The prevalence and predictors of herbal medicines usage among adult rheumatoid arthritis patients: A case-control study

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ABSTRACT

Objectives: This study was performed to evaluate the prevalence and predictors of herbal medicines usage among adult Rheumatoid Arthritis (RA) patients.

Design: In this cross-sectional, case-control study, the case group included 500 RA patients and the control group contained 500 control individuals.

Setting: The study was performed in three rheumatology, surgical, and orthopedic clinics affiliated to Shiraz University of Medical Sciences.

Main outcome measures: The pattern of herbal medicines usage was assessed by a researcher-made questionnaire.

Results: In this study, 51.4% of the subjects in the RA group and 36.4% of those in the control group used herbal medicines. The most frequently used herbal medicines were thyme (43.4%), chamomile (36.9%), borage (36.8%), lavender (31.2%), ginger (28.5%), and cinnamon (21.5%) among RA patients. The results showed a significant difference between the two groups with regard to usage of herbal medicines, such as chamomile, cinnamon, and ginger. Besides, the results of logistic regression analysis on RA patients showed that males (odds ratio = 0.50, \( p = 0.001 \)) used herbal medicines less compared to females. Additionally, married RA patients (odds ratio = 0.35, \( p = 0.03 \)), illiterate ones (odds ratio = 2.45, \( p = 0.001 \)), and those with high school diplomas (odds ratio = 1.64, \( p = 0.02 \)) used herbal medicines more compared to other patients.

Conclusion: This study showed that more than half of RA patients used herbal medicines. All herbal medicines have to be conducted to evaluate the efficacy and safety of herbal medicines usage in RA patients.

1. Introduction

Rheumatoid Arthritis (RA), as a chronic autoimmune disease, leads to joint synovial inflammation and progressive cartilage and bone destruction. Most of drugs used for treatment of RA have severe side effects and are highly expensive. Therefore, the proportion of patients who use Complementary and Alternative Medicine (CAM) has been increasing recently.¹ The prevalence of CAM usage varied from 28% to 90% in RA patients.⁶ It has been reported that the most frequently used CAM was biological products, such as honey, and herbal medicines.³ Recently, 90% of arthritic patients used alternative therapies, such as herbal medicines.⁴

It has been maintained that rosemary, ginger, borage,⁴,⁶ and subspecies such as ursica dioica, uncaria tomentosa, vaccinium myrtillus, and olea europaea might have anti-inflammatory effects and were the most common herbal medicines ⁶ that could be used in RA patients. This is due to the fact that herbal medicines are easily available, have low or no adverse effects, are cheap, and may be safe and efficient.⁶

Some researchers have indicated that herbal medicines and dietary products had preventive effects against some diseases. For example, some kinds of vitamins might prevent cognitive impairments.⁷ Moreover, consumption of coffee and green tea might prevent the development of RA.⁸ Other studies also indicated that herbal remedies, medicinal plants, and functional foods as natural products might be used to treat chronic inflammatory diseases, such as RA.⁹ RA patients used medicinal plants to cure diseases or relieve symptoms.⁹ They used CAM, such as herbal medicines, to reduce pain,⁹,¹⁰ edema,¹⁰ inflammation,¹¹ and extra-articular complications.¹² In fact, some types of foods and diets decreased inflammatory cytokines levels in RA patients, which might be effective in RA management.¹³ Although a limited number of...
Studies have maintained that RA patients consumed herbal medicines, the prevalence of herbal medicines usage among RA patients is not clear. Moreover, no studies have assessed the predictors of herbal medicines usage among adult RA patients. Therefore, this study aims to determine the prevalence and predictors of herbal medicines usage among adult RA patients.

2. Methods

In this cross-sectional, case-control study, the case group included 500 RA patients and the control group contained 500 control individuals selected through convenience sampling. The case group participants were selected from three rheumatology clinics in Hafez, Motahari, and Imam Reza centers affiliated to Shiraz University of Medical Sciences. The control group participants were also selected from surgical and orthopedic clinics in Motahari center. The inclusion criteria for the case group included confirmation of RA by a rheumatologist, aging 18 years or above, and prognosis of at least 6 months. The control group included control subjects without RA or other autoimmune diseases. It should be noted that the cases and controls were matched with regard to age and gender.

The sample size was determined based on a pilot study. On the basis of the pilot study and considering two-sided confidence level of 95%, power of 90%, controls/cases ratio of 1, hypothetical proportion of controls who used herbal medicines as 36, hypothetical proportion of cases who used herbal medicines as 46.25, and least extreme odds ratio to be detected as 1.53, the sample size was estimated as 484 subjects in each group, which was raised to 500 subjects in each group.

The study data were collected using a demographic and clinical characteristics form, including information about age, gender, education level, marital status, and having other diseases or medical problems. In addition, they were asked “Which supplementary do you use or have you used in the past (vitamin E, vitamin D, calcium, zinc sulfate, and ferrous sulfate)”. Moreover, the pattern of herbal medicines usage was assessed by a researcher-made questionnaire designed based on the study by Hughes et al. In this questionnaire, the subjects were asked to answer the following questions:

“Are you using any herbal medicines? (Yes / No)"
“What types of herbal medicines are you taking?""n
“How often are you taking each herbal medicine?""
“How many herbal medicines are you taking currently?”

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (code: EC-P-93-76-7276). Written informed consent forms were obtained from all participants. The participants were informed about the study objectives and procedures verbally and in written. They were also reassured that participation/non-participation in the study was voluntary and that the information would be published as a whole.

The data were analyzed using the SPSS statistical software, version 21. Descriptive statistics, such as frequency, were used to determine demographic characteristics and usage of herbal medicines. Chi-square test was used to compare RA and control groups with regard to qualitative variables. In this study, “having other diseases or medical problems” was considered as the covariate that might impact the use of herbal medicines. Therefore, ANCOVA was used. In addition, logistic regression analysis was employed to determine the predictors of herbal medicines usage in RA patients. P < 0.05 was considered to be statistically significant.

3. Results

The mean age of the subjects in the RA and control groups was 46.16 (SD = 9.09) and 47.29 (SD = 14.19) years, respectively. The two groups were similar regarding the subjects’ age (t = -1.49, p = 0.13). Moreover, the study participants in the RA and control groups were predominantly female (cases: n = 411, 83.5% vs. controls: n = 434, 86.8%), married (cases: n = 376, 76.7% vs. controls: n = 379, 76.6%), and illiterate or had primary or secondary school education levels (cases: n = 264, 54.8% vs. controls: n = 294, 59.1%). Furthermore, 56.6% of the patients in the case group did not have other diseases or medical problems. Also, more than half of the subjects in the control group did not have any diseases or medical problems. The results showed no significant differences between the two groups regarding demographic and clinical characteristics. The demographic and clinical characteristics of the subjects in the RA and control groups have been presented in Table 1.

According to Table 2, the two groups were significantly different with regard to consumption of vitamin D, calcium, zinc sulfate, and ferrous sulfate (p < 0.05). Accordingly, a higher percentage of the participants in the case group consumed vitamin D, calcium, zinc sulfate, and ferrous sulfate. However, there were no significant differences between the two groups regarding vitamin E intake (p > 0.05). The results also showed a significant difference between the two groups with respect to the number of calcium and zinc sulfate supplements intakes (p < 0.05). Nonetheless, the two groups were similar concerning the number of intakes of vitamins D and E and zinc sulfate supplements (p > 0.05). In this study, 257 subjects (51.4%) in the RA and 182 ones (36.4%) in the control group used herbal medicines, and the difference was statistically significant (χ² = 22.84, p < 0.001). The results also showed a significant difference between the two groups with regard to the types of herbal medicines (χ² = 6.13, p = 0.04) (Table 3).

As shown in Table 3, a significant difference was observed between the RA and control groups regarding the usage of herbal medicines, such as chamomile, cinnamon, and ginger. Based on the results of chi-square test, the percentage of using chamomile was lower in the RA group compared to the control group (p = 0.04). However, the percentage of using cinnamon and ginger was higher in the RA than in the control group (p < 0.05).

According to Fig. 1, the most frequently used herbal medicines among RA patients were thyme (43.4%), chamomile (36.9%), borage (36.8%), lavender (31.2%), ginger (28.5%), and cinnamon (21.5%).

Based on Table 4, after controlling “having other diseases or medical problems” as a covariate, a significant association was found between using herbal medicines and age (F = 1.90, p < 0.001), gender (F = 10.57, p = 0.001), marital status (F = 4.01, p = 0.008), and education level (F = 2.46, p = 0.04). Accordingly, after controlling the covariate, the RA subjects who were female, old, and married and had
high school diplomas used herbal medicines more frequently. According to Table 4, the results of logistic regression analysis on RA patients showed that older individuals used more herbal medicines (odds ratio = 0.98; 95% CI: 0.97–1.00; p = 0.04). Moreover, males used herbal medicines less compared to females (odds ratio = 0.50; 95% CI: 0.34-0.75; p = 0.001). Additionally, married RA patients (odds ratio = 0.98; 95% CI: 0.97–0.99; p = 0.03) used herbal medicines more compared to divorced patients. Furthermore, usage of herbal medicines was 2.45 and 1.64 folds higher among illiterate patients and those with high school diplomas, respectively. Therefore, using herbal medicines was predicted by age, gender, marital status, and education level.

4. Discussion

The present study results showed that the prevalence of herbal medicines usage was higher in the RA group in comparison to the control group. Accordingly, more than half of RA patients used herbal medicines. Consistently, individuals with chronic diseases used herbal medicines usage was higher in the RA group in comparison to the control group. Accordingly, more than half of RA patients used herbal medicines. Consistently, individuals with chronic diseases used herbal medicines.16 According to Table 4, the results of logistic regression analysis on RA patients showed that older individuals used more herbal medicines (odds ratio = 0.98; 95% CI: 0.97–1.00; p = 0.04). Moreover, males used herbal medicines less compared to females (odds ratio = 0.50; 95% CI: 0.34-0.75; p = 0.001). Additionally, married RA patients (odds ratio = 0.98; 95% CI: 0.97–0.99; p = 0.03) used herbal medicines more compared to divorced patients. Furthermore, usage of herbal medicines was 2.45 and 1.64 folds higher among illiterate patients and those with high school diplomas, respectively. Therefore, using herbal medicines was predicted by age, gender, marital status, and education level.

Table 2

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups</th>
<th>Test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E, n (%)</td>
<td>RA</td>
<td>52 (16.3)</td>
<td>63 (14.0)</td>
</tr>
<tr>
<td>Number of vitamin E,</td>
<td>Mean (SD)</td>
<td>16.84</td>
<td>14.87</td>
</tr>
<tr>
<td>Vitamin D, n (%)</td>
<td>RA</td>
<td>126 (36.0)</td>
<td>82 (18.5)</td>
</tr>
<tr>
<td>Number of vitamin D,</td>
<td>Mean (SD)</td>
<td>22.09</td>
<td>19.01</td>
</tr>
<tr>
<td>Calcium, n (%)</td>
<td>RA</td>
<td>299 (70.2)</td>
<td>135 (29.6)</td>
</tr>
<tr>
<td>Number of calcium,</td>
<td>Mean (SD)</td>
<td>26.14</td>
<td>19.03</td>
</tr>
<tr>
<td>Zinc sulfate, n (%)</td>
<td>RA</td>
<td>71 (22.9)</td>
<td>46 (10.5)</td>
</tr>
<tr>
<td>Number of zinc sulfate,</td>
<td>Mean (SD)</td>
<td>239 (77.1)</td>
<td>392 (89.5)</td>
</tr>
<tr>
<td>Ferrous sulfate, n (%)</td>
<td>RA</td>
<td>181 (47.3)</td>
<td>160 (34.9)</td>
</tr>
<tr>
<td>Number of ferrous sulfate,</td>
<td>Mean (SD)</td>
<td>25.52</td>
<td>15.00</td>
</tr>
</tbody>
</table>

1 Intake every month.

Table 3

Comparison of rheumatoid arthritis and control groups regarding the pattern of herbal medicines usage.

<table>
<thead>
<tr>
<th>Herbal medicines</th>
<th>Groups</th>
<th>χ²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using herbal medicines</td>
<td>RA</td>
<td>257 (51.4)</td>
<td>182 (36.4)</td>
</tr>
<tr>
<td>No</td>
<td>243 (48.6)</td>
<td>318 (63.6)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Type of herbal medicines usage</td>
<td>RA</td>
<td>59 (22.7)</td>
<td>55 (30.2)</td>
</tr>
<tr>
<td>1</td>
<td>94 (36.2)</td>
<td>47 (25.8)</td>
<td>p = 0.04</td>
</tr>
<tr>
<td>2</td>
<td>107 (41.2)</td>
<td>80 (44.0)</td>
<td>p = 0.36</td>
</tr>
<tr>
<td>≥ 3</td>
<td>179 (68.8)</td>
<td>123 (67.6)</td>
<td>p = 0.77</td>
</tr>
</tbody>
</table>

4. Discussion

The present study results showed that the prevalence of herbal medicines usage was higher in the RA group in comparison to the control group. Accordingly, more than half of RA patients used herbal medicines. Consistently, individuals with chronic diseases used herbal medicines more compared to the general population. Moreover, it has been reported that arthritis and breathing problems were associated with use of herbal medicines. Furthermore, two-thirds and 39% of RA patients used CAM currently or in the past, with nutritional supplements being the most common form. Some CAM, such as herbal medicines, reduced pain. Indeed, herbal medicines might change the balance between inflammatory and anti-inflammatory cytokines, control angiogenesis, inhibit the migration of arthritogenic leukocytes into the joints, and control the level and quality of immune reactions. Therefore, various types of herbal products might be effective in management of RA and prevention of RA symptoms and complications.

In the current study, 36.4% of the control adults used herbal medicines. Similarly, Rashash et al conducted a study on adults in the United States and reported that 35% of subjects used herbal medicines. In the present study, approximately two-thirds of RA patients used two or more types of herbal medicines. The most commonly used herbal medicines were thyme, chamomile, borage, lavender, ginger, and cinnamon. Thyme might decline the production and gene expression of pro-inflammatory mediators, including Tumor Necrosis Factor-α (TNF-α), interleukin- (IL) 1B, and IL-6, and elevate the markers on the anti-inflammatory IL-10 cytokine. Chamomile was also used for treatment of inflammatory diseases. Borage is full of gamma linoleic acid, which suppresses TNF-α. It elevates prostaglandin-E level that leads to cyclic adenosine monophosphate augmentation. The mechanism clarifies the anti-inflammatory effect of borage on RA. Ginger, as a common

Fig. 1. Pattern of herbal medicines usage among rheumatoid arthritis patients.
Although it was not clear who had recommended sulfate supplements, intakes was higher in the case group in comparison. Furthermore, the number of calcium and zinc participants in the case group consumed vitamin D, calcium, zinc sulfate, and ferrous sulfate. Moreover, the number of calcium and zinc sulfate supplements intakes was higher in the case group in comparison to the control group. Although it was not clear who had recommended the subjects to use these supplements, vitamin D and calcium were used to prevent osteoporosis as a side effect of prednisolone, which is a common drug used by RA patients. Moreover, since some RA patients have anemia, they have to use ferrous sulfate. Therefore, it could be expected that the RA subjects used these supplements more compared to the control group.

Although half of the RA patients in the present study used herbal medicines, no evidence was available regarding their efficacy and safety. Thus, further studies are recommended to be conducted in this regard.

This study had some limitations, the first of which being its cross-sectional design and short duration. Therefore, other longitudinal studies have to determine herbal medicines habit among adult RA patients. Another study limitation was that dose and length of using each herbal medicine was not assessed. Therefore, due attention has to be paid to these variables in future studies. The third limitation was that the subjects were not questioned about the individuals who had recommended them to use the supplements and herbal medicines (physicians, pharmacists, friends, and relatives), their reasons for using or not using herbal medicines, their sources of information about herbal medicines, and their satisfaction with herbal medicines usage. These are suggested to be evaluated in further studies. The forth study limitation was that the subjects were not asked about the way they prepared the herbal medicines. Moreover, some variables, such as concomitant diseases that might have triggered herbal medicines use, were not controlled in this study. Therefore, future studies are recommended to be conducted on RA and control groups without concomitant diseases.

Table 4
The demographic and clinical predictors of herbal medicines usage after controlling for “having other diseases or medical problems” in RA patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Using herbal medicines</th>
<th>Test†</th>
<th>P-value</th>
<th>Logistic regression analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n)</td>
<td>No (n)</td>
<td>F = 2.46</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Age (Mean (SD))</td>
<td>47.00 (13.65)</td>
<td>47.61 (14.77)</td>
<td>F = 1.90, p &lt; 0.001</td>
<td>−0.13 (0.98)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>226 (88.6)</td>
<td>185 (78.1)</td>
<td>F = 10.57, p = 0.001</td>
<td>R (R)</td>
</tr>
<tr>
<td>Female</td>
<td>29 (11.4)</td>
<td>52 (21.9)</td>
<td>p &lt; 0.001</td>
<td>R (R)</td>
</tr>
<tr>
<td>Male</td>
<td>204 (81.9)</td>
<td>172 (71.4)</td>
<td>F = 0.008</td>
<td>−0.36 (0.69)</td>
</tr>
<tr>
<td>Marital status</td>
<td>14 (5.7)</td>
<td>21 (8.7)</td>
<td>R (R)</td>
<td>0.42 (0.25-1.91)</td>
</tr>
<tr>
<td>Single</td>
<td>2 (0.8)</td>
<td>10 (4.1)</td>
<td>p = 0.001</td>
<td>−0.61 (0.54)</td>
</tr>
<tr>
<td>Widowed</td>
<td>2 (0.8)</td>
<td>10 (4.1)</td>
<td>R (R)</td>
<td>0.27 (0.18-1.61)</td>
</tr>
<tr>
<td>Divorced</td>
<td>26 (10.5)</td>
<td>48 (20.4)</td>
<td>F = 2.46</td>
<td>0.09 (2.45)</td>
</tr>
<tr>
<td>Education level</td>
<td>40 (16.2)</td>
<td>27 (11.5)</td>
<td>p = 0.04</td>
<td>1.43-4.20</td>
</tr>
<tr>
<td>Illiterate</td>
<td>68 (27.5)</td>
<td>55 (23.4)</td>
<td>R (R)</td>
<td>R (R)</td>
</tr>
<tr>
<td>Primary school</td>
<td>26 (10.5)</td>
<td>48 (20.4)</td>
<td>F = 4.01</td>
<td>0.89 (2.45)</td>
</tr>
<tr>
<td>Secondary school</td>
<td>76 (30.8)</td>
<td>64 (27.2)</td>
<td>R (R)</td>
<td>0.001</td>
</tr>
<tr>
<td>High School</td>
<td>37 (15.0)</td>
<td>41 (17.4)</td>
<td>0.001</td>
<td>1.43-4.20</td>
</tr>
<tr>
<td>Academic</td>
<td>37 (15.0)</td>
<td>41 (17.4)</td>
<td>p = 0.001</td>
<td>R (R)</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.
† ANCOVA and “having other diseases or medical problems” as a covariate.

The results of this study indicated that a higher percentage of the participants in the case group consumed vitamin D, calcium, zinc sulfate, and ferrous sulfate. Furthermore, the number of calcium and zinc sulfate supplements intakes was higher in the case group in comparison to the control group. Although it was not clear who had recommended dietary constituent, has antioxidant and anti-inflammatory properties and has been used to treat inflammatory diseases for thousands of years. It has also been used to prevent or reduce RA signs, symptoms, and extra-articular complications and decrease pain in osteoarthritis patients. Researchers believed that cinnamon had anti-inflammatory and anti-arthritis potentials. Cinnamon changed ankle diameter, arthritic score, and C-reactive protein serum levels. In addition to these scientific data, Iranian tradition has suggested the use of lavender for arthritis, chamomile for muscle tightness, peppermint for inflammation, cinnamon for inflammation, arthralgia, and headache, ginger for general pain, and valerian for pain and inflammation. Since RA is an inflammatory disease with pain and the above-mentioned herbal products have anti-inflammatory effects, RA patients might be encouraged to use them more.

Lavender was another herbal medicine used by the study subjects. Lavender could reduce stress, anxiety, and pain in osteoarthritis patients. It was reported that 60% and 62% of RA patients suffered from depression and anxiety, respectively. Moreover, approximately one-third of female RA patients suffered from neuropathic pain. Global pain at rest was also higher in the RA than in the control subjects. Lavender has anti-inflammatory effects. These might be due to an antagonism on the n-methyl-D-aspartate receptor and inhibition of serotonin transporter. In addition, lavender had anti-inflammatory activities and decreased edema. Therefore, RA patients tend to use lavender in their daily diets.

The current study showed that female, married, and old patients and those with high school diplomas tended to use herbal medicines more compared to males, non-married patients, and those with academic degrees. Similarly, it has been reported that women and individuals with higher education levels suffering from chronic diseases were most likely to use CAM. Researchers also reported a significant association between using CAM or herbal medicines and age, gender, marital status, and education level. Generally, women prefer to address their health problems by herbal medicines. This might be attributed to their easier access to social networking to purchase herbal medicines. Moreover, individuals with higher education levels may have higher tendency to explore other therapies. Therefore, they prefer to use herbal medicines more than other people.

5. Conclusion
This study showed that 51.4% of the subjects in the RA group and 36.4% of those in the control group used herbal medicines. The most common herbal medicines used by the RA subjects were thyme, chamomile, borage, lavender, ginger, and cinnamon. In addition, males used herbal medicines less compared to females. Besides, married RA patients used herbal medicines more compared to divorced patients. Moreover, illiterate patients and those with high school diplomas were more likely to use herbal medicines. Yet, further studies are required to evaluate the efficacy and safety of herbal medicines in RA patients.
Declaration of conflict and interest

None declared.

Acknowledgments

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