TANG HUMANITAS MEDICINE

Brief Communication

Paulinia cupana (Guaraná) for the treatment of cancer related fatigue in patients undergoing radiation therapy or chemotherapy: a meta-analysis of three clinical trials

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ABSTRACT

For cancer patients undergoing radiation therapy (RT) or systemic chemotherapy (CHT), cancer-related fatigue (CRF) is a common problem that can negatively impact their quality of life. Guarana (*Paullinia cupana*) is a plant native to the Amazon basin that has been used as a stimulant since pre-Columbian times. PURPOSE: To evaluate the effectiveness of guarana extract on fatigue in BC patients undergoing either CHT or RT. A total of 137 cancer patients (85% with Breast Cancer) undergoing either CHT (101) or RT (36) were randomized to receive either a placebo or guarana. In all 3 studies, the guarana was given as an unmanipulated dry extract at a dose of 75 mg PO QD in the first two studies or 50 mg PO BID in the third study. Patients were crossed over to the other experimental arm, and we evaluated fatigue with the Chalder Scale in all three studies. Guarana significantly improved the The Chalder Scale Global Scores (- 0.85; 95% CI:-1.31 to - 0.40; p = 0.0002); Physical Fatigue Scores (- 0.44; 95% CI: - 0.74 to - 0.13; p = 0.005) and Mental Fatigue Scores (- 0.93; 95% CI: - 1.14 to - 0.72; p < 0.00001). Guarana did not produce any CTCAE grades 3 or 4 toxicities in any of the studies. Guarana is an effective, cheap and non-toxic alternative for the treatment of fatigue in cancer patients undergoing treatment.

Keywords *Paulinia cupana*, radiation therapy, chemotherapy

INTRODUCTION

Fatigue is a common and very distressing symptom for cancer patients (Cheville et al., 2009; Madden et al., 2006). Cancer Related Fatigue (CRF) can be defined as an unusual, persistent, and subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning (Madden et al., 2006). CRF can affect 70% to 80% of cancer patients depending on the type of treatment, study design, patient population, and the evaluation instrument employed (Cheville et al., 2009). CRF pathophysiology is poorly understood (Wang et al., 2008) and its pharmacologic treatment is so far unsatisfactory (Minton et al., 2008). In fact, a recent meta-analysis (Minton et al., 2008) reported that methylphenidate and erythropoietin seem to offer some benefit to fatigued cancer patients, but the thrombogenic and potential tumor stimulatory activities of Erythropoietin (Bohlius et al., 2009) and the toxicities related to methylphenidate limit their wider application to cancer patients.

Guarana (paullinia cupana) is a plant native to the Amazon basin. Roasted seed extracts have been used in medicinal beverages since pre-Columbian times as stimulants, aphrodisiacs, and tonics (Smith et al., 2007). Interestingly, guarana at doses of 75 mg daily demonstrated favorable effects on memory and cognition in a small, randomized placebo-controlled trial (Haskel et al., 2007). We conducted 3 previous studies (da Costa. et al., 2008; da Costa et al., 2009; de Oliveira Campos MP. et al., 2011) in patients with cancer aiming at evaluating guarana's effects in CRF and we report here a metaanalysis of these 3 studies.

MATERIALS AND METHODS

We have conducted to date 3 studies to evaluate guarana´s effects compared to a placebo for the treatment of Cancer Related Fatigue in patients with solid tumors undergoing either chemotherapy or radiation therapy. To our knowledge, there are no other studies addressing fatigue in this population of cancer patients treated with guarana, so this meta-analysis includes all the published studies in this subject. The first study contained 26 patients with several types of solid tumors (16% with Breast Cancer) undergoing chemotherapy; whereas the second and third studies included only non-metastatic breast cancer patients who received adjuvant radiation therapy and chemotherapy, respectively. In all 3 studies, patients were randomized to receive either the placebo or guarana followed by a cross over to the other experimental arm. Patients were crossed over to the other experimental arm after one cycle of treatment in the first study, in the middle of radiation therapy in the second study and after 21 days of treatment followed by a 7 days washout period in the third study. Guarana was given as an unmanipulated dry extract at a dose of 75 mg by mouth once daily in the first two studies or 50 mg by mouth twice daily in the third study (Table1).

The guarana standardized dried extract from Paullinia cupana was acquired from Cathedral Pharmaceutical Industry (NovaPampulha, Vespasiano, Minas Gerais, Brasil).Cornstarch was used as an excipient.

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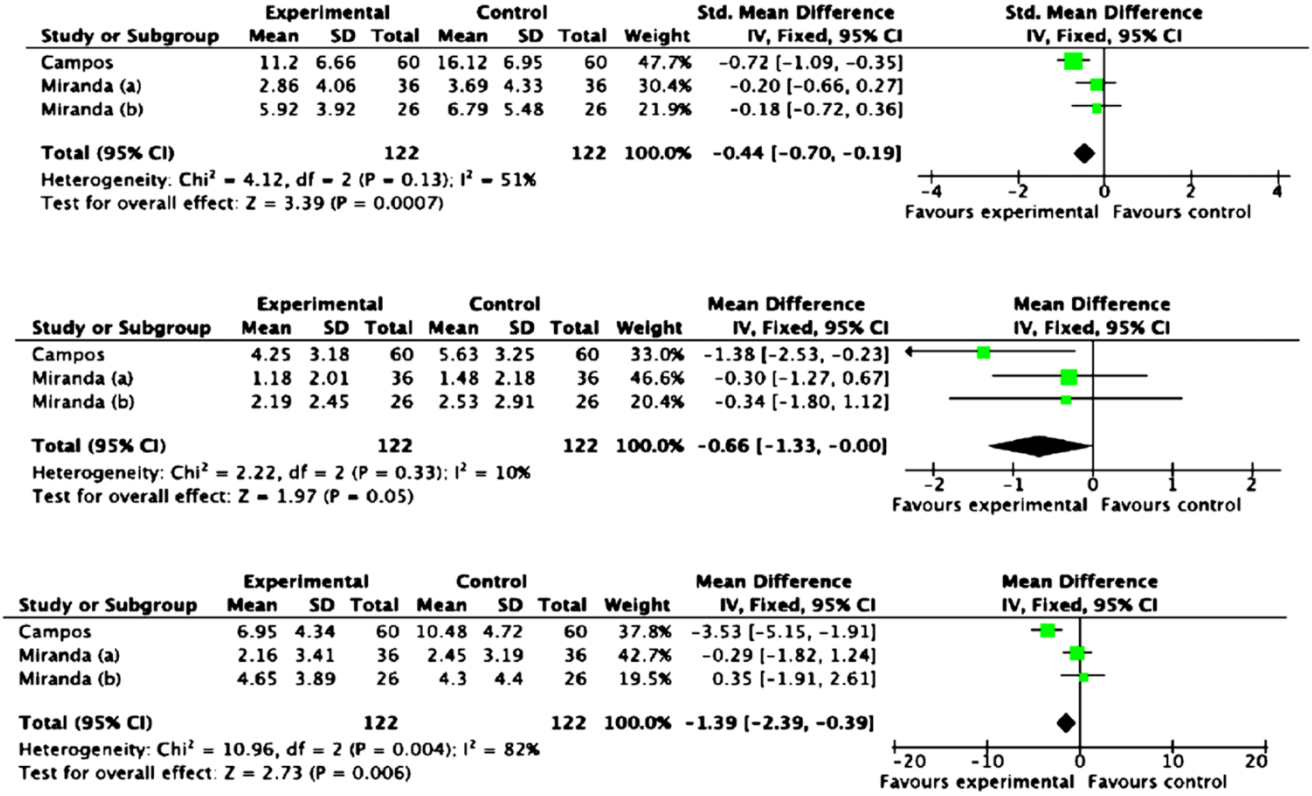

Fig. 1. Adjusted risk ratios of fatigue for patients using guarana (experimental arm) compared with placebo (control). Global scores are presented in the upper forest plot, mental scores in the middle and physical Chalder Scale scores in the lower forest plot.

All three studies employed the Chalder Scale which was already validated in Portuguese. The Chalder Fatigue Scale is a self-rated measure of fatigue severity for both physical and mental symptoms that is scored in a Likert format with response options ranging from better than usual to much worse than usual, with a total score of 26. To identify physical or mental fatigue, the patient must score at least 8 or 5, respectively, and the presence of both high scores is considered "global fatigue" (Cho et al., 2007; Morriss et al., 1998).

The overall effects for each trial represent the aggregate of all patients treated with guarana whenever that happened (first or second phase of the study) in relation to those treated with the placebo whenever that happened (first or second phase of the study) (Elbourne et al., 2002). We computed a pooled estimate of the RRs of the individual studies using a fixed

Table 1. General characteristics of the studies

Study	Number of Participants (Mean Global Chalder Scores at entry ± SE)	Study Design	Oncologic Treatment/Guaraná dose	Patient's Tumour Types	Questionnaires
de Oliveira Campos MP	75 (11.82 ± 0.96)	Phase II RDBPCC	Chemotherapy Guarana, 50 mg/twice a day (21 days)	Breast	CFS BFI FACIT-F FACIT-ES PSQI HADS CTCAE
Miranda VC	36 (4.29 ± 0.76)	Phase II RDBPCC	Radiotherapy Guarana, 75 mg/day (21 days)	Breast	CFS BDI BFI
Miranda VCb	26 (8.46 ± 1.2)	Phase II RDBPCC	Chemotherapy Guarana, 75 mg/day (21 days)	Solid Tumors (Breast 16%)	CFS BDI BFI

RDBPCC: Randomized, double-blind, placebo-controlled crossover trial; CFS: Chalder fatigue scale; BFI: Brief fatigue inventory; FACIT-F: Functional assessment of chronic illness therapy-fatigue; FACIT-ES: FACIT for endocryne symptoms; PSQI: Pittsburgh sleep quality index; HADS: Hospital anxiety and depression scale; CTCAE: Common terminology criteria for adverse events; BDI: Beck depression inventory; SE: Standard Error.

effect model according to Mantel and Haenszel and graphically represented these results using forest plot graphs (Fig. 1). The homogeneity assumption was checked by a $\chi 2$ test with a df equal to the number of analyzed studies minus 1. We employed for all metaanalysis calculations the Review Manager software (http://www.cc-ims.net/revman).

RESULTS

These 3 studies in aggregate contained 137 patients with histologically diagnosed breast cancer undergoing either chemotherapy (26) or radiation therapy (36) in two studies not required to have baseline fatigue at entry and patients (75) with fatigue after their first cycle of chemotherapy in a third study.

Guarana significantly improved the Chalder Scale Global Scores (- 0.85; 95% CI: - 1.31 to - 0.40; $p = 0.0002$); Physical Fatigue Scores (- 0.44; 95% CI: - 0.74 to -0.13; $p = 0.005$) and Mental Fatigue Scores (- 0.93; 95% CI: - 1.14 to - 0.72; $p < 0.00001$) (Fig. 1). There was no statistically significant heterogeneity noted in all Chalder Scale Dominion scores' analysis (global, physical and mental).

Guarana did not produce any CTCAE grades 3 or 4 toxicities in any of these three studies and did not worsen sleep quality or cause anxiety or depression in the third one in which the HADS and Pittsburg Sleep Inventory Scales were employed.

DISCUSSION

Pharmacologic and non-pharmacologic treatments have all been proposed to treat CRF such as exercise, erythropoietin, methylphenidate (Minton et al., 2008), and acupuncture. However, the results of such therapies are modest at best. In fact, regarding methylphenidate, a well-conducted double-blind randomized study of methylphenidate versus a placebo produced negative results (Bruera et al., 2006). Furthermore, recent concerns voiced regarding the potential tumor stimulatory proprieties of erythropoietin (Bohlius et al., 2009) also limit the use of this drug.

This metaanalysis shows that in 137 patients, mostly with early breast cancer undergoing either radiation or chemotherapy, guarana was effective for CRF in comparison with the placebo. We were unable to identify any significant fatigue improvement with guarana (da Costa Miranda et al., 2008; da Costa Miranda et al., 2009) in the first two studies. Possible reasons are that in these two studies we included patients prior to starting radiation or chemotherapy, regardless of the presence of baseline fatigue. In fact, as can be seen in Table 1, the Chalder Global Scores at entry were higher for the patients included in the third study as compared to the first two. Furthermore, the dose of guarana used in the first two studies was lower than the one used in the third study (75 mg given once daily versus 50 mg twice daily) (de Oliveira Campos MP. et al., 2011). In addition to a 33% dose increase in Guarana's dose, 50 mg twice daily may have allowed for a more even distribution of its effects throughout the day. The small sample size of those two first studies (Table 1) also may have precluded the finding of a clinically significant effect.

Guaraná seeds contain 4-8% caffeine, as well as trace amounts of theophylline and theobromine together with large quantities of alkaloids, terpenes, tannins, flavonoids, starch, saponins, and resinous substances. The xanthine alkaloids (caffeine, theophylline, theobromine) are believed to contribute significantly to guaraná's psychostimulant activities in clinical studies (Taylor et al., 2005). Even though guarana's caffeine content is large relative to other plants such as coffee, black tea and mate, the amount of caffeine present in the dosages of 75 to 100 mg used in the studies included in this meta-analysis may be insufficient to explain the anti-fatigue activity of this plant. It is possible that other activities of guarana yet unknown may be responsible for its anti-fatigue effects that we observed clinically in patients with cancer.

Here we showed that using a meta-analytic approach we were able to observe a significant and consistent improvement in all the Chalder Fatigue Scale dominions (global, mental and physical fatigue) with guarana when compared to a placebo when we analyzed all 3 studies in aggregate. Furthermore, no clinically significant side effects were seen in any of the 3 studies included in this meta-analysis. We thus conclude that guarana is an effective, cheap and non-toxic alternative for the treatment of fatigue in cancer patients undergoing treatment.

CONFLICT OF INTEREST

The authors do not have any conflict of interest in the present study.

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