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**Are CAMs Safe and Effective in Improving Symptoms of Adult Patients Over the Age of 18 With Active Crohn Disease?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## **ABSTRACT**

**Objective:** The objective of this selective EBM review is to determine whether or not complimentary and alternative medicines are safe and effective in improving symptoms of adult patients over the age of 18 with active Crohn disease.

**Study design:** A review of three published, randomized controlled trials (RCTs), one published in 2010, and the second and third in 2014. All English language.

**Data source:** All 3 RCT's were found using PubMed.

**Outcomes measured:** All three studies measured improvement of Crohn disease symptoms through the Crohn Disease Activity Index (CDAI), Hamilton's Depression Scale (HAMD), the Inflammatory Bowel Disease Questionnaire (IBDQ) and the Partial Harvey Bradshaw Index (pHBI).

**Results:** Patient reported improved health-related quality of life and gastrointestinal function

**Conclusions:** The studies demonstrate some evidence that Complimentary and Alternative Medicines may improve acute symptoms of Crohn disease and an increased quality of life. However, it is inconclusive whether these therapies actually provide long-term results in healing patients with chronic disease.

**Key words:** "Crohn Disease" & "Complimentary Therapies"

## Introduction

Crohn Disease (CD) is an inflammatory bowel disease (IBD) that can affect any part of the gastrointestinal (GI) tract from mouth to anus.<sup>1</sup> IBD is comprised of CD and ulcerative colitis (UC). CD is a chronic, relapsing and remitting disease characterized by chronic diarrhea, abdominal pain and weight loss. Complementary and alternative medicine (CAM) is a term used to describe health and wellness therapies that have typically not been part of conventional Western medicine. “Complementary” suggest therapies that are used in conjunction with conventional medicine. “Alternative” suggests therapies used in substitution to conventional medicine.<sup>2</sup> This study evaluates the efficacy of CAMs in improving the symptoms associated with active CD.

Collectively, it is estimated that 1 in 200 Americans live with IBD.<sup>3</sup> The incidence is evenly divided between CD and UC in the US. Studies have extrapolated that the direct medical costs based on insurance claims for all patients treated for IBD estimated up to 28 billion dollars in 2014.<sup>6</sup> These costs include hospitalizations, prescription drugs, over the counter medications, hospital and physician services. Between 2011-2013, health plans estimated to pay out costs of \$18,637 per patient with CD.<sup>6</sup> Considering that the most common presenting symptom of CD is abdominal pain, this disease remains to be a diagnostic challenge for many clinicians across the medical landscape.<sup>4</sup>

With the increasing popularity and influence of eastern medicine on western medicine, patients have greater access to complimentary and alternative therapies. The trend of “natural” remedies or holistic medicine has a place in today’s advancing medicine for both the patient and the consumer. Some of the most popular internet searches for alternative therapies include

acupuncture, Ayurveda medicine, chiropractic care and biofeedback. The utilization of CAMs in clinical trials offer insight to their safety and efficacy in treating a myriad of conditions.

There are many natural remedies to treating abdominal pain. However, CAM interventions used in studies to treat CD aim at targeting more symptoms of the disease. Examples include the herb *Artemisia absinthium*, commonly known as wormwood; it is best known as the main ingredient in the alcoholic drink, absinthe. Another is acupuncture, a therapy that inserts small needles into specific zones of the body in order to stimulate an immune response. Moxibustion, or dried mugwort, is traditional Chinese herb used to augment medical therapies to increase healing.<sup>5</sup> Lastly, diet is not well understood in CD. Some foods have been linked to inflammation, which has a direct affect with symptoms of CD.<sup>6</sup>

The exact cause of CD is unknown, however it is understood to be involve interacting factors such as genetics, immune system and our personal environments.<sup>6</sup> The emotional impact from sudden flair ups to embarrassing GI symptoms increases stress levels, which can weaken immune systems. Like many disease states of dysfunctional immune systems, there is no cure; or one specific treatment that is effective in all patients. Treatment approach is highly complex. Biologic agents such as TNF inhibitors are one of the current emerging treatments for CD. They have been shown to induce and maintain clinical remission in patients with moderate to severe CD.<sup>6</sup> The many side effects and the administration of these drugs make them less appealing to some patients.

## **Objective**

The objective of this selective EBM review is to determine whether or not CAMs are safe and effective in improving symptoms of adult patients over the age of 18 with active CD.

## **Methods**

The criteria used as a basis to this study included participant population, interventions used, comparison analysis between control groups and measurable outcomes. This review focused on a population of participants over the age of 18 with active CD. The interventions used in all three RCT's were different types of complimentary and alternative medicines. These interventions were analyzed in comparison to participants over the age of 18 with active CD utilizing a placebo specific to each respective study. The outcomes that are measured include improvement of gastrointestinal-related and general symptoms of CD, improvement in healing, and an increased quality of life.

The intervention used in the study Krebs *et al.*, included powdered wormwood capsules versus the control placebo.<sup>7</sup> Bao *et al.*, compared the study group of participants receiving a combination of acupuncture augmented with moxibustion, against a control group of participants receiving placebo “superficial” acupuncture and moxibustion.<sup>8</sup> Interventions addressed in the Brotherton *et al.* study focused on patients consuming a high fiber, low refined carbohydrate diet, with specific daily consumption of whole wheat bran cereal. This was compared against a control group consuming a modified elimination diet.<sup>9</sup>

Article search and selection for this selective EBM review was conducted through PubMed. The key words used in the search were “Crohn Disease” and “Complimentary Therapies”. The studies chosen were all published in peer-review journals between 2010 and 2014. All 3 studies were written in English and selected based on the preceding criteria, being patient-oriented evidence, as well as the clinical relevance to my question. Statistical data reported to determine clinical importance included p-value, relative risk reduction (RRR), absolute risk reduction (ARR), and number needed to treat (NNT)

Table 1 Demographics &amp; Characteristics of included studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
<b>Krebs <i>et al.</i>, 2010</b>	RCT	20	18-80 years	Between the age of 18-80  Prior CDAI score of at least 200 for 3 mo	Participants receiving TNF-alpha inhibitors	0	Powdered wormwood ( <i>Artemisia absinthium</i> ) 750mg x3 qd
<b>Bao <i>et al.</i>, 2014</b>	RCT	92	18-80 years	Diagnosis of mild or moderate CD; Negative history of salicylic acid and/or prednisone (at a dose $\leq$ 15 mg) for at least 1 month, and immunosuppressant or used anti-TNF- $\alpha$ biological agents for 3 months prior to enrollment.	Pregnant or lactating, heart, brain, liver, kidney, or hematopoietic disease, mental illness, other severe diseases.	15	Acupuncture and moxibustion
<b>Brotherton <i>et al.</i>, 2014</b>	RCT	7	18-64 years	Diagnosed with CD via colonoscopy and biopsy.  Aged 18 to 64 years  pHBI score $\geq$ 3  At least 4 weeks of stable pharmacologic therapy.	Use of Biologics, diverticulitis, short bowel syndrome, clinically significant, penetrating or stricturing CD, Special dietary restrictions, any disorder that might interfere with the ability to follow detailed dietary instructions over time, pregnancy; cancer, uncontrolled kidney or CVD, pHBI score $>$ 9. decompensated liver disease.	0	High fiber and low refined carbohydrate diet; including consumption of whole wheat bran cereal.

### Outcomes Measured

The main outcome in the Krebs *et al.* study was the improvement of CD symptoms measured through the Crohn Disease Activity Index (CDAI).<sup>7</sup> Participants were required to have a minimum CDAI score of at least 200 at baseline.<sup>7</sup> This study also collected secondary outcomes of improved mood, measured by the Hamilton Depression Scale (HAMD) and serum

inflammatory markers.<sup>7</sup> Outcomes measured in the Bao *et al.* study were also aimed at improvement of symptoms through CDAI.<sup>8</sup> The study measured quality of life scores as secondary outcome through the Inflammatory Bowel Disease Questionnaire (IBDQ).<sup>8</sup> The Brotherton *et al.* study addresses the effects of a high fiber diet on both the quality of life and gastrointestinal function of participants with CD.<sup>9</sup> These effects were measured through IBDQ and the partial Harvey Bradshaw Index (pHBI).<sup>9</sup> Systemic inflammation was measured in the blood as secondary outcome for this study.

## Results

A total of 20 participants were enrolled in the Krebs *et al.* study with zero withdrawal during the 6-week trial.<sup>7</sup> Ten participants were randomly selected and divided into the group receiving wormwood, and the remaining ten were instructed not to take any additional medications, as comparison.<sup>7</sup> Participants who were being actively treated for CD with either 5-aminosalicylates, azathioprine or steroids, were kept on a stable dosage prior to the start of the trial.<sup>7</sup> This study excluded patients who were taking TNF inhibitors to avoid comparison from a pharmacologic prospective.<sup>7</sup> There were no significant differences between each participant in regards to age, duration of disease, extra-intestinal manifestations, and current medications.<sup>7</sup>

Participants in the wormwood group were instructed to take one 750mg capsule containing powdered wormwood three times daily for 6 weeks.<sup>7</sup> A significant improvement was defined by the author as a decrease in CDAI score of 70 points or decrease in HAMD scores of 50% from baseline.<sup>7</sup> At the end of 6 weeks, CDAI scores for the wormwood group decreased by an average of 100 points, with remission of symptoms in 8 participants.<sup>7</sup> Based on the outcomes measured, this was deemed a significant improvement as compared to a decrease of only 22 points in the control group.<sup>7</sup> Control also reports remission of 2 patients at the end of the 6 week

trial.

Of the secondary outcomes measured, there were reported improvements in mood symptoms. Participants in the wormwood group showed a decrease in their HAMD scores by an average of 9.9 points, as compared to the placebo group with a decrease of 3.5 points.<sup>7</sup> To scientifically measure the reduction in pro-inflammatory cytokines, TNF-a levels were drawn at baseline, 3 and 6 weeks.<sup>7</sup> By the sixth week, serum levels reduced an average of 17.5pg/ml for wormwood, whereas only 2.6pg/ml for control.<sup>7</sup> Based on all reported data in Krebs *et al.* study, the relative risk reduction (RRR) was 3%, the absolute risk reduction (ARR) was 60% and the numbers needed to treat (NNT) was 2.<sup>7</sup> Table 2 and 2a summarizes the primary outcome and efficacy of treatment.

Table 2: Krebs *et al.* primary outcome: improve symptoms of CD per CDAI scores.

Table 2a: efficacy of wormwood treatment on CD symptoms

	Wormwood Group (n=10)			Control Group (n=10)		
Score	<i>Baseline</i>	<i>6 weeks</i>	<i>Mean</i>	<i>Baseline</i>	<i>6 weeks</i>	<i>Mean</i>
CDAI	275 ± 15	175 ± 12	100	282 ± 11	260 ± 14	22
<b>CER</b>	<b>EER</b>		<b>RRR</b>	<b>ARR</b>	<b>NNT</b>	
20%	80%		3%	60%	2	

There were 92 participants between the ages of 18-80 enrolled in the 12 week Bao *et al.* study with 7 withdrawals before completion.<sup>8</sup> Treatment versus placebo were divided between 43 and 42 participants, respectively.<sup>8</sup> Of those, 40 of the treatment group and 37 of the control group completed a follow-up study at week 24.<sup>8</sup> There were no significant differences in participants in terms of baseline data.<sup>8</sup> There were two adverse events reported in the study. One treatment participant reported pain, and one control participant reported burning.<sup>8</sup> At the conclusion, there was a 13% loss to follow up of the subjects who entered the trial.<sup>8</sup>

Based on the results, CDAI scores from both groups reduced by the end of 12 weeks and

scores remained low for the treatment group by the 24 week follow up.<sup>8</sup> Clinical significance is determined by a decrease in 70 points on the CDAI scale. There was 83.7% improvement of symptoms for the treatment group and 40.5% for the control.<sup>8</sup> Based on this reported data the RRR was 1.1%, the ARR was 41.3% and NNT was 2.<sup>8</sup> While both groups reported increase in quality of life through their IBDQ scores, the treatment group score was statistically greater with a difference of p-value,  $P = 0.017$ .<sup>8</sup> The study found statistical evidence ( $p < 0.001$ ) that treatment with acupuncture and moxibustion did improve symptoms of CD per CDAI scores. Table 3 summarizes these results.

Table 3: Bao *et al.* mean values of CDAI and IBDQ scores.

Table 3a: Efficacy of acupuncture and moxibustion treatment on CD symptoms

	Treatment Group (n=43)			Control Group (n=42)		
	<i>Baseline</i>	<i>12 weeks</i>	<i>24 weeks</i>	<i>Baseline</i>	<i>12 weeks</i>	<i>24 weeks</i>
<b>CDAI</b>	210.84 ± 48.03	-115.35 ± 55.05	-128.93 ± 64.46	201.04 ± 57.13	-35.68 ± 46.91	-14.32 ± 52.09
<b>CER</b>	<b>EER</b>		<b>RRR</b>	<b>ARR</b>	<b>NNT</b>	
40.5%	83.7%		1.1%	43.2%	2	

Seven participants between ages 18-64 years were enrolled into the Brotherton *et al.* study.<sup>9</sup> The participants had active CD symptoms and treated as outpatient clinic setting.<sup>9</sup> Four participants were instructed on the intervention diet, which consisted of high fiber, including 0.5 cup of wheat bran cereal, and low refined carbohydrate diet.<sup>9</sup> The remaining three participants in the control group were instructed on a modified elimination diet based on “problematic foods” as per the Crohn and Colitis Foundation of America. Examples included whole grains, dairy products, and spicy foods.<sup>10</sup> Due to lack of variability in participant pool, only females were enrolled into the control group. There were no adverse events reported in the study.<sup>9</sup>

The author reports quality of life of the patients through IBDQ scores, with the range from 32-224.<sup>9</sup> IBDQ measures bowel symptoms, systemic symptoms, emotional function, and

social function.<sup>9</sup> Clinical significance is determined by a score of  $\geq 32$ -points.<sup>9</sup> Clinical remission has been set at  $\geq 170$  points.<sup>9</sup> With a baseline mean of 158.3, the treatment group improved their scores by 44.25 points. The control group had a baseline of 157.7 and increased by 19 points.<sup>9</sup> The increase in treatment scores were statistically significant over control ( $p = 0.028$ ). All patients enrolled achieved clinical remission based on the IBDQ scale.<sup>9</sup> Based on this reported data the RRR was 0, the ARR was 100%, and NNT was 10.<sup>9</sup>

The pHBI scores measured general well-being, abdominal pain, and number of liquid stools per day.<sup>9</sup> This particular study required baseline scores to range between 3-9.<sup>9</sup> Improved GI function was statistically significant ( $p = 0.008$ ) with all participants of the treatment group reporting scores of zero, and control group reported scores of three at the end of the 4 week trial.<sup>9</sup> Systemic inflammation was measured in the blood as secondary outcome for this study. This data was dismissed due to lab mishandling. After the 4 weeks, there were no significant differences reported in CRP ( $p$ -value = 0.125) and ESR ( $p$ -value = 0.788) values.<sup>9</sup>

Table 4: Brotherton *et al.*. primary outcomes: increased quality of life through IBDQ and improved GI symptoms through pHBI.

Table 4a: Efficacy of wheat bran diet on CD symptoms

	Wheat Bran Group (n=4)		Control Group (n=3)		<i>p</i> -value
	<i>Baseline</i>	<i>4 wks</i>	<i>Baseline</i>	<i>4 wks</i>	
<b>IBDQ</b>	158.3 $\pm$ 20.1	+44.25	157.7 $\pm$ 32.0	+19	0.028
<b>pHBI</b>	5.3 $\pm$ 1.3	0	4.7 $\pm$ 1.5	3	0.008

## Discussion

The primary aim of the Krebs *et al.* study demonstrates not only improvement of symptoms symptoms of CD, but also clinical remission of 80% of participants who received treatment. This study suggests that a natural product could provide patients with an alternative therapy to injectable biologics agents and specifically excluded patients already administering

them. A potential limitation to using a natural supplement to augment or treat any disease would be the safety in regulation and validity in its manufacturing. Most dietary products regulated by the FDA are done so differently than most food and drug products.<sup>11</sup> The correlation between wormwood and the observed improvement in mood seen in HAMD scores is unclear as there is little evidence that wormwood may have some anti-depressant effect.<sup>7</sup>

Overall, the use of intervention in the Bao *et al.* study, provided some observable benefits for patients suffering from gastrointestinal symptoms secondary to CD. It is said that acupuncture has been utilized in Chinese internal medicine as a treatment since 100 B.C.<sup>12</sup> This ancient therapy has reputation for alleviating many sub-clinical ailments and boasts little side effects or adverse reactions.<sup>12</sup> As an alternative therapy in combination with partitioned moxibustion, this appears to be an effective treatment for this particular patient population.

The limitations of this study were observed in the outcomes measured. Unlike the CDAI scores, the IBDQ and other laboratory values were only recorded post-treatment.<sup>8</sup> The primary efficacy indicator, CDAI, was documented at the 12 and 24 week follow up to ascertain progress and stability.<sup>8</sup> This study also did not address any mood or affective symptoms that are commonly associated with CD and IBD.

As a whole, the Brotherton *et al.* study demonstrated ease of implementing an affordable and tolerable whole wheat food into daily diet, which is beneficial to a population with advancing need for alternatives in health care. As a complex carbohydrate, wheat bran is fermentable, which allows it to provide the gut with a rich source of microbiota that would enhance the natural flora.<sup>9</sup> It is also rich in fiber, which slows gastric transit time and increases the water-binding capacity of luminal contents, ultimately reducing the frequency of diarrhea and constipation associated symptoms of CD.

This study was limited by its small sample size and potentially by the duration of the study. There were numerous exclusion criteria, as well as an exclusively female control group. In the results section, the author comments on the unreliability pertaining to the secondary aim of this study regarding the measurements in inflammatory markers. CRP and ESR are both non-specific lab markers and provide little insight regarding specifics of gastrointestinal inflammation.<sup>9</sup>

### **Conclusion**

The three studies reviewed in order to support the question, “Are CAMs safe and effective in improving symptoms of adult patients over the age of 18 with active Crohn disease?” demonstrate some evidence that CAMs may improve acute symptoms of Crohn disease and an increased quality of life. However, it is inconclusive whether these therapies actually provide long-term results in healing patients with CD. This review is ultimately limited by the use of different types of CAMs in each of the articles. With no identifiable harms in the above studies, the discussed interventions could be an alternative option to augment traditional medical treatment for patients suffering from this chronic and incurable disease. It would benefit future studies like these to observe participants over a longer period of time, as well as scheduled follow up visits for those who achieve early remission.

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