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Original Article

# Randomized controlled trial of *Panax ginseng* in patients with irritable bowel syndrome

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ABSTRACT

The irritable bowel syndrome is defined as the presence of continuing or recurrent abdominal pain and it is associated with altered bowel habit. Experimental studies with *Panax ginseng* C.A. Mey., Araliaceae, have demonstrated the antinociceptive action on calcium and sodium channels, as well as on primary sensory neurons. A clinical double-blind, randomized, prospective and experimental trial was conducted for sixty days, comparing the action of dry extract of *P. ginseng* (300 mg/day) with trimebutine (600 mg/day). Patients were assessed at four visits for abdominal pain, using the Likert scale, and adverse events. Twenty-four patients completed the study, being 87.5% female and mean age of 47.41 years. There was improvement in abdominal pain, through Likert scale values, in patients who used *P. ginseng*. This group started from a median basal of −5 to 2.5, 3 and 5 in the 1st, 4th and 8th weeks of treatment, respectively, with a statistically significant difference. Similar results were achieved in those patients who used trimebutine. The only adverse effect observed was the occurrence of headache in two patients (16.66%) in the group that used the herbal. The research suggests that *P. ginseng* was effective in the control of abdominal pain in irritable bowel syndrome patients, analogous to trimebutin, and may be used in future studies for a better evaluation of the obtained results.



## Introduction

Irritable bowel syndrome (IBS) is a functional chronic and relapsing disorder of the gastrointestinal tract, clinically characterized by abdominal pain associated with defecation or abnormalities of bowel habit (constipation and/or diarrhea), in the absence of demonstrable organic or biochemical alteration (Lacy et al., 2016). Although the denomination suggests limited alterations to the intestines, the symptomatic manifestations can come from the entire digestive tract (Dalrymple and Bullock, 2008).

This nosological entity affects about 10–15% of the population of the western countries and it is considered one of the most prevalent gastrointestinal conditions. It affects mainly the female sex between the third and fifth decades of life (Valenzuela et al., 2004; Hammerle and Surawicz, 2008). IBS is considered a multifactorial disorder with a heterogeneous and complex pathophysiological process. Genetic, environmental and psychosocial factors increase the risk of developing this condition. The resulting pathogenic mechanisms are variable and they include visceral hypersensitivity, dysregulation in the bowel-brain axis, dysbiosis, food intolerance, increased intestinal permeability, immune activation in the intestinal mucosa and gastrointestinal motility disorders (Chey et al., 2015; Lacy et al., 2016).

The difficulty of finding an effective therapy with traditional medicine guides IBS patients to seek complementary medicine as a treatment possibility, estimating that 50% of them migrate to this line (Birtwhistle, 2009).

Phytotherapy emerges as one of the most known and widespread modalities, considering that approximately 80% of the population of developing countries use herbs for health problems (Guo et al., 2007; Chang and Lu, 2009).

*Panax ginseng* C.A. Mey., Araliaceae, is one of the most well-known Oriental herbs. The available commercial product is a light yellow powder with a characteristic odor from which capsules or

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tablets are made (Auricchio et al., 2007; Braga et al., 2010). This herbal medicine has ginsenosides (approximately 38 types have been identified) or triterpenoid saponins as main active components (Rhim et al., 2002; Leung et al., 2007; Choi, 2008).

Different beneficial activities are attributed to *P. ginseng* as a therapeutic alternative to improve physical, psychomotor and cognitive performance, enhancing vitality through its anti-inflammatory and antioxidant action. There is also an improvement in the cardiovascular, immunological, endocrine, reproductive and nervous systems and, in some reports, a reduction in the risk of certain types of tumors is observed (Voces et al., 2004; Radad et al., 2006).

It is a well-tolerated compound with mild and reversible adverse effects from the use suspension (Kiefer and Pantuso, 2003). However, so far, there have been no studies in the literature that correlate it with the IBS treatment.

Thus, the establishment of these premises led to the development of a clinical study on the action of *P. ginseng* concerning the therapeutic approach of patients with IBS. This aimed to expanding the treatment alternatives for this group of patients.

## Materials and methods

This piece of research was characterized as a double-blind, randomized, prospective and experimental study, with intervention in the conduction of the disease. The patients were seen at the Gastroenterology outpatient clinic of the Lauro Wanderley University Hospital of the Federal University of Paraíba, located in the municipality of João Pessoa, Paraíba, Brazil.

The sample was carried out between November 2010 and September 2013. It consisted initially of 40 patients, but only 26 remained in the research due to the inclusion and exclusion criteria. All participants signed the informed consent form.

The established inclusion criteria were: diagnosis of irritable bowel syndrome (IBS), according to the criteria defined by the Rome III Consensus; must be over 18 years of age; do not present cognitive deficit; and fit the normal laboratory standards. To be included in the research, patients using analgesics, opioids, anti-inflammatory drugs or sleep inducers had to discontinue such medications for a minimum of three weeks before starting the study.

The exclusion criteria consisted of patients with the following disorders: inflammatory bowel disease (IBD), colon cancer, intestinal mal absorption, celiac disease, lactose intolerance, thyroid dysfunction, gastroenteric neuroendocrine tumors, intestinal parasitic diseases, long-course intestinal bacterial infections, arterial hypertension and acute bronchial asthma; those who had used tricyclic antidepressants in the last three months, as well as those using warfarin and pregnant women; individuals who are hypersensitive to ginseng or its components, with hemorrhage, schizophrenia and hormonal treatments; and those who used steroids or antipsychotic drugs, since they are contraindicated for concomitant use with ginseng.

The clinical trial was developed following the regulating guidelines and norms of research involving human beings contained in the Resolutions number 196/96 and number 251/97 of the National Health Council of the Ministry of Health. The project was submitted to the Research Ethics Committee of the Lauro Wanderley University Hospital of the Federal University of Paraíba, being approved in session held on May 25$^{th}$, 2010, under protocol number 287/10.

Patients were randomly selected and divided into two groups, by draw, with a ratio of 1:1; and they were given the identically encapsulated medicines: trimebutine (600 mg/day) and *P. ginseng* at a dose of 300 mg/day (standardized to 26.66% ginsenosides), in double-blind test, separated in hermetically sealed white bottles and after label removal. The control and delivery of the bottles were performed by the secretary of the Gastroenterology Outpatient Clinic of the Lauro Wanderley University Hospital and they were handed to the selected patients at the beginning of the study and after completing thirty days of treatment. Each patient remained in the study for 60 days. They were instructed to take the medication in three daily doses, thirty min before the main meals.

During the study, the use of dipyrone (500 mg up to 4 times a day) was allowed only on those days when more severe abdominal pain occurred; consequently, the researcher should be informed about it. A hypolipidemic as well as a short-chain low-carbohydrate diet (oligosaccharides, disaccharides and monosaccharides) were also recommended for both groups.

Ginseng was encapsulated in the form of dried extract of stem and leaves of *Panax ginseng* C.A. Mey., Araliaceae, from China, containing 26.66% of total ginsenosides, Manufacturing Lot No. C20110809. After receiving the capsules on day zero (baseline), the patients were evaluated after one week, thirty and sixty days after starting treatment, totalizing four visits (0–1–4–8 weeks).

The Likert scale was used, at baseline, to grade the intensity of pain. After the use of the drugs, it was reused in the first, fourth and eighth weeks of treatment to see if there was a modification of the pain pattern mentioned initially. An adaptation of the Likert scale was made (Freire, 2008), in which fifteen options were formulated, subjectively evaluating the intensity of abdominal pain. The lowest score (−7) indicated high intensity of abdominal pain and the highest score (+7) indicated absence of the painful symptom. During the consultation, the scale was presented to the patient and then asked how he felt about abdominal pain and was requested to record the intensity of the pain in the instrument cited, after due explanation.

Data analysis of epidemiology and clinical manifestations of irritable bowel syndrome was performed using Fisher's test. The analysis of the data to assess the intensity of pain in the groups was performed by the Mann–Whitney test and the Friedman test, followed by Dunn's post-test for multiple comparisons. The results will be presented in the median of the scores attributed by the participants. It was used the GraphPad Prism, version 6.0 for Windows, GraphPad Software, San Diego, California, United States. Differences were considered statistically significant when $p < 0.05$.

## Results

The sample consisted of 26 patients ($n = 26$), of whom 24 completed the study protocol and two gave up after the first week of treatment, one due to private issues and the other because of an adverse effect (diarrhea).

The selected patients were divided into two groups of twelve patients each. In one group, ginseng was used and in the other one, trimebutine. The characteristics of each group are described in Table 1. In both groups, the female predominance is verified. The mean age was approximately 43.33 years for the ginseng group and 51.5 for the trimebutine group, highlighting relative homogeneity in both groups. This fact was also repeated when the duration of the signs and symptoms was analyzed, except in the group with symptoms up to 2 years ($p < 0.05$). Regarding schooling, patients with higher education level were prevalent in the ginseng group.

In the process of investigating the clinical manifestations, there was a relative predominance of IBS with constipation and IBS with mixed bowel habits in the ginseng group, whereas a fair distribution of the manifestations occurred in the trimebutine group. Comparing the two groups, a homogeneous division was observed in relation to the symptomatology (Table 2).

The evaluation of the *P. ginseng* therapeutic efficacy in the control of abdominal pain was carried out in the first, fourth and eighth weeks of treatment in relation to the beginning of therapy, using the Likert scale as parameter.

**Table 1**
Epidemiological and clinical characteristics of the groups.

| Groups/variables | | *Panax ginseng* ($n = 12$) | Trimebutine ($n = 12$) |
|---|---|---|---|
| Sex | Female | 11 (91.66%) | 10 (83.33%) |
| | Male | 01 (8.34%) | 02 (16.67%) |
| Age (Mean ± SD[a]) | | 43.33 ± 14.9 | 51.5 ± 8.1 |
| Education level | Elementary | 02 (16.66%) | 03 (25.00%) |
| | High school | 06 (50.00%) | 06 (50.00%) |
| | Higher level | 04 (33.33%) | 03 (25.00%) |
| Symptoms | Upto 2 years[b] | 05 (41.66%) | 03 (25.00%) |
| | >2 and ≤5 years | 01 (8.33%) | 02 (16.66%) |
| | >5 years | 06 (50.00%) | 07 (58.33%) |

[a] SD, standard deviation.
[b] $p < 0.05$.

**Table 2**
Presentation of IBS according to the research groups.

| Groups/clinical manifestations | *Panax ginseng* ($n = 12$) | Trimebutine ($n = 12$) |
|---|---|---|
| IBS-D[a] | 03 (25%) | 04 (33.33%) |
| IBS-C[b] | 04 (33.33%) | 04 (33.33%) |
| IBS-M[c] | 05 (41.66%) | 04 (33.33%) |

[a] IBS-D, IBS with diarrhea.
[b] IBS-C, IBS with constipation.
[c] IBS-M, IBS with mixed bowel habits.

Analysis of the pre-treatment (baseline) scores shows a median for this group of −5, with the 25th percentile of −6 and the 75th percentile of −2.25. Therefore, all patients presented negative values in the Likert scores, including maximum and minimum values, prior to *P. ginseng* administration.

From the first week of treatment, changes were observed regarding the scores. It was realized that the median changed to 2.5. Thus, a significant gain in the scores of 7.5 points was verified. The 25th and 75th percentiles, respectively, were 1 and 3.75, having been observed a minimum value of −2. This means that only three patients scored less than or equal to 1. The remaining nine patients had high positive scores, clearly demonstrating the *P. ginseng* efficacy, from the first week, in relieving IBS abdominal pain.

In the fourth week, ginseng efficacy could still be observed with behavior similar to that detected in the first week. This occurred because the median was equal to 3, with percentiles for positive values. Three patients presented values less than or equal to 0.25. Of this total, only one had a negative score and the remaining nine scored positively.

In the eighth week, there was a ten-point significant gain in the scores. Thus, the median became 5 as opposed to the median observed at baseline, which was −5. The analysis of the percentiles as well as of the maximum and minimum values showed that all twelve patients had positive scores; this, once again, corroborates the *P. ginseng* therapeutic action.

The values derived from the Likert scale scores for the group treated with *P. ginseng* are plotted in Fig. 1. They were considered significant when $p < 0.05$, using the Friedman test. The therapeutic effects of this product were analyzed, being based on the standard drug: trimebutine.

Trimebutine was effective in relieving the painful symptom of irritable bowel syndrome from the first week. In this way, an eight-point reversion in the median value was observed from −5.5 (baseline) to 2.5 with the 25th and 75th percentiles, respectively, of 1.25 and 3.75, so that the majority of patients presented positive scores.

In the fourth and eighth weeks, it was noticed that one particular patient still had a negative score. However, the remaining eleven

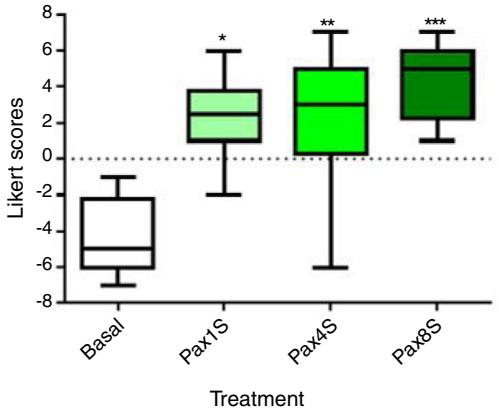


**Fig. 1.** Effect of *Panax ginseng* administrated orally for eight weeks at a dose of 300 mg/day, according to the Likert scale scores. Data presented as median (the 25th and 75th percentiles), maximum and minimum values. Friedman's test followed by Dunn's multiple comparison post-test. $n = 12$. $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$. (Pax, *P. ginseng*; 1S, 1st week; 4S, 4th week; 8S, 8th week).

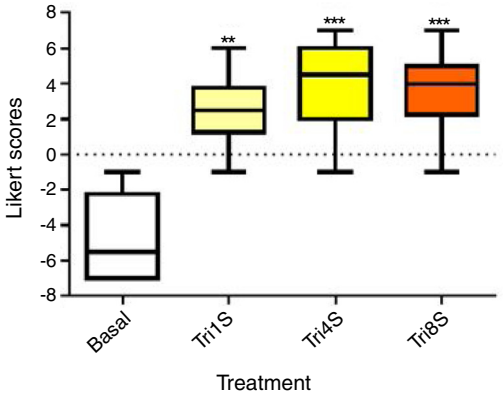


**Fig. 2.** Effect of trimebutine given orally for eight weeks at a dose of 600 mg/day according to the Likert scale scores. Data presented as median (the 25th and 75th percentiles), maximum and minimum values. Friedman's test followed by Dunn's multiple comparison post-test. $n = 12$. $^{**}p < 0.01$ and $^{***}p < 0.01$ (Tri, trimebutine; 1S, 1st week; 4S, 4th week; 8S, 8th week).

patients presented positive values in these two weeks. The median, in the fourth and eighth weeks, was 4.5 and 4.0, respectively. There was a significant mean gain of ten points compared to the baseline median (−5.5). The 25th and 75th percentiles, as well as the minimum and maximum values, were all positive. Thus, trimebutine was effective in relieving abdominal pain in IBS patients.

The values obtained from the Likert scores for the group treated with trimebutine are plotted in Fig. 2. They were considered significant when $p < 0.05$, by using the Friedman test.

The analysis of the effects of treatment with *P. ginseng*, comparing with the effects of trimebutine, did not show a significant difference when using the Mann–Whitney statistical test, during the weeks of treatment (Fig. 3). Therefore, both treatments proved to be effective and apparently equivalent to relieving abdominal pain in the irritable bowel syndrome.

Finally, it should be noted that the occurrence of side or adverse effects was small. In the group that received *P. ginseng*, there was a report of headache, in a discreet manner, in two patients (16.66%). In the group treated with trimebutine, there was a record of fleeting diarrhea in one of the individuals (8.33%). Such clinical manifestations did not require therapeutic intervention. It is important to mention that there was no need for the use of dipyrone in the groups.

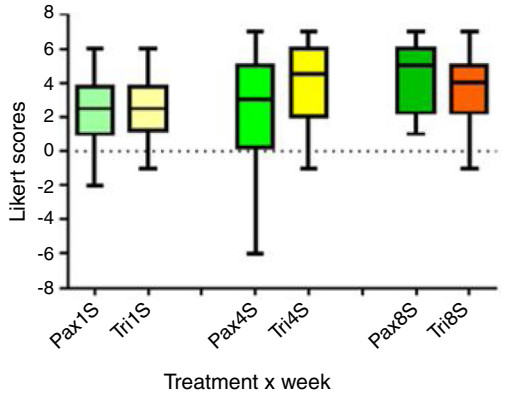


**Fig. 3.** Comparison of the effects, per week, of *Panax ginseng* at a dose of 300 mg/day with the effects of 600 mg/day of trimebutine. Data are expressed as median, the 25th and 75th percentiles, minimum and maximum values ($n = 12$). Mann–Whitney test for comparisons of two groups in the same week. (Pax, *P. ginseng*; Tri, trimebutine; 1S, 1st week; 4S, 4th week; 8S, 8th week).

## Discussion

The use of plants for therapeutic purpose is one of the oldest practices of mankind (Ministério da Saúde, 2012). Most of these practices are due to the development of empirical experiments using the common sense of various ethnic communities (Ministério da Saúde, 2006). Historically, medicinal plants are used in a considerable way as phytotherapeutics and in the discovery of new drugs (Ministério da Saúde, 2012).

As it is a country of continental dimensions, Brazil has a very rich and significant natural diversity. This biodiversity makes it a vast field of scientific research. Therefore, medicinal plants and their derivatives are among the main therapeutic resources, both in the traditional medicine and alternative and complementary medicine, being used in the public programs of phytotherapy (Ministério da Saúde, 2012).

Alternative and complementary medicine refers to medical practice that is not considered as part of conventional allopathic medicine. Some factors have contributed to the growing interest in this practice, aiming at the treatment of irritable bowel syndrome. It can be mentioned, for example, the relative efficacy that the traditional medicine provides in relation to the placebo therapeutic benefit in a rate from 7 to 15%. It is also observed the progressive desire of part of the population, from several Western countries, for a more natural and holistic therapeutic option due to the concern with the safety of the medicine prescriptions (Chey et al., 2011).

Some studies on plants and herbs for the IBS treatment have been developed in recent years. *Cynarascolymus* leaf extract was used in two hundred and eight patients with IBS-M for two months. It was observed that 26.4% of these patients had a significant reduction in the intensity of symptoms (Bundy et al., 2004) through the antispasmodic activity and the intervention of the herbal remedy in the intestinal flora (Emendörfer et al., 2005; Costabile et al., 2010). In a pilot study with eleven patients with IBS-D, the arrowroot was given in powder form three times a day for thirty days, proving to be effective in controlling diarrhea and relieving abdominal pain. Its action mechanism must be related to an increase in the fecal bolus and, consequently, to a more efficient intestinal action (Cooke et al., 2000).

Ginseng has been used for centuries by Oriental medicine as a body tonic. Nevertheless, there are no reports of its use in the IBS treatment, according to an international literature survey, although there are publications reporting its antinociceptive action (Ramarao and Bhargava, 1990; Nah and McCleskey, 1994; Mogil et al., 1998; Nah et al., 2000; Rhim et al., 2002; Choi, 2008)

More recently, in an experimental study in mice that developed femur tumor, attenuation in the pain intensity related to bone cancer was observed after intrathecal administration of ginsenosides. The authors concluded that, by means of this use, ginseng could be an analgesic alternative for the treatment of pain in bone neoplasia (Yoon et al., 2010).

Regarding the sample, there was predominance of females (87.5%), which reflects the higher prevalence of the disease in this gender (Saito et al., 2002). The mean age of study participants was 47.41 years, with extremes between 22 and 68 years and with preponderance of the symptoms over a five-year period. These data confirmed the epidemiological and clinical features of this disease, which usually occurs between the third and fifth decades of life, and it has a chronic evolutionary behavior (Hammerle and Surawicz, 2008).

It is important to mention the difficulty in selecting patients. Excluding the cases of non-acceptance in the study participation (four subjects), ten patients could not be included, since they used concomitantly anxiolytic and antidepressant drugs. This is a relatively common fact in IBS patients (Halpert et al., 2005; Jackson et al., 2000).

Pain is the most frequently observed symptom in IBS, and its control is fundamental to the improvement of the patients' quality of life. The painful phenomenon is mainly related to the increased visceral sensitivity. Although the pathophysiology of visceral hypersensitivity is not clearly defined, several mechanisms have been proposed, such as: the inflammatory nature, the participation of psychosocial factors and the alterations in the sensory-motor function of the digestive tract. For the last one, it was assigned a relevant role in the peripheral and central sensitization of afferent visceral neuronal pathways (Akbar et al., 2009).

There are several channels and receptors involved in the genesis of irritable bowel syndrome, among which we can mention: the transient receptor potential vanilloid1 (TRPV1); ATP-dependent ion channels (P2X); voltage-dependent sodium channels (NaV); protease-activated receptors (PAR); serotonin (5-HT) receptors; voltage-dependent calcium channels (CaV); cholecystokinin receptors and cannabinoid receptors (Akbar et al., 2009).

According to experimental studies, ginseng presents antinociceptive action in the CaV (Nah and McCleskey, 1994; Mogil et al., 1998; Rhim et al., 2002) and NaV (Choi, 2008), in the area of the primary sensory neurons (located in the dorsal region of the spinal cord). There are also reports of an antinociceptive action of ginsenosides in the spinal or supraspinatus region (Shin et al., 1999; Nah et al., 2000). This study suggests that *P. ginseng* was effective in controlling abdominal pain in IBS patients during the 60-day treatment period.

When abdominal pain improvement through the Likert scale was analyzed, a positive evolution was noticed in patients who used *P. ginseng*. This group ranged from a median baseline of −5 to 2.5, 3 and 5, in the first, fourth and eighth weeks of treatment, respectively. Therefore, there was a ten-point variation in the median between the pre-treatment period and the end of the study. In practice, there was a significant relief of the painful symptom.

Patients who used trimebutine presented an expected response, confirming the efficacy of this drug in the IBS treatment. This drug has its actions modulated by its agonist effect of peripheral opioid receptors. In addition, it causes the release of motilin and induces the appearance of migrating motor complexes (MMC), increasing the contractile activity of the large intestine (Schang et al., 1993).

The occurrence of side or adverse effects through the use of ginseng, in the present study, was small and it was represented by two patients. It was transient and it did not cause discontinuity of the research, as it has been previously described in the literature (WHO, 2001; Coon and Ernst, 2002; Kiefer and Pantuso, 2003; Shergis et al., 2013).

## Conclusion

The results obtained in this research, unique in the evaluation of *Panax ginseng* use in the treatment of patients with IBS, showed that this herbal medicine, when administered orally, has been shown to be efficient in the control of abdominal pain. It was well tolerated and it may represent a potential therapeutic alternative for this disease. It should also be taken into consideration the fact that it is a cheaper pharmaceutical product, when compared to the therapeutic options commercially available in the Brazilian market for the approach of this nosological entity.

Finally, it should be noted that this study was based on a small sampling with an excessive predominance of women. For these reasons, additional clinical trials with a greater number of patients and a major balance between the genders are necessary for a better evaluation of the obtained results.

## Authors' contributions

TVR and FJFN contributed to collecting and performing lab work. HACR, supervised the laboratory work and contributed writing the manuscript. JMD and MFFMD contributed to the design of the study. LCSM co-contributed to the critical statistical analysis of the study. All authors read the final manuscript and approved the submission.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

## Conflicts of interest

The authors declare no conflicts of interest.

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