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Pharmacological and Clinical Effectiveness of *Zingiber officinale* and *Alpinia galanga* in Patients with Osteoarthritis

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1. Introduction

Osteoarthritis (OA) is a progressive degenerative joint disease that has a major impact on joint function and quality of life. OA is a painful condition caused by a gradual loss of cartilage from the joints and, in some people, joint inflammation [1]. Pain, stiffness, and difficulty moving the joint easily are common symptoms of OA. Non-drug treatments for osteoarthritis have gained popularity according to the American College of Rheumatology (ACR) [2] and can often reduce the symptoms. Therefore, there is a significant need to improve current osteoarthritis therapies and to search for novel therapies. Nutraceuticals and dietary supplements derived from herbs have long been used in traditional medicine. Though they aren't recognized as drugs, herbal and natural remedies are used for a drug-like effect, and they can potentially cause the same reactions and complications prescription drugs can cause. There is considerable evidence that nutraceuticals may play an important role in inflammation and joint destruction in OA. The World Health Organization (WHO) [3] has taken an interest in the indigenous system of medicine; particularly, plant remedies. Ginger is widely used as a spice, an antiemetic and carminative agent, and for its essential oils. Gingerols, in particular 6-gingerol, are the active components of ginger. Proposed mechanisms include direct stimulation of the gastrointestinal tract, or serotonin antagonism in the gut or central nervous system [4, 5]. A study on 6-gingerol was shown to significantly inhibit the production of nitric oxide, a highly reactive nitrogen molecule that quickly forms a very damaging free radical called peroxynitrite and greatly lessened depletion of glutathione [6]. Other reports suggest that ginger produces its

anti-inflammatory effect by inhibiting arachidonic acid metabolism [4, 7], induce apoptosis in HL-60 leukemia [8], non-small cell lung cancer cells [9] and against acute monocytic leukemia [10]. It is also reported to be chemopreventive and anti-inflammatory [11, 12]. The antioxidant, antimicrobial and cytotoxic activities of *Zingiber officinale* displayed specific inhibition on *Escherichia coli* was also studied [13]. Gingerols also promoted significant reduction in mRNA transcription of TNF- α , IL-2 and INF- γ [14]. Ginsenoside Rg5 (Rg5), an abundant natural compound in *Panax ginseng*, has been found to be beneficial in treating AD [15]. Pharmacologic studies in the last decades have shown that ginsenosides (ginseng saponins) are primarily responsible for the actions of ginseng [16]. In diabetes ginger supplementation in oral administration reduced inflammation in type 2 diabetic patients [17]. Other studies have shown that ginger may benefit musculoskeletal disorder treatment [18] nausea and vomiting [19], inflammation or inflammatory states [20, 21] such as osteoarthritis [20-22], migraine [23], cancer [24], hyperlipidemia and hyperglycemia [25, 26]. In vitro studies suggest that ginger produces its anti-inflammatory effect by inhibiting arachidonic acid metabolism^{4, 7}. This chapter intends to give a brief outline of ginger health benefit and to investigate the ability of ginger tablets to reduce postoperative pain in patients with osteoarthritis.

1.1. History

The earliest evidence of humans' use of plants for healing dates back to the Neanderthal period [27]. In the 16th century, botanical gardens were created to grow medicinal plants for medical schools [28]. Herbal medicine practice flourished until the 17th century when more "scientific" pharmacological remedies were favoured [29]. The use of plants for healing purposes predates human history and forms the origin of much modern medicine. Many conventional drugs originate from plant sources: a century ago, most of the few effective drugs were plant based. Examples include aspirin (from willow bark), digoxin (from foxglove), quinine (from cinchona bark), and morphine (from the opium poppy). The development of drugs from plants continues, with drug companies engaged in large scale pharmacological screening of herbs.

1.2. Therapeutic scope

Although herbal preparations are widely used as self-medication for acute conditions, practitioners of herbal medicine tend to concentrate on treating chronic conditions. A typical caseload might include asthma, eczema, premenstrual syndrome, rheumatoid arthritis, migraine, menopausal symptoms, chronic fatigue, irritable bowel syndrome and lately to treat mental or musculoskeletal disorders.

1.3. Safety

Many plants are highly toxic. Herbal medicine probably presents a greater risk of adverse effects and interactions than any other complementary therapy. There are case reports of serious adverse events after administration of herbal products. In most cases the herbs involved were self-prescribed and bought over the counter or obtained from a source other than a registered practitioner. In the most notorious instance, several women developed

rapidly progressive interstitial renal fibrosis after taking Chinese herbs prescribed by a slimming clinic

2. Method and subjects

2.1. Method

Fourthly patients with OA of the knee and moderate-to-severe pain were enrolled in a randomised, double-blind, placebo-controlled, two-center, parallel group, 12-week study. The primary efficacy variable was the proportion of responders experiencing a reduction in “knee pain on standing” using a visual analog scale.

The study was approved by the ethics committee of the Latvian Institute of Cardiology for clinical and physiological research, drug and pharmaceuticals product clinical investigation.

Only those willing to participate and after getting their informed consent will be involved in the investigation

2.2. Subjects

Elderly patients with clinical diagnosis of osteoarthritis (OA) of the knee, defined as knee (articular and not periarticular or referred) pain for most days of the prior month and radiographic osteophytes at the tibiofemoral joint margins were involved in the study. All involved patients had a baseline pain score > 40 mm and < 90 mm on a 100-mm Visual Analogue Scale (VAS) at the time of randomization, when evaluating pain on standing during the last 24 hours. Both men and women were included.

Exclusion Characteristics

- No NSAID's or other medication before intervention start-or consider including one week wash-out period.
- History of allergy to ginger;
- History of rheumatoid disease;
- History of asthma, if the patient needs treatment with steroids;
- Treatment with oral corticosteroids within four weeks prior to screening;
- Treatment with intra-articular corticosteroids;
- Treatment with intra-articular hyaluronic acid within 6 months prior screening;
- Prior treatment with immuno-suppressive drugs, cytostatic drugs, gold or penicillamine;
- Other investigational drugs within one month prior to screening;
- History or clinical signs of impaired kidney function;

- Clinical signs of liver disorders;
- Severe neurological diseases;
- Increased oral temperature, (37,5 C) at the time of screening;
- Affection of the hip to an extent that would influence the ratings done at the visits";
- History of fibromyalgia;
- Gout;
- Recurrent or active pseudo-gout;

2.2.1. Study design

The study was 12 weeks, double blind, and placebo-controlled, parallel group trial performed in two social care centres for elderly people. The study was approved by the ethics committee of the Latvian Institute of Cardiology for clinical and physiological research, drug and pharmaceuticals product clinical investigation. Only those willing to participate and after getting their informed consent will be involved in the investigation. Patients were randomised to receive treatment and both investigators and the patients were blind to treatment assignment.

2.2.2. Treatment

During the 12-week period, patients ingested 1 capsule twice daily, morning and evening. Each capsule contained 150 mg Ginger rhizome (*lat. Zingiberis officinale rhizome*) powdered extract and 125 mg Galangae rhizome (*Alpinia officinarum rhizome*) dry extract. 22 patients were got tablets with "A" and 18 patients got tablets with "B". Examination was done at the baseline, after 6 weeks and after 12 weeks.

2.2.3. Results

Characteristics of the subjects

Forty patients were included in the study (for group "A"-mean age \pm SD 69 \pm 13,7 and for group "B"-mean age \pm SD 75 \pm 8,6). There were ten males (35 %) and thirty females (75%). The patients in both groups were generally overweight, since the average was >28 kg/m² (range 43 – 120 kg).

2.2.4. Assessments

The primary efficacy parameter was proportion of respondents experiencing at least a 15-mm reduction in pain between baseline and the final examination for knee pain on standing and walking during preceding 24 hours, as measured by a 100-mm, VAS.

The secondary measurement was mean \pm SE of measurements for knee pain on standing and walking.

	"A" group (n=22)	"B" group (n=18)
Age, mean ± SD years	69 ± 13,7	75 ± 8,6
Sex %		
Men	23	28
Women	77	72
Body mass index ± SD kg/m ²	29.31 ± 7,7	28 ± 7,0
Waste/hip ratio ± SD	0,88 ± 0,04	0,91 ± 0,04

Table 1. Demographic characteristics

	Baseline data		After 6 weeks		after 12 weeks	
	A	B	A	B	A	B
	n=22	n=18	n=20	n=18	n=20	n=18
Pain on standing and walking (%)						
> 15 mm	-	-	-	-	50	44
0 – 15 mm	-	-	-	-	41	50
≤ 0	-	-	-	-	9	6
Pain on standing, mean ± SE (mm)	62.95±2.2	57.11±2.5	56.65±2.3	49.52±2.5	51.2±2.3	43.88±2.5
Pain on walking, mean ± SE (mm)	61.68±2.4	60.64±2.7	54.85±2.5	54±2.7	49.25±2.5	49.23±2.7

Table 2. Measurements for knee pain between group "A" and group "B"

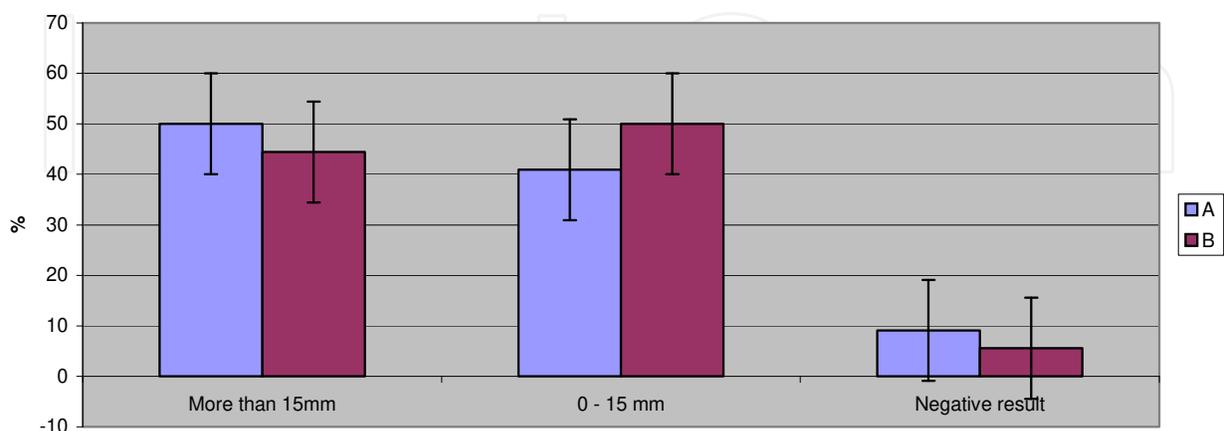


Figure 1. Pain on standing and walking after using of Ginger containing food supplements

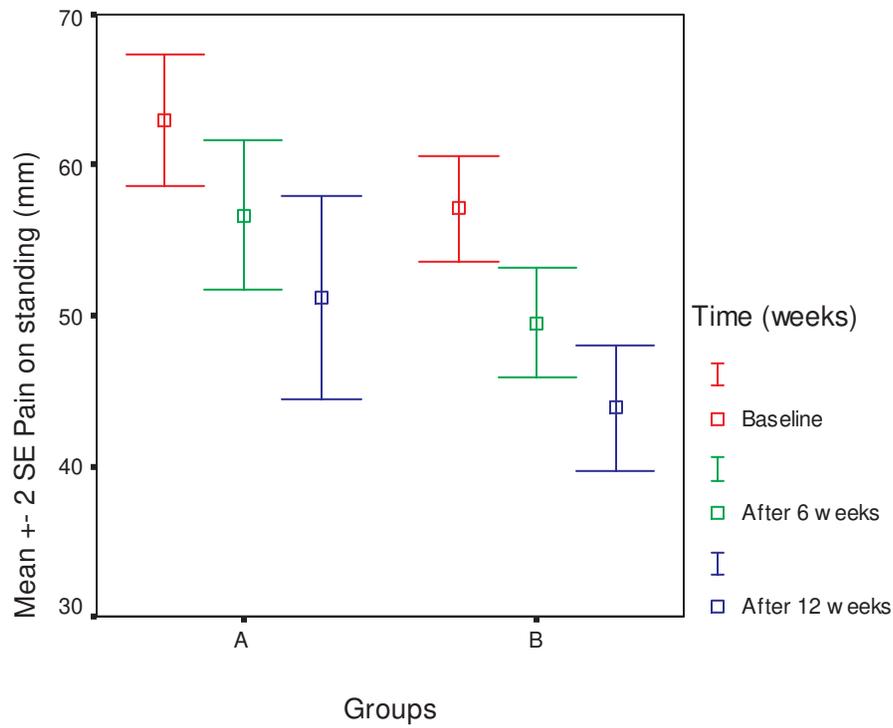


Figure 2. Knee pain on standing as measured by 100-mm visual analog scale at baseline and after 6 weeks and 12 weeks. Bars shows means with 2 SE (mm)

Additionally blood sample was checked in both groups. There were no statistically significant changes between groups.

	Baseline data		After 12 weeks	
	A	B	A	B
	n=22	n=18	n=20	n=18
Erythrocytes, Mean±SE, (10 ¹² /L)	4.42±0.9	4.46±1	4.31±0.09	4.2±1
Hb Mean±SE, (g/L)	131.66±5.8	135.8±6.5	134.8±5.9	113.15±6.5
Hematocrit Mean±SE (%)	39.28±0.9	40.03±1.0	38.8±0.9	37.85±1.0
WBC Mean±SE (10 ⁹ /L)	7.7±0.5	6.4±0.5	6.38±0.5	5.6±0.5
ESR Mean±SE (mm/h)	23.77±3.6	20.06±4.0	19.31±3.8	18.76±4.1

Table 3. Comparison of blood samples between both groups in the study.

3. Discussion and conclusion

Ginger (*Zingiber officinale* Roscoe), a well-known spice plant, has been used traditionally in a wide variety of ailments including hypertension and osteoarthritis. Gingerol, the active components of ginger, derivatives are currently under investigation as potential drug therapy for disorders of platelet function, but the small amounts consumed in the diet are unlikely to influence platelet function. We report here the osteoarthritis effects of *Zingiber officinale* and *Alpinia galanga* tablets under controlled experimental conditions.

Osteoarthritis, the most common form of arthritis, is a debilitating progressive disease principally affecting the elderly. Osteoarthritis therapy has evolved in the past few decades from symptomatic treatment to possible disease-modifying solutions. Osteoarthritis continues to be a difficult disorder to treat, as there is no cure as such and current treatments focus mainly on relieving pain and maintaining joint function. The search nevertheless continues for management regimens that can slow, alter or reverse the degenerative processes of osteoarthritis. Experimental therapies that seek to modify the course of osteoarthritis. These include such medications as colchicine, bisphosphonates and hormones. Dietary therapeutics, such as ginger extract also has been suggested. Current approaches to treating osteoarthritis-i.e. medications; nonpharmacological modalities, such as physical therapy, exercise, weight management and orthotics; and (as a last resort) surgery-focus on reducing pain and improving (or at least maintaining) mobility

Musculoskeletal conditions are prevalent and their impact is pervasive. They are the most common cause of severe long-term pain and physical disability. The prevalence of many of these conditions increases markedly with age, and many are affected by lifestyle factors, such as obesity and lack of physical activity. The increasing number of older people and the changes in lifestyle throughout the world mean that the burden on people and society will increase dramatically. This has been recognized by the United Nations and WHO, with their endorsement of Bone and Joint Decade 2000–2010 [30]. Osteoarthritis was estimated to be the eighth leading non-fatal burden of disease in the world in 1990, accounting for 2.8% of total years of living with disability, around the same percentage as schizophrenia and congenital anomalies [31]. It was the sixth leading cause of years of living with disability at the global level, accounting for 3% of the total global years of living with disability [32], [33], [34]. According to the American Holistic Medical Association it is believed that the spiritual element should also be taken into account when assessing a person's overall well-being [35], [36]. Ginger is an herb which has been used for centuries in Ayurvedic medicine to relieve the pain of arthritis although few studies are available to demonstrate its benefits. There appears to be good evidence from epidemiological studies and clinical trials that *Zingiber officinale* and *Alpinia galanga* tablets lower osteoarthritis tendency. The mechanism of action is believed to be due to the inhibition of prostaglandin and leukotriene synthesis. *Zingiber officinale* and *Alpinia galanga* was also tested for antibacterial activities by evaluating growth delays using human strains of the genera *Staphylococcus* and *Micrococcus*. *Staphylococcus aureus* was found to be sensitive to the ginger extract. When the extract was tested for the haemolytic effect, no lytic effects on procaryotic cells were found. Patients suffering from such disorders reported relief

in pain and associated symptoms on extract administration. No significant side effects of supplementation were noted, which may be considered as adjuvant therapy in patients with osteoarthritis of the knee. In this study ginger extract may have a beneficial effective in treatment for osteoarthritis. However, more observational studies, with a larger sample size, are needed to confirm the encouraging preliminary data on effectiveness and safety. The use of *Zingiber officinale* and *Alpinia galanga* in osteoarthritis will reduce the symptoms to an equivalent extent in elderly people with osteoarthritis.

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