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Clinical Trials

Ginseng Efficacy in the Clinical Improvement of Brucellosis

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Abstract

Background and Aim: Brucellosis, which is considered as one of the most prevalent zoonoses worldwide, is a major public health problem in several developing countries. The aim of the present study was to conduct an objective evaluation of ginseng's potential to improve the symptoms of brucellosis.

Materials and Methods: In a randomized controlled single-blind study, 62 patients with acute brucellosis after taking informed consent were randomly categorized into two therapeutic groups, namely the ginseng group and the control group. All the patients were examined to check their clinical response at the days 0, 3, 7, 14. The patients were followed for recurrence until 9 month after the initiation of treatment. The required data were collected and analyzed with SPSS software (ver. 18).

Results: Sixty-two patients participated in the study. The most prevalent findings were fever (90.2%), sweating (77.2%), fatigue and malaise symptoms (73.9%), arthritis and arthralgia (70.79%). The efficacy of ginseng compared to the control group to improve symptoms after one week was as follows: fever (P value = 0.083), sweating (P value = 0.19), fatigue and malaise (P value = 0.021), arthritis, and arthralgia (P value = 0.013). The relapse rate did not differ significantly between the two groups in nine-month follow up (P value = 0.693).

Conclusion: Ginseng might be efficient in the improvement of clinical signs and symptoms in patients and also in the rise of patients' compliance with treatment. Moreover, it has no serious side effects.

Keywords: Brucellosis, Efficacy, Ginseng, Supplement

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Introduction

Brucellosis is a widespread zoonosis that causes a severe health problem in both humans and animals. The causative agents of brucellosis are bacteria of the genus *Brucellae*. They are facultative, gram-negative, non-spore forming, non-capsulated, and intracellular coccobacilli. Brucellosis are capable of affecting various organs, tissues, and systems (1). In humans, four of the species have been noticed to be the most pathogenic cases that include *B. melitensis*, *B. abortus*, *B. suis* and *B. Canis*. They are transmitted to humans from animal reservoirs (2). Different species of *Brucellae* tend to affect certain animal hosts, and are more common in specific geographical locations. The global annual incidence of human brucellosis is not truly known owing to variation and inadequate surveillance systems between countries, but is thought to exceed 10 per 100,000 in certain populations. Major endemic areas worldwide include the Mediterranean,

Central Asia, and parts of Central and South America (3-5). Following the ingestion or inoculation, *Brucellae* species encroach to the mucosa, where polymorphonuclear leukocytes and activated macrophages are engaged in the annihilation of the bacteria. However, *Brucellae* are able to increase in number and survive intracellularly by hindering and counteracting bactericidal effects in the phagosome (6).

The development of an efficient medical treatment for the ailment is not easy due to its intracellular replication properties that lead to chronic infections (1, 7). The combinations of antibiotics that are used to treat this disease are hindered by several difficulties such as financial issues, therapeutic failures, and health as well as safety concerns. Ginseng (the root of Panax ginseng) is a significant medicinal plant which is widely used as a supplementary herbal medicine to treat cancer, diabetes, and atherosclerosis. Ginseng contains several active compounds. The major compounds include ginsenosides whose antidiabetic, anticancer and anti-inflammatory impacts have been confirmed (8, 9). Other active components include acidic polysaccharides. Investigations have indicated that they possess either immunostimulatory or immunosuppressive impacts depending on the length of therapy and disease condition (10). Ginseng acidic polysaccharides are able to increase the production of cytotoxic cells that could be used against tumors. Moreover, they trigger macrophages to produce T helper types 1 and 2 (Th1 and Th2), modulate antioxidant defense systems, and suppress acute inflammatory reaction at an early stage of Staphylococcus aureus infection (10). Ginseng acidic polysaccharides is able to disturb the phagocytic activity of B. abortus by preventing the activity of mitogen-activated protein kinases (MAPKs) signaling proteins ERK, JNK and p38 levels, and also by inhibiting the intracellular replication of B. abortus via enhancing phagolysosome fusion that might provide an alternative control of brucellosis (11). The inhibitory impacts of ginsenoside Rg3 against intracellular parasitic Brucella infection were examined via bacterial infection and adherence tests. The internalization, intracellular growth, and adherence of Brucella abortus in Rg3-treated RAW 264.7 cells remarkably reduced in comparison with the Rg3-untreated control. These results indicate that ginsenoside Rg3 hinders B. abortus infection in mammalian cells and could be used as an alternative remedy in the treatment of brucellosis (12). Another research revealed that Korean red ginseng oil (RGO) could attenuate Brucella abortus infection in a murine model as a host immune-enhancing agent. It was also shown in this study that RGO could have protective effects against B. abortus infection in vitro and in vivo. It is indeed a confirmation of the beneficial impacts of RGO in the prevention and treatment of brucellosis (13). This research sought to examine the efficacy of ginseng supplements on reliving the symptoms and physical performance enhancement in brucellosis.

Materials and Methods

According to the data provided by one of the previous studies, the symptom relief for brucellosis treatment by Doxycycline plus Rifampin was equal to 88.2% ($p = 0.882$) [14]. Moreover, based on a confidence interval of 95% ($\alpha = 0.05$) and a study power of 80% ($\beta = 0.20$), the sample size was assessed as follows:

$$N_1 = N_2 = Z_{(1-\alpha/2)^2} \times p \times q \div d^2 = 30$$

The result of the calculation of the sample size indicated that this number was 30 for each group. Given the 15% dropout, a total of 70 patients were enlisted in two groups, namely the standard and the ginseng group. The randomization was 1: 1 for the two groups and participants were assigned using computer-generated randomization (Figure 1).

In a randomized controlled single-blind study, seventy patients entered the study. In order to carry out the random allocation of the cases equally into two groups, 70 chits writing “C” (for the control group) on 35 chits and “T” (for the trial group) on the other 35 chits were prepared. The control group received doxycycline (RAZAK Co.) 100mg twice daily and 600mg Rifampin (ALHAVI Co.) once daily for 6 weeks, and the trial group received doxycycline 100mg twice daily and 600mg Rifampin once daily for 6 weeks with ginseng (GOLDARU Co.), 250mg (each capsule contains roughly 7 milligrams of $ginsenosides_{Rg1}$) twice daily for one week. All the patients were unaware about the received drugs. During the study, four patients were excluded from

every group and finally, 62 patients completed the study. The patients were compared for the disappearance of symptoms (fever, arthralgia, malaise) and decrease in CRP. They were followed for 9 months for relapse. The inclusion criteria included the clinical symptoms of severe brucellosis and the positive serology of standard tube agglutination (wright test) ≥1:160 and 2-ME (2-mercaptoethanol) ≥ 1:40, age > 15yrs. No history of brucellosis treatment within the past three years or chronic and local brucellosis, and no pregnancy acquired or innate immunodeficiency or concurrent advanced illness like chronic renal, cardiac, pulmonary or hepatic diseases were observed. The exclusion criteria were a history of allergy to ginseng, tetracycline or rifampin, discontinuation of treatment, withdrawal from study participation, patient migration or death. Patients in both groups were clinically followed and continuously examined. The questionnaires that were filled out contained demographic information and outcome variables that included subjective symptoms such as fever, chills, sweating, anorexia, arthralgia, myalgia, anorexia, and objective signs such as fever, arthritis, recurrence rate and also laboratory findings. Data were analyzed using the SPSS statistical package (ver.18). In the analytical part, the distinctions between the treatment groups were compared by the chi-square or Fisher exact test for categorical variables. Moreover, a two-sample t-test or Mann–Whitney test for continuous variables and R-squared linear regression were used to depict the strength of a correlation between the two variables. The P-value of less than 0.05 was considered significant. This research was authorized by the Research and Ethics Committee of Arak University of Medical Sciences (ethical code: 93-168-4), and registered with www.irct.ir by the IRCT201412219855N8. Written informed consent obtained from all patients to enter the study and all formal ethical rules were considered.

Results and Discussion

Seventy patients were included in this study, but 62 patients eventually completed the research. The mean age of the standard group was 36.8±14.5, and in the ginseng group mean age was 37.1±15.7. About 64.5% of the standard and 71% in the ginseng group were male and 74.4% of the standard and 71% in the ginseng group were rural. Furthermore, 48.4% in the standard group and 45.2% in the ginseng group were found to have a history of being in touch with cattle and had consumed unpasteurized dairy (Table 1).

The most prevalent findings were fever (90.2%), sweating (77.2%), fatigue and malaise symptoms (73.9%), arthritis and arthralgia (70.79%). The most common laboratory finding was positive CRP in 88.5% of the patients. The function of ginseng in improving fever, sweating, fatigue and, malaise, arthritis, arthralgia, and CRP was better than the placebo group during the treatment. Clinical and laboratory findings have been indicated in table 2.

The relapse rate after nine-month follow up was 12.9% in the standard group and 9.7% in the ginseng group (Figure 2).

Brucella spp. is able to reproduce itself inside various mammalian cell types characterized by an intracellular lifestyle. Moreover, Brucella spp. could limit the exposure to the host innate and adaptive immune response, drive the distinctive feature of pathology in infected hosts, and finally insulate the hosts from the impacts of antibiotics (6). The establishment of infection requires microbial adhesion to host cells. It depends on specific cell-to-bacteria interactions. Several researches have indicated that the efficacy of ginseng is primarily due to its polysaccharide components, which disrupt the adhesion of several pathogens to host cells, such as Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Propionibacterium acnes, and Staphylococcus aureus, in order to prevent the occurrence of infectious diseases (15). The intracellular lifestyle of Brucella restricts its exposure to host innate and adaptive immune responses that protect the organism from the impacts of antibiotics (6). B. abortus steadily hinders phagosome-lysosome fusion and Brucella-containing phagosome (BCP) maturation into replicative phagosomes (16). As a host defense, lysosome-associated membrane proteins (LAMPs), including LAMP-1, are transmembrane proteins given to phagosomes during the phagosome maturation process for phagosome-lysosome fusion. Consequently, an organelle with degradative and antimicrobial components that are necessary for the destruction of internalized microorganisms is created (17). In a

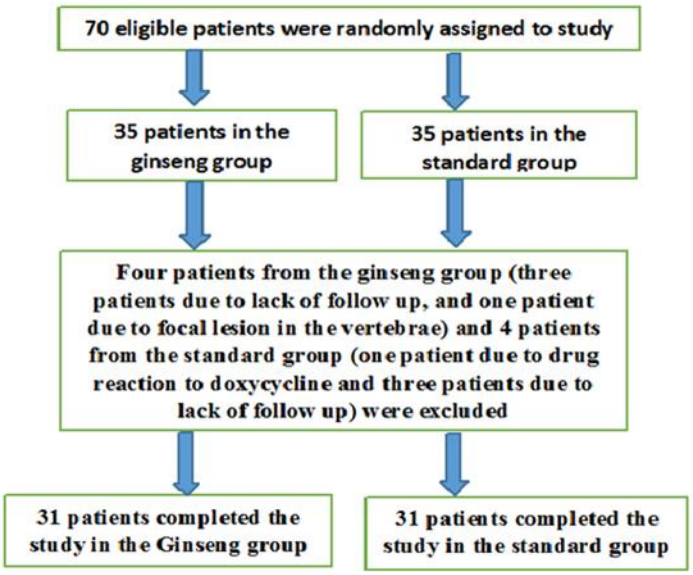

Figure 1. Flowchart of patients participating in the study.

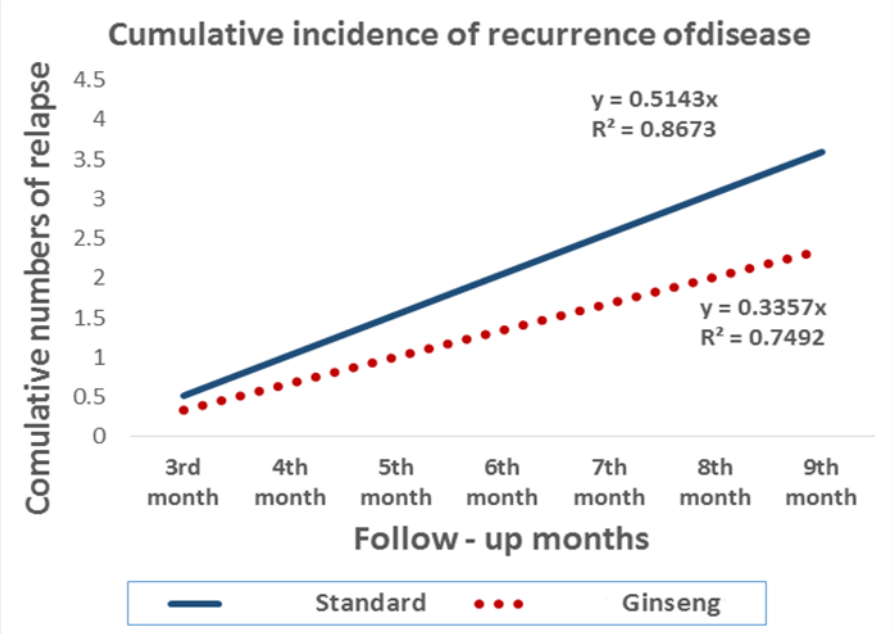

Figure 2. Cumulative incidence of relapse in two groups.

research carried out by Park *et al.* (18), the use of a red ginseng-containing diet resulted in the protection of mice from fatal infection with a highly pathogenic H5N1 influenza virus, and remarkably induced the production of the antiviral cytokine IFN-γ in the lungs. This phenomenon suggests that red ginseng is an immune-enhancing agent. IL-10 was noticeably reduced during infection, which seemed to be beneficial for the animals. IL-10 hinders cell-mediated responses and prevents further tissue damage. Hence, mice that lack T cell-derived IL-10 had a greater ability to control B. abortus infection (19).

Ginseng is found in two major species, namely Korean ginseng (Panax ginseng) and American ginseng

Table 1: Comparison of demographic characteristics of patients in two groups.

Variable		Trial	Control	P-value
Age (years) (mean + SD)		37.1±15.7	36.8±14.5	0.9378
Gender (%)	**male**	22(71)	20(64.5)	0.5871
	female	9(29)	11(35.5)	
Location	**Urban**	9(29)	8(25.8)	0.7793
	rural	22(71)	23(74.2)	
Contact the livestock	**yes**	14(45.2)	15(48.4)	0.5679
	No	17(54.8)	16(51.6)	

Table 2: Comparison of the treatment outcome of patients in two groups.

Variable		Ginseng	Standard	P-value
Fever (No. of patients)	**Day zero**	28(90.3)	27(87.1)	0.6931
	third day	17(54.8)	23(74.2)	0.1134
	seventh day	5(16.1)	11(35.5)	0.0834
	Fourteenth day	1(3.2)	2(6.5)	0.5486
Sweating (No. of patients)	**Day zero**	23(74.2)	24(77.4)	0.5486
	third day	16(51.6)	20(64.5)	0.3073
	seventh day	9(29)	14(45.2)	0.1903
	Fourteenth day	3(9.7)	8(25.8)	0.0999
Arthritis and Arthralgia (No. of patients)	**Day zero**	23(74.2)	22(71)	0.7793
	third day	14(45.2)	18(58.1)	0.3134
	seventh day	5(16.1)	14(45.2)	0.0137
	Fourteenth day	1(3.2)	7(22.6)	0.0238
fatigue and malaise (No. of patients)	**Day zero**	24(77.4)	23(74.2)	0.7705
	third day	11(35.5)	19(61.3)	0.0438
	seventh day	4(12.9)	12(38.7)	0.0213
	Fourteenth day	1(3.2)	7(23.3)	0.0206
Average CRP (mg/L) (mean±SD)	**Day zero**	48.5±25.1	47.7±23.3	0.8966
	third day	39.9±21.6	42.5±22.8	0.646
	seventh day	21.3±11.4	29.4±13.7	0.0142
	Fourteenth day	12.7±6.5	17.9±8.4	0.0088
Cumulative recurrence at the end of the ninth month		3(9.7)	4(12.9)	0.6931

(Panax quinquefolius). They vary in terms of both amount and ingredients, and mainly include ginsenosides as their most significant ingredients (8). Many active compounds such as approximately 40 ginsenosides have been identified in P. ginseng with several pharmacological activities, including its impacts on chemical stress, immune modulation in animal studies, antitumor activities, as well as glucose metabolism and the development of cognitive performance (20, 21). Several randomized controlled trials have reported the beneficial impacts of ginseng supplements on the relief of fatigue (22-25) and physical performance enhancement (26-28) so far. Consequently, RGO could be considered an immunomodulator that brings about certain alterations in the immune system, possibly by regulating the adhesion molecules, nitric oxide, and cytokines, that in turn protect mice against brucellosis. These findings indicate that the daily consumption of RGO might contribute to the prevention and treatment of brucellosis. However, further investigations are required to validate its therapeutic use in animal hosts. In the present study and during the treatment, ginseng-related side effects were not observed.

Conclusion

This study exhibited that the therapeutic effect of ginseng was significant in the symptom improvement of brucellosis. Moreover, in the follow up for failure and recurrence, there was no significant difference in the standard and the ginseng groups. The efficacy of

ginseng in the treatment of human brucellosis has not been investigated in previous studies. Hence, our study could be considered a novel research conducted on this issue. The use of ginseng might improve clinical signs and symptoms of brucellosis patients and increase the patients' compliance with treatment. Furthermore, it has no serious side effects. However, the present study is a clinical research, and the authors hold that further basic and clinical studies of the mechanism of ginseng in brucellosis are required. In conclusion, the authors demonstrated that ginseng might be a beneficial medicinal herb that could be used as a supplementary herbal medicine for the management of brucellosis.

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Conflict of Interest

The authors declare that they have no competing interests.

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