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The effects of Zintona EC (a ginger extract) on symptomatic gonarthritis

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Summary

Objective: Evaluation of the effect of a ginger extract (Zintona EC) on patients suffering from gonarthritis.

Material and methods: Twenty-nine patients (6 men and 23 women) with symptomatic gonarthritis (ACR criteria), in the age range 42–85 years, were included after randomization in a double blind, placebo controlled, crossover study of 6 months' duration. The treatment group was given a ginger extract (250 mg of Zingiberis Rhizoma per capsule, qid), while the placebo group received the same number of identical looking capsules per day. The crossover occurred after 3 months of therapy. Results were evaluated by a 100 mm visual analog scale (VAS) of pain on movement and of handicap.

Results: Eight patients dropped out because of inefficacy, three from group 1 (ginger extract first) and five from group 2 (placebo first). One patient from group 1 and one from group 2 dropped out because of heartburn (while they were on ginger extract). Twenty patients completed the study period of 24 weeks and 19 that of 48 weeks follow-up. By the end of 24 weeks there was a highly statistically significant difference between the VAS of pain and handicap of the two groups ($P<0.001$). However, at crossover both groups showed a statistically significant decrease in VAS of pain on movement and of handicap, but the differences between the groups did not reach statistical significance.

Conclusions: Zintona EC was as effective as placebo during the first 3 months of the study, but at the end of 6 months, 3 months after crossover, the ginger extract group showed a significant superiority over the placebo group.

Key words: Ginger extract, Gonarthritis, Zintona EC.

Introduction

Osteoarthritis (OA) is the most common rheumatic disease, the prevalence of which increases with advancing age[1,2]. The 1995 American College of Rheumatology (ACR) recommendations for the management of OA of the hip and knee outlined both the use of nonpharmacological modalities as well as that of pharmacological agents[3]. The 2000 ACR update of these recommendations[4,5] includes a discussion of the place of acetaminophen, COX-2 inhibitors and nonselective NSAIDs, tramadol, opioids, intra-articular glucocorticoids and hyaluronan, topical capsaicin and methylsalicylate in OA management. Agents under investigation, such as glucosamine, chondroitin sulfate and others, are also discussed. Altman and Marcussen[6] recently reported a statistically significant effect of a ginger extract on reduction of knee pain in patients with OA. Their study was a 6-week double blind placebo controlled parallel-group study.

We report here the effects of a ginger extract on symptomatic OA of the knee in a double blind placebo controlled, crossover study of 6 months' duration.

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Patients and methods

STUDY DESIGN

Twenty-nine patients (six men and 23 women) aged 42–85 years were included in the study after they signed an informed consent according to the Ethics Committee requirement.

INCLUSION CRITERIA

Patients aged 40–85 years of both genders, with a diagnosis of OA of the knee according to the ACR criteria[7] (showing at least one osteophyte on X-ray) and corresponding to OA grades 2, 3 or 4 by the Kellgren and Lawrence criteria[8], were considered for inclusion. They had to report pain on knee movement on a 100 mm visual analog scale (VAS) of at least 35 mm (VA≥35 mm) after a 4 day washout period of any previous medication. Patients were excluded from the trial if pregnant or lactating or not using acceptable contraception, if they had participated in any other drug trial during the preceding 3 months, if they had intra-articular injections of corticosteroids or hyaluronan within the preceding 3 months, if they were on glucosamine/chondroitin preparations or diacerein less than a month before the trial onset, if they were on anticoagulants except for mini-aspirin (75–325 mg/day), if they had, besides OA, a concomitant rheumatic disease or secondary OA, or recent surgical orthopedic intervention in the lower limbs (within 6 months prior to trial onset). They were also excluded if mentally incapable of understanding or complying with the study protocol or for failing to sign the informed consent.

Table I
Demographic characteristics of patients and radiographic classification of knee OA

	Group 1 (ginger first)	Group 2 (placebo first)
Age: mean (range, years)	64.7 (47–85)	59.3 (42–81)
Sex: male/female ratio	1/13	5/10
Disease (OA) duration: mean years±SD	8±4.8	5.9±3.4
Radiographic classification of knee OA		
Stage 2	3	2
Stage 3	7	10
Stage 4	4	3

No active physiotherapy or balneotherapy for the knees was allowed during the trial period.

After randomization by computer-generated allocation schedule they were divided into two groups: group 1 (14 patients, who received the ginger extract first) and group 2 (15 patients who received placebo first). Both patients and investigators were blinded to treatment assignment. After 12 weeks, group 1 was switched to placebo and group 2 was given ginger extract for an additional 12 weeks. By the end of the double blind trial at week 24 the code was broken and interested study participants continued on ginger extract and were followed for an additional 24 weeks.

Demographic characteristics of patients included in the study and radiographic classification of the target knee are described in Table I.

TREATMENT

Following discontinuation of any NSAID treatment for 4 days (washout period) patients were allocated to either Zintona EC (enteric coated) or placebo which were administered qid in identical opaque capsules. Paracetamol, up to four tablets per day, was allowed throughout the study except for a 12 h period before every point of clinical evaluation (weeks 4, 12, 16, 24, 32, 40 and 48) and their consumption recorded. The preparation Zintona EC (enteric coated ginger extract) was produced by Dalidar Pharma (Beer Sheva). It is a preparation (250 mg per enteric coated capsule) based on an extract of the plant ginger (*Zingiber officinale*). The plant root was subjected to extraction by liquid carbon dioxide under supercritical conditions. The liquid extract was absorbed on maltodextrin and microencapsulated to form an enteric coated product. The potency of the preparation was followed by analysis with HPLC on the active molecule gingerol. The dissolution of the preparation was done in a USP type 2 dissolution apparatus in gastric fluid (0.1 M HCl) for 1 h and the pH was rapidly increased to that of intestinal fluid (phosphate buffer pH=7.4). The release of gingerol was followed at several time points by HPLC analysis. The preparation was designed to release 20% under acidic gastric conditions in 2 h and the rest of the active material under intestinal conditions. Each capsule was filled to contain 10 mg gingerol. Placebo capsules contained maltodextrin only.

ASSESSMENTS AND STATISTICAL ANALYSIS

VAS of pain and handicap were determined by the Hebrew validated version of WOMAC[9]. Knee circumference was measured by tape at the level of the patellar center. Means of VAS of pain on movement, handicap and target knee circumference were calculated at each visit while stratifying for treatment group. The means of each of these visits were compared to the baseline mean (the second visit, after 4 days of washout). Statistical significance of these comparisons was calculated by the paired *t*-test. At each visit the differences from baseline of the means of VAS of pain on movement, handicap and target knee circumference were compared between the treatment groups. The statistical significance of these comparisons was calculated by independent sample *t*-test.

Data concerning pain on movement, handicap and knee circumference reduction were analyzed by intention to treat. Since we could not compare means because the results concerning those who were lost to follow-up were not available, the intention to treat analysis was done for success versus failure, while referring to those who were lost to follow-up as treatment failures. Patients who reported more than 30% reduction in pain and handicap or presented more than 5% reduction in knee circumference were regarded as treatment success. The proportion of treatment success was calculated at each visit, while those who were lost to follow-up were regarded as treatment failure. These proportions were compared between treatment groups. Statistical significance was calculated by Fisher's exact test.

Results

The means of VAS of pain on movement and handicap at each visit, according to treatment group, are presented in Figs. 1 and 2 and Table II. During the first 12 weeks of the trial (phase one), VAS of pain on movement and VAS of handicap were reduced in both treatment groups. By the 12th week, in those treated with Zintona EC, the mean VAS of pain on movement was reduced from 76.14 (95% CI: 67.69–84.60) at baseline to 41.00 (95% CI: 22.50–59.49) (P=0.001) and that of handicap was reduced from 75.86 (95% CI: 68.00–83.72) at baseline to 39.72 (95% CI: 22.24–57.22) (P=0.001). In those who were treated with placebo, the mean VAS of pain on movement decreased from 76.87 (95% CI: 71.64–82.09) at baseline to 50.00 (95% CI: 33.46–66.53) (P=0.001) and that of handicap decreased from 73.47 (95% CI: 66.66–80.28) to 46.08 (95% CI: 29.75–62.40) (P=0.002). The differences between groups were not statistically significant. At phase two (after crossover) VAS of pain on movement and of handicap continued to decrease in the group that switched from placebo to Zintona EC, with means of 9.30 (95% CI: 3.29–15.31) and 10.00 (95% CI: 3.84–16.16), respectively, at the 24th week. In the groups that switched from Zintona EC to placebo, these means started rising, with the mean VAS of pain on movement and of handicap reaching 82.10 (95% CI: 69.81–94.39) and 80.80 (95% CI: 68.47–93.12), respectively, at the 24th week. The differences at this time were found to be statistically significant (P<0.001 for both comparisons). At phase three, when patients from both groups received Zintona EC, VAS of pain on movement and of handicap remained low in the group that continued Zintona EC from phase two, and decreased again in the group that received placebo at phase two. Both groups reached a low mean, which was statistically different from the baseline mean. No statistically significant difference was observed between the groups at this phase.

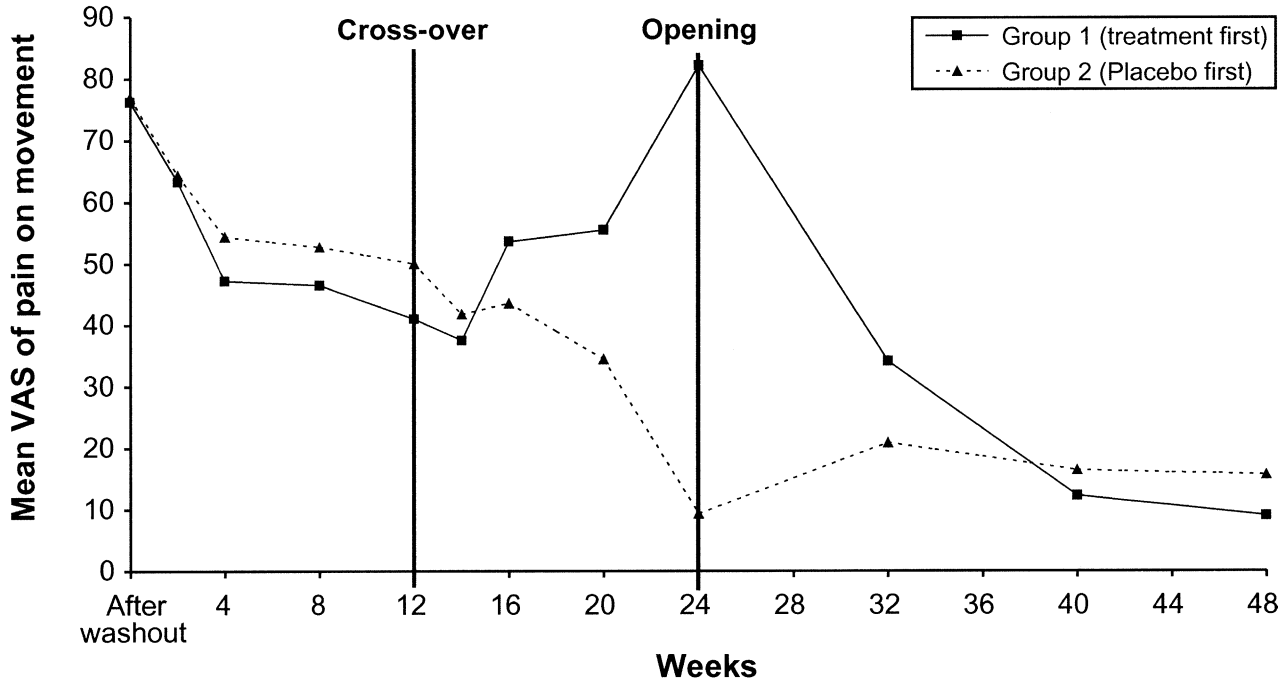

Fig. 1. Comparison of mean VAS of pain on movement in the two treatment groups.

At phase one, knee circumference was reduced in both treatment groups (Fig. 3). In those who were treated with Zintona EC, the mean target knee circumference decreased from 43.25 cm (95% CI: 40.37–46.13) at baseline to 39.36 cm (95% CI: 36.77–41.95) at the 12th week ($P=0.003$), while in those who were treated with placebo, it decreased from 41.27 cm (95% CI: 39.52–43.01) to 38.58 cm (95% CI: 36.71–40.45) at the 12th week ($P<0.001$). However, reduction of knee circumference in the group treated with Zintona EC was greater, though the difference was not statistically significant ($P=0.15$). At phase two (after crossover), the target knee circumference stopped decreasing and even increased in the group that moved from Zintona EC to placebo, while it continued to decrease in the group that moved from placebo to Zintona EC. At phase three, when both groups received Zintona EC, the mean target knee circumference continued to decrease in both groups. Groups 1 and 2 reached a low

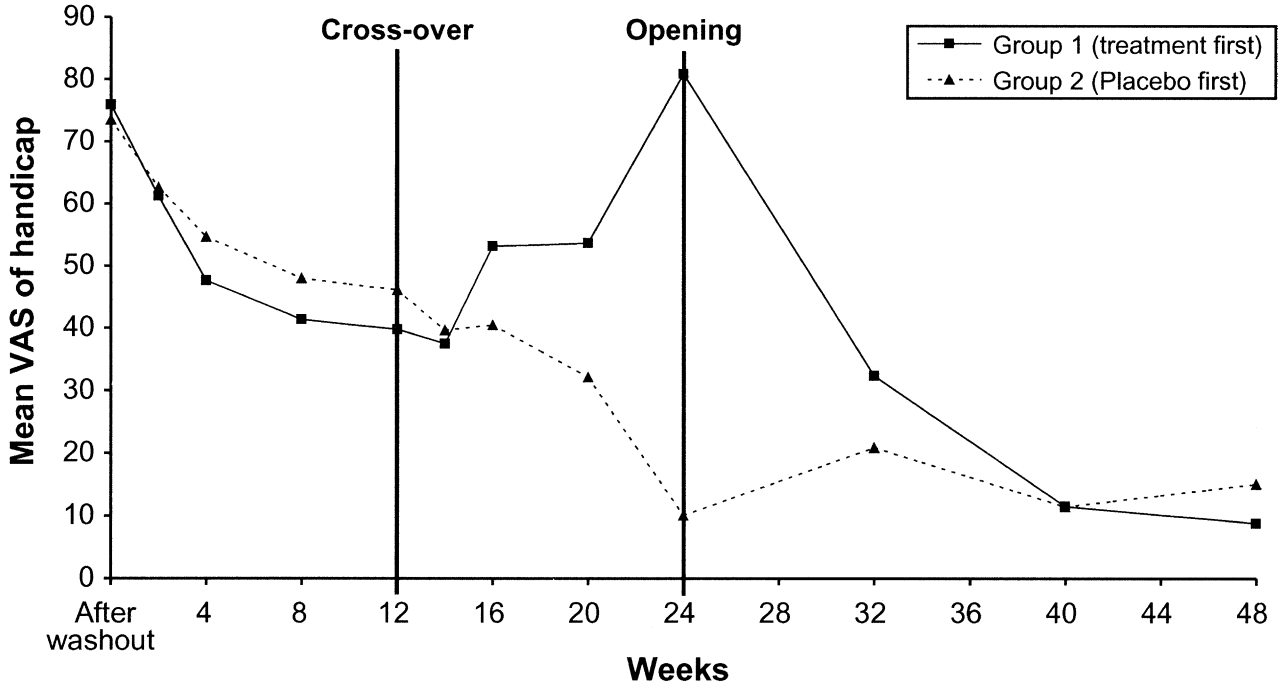

Fig. 2. Comparison of mean VAS of handicap in the two treatment groups.

Table II
Mean VAS of pain on movement and handicap at each visit, according to treatment group

Time	*N*		Mean VAS of pain on movement					Mean VAS of handicap				
	Group 1*	Group 2*	Group 1*		Group 2*			Group 1*		Group 2*		
			Mean	*P*-value†	Mean	*P*-value†	*P*-value‡	Mean	*P*-value†	Mean	*P*-value†	*P*-value‡
–4 days	14	15	70.43	–	76.00	–	0.233	70.21	–	72.13	–	0.691
0 (baseline)	14	15	76.14	–	76.87	–	0.875	75.86	–	73.47	–	0.623
2 weeks	13	15	63.23	0.017	64.27	0.038	0.895	61.15	0.010	62.53	0.087	0.862
4 weeks	12	15	47.17	<0.001	54.33	0.005	0.411	47.58	<0.001	54.60	0.033	0.438
8 weeks	12	15	46.47	0.005	52.67	0.013	0.559	41.33	<0.001	47.93	0.008	0.568
12 weeks (crossover)	11	13	41.00	0.001	50.00	0.001	0.432	39.72	0.001	46.08	0.002	0.566
14 weeks	11	13	37.55	0.001	41.77	<0.001	0.734	37.45	0.001	39.62	<0.001	0.858
16 weeks	11	12	53.55	0.009	43.58	0.005	0.496	53.09	0.011	40.42	0.002	0.377
20 weeks	11	11	55.45	0.061	34.45	0.002	0.133	53.55	0.057	32.09	<0.001	0.113
24 weeks (opening)	10	10	82.10	0.930	9.30	<0.001	<0.001	80.80	1.000	10.00	<0.001	<0.001
32 weeks	10	8	34.10	0.004	20.88	0.001	0.413	32.33	0.003	20.88	0.001	0.468
40 weeks	9	8	12.22	<0.001	16.38	<0.001	0.627	11.44	<0.001	11.38	<0.001	0.992
48 weeks	9	8	9.00	<0.001	15.63	<0.001	0.491	8.78	<0.001	15.00	<0.001	0.515

*Group 1: treatment first (until week 12), then placebo (until week 24). Group 2: placebo first (until week 12), then treatment (until week 24). Both groups received treatment from week 25 through week 48.

† *P*-values for the difference between each visit and the baseline within the same group (paired *t*-test).

‡ *P*-values for the difference between each group mean at the same visit (independent *t*-test).

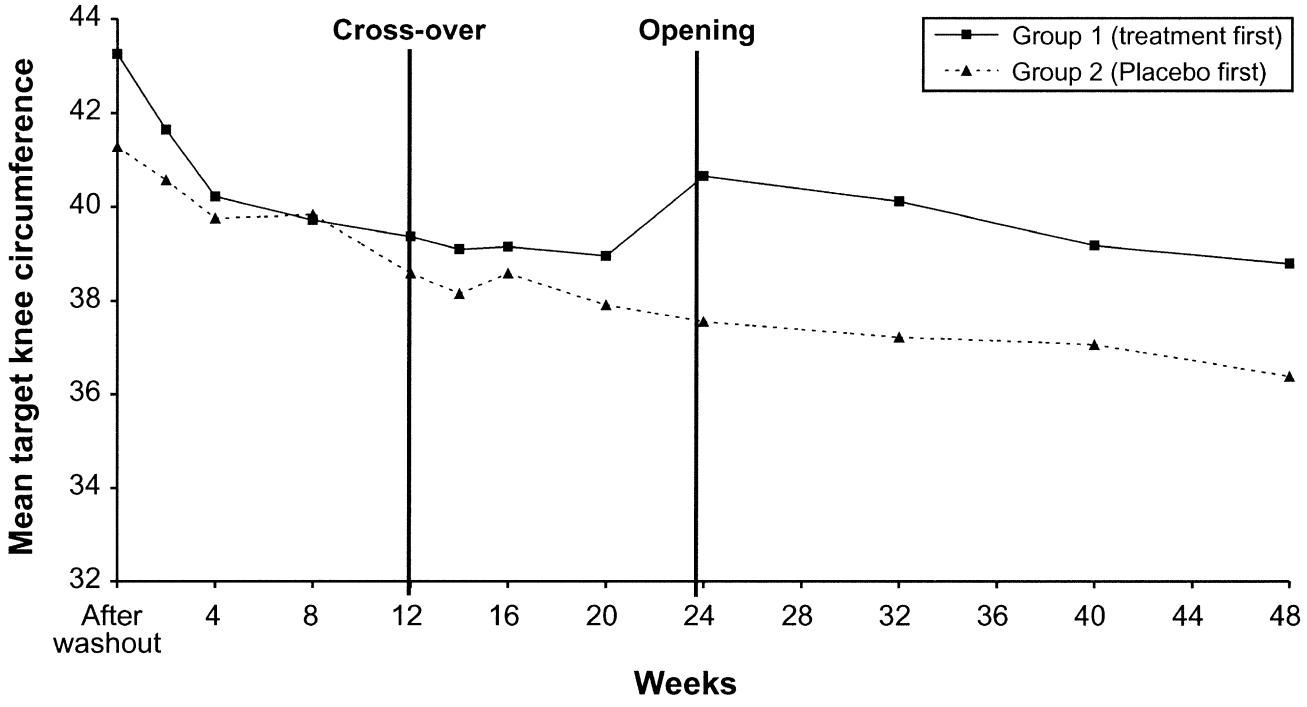

Fig. 3. Comparison of target knee circumference in the two treatment groups.

mean of 38.78 cm (95% CI: 34.84–42.72) and 36.38 cm (95% CI: 32.94–39.81), respectively, which was statistically different from the baseline mean ($P=0.008$ and $P<0.001$, respectively). No statistically significant differences were observed between the groups at this phase ($P=0.971$).

INTENTION TO TREAT ANALYSIS

The proportion of patients who reported more than 30% reduction in pain on movement and handicap was compared between treatment groups. The only statistically significant difference between the groups was found at the 24th week. Ten of the 15 patients in the group which started with placebo and finished with Zintona EC reported treatment success for both parameters as defined above. Only one patient in the other group reported treatment success at the end of the second phase ($P=0.001$).

When comparing the proportion of patients with more than 5% reduction in target knee circumference, no statistically significant difference was observed between the groups.

ADVERSE EVENTS

The only adverse effect was heartburn experienced by two patients: one patient from group 1 who dropped out after 1 week of treatment with Zintona EC and one from group 2 who dropped out in week 48 while on Zintona EC.

INEFFICACY AND DROPOUT

In the first phase, three Zintona EC patients and two placebo patients dropped out. In the second phase, three Zintona patients and one placebo patient dropped out. Altogether six Zintona patients and three placebo patients dropped out before breaking the code. After code breaking, three more patients dropped out of the study.

Discussion

Our data show that Zintona EC as used in the present study was effective in reducing pain on movement, handicap and knee circumference in patients with gonarthritis.

During the first 12 week phase of the study this effect was not statistically different from that of placebo. However, after crossover the difference between the group switched from Zintona EC to placebo and the group switched from placebo to Zintona EC became highly statistically significant at 24 weeks in both VAS of pain on movement and of handicap. The target knee circumference, though significantly lower at 24 weeks in the group switched from placebo to Zintona EC (as compared to baseline), was not significantly different from the group switched from Zintona EC to placebo. During the additional 24 week open study the patients switched from placebo to Zintona EC again showed statistically significant improvement (from baseline) at week 48.

The fact that a statistically significant difference between groups was reached only at week 24 could be explained as follows: In the first phase, no significant difference was observed because of the remarkable placebo effect of different remedies used in OA[10]. In the second phase (after crossover) the groups reached a statistically significant difference only at week 24 because of a delayed effect of Zintona EC and lack of a washout period. In the third phase (after opening), when both groups received Zintona EC, similar results were observed in both groups, as expected.

The higher dropout rate while on Zintona EC could be related to possible side effects. In fact, two of the patients (one in each phase) dropped out due to heartburn. It could

be that the other patients who were lost to follow-up suffered from heartburn or other side effects.

Routine laboratory evaluations, including blood counts, liver tests and creatinine performed on day 0 and weeks 4, 12, 16, 24, 32, 40 and 48, remained within normal limits.

Our observations are in accord with those of Altman and Marcussen[6] and Bliddal *et al.*[11] and support the need for studies of longer duration than those previously published[6,11]. In addition, data provided suggest lack of toxicity of prolonged ginger extract therapy (48 weeks) as evaluated by routine blood counts, liver and renal function tests. However, a sound comparison between results of different studies of ginger extracts is difficult because we do not know the exact nature and dose of the active material in this plant extract. Previous studies have attributed an anti-prostaglandin and anti-inflammatory effect[12,13] as well as an anti-TNFα effect[14] to ginger preparations. The reduction of target knee circumference observed in our study may suggest an anti-inflammatory effect of Zintona EC.

Our study has several limitations. The first is the absence of a washout period at crossover. However, in the group that started with placebo, a washout period is not needed, since these patients did not receive any active medication during the first phase. As for the second group, with the absence of a washout period the effect of the drug (Zintona EC) could continue after moving to placebo. This could explain the fact that the patients in this group continued to improve 2 weeks after starting on placebo and the onset of deterioration was noticed only after 4 weeks (week 16 of the study). We believe that this observation indicates a positive effect of Zintona EC. Since two patients who were on Zintona EC complained of heartburn one can speculate that some after taste or other sensation would result in unblinding. However, the patients who complained of heartburn were removed from the study and the researchers remained blinded to the end of the controlled study at week 24. We believe that all other patients did not identify the drug they received in each phase. Measuring of knee circumference using a tape may not be valid. However, since the investigators were blinded to the treatment module, this measurement method could lead to a non-differential bias. In that case, the size of the difference between the study's arms should be less than the real difference. This could explain the nonsignificant difference between the study groups observed for this parameter. Finally, a higher dropout rate was observed in the patients who were on Zintona EC, as compared to placebo. Six Zintona EC patients and three placebo patients dropped out before opening at week 24. Since we could not compare means because the results concerning those who were lost to follow-up were not available, we performed an intention to treat analysis for success versus failure, referring to those lost to follow-up as treatment failures. This assumption could lead to bias. If some of the patients who were lost to follow-up in the placebo group had treatment success, it could be that the difference between the groups was smaller. On the other hand, if patients in the Zintona EC group (in which most of the dropouts occurred) who were lost to follow-up had treatment success, the difference between groups could be larger.

Herbal medicinals are widely used in the United States and elsewhere[15,16]. Ginger is considered one of the commonly used herbal medicinals[17]. It has been used for vertigo[18], motion sickness[19] and as an antiemetic[20]. Evidence is now provided suggesting that it may have a place in the management of OA of the knee. Official recommendations for the management of knee OA are periodically revised[3–5]. Coated ginger extract may be considered for this purpose in the future.

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