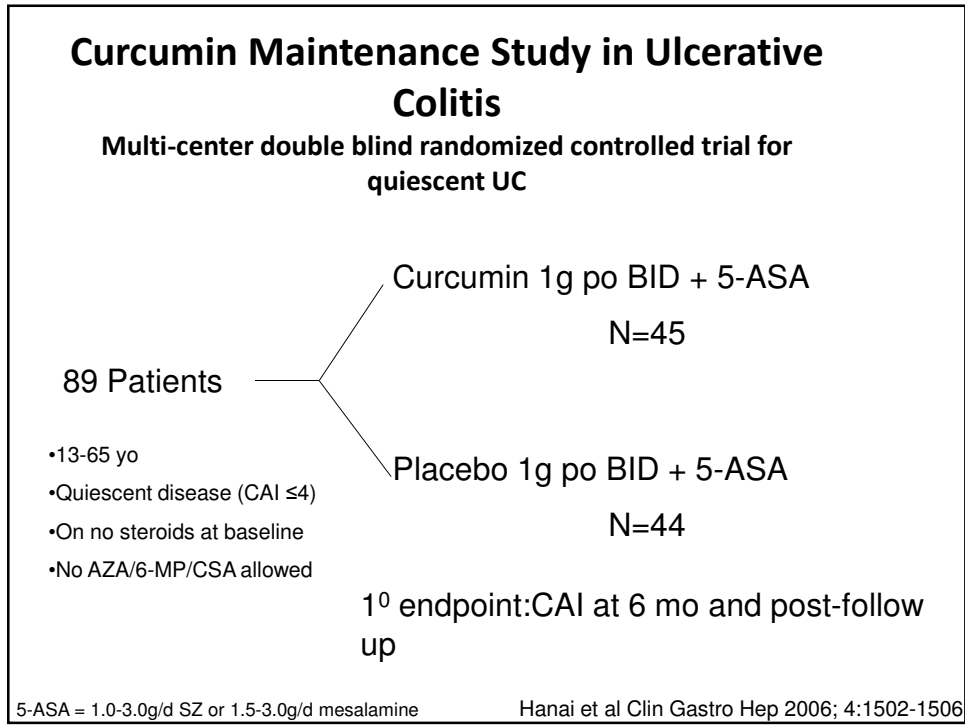
Comments

- Lack of statistical comparisons
- Mechanism of action unclear

- Prolonged steroid sparing after cessation
- Improvement in CDAI and IBDQ
- ?Something there
- Needs and warrants further study

Curcumin

- Found in South Asian spice tumeric
- Potential anti-inflammatory effect
- Most clinical studies in a variety of disease states have been negative



What is FMT?

- Acquisition of fecal material from a healthy donor
- Preparation of diluent
- Delivery to recipient
 - N-G
 - Colonoscopy
 - Enema
 - Pill form (desiccant)

Fecal Microbiota Transplantation (FMT) in IBD patients

- Some promising case reports and case series in UC
- No controlled trials
- Heterogeneity of patient types and severity
- Variable outcomes
- Limited post-transplant assessment of microbiome
- 2 Categories of FMT studies in IBD patients:
 - FMT as primary therapy for IBD
 - FMT as therapy for *Clostridium difficile* infection in IBD patients

Efficacy of FMT in IBD

- No controlled trials
- Several case reports with high free disease activity rate post-FMT of 63% (up to 2012).¹
- 7 reported cohort studies (6/7 reported in 2013).
- Clinical remission rate of case studies + cohort studies: 54%²
- Meta-analysis of these 7 cohort studies demonstrates only an overall pooled estimate of 32% (95%CI 11%-64%).²
 - Only 3 studies reported patients that achieved clinical remission.
 - 2 of the 3 studies included peds population (age 7-20).

¹Anderson JL et al. *Aliment Pharmacol Ther.* 2012;36(6):503-16.

²Colman RJ and Rubin DT Submitted.

Safety of FMT in Inflammatory Bowel Disease

- Some safety concerns remain
 - Common to have transient fever and some non-specific GI symptoms after FMT
 - Reports of worsening IBD after FMT^{1,2}
 - Lack of efficacy is a safety concern
 - Other safety outcomes have been described in non-IBD: new immune conditions (ITP, RA, peripheral neuropathy, Sjogrens)³
- Unknown consequences of patients doing this at home

IND through FDA Center for Biologic Evaluation & Research required in order to perform FMT in IBD

Current sponsors:

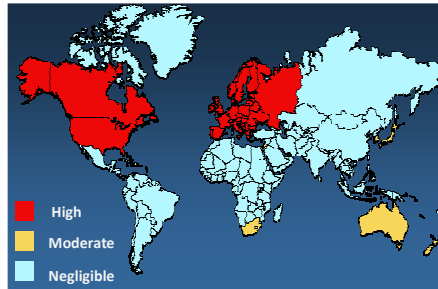
David Rubin, University of Chicago (UC)

Alan Moss, Beth Israel-Deaconess in Boston (CD)

1. de Leon LM et al. *Clin Gastroenterol Hepatol.* 2013;11(8):1036-8.
2. Angelberger, et al. *Am J Gastroenterol.* 2013, in press.
3. Brandt, et al. *Am J Gastroenterol* 2012 Mar 27. doi: 10.1038/ajg.2012.60.

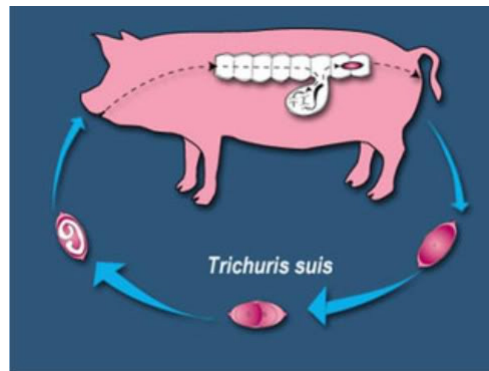
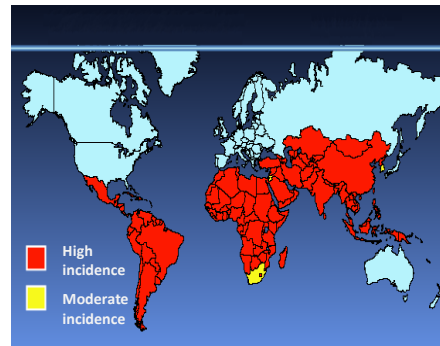
Why Parasites Might be the Answer (or just the question)

Autoimmune disorders incidence



Countries with *low* rates of
helminthic infections:
have high autoimmune
disease rates

Helminthes infestation incidence



Trichuris suis ova (worm eggs)

2 RCTs of Trichuris suis ova for IBD

Safety and Tolerability of Trichuris ova in CD¹

Results:

- 36 patients (2 to 6 mo F/U)

Adverse events:

- GI symptoms: 7(25.9%) in ova vs 3 (33.3%) in placebo group.
- No dose dependent relationship.
- No clinically meaningful changes in GI signs and symptoms.

Trichuris suis therapy for active UC²

Results:

- 54 pts (12 wk Tx)

Clinical Outcomes	TSO (n=30)	Placebo (n=24)	P-value
Clinical response (↓UCDAI ≥ 4)	43% (13/30)	16.7% (4/24)	0.04

1. Sandborn W et al. Aliment Pharmacol Ther. 2013;38(3):255-63.
2. Summers RW et al. Gastroenterology 2005;128(4):825-32.

Ongoing Study

- Phase II – RCT of Suis Ova Treatment in left-sided UC and its effects on Mucosal Immune State and Microbiota (NCT01953354)

Treatment arms:

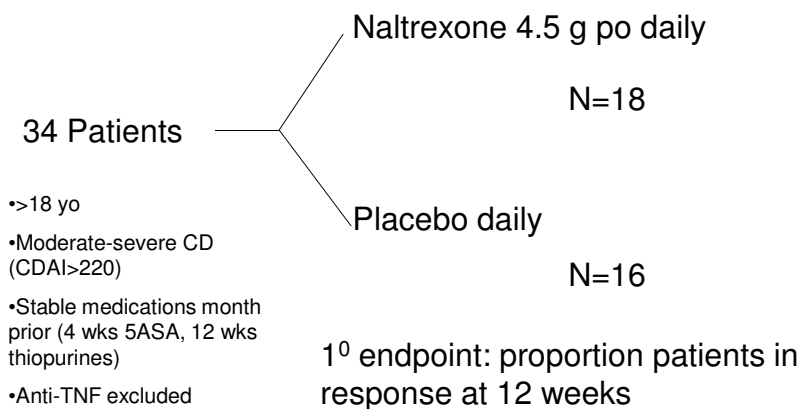
- 7500 Trichuris suis ova every 2 weeks for 10 weeks versus placebo

Naltrexone

- Opioid peptides play role in inflammation
- Naltrexone antagonizes the opioid pathways
- Advocacy for it, websites
- Recommended dosage is 4.5 mg once daily taking at night
 - This is low dose because full dose is 50 mg
- Typically made by compounding pharmacy
- Few side effects, but since blocks opioid receptors, avoid use in patients on narcotics

Naltrexone Study

Single center double blind randomized controlled trial for active Crohn's



5-ASA = 1.0-3.0g/d SZ or 1.5-3.0g/d mesalamine

Smith JP et al Dig Dis Sci 2011; 56:1653-7

Data for Low Dose Naltrexone

- Remission: 30% (CAM) vs. 18% (PBO), p=NS
- Response: 88% (CAM) vs 40% (PBO), p=0.009*
- Endoscopic response: 62% (CAM) vs. 25%(PBO), p<0.05
- Great! Right?
 - One small study
 - Data insufficient for firm conclusions
 - No specific adverse events
- RCT planned (NCT01810185)

Cannabis



Mechanism of Cannabinoid Derivatives in IBD

- Unknown
- Appetite stimulant
- Bowel relaxant/anticholinergic
- No evidence that it is anti-inflammatory (even though opioid system may promote inflammation)

[http://en.wikipedia.org/wiki/Cannabis_\(drug\)](http://en.wikipedia.org/wiki/Cannabis_(drug))
accessed March 21, 2014

Bodily effects of Cannabis

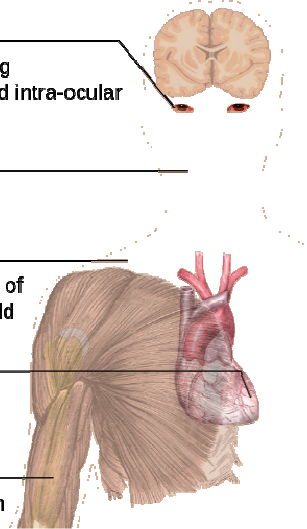
Eyes:
- Reddening
- Decreased intra-ocular pressure

Mouth:
- Dryness

Skin:
- Sensation of heat or cold

Heart:
- Increased heart rate

Muscles:
- Relaxation



Cannabidiol (CBD) No More Effective Than Placebo Active Crohn's Disease

- CBD one of 60 active substances in cannabis and thought to have greater scope medical applications than THC
- Evaluated 20 patients CDAI > 200
 - No prior marijuana use (per history)
- CBD 10mg BID vs. Placebo x 8 weeks
- No change vs placebo for CDAI
 - CBD 337 +/- 108 → 220 +/- 112
 - Placebo 308 +/- 96 → 216 +/- 121
 - Hemoglobin, albumin, kidney/liver function remained unchanged
- Cannabidiol does not produce psychotropic effect
- Cannabidiol does not seem to be effective compared to placebo in this small study
 - Dose?

Naftali T, et al. Presented at DDW May 2013, Abstract 983.

Controlled Trial of THC in Crohn's Disease

- Inclusion: IBD patients with C steroids, IMMs or anti-TNFs.
- RCT of $\Delta 9$ -tetrahydrocannabinol
- Cigarettes with 115mg THC vs
- Primary endpoint complete re

Clinical or laboratory variable
Number of liquid or soft stools each day for seven days
Abdominal pain (graded from 0-3 on severity) each day for seven days
General well being, subjectively assessed from 0 (well) to 4 (terrible) each day for seven days
Presence of complications*
Taking Lomotil or opiates for diarrhea
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite)
Hematocrit of <0.47 in men and <0.42 in women
Percentage deviation from standard weight

Clinical Outcomes	THC (n=11)	Placebo (n=10)	P-value
Clinical remission	45% (5/11)	10% (1/10)	0.43
Clinical response (CDAI \downarrow >100)	90% (10/11)	40% (4/10)	0.028

Naftali T et al. Clin Gastroenterol Hepatol 2013;11:1276-1280.

Alternative therapies in IBD

Compound	Conclusion
Aloe Vera	Superior in UC activity index but no endoscopic change
Wheat grass juice	Improved disease activity index, but no clear biologic reason to work
Andrographis paniculata	Promising, RCT ongoing, perhaps first herbal backed by real clinical trial data
Wormwood	No clear statistical comparisons, looked promising
Curcumin	Improvement at 6 months, reasonable data
FMT	No controlled studies, no reliable or sustained results Need to distinguish success in Cdiff vs IBD vs Cdiff/IBD
Trichuris suis	Study ongoing in UC
Low dose naltrexone	Limited data, positive study, low side effect profile, need real trial
Cannabis	No benefit in remission but yes in symptom improvement.

CAM Therapy in IBD
 “First Principles”

- First, do no harm;
- Ensure no opportunity cost (ie, do not delay treating a serious illness for which there is known effective therapy);
- If the CAM therapy carries little risk of harm, then consider its use and follow the patient closely;
- If the CAM therapy carries serious risk of harm, advise the patient accordingly and follow the patient closely;
- Where possible, it is recommended to try to follow an evidence-based rationale for therapy; and
- Where the evidence is lacking, try to maintain an open mind and a balanced approach.

References

1. Canadian Pediatric Society, D'Haeseleer. Children and natural health products: what a clinician should know. Paediatrics Child Health 2005;10: 227-232.

Data for aloe vera

- Author/Study/Yr: Langmead, UK, 2004
- Population: mild-moderate UC, active
- Patients: 44
- CAM: 100 ml twice per day
- Comparator: PBO
- Duration: 4 weeks
- Remission/Response:
 - 30% (CAM) vs 7% (PBO), $p=0.09$
 - 47% (CAM) vs. 14% (PBO), $p<0.05^*$
- Conclusion: greater response than PBO

Data for Boswellia serrata extract PS0201Bo

- Author/Study/Yr: Holtmeier, Germany, 2010
- Population: CD in remission
- Patients: 108
- CAM: 1200 mg twice per day
- Comparator: PBO
- Duration: 52 weeks
- Remission:
 - 60% (CAM) vs 55% (PBO), $p=0.85$

Boswellia serrata gum resin

- Anti-inflammatory effects

Data for *Boswellia serrata*

- Author/Study/Yr: Gupta, India, 2001
- Population: Active UC, open label
- Patients: 30
- CAM: 300 mg three times per day
- Comparator: Sulfasalazine 1g three times per day
- Duration: 6 weeks
- Remission/Response:
 - 70% (CAM) vs 40% (Sulfasalazine) (no p values)
 - 90% (CAM) vs 60% (sulfasalazine)

Data for *Boswellia serrata* extract H15

- Author/Study/Yr: Gerhardt, Germany, 2001
- Population: Active Crohn's
- Patients: 102
- CAM:
- Comparator: mesalamine
- Duration: 8 weeks
- Remission:
 - 36% (CAM) vs 31% (mesalamine)

Data for Wormwood 1

- Author/Study/Yr: Omer, Germany, 2007
- Population: active Crohn's
- Patients: 40
- CAM: 500 mg three times per day
- Comparator: PBO
- Duration: 10 weeks
- Remission:
 - 65% (CAM) vs 0% (PBO), no p value

Data for Curcumin

- Author/Study/Yr: Hanai, Japan, 2006
- Population: UC in remission
- Patients: 89
- CAM: 1 gram after breakfast and dinner plus sulfasalazine or mesalamine
- Comparator: PBO plus sulfasalazine or mesalamine
- Duration: 6 months
- Remission/Response:
 - 6mo: 95% (CAM) vs 79% (Sulfasalazine), p=0.049*

Boswellia serrata

- Plant that produces frankincense
- Plant native to India
- Used for 100s of years to treat arthritis (anti-inflammatory properties)
- Wokvel is a name brand