Research Article

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Safety, efficacy and tolerability of a combination micronutrient and polyherbal preparation (*GoutFighter*TM) for gout: a single-arm open-label pilot study

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Abstract

Background: To evaluate the safety, efficacy and tolerability of a combination micronutrient and polyherbal preparation (*GoutFighter*TM) for gout management.

Methods: A single arm, open-label pilot study was conducted at the National Hospital for Traditional Medicine in Vietnam. Participants (n=35 recruited) diagnosed with chronic gout received four tablets of *GoutFighter*TM daily over a 45-day period. Efficacy was assessed by changes in pain, swelling and blood uric acid levels, with concurrent safety and tolerability assessments.

Results: A total of 27 (85.2% male) participants (mean $\pm$ SD age, 54.2 $\pm$ 12.5 years; BMI, 24.2 $\pm$ 3.6 kg/m²) with gout (median [IQR], years since diagnosis 4.0 [3.0–8.0]) completed intervention. In relation to safety, there were no significant changes in vital signs, blood biochemistry or cell counts. In regard to efficacy, the degree of perceived pain and frequency of joint swelling significantly declined after 15 and 30 days of treatment, respectively, and remained so until the end of trial. Mean blood uric acid levels also declined by 25.8 μ mol/L (95% CI, 3.7 to 48.0, p=0.024). Overall, the predominance of participants (96.3%) responded favorably to treatment (p<0.0001) and *GoutFighter*TM was well tolerated, with no serious adverse events.

Conclusion: Clinically relevant doses of *GoutFighter*TM were found to be generally safe, well-tolerated and effective for the short-term, symptomatic relief of chronic gout. *GoutFighter*TM appears to be suitable as an adjunctive treatment in lifestyle programs for gout management, and further investigation in placebo-controlled trials is therefore warranted.

Keywords: complementary medicine; gout; micronutrients; phytochemicals.

Introduction

Gout is a common, chronic inflammatory disease whose burden continues to rise with the increased aging population throughout the world. Globally, gout affects 0.08% of the population [1], with a growing prevalence throughout Western and Southeast Asian countries [2], producing increased healthcare costs and reducing the quality of life in those affected [3]. The onset of gout is preceded by hyperuricemia and the chronic deposition of uric acid crystals in joint tissues, causing recurrent acute flares of inflammation, swelling and pain, as well as functional impairment and disability [4]. Current management is achieved through pharmacotherapy; however, conventional gout-specific medications may be contraindicated in the presence of various comorbidities including diabetes, chronic kidney disease and metabolic syndrome [5]. Consequently, alternative strategies are under ongoing development, many of which have a basis in traditional and complementary paradigms.

A wide range of micronutrients and naturally derived substances have been identified to exert anti-gout and analgesic activities [6–9]. Phytochemicals from the fruit of *Prunus cerasus* (tart cherry) and the seed of *Apium graveolens* (celery), as well as the micronutrients folic acid and potassium citrate appear to mitigate gout pathogenesis

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and/or pathophysiology [10–13], while ascorbic acid has been associated with uricosuric activity when used as a supplement to dietary intake [14]. Additionally, extracts of *Harpagophytum procumbens* (devil's claw) tuber have been reported to elicit anti-inflammatory [15] and analgesic effects [16, 17], which may be beneficial for the management of gout-related pain. Collectively, evidence from traditional medicine practice as well as current research indicates that these candidates may be independently beneficial in the prevention and/or treatment of hyperuricemia and gout [6–8, 11], however there have been no studies to date that have examined them in combination. The present study was therefore performed to evaluate the efficacy, safety and tolerability of a clinically relevant dose of a commercially available preparation that combines these ingredients in a single oral format for the management of gout symptoms.

Materials and methods

Clinical study design

This study was an open-label single-arm pilot trial conducted on outpatients at the National Hospital for Traditional Medicine in Hanoi, Vietnam, throughout 2017 and 2018. The study protocol was approved by the National Hospital for Traditional Medicine institutional review board and conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and local regulatory requirements. The study consisted of a 45-day implementation with *GoutFighter™* as a stand-alone oral medicine, with three 15-day follow-ups from baseline (Figure 1). The primary objective was to evaluate the safety of *GoutFighter™* in patients with moderate to severe gout. Secondary objectives concerned the efficacy of the investigational material for its potential effects on pain management and uric acid levels as well as its tolerability.

Patients

Adult patients (age ≥ 18 years) were eligible to be included if they had a history of chronic gout, and which was indicated at the time of screening at the physician's discretion. Symptoms were assessed according to the Vietnam Ministry of Health practice guidelines for the treatment of rheumatic diseases [18] which are based on criteria outlined by Bennet and Wood [19], and more recently the ILAR and OMERACT criteria [20]. These included evidence of chronic gout with or without a flare (defined as a sudden onset of severe pain, swelling) and hyperuricemia (defined as male: $>420 \mu\text{mol/L}$; female: $>360 \mu\text{mol/L}$), or pain related to chronic gout (defined as pain plus hyperuricemia), with or without inclusion of tophus crystals in one or more affected joints, as determined radiographically. Participants were excluded if they were already taking other forms of gout medication or suffered from other acute arthritic disorders or chronic inflammatory disease. Participation in the study was voluntary and outpatients were

permitted to withdraw at any time if they did not wish to continue. During screening, prospective participants were counselled on the mechanisms of action, usage and possible side effects of the interventional material in relation to their condition, before providing informed consent.

Treatment

Following inclusion and baseline clinical assessment, patients were allocated without blinding a total of four tablets of investigational material per day, consumed orally (2 after each of breakfast and lunch). Each tablet of *GoutFighter™* (Max Biocare Pty Ltd, Melbourne, Australia, manufactured under TGA-licensed pharmaceutical conditions, AUST-L No 295855) contained the following active ingredients: *P. cerasus* fruit extract (100 mg; extract ratio 25:1); *A. graveolens* seed extract (300 mg; extract ratio 10:1); *H. procumbens* tuber extract (150 mg, extract ratio 3.8:1, standardized to 2% harpagosides); potassium citrate (50 mg); ascorbic acid (50 mg) and folic acid (90 μg). Botanical concentrates were pharmaceutical grade hydroalcoholic extracts manufactured for oral use and compliant with British and US pharmacopoeia standards. Patients were allocated rescue analgesics as per investigator discretion and automatically withdrawn from the study in the event that adequate pain relief was not readily achieved during the treatment.

Efficacy, safety and tolerability

Patients rated the intensity of pain in affected joint(s) according to a simplified, 4-point visual analog scale (VAS, 0 = none, 1 = mild, 2 = moderate, 3 = severe). The percentage of participants with

Figure 1: Study design (A) and CONSORT flowchart (B) of the single-arm, open-label clinical trial examining the safety, efficacy and tolerability of *GoutFighter™* on patients diagnosed with gout. VAS, visual analog pain scale.

swelling, redness and warmth were also recorded as either present or absent. Additionally, using the same scale, patients rated the intensity of pain in specific joints, including index (metatarsophalangeal or metacarpophalangeal) joints, and/or ankle, knee or elbow, as well as their heel; ratings were recorded at baseline (day 0) and follow-up days 15, 30 and 45. The primary efficacy endpoint was the change in global visual analogue scale (VAS) pain intensity across these time points. At day 45, the investigators further evaluated the global efficacy of treatment based on a single assessment rating that combined the degree of blood uric acid decline with the alleviation of clinical symptoms. Major responders to treatment were defined as those showing a reduction of blood uric acid of $>120 \mu\text{mol/L}$ and complete dissipation of pain and swelling (in those with accompanying symptoms); moderate responders were defined as those showing a reduction of blood uric acid of 60 to $120 \mu\text{mol/L}$ and complete dissipation of pain and swelling (in those with accompanying symptoms); mild responders were defined as those showing a reduction of blood uric acid of $<60 \mu\text{mol/L}$ and/or the complete dissipation of pain and swelling; while non-responders were defined as those that showing no reduction in blood uric acid, pain or swelling. Safety was assessed throughout the study duration by monitoring of vital signs and clinical laboratory investigations (hematology, clinical chemistry). Tolerability was assessed by the frequency of adverse events (e. g. vomiting, nausea, constipation, itching, dizziness, headache and insomnia) throughout the treatment period by day 45.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 16.0 and figures were constructed using GraphPad Prism version 8. Checking of the data was performed to identify missing values, outliers ($\leq Q1 - 3 \times \text{IQR}$ or $\geq Q3 + 3 \times \text{IQR}$, where $\text{IQR} = Q3 - Q1$) or non-normally distributed data (Shapiro-Wilk test). There were no missing values. Non-parametric tests were used if the data were not normally distributed or contained outliers. For hematological bio-markers (with continuous characteristics), differences between baseline and day 45 were tested through the use of paired t-tests or non-parametric sign tests. For hematological biomarkers measured on dichotomous scales, McNemar's test was used. To test for differences in vital signs between baseline, day 30 and day 45, Friedman's test was used with Bonferroni's post hoc for multiple comparisons. Differences in Likert scores between timepoints were also tested using Friedman's test. To assess the global efficacy of treatment, a one sample chi-square goodness-of-fit test was conducted to determine if the proportion of participants responding to treatment was the same as those who did not respond. To assess the percent of patients with clinical evidence of joint swelling across timepoints, Cochran's Q test was used with prior confirmation of both assumptions of sample size adequacy, and post hoc testing using Dunn's procedure with Bonferroni's correction for multiple comparisons. All comparisons were considered biologically significant at a two-tailed p-Value of 0.05 or less and all post hoc p-Values presented are following Bonferroni adjustment. All variables are presented as mean $\pm$ SD for parametric analysis and median (IQR, 25th–75th percentile) for non-parametric analysis unless stated. All data points were used in all analyses, we did not transform any data, and no data points were removed (n=27).

Table 1: Baseline characteristics of study participants completing trial (n=27)^a.

Variable	Value
General Characteristics	
Age (y)	54.2 $\pm$ 12.5
Gender	
Male	23 (85.2)
Female	4 (14.8)
BMI (kg/m^2)	24.2 $\pm$ 3.6
Risk factors for gout	
High protein diet	16 (59.2)
High alcohol intake	14 (51.9)
BMI $> 23 \text{ kg/m}^2$	14 (51.9)
Family history of gout	4 (14.8)
Co-existing conditions	
Diabetes	1 (3.7)
Hypertension	10 (37.0)
Gout characteristics	
Duration since diagnosis (y)	4.0 (3.0–8.0)
Category	
1–5 years	17 (63.0)
6–10 years	6 (22.2)
11–15 years	2 (7.4)
>16 years	2 (7.4)
Patients with flare on enrolment	8 (29.6)
Joint features, participants with:	
No pain	5 (18.5)
Pain in one joint	15 (55.5)
Pain in $\geq$ two joints	7 (25.9)
Swelling	8 (29.6)
Tophus particles	2 (7.4)
Articular bone damage	8 (29.6)

^aData presented as mean $\pm$ SD, n (%) or median (IQR, 25th–75th percentile).

Results

Of the 35 participants enrolled, five voluntarily withdrew within ~2 to 3 days of starting intervention in preference of being prescribed conventional analgesics, while another three were withdrawn by the trial physician due to unrelated co-morbidity complications, leaving 27 participants who completed the trial (summarised in Figure 1). The treatment group that completed the trial was predominately male (85.2%), with a majority of subjects >50 years old (63.0%), with chronic gout for >3 years (63.0%). Most participants had lifestyle risk factors for gout, with many existing cardiovascular co-morbidities (Table 1). Just under a third of participants (29.6%) who completed the trial were experiencing a gout flare at the time of enrolment, whose onset had occurred within the previous ~2 days. About half (51.9%) had pain associated with chronic gout at the time of enrolment while 18.5% showed a history of chronic gout.

Safety and tolerability

In relation to safety, there were no significant differences in vital signs, serum biochemistry or blood cell counts between day 0 and day 45 of treatment (Table 2). In particular, there were no significant differences in pro-inflammatory markers or liver enzyme levels. *GoutFighter*[™] consumption was associated with minimal adverse events, none of which was serious, including constipation in three of the 27 treated participants (11%) (Table 3).

Efficacy

In regard to primary efficacy outcomes, throughout treatment there was a reduction in global VAS pain, $\chi^2 [3] = 59.4$, $p \leq 0.0001$, as well as in the percentage of participants experiencing swollen joints, $\chi^2 [3] = 19.0$, $p \leq 0.0001$ (Figure 2). VAS pain began to decline in the first 2 weeks, reaching zero by day 15 follow-up, to remain at this level

until the end of treatment, with post hoc pair-wise comparisons revealing significance between baseline (median [IQR], 2 [0–3]) and each of day 15 (0 [0–2], $p = 0.0003$), day 30 and day 45 (both 0 [0–0], $p < 0.0001$) VAS pain values (Figure 2A). Post hoc pair-wise comparison of the percentage of participants experiencing swollen joints showed a trend toward a decline between baseline (29.6%) and day 15 (11%, $p = 0.111$), which achieved significance by days 30 and 45 (0%, $p = 0.001$) (Figure 2B). Sub-analysis was conducted on pain detected in six different joints and of these, participants reported reduced pain in their metatarsophalangeal joint $\chi^2 [3] = 32.4$, $p \leq 0.0001$, ankles $\chi^2 [3] = 18.2$, $p \leq 0.0001$, knees $\chi^2 [3] = 21.9$, $p \leq 0.0001$, heels $\chi^2 [3] = 13.6$, $p = 0.003$, metacarpophalangeal joint $\chi^2 [3] = 9.0$, $p = 0.029$ and elbows $\chi^2 [3] = 9.0$, $p = 0.029$. We also evaluated whether the total number of joints with pain decreased between baseline and day 45 and found there was a statistically significant difference throughout, $\chi^2 [3] = 47.1$, $p < 0.0001$. Post hoc analysis revealed the total number of joints with pain had declined from a median of 1 (range,

Table 2: Safety assessment of *Goutfighter*[™] on vital signs and hematological characteristics after 45 days of treatment in those with diagnosed gout^a.

Variable	Time-points			P ^b
	Baseline	Day 30	Day 45	
Vital signs				
Heart rate (beat/ min)	78 (75–80)	78 (77–78)	77 (76–78)	0.351
Temperature (°C)	36.5 (36.5–36.6)	36.5 (36.4–36.8)	36.5 (36.4–36.7)	0.723
Blood pressure				
Systolic (mmHg)	120 (115–120)	125 (115–125)	120 (115–120)	0.289
Diastolic (mmHg)	80 (70–80)	80 (70–85)	75 (75–80)	0.903
Hematology				
WBC (G/L)	7.2 (6.2–8.1)		7.5 (6.1–8.6)	0.230 [†]
RBC (T/L)	5.0 ± 0.6		4.9 ± 0.5	0.537
PLT (G/L)	261.3 ± 62.7		270.9 ± 71.1	0.238
Urea (mmol/L)	6.4 (5.3–7.1)		5.6 (4.9–6.3)	0.078
Glucose (mmol/L)	5.6 ± 0.8		5.7 ± 0.8	0.579
Creatinine (μmol/L)	94.7 ± 18.3		90.7 ± 19.3	0.078
AST (U/L)	30.0 (24.0–38.0)		27 (23.0–33.0)	0.152 [†]
ALT (U/L)	54.0 (42.0–62.0)		46.0 (42.0–52.0)	0.230 [†]
CRP-positive (n (%))	2 (16.7)		1 (13.3)	0.999 [†]
Triglycerides (mmol/L)	2.2 (1.8–3.2)		2.1 (1.2–2.5)	0.556
Cholesterol (mmol/L)	5.1 ± 0.9		5.1 ± 1.1	0.637
HDL (mmol/L)	1.1 ± 0.3		1.2 ± 0.3	0.219
LDL (mmol/L)	3.0 ± 0.6		2.8 ± 0.8	0.189
ESR _{1-hr} (Mm/h)	7.0 (3.0–9.0)		6.0 (3.0–9.0)	0.064 [†]
ESR _{2-hr} (Mm/h)	25.0 (6.0–40.0)		20.0 (7.0–30.0)	0.286 [†]

^aData presented as mean ± SD or median (IQR, 25th–75th percentile) for parametric and non-parametric analysis respectively unless stated. WBC, white blood cell; RBC, red blood cells; PLT, platelet; AST, aspartateaminotransferase; ALT, alanine aminotransferase; HDL, high density lipoprotein; LDL, low density lipoprotein; ESR, erythrocyte sedimentation rate where sub-script pertains to the rate in the first and second hours.

^bDifference between time points assessed using Friedman's test, paired t-test, sign test or McNemar's test where applicable. $p \leq 0.05$ two tailed was considered significant and exact p-Values[†] are given where appropriate. All data was used in all analyses and no data points were removed (n=27).

Figure 2: Efficacy of *Goutfighter™* on perceived (median [range]) joint pain (visual analog scale of pain, VAS) (A) and percent of patients with clinical evidence of joint swelling (B) after 45 days of supplementation in subjects diagnosed with gout. Differences assessed using Friedman's test (panel A) and Cochran's Q test (panel B), both with Bonferroni's post hoc corrected p-values presented. **exact $p < 0.001$, *** $p < 0.0001$. All data was used in all analyses and no data points were removed ($n = 27$).

0 to 6) to 0 (0, 6) by day 15 ($p < 0.0001$) and remained so throughout treatment until day 45 ($p < 0.0001$). The mean $\pm$ SD of blood uric acid levels also declined between baseline ($489.0 \pm 79.9 \mu\text{mol/L}$) and day 45 follow-up assessment ($463.1 \pm 78.0 \mu\text{mol/L}$) with a statistically significant reduction of 25.8 (95% CI, 3.7 to 48.0) $\mu\text{mol/L}$ [t [26] = 2.402, $p = 0.024$, $d = 0.462$] (Figure 3A). Based on this and the alleviation of clinical symptoms, an assessment of the global efficacy of treatment showed that of the 27 participants who completed the study, 96.3% responded to treatment ($\chi^2[1] = 23.148$, $p < 0.0001$) (Figure 3B).

Discussion

The use of complementary and alternative medicines for the management of gout is becoming increasingly prevalent [21]. Several studies have investigated the efficacy of traditional Chinese medicines [22], Western herbal

therapies [7], nutraceuticals and dietary strategies [6] for the prevention and/or treatment of hyperuricemia and/or gout. Our study is the first clinical trial to assess the therapeutic suitability of *GoutFighter™* for the treatment of chronic gout in a Vietnamese cohort. The unique combination formula of micronutrients and botanical extracts was selected for their reported gout-protective and analgesic effects throughout traditional medicine practice and medical research [6–8, 11]. *Goutfighter™* was found to be generally safe and effective for the amelioration of joint pain and swelling, with concomitant improvement in serum uric acid levels and no change in vital signs or blood biochemistry.

In our cohort, *GoutFighter™* was well tolerated and displayed a good safety profile, with only low-level gastrointestinal events. The assessment of safety is important because some botanical substances used in complimentary therapies are known to induce adverse reactions (e.g. allergies) or toxicity (e.g. liver reactions) with variable frequency and severity [23]. In this trial, there were no changes in vital signs, hematological characteristics or liver enzymes (AST and ALT), indicating an absence of liver toxicity. This latter observation is of particular significance, given the active ingredients in *GoutFighter™* can act specifically on liver xanthine oxidase. Treatment also showed no evidence of an inflammatory reaction, as indicated by stable ESR and CRP levels. In addition, no evidence of intolerance reactions such as vomiting, nausea, or other feelings of malaise occurred. The three cases of constipation are difficult to explain, however gastrointestinal complaints for botanical ingredients are amongst the most commonly reported side effects [24]. In addition,

Table 3: Summary of adverse events throughout the intervention period with *Goutfighter™* ($n = 27$)^a.

Variable	Value
Adverse events [n (%)]	
Vomiting	0 (0)
Nausea	0 (0)
Constipation	3 (11.1)
Itching	0 (0)
Dizziness	0 (0)
Headache	0 (0)
Insomnia	0 (0)

^aData presented as n (%).

Figure 3: Efficacy of *Goutfighter*™ on plasma (mean $\pm$ SD) uric acid with individual patient changes shown (A) and global efficacy of treatment (B) after 45 days of supplementation in subjects diagnosed with gout. Differences assessed using paired t-test (panel A) and one sample chi-square goodness-of-fit (unequal) test (panel B), * $p < 0.05$, *** $p < 0.0001$. All data was used in all analyses and no data points were removed ($n = 27$).

limited mobility in some subjects owing to their condition, or dietary intake and age-related factors could all be confounders in these cases.

Following treatment with *GoutFighter*™, pain and swelling in all participants generally declined within 15 days and was sustained until trial completion. Our findings are in agreement with other human trials that have reported on the analgesic and anti-inflammatory effects of the individual bioactive ingredients in *GoutFighter*™. Specifically, a review of double-blind, placebo controlled, randomized trials ($n = 4$ studies with 285 participants) reported significant reductions in pain across most trials (measured using a variety of VAS and Likert scales) following treatment with devil's claw extract in patients with rheumatic diseases [17]. The biological activity of devil's claw is generally ascribed to its phytochemical content of iridoid glycosides, such as harpagoside, of which *GoutFighter*™ contains a standardized concentration. The phytochemical derivatives from devil's claw tuber appear to elicit anti-inflammatory effects by inhibiting nuclear factor-kappa B, activator protein 1, tumor necrosis factor- α , interleukin-6, interleukin-1 β and prostaglandin E2 pathways [15], as well as analgesic action via cyclooxygenase-2 (COX-2) modulation [25], which is the major target of paracetamol and NSAIDs. Other ingredients in *GoutFighter*™ have also shown anti-inflammatory activity *in vivo* and may have further contributed to the observed

reductions in pain and swelling. Specifically, tart cherries contain high concentrations of phenolics and anthocyanins, whose catabolites are reported to interact with COX-1 and COX-2 to attenuate pain and swelling [26]. Across human clinical trials intervening with tart cherry products for a variety of conditions, significant declines in pain (as measured by VAS and WOMAC scores) have been observed [27], however responses tend to be variable [28]. Moreover, vitamin C supplementation has shown analgesic properties in some clinical conditions, potentially mediating this effect through antioxidant and anti-inflammatory mechanisms [29]. Collectively, these three bioactives in *GoutFighter*™ may produce an additive and/or synergistic effect, to interact with multiple inflammatory pathways to reduce pain and swelling in gout.

We observed a significant reduction of blood uric acid, which is the main diagnostic and pathophysiological hallmark of gout. Our findings are encouraging and compare favorably with existing literature reporting on the effects of several ingredients used in *GoutFighter*™. For example, in a meta-analysis of thirteen ($n = 556$) randomized trials, ascorbic acid was reported to decreased blood uric acid concentration (pooled effect size $-20.8 \mu\text{mol/L}$, $p = 0.032$) [14]. The effect of vitamin C on plasma uric acid is thought to occur through the modulation of uric acid transporter 1 and the Na^+ -dependent anion cotransporters, which increase its excretion [14]. Urine

alkalization also facilitates uric acid excretion and thus interventions with alkali salts promote uricosuric effects [30]. Potassium-citrate is one such type of alkali salt, whose citrate portion is known to promote uric acid excretion and may have also contributed to the decline in uric acid observed in this study [13]. Moreover, in acute feeding studies, both Jacob et al. and Bell et al. reported that the consumption of cherry products significantly decreased serum urate by 31 $\mu\text{mol/L}$ ($p < 0.05$) and 178 $\mu\text{mol/L}$ ($p < 0.001$) at 5 and 8 h post-dose respectively [31, 32]. Jacob et al. intervened with a 280 g bowl of cherries, while Bell et al. administered a 60 ml shot of cherry juice concentrate, reportedly equivalent to 180 whole cherries, which may explain the differences in effect sizes. Other ingredients in *GoutFighter*TM have also been found to lower plasma uric acid in humans. In a study of 15,364 hypertensive patients randomly assigned to Enalapril with or without folic acid, after 4.4 years of treatment, the difference between each group in plasma uric acid was $-4.0 \mu\text{mol/L}$ (95% CI: -6.5 to $-1.6 \mu\text{mol/L}$, $p = 0.001$) in favor of the folic acid combination, indicating folate treatment effectively attenuated uric acid accumulation [11]. Moreover, in a survey of herbalist practices, celery seed extracts were found to be the most commonly prescribed natural product for the treatment of gout due to its reputed uric acid lowering effects [7]. While clinical trials are lacking, celery seed has been reported to effectively lower uric acid in rodent models [12]. The aforementioned products of tart cherry, folic acid and celery seed have all been shown to inhibit xanthine oxidase and/or xanthine dehydrogenase activity, which impedes production of uric acid from purines, which may explain their effect on uric acid status [10, 12, 33]. Collectively, the ingredients provided in *GoutFighter*TM are likely to limit the opportunity for uric acid to accumulate and condense into urate crystals and deposits within the peripheral joints.

The limitations of the present study include possible measurement error relating to the use of visual scales and a modest sample size. The use of an open-label single arm design also makes it difficult to determine whether any treatment effect is greater than placebo. Despite this, the time dependent declines in pain, swelling and uric acid levels suggest that *GoutFighter*TM alone induces clinically relevant effects in the absence of conflicting effects from other medications or lifestyle treatments. Although the change in uric acid may appear modest, it is in-line with other intervention studies of diet and lifestyle change such as weight loss. For example, in an intervention study of the Dietary Approach to Stopping Hypertension (DASH study), serum uric acid decreased by 29.7 $\mu\text{mol/L}$ from baseline after 30 and 90 days ($p = 0.07$ and 0.06 respectively) of treatment [34], while a low purine diet was reported to decrease plasma

uric acid by 59 $\mu\text{mol/L}$ to 118 $\mu\text{mol/L}$ [9]. At the same time, the MRFIT weight reduction RCT [35], found that declines in weight of $\leq 4.9 \text{ kg}$ ($n = 2,866$), five to 9.9 ($n = 1,334$) and $\geq 10 \text{ kg}$ ($n = 412$) were accompanied by a reduction of serum urate levels by 7, 19 and 37 $\mu\text{mol/L}$ respectively. Collectively, this suggests that the combined ingredients of *GoutFighter*TM might mitigate gout pathophysiology as efficaciously as other non-pharmacological approaches, suggesting that *GoutFighter*TM may be useful as an adjunctive treatment in comprehensive lifestyle management programs. While the use of *GoutFighter*TM in this study is isolated to efficacy in Vietnamese gout sufferers, which would be valuable for Vietnamese and possibly Eastern Asian practitioners, further studies on western ethnicities would need to be performed to assess its broader applicability.

In conclusion, the combination of tart cherry fruit, celery seed, devil's claw tuber, potassium, ascorbic acid and folic acid in *GoutFighter*TM was found to reduce participant pain, swelling and plasma uric acid status and was safe and well tolerated. These results suggest that *GoutFighter*TM is effective for the short-term, symptomatic relief of moderate to severe gout, potentially making it suitable as an adjunct treatment to lifestyle interventions and warrants further investigation in larger, placebo controlled, long-term clinical trials.

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Competing interests: MaxBiocare Pty. Ltd. is a company engaged in micronutrient and phytochemical research and complementary medicine related commercial activities.

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