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Original Article

A Pilot Clinical Study of the Efficacy and Safety of Phellinus Linteus (Sanghuang) Extract Treatment for Knee Osteoarthritis

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ABSTRACT

Background: To evaluate the efficacy and safety of Phellinus linteus (PL) extract for the treatment of knee osteoarthritis (KOA) a pilot clinical study was performed.

Methods: There were 24 patients with KOA who enrolled in this double-blind, randomized, controlled, clinical trial. There were 3 groups: PL 1,000 mg/day (PL 1,000), PL 1,500 mg/day (PL 1,500), and dextrin 3,000 mg/day (placebo). Patients took capsules twice a day, 3 capsules at a time, over 8 weeks. Patients were monitored prior to treatment (Visit 1: Week 0), and followed up every 4 weeks (Visit 2: Week 4 and Visit 3: Week 8) where outcome measurements were taken. The primary outcome measure was the score from the Korean version of the Western Ontario and McMasters Universities from baseline to Week 8. The secondary outcomes were measurements from the visual analog scale, quality of life scale, erythrocyte sedimentation, and c-reactive protein. Adverse events were recorded at every visit.

Results: The Korean version of the Western Ontario and McMasters Universities score showed the greatest improvement in symptoms of KOA in the PL 1,500 group compared with the placebo group. The erythrocyte sedimentation tended to decrease in the PL 1,500 group compared with the placebo group (which was within the normal range). The visual analog scale score decreased in all groups, with no significant differences between groups. No adverse events related to PL were reported. There were no abnormal hematological or physical findings.

Conclusion: This pilot clinical trial was the first step to assess the efficacy and safety of PL used in the treatment of patients with KOA.

Introduction

In modern society, as society gradually becomes an aging society, the problem of chronic disease is also emerging. Knee osteoarthritis (KOA) is the most common form of degenerative arthritis. It is characterized by pain and functional limitations due to wear of articular cartilage, and affects the patient's physical, mental, and social health [1]. Degenerative changes in articular cartilage occur mostly in elderly people over the age of 55 and are exacerbated by aging, knee joint lesions and injuries, varus and valgus deformities, infections, or other mechanical load associated with arthritis. Initially pain and discomfort in the knee joint appears and as arthritis progresses, it is difficult to walk or stand, and synovial hypertrophy, joint effusion, muscle spasms, muscle atrophy, restriction of motion, and joint lock may occur [2].

Currently, treatment of osteoarthritis focuses on relieving symptoms by reducing the pain and swelling. Treatment methods commonly used include pharmacological drugs, physical treatment, surgery, steroid injection treatment, and non-steroidal anti-inflammatory drugs (NSAIDs) [3,4]. Osteoarthritis is a chronic

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disease where most NSAIDs are taken for a long time which may cause side effects such as gastrointestinal side effects and kidney toxicity [5]. For this reason, the demand for medicines that are safe for long-term use and are effective is gradually increasing [6,7]. In line with this trend, various studies on osteoarthritis using herbal medicines or natural products have recently been conducted in Korea [8].

Phellinus linteus (PL) sanghuang is a medicinal mushroom extract known for anticancer and immune enhancing properties. Ergosterol, contained in PL, inhibits the formation of new blood vessels and blocks the supply of nutrients to growing tumors, thereby inhibiting the growth of cancer [9]. In a study where a rat model of osteoarthritis (MIA-induced) examined the effect of PL treatment by measuring changes in hind limb weight bearing, a significant beneficial difference was reported between treatment and control conditions [10]. The effect of PL in osteoarthritis has not been determined in clinical studies in Korea.

To investigate the efficacy of PL on KOA (in patients had knee pain for more than 6 months), a pilot clinical study was performed using PL 1,000 mg/day or PL 1,500 mg/day or dextrin 3,000 mg/day for 8 weeks and outcome measures [Korean Western Ontario and Mcmaster Universities (K-WOMAC), visual analogue scale (VAS), Euro quality-of-life 5 dimension (EQ-5D), erythrocyte sedimentation (ESR), and c-reactive protein (CRP)] were assessed.

Materials and Methods

Patients

Patients were openly recruited from March 13, 2020 to June 5, 2020 through the ins and out-of-hospital recruitment announcements of Cheonan Korean Medicine Hospital of Daejeon University. Inclusion and exclusion criteria are shown in Table 1. Patients who participated received a detailed explanation, gave signed written consent, and were enrolled into the study. The double-blind, randomized, controlled, clinical trial was conducted at the clinical trial center of Cheonan Korean Medicine Hospital of Daejeon University, and was conducted under the approval of the Institutional Bioethics Committee of Cheonan Korean Medicine Hospital of Daejeon University based on the declaration of Helsinki (approval no.: DJUMC-2019-BM-11-2).

Materials

The PL [Korea New Drug Co., Ltd. (www.hsp.co.kr, Korea)] strains were isolated from the fruiting bodies of PL and were passaged (yeast extract 4, malt extract 10, and glucose 4 g/L medium), and incubated at 29 ± 1°C for about 15 days. Thereafter, the sub cultured strain was fragmented using a cork borer, suspended in sterilized distilled water, and cultured in a shaking incubator at 29 ± 1°C for 6 days. The cultured primary seed was inoculated into a 14 L fermenter, and purified water was added 10 times to the mycelium obtained by mass cultivation, followed by extraction at 100°C for 15 hours. After filtering the extract, it was concentrated to 30 brix at a rate of 2 kL per hour. After adding alcohol, the precipitated precipitate, and an excipient (dextrin) were mixed, spray-dried, and collected to be used.

Study design

This pilot clinical trial was conducted as a double-blind, randomized, and controlled comparative trial. For randomization, patients were assigned 1:1:1 to the test group and the control group using a block randomization method. The randomization

Table 1. Study Criteria.

Inclusion criteria
1. 40-75-year-old male and female with knee pain for 6 mo or more
2. A Kellgren-Lawrence grading scale of Grade 1 or Grade 2 on both knees using X-ray examinations
3. If patient is taking arthritic medications, patient has not changed his/her medication within the past mo
4. Patient who agrees to participate in the study and signs the informed consent form

Exclusion criteria
1. A patient who is currently being treated for clinically significant acute or chronic conditions/diseases: cardiocerebrovascular system, immune system, respiratory system, hepatobiliary system, kidney and urinary system, nervous system, musculoskeletal disorders, mental, infectious, and blood and tumor
2. A person whose arthritis is due to a specific factor other than degenerative
3. Those who have a history of fractures of the lower limb within the last 3 mo
4. Those who have creatinine level in the blood that is > twice the normal upper limit of the organ
5. A patient who has received an intra-articular injection with hyaluronic acid or steroids within 3 mo of the study
6. Those who have an AST or ALT level that is 3 x higher than normal upper limit in the blood
7. Those who have uncontrolled hypertension (over 160/100 mmHg)
8. Patients taking medication for psychiatric disorders
9. Those who have been taking herbal medicine for the last 2 w
10. Those who have received other research drugs within the last 4 w
11. Individuals who must continue to take drugs that they think may affect the results of this clinical trial
12. Those who have a history of gastrointestinal resection
13. Those who have had artificial joint surgery
14. Those who are pregnant or breastfeeding
15. Is an alcoholic or has alcoholic drinks > 4 times/w
16. Persons with hypersensitivity to the research food or its components
17. Any other researcher deemed inappropriate for this test

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

details were generated by a statistician using nQuery Advisor 7.0 (or SAS Version 9.0 or SPSS Version 21.0), and the statistician put the randomization details for each patient in a non-permeable bag which was sealed, and supplied to the research manager. The test group and the control group were classified into 3 groups (Table 2), and 8 patients were assigned to each group. Patients took capsules for clinical trials twice a day, 3 capsules at a time, and the total duration of drug administration for each participant was 8 weeks (Table 3).

The primary outcome measure was the K-WOMAC scores from baseline to Week 8. The secondary outcomes were scores

Table 2. Intervention Description.

Treatment	Group 1 (PL 1,000) (500 mg per 1 capsule = PL 167 mg, dextrin 333 mg)	PL 1,000 mg/d
	Group 2 (PL 1,500) (500 mg per 1 capsule = PL 250 mg, dextrin 250 mg)	PL 1,500 mg/d
Control	Placebo (500 mg per 1 capsule = dextrin 500 mg)	Dextrin 3,000 mg/d

PL, Phellinus linteus.

Table 3. Study Schedule and Outcome Measurements.

	Study period			
	Screening	Visit 1	Visit 2	Visit 3
	-2-0	Week* 0	Week 4*	Week 8*
Enrollment				
Investigation of demographic information	√			
Eligibility screen	√			
Informed consent	√			
Allocation		√		
Interventions				
PL 1,000 mg		√	√	
PL 1,500 mg		√	√	
Placebo		√	√	
Assessments				
K-WOMAC		√	√	√
EQ-5D		√	√	√
VAS		√	√	√
Checking both knee X-ray	√			
AST, ALT, ALP, GGT, total cholesterol, glucose, total bilirubin, BUN, creatinine, CRP, ESR, CBC	√		√	√
RA factor, uric acid	√			
TG, HDL, LDL, Na, K, Cl	√			√
Checked for adverse events			√	√
Confirmation of concomitant medicine change		√	√	√
Confirmation of medication adherence			√	√

* The error range for each visit was set to ± 8 days.
√, scheduled interventions or assessments were conducted.
K-WOMAC, Korean Western Ontario and Mcmaster Universities; VAS, visual analogue scale; EQ-5D, Euro quality-of-life 5 dimension; ASL, aspartate transferase; ALT, alanine transferase; ALP, alkaline phosphatase; GGT, ; BUN, blood urea nitrogen; CBC, complete blood count; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ESR, erythrocyte sedimentation; CRP, c-reactive protein.

from the VAS, EQ-5D-3L, the ESR, and the level of CRP. The outcomes were measured values before treatment (Visit 1), during (Visit 2), and at the end of treatment (Visit 3). In addition, in order to compensate for the small number of patients, the pooled standard deviation and effect size of the validity evaluation variables were calculated. In this pilot study, the effect size was presented as Cohen's d value calculated by dividing the difference between the mean values of the 2 groups by the integrated standard deviation in order to standardize the difference between the means of the groups to be compared as previously described [11].

Statistical analysis

For statistical analysis, an independent t test was performed when the data were normally distributed to test the difference in the continuous variable between the 2 groups, and the Analysis of Variance (ANOVA) test was performed otherwise. To test the difference according to the timepoint within the group, a paired t test was performed if the data followed a normal distribution, and a Wilcoxon's signed rank test was performed otherwise. Shapiro–Wilk's test was used to test the normality of continuous variables, and the significance level for statistical significance test was 5%. When a missing value occurs for an evaluation variable or when a patient dropped out before the end of the trial, data analysis was performed with the most recently measured data as if it were obtained at that point in time (Last Observation Carried Forward Analysis).

Results

Patients' general characteristics

There were 25 individuals recruited for this clinical trial who were screened, of which 24 were enrolled and randomized to a group: PL 1,000, $n = 8$; PL 1,500, $n = 8$; and Placebo: $n = 8$. During the study, 2 individuals from the placebo group and 1 from the PL 1,500 group dropped out, leaving a total of 21 who completed the study (Fig. 1). There was no statistically significant difference in the patients' general characteristics and baseline assessment values (Tables 4, S1 and S2).

K-WOMAC

There was a difference in homogeneity between the 3 groups on Visit 1 using the primary outcome assessment K-WOMAC, so the results were analyzed using the amount of change between groups. In comparison between groups using K-WOMAC scores, the amount
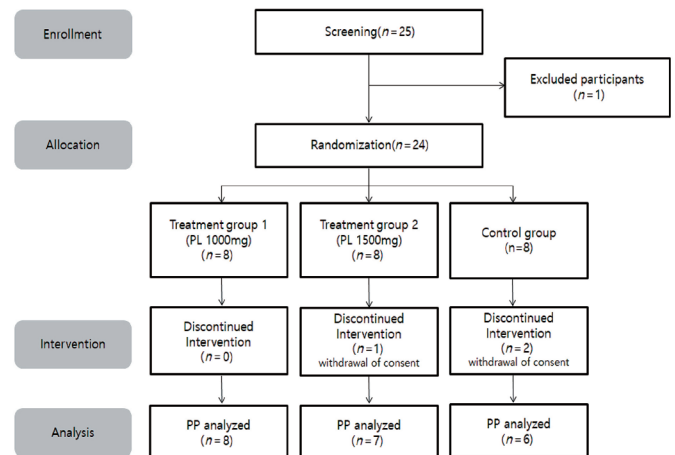

Fig. 1. Study flow chart.

Table 4. Demographic Characteristics.

Variable		Placebo ($n = 6$)	PL 1,000 ($n = 8$)	PL 1,500 ($n = 7$)	p
Sex	Male	0 (0.0)	1 (12.5)	0 (0.0)	0.426*
	Female	6 (100.0)	7 (87.5)	7 (100.0)	
Alcohol consumption	No	5 (83.3)	7 (87.5)	7 (100.0)	
	Moderate	1 (16.7)	1 (12.5)	0 (0.0)	0.556*
	Heavy	0 (0.0)	0 (0.0)	0 (0.0)	
Smoking	No	6 (100.0)	7 (87.5)	7 (100.0)	
	Past	0 (0.0)	1 (12.5)	0 (0.0)	0.426*
	Present	0 (0.0)	0 (0.0)	0 (0.0)	
Age (y)		56.83 ± 7.78	56.13 ± 8.61	57.29 ± 3.77	0.950†
Weight (kg)		60.48 ± 10.66	60.65 ± 7.04	56.19 ± 8.71	0.564†
Height (cm)		154.20 ± 5.75	155.96 ± 5.21	155.49 ± 4.02	0.950‡

Data are presented as n (%) or mean ± SD.
* p values were derived from Chi-square test.
† p values were derived from ANOVA.
‡ p values were derived from Kruskal-Wallis test.

of change was −6.67 ± 19.71 in the placebo group, −0.5 ± 8.47 in the PL 1,000 group, and −17.14 ± 19.10 in the PL 1,500 group. The mean difference between the treatment group and the placebo group was 10.47. In the PL 1,500 group, the K-WOMAC value showed a tendency to decrease after 8 weeks compared with the baseline. There was no significant difference between the groups (S3 and 4).

VAS

In the intra-group comparison, the amount of VAS score change was −20.17 ± 16.59 (p = 0.031) in the placebo group, −19.38 ± 10.88 (p = 0.001) in the PL 1,000 group, and −20.14 ± 29.78 in the PL 1,500 group. In all 3 groups, the VAS value showed a tendency to decrease after 8 weeks compared with the baseline, but there was no significant difference between the groups (S3 and 4).

ESR

In comparison between groups, the amount of ESR change was 1.83 ± 4.26 in the placebo group, −0.38 ± 2.88 in the PL 1,000 group, and −1.86 ± 4.1 in the PL 1,500 group. In the PL 1,500 group, the ESR value decreased most significantly after 8 weeks compared with the baseline and compared with the placebo group (S3 and 4).

EQ-5D-3L

The amount of EQ-5D-3L change within and between groups was −0.01 ± 0.09 in the placebo group, 0.03 ± 0.08 in the PL 1,000 group, and 0.07 ± 0.09 in the PL 1,500 group. There was no significant difference between groups (S3 and 4).

CRP

In the intra-group and inter-group comparisons, the amount of CRP change was −0.05 ± 0.62 in the placebo group, −0.01 ± 0.12 in the PL 1,000 group, and 0.27 ± 0.47 in the PL 1,500 group. There was no significant difference between groups (S3 and 4).

Safety assessment

In this clinical trial, a total of 3 adverse reactions were reported in 3 patients (12.5%), and the details are shown in Table 5. Mild adverse reactions included symptoms of indigestion and constipation, but it was judged that there was no causal relationship with PL. There were no serious adverse reactions (S3 and 4).

Discussion

Osteoarthritis, also referred to as degenerative osteoarthritis, is one of the most common types of arthritis, resulting in pain and inflammation mainly due to degenerative damage to the cartilage, which plays a role in protecting joints [12]. Among the commonly used pharmaceutical drug treatments for osteoarthritis, NSAIDs inhibit cyclooxygenase-2 (COX-2) [13]. COX-2 is an inducible enzyme expressed by inflammatory cells and is not present in normal tissues. It regulates the production of prostaglandin, which plays an important role in inflammation or pain, and the expression of COX-2 has been reported to be increased 10 to 80 times in the inflamed area [14]. However, long-term use of NSAIDs has been reported to worsen arthritis by reducing the synthesis of glycosaminoglycans, and this is in addition to an increased risk of heart failure and kidney impairment in some types of patients [15]. For these reasons, interest in safe and effective natural products is gradually increasing.

The main components of PL (sanghuang) are polysaccharides which have antitumor, immune enhancement, and anti-inflammatory effects [16]. In general, the polysaccharides contained in PL include glucans, schizophyllan, heteroglycan, lentinan, krestin, and galactomannan, and their efficacy in treating a condition/disease may vary depending on the relative content of these ingredients [17]. PL has been reported to have anti-cancer and immune functions with detailed mechanisms for anti-inflammatory functions being actively pursued [18]. Beta-glucan is a key ingredient in the anti-inflammatory effect of PL, and it is thought that the polysaccharides from PL determine the efficacy of PL [19].

As such, several studies have revealed the anti-inflammatory effect of PL, but no clinical studies in Korea that evaluated the efficacy of PL on the human body have been reported. Therefore, this pilot clinical trial planned to investigate the effect of PL on KOA. In this pilot study, the efficacy and safety were measured and compared in adults aged 40 to 75 years with knee pain (6 months or longer) after taking PL or placebo for 8 weeks.

Table 5. Adverse Events.

Symptom	No. of occurrences			Severity*	Causal relationship with test drug†	Group
	Number	%	R-number			
Indigestion	1	33.3	001	A	3	PL 1,000
Constipation	1	33.3	018	A	4	PL 1,500
Cystitis	1	33.3	019	B	5	PL 1,000
Total	3	100	–	–	–	–

* A-Mild, B-Moderate, C-Severe.
† 1-Clearly related, 2-Thought to be relevant, 3-Likely to be related, 4-Not considered relevant, 5-Clearly not relevant, 6-Unknown.

K-WOMAC was selected as a tool to evaluate the efficacy of PL treatment on KOA. It is a questionnaire for arthritis and joint disease, and it is reported that the reliability and validity of pain measurement are high due to the instrument validity and sensitivity to change [20]. In addition, unlike other survey tools, the WOMAC index consists of 24 questions on functional limitations related to knee pain, and can be evaluated in detail by integrating functional disorders related to knee pain and the degree of restriction of specific movements [21]. This assessment tool measures 5 types of pain-related activities, 2 types of stiffness, and 17 types of physical activity. The higher the score, the worse the symptoms and the more restricted the individual's activity [22]. Due to these characteristics, K-WOMAC is widely used as a tool to evaluate pain and daily living functions in patients with arthritis knee pain. In this study, as a result of analyzing the amount of change in K-WOMAC scores before/after taking PL, the PL 1,500 group showed a tendency to change significantly compared with the placebo group.

To measure changes in knee pain, the VAS was selected as the secondary outcome evaluation of efficacy. This is a method in which the patient indicates the level of pain on a straight 10 cm line with the worst imaginable pain to the far right (VAS score of 10). The VAS is often used as a pain evaluation index because it is easy to use for the patient, and scoring can minimize the involvement of the researcher. It has been reported to be statistically sensitive, such that it can confer significance even when the target group is small or the difference between groups is small [23]. In this study, as a result of analyzing the amount of change in the VAS score before/after treatment, the VAS value in all 3 groups showed a tendency to decrease after 8 weeks compared with the baseline. The change before/after treatment was statistically significant in the placebo group, and the PL 1,000 group, but not statistically significant in the comparison between groups.

The EQ-5D-3L was selected as an outcome evaluation tool to measure quality of life. Among several tools for measuring health-related quality of life, EQ-5D-3L is one of the most widely used tools because it is simple and it is easy to measure overall health-related quality of life [24,25]. In this study, the change in the EQ-5D-3L score before/after treatment was not statistically significantly different when comparing within and between groups.

When the results of the K-WOMAC, VAS, and EQ-5D-3L were analyzed, the results of the 3 efficacy evaluation variables showed different trends for each of the 3 groups. This may be because the study was conducted with a small sample size. Since the purpose of this pilot study was to explore the efficacy of PL, it seems appropriate to report the tendency of change after taking PL.

In addition, CRP and ESR were selected as secondary outcome evaluation variables measuring efficacy for the evaluation of arthritis. ESR is an indirect indicator of inflammation and is affected by fibrinogen, immunoglobulins, rheumatoid factors, age, sex, and anemia [26]. On the other hand, CRP, as a direct indicator of inflammation, is mainly produced in the liver by interleukin-1 and interleukin-2, and unlike ESR, it is not affected by other factors [27]. Since normal levels of ESR and CRP are the standard for knee osteoarthritis, it seems appropriate to maintain normal ESR and CRP values before/after taking the drug. As a result of analyzing the amount of change in ESR and CRP before/after drug administration in this study, both ESR and CRP changed within the normal range in all 3 groups.

During the test period, 8 patients in the PL 1,000 group, 8 patients in the PL 1,500 group, and 8 patients in the placebo group who took the test drug (at least once) were evaluated for safety by evaluating vital signs and performing hematological tests during the test period. There were cases of adverse reactions occurring during the trial period, but it was judged that there was no association with the investigational drug, and there were no serious adverse reactions. There were no dropouts due to adverse reactions. In addition, safety was confirmed by analysis of hematological test results and physical examination.

In this pilot clinical study, not only the p value but also the effect size was calculated when statistically analyzing the efficacy evaluation variable (Table 6). The p value commonly used in medical research provides only a binary judgment of statistical significance and has a limitation that it is affected by the number of samples. In contrast, the effect size can be interpreted on a continuous line, and is not affected by the number of samples, so even in clinical studies with a small number of samples, the actual difference between the groups to be compared can be determined [11]. As a result of calculating the effect size in this study, the effect size for the K-WOMAC amount of change in the PL 1,500 group was 0.54, which suggests the possibility that PL would be effective

Table 6. Effect Size and Pooled SD for Outcome Variables.

Variable	PL 1,000		PL 1,500	
	pooled SD	effect size	pooled SD	effect size
K-WOMAC	13.15	−0.47*	19.38	0.54*
VAS	13.26	−0.06*	23.78	0.00*
ESR	3.46	0.64*	4.17	0.88*
EQ-5D-3L	0.08	−0.48*	0.09	−0.89*
CRP	0.33	−0.12*	0.54	−0.59*

K-WOMAC, Korean Western Ontario and Mcmaster Universities; VAS, visual analogue scale; ESR, erythrocyte sedimentation; EQ-5D-3L, Euro quality-of-life 5 dimension; CRP, c-reactive protein.
* Effect sizes were derived from Cohen's d and compared with the placebo group.

for KOA even if it was not statistically significant.

Comprehensively, as a result of analyzing the amount of change in the K-WOMAC, VAS, EQ-5D-3L, ESR and CRP, it is expected that PL can help ease the symptoms of knee arthritis. In particular, in the K-WOMAC scores, it was confirmed that the PL 1,500 group had a greater tendency to change than the placebo group and had a considerable effect size. However, there was not homogeneity between the 3 groups using the K-WOMAC scores. It seems that errors should be prevented by including not only the Kellgren and Lawrence grade but also the intensity of pain such as the VAS score or Numeral Rating Scale score in the inclusion criteria. In addition, this clinical trial was limited in its power which was low due to its small sample size, but this clinical trial was a pilot clinical study, and its purpose is to explore efficacy and safety, and to estimate the dose and sample size of future clinical studies. In addition, the effect size of 0.54 was confirmed in the K-WOMAC scores among the efficacy evaluation variables, and safety for mid- to long-term administration was also confirmed by recording adverse reactions, clinical laboratory tests, and interviews. As a result of the exploration for the efficacy of PL for confirmatory clinical studies in the future, it is appropriate to set the dosage of PL to 1,500 mg/day, the dose of the PL 1,500 group, which showed a tendency to change significantly more than the placebo group in the amount of change in the K-WOMAC score. Based on this pilot clinical study, the efficacy PL on KOA may be determined in the future with larger, randomized controlled trials.

Supplementary Materials

Supplementary material is available at doi:https://doi.org/ 10.13045/jar.2022.00010 .

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Ethical Statement

This research did not involve any human or animal experiments.

Data Availability

All relevant data are included in this manuscript.

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