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Wheat Grass Juice in the Treatment of Active Distal Ulcerative Colitis

A Randomized Double-blind Placebo-controlled Trial

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Background: The use of wheat grass (*Triticum aestivum*) juice for treatment of various gastrointestinal and other conditions had been suggested by its proponents for more than 30 years, but was never clinically assessed in a controlled trial. A preliminary unpublished pilot study suggested efficacy of wheat grass juice in the treatment of ulcerative colitis (UC). **Methods:** A randomized, double-blind, placebo-controlled study. One gastroenterology unit in a tertiary hospital and three study coordinating centers in three major cities in Israel. Twenty-three patients diagnosed clinically and sigmoidoscopically with active distal UC were randomly allocated to receive either 100 cc of wheat grass juice, or a matching placebo, daily for 1 month. Efficacy of treatment was assessed by a 4-fold disease activity index that included rectal bleeding and number of bowel movements as determined from patient diary records, a sigmoidoscopic evaluation, and global assessment by a physician. **Results.** Twenty-one patients completed the study, and full information was available on 19 of them. Treatment with wheat grass juice was associated with significant reductions in the overall disease activity index ($P = 0.031$) and in the severity of rectal bleeding ($P = 0.025$). No serious side effects were found. Fresh extract of wheat grass demonstrated a prominent tracing in cyclic voltammetry methodology, presumably corresponding to four groups of compounds that exhibit anti-oxidative properties. **Conclusion.** Wheat grass juice appeared effective and safe as a single or adjuvant treatment of active distal UC.

Key words: Clinical trial; complementary alternative medicine (CAM); randomized; ulcerative colitis; wheat grass juice

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Wheat grass juice is an extract squeezed from mature sprouts of wheat seeds (*Triticum aestivum*). The use of wheat grass juice for therapeutic purposes was developed and popularized by Dr. Ann Wigmore (1). Although proponents of wheat grass juice have recommended it for three decades as a treatment for various ailments, including chronic inflammatory conditions and malignancies, to date no clinical trials exist. The juice is believed to possess therapeutic qualities only when fresh and is therefore consumed immediately after extraction, on an empty stomach. The therapeutic qualities of wheat grass juice have been attributed to its rich nutritional content—chlorophyll, vitamins (A, C and E), bioflavenoids, minerals (iron, calcium and magnesium), and 17 amino acids, 8 of which are essential (2). Several studies have assessed an anti-mutagenic activity of wheat grass juice. In 1978, Lai et al. demonstrated an anti-mutagenic activity of wheat grass extract in the Ames test system and attributed it to chlorophyll (3). In 1992, Peryt showed its anti-mutagenic activity against cyclophosphamide and ethidium bromide, which was related to flavonoids, particularly apigenin (4).

Clinical aspects of ulcerative colitis (UC) have been studied thoroughly, and there have been recent advances in drug therapy (5). Yet many patients, particularly in younger age groups, suffer from symptoms that are difficult to treat: the emotional distress of feeling controlled by the disease rather than controlling it (as they constantly seek the nearest rest-room); the experience of blood in the stool and constant concern about neoplastic changes; the side effects of second-line drugs; and the physical and psychological distress of multiple endoscopic procedures (6).

The use of wheat grass juice in the treatment of UC was brought to our attention by several patients with UC who attributed their improvement to regular use of the extract. In a pilot study, we gave 100 cc of wheat grass juice for 14 days to 10 previously diagnosed UC patients during relapse. Eight

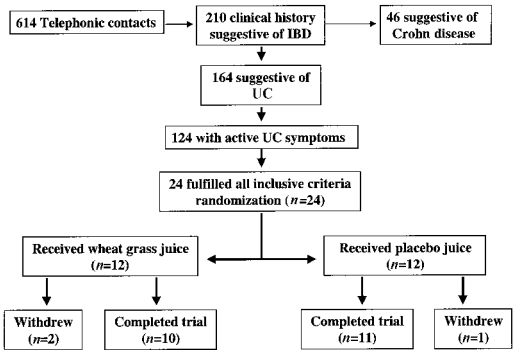

Fig. 1. Flow chart describing progress of patients through the trial.

patients described clinical improvement, one had no change, and one got worse. This study was never published. The present randomized, double-blind, placebo-controlled trial was designed to examine the effects of wheat grass juice in patients with active distal UC.

Methods

Patients

Patients were recruited from a variety of sources: media publicity, an inflammatory bowel disease (IBD) support group, and referrals from gastroenterologists and general practitioners (Fig. 1). Of the 614 individuals who contacted the research team, 210 presented with clinical histories suggestive of IBD (164 compatible with UC and 46 with Crohn disease). Active symptoms of UC were present in 124 patients. However, only 24 fulfilled the clinical inclusion criteria (Table I) as well as were willing to undergo two sigmidoscopies, resided within reasonable travel distance, and were able to enlist the full collaboration of their physicians. These 24 patients (15 men and 9 women), with a mean age of 35 and a mean duration of UC of 6.8 years, were randomized to receive either true wheat grass juice or a placebo of similar color and amount. There were no significant differences between the two groups in the baseline patient characteristics, clinical and sigmoidoscopic assessment and current treatment (Table II).

The protocol was approved by the Hadassah Hospital ethics committee in Jerusalem and by the Israeli Ministry of Health in accordance with the Declaration of Helsinki II. All patients signed an informed consent. Patients with clinical symptoms of UC underwent a baseline endoscopic assessment upon entry.

Table I. Inclusion criteria

Age >18 years
Sigmoidoscopic finding of active Ulcerative Colitis that involves the left colon
Clinical activity comparable with Ulcerative Colitis
No change in drug treatment (type and dosage) in the month prior to entry
Lack of serious systemic involvement–fever >38 °C, erythema nodosum, arthritis
Blood hemoglobin >11 g%
Negative stool culture and test for ova and parasites

Table II. Patient characteristics

Variable	Placebo	Wheat grass	*P* value
No. of patients	12	11	
Age (years)	33.3 ± 10.3	37.4 ± 12.8	0.402
Sex (male/female)	9/3	6/5	
Years of disease	6.6 ± 9.4	7.0 ± 9.4	0.924
Sigmoidoscopic score: (no. of patients)			
Mild (score 1)	5	4	
Moderate (score 2)	6	4	
Severe (score 3)	1	3	
Severity of disease by patient assessment			
Rectal bleeding (score 0–3)	0.7 ± 0.4	1.4 ± 0.9	0.006
Bowel Movements (no.)	4.4 ± 2.4	3.6 ± 2.5	0.083
Hemoglobin (g/dl)	13.6 ± 1.9	14.0 ± 1.9	0.644
Pre-study medication: (no. of patients)			
None	3	3	
5-amino-salicylic acid oral (enema)	8 (4)	8 (3)	
Prednisone oral (enema)	1 (1)	0	

Assessment of patients

Although there is a correlation between sigmoidoscopic evaluation and clinically active UC, one cannot predict the severity of the symptoms based on the sigmoidoscopic examination alone. Therefore, disease activity assessments in UC require a combination of subjective and objective parameters. Disease activity was assessed in three ways: symptom diary, sigmoidoscopy, and subjective improvement scale (7).

The symptom diary consisted of eight symptoms which patients graded daily on a 0–3 scale (no activity, mild, moderate, or severe, respectively). The eight symptoms were rectal bleeding, stool frequency, urgency, pain (rectal or abdominal), distention, mucous, general well-being, and appetite. Baseline diary information was recorded for 3–7 days prior to the beginning of treatment. Symptomatic changes were assessed by comparing the average scores of the first week of diary entry to the average scores in the last week of diary entry for each symptom.

Sigmoidoscopies were performed on each participant within a week prior to starting treatment and within 3 days following the termination of treatment. Sigmoidoscopic results were rated on a 0–3 scale as no activity, mild, moderate or severe, respectively. Pretreatment and posttreatment scores were compared for each participant. All sigmoidoscopies were performed, assessed and rated by gastroenterologists from the Gastroenterology Unit in Hadassah Hospital in Jerusalem who were blinded as to whether the patients were treated with wheat grass or placebo.

The subjective global assessment consisted of both the physician's and participant's estimation of change in disease activity. It was performed upon treatment termination separately and graded on a −3 to +3 scale.

A disease activity index (DAI) was created by combining the four most accepted measures (according to Sutherland (7)): stool frequency, rectal bleeding, sigmoidoscopic score and physician's assessment of disease activity.

Trial design and treatment

Patients were randomly allocated, through a centralized randomization process, to receive either 100 cc of wheat grass juice or matching placebo for 1 month. To ensure high quality, special methods of preparing and distributing the wheat grass juice and the placebo were designed. Wheat seeds were grown organically in indirect sunlight on a substrate composed of soil, volcanic tuff and compost. The wheat grass was harvested at the height of 20 cm, packaged and distributed in a refrigerated vehicle twice weekly to the three study coordinating centers in three main cities in Israel. Every morning, at about 0500, workers at each study coordinating center extracted the wheat grass juice using a manually operated juice machine. Then both the true wheat grass juice and the placebo were packaged in coded, identical, sealed, opaque containers. A driver, blinded to the allocation scheme and given only the addresses for each package, then distributed all the packages. All containers were delivered within an hour of extraction to ensure freshness. The patients were instructed to take the juice immediately. The doses of both the true juice and the placebo were increased gradually from an initial dose of 20 cc on the first day to an increase of 20 cc on each successive day. By the fifth day the optimal daily dose of 100 cc was achieved and given thereafter.

The placebo juice was manufactured from 0.18% normal saline with a mixture of under 0.5% weight kaolin and tragacanth, and tinted with food color (Fast Green FCF). The placebo juice was prepared in a centralized location and distributed monthly to the study coordinating centers. The placebo juice was similar to wheat grass juice in appearance, but not in taste and smell.

Data collection and scoring

Patients' diaries and final subjective assessment of change were collected upon treatment completion. Each final subjective assessment score (after 1 month of drug or placebo) was subtracted from the initial subjective score for each patient. The values for the two groups were compared. The proportions of persons who improved or deteriorated are shown in Figs 2 and 3. Table III specifies the results in various parameters. A change in a parameter (improvement or aggravation) was defined as larger than 0.4 in an analog scale where −3 designates the lowest score of aggravation, 0 no change, and +3 highest score of improvement. The parameter change for the number of bowel movements was defined as greater than 2 in absolute numbers.

Statistical analysis

A between-groups analysis (two-tailed, Fisher exact test) was done on the four components of the DAI: rectal bleeding, stool frequency, sigmoidoscopic score and physician's assessment of disease activity (Table III). Analyses were confined to the 21 patients who completed the trial. The physician's assessment of disease activity was compared to the stool frequency, rectal bleeding, sigmoidoscopic score and the patient's retrospective assessment score using the Spearman rank correlation (Table IV).

Results

Withdrawals and drop-outs

Of the 24 patients who were randomized, 21 completed the double-blind study. Three withdrew early. One patient (from the treatment group) withdrew within 1 day of commencing treatment, because she was unable to tolerate the taste of the juice (Fig. 1). Another patient (treatment group) withdrew after 10 days, convinced she was receiving a placebo. The third patient (placebo group) withdrew after 14 days, due to deterioration in her illness. Of the 21 patients who completed the 1-month trial, 19 were evaluated with a second sigmoidoscopy within 3 days after completion of the study.

Significant differences in improvements in rectal bleeding ($P = 0.025$), abdominal pain ($P = 0.019$), the DAI score

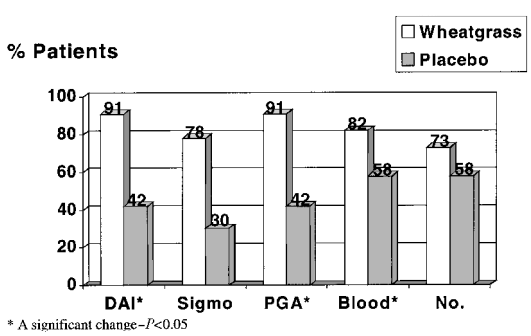

Fig. 2. Percentage improvement in DAI (disease activity index) and in its 4 constituents: Sigmo (score), PGA (physician global assessment), Blood (rectal bleeding-diary), No. (daily bowel movements-diary).

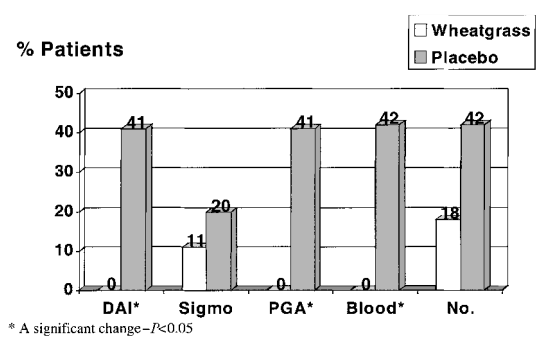

Fig. 3. Percentage deterioration in DAI (disease activity index) and in its 4 constituents: Sigmo (score), PGA (physician global assessment), Blood (rectal bleeding-diary), No. (daily bowel movements-diary).

Table III. Clinical state after 1 month of treatment

Variable	Study group	Improved	No change	Worsened	*P* value
Disease Activity Index (DAI)	Treatment (T)	10	1	0	0.0312
	Placebo (P)	5	2	5	
1. Rectal bleeding	T	9	2	0	0.0254
	P	7	0	5	
2. Bowel movements (No.)	T	8	1	2	0.37
	P	7	0	5	
3. Sigmoidoscopic assessment*	T	7	1	1	0.127
	P	3	5	2	
4. Physician global assessment (PGA)	T	10	1	0	0.0312
	P	5	2	5	
Other indices of activity (Diary)					
Mucous	T	5	2	3	0.167
	P	8	4	0	
Pain	T	8	1	0	0.0191
	P	3	4	5	
Abdominal bloating	T	7	3	1	0.376
	P	3	2	7	
Patient's retrospective evaluation	T	10	0	0	0.0053
	P	5	3	4	

* 10 patients in placebo and 9 in treatment group.

($P = 0.031$), the PGA ($P = 0.031$), and patients' retrospective evaluation ($P = 0.0053$) were demonstrated in the treatment versus the placebo groups (Table III). No significant differences were found in the number of bowel movements or sense of abdominal bloating between the two groups. A greater proportion of participants improved on the sigmoidoscopic evaluation in the treatment group (7 of the 9 patients (78%)), compared to the placebo group (3 of the 10 patients (30%)). However, this difference was not significant ($P = 0.13$).

Credibility of blindness was assessed by a questionnaire at the end of the study. In the treatment group, 6 of 11 patients believed they were getting wheat grass juice, and attributed it to their improved well-being; three were convinced they were getting placebo, and two did not give a definite answer. In the placebo group, 7 out of 12 patients did not give a definite answer, 2 believed they were getting wheat grass, and 3 believed they were taking placebo.

Table V summarizes both the positive and the negative effects, which were reported by participants who received wheat grass juice. Nausea was found to be the most adverse effect (33%). A prominent positive side effect was increased vitality (41%). No side effects were reported in the placebo group.

An attempt was made to identify likely bioactive compounds that might explain some of the activity of wheat grass juice. Reactive oxygen species (ROS) have been suggested to be involved in the induction and prognosis of UC. Antioxidants were demonstrated to be beneficial in preventing intestinal injury in general, and UC in particular. A significant reduction in the activity of the colonic low molecular weight anti-oxidants (LMWA) has already been reported (8); therefore, in this study we evaluated the overall LMWA capacity of the wheat grass juice to see its profile. The cyclic voltammetry (CV) methodology was used for this purpose, as described in detail elsewhere (Chevion et al.) (9). Fresh extract of wheat grass demonstrated a prominent tracing with at least four peaks (Fig. 4), presumably corresponding to four groups of compounds that exhibit anti-oxidative properties. These four peaks decreased in number and amplitude over time (Fig. 5).

Table IV. Correlation between physician global assessment and other parameters of disease activity

Variable	No. of subjects	Correlation rho	*P* value
Bowel movements	33	0.410	0.0178
Rectal bleeding	33	0.775	0.0001
Retrospective patient assessment	33	0.773	0.0001
Sigmoidoscopic appearance	30	0.618	0.0003

Discussion

The results of this double-blind study indicate that wheat grass juice has a therapeutic role in treating patients with active restricted left colon UC. We have demonstrated that wheat grass is a generally safe substance, with few side effects (Table V).

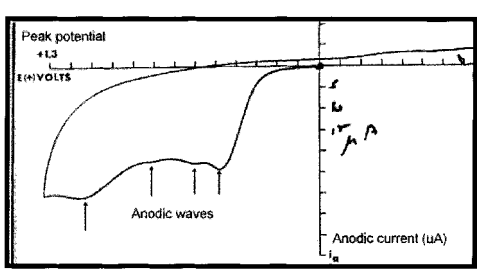

Fig. 4. Cyclic voltammetry of fresh wheat grass juice.

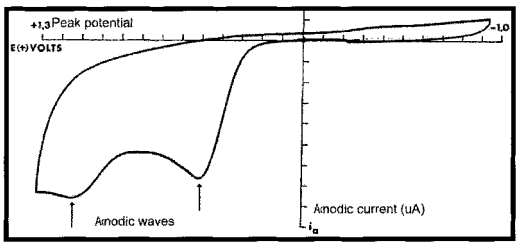

Fig. 5. Cyclic voltammetry of non-fresh wheat grass juice.

Both subjective and objective parameters are important in the clinical evaluation of UC. Various disease activity assessments that combine these parameters have been developed in the past 40 years, initially by Truelove & Witts in 1955 (10) and later by Seo et al. (11) and Sutherland (7). It is notable that the correlation between sigmoidoscopic evaluation and clinical activity in UC is well established but not absolute, as the length of the inflamed colon does not always correspond with the severity of the clinical appearance (12). According to the four parameters of the DAI we used [based on Sutherland (7)], overall clinical evaluation of the treatment group demonstrated a significant improvement compared to the placebo group. Although sigmoidoscopy did not demonstrate a significant improvement, there was a distinct trend toward improvement.

The present study indicates a possible clinical efficacy of wheat grass juice in treating UC. Several questions emerge. First, does wheat grass possess anti-inflammatory properties? If so, which components are the active ones? Second, does the active substance exert a general anti-inflammatory effect via proximal intestinal absorption, or does it act locally at the inflamed site itself?

When wheat grass juice has been analyzed using cyclic voltammetry, four distinct peaks emerge. These four peaks may indicate that there are at least four groups of active ingredients that possess redox potentials and anti-oxidative properties. There is growing evidence that free radicals play a role in the pathogenesis of UC (8). If this is the case, then anti-oxidative agents may be beneficial therapy.

One mechanism by which wheat grass juice may improve the symptoms of UC can involve flavonoids, specifically apigenin, a known ingredient of wheat grass juice (4). The well-established biological activity of flavonoids includes anti-inflammation (via the arachidonic acid pathway (13)) and anti-oxidation (14). Apigenin, a potent bio-flavonoid found in wheat grass juice, has been shown to be an anti-oxidant in the xantine/xantine oxidase system (15), anti-inflammatory in inhibiting adhesion of leukocytes to endothelia (16), anti-mutagenic in the Ames Test (17) and inhibiting towards colon motility (18).

Table V. Side effects of wheat grass juice administration

	No. of patients (%)
Nausea	
Mild	3 (25)
Severe	1 (8.3)
Decreased morning appetite	2 (16.6)
Constipation	1 (8.3)
Increased vitality	5 (41.6)

No answer is available at present as to the site of wheat grass juice action. This question can be addressed in future studies by administration of wheat grass juice in enemas or suppositories. Many other questions are raised by our results. For example, does wheat grass juice have a therapeutic advantage over other modes of treatment for UC as a stand-alone treatment or an adjunct to drug administration? Does it have any role in prophylaxis or only in acute attacks? Should it be offered to patients with extensive UC or Crohn colitis as well? What are optimum doses and modes of administration, and are there interactions with other drugs? The authors believe that these questions should be tested in future studies.

Although it is noteworthy that significant findings emerge from the study with such a small sample size, there are some limitations of this study because of its small sample. For example, the sample was too small to be able to identify characteristic of responders. Secondly, the study required participants to undergo two sigmoidoscopies, use an unconventional treatment, and travel. Given these requirements, the study participants may be a non-representative, highly motivated sample of UC patients. Another trial with a larger group of patients could address both of these shortcomings.

We can also, in retrospect, identify at least two ways that future trials can improve on this study. First, it is recommended that the sigmoidoscopy films be read by two independent readers blinded to each other's assessment, and that inter-rater agreements be calculated. This would highlight, and minimize, single-reader bias. Secondly, an assessment of whether participants believe they are receiving the placebo or the true juice before there is any chance of a change in the disease activity, for example at about 3 days.

We believe that wheat grass juice offers a genuine therapeutic advantage in the disabling disease of UC. Besides apparent efficacy, adverse effects were relatively benign. Notable is the potential of this regimen of empowering the patient in becoming an active participant in the therapeutic process. The effort of obtaining or growing wheat grass and the daily production of fresh juice may be important in enhancing the patients' sense of control and alleviating some of the patient distress described earlier. In any case, use of wheat grass juice in subsets of patients, as single or adjuvant remedy in acute left-sided UC, may prove to be beneficial therapeutically.

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