Aqueous Extract of Dried Fruit of *Berberis vulgaris* L. in Acne vulgaris, a Clinical Trial

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**ABSTRACT.** *Berberis vulgaris* L. (barberry) is a very well-known herb in traditional medicine. Apart from its anti-inflammatory and antibacterial properties, the antilipogogenic effect of barberry on the sebaceous glands in animals may further suggest it could be employed as an anti-acne agent. This study examined the effect of oral aqueous extract of barberry on acne vulgaris. Adolescents aged 12–17 years with moderate to severe acne vulgaris were randomly given oral gelatin capsules containing either aqueous extract of dried barberry (600 mg daily for 4 weeks, *n* = 25) or placebo (*n* = 24). Counts of facial noninflamed, inflamed, and total acne lesions, as well as the Michaelson's acne severity score were documented at baseline and at weeks 2 and 4. Both groups were comparable in terms of the patients’ characteristics and baseline variables. After 4 weeks, the mean number of noninflamed, inflamed, and total lesions as well as mean Michaelson's acne severity score declined significantly by 43.25 ± 10.88% (median: 42.11%), 44.53 ± 11.78% (median: 45.45%), 44.64 ± 8.46% (median: 46.15%), and 44.38 ± 8.25% (median: 44.07%), respectively, among the extract receivers (*p* < .001 for all the changes). Similar changes were not significant in the placebo group. No notable complication or side effect was reported in relation to barberry. In conclusion, oral aqueous extract of dried barberry is a safe, well-tolerated, and effective choice in teenagers with moderate to severe acne vulgaris.

**KEYWORDS.** Acne vulgaris, *Berberis vulgaris*, Michaelson's acne severity score

**INTRODUCTION**

*Berberis vulgaris* L. (family Berberidaceae) is a rather ubiquitous plant as it grows in vast areas in Asia, Europe, and America. It is also well known in Iran, first for its dried fruits, which are widely used as a food additive in culinary dishes, and second, for its root, bark, leaf, and fruit, which have become famous herbal materials in folk medicine (Zargari, 1993). This 1–3 m tall shrub has yellow wood, obovate leaves, pendulous yellow flowers, and oblong red fruits (*barberry* or *Zereshk*) (Shamsa, Ahmadiani, Khosrokhavar, 1999). Some pharmacological research has suggested that various therapeutic effects of *Berberis vulgaris* L. are related mainly to its iso-
quinoline alkaloids, particularly berberine. Anti-inflammatory, antimicrobial and antioxidant properties have been documented in previous studies (Imanshahidi & Hosseinzadeh, 2008; Local Food-Nutraceuticals Consortium, 2005; Tomosaka et al., 2008). Besides its dried fruit, the juice of fresh barberry has recently gained popularity as a cold refresher among Iranian people and teenagers, in particular. Surprisingly, a considerable number of the consumers report alleviation or even cure of their acne lesions after ingestion of the juice. It is previously reported that berberine could effectively suppress lipogenesis in the sebaceous glands of hamster (Seki & Morohashi, 1993). However, no related clinical trial was found in the literature. The objective of the present study was to investigate the effect of crude aqueous extract of barberry in adolescents with moderate to severe acne vulgaris.

**MATERIALS AND METHODS**

**Study Design and Participants**

In this double blind, randomized, placebo-controlled clinical trial 50 adolescents with moderate to severe acne vulgaris based on physician clinical assessment were recruited from a teaching dermatological center from February 2011 to August 2011. All participants and parents or guardians provided written informed consent. The exclusion criteria were acne due to secondary causes, pregnancy, the presence of other dermatological disease of the face, and any other acne treatment within the previous 3 months.

**Preparation of Aqueous Extract of Berberis vulgaris L. and Placebo**

Air dried fruits of *Berberis vulgaris L.* (Figure 1) were obtained from a local market. Although dried barberry is a well-known and routinely used additive in Persian cuisine, the obtained product was identified and authenticated by a skilled botanist (Professor Moafeghi).

The product (100 g) was lightly boiled in 1,000 ml of distilled water for 30 min, filtered and concentrated in a rotary vacuum evaporator, yielding 10 g of aqueous extract of *Berberis vulgaris L.* Gelatinous capsules were filled by 200 mg of this extract and famed. The placebo (lactose) was packed in identical capsules. Fifty packs containing 84 capsules in each were prepared by a pharmacologist who was not involved in the study. Each pack was labeled as “A” or “B,” containing active agent or placebo. The code was not disclosed for the investigator until after completion of data analysis.

**Groups and Variables**

Patients randomly received capsules containing either 200 mg of aqueous extract of *Berberis vulgaris L.* three times a day for 4 weeks (the treatment group, \( n = 25 \)) or placebo in the same fashion (the control group, \( n = 25 \)). This dose was selected based on the traditional Persian pharmacological literature. Numbers of inflamed, noninflamed and total acne lesions on the face, as well as the Michaelson’s acne severity score (Michaëlsson, Juhlin, Vahlquist, 1977) were determined at baseline and at weeks 2 and 4 after starting study by a skilled physician unaware of grouping of the patients. No concomitant acne medications were permitted within the
study period. The participants were given specific instructions about their diet, activity and hygiene in this period. For this purpose, the participants were requested to follow a low-glycemic load, junk/processed/spicy food-free diet with skimmed milk only during the study period (Adebamowo et al., 2005; Smith, Mann, Braue, Mäkeläinen, Varigos, 2007). They were also recommended to avoid strenuous activities, sun exposure, and stressful events as much as possible (Pappas, 2009) and instructed to wash their face with regular soap and water only twice daily and after exercise.

All patients completed the study period except for one in the control group, leaving 24 patients available in this group for final analysis. This patient dropped out due to the death of his mother during the study period.

**Statistical Analysis**

Analysis of data was performed with the SPSS for Windows V 15.0 (SPSS Inc., Il, USA). Based on the results of the Shapiro-Wilk W test and the quantile-quantile plot (Q-Q plot), all quantitative data were distributed normally, except for changes of variables at baseline and after 4 weeks. Statistical methods included the Chi-square test, independent samples t tests, Mann-Whitney U test, and Repeated Measures Analysis (RMA). P-values ≤ .05 were considered as significant.

**RESULTS**

There were 11 males (44%) and 14 females (56%) with a mean age of 14.40±1.63 (range: 12–17) years in the treatment group vs. 15 males (62.5%) and 9 females (37.5%) with a mean age of 13.88 ± 1.62 (range: 12–17) in the control group. The
groups were matched for the patients’ gender (Chi-square test, \( p = .20 \)) and age (Independent samples \( t \) test, \( p = .27 \)).

Mean duration of disease was 2.00 \( \pm \) 0.65 (range: 1–3) years in the treatment and 1.83 \( \pm \) 0.70 (range: 1–3) years in the control group, again with no significant difference between the two (Independent samples \( t \) test, \( p = .17 \)).

The mean number of acne lesions, as well as the mean Michaelson’s acne severity score (which was analyzed using the RMA model) are outlined in Table 1.

Comparing with the baseline values, the model showed that the mean numbers of noninflamed, inflamed, and total lesions, as well as the mean Michaelson’s acne severity score declined significantly by weeks 2 and 4 in the treatment group. Comparing the results at 4 weeks with baseline, there was a significant decline in the mean count of noninflamed (20.20 \( \pm \) 4.79\% (14–30), median: 19.29 \( \pm \) 4.52\% (13–29), \( p = .50 \)) and inflamed (24.28 \( \pm \) 3.40\% (18–31), median: 22.79 \( \pm \) 5.04\% (17–36), \( p = .23 \)) lesions, as well as in the mean Michaelson’s acne severity score (53.84 \( \pm \) 5.06\% (46–62), median: 51.04 \( \pm \) 8.66\% (41–75), \( p = .17 \)) in the treatment group.

In the control group, however, similar changes did not reach a statistically significant level. The mean number of noninflamed lesions was increased (2.06 \( \pm \) 13.72\% (14 to 20.83\% decrease)) at week 4, whereas there was a decline in the mean count of inflamed (2.06 \( \pm \) 13.72\% (15–36), median: 21.79 \( \pm \) 5.48\% (13–36), \( p = .003 \)) and total (4.48 \( \pm \) 5.16\% (37–53), median: 4.00 \( \pm \) 7.49\% (30–59), \( p = .001 \)) lesions, as well as in the mean Michaelson’s acne severity score (4.48 \( \pm \) 5.16\% (37–53), median: 4.00 \( \pm \) 7.49\% (30–59), \( p = .001 \)) in the treatment group.

### Table 1. Number of Noninflamed, Inflamed, and Total Acne Lesions, and the Michaelson's Acne Severity Score at Baseline and at weeks 2 and 4 in the Case and Control Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case Group (( n = 25 ))</th>
<th>Control Group (( n = 24 ))</th>
<th>( p )-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninflamed lesions count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>20.20 ( \pm ) 4.79 (14–30)</td>
<td>19.29 ( \pm ) 4.52 (13–29)</td>
<td>.50</td>
</tr>
<tr>
<td>Week 2</td>
<td>16.32 ( \pm ) 2.73 (12–22)</td>
<td>19.50 ( \pm ) 4.38 (12–27)</td>
<td>.001</td>
</tr>
<tr>
<td>Week 4</td>
<td>11.08 ( \pm ) 1.61 (8–14)</td>
<td>19.21 ( \pm ) 3.95 (13–27)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>( p )-value**</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>&lt;.001</td>
<td></td>
<td>.86</td>
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<tr>
<td>Inflamed lesions count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>24.28 ( \pm ) 3.40 (18–31)</td>
<td>22.79 ( \pm ) 5.04 (17–36)</td>
<td>.23</td>
</tr>
<tr>
<td>Week 2</td>
<td>18.92 ( \pm ) 2.71 (15–24)</td>
<td>22.08 ( \pm ) 5.44 (15–36)</td>
<td>.003</td>
</tr>
<tr>
<td>Week 4</td>
<td>13.24 ( \pm ) 2.26 (9–18)</td>
<td>21.79 ( \pm ) 5.48 (13–36)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>( p )-value**</td>
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<td></td>
<td>&lt;.001</td>
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<td>.92</td>
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<tr>
<td>Total lesions count</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>44.48 ( \pm ) 5.16 (37–53)</td>
<td>42.08 ( \pm ) 7.95 (32–63)</td>
<td>.22</td>
</tr>
<tr>
<td>Week 2</td>
<td>35.24 ( \pm ) 3.81 (30–43)</td>
<td>41.58 ( \pm ) 8.19 (30–61)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Week 4</td>
<td>24.32 ( \pm ) 2.58 (21–30)</td>
<td>41.00 ( \pm ) 7.49 (30–59)</td>
<td>&lt;.001</td>
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<tr>
<td>( p )-value**</td>
<td></td>
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<tr>
<td></td>
<td>&lt;.001</td>
<td></td>
<td>.93</td>
</tr>
<tr>
<td>Michaelson’s score</td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>53.84 ( \pm ) 5.06 (46–62)</td>
<td>51.04 ( \pm ) 8.66 (41–75)</td>
<td>.17</td>
</tr>
<tr>
<td>Week 2</td>
<td>40.54 ( \pm ) 4.26 (35–49)</td>
<td>50.52 ( \pm ) 7.88 (39–70)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Week 4</td>
<td>29.40 ( \pm ) 3.37 (24–36)</td>
<td>50.27 ( \pm ) 7.71 (38–65)</td>
<td>&lt;.001</td>
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<td>( p )-value**</td>
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<td></td>
<td>&lt;.001</td>
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<td>.91</td>
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</table>

Data presented as mean \( \pm \) standard deviation (range).

* Between-group.

** Within-group.
range: 22.86% increase to 13.51% decrease) lesions, as well as in the mean Michaelson's acne severity score (0.22 ± 8.04%, median: 0.85%, range: 15.22% increase to 14.29% decrease).

All the changes were significantly higher in the treatment than in the control group (Mann-Whitney U test, \( p < .001 \) for all comparisons) (Figure 2).

In addition, the between-group analysis showed that the resolution of noninflamed, inflamed, and total lesions, as well as the decrease in the Michaelson's acne severity score was significantly more prominent in the treatment than in the control group (Table 1).

No significant side effects or complications were reported by the participants within the study period.

**DISCUSSION**

In this study, oral intake of aqueous extract of barberry in gelatin capsules (600 mg per day) decreased the counts of both inflamed and noninflamed lesions by roughly
44% at week 4 in a group of teenagers (12–17 years) with acne vulgaris. Studies on the chemical composition of extracts from *Berberis vulgaris* fruit have reported various compounds such as isoquinoline alkaloids (berberine, palmatine), flavonoids (chrysanthemin, pelargonin, petunidin-3-o-beta-d-glucoside), phenylpropanoids (caffeic acid, chlorogenic acid), carbohydrates (pectin, sucrose), coumarin (asculetin), vitamin (ascorbic acid), flavonol (hyperoside), alkane to c4, triterpene (ursolic acid), and tannin (Imanshahidi & Hosseinzadeh, 2008; Ivanovska & Philipov, 1996; Pizzorno & Murray, 2005; Pozniakovskii, Golub, Popova, & Kovalevskaia, 2003). Among these compounds, berberine is apparently the most important one, which is generally believed to be responsible for many beneficial effects of the plant (Küpeli, Koşar, Yeşilada, Hüsnü, & Başer, 2002; Yeşilada & Küpeli, 2002). In a study by Seki and Morohashi, it was shown that the lipogenesis in hamster sebaceous glands was suppressed 63% by 10(-4) M berberine (Seki & Morohashi, 1993). Resolution of acne lesions after 4-week treatment with aqueous extract of barberry in our series supports this finding. However, it should be borne in mind that acne vulgaris is a multifactorial skin disease and other mechanisms may underlie its pathogenesis. For instance, an anti-inflammatory activity with unknown exact mechanism has been proposed to be exerted by the alkaloid fraction of *Berberis vulgaris* and berberine (Imanshahidi & Hosseinzadeh, 2008). This is in line with the significant decrease in number of inflamed lesions found in our patients who received the extract of barberry.

On the other hand, the plant has displayed a significant antibacterial, antifungal, and antiparasitic activity against different species such as *Staphylococcus* and *Candida* (Freile et al., 2003; Stermitz, Beeson, Mueller, Hsiang, & Lewis, 2001), as well as *Entamoeba histolytica*, *Giardia lamblia*, *Trichomonas vaginalis* (Kaneda, Torii, Tanaka, & Aikawa, 1991), *Helicobacter pylori* (Mahady, Pendland, Stoia, & Chadwick, 2003) and *Leishmania donovani* (Ghosh, Bhattacharyya, & Ghosh, 1985). Although *Propionibacterium acne*, the main bacterial culprit in pathogenesis of acne vulgaris (Khodaeiani et al., 2012), is not mentioned in this list, the antibacterial activity of berberine against this microorganism could not be definitely denied due to lack of data. The oxidative stress and lipid peroxidation, in particular, are now believed to play a pivotal role in pathogenesis of acne vulgaris (Bowe & Logan, 2010). Interestingly, *Berberis vulgaris* is also very well known for its antioxidant profile. Methanol extracts of its leaves, fruits, and stem, have been reported to be active in radical-scavenging and inhibiting lipid peroxidation. Apparently, these effects are linked to the action of the phenolic compounds such as tyramine, cannabisin, and lyoniresinol, which are all detectable in extracts from barberry (Tomasaka et al., 2008).

Last but not least, it is proposed that berberine may exert an anxiolytic effect (Peng et al., 2004). This may also contribute to the antiacne activity connected with the extract of barberry, because it has been previously suggested that psychological stress and anxiety may be associated with the development and exacerbation of acne vulgaris (Yosipovitch et al., 2007) by alteration of the immune system of the skin (Dhabhar, 2003) and the cutaneous barrier function (Garg et al., 2001). Nevertheless, whatever the exact antiacne mechanism of barberry is, the clinical outcome was excellent in the present study. No significant side effects or complications were reported by the barberry receivers. Safety of the extract was already
anticipated, because it was previously confirmed in various clinical situations that berberine is not toxic at routine doses (i.e., 200 mg orally two to four times daily) (Birdsall & Kelly, 1997). Likewise, as mentioned before, the barberry juice is a routinely consumed refresher by many people even at much higher doses than that we used in this clinical trial, with no significant side effects or complications. This finding is outstanding, because many other medications being prescribed in treating acne vulgaris are not entirely safe or tolerable especially by teenagers (Babaeinejad, Khodaeiani, & Fouladi, 2011; Eichenfield & Wortzman, 2009; Kus, Gün, Demirçay, & Sur, 2005). To the best of our knowledge, this is the first clinical trial with regard to the effectiveness of barberry in acne vulgaris. As a pioneer, we recommend further studies particularly in terms of combination therapy with other medications in these patients (Han & Lee, 2005; Oh KB, Oh MN, Kim, Shin DS, & Shin J, 2006; Soffar, Metwali, Abdel-Aziz, el-Wakil, & Saad, 2001; Sun, Courtney, & Beachey, 1988a; Sun, Abraham, & Beachey, 1988b). In addition, more studies are needed to effectively report the optimal dose of the extract. Short study period could be acknowledged as a limitation in this study, albeit significant findings in this apparently short period even further consolidate the importance of barberry in acne vulgaris. More long-term follow-ups, however, are recommended in future studies.

**Declaration of interests:** The author reports no conflicts of interest.

**ABOUT THE AUTHOR**

**Rohollah F. Fouladi**, MD graduated from the Tabriz University of Medical Sciences and has worked as a researcher in various fields of medicine and dentistry for over 6 years. By now, he has participated in over 600 research projects and served as reviewer in a number of international medical journals.

**REFERENCES**


