Therapeutic effectiveness of oral homeopathic remedy in management of knee osteoarthritis via attenuation of oxidative and inflammatory pathway

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Background
Osteoarthritis (OA) is the most common prevalent condition that affects joints and causes erosion of the cartilage. Many conventional medications show evidence of short-term effectiveness. However, they are associated with numerous adverse effects.
Objective
As homeopathy is a complementary modality, thus this study aimed to explore the therapeutic effectiveness of homeopathic remedies in management of knee OA that proved efficiency in management of knee OA without health hazards.
Patients and methods
Thirty cases (25 females, five males) were complaining of bilateral grade 2 or 3 knee OA were included in the study. Each patient was taken as her/his control. One milliliter of a diluted complex of four homeopathic remedies (Arnica Montana, Ledum Palustre, Rhus Tox, and Ruta Graveolens) was taken orally by each patient for 6 weeks in ascending potency.
Results
All clinical parameters showed significant improvement after the end of therapy. Visual analog scale, number of tender points, tenderness score (TS), angle of knee flexion, heel to hip distance Western Ontario and McMaster universities osteoarthritis index score and Lequesne index ($P \leq 0.05$). In addition, there was significant improvement in laboratory markers as significant increase in serum enkephalin and interleukin-4 and decreasing in erythrocyte sedimentation rate ($P \leq 0.05$).
Conclusion
The study showed efficiency of four homeopathic remedies in decreasing pain, tenderness, improving knee flexion and quality of life supported with improvement in serum levels of encephalin, interleukin-4 and erythrocyte sedimentation rate in grade 2 or 3 OA patients.

Keywords:
cytokines, homeopathy, osteoarthritis, pain

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Introduction

Osteoarthritis (OA) is considered as one of the most prevalent forms of arthritis and the most common orthopedic disorder [1]. It is a major health issue that affects 22.9% of the general population worldwide [2]. Globally, it is a leading cause of impaired joint function, disability and poor quality of life due to functional limitations and musculoskeletal pain especially in older patients [3]. In 2022, a number of 240 million people were recorded worldwide as having symptomatic OA, including 18% of women and10% of men aged 60 and older [4].

In the Middle East and North Africa (MENA) region, there were 2.3 million cases of OA in 2019 [5]. From 1990 to 2019, the age-standardized rate of incidence of OA grew by 9.4%. OA affects 52.5 million Americans, half of whom are 65 years of age or older. Eighty percent of the population is thought to have OA, even though only 60% of them will experience symptoms. In 2040, 78 million Americans (26% of the population) are projected to have OA [6].

OA is characterized by cartilage erosion; osteophytes formation and alterations occur in the synovial fluid and subchondral bone leading to localized inflammation of knee [7]. Increasing age, nutritional (diet), environmental (smoking), obesity, and hormonal (female sex) factors, genetics, and

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epigenetics trigger the activation of the synovium releasing pro-inflammatory cytokines in the joint synovial fluid that leads to chronic inflammation (synovitis) resulting in pain, swelling, stiffness, and eventually damage and disability [8].

The primary signs and symptoms of OA of the knee are pain, which limits joint motion, and stiffness. In general, 'pain' is described as a sharp pain or a burning sensation that induces irritability, depression, insomnia, and other psychological and physical changes.

Long-term activity usually makes it worse, while rest usually makes it better. The stiffness is more prevalent in the morning and usually lasts less than 30 min, but it can come back after periods of inactivity. Also, OA can cause crepitus (crackling noise). Patients may feel contractions in the tendons and muscular spasms when the affected joint is manipulated or touched [9].

Radiologically, knee OA is classified to five grades by Kellgren and Lawrence System in 1957 and accepted by WHO in 1961. It was stated as grade 0: no radiographic signs of OA are found in patients; grade 1: possible osteophytes lipping and dubious joint space narrowing (JSN); grade 2: anteroposterior weight-bearing radiograph shows obvious osteophytes and a potential JSN; grade 3: sclerosis, multiple osteophytes, obvious JSN and may be deformed bones; grade 4: significant bony deformities, prominent JSN, massive osteophytes, and severe sclerosis [10].

While short-term evidence suggests that pharmaceutical therapy for OA is beneficial, it is also associated with a variety of side effects. Finding a medicine that offers a clear, overall, net advantage is challenging due to the complex balance between benefits and hazards. NSAIDs and glucocorticoids are very commonly used in treatment of OA but are not optimal because of moderate efficiency and serious side-effects in long-term use [11].

NSAIDs are more likely to cause stomach problems than COX-2 selective inhibitors, but myocardial infarction and other cardiovascular disorders are more common. In addition to NSAIDs-induced renal toxicity through interstitial nephritis and renal papillary necrosis. Patients with severe renal and hepatic impairment should not use NSAIDs. Previous research has revealed that medication toxicity is the cause of 5–7% of hospital admissions, with non-aspirin NSAIDs accounting for 11–12% of those admissions [12]. Tramadol and other opioids are often given, but their effectiveness is limited by a number of hazards. Patients with knee OA, intra-articular corticosteroid injections can lower pain by 20% over the course of 1–3 weeks. Patients with diabetes mellitus, intra-articular injections might lead to joint infections and hyperglycemia for 2–3 days. Injections should not be frequently used more than every 3 months [13]. Joint replacement surgery, such as a knee arthroplasty, is advised in cases with severe OA, but there are hazards involved, especially for elderly people who often suffer from comorbid health problems. Some people after surgery were affected by long-lasting pain, swelling, stiffness, clicking sounds, poorly positioned or loose prostheses, infection, inflammatory, thrombosis, and potential for fractures [14]. There seems to be a general demand for medical drugs with high efficacy and minimal toxicity for treatment of patients with OA, especially, there is an urgent need for alternative medications by patients who do not respond well to conventional drugs and who are not eligible for surgery or refuse it. A growing number of OA patients are turning to complementary medicines. According to research, 80–90% of arthritis patients use some form of Complementary Alternative Medicine (CAM) to treat their symptoms and those who choose CAM treatment most commonly are expecting symptom relief from it and believe that these approaches are free from side effects [15]. Homeopathy is the most popular alternative medicine, the efficiency of homeopathic medicine in general becomes wide spread and confidence is growing among the public and physicians, even partly integrated into many healthcare systems [16].

Homoeopathy is a branch of nanopharmacology, sometimes known as 'medical biomimicry,' in which extremely small and carefully formulated doses of diverse substances from the chemical, mineral, animal, and plant kingdoms are given to cure particular disorders they are known to produce in overdose. Homeopathic medications are not conventional drugs. Conventional drugs act through mechanistically targeted, biochemical, specific direct local effects. In contrast, homeopathic medications serve as a low-dose stimulus to induce patterns of functional adaptive changes locally and globally in the body. Homoeopathic medications are given to replicate and enhance the patient's immunological response and natural defenses as opposed to pharmacological medications, which are intended to inhibit or suppress a patient's symptoms [17].

Homoeopathic medications are said to be quite safe and nonhabit forming, allowing them to be taken for a prolonged time (which is necessary in cases of OA), the medicine can aid in both pain management and increased joint mobility [18]. Homeopathic remedies offer patients an alternative treatment option and can provide relief of symptoms in a natural way [19]. Homoeopathy is the only system of medicine that uses constitutional individualized therapy. Individualized homoeopathy could improve patients' quality of life and offer more relief, but studies on homoeopathy were generally of lower quality and have not significantly improved over research on conventional treatments [20]. Homeopathic remedies that proved effective in treatment of OA were Arnica Montana, Rhus Toxicodendron, Ruta Graveolens, and Ledum Palustre. Arnica Montana is a herb that has been prescribed to treat trauma-related edema and pain associated with knee OA [21]. It contains polyphenolic compounds such sesquiterpene lactones and flavonoids, that has been proved to suppress the inflammatory process [22]. It additionally suppresses neutrophil migration, reduces 5-lipoxygenase and leukotriene C4 synthase that has been linked with an increase in pain and inflammation. Arnica Montana stimulates production of fibronectin, a protein involved in the process of tendon repair. Therefore, Arnica Montana may not only decrease the pain but also aid muscle and cartilage repair if given for longer period [23].

Ledum Palustre has flavonoids that have antioxidant effect controlling inflammation and pain [24]. Rhus Toxicodendron suppresses the pro-inflammatory effect of interleukin-6 (IL6) [25]. Ruta Graveolens has rutin and quercetin as the main active flavonoids, they apply their anti-inflammatory effect through suppressing the mediators that aggravate inflammation such as: prostaglandin, histamine, and serotonin [26]. Ruta Graveolens also has antineoplastic and immunomodulatory effect [27].

The aim of this study was to investigate the effect of combined four homeopathic remedies known for their benefits on symptoms management in patients with knee OA.

Patients and methods

Study design

All cases presented with knee OA at the complementary medicine clinic, National Research Centre, Cairo, Egypt were examined. Forty-five cases complaining of bilateral grade 2 or 3 knee OA were selected. Grade 2 (mild) or 3 (moderate) knee OA was diagnosed by plain radiograph. Patients selected were not suffering from renal or hepatic impairment or recent heart attack or stroke. Also, patients receiving chemotherapy or cortisol were not included in the study.

Ethical consideration

Before the start of the study, written informed consents were obtained from all patients in accordance with Helsinki declaration 1964. This study was approved by the medical research ethics committee of the National Research Centre, Cairo, Egypt, with approval number 16/337.

Methods

During the first visit and at the end of the study, each patient was subjected to:

(1) General clinical examination.
(2) Radiograph examination (posteroanteroir view) to determine the grade of knee OA
(3) Pain intensity on visual analog scale (VAS): it is the visual representation of the range of pain that a patient may experience. The range is represented by a line, usually 10 cm in length with or without marks at each centimeter. One represents no pain while 10 represents the worst pain the patient can imagine [28].
(4) Western Ontario and McMaster universities osteoarthritis index (WOMAC) questionnaire (Table 1): it helps to assess pain, stiffness, and physical function of the joint. It consists of 24 items divided into three subscales:
    (a) Pain (five items): during walking, using stairs, in bed, sitting or lying, and standing (score ranges from 0 to 20).
        (1) Two instances of stiffness: right after waking and later in the day (range: 0–8 points).
        (2) Physical function (17 items): using stairs, getting up from a chair, standing, bending, walking, getting in and out of a car, shopping, putting on/removing socks, rising from a lying position, bathing, sitting, using the toilet, heavy and light housework (score from 0 to 68) [29].

Tender score: firm pressure is used to measure the knee's tenderness, and the result is scored as follow:

Score 0: the sufferer experiences no discomfort.
Score 1: according to the patient, it hurts.

Table 1 Western Ontario and McMaster Universities Osteoarthritis Index questionnaire

Name:					Date:		
Instructions: please, rate the activities in each category according to the following scale of difficulty:							
0=None, 1= Slight, 2=Moderate, 3=Very, 4=Extremely							
Pain	1.	Walking	0	1	2	3	4
	2.	Stair Climbing	0	1	2	3	4
	3.	Nocturnal	0	1	2	3	4
	4.	Rest	0	1	2	3	4
	5.	Weight bearing	0	1	2	3	4
Stiffness	1.	Morning stiffness	0	1	2	3	4
	2.	Stiffness occurring later in the day	0	1	2	3	4
Physical function	1.	Descending stairs	0	1	2	3	4
	2.	Ascending stairs	0	1	2	3	4
	3.	Rising from sitting	0	1	2	3	4
	4.	Standing	0	1	2	3	4
	5.	Bending to floor	0	1	2	3	4
	6.	Walking on flat surface	0	1	2	3	4
	7.	Getting in/out of car	0	1	2	3	4
	8.	Going shopping	0	1	2	3	4
	9.	Putting on socks	0	1	2	3	4
	10.	Lying in bed	0	1	2	3	4
	11.	Taking off socks	0	1	2	3	4
	12.	Rising from bed	0	1	2	3	4
	13.	Getting in/out of bath	0	1	2	3	4
	14.	Slitting	0	1	2	3	4
	15.	Getting in/out of toilet	0	1	2	3	4
	16.	Heavy domestic duties	0	1	2	3	4
	17.	Light domestic duties	0	1	2	3	4
Total score:		. . . . . /95= . . . . . %					
Comments/interpretation (to completed by therapist only):							

Score 2: the patient groans and declares it to be painful. Score 3: the patient mutters, winces, and pulls the limb away.

The mean tenderness score (TS) of these places are calculated when this is applied to each of the following sites: suprapatellar, infrapatellar, medial collateral ligament, lateral collateral ligament, and popliteal fossa.

On a scale of 0–3, tenderness on palpation can be graded as having no pain, mild, moderate, or severe tenderness, respectively. The number of tender points (NTP) of the knee joint were also recorded [30].

Lequesne index

It is an index of severity for OA for the knee, done also before the start of treatment and after its end. It tests pain or discomfort, maximum distance walked and activities of daily living. The index score ranges from 0 to 24 detecting the degree of handicap as 1–4 (mild), 5–7 (moderate), 8–10 (severe), 11–13 (very severe), and 14 or higher (extremely very severe) [31].

Goniometry of knee range of motion

Goniometry of knee range of motion was measured with a universal goniometer from the manufacturer CARCI. Active extension was measured with the participant in a supine position with extended legs. For goniometry of active flexion, the participant was in the prone position with the contralateral lower limb in extension. Range of painless movement (flexion) measures the range of flexion in degrees starting from the zero position of normal full extension. Flexion of 135 and over is regarded as normal [32].

Heel to hip distance

The distance between the hip and heel in supine position with knee flexion was measured.

Pain (VAS), WOMAC questionnaire, tender score, NTPs, Lequesne index, angle of knee flexion, and heel to hip distance were documented for each patient before and after therapy.

Laboratory analyses

The laboratory tests that were performed just before the start of the therapy were: aspartate aminotransferase, alanine aminotransferase, urea, creatinine, and uric acid. They were done to exclude patients having hepatic or renal impairment. Before and after homeopathy treatment, blood samples (5 ml)

were withdrawn from each patient. A part (2 ml) from each blood sample was used in determination of erythrocyte sedimentation rate, while the other part (3 ml) was left to coagulate, then centrifuged at 300 rpm; the sera were separated into aliquots and stored at −80°C. Using enzyme linked immunosorbent assay (ELISA), serum IL4 concentration was assayed using human IL4 ELISA kit (IL431-K01) purchased from Eagle Biosciences Int. (Amherst, NH 03031, USA). Serum enkephalin concentration was determined using human enkephalin ELISA kit (CSB-E09117h) purchased from CUSABIO (Houston, Texas, USA) [33].

Homeopathic treatment

Complexes four homeopathic remedies, known by their effect on OA were selected. The four remedies were Arnica Montana, Ledum Palustre, Rhus Toxicodendron, and Ruta Graveolens. The remedies were produced by Helios homeopathic pharmacy, UK in the form of granules which were made from pure sucrose 250/g with approximately a diameter of 1.5 mm for each granule. Patients received a medication bottle, containing five granules of each remedy, all dissolved in sterile water. The mixture had to be taken orally in the Hahnemannian scale of ascending potency as following: first 2 weeks we used remedies of 12C potency, second 2 weeks we used remedies of 30C potency and last 2 weeks we used remedies of 200C potency. Dosage is 1 ml daily for 6 weeks, patients were advised to refrain from handling the solution, eating, drinking, smoking, or brushing teeth within 20 min of taking the mixture and were asked to keep the solution in their mouth for few seconds. Patients were instructed to report any reactions after starting treatment and to come for follow-up every 2 weeks over the course of 6 weeks plus extra visits and telephone consultations as necessary, according to normal practice. We followed-up the patients (n=9) who felt better during the first month, but they did not complete the end of the second month. Other patients (n=6) missed many doses, did not show regularly for examination and lost interest in the study. Those cases (n=15) were excluded from the study. The remaining 30 cases (25 females, five males) were taken as her/his control.

Statistical analysis

Multiple intergroup comparisons were made by using one-way analysis of variance. If a significant change was found in intergroup comparisons, post-hoc multiple comparison analysis with Duncan multiple comparison test was performed using statistical analysis system (SAS) program software (copyright (c) 1998 by SAS Institute Inc., Cary, North Carolina, USA). The difference is considered significant at P value less than or equal to 0.05.

Results

Demographic data illustrated in Table 1 for the studied group 30 patients (25 females, five males) complaining of bilateral grade 2 or 3 knee OA were given a mixture of oral homeopathic remedies. Their ages ranged between 30 and 60 years (mean: 47.66). Mean of weight was 87.11 kg, mean of height 159.11 cm, mean of BMI 35.58 kg/square height and mean of duration of the disease 3.6 month.

The data recorded in Table 2 illustrated values of the clinical characteristics of knee osteoarthritic patients, prehomeopathy and posthomeopathy treatment.

After homeopathic treatment there was a significant decrease in VAS, NTP, TS, heel to hip distance, WOMAC score and Lequesne index and there was a significant increase in angle knee flexion ($P \leq 0.05$).

As shown in Table 3, the laboratory parameters of knee osteoarthritic patients; pretreatment and posttreatment with homeopathy; there was a significant elevation in serum enkephalin and IL4 associated with a significant decrease in erythrocyte sedimentation rate (Table 4).

Table 2 Demographic characteristics of patients with knee osteoarthritis in homeopathy group

	Mean (minimum–maximum)
Sex	
Male	5
Female	25
Age (year)	47.66 (30/60)
Weight (kg)	87.11 (60/128)
Height (cm)	159.11 (150/173)
BMI (kg/square height)	35.58 (22/49.7)
Duration of the disease (month)	3.63 (0.5/10)

Table 3 Clinical characteristics of knee osteoarthritic patients: prehomeopathy and posthomeopathy treatment

	Before treatment	After treatment
VAS	7.89±1.64	3.3±1.49*
NTP	4.48±1.96	1.11±0.22*
TS	2.51±0.64	0.52±0.11*
Angle of knee flexion	92.5±16.3	117±14*
Heel to hip distance	32.5±7.3	21.96±5.6*
WOMAC score	47.6±18	17.04±2.4*
Lequesne index	13.3±3.3	4.8±3.12*

Data are presented as mean±SD. NTP, number of tender points; TS, tenderness score; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster universities osteoarthritis index.
*Significant at P value less than or equal to 0.05.

Table 4 Laboratory parameters of knee osteoarthritic patients: pretreatment and posttreatment with homeopathy

	Before treatment	After treatment
Serum enkephalin (pg/ml)	37.7±17.4	53.1±26*
Serum IL 4 (ng/l)	3.12±2.6	4.72±4.5*
Blood ESR 2nd h(mm/h)	28±19	15.3±9.5*

Data are presented as mean±SD. ESR, erythrocyte sedimentation rate. *Significant at *P* value less than or equal to 0.05.

Discussion

Many patients use CAM, including homeopathy, to prevent, control, and manage OA. Most conventional medical treatments manage pain, but, many encounters serious side-effects, leading patients to seek other alternatives [34]. Although homeopathy is based on individualized treatment for each patient, many remedies could be used for specific diseases as conventional medicine.

In our study, all patients (n=30) suffering from OA (grade 2 or 3) received a mixture of four homeopathic remedies known by their effects on pain management for 6 weeks. Those remedies are Arnica Montana, Ledum Palustre, Rhus Toxicodendron, and Ruta Graveolens. Our results showed that pain (VAS), TS, angle of knee flexion, WOMAC and Lequesne index were significantly improved during and after treatment with the oral mixture ($P \leq 0.05$). In agreement with our results, it was reported that a mixture of Arnica Montana, Rhus Toxicodendron, and Ruta Graveolens significantly improved pain (VAS) and WOMAC index in 25 patients with grade 2 knee OA [35]. Other studies supported our results but using different approaches. Some studies used individualized homeopathy and others used a local gel containing the same ingredients we used in the oral mixture. In a prospective, observational study found that daily activities of OA patients can potentially be improved by individualized homoeopathic medications, as proved by WOMAC OA index and stiffness, and limiting progress of the disease without any adverse systemic effects and can safely be employed as a comprehensive health care therapeutics [36].

Many studies used topical applications using either a single remedy or a complex form. A pooled individual patient data meta-analysis of three randomized trials examined the efficacy of a homeopathic gel containing Rhus Toxicodendron as a key element in OA of the knee and acute low back pain. The 284 patients in the gel group and the 275 patients in the control group made up the pooled dataset. A statistically significant effect for the symptoms was discovered after controlling for pain at baseline [37].

A homeopathic gel formed of a mixture of Rhus Toxicodendron, Ledum Palustre, *Symphytum officinale* significantly decreased pain by VAS in 86 patients complaining of knee OA. The gel was applied three times daily for 4 weeks. The effect of the homeopathic gel was statistically the same as piroxicam (NSAID) gel [38]. Local application of Arnica gel significantly improves pain (VAS) and the function in patients complaining of hand OA after 3 weeks of treatment. Its effect was similar to that of ibuprofen gel [39].

Another study accomplished on 592 grades 1 and 2 knee OA patients proved that Zeel comp. N tablet which contain homeopathic mixture of these remedies (Arnica Montana, Rhus Toxicodendron in addition to Solanum Dulcamara, Sanguinaria Canadensis, and sulfur) improved significantly WOMAC index after 4 weeks of treatment. The homeopathic mixture was as effective as Cox2 inhibitors given to the other group [40].

Serum enkephalin had been significantly increased after the end of the therapy in our study. Enkephalins are peptides secreted in the brain, spinal cord, and the adrenal gland, they reduce pain by binding with opioid receptors and inhibiting the release of substance P which is a neurotransmitter that aggravates pain sensation, enkephalins also inhibits the secretion of pro-inflammatory IL1 β, and tumor necrosis factor [41]. To our knowledge, this is the first study in literature demonstrating the relation between homeopathic remedies and enkephalin. Serum IL4 had also been significantly increased after the end of the treatment, IL4 was known to have anti-inflammatory effect through inhibiting the secretion of tumor necrosis factor and IL1 β [42]. It was proved that Arnica stimulates the production of IL4 that helps to reduce inflammation and pain [43].

In contrast to our results, a prospective, parallel arm, double-blind randomized, and placebo-controlled study was conducted involving patients who were suffering from acute painful episodes of knee OA. Statistically significant decrease was reported in three VASs (measuring pain, stiffness, and loss of function) and Osteoarthritis Research Society International scores in both groups over 2 weeks ($P \leq 0.05$); however, group differences were not significant ($P > 0.05$). Overall, homeopathy did not appear to be superior to placebo [44]. As for the

occurrence of side effects, many studies reported aggravation of symptoms on starting treatment with homeopathy, which fades away after few hours [45]. In our study, we tried to avoid this as mentioned in methodology by adopting the Hahnemannian scale of ascending potency (12C for 2 weeks, 30C next 2 weeks then 200C for last 2 weeks).

Conclusion

The study was carried out for 6 weeks. Many parameters were used for the assessment of effectiveness of an oral homoeopathic complex (Arnica Montana, Ledum Palustre, Rhus Toxicodendron, and Ruta Graveolens) on knee OA. All parameters showed a significant improvement after treatment.

Limitations of the study

In the above study, the duration of treatment was 6 weeks which is too short for a chronic disease as OA. Although there was significant improvement in all cases, but, we needed a longer duration of observation to avoid recurrence and a control group of patients using conventional medications. It is the policy of the medical ethical committee that blood samples should not be withdrawn from healthy people or patients taken as control as long as they will not benefit from the study. In case of taking patients as controls, previous treatment will be stopped also without giving any alternative, which may worsen the case, that is why we did not take a control group. This study will contribute evidence of using this modality in clinical practice and will provide additional insights for the complementary treatment options.

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Conflicts of interest

There are no conflicts of interest.

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