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Treatment of Patients with Refractory Functional Dyspepsia Using *Nardostachys jatamansi* (D.Don) DC. Hydroalcoholic Extract: A Case Series

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Abstract

Functional dyspepsia (FD) is a highly prevalent condition with high impact on healthcare costs. Considering the complimentary therapies options like phytotherapy, this study aimed to investigate the efficacy and safety of *Nardostachys jatamansi* (D.Don) DC. extract in sixteen FD patients. The subjects received capsules of 500 mg *N. Jatamansi*, 3 times daily before meals for 30 days. The severity of early satiation and postprandial fullness were assessed by self-report of improvement at least 50% of symptoms and other FD symptoms assessed by Gastrointestinal Symptom Rating Scale (GSRS) before intervention and at end of treatment. The mean GSRS score level decreased significantly after intervention among study population. Five patients had chief complaint of early satiety and post prandial fullness who all of them reported 50% improvement. According to the results *N. jatamansi* seems to be effective in patients with refractory FD. Randomized clinical studies seem to be required.

Keywords: Dyspepsia; Herbal medicine; *N. jatamansi*; Traditional medicine

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Introduction

Functional dyspepsia (FD) is a highly prevalent condition with high impact on socio-economic and healthcare costs. Its diagnosis is generally based on four symptoms including epigastric pain and burning, early satiety, postprandial fullness, for three months with symptom onset more than six months, without evidence of other organic, systemic, metabolic or structural disease [1-3].

The reported prevalence of dyspepsia varies depending on geographical definition and location and it is represented in a systematic review in the range of 10-40% [4,5]. Dyspepsia is estimated to affect up to 29.9% of the Iranian population [6]. According to the Rome III criteria, FD patients were divided in to two groups, including subjects with "epigastric pain syndrome (EPS)" and those with "postprandial distress syndrome (PDS)"[7]. The overlap of PDS and EPS is considered as a new variant in Rome IV criteria [8]. The underlying pathophysiology of these two categories might be heterogeneous so it is required to have different approaches in treatments [9]. Delayed gastric emptying of solids is reported in a large proportion (up to 40%) of patients with functional dyspepsia and mainly treated with prokinetic drugs [10,11]. However, the results of prokinetic medications efficacy in the treatment of FD patients are unclear [12].

Generally, several complimentary therapies options like phytotherapy are available for managing patients with functional dyspepsia [13]. Some natural products have been traditionally used in Persian Medicine (PM) with a long history of use in the treatment of gastrointestinal diseases. They have also gained patients' better acceptance than conventional therapeutic agents [14-17]. Today, there are some clinical studies based on PM in treatment of FD [18-21].

N. jatamansi has long been used as a remedy in treatment of some diseases like central nervous system (CNS) disorders [22]. The medicinal properties of its rhizome are well-documented in traditional medicinal systems including Ayurveda, Persian and Chinese medicine for the treatment of digestive and neuro-psychiatric disorders [23,24]. Along with many studies representing its efficacy in CNS diseases [25], there are only some animal studies that indicate its effect in gastrointestinal filed [23,26].

Therefore, this pilot study aimed to investigate the therapeutic efficacy and safety of *N. jatamansi* hydroalcolic extract in patients with functional dyspepsia.

Methods

Study design and subjects

This pilot clinical trial study was conducted on sixteen FD patients, in Persian medicine clinic, Babol, Iran. FD was diagnosed clinically by a gastroenterologist, according to Rome IV criteria. Endoscopy was performed for patients over the age of 55 years and patients with symptoms including unexplained weight loss, odynophagia, dysphagia, family history of gastrointestinal cancer. These patients had symptoms of FD in the last six months before this study, and some of them were taken the routine treatments like antacid drugs or prokinetic agent, etc., without satisfactory effect. Individuals taking routine medication were included in this study and patients with problems such as drug resistance, under the supervision of a gastroenterologist, their routine medication was discontinued. All patient's voluntary entered the study after the complete explanation of the drug safety profile. Written informed consent was obtained from all of them. We reassured all patients that they will access trained traditional medicine doctor by telephone during the study.

The exclusion criteria were: drug consumption with GI effect like prokinetics, acid-reducing drugs, bismuth, sedatives, laxatives, and drugs affecting the cholinergic system, macrolide an-

tibiotics, aspirin (> 325 mg/day), spasmolytics; any documented history of endoscopic esophagitis and peptic ulcer disease; concurrent major physical illness including cardiac or liver disease, inflammatory bowel disease, active thyroid disease, and vasculitis.

Intervention

The hydro-alcoholic (70%; ethanol/water) extract of the rhizomes of *N. jatamansi* in a form of fine brown powder was purchased from Soha-Jissa (plantation industries and medicinal plants processing Co. Mazandaran, Iran; Batch Number: 204086). The extract was chemically standardized as follows: valerenic acid: 0.26 %, total valepotriate: 8.69%, total phenolic content: 6.84% Gallic acid equivalent. The microbial limit tests were performed in accordance with the British pharmacopeia for herbal preparations [27]. Microbial count of the extract was below the standard limit based on the BP criteria for herbal preparations. Patients were asked to take 500mg *N. Jatamansi* capsules, 3 times daily before meals (1500 mg daily) for 30 days.

Assessments

The initial severity of the symptoms was assessed by the Gastrointestinal Symptom Rating Scale (GSRS). It was the only valid and reliable Persian version of existing questioner about the GI problem [28]. It contains 15 questions about the symptoms including: pain or discomfort in upper abdomen, heartburn, acid reflux, hunger pains, nausea, rumbling, bloating, burping(-belching), passing gas or flatus, constipation, diarrhea, loose stools, hard stools, urgent need to have a bowel movement, sensation of not completely emptying the bowels. For two main symptoms, early satiation and postprandial fullness we used a self-report of improvement at least 50% of symptoms. All patients were visited before the intervention and at week 4 (at the end of the treatment).

Statistical analysis

Data are shown as mean and standard deviation (SD) for the continuous variable and n (%) for the categorical variable. P-value was calculated using Wilcoxon Signed Ranks Test and Mann Whitney u test as appropriate. Statistical analyses were done using SPSS version 20.0. $P<0.05$ was considered as statistically significant.

Results

Of all 16 participants 56.2% (n = 9) were female, with the mean (SD) age of 47.3(9.4) years. The mean (SD) age of male was 49.6 (10.0) years. After intervention 2 male patients with heartburn were discontinued medication due to exacerbation of symptoms on the first day of treatment. General information for each of the remaining 14 patients has been reported in table 1.

Table 1: Demographic and general information for each patient

Patient ID	Age, years	Sex	History of comorbidities	History of pervious treatment	Chief complaint	Initial GSRS total score
1	60	female	Hyper TG, cholesterol,	Omeprazole, domperidone	Sever bloating	52
2	55	male	No	Mebeverine, rulax® (*Cassia angustifolia)*	Sever bloating and constipation	65
3	54	male	DM	ALMG, omeprazole	Belching and postprandial fullness	34
4	48	female	History of breast cancer surgery	Pantoprazole	Belching, bloating	38

5	60	female	HTN, hyper TG	Domperidone	Bloating	36
6	32	female	No	Domperidone, pantoprazole	Bloating	54
7	39	male	No	Domperidone	Bleching and Post prandial fullness	41
8	39	male	No	Asacol, gabapentin	Epigastric pain and burning	43
9	39	female	MDD	Omeprazole, domperidone	Epigastric burning	37
10	52	female	Hypothyroidism, MDD	Domperidone	Bloating and belching and anorexia	50
11	41	female	Hyper cholestrolemia	anti-*helicobacter pylori* regimen	Bloating ,belching ,early satiety	35
12	51	female	Hyperthyroidism	Metronidazole, clarithromycin, dimethicone	Bloating and post prandial fullness	29
13	61	male	HTN, and 2 MIs	Domperidone, pantoprazole	Belching	21
14	43	female	No	Domperidone	Bloating, early satiety	43

HTN: hypertension, MI: myocardial infarction, MDD: major depressive disorder, hyper TG: hypertriglyceridemia, DM: diabetes mellitus.

The mean (SD) GSRS score of the patients at baseline and follow-up (after 1 months) measurement was 41.30 (11.2) and 28.8 (10.3) respectively (with a difference of 12.5 (6.6); P-value = 0.001). This indicates that the GSRS score level decreased significantly after intervention among study population (30% decreases). Overall GSRS score at baseline and follow-up for each patient separately were shown in the figure 1.

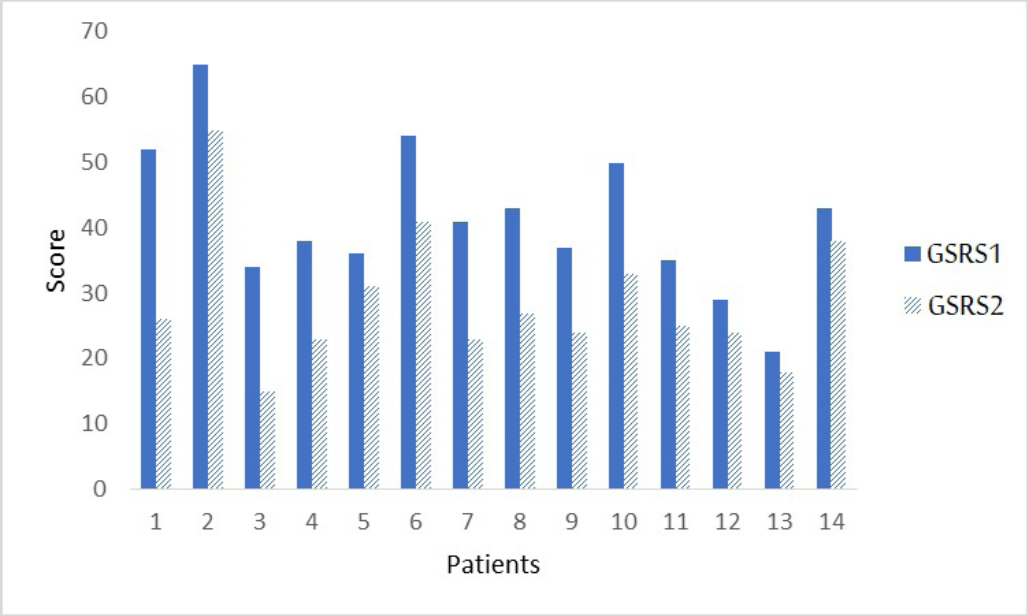

Figure 1: Overall GSRS score separately measured for each patient at baseline (GSRS1) and follow-up (GSRS2)

The biggest difference between two measurements of GSRS was seen in the first patient who had severe bloating as chief complaint (Table1). The comparison of the mean score of each questions before and after intervention showed that the decrease of symptoms score in questions 1 (pain or discomfort in upper abdomen), 2 (heartburn), 6 (rumbling), 7 (bloating), 8 (belching), 9 (passing gas) and 15 (sensation of not completely emptying the bowels) were statistically significant (Table 2).

Table 2: Mean score of each question of the GSRS of all patients at baseline and follow-up measurement as well as their difference

	GSRS questions	Baseline measurement [A]	Folow-up measurement (after 1 months)	Difference	P-value [B]
Q 1	pain or discomfort in upper abdomen	3.71 (1.81)	2.36(1.86)	-1.35(1.15)	0.004
Q2	heartburn	2.6(1.87)	1.71(1.32)	-0.86(1.35)	0.042
Q3	acid reflux	1.86(1.10)	1.86(1.10)	0.00 (1.03)	0.89
Q4	hunger pains	2.43(1.65)	1.79(1.48)	-0.64(1.39)	0.11
Q5	nausea	1.71(1.27)	1.28(0.47)	-0.43(1.09)	0.16
Q6	rumbling	2.21(1.05)	1.28(0.61)	-0.93(0.83)	0.006
Q7	bloating	4.93(1.98)	2.71(1.49)	-2.21(1.31)	0.001
Q8	burping(belching)	3.50(1.83)	2.00(1.30)	-1.50(1.22)	0.003
Q9	passing gas or flatus	5.21(1.93)	2.71(1.49)	-2.50(1.34)	0.001
Q10	constipation	3.36(2.27)	3.00(1.88)	-0.36(1.21)	0.26
Q11	diarrhea	1.21(0.80)	1.07(0.27)	-0.14(0.53)	0.32
Q12	loose stools	1.21(0.80)	1.07(0.27)	-0.14(0.53)	0.32
Q13	hard stools	3.07(2.23)	2.78(1.85)	-0.28(1.14)	0.36
Q14	urgent need to have a bowel movement	1.28(0.82)	1.07(0.27)	-0.21 (0.58)	0.18
Q15	sensation of not completely emptying the bowels	3.0(2.29)	2.07(1.49)	-0. 93(1.49)	0.041

A: Data are shown as mean (SD)
B: P-value was calculated according to the Wilcoxon Signed Ranks Test

But symptoms like acid reflux, hunger pains, nausea, constipation, diarrhea, were not statistically significant. All of the patients who had chief complaint of early satiety and postprandial fullness (n = 5) reported complete relief of symptoms at the end of treatment period.

Discussion and Conclusion

In recent years some studies have demonstrated the increase of patients' requests for holistic approach as well as alternative therapies for treatment of FD [29,30]. The effectiveness of phytotherapy, as one of main kinds of alternative treatments, on FD has not systematically been clarified. In this way, the assessment of the efficacy and safety of these herbal medications seems to be worthwhile.

Persian medicine, has recommended numerous herbs for the treatment of dyspepsia symptoms which Indian valerian (*N. jatamansi*) is one of the most repetitive ones [31]. The main reported therapeutic effects of *N. jatamnsi* in PM text books are in two main organs, stomach and brain [32]. Newly available reports of Indian valerian are mainly related to its effects on CNS [33,34]. Also, no clinical evidence of its effect

on gastrointestinal (GI) diseases have found in recent studies. Thus, this study would be considerable as first report of *N.jatamansi* effect on GI disorders in human.

There are some studies indicating phytotherapeutical approaches to dyspepsia mostly with the polyherbal formulations [35,36]. Many clinical studies have been performed on the STW5, a combination of nine plant extracts as a traditional Chinese herbal formula [37-39]. Comparing the results of different studies with results of this study, because of the difference in poly- and mono- herbal formulations and difference in outcome measurement tool, may not be correct. Bortolotti and his colleagues studied the efficacy of red pepper powder (2.5 g/day; before meals, for 5 weeks) in 30 patients with non-ulcer dyspepsia. They reported a decrease about 60% in the overall symptom score and the epigastric pain, fullness and nausea scores of the red pepper group at the end of the treatment**.** The present study demonstrated significant improvement of dyspeptic symptoms with decrease about 30% during the treatment with *N. jatamansi* hydroalcoholic extract in all 14 patients. However, the outcomes measurement tools of the two studies are not the same and the comparison may be incomplete. Other effective treatments were also reported with monoherbal formulations like artichoke leaf extract [40], *Glycyrrhiza glabra* [41], and with herb combinations like peppermint oil and caraway oil [14]. Whereas, most patients in the present study had refractory functional dyspepsia and experienced other therapeutic options, the results of this study could be the basis for further studies to reach the appropriate dosage form. We had two cases of patients with increased heartburn who had to stop taking medication. On the other hand, there was an increase in symptoms of epigastric pain and burning in some patients, but they were not willing to stop medication because of the satisfaction of the reduction of other symptoms like; rumbling, bloating, burping (belching), passing gas or flatus and sensation of not completely emptying the bowels. All patients with complaints of post prandial fullness and early satiety were reported more than 50% decrease in their symptoms. According to these results and some animal studies support the gastroprotective effect of the hydroalcoholic extract of *N. jatamansi* [26], we can hypothesize that this drug is more effective in people with postprandial distress symptoms versus epigastric pain syndrome.

In this case series we had 2 patients who had simultaneous functional dyspepsia and psychological disorder that had been under the appropriate treatment. After the treatment with *N.jatamansi* for their FD related problems, patients reported a decrease in psychological symptoms (such as improving sleep status and decreasing stress). We did not define the improvement of psychological symptoms with appropriate measurement tool since the beginning of the study, thus we cannot accurately comment on this section at this time. However, *N. jatamansi* has been shown to have antidepressant activity in preclinical studies [42]. In a mechanistic view, its extract has been indicated to cause an overall increase in the norepinephrine, dopamine, serotonin, 5-hydroxyindoleacetic acid (5-HIAA), and gamma-aminobutyric acid (GABA), in rats [43]. Evidence from recent researches has also demonstrated that *N. jatamansi* may increase levels of neurotransmitter acetylcholine in the synaptic space, and improve cholinergic functions via acetylcholinesterase inhibitory effect [44]. The neurotransmitters of autonomic nervous system and cholinergic system might influence gastric accommodation and emptying [45]. As gastric dysmotility has been indicated as supposed cause of FD, acetylcholinesterase inhibitors might effectively treat patients with FD [46]. Considering the simultaneous effect of *N.jatamansi* in the field of CNS and GI and respect to the importance of gut–brain axis and

the role of psychological disorders, especially the anxiety and depression, in pathophysiology of functional dyspepsia [47-50], we can hypothesize the effectiveness of *N.jatamansi* on patients with simultaneous digestive and neurological involvement.

Additionally, *N. jatamansi* has been shown to have pharmacological activities such as anti-hyperglycemic, anti-hypertensive and anti-inflammatory effects through the inhibitory activities on each respectively related key enzymes like α-amylase, angiotensin-converting enzyme and lipoxygenase [51,52]. Whereas, any side effect report has not reported by patients with other underlying conditions such as hypothyroidism, high blood pressure and diabetes, it has suggested that *N.jatamansi* be used for further studies in FD patients with these underling diseases.

Statement of Ethics

The study protocol was approved by the Ethics Committee of Babol University of Medical Sciences, Babol, Iran.

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Conflict of Interest

None.

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None.

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