Original Article

Clinical effect of continuous nursing combined with total glucosides of paeony on rheumatoid arthritis

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Abstract

Background: The dried root of *Paeonia lactiflora* has been used to treat arthritis and diseases like hepatitis in countries like Japan, Korea, and China. This practice of treatment with plant roots is ancient and has been used for more than 1200 years. Water or ethanolic extract of the plant root is known as the glucosides of paeony containing more than 15 different components. Paeony effects mainly through receptors like TGF-beta IL-2 receptors.

Objective: This paper aims to identify the effectiveness of paeony as compared to other medications in the treatment of arthritis.

Method: A systematic review of previously published articles in the past ten years, which were published on rheumatoid arthritis were reviewed and a meta-analysis was performed, which included the paeony treated group and any other medication group used in the treatment of arthritis, using the R statistical software. The results obtained were summarized.

Result: After conducting the meta-analysis, a significant difference was found in the serum level of Erythrocyte Sedimentation rate (ESR) in the glucosidic (GP) and leflunomide (LF) combination or only leflunomide groups (at 95% CI (Confidence interval) GP+LF value -8.67 and only LF value is -3.68), for C reactive protein (at 95% CI) GP+LF value -8.67 and only LF value is -3.04) and rheumatoid factor (at 95% CI GP+LF value -21.81 and only LF value is -8.15).

Conclusion: The analysis indicates that paeony and other medicine combined therapies are more beneficial as compared to therapies which utilize only medication. These finding has been supported by other research findings. Though this study has been conducted using a small sample, it indicates a beneficial outcome for arthritis treatment. These findings may be beneficial in the future and may prove to be a promising treatment for arthritis patients. [*Ethiop. J. Health Dev.* 2021: 35(4) 375-379]

Keywords: Paeony, rheumatoid arthritis, ESR, CRP, rheumatoid factor

Introduction

Rheumatoid arthritis is a chronic disease that affects the muscles, connective, fibrous tissue, and tendons. It generally happens during the age groups of 20 to 40 years of age. This disease can cause pain and deformity in the affected area. The significant pathological alterations of arthritis are chronic inflammation in the synovial area (1-4). Inflammation also spreads in the ligaments; the subchondral bone destroys the articular cartilage, joint capsule, and bones and causes various other symptoms (5, 6). The main characteristics of the disease are progressive exacerbation and easy recurrence which is incurable. In China, the arthritis patients' disability rate has increased as follows; in 5 years, to about 9% in 10 years to about 43% and in 15 years up to about 61%, which increases with disease duration (7-10). Arthritis not only reduces patients' physical condition but also causes economic burdens in the family. Delaying the progression of arthritis and finding a cure is imperative for researchers and health professionals (11). There is a long history of the use of Chinese medicine to treat arthritis, with many associated benefits. White is traditional medicine broadly used by doctors of China. It has been found that the main constituent of the group is glucosides, which is known as white glucosides. Nowadays, Glucosides has been processed into a patent drug in China and well utilized in the treatment of arthritis. In an animal experiment, total glucosides have been found to treat inflammation and autoimmune response. Glucoside effects via interleukin one inhibition, TNF-α (tumor necrosis necrosis factor- α) inhibition factor-a) inhibition, and the proliferation of Synovial cell, NF-kβ signaling and Interleukin-2 regulation pathways (12, 13). While in the trial phase, glucoside inhibits rheumatoid factor, ESR or erythrocyte sedimentation rate and C-reactive protein, which decreases inflammation and controls arthritis. The combined effect of glucoside and another medication is more effective than any other individual treatment (14-17) though some defects exist in this research. Due to the limitations of a systematic review, this research includes a meta-analysis of the clinical effectiveness of glucoside in arthritis therapy.

Components of Glucosidic Paeony:

Extracts from *Radix Paeoniae Alba* is called total glucosides of paeony. These extracts are either ethanolic extract or water extract, which contains 15 components such as, oxy benzoyl-paeoniflorin, lactoferrin, paeoniflorin, phenol (18, 19). Major compounds are monoterpene structure. The major component of the glucoside of paeony is shown in figure 1. Paeoniflorin ($C_{23}H_{28}O_{11}$) is the most abundant; the water-soluble compound has a pharmacological property. A preparation for glucosides of paeony was accepted by FDA China for arthritis treatment. Recently much research has been organized on the glucosides of paeony for their different pharmacological properties.

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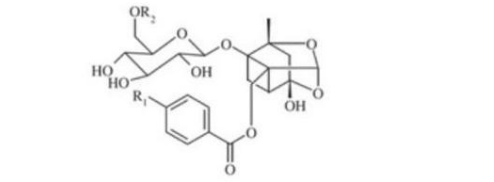
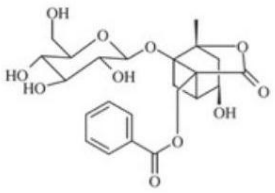
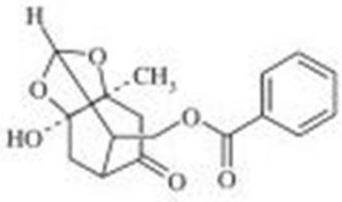


Paeoniflorin: R_1=H; R_2=H
Oxypaeoniflorin: R_1=OH; R_2=H
Benzoyl-paeoniflorin: R_1=H; R_2=Benzoyl (C_6H_5CO)
Oxybenzoyl-paeoniflorin: R_1=H; R_2= 4-OH-benzoyl



ALBIFLORIN

LACTIFLORIN



PAEONIFLORIGENONE

Figure 1: The components of total glucosides of paeony

Materials and Methods

In this meta-analysis study, patients (age group-20-40 years) with rheumatoid arthritis are included. The patients were included in a randomized controlled trial with a specific dose of Glucoside capsules daily, which were available at the market (standard 0.3g). Each capsule contains 104mg paeoniflorin. As these capsules contain volatile oil, therefore, in this study, no alcohol extract or water extract was included, whether in a single capsule or combined with other doses of the capsule. The control group included a placebo or any other conventional treatment. In this study, leflunomide (LF) was taken in the other treatment group. In this study, relevant research and review articles were collected from 2010-2019. Abstract only and conference proceedings were not included in this study. From the internet databases such as Embase, control trial register, PubMed, ClinicalTrials.gov, etc. Articles of interest were downloaded and stored based on their relevance which was assessed from reviewing the abstract and literature, and any queries related to the literature was resolved through consultation with the authors of the published articles and/or other experts in the field. However, if a decision around the problem was not reached through consultation, then the literature was classified as pending. Data was extracted from databases and studied in a systematic and well-defined manner. The first author extracted the following information for all the articles of interest; name, trail group number, control group number, place (Country), Publication period, study type, significant outcome, minor outcomes, and adverse events. For further information, if necessary, communication was carried out with the respective authors (20).

Clinical effective rate considered as Major outcomes and Rheumatoid factor of serum, C-reactive protein and Erythrocyte sedimentation rate was considered, McMaster and Western Ontario, and the antagonistic effect was considered minor outcomes for this study. The Cochrane risk-of-bias tool (version 2) was also utilized in this study (21). All data analysis was done using RStudio (version 1.3.1056). Binary variables are denoted by the risk ratio (RR) and a 95% CI (confidence interval) was used, while the continuous variable was denoted by a 95% CI and a mean difference (22). A chi-squared test was done for testing the heterogeneity with a 0.1 significance level (α=0.1). Simultaneously I^2 tests were done for heterogeneity quantification. $I^2 \geq$ 50% was taken as heterogeneity significant (23). A subgroup analysis was also conducted for finding heterogeneity within studies. Gender, control group, and treatment duration were also included in the subgroup hypothesis. A Sensitivity analysis was carried out to find the result's robustness utilizing effective measures (Odd ratio and risk ratio) and statistical models (random effect or fixed effect). Publication bias was assessed using the Egger test. A value of $P<0.05$ indicated that the publication bias was in existence. The evaluation quality was rated as high, medium, or low.

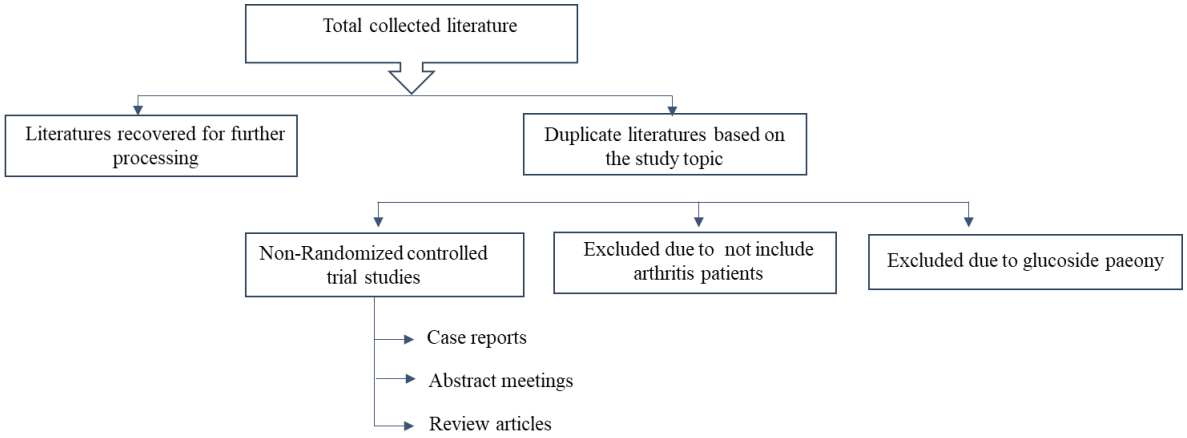


Figure 1. Express of Study chart as per PRISMA guidelines

Table 1. list if literatures included in final meta-analysis

Total Collected literature	Duplicate study			Literatures for further processing
75	19			56
	Abstract meeting	**Review articles**	**Non-Randomized controlled trails**	
	6	**4**	**9**	

Results

A total of 75 articles were selected during the literature search. 19 pieces of literature were recognized as duplicate based on the study topic and 56 pieces of literature were recovered for further processing. Post-content review included nine non-Randomized controlled trial studies, which included case reports, six abstract meetings, and four review articles were excluded from further analysis. Additionally, seven studies were excluded due as they did not include arthritis patients and 24 studies where glucoside paeony was not applied were excluded from the meta-analysis. A total of 9 publisher trials, including 320 cases and 325 controls were considered for meta-analysis. All included literature was available from 2010 to 2019. All 9 Randomized control trials occurred in China and were published in Chinese articles. The participant numbers varied from between 39 to 120. The duration of the treatment in the considered studies varied from 6 to 30 weeks. 5 studies had a therapeutic effect that were assessed as follows; "Significant effective," "Effective," and "non-effective." seven trials reported adverse events. Additionally, seven trails reported an erythrocyte sedimentation rate. While five trials reported a rheumatoid factor lastly, four trials reported C-reactive proteins.

The study quality was found to be very poor after conducting the bias assessment risk, for all seven reported randomizations. This was due to neither of them reporting their specific methods used. Furthermore, seven studies did not mention the study's location, participant number, and nine studies indicated an incomplete outcome despite not having an identifiable bias. To evaluate the effect of the glucosidic and leflunomide combination effect or leflunomide alone, data was taken from the five trials, which considered 319 patients in the 20-to-40-year age group. As no heterogeneity was observed, A fixed-effect model approach was undertaken to pool data (I^2 value 0% and P-value is 0.89).

A significantly higher effectivity rate was recognized in the leflunomide group as compared to the leflunomide combination group (Odd ratio=4.30, CI at 95% is 2.01 to 9.17 and P-value 0.001). Seven trials reported glucosidic and leflunomide combinations or only leflunomide trials on serum level of the Erythrocyte Sedimentation rate (ESR), and two trials reported on C-related proteins. At the same time, five trials reported on the rheumatic factor. Furthermore, a random effect model was used for analysis. The results indicated a significant difference in the serum level of the Erythrocyte Sedimentation rate (ESR) in the glucoside (GP) and leflunomide (LF) combination or only leflunomide groups (at 95% CI (Confidence interval) GP+LF value -8.67 and only LF value is -3.68), for C reactive proteins (at 95% CI (Confidence interval) GP+LF value -8.67 and only LF value is -3.04) and rheumatoid factor (at 95% CI (Confidence interval) GP+LF value -21.81 and only LF value is -8.15). For all trials, safety profiles were also assessed. The major adverse events, which included liver abnormalities, defined as alanine aminotransferase, or

aspartate aminotransferase was >1.5 times more than the upper limit in the serum level gastrointestinal abnormalities with emesis, nausea, and diarrhoea. A fixed-effect model was considered for data analysis due to no heterogeneity in data being observed (P value>0.1 and I^2 value is <50%). Analysis results indicated very high liver abnormalities (Odd ratio= 0.31, 95% Confidence interval = 0.11 to 0.83 and P-value is 0.01). in the LF group as compared to the GP and LF combined groups. No significant variation in gastrointestinal abnormalities was found (Odd ratio is 0.16, 95% Confidence interval is o.80 to 3.08, and P-value is 0.17).

Discussion

In this analysis, nine trials, including 320 cases and 325 controls were considered for meta-analysis. The results indicate a favorable result for only leflunomide therapy as compared to glucosidic and leflunomide combination therapy. The practical evaluation system grounded on the developed sign and symptom may be leading to heterogeneity (24-25). Only one study explained the clinical results defined by ACR or American College of Rheumatology criteria. This study indicates a high response rate in the GP and LF combination groups as compared to the LF only group (26).

Additionally, according to the European League Against Rheumatism (EULAR), a guided trial indicated a better treatment effect in GP and LF combinations as compared to only LF combinations (27). This study also incorporated standardizations like EULAR or ACR and increased the sample size for more GP and LF combination studies in arthritis treatments (28). The data indicates that GP and LF combination therapy has a better effect as compared to only LF therapy. To examine drug safety, adverse events must be considered. A significant amount of arthritis patients who were treated with only LF, had more liver abnormality as compared to GP and LF combination therapy. However, no significant gastrointestinal abnormality was found.

This study's primary limitation was the trial number, and patient numbers which were minimal in the studies selected for review. In the bias assessment analysis, the analysis result was limited due to the smaller number of patients and trials. Some studies were of inferior quality. However, all trials were randomly designed and only a few of them reported the randomization procedure. In some literature, the location and participant numbers were not available, which resulted in higher bias detection. Heterogeneity was identified and included in the trials. Apart from all these limitations, dose differences, treatment period and evaluation criteria were the primary sources of heterogeneity. Additionally, all the trials in the present meta-analysis occurred in China, which resulted in an increased bias. Therefore, this meta-analysis should be considered for further analysis in the future.

Conclusion

Even though Glucosidic paeony therapeutic effect combined with other medicine combinations may not be better than a single medicine therapy, still a combination therapy of Glucosidic paeony and leflunomide significantly reduces the Erythrocyte Sedimentation rate, C reactive protein, and the rheumatoid factor. Additionally, this combination of therapy is very safe as compared to a single medicine therapy. This result has been verified by the small sample in this study and may benefit further from a larger sample.

Abbreviation

GP: Glucoside paeony; **ESR**-Erythrocyte Sedimentation rate; **CRP**-C reactive protein; **RF**-rheumatoid factor; **EULAR**-European League Against Rheumatism; **LF** -Leflunomide; **FDA**- Food and drug administration.; **CI-** confidence interval; **RR**-Risk Ratio.

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