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ScienceDirect
Journal of Ethnopharmacology 110 (2007) 305–310
Journal of ETHNO-PHARMACOLOGY
www.elsevier.com/locate/jethpharm

# Effect of a *Psidii guajavae folium* extract in the treatment of primary dysmenorrhea: A randomized clinical trial

Svetlana Vladislavovna Doubova[a], Hortensia Reyes Morales[a], Sergio Flores Hernández[b,*], María del Carmen Martínez-García[c], Marcela González de Cossío Ortiz[d], Marco A. Chávez Soto[e], Erika Rivera Arce[e], Xavier Lozoya[e]

[a] *Epidemiology and Health Services Research Unit "Centro Medico Nacional Siglo XXI", Mexican Institute of Social Security (IMSS), Mexico*
[b] *Coordination of Health Research, Mexican Institute of Social Security (IMSS), Mexico*
[c] *Pediatric Hospital, "Centro Medico Nacional Siglo XXI", Mexican Institute of Social Security (IMSS), Mexico*
[d] *Research and Human Development, Medical Center of National Autonomous University of Mexico (UNAM), Mexico*
[e] *Phyto-drugs Technology Research and Development Laboratory, Mexican Institute of Social Security (IMSS), Mexico*

Received 17 May 2006; received in revised form 15 September 2006; accepted 22 September 2006
Available online 13 October 2006

**Abstract**

*Objective:* To assess the efficacy of two different doses of a *Psidii guajavae folium* extract in the management of primary dysmenorrhea.
*Methodology:* A double-blinded randomized clinical trial was conducted in 197 women with primary dysmenorrhea. Four intervention groups were defined: two extract doses (3 and 6 mg/day); ibuprofen (1200 mg/day); placebo (3 mg/day). Participants were followed-up individually for 4 months. The main outcome variable was abdominal pain intensity measured according to a visual analogue scale (VAS).
*Results:* The average age of participants was 19 years; menarche occurred around age 12 years. Participants had menstrual cycles of 28 or 29 days, with menstruation lasting 5 days and mean of pain intensity of 8.2 on the VAS. During each successive treatment cycle, participants experienced a lower pain intensity score. Multiple regression analysis, after adjusting each cycle for baseline pain, treatment compliance and other variables, showed that the group receiving 6 mg/day extract had significantly reduced pain intensity ($p < 0.001$). This effect was maintained in cycles 2 and 3, although the reduction in the mean of pain intensity was lower. The group receiving the 3 mg/day extract did not show a consistent effect throughout the three cycles.
*Conclusion:* At a dose of 6 mg/day, the standardized phyto-drug (*Psidii guajavae folium* extract) reduced menstrual pain significantly compared with conventional treatment and placebo.


*Keywords:* *Psidii guajavae folium*; Primary dysmenorrhea; Phytodrug

## 1. Introduction

Primary dysmenorrhea is one of the most frequent gynecological disorders in young women. In Mexico, the prevalence of dysmenorrhea is 52.1% for women younger than 15 years of age, 63.8% for the group between 15 and 19 years, and 52.3% for women of 20–24 years and it is similar to other countries (Klein and Litt, 1981; Pedrón-Nuevo et al., 1998). The menstrual pain of women with this condition occurs in the absence of any identifiable pelvic lesion and is due to intrinsic factors of the uterus. Women with primary dysmenorrhea have been found to produce higher levels of prostaglandins (PGF2-alpha) in the endometrium, which increases the uterus tone and causes exaggerated contractility by stimulating the adrenergic smooth muscle receptors (Speroff et al., 1999).

It has been estimated that more than 50% of post-menarche women have primary dysmenorrhea, with 10% experiencing severe pain intensity that disables them for 1–3 days per month (Bergsjo, 1979; Dawood, 1983). Automated medical examinations of 13,000 women in high school and 7500 first year university students in years 2002, 2003 and 2004 at the National Autonomous University of Mexico (UNAM) found that 23%

* Corresponding author. Instituto Mexicano del Seguro Social, Centro Médico Nacional Siglo XXI, Coordinación de Investigación en Salud, Av. Cuauhtémoc 330, Col. Doctores, CP06725 México D.F., México.
Tel.: +52 55 562 76900x21230.
*E-mail address:* sfloresh@cis.gob.mx (S.F. Hernández).

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doi:10.1016/j.jep.2006.09.033

and 27.3% of women in these groups reported dysmenorrhea. At present, conventional treatment for the management of this problem has been the administration of non-steroidal anti-inflammatory agents during the painful stages of the menstrual cycle (Dawood, 1988; Marjoribanks et al., 2005).

The use of a water infusion prepared with the leaves of the plant species *Psidium guajava* L. (Myrtaceae) as a popular therapeutic resource for the relief of some menstrual disorders that come with abdominal cramps and discomfort has been documented since ancient times both in Mexico and in other countries (Mahabir, 1995). In Mexican Traditional Medicine the existence of abdominal pain in women if frequently associated with a "cold state of the uterus", a condition that is recognized as previous to the arrival of another, the "hot state" of this organ recognized by the appearance of menstrual blooding. 'Cold condition' is also associated with diarrhea, intestinal discomfort, the presence of cramps and abdominal distention (Aguilar et al., 1994; Argueta et al., 1994; Oblitas, 1992; Castañeda, 1995; Lozoya, 1999). The guava leaf infusion is classified as a "hot remedy" useful and safe for the treatment of both mentioned conditions, however, in the past only the gastro-intestinal properties attributed to this herbal remedy had been explored by experimental scientific studies.

The abundant scientific research on the gastro-intestinal beneficial properties of products manufactured with this plant-based drug, *Psidii guajavae folium* described in the literature, have consecutively shown that the extracts possess: antimicrobial, anti-diarrheal, antispasmodic, anti-inflammatory, anti-oxidant and neuro-sedative actions, according to the modern evolution in the understanding of pathophysiological conditions that characterize intestinal motility disorders (Lutterodt, 1989; Lozoya et al., 2005; Morales and Lozoya, 1994; Morales et al., 1994; Meckes et al., 1996). The therapeutic properties of the phyto-drug are mainly attributed to the presence in the guava leaf extracts of five quercetin-derived flavonols that act as calcium antagonists at the intestinal smooth muscle and as anti-oxidants. Some terpenoids present in the extract, have been described to have an antispasmodic effect on other smooth muscle and to inhibit inflammation through the prostaglandin-synthesis enzymatic system. In the stomach, quercetin glucosides are hydrolyzed due to acid pH; quercetin is being able to be freed and absorbed up to 50%, its toxicity practically null (Graefe et al., 1999; Crespy et al., 1999).

Recently, the intestinal analgesic–antispasmodic property of the extract has been clinically demonstrated. The efficacy of the guava leaf extract was found in China in the treatment of infantile retroviral acute diarrhea (Wei et al., 2000). Ambulatory adult patients with acute diarrheic syndrome (ADS) were successfully treated in Mexico with a standardized guava leaf extract at a dose of 3 mg/day, showing the efficacy of this product (Lozoya et al., 2002).

The combined antispasmodic, anti-inflammatory and analgesic effects described for this plant extract support the clinical efficacy observed in the treatment of gastro-intestinal disorders. However, their therapeutic analgesic–antispasmodic efficacy at other smooth muscle sites as in the case of dysmenorrheal syndrome has not been clinically explored.

Due to the epidemiological importance of primary dysmenorrhea and the need for a safe, widely accepted agent, we assessed the therapeutic efficacy of two doses of a *Psidii guajavae folium*-based extract for the symptomatic management of this disorder and compared it with placebo and ibuprofen, a non-steroidal anti-inflammatory analgesic commonly used for the treatment of primary dysmenorrhea. Additionally, we explored the dose–response effect by duplicating the guava leaf extract dose of 3 mg/day, based on the assumption of only 50% of absorption.

## 2. Methodology

We randomly selected 220 of the 2758 female students at the UNAM who had been subjected to an automated medical examination and who reported dysmenorrhea. All subjects were aged between 17 and 25 years; had regular menstrual cycles; primary dysmenorrhea, defined as regular pain since the first menstrual period (menarche) during at least 1 day of the menstruation, with no medical history of other gynecological diseases; moderate to severe pain intensity, varying from 5.0 to 10.0 on the visual analogue scale (VAS) (Murphy et al., 1988); an absence of hormonal treatment; oral contraceptives or intrauterine devices.

Previous informed consent subjects were randomly assigned to one of four treatment groups. Groups 1 and 2 subjects received one or two capsules, respectively, of *Psidii guajavae folium* extract with standardized flavonol content (1 mg of active ingredient in 300 mg of extract) administered q 8 h (3 and 6 mg/day); Group 3 subjects received one capsule of placebo q 8 h (300 mg/day starch); Group 4 subjects received one 400 mg capsule of ibuprofen q 8 h (1200 mg/day). All treatments were for 5 days, beginning 24 h before menstruation, for three consecutive menstrual cycles.

The outcome variable was intensity of pain measured by a 0.0–10.0 VAS, where 0 was pain-free and 10 was severe pain. Co-variables were age at menarche, duration of bleeding and menstrual cycle, active sexual life, exercising during menstruation, current intake of alcoholic beverages, smoking and symptomatic medication during menstruation. Age, gynecological history and regular exercising habits were registered as general variables.

The phyto-drug, ibuprofen and placebo were manufactured, standardized and packaged at Phyto-drugs Technology Research and Development Laboratory of the Mexican Institute of Social Security. The manufacturing of the phyto-drug, including the use of dry leaves of *Psidium guajava* L., has been authenticated and corroborated with regards to its chemical and morphological features; quality control methods were applied throughout, and chemical content was standardized during the ethanolic extract process and its pharmaceutical formulation. All vials of medication (extract, placebo or ibuprofen) were identical and labeled with codes, which were known only to the investigators who manufactured the products.

Subjects were monitored through four menstrual cycles, one at baseline and three during treatment (five medical consultations in total, including enrollment). Subjects were interviewed at each consultation, variables of interest were recorded and the corresponding supply of drugs was provided. The first consul-

tation was with a physician and nurse previously trained and specifically devoted to the trial, and written informed consent was obtained at this time.

During the first month, each participant kept a diary to record baseline menstrual cycle conditions. Three times per day, each subject recorded the intensity and duration of menstrual pain, the drugs taken and the exercises practiced. After this first month, during the second consultation, each participant was randomly assigned to one of the treatment groups, through a table of codes that was *ex profeso* designed with random numbers. The diary was replaced, and a third consultation was scheduled for the following month. Compliance with treatment and with visits was ensured through reminder phone calls, performed by a nurse a day prior to each expected menstrual period. If a subject did not keep an appointment, follow up was carried out via phone calls to give a new appointment. For the purpose of this study, compliance was defined as the ingestion of at least 80% of the total amount of drug prescribed for the corresponding cycles.

### 2.1. Sample size

The sample size was estimated through a formula for a continuous outcome measures (Meinert, 1986) that assumed that the difference in the reduction in the mean of pain intensity between groups was 2.0 VAS scores (the reduction in the mean of pain intensity for ibuprofen was 5.0 VAS scores (Pedrón et al., 1998) and for phyto-drug was 3.0 VAS scores (Lozoya et al., 2002)), with $\alpha = 0.05$ (one side) and the power of 80%. The number of participants by group, allowing for 20% lost participants, was 53.

### 2.2. Statistical analysis

Proportions, central trend measurements and dispersion according to the distribution of each variable were obtained. The Mann–Whitney *U*-test was used for continuous variables and the Chi-square test or Fisher exact test for categorical variables.

Since the study assessed baseline pain intensity for 5 days and for three subsequent menstrual cycles, we performed an analysis for each cycle. One-way ANOVA was used to compare the mean of pain intensity in the treatment groups. In addition, to control potential confounding or effect modification variables, multiple regression analysis was performed for each cycle, by comparing the analgesic effect of each treatment *versus* placebo adjusted for the intensity of pain reported during the baseline cycle, therapeutic compliance, age at menarche, having sexual activity, and alcohol consumption habits. Due to the fact that compliance with medication regimes may affect the outcome variable, interaction between therapeutic compliance and the type of treatment per menstrual cycle was also assessed. The method used for the modeling was the *backward* method through the Stata 8.0 special version statistical program.

## 3. Results

Of the 197 women with primary dysmenorrhea who met the inclusion criteria, 52 were treated with 3 mg/day extract, 57 with 6 mg/day extract, 42 with placebo, and 46 with 1200 mg/day ibuprofen. All 197 female students were single and their average age was 19 years. Their first menstrual period occurred around age 12 years and they reported a 5-day average menstrual duration with menstrual cycles every 28 or 29 days. Most reported a family history of dysmenorrhea and a history of analgesics use for alleviation of menstrual pain. Most exercised on a regular basis and a low percentage reported smoking at the time of study and occasional drinking of alcoholic beverages (Table 1). During the study, 12 participants taking 3 mg/day extract (23.1%), 19 taking 6 mg/day extract (33.4%), 11 tak-

Table 1
General characteristics and gynecological history

| Characteristics | Phyto-drug: 3 mg/day, $n = 52$ (mean ± S.D.[a]) | Phyto-drug: 6 mg/day, $n = 57$ (mean ± S.D.) | Placebo: 3 mg/day, $n = 42$ (mean ± S.D.) | Ibuprofen: 1200 mg/day, $n = 46$ (mean ± S.D.) |
|---|---|---|---|---|
| Age (years) | 19.6 ± 2.0 | 19.4 ± 1.7 | 19.5 ± 1.9 | 19.9 ± 2.2 |
| Gynecological history | | | | |
| Age at menarche (years) | 11.9 ± 1.6 | 12.1 ± 1.2 | 11.7 ± 1.4 | 12.1 ± 1.6 |
| Menstruation (days) | 4.9 ± 1.0 | 5.5 ± 1.4 | 5.4 ± 1.3 | 5.4 ± 1.4 |
| Menstrual cycle (days) | 29.2 ± 1.9 | 28.9 ± 1.5 | 28.7 ± 1.8 | 29.0 ± 1.9 |
| Age at first dysmenorrhea (years) | 13.5 ± 2.1 | 13.9 ± 2.6 | 13.2 ± 3.5 | 14.1 ± 3.1 |
| Intensity of menstrual pain | 8.2 ± 1.4 | 8.4 ± 1.3 | 8.4 ± 1.4 | 8.2 ± 1.7 |
| Characteristics | Phyto-drug: 3 mg/day, $n = 52$ ($n$, %) | Phyto-drug: 6 mg/day, $n = 57$ ($n$, %) | Placebo: 3 mg/day, $n = 42$ ($n$, %) | Ibuprofen: 1200 mg/day, $n = 46$ ($n$, %) |
| Family history of dysmenorrhea | 39 (75.0) | 44 (77.2) | 30 (71.4) | 27 (58.7) |
| Having sexual activity | 26 (50.0) | 24 (42.1) | 20 (47.6) | 18 (39.1) |
| Analgesic use during menstruation | 39 (75.0) | 44 (77.2) | 32 (76.2) | 39 (84.8) |
| Habits | | | | |
| Exercise during menstruation | 21 (40.4) | 23 (40.4) | 18 (42.9) | 19 (41.3) |
| Actual smoking | 8 (15.4) | 13 (22.8) | 6 (14.3) | 9 (19.6) |
| Alcohol consumption[b] | 9 (17.3) | 22 (38.6) | 7 (16.7) | 11 (23.9) |

[a] S.D.: standard deviation.
[b] $p < 0.05$.

Table 2
Comparison of means for menstrual pain intensity during the first two days of each menstrual cycle, by group

| Menstrual cycle | Phyto-drug: 3 mg/day, $n=52$ (mean ± S.D.[a]) | Phyto-drug: 6 mg/day, $n=57$ (mean ± S.D.) | Placebo: 3 mg/day, $n=42$ (mean ± S.D.) | Ibuprofen: 1200 mg/day, $n=46$ (mean ± S.D.) |
|---|---|---|---|---|
| Baseline cycle | 5.37 ± 2.12 | 5.59 ± 2.28 | 4.75 ± 1.91 | 4.83 ± 2.43 |
| Cycle 1[b] | 4.31 ± 2.42 | 5.13 ± 2.23 | 4.13 ± 1.96 | 3.55 ± 2.19 |
| Cycle 2[b] | 3.73 ± 2.31 | 4.30 ± 2.43 | 3.32 ± 1.96 | 3.00 ± 1.94 |
| Cycle 3 | 3.39 ± 2.18 | 4.31 ± 2.50 | 3.18 ± 2.08 | 3.22 ± 2.05 |

[a] S.D.: standard deviation.
[b] $p<0.05$ between phyto-drug 6 mg/day and ibuprofen (one-way ANOVA, and Bonferroni test).

Table 3
Analgesic effect of each treatment compared with placebo during menstrual cycle 1 (final model)

| | Coefficient | 95% confidence intervals | $p$ |
|---|---|---|---|
| Phyto-drug (3 mg/day) | −0.19 | −0.58, 0.19 | 0.32 |
| Phyto-drug (6 mg/day) | 2.04 | 1.45, 2.64 | 0.00 |
| Ibuprofen | −0.85 | −1.23, −0.45 | 0.00 |
| Intensity of pain reported during the baseline cycle | 0.42 | 0.34, 0.49 | 0.00 |
| Treatment compliance | 0.77 | 0.33, 1.21 | 0.00 |
| Treatment x compliance in phyto-drug (6 mg/day group)[a] | −1.81 | −2.49, −1.13 | 0.00 |
| Age at menarche | 0.19 | 0.10, 0.29 | 0.00 |
| Having sexual activity | −0.41 | −0.68, −0.13 | 0.00 |
| Exercise during menstruation | −0.29 | −0.60, 0.001 | 0.051 |
| Alcohol consumption | 0.72 | 0.39, 1.04 | 0.00 |

Multiple regression analysis.
[a] Interaction term including compliance and treatment at 6 mg/day phyto-drug group.

ing placebo (26.2%) and 12 taking ibuprofen (26%) abandoned the study. In all cases, the reason cited for abandonment was lack of time. No statistically significant differences in demographic characteristics, gynecological history and characteristics of dysmenorrhea were observed between students who abandoned the study and those who completed it. In all groups the compliance with treatment was good; ibuprofen compliance varied from 91.9 to 97.1%, phyto-drug 3 mg was 80.0–85.7%, phyto-drug 6 mg was 72.0–92.0% and placebo was 74.0–97.0%. Table 2 shows the comparison of means for menstrual pain intensity during the first 2 days of each menstrual cycle, by group; the four groups had similar means of pain intensity at baseline. During cycles 1 and 2, however, a significant difference was observed between the groups that received 6 mg/day extract and ibuprofen. In each treatment group, there was a reduction in the mean of pain intensity between baseline and cycle 3.

Table 3 presents the results of the multiple regression model for cycle 1. After adjusting for other variables associated with the effect from extract and/or intensity of pain (baseline pain, treatment compliance, age at menarche, sexual activity, exercise during menstruation and alcohol consumption habits), we found that women exhibited at least 80% of the total amount of phyto-drug 6 mg/day prescribed for the corresponding cycle showed the significantly major reduction in the intensity of pain (interaction term including compliance and treatment at 6 mg/day phyto-drug group) (−1.81, $p<0.001$). This effect was maintained in cycles 2 and 3, although the reduction in the mean of pain intensity was less (Tables 4 and 5). In contrast, a consistent effect was not observed in subjects receiving 3 mg/day extract throughout the three cycles.

With regard to probable adverse events, one subject taking 3 mg/day extract, two taking 6 mg/day extract and two taking

Table 4
Analgesic effect of each treatment compared with placebo during menstrual cycle 2 (final model)

| | Coefficient | 95% confidence intervals | $p$ |
|---|---|---|---|
| Phyto-drug (3 mg/day) | 1.01 | 0.18, 1.83 | 0.02 |
| Phyto-drug (6 mg/day) | 1.28 | 0.18, 2.37 | 0.02 |
| Ibuprofen | −0.51 | −0.93, −0.09 | 0.02 |
| Intensity of pain reported during the baseline cycle | 0.53 | 0.46, 0.59 | 0.00 |
| Treatment compliance | 0.43 | 0.01, 0.84 | 0.04 |
| Treatment x compliance in phyto-drug (3 mg/day group)[a] | −1.06 | −1.95, −0.16 | 0.02 |
| Treatment x compliance in phyto-drug (6 mg/day group)[b] | −0.99 | −2.11, 0.13 | 0.08 |
| Age at menarche | 0.34 | 0. 23, 0.44 | 0.00 |
| Exercise during menstruation | 0.45 | 0.12, 0.77 | 0.00 |

Multiple regression analysis.
[a] Interaction term including compliance and treatment at 3 mg/day phyto-drug group.
[b] Interaction term including compliance and treatment at 6 mg/day phyto-drug group.

Table 5
Analgesic effect of each treatment compared with placebo during menstrual cycle 3 (final model)

| | Coefficient | 95% confidence intervals | *p* |
|---|---|---|---|
| Phyto-drug (3 mg/day) | −0.16 | −0.65, 0.31 | 0.49 |
| Phyto-drug (6 mg/day) | 1.75 | 0.89, 2.61 | 0.00 |
| Ibuprofen | −0.15 | −0.63, 0.33 | 0.54 |
| Intensity of pain reported during the baseline cycle | 0.53 | 0.46, 0.60 | 0.00 |
| Treatment compliance | −0.51 | −0.94, −0.08 | 0.02 |
| Treatment x compliance in phyto-drug (6 mg/day group)[a] | −0.93 | −1.77, −0.09 | 0.03 |
| Age at menarche | 0.36 | 0.27, 0.45 | 0.00 |
| Alcohol consumption | 1.14 | 0.74, 1.52 | 0.00 |

Multiple regression analysis.
[a] Interaction term including compliance and treatment at 6 mg/day phyto-drug group.

ibuprofen reported abdominal pain and/or nausea. In all cases, however, these effects were mild and transitory, and there was no need to modify the treatment regimen.

## 4. Discussion and conclusions

This study is the first clinical trial on the efficacy of a chemically standardized extract from *Psidii guajavae folium* in the treatment of dysmenorrhea. Although all four intervention groups showed a decreased intensity of menstrual pain during each treatment cycle compared with baseline, the difference was not statistically significant. This finding could be explained by a perceived placebo effect that has been recognized previously (Ernst and Resch, 1995; Hrobjartsson and Gotzsche, 2006).

The analgesic–antispasmodic effect of the extract *versus* placebo was stronger in women with therapeutic compliance, and it was consistent throughout the three cycles. Since the extract has been previously reported to have a clinical effect only on intestinal smooth muscle fibers (Lozoya et al., 2002; Wei et al., 2000), our findings suggest that this extract has a broader clinical effect than this antispasmodic action. Therefore, this extract could be recommended as a therapeutic alternative to non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, in the treatment of dysmenorrhea.

Although NSAIDs are effective in treating dysmenorrhea (Chan et al., 1979; Dawood, 1999; Morrison et al., 1980; Murphy et al., 1988), a result corroborated in this study, about 30% of women with primary dysmenorrhea would rather not take these drugs, due to the absence of therapeutic response or intolerance to gastro-intestinal adverse events (Campbell and McGrath, 1997). About half of the women in this study had a history of NSAID use to combat menstrual pain, with the remaining subjects not using any type of medication, despite moderate to severe dysmenorrhea, justifying the search for other regimens that may have a higher acceptability rate.

A potential advantage of this extract may arise from the different mechanism of action of its active ingredient from that of NSAIDs. Women with primary dysmenorrhea have increased levels of prostaglandins in the endometrium and in menstrual blood. NSAIDs suppress menstrual pain by inhibiting prostaglandin synthesis by cyclo-oxygenases 1 and 2; however, this mechanism is responsible for the adverse effects of these drugs (Dawood, 1981). In contrast, the flavonols in the extract act primarily as antispasmodic agents, while also having anti-oxidant and anti-inflammatory properties, whereas other components in this extract have sedative and analgesic effects. At this time, however, the compound(s) or mechanism(s) of action involved in the ability of the extract to relieve menstrual pain are not known. Its therapeutic activity in the treatment of menstrual pain in patients with dysmenorrhea suggests that its analgesic effects may involve the anti-oxidant and anti-inflammatory actions of *Psidii guajavae folium* flavonols derived from quercetin and morin (Camuesco et al., 2004; Delporte et al., 2005; Guardia et al., 2001; Kim et al., 2005; Theoharides et al., 2001).

In conclusion, we have shown here that the phyto-drug, at a dose of 6 mg/day, can be used therapeutically to reduce menstrual pain in women with primary dysmenorrhea.

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