Original Article

Evaluating the Anti-Arthritic Potential of Nerolidol Using In-Vitro and In-Vivo Models

Shanila Akhter[1], Hafiz Muhammad Irfan[2], Asma Nafisa[3], Zaid Mustafa[4], Asma Umar Khayam[5], Attiya Munir[6]

Abstract

Objective: The current study's objective was to assess nerolidol's anti-arthritic effects by using both in vitro and in vivo animal models.

Methods: In vitro methods included the denaturation of the egg albumin protein, bovine serum, as well as the human red blood cell membrane stabilisation assay at concentrations of 50, 100, 200, 400, 800, 1600, 3200, and 6400 µg/ml. The in vivo method involved the induction of non-immunological arthritis by formaldehyde at doses of 200, 400, and 800 mg/kg.

Results: Nerolidol inhibited the denaturation of protein and neutralised the human red blood cell membrane in a concentration-dependent manner, with maximum consequence attained at 6400ug/ml ($p < 0.001$). Likewise, formaldehyde induced model reduced the paw volume and an extreme reduction was obtained at 800mg/kg ($p< 0.001$).

Conclusion: These findings form a base to conclude that nerolidol supports the folklore claim of providing fortification against arthritis.

Keywords: Arthritis, Nerolidol, in vitro, in vivo, protein denaturation.

Introduction

One of the main causes of incapacity and a dangerous medical condition is arthritis. Arthritis can be defined as a chronic and systemic inflammatory autoimmune malady followed by swelling, rigidity and pain in the synovial joints.[1] It is common in 0.5% of people worldwide and results in joint impairment. Numerous forms of arthritis exist, including rheumatoid arthritis, psoriatic arthritis, fibromyalgia, osteoarthritis, and gout.[2] Osteoarthritis (OA) is characterised by cartilage damage of the hip and knee joints. The risk for OA of the knee is 40% in men and 47% in women, and its incidence increases with obesity and ageing.[3] Chronic inflammatory and systemic disease, rheumatoid arthritis (RA), is characterised by joint inflammation that results in bone and cartilage loss, systemic problems, debility, and elevated morbidity and mortality. The immune system becomes activated due to autoimmune disease, and this sudden release of pro-inflammatory cytokines results in synovitis and the decomposition of bone and cartilage.[4] Environmental, genetic circumstances and autoimmunity are involved in the pathogenesis of RA.[5] Pharmacological management of RA provides symptomatic relief of pain and inflammation. Synthetic drugs which are used against rheumatoid arthritis include DMARDs, IL-1 receptor antagonist, NSAIDs, glucocorticoids and TNF-α inhibitors. However, these drugs have plenty of adverse effects, which include, but are not limited to the opportunistic infection and immunosuppression. Thus, there is a great need to develop therapeutic compounds against arthritis that are economical and have the least adverse effects.

Synthetic drugs are used to treat abnormal disorders, but they have certain side effects, like osteoporosis and gastric bleeding. Herbal drugs, which are developed from medicinal plants, are more frequently used in place of synthetic drugs due to their less toxic effects.[2] Plants are a rich source of drugs which are used in traditional medicine, neutraceuticals, and pharmaceutical intermediates and as a therapeutic agent for the preparation of commercial drugs.[6] Medicinal plants contain several bioactive compounds like dihydroflavonols, flavones, terpenes, alkaloids, sesquiterpenes, phytoestrogens and anthraquinones, which play a central role in ameliorating the effects of arthritis. Scientists explore basic mechanisms of action of herbal drugs, which are used in the treatment of arthritis, like inhibition of cartilage degradation and protein denaturation, HRBCs membrane stabilisation and downregulation of inflammatory mediators in formaldehyde-induced arthritis.

Isolation and formulation of phytochemicals in modern drug discovery and development started in the 19th century. Curcumin isolated from *Curcuma longa* and its effect against inflammation is mediated through its ability to inhibit cyclooxygenase-2 and lipoxygenase.[7] Nerolidol is derived from the essential oils of *Peperomia Serpens. In Brazil, folk medicine uses its leaves extensively to treat inflammation, discomfort, and asthma.*[8] Previous reports have indicated that α-humulene has an anti-inflammatory impact.[9] An acyclic sesquiterpene called nerolidol is a lead chemical found in essential oils. Studies have demonstrated that nerolidol can modulate the immune response by downregulating pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, while upregulating anti-inflammatory cytokines like IL-10 and IL-4. This dual action

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contributes to its potential in alleviating inflammatory conditions like rheumatoid arthritis. Since an investigation was carried out, it was carried out using both in vitro and in vivo animal models to assess the anti-arthritic efficacy of nerolidol.

Materials And Methods

Nerolidol (Sigma Aldrich, Steinhem USA), Aspirin (Sigma Aldrich, Steinhem USA), egg albumin (hens egg), Formaldehyde, Potassium dihydrogen phosphate (Riedel-de-Haen, USA) Diclofenac sodium (Sigma Aldrich, Steinhem USA), Sodium hydroxide (Sigma Aldrich, Steinhem USA), BSA (Sigma Aldrich, USA), Disodium hydrogen phosphate (Merck), Naproxen (Sigma Aldrich, Steinhem USA), Sodium chloride (Sigma-Aldrich, USA).

For the experiments, Sprague Dawley rats were employed. Few removed for blind review maintained an ordered temperature for their animals. Water and a regular diet pellet were provided to the animals. The National Research Council's (2010) standards were strictly adhered to when conducting the tests.

The assay combination (5 mL) consisted of 2.8 mL of phosphate buffer (pH 6.4), 0.2 mL of egg albumin, and 2 mL of Nerolidol at doses ranging from 50 to 6400 µg/mL, as well as a reference medication, aspirin. Afterwards mixture was incubated for 15 min. was incubated in an incubator at (37±2) ºC and then heated for 5 minutes at 70ºC. After the solution was cooled, measured absorbance was measured at 660nm using a UV Spectrophotometer.[10] Per cent inhibition of denaturation was measured by under under-mentioned formula.

Inhibition (%) = (Abs of arthritic control- Abs of test samples) × 100/ Abs of arthritic control

In accordance with this method test solution (0.5ml) contains 0.05ml of the following concentrations: 50, 100, 200, 400, 800, 1600, 3200, 6400 ug/ml of Nerolidol, and 0.45ml of 0.5% BSA, and standard medication, aspirin, was prepared in each case. Whereas the test control contained 0.45ml of bovine serum albumin and 0.05ml of distilled water, the product control contained 0.45 millilitres of distilled water and 0.05 ml of each dilution of test samples. pH of the mixture was attuned to 6.3 with 1N NaOH and HCl. Then, test samples were incubated at 37ºC for 20 minutes and successively heated at 57ºC for 30 minutes. After this, these samples were cooled at room temperature and 2.5 mL of phosphate buffer saline with pH 6.3 in each test tube. The optical density was measured at 660nm using UV UV-visible spectrophotometer [(10)]. Inhibition percentage was measured as follows

$$\text{Inhibition (\%)} = 100 - \frac{\text{Absorbance of Ts} - \text{Absorbance of PC}}{\text{Absorbance of Test control}} \times 100$$

Ts = test solution, PC = product control

Anti-arthritic efficacy was also evaluated by using a stabilisation assay. Blood was drawn from volunteers who hadn't taken an NSAID for the 14 days before the test, and the blood was divided equally among the subjects using Alsever's solution. The blood samples were centrifuged for 15 minutes at 3000 rpm. The supernatant was removed, and the packed cells were then cleaned with a 10% v/v isosmotic saline solution. Isosoline solution was used to prepare a 10% v/v HRBC solution. The test solution contained hypotonic saline (2ml), phosphate buffer (1ml), RBC suspension (0.5ml) and 0.5ml of Nerolidol with the following concentrations: 50, 100, 200, 400, 800, 1600, 3200, 6400ug/ml, and standard diclofenac sodium, respectively. Instead of nerolidol, 0.5 ml of distilled water was added to the test control solution. Following a 30-minute incubation period at 37ºC, the mixtures were centrifuged for five minutes at 3000 rpm. Using a UV-visible spectrophotometer, the liquid supernatant was decanted, and the absorbance at 560 nm was measured.[10] Using the formula below, the protection % against hemolysis was calculated.

$$\text{Inhibition (\%)} = 100 - \frac{\text{optical density of Test samples}}{\text{optical density of Test control}} \times 100$$

BOX 1: **Induction of arthritis by Formaldehyde in rats**

Principal

The purpose of the study was to determine nerolidol's anti-arthritic efficacy against non-immunologically generated arthritis in rats using formaldehyde.

Requirements

Sprague Dawley rats, Plathysmometer, Nerolidol, Tween 80, Formaldehyde

Procedure

Step 1: Rats were split up into five groups (n=5).

Group 1 was designated as a control group and received 2% solution of Tween 80 (3ml/kg).

Group 2 received 20mg/kg naproxen sodium.

Group C, D, and E received 200, 400, and 800mg/kg Nerolidol, respectively.

Step 2: The dosage was given orally to the rats. Non-immunological arthritis was first created on day 1 by injecting 0.1 ml of formaldehyde subplantarly into the left paw, followed by 30 minutes of oral test material administration. This procedure was repeated on day 3. Ten days of drug administration were spent.

Step 3: Paw volume was determined by using plathysmometer.

Step 4: The Inhibition percentage of paw size was equated with arthritic control.

Inhibition (%) = $\frac{Vc-Vt}{Vc} \times 100$

Vc = paw volume of arthritic control, Vt =paw volume of test substance

Refrences

(10).

The findings were reported as mean ± (S.E.M). The two-way ANOVA of variance test using GraphPad Prism 5 was used for the statistical analysis, which was then followed by a Bonferroni posttest. The threshold for significance was set at ap<0.001, bp<0.01, and cp<0.001.

Results

Anti-arthritic activity of Nerolidol was evaluated against fresh hen egg albumin protein denaturation. Nerolidol shows an effect against protein denaturation in concentration concentration-dependent manner, 50 -6400ug/ml. Nerolidol gives maximum inhibition (97.270%) at a concentration of 6400 µg/ml, which is greater than the percentage inhibition (93.373%) exhibited by the standard drug (Aspirin) at the same concentrations as shown in Table 1.

Table 1: Inhibition of protein denaturation by Nerolidol with egg albumin

	Percentage inhibition of protein denaturation							
Treatment groups	**50ug/mL**	**100ug/mL**	**200ug/mL**	**400ug/mL**	**800ug/mL**	**1600ug/mL**	**3200ug/mL**	**6400ug/mL**
Aspirin (Standard)	43.380 ± 1.156	53.877 ± 0.658	62.970 ± 0.177	66.017 ± 0.348	72.817 ± 0.098	80.368 ± 0.286	85.553 ± 0.310	93.373 ± 0.772
Nerolidol	52.173 ± 1.179 [a]	72.787 ± 0.268 [a]	75.647 ± 0.173 [a]	79.977 ± 0.580 [a]	86.457 ± 0.973 [a]	87.870 ± 0.062 [a]	92.763 ± 0.112 [a]	97.270 ± 0.095 [a]

Similarly, Nerolidol at different concentrations yield considerable protection against protein denaturation induced by bovine serum albumin. In addition, at a dosage of 6400 µg/ml, nerolidol offered the highest level of protection (96.833%) against thermally induced denaturation of proteins, surpassing the protection offered by the conventional medication aspirin (82.436%). As a result, nerolidol was found to be more effective against denaturation per cent inhibition as shown in Table 2.

Table 2: Per cent Inhibition of Nerolidol on protein denaturation

	Per cent inhibition on denaturation							
Treatment groups	**50ug/mL**	**100ug/mL**	**200ug/mL**	**400ug/mL**	**800ug/mL**	**1600ug/mL**	**3200ug/mL**	**6400ug/mL**
Aspirin (standard)	37.983 ± 2.296	52.070 ± 0.590	58.113 ± 4.028	59.550 ± 2.003	65.516 ± 0.612	78.316 ± 2.168	80.426 ± 0.397	82.436 ± 1.716
Nerolidol	57.926 ± 2.457 [a]	66.383 ± 0.808 [a]	70.656 ± 0.270 [a]	73.876 ± 0.643 [a]	80.610 ± 0.742 [a]	87.336 ± 0.338 [b]	92.210 ± 0.830 [a]	96.833 ± 0.606 [a]

As seen in Table 3, the erythrocytes in the membrane were shielded against lysis by heat and hypotonic solution by nerolidol in a concentration-dependent manner that ranged from 50 to 6400 µg/ml. The HRBC was maximally protected (79.973%) by nerolidol at a dose of 6400 µg/ml. When diclofenac sodium was added to all the results, the protection of HRBC in a hypotonic solution at values of 6400 µg/ml was found to be 63.843%. Consequently, nerolidol had a greater efficacy than diclofenac sodium.

Table 3: Protection against hemolysis by Nerolidol using the Stabilisation method.

	Per cent inhibition on protein denaturation							
Treatment groups	**50ug/mL**	**100ug/mL**	**200ug/mL**	**400ug/mL**	**800ug/mL**	**1600ug/mL**	**3200ug/mL**	**6400ug/mL**
Aspirin (standard)	25.770 ± 0.111	29.820 ± 0.251	32.840 ± 0.035	37.596 ± 0.193	43.750 ± 0.201	47.973 ± 0.029	54.583 ± 0.324	63.843 ± 0.126
Nerolidol	47.383 ± 0.308[a]	47.936 ± 0.042 [a]	51.770 ± 0.069 [a]	56.333 ± 0.083 [a]	62.610 ± 0.180 [a]	70.640 ± 0.175 [a]	74.720 ± 0.150 [a]	79.973 ± 0.052 [a]

Table 4: Effect of Nerolidol on paw volume in the formaldehyde-induced animal model

Treatment groups	**2nd day**	**4th day**	**6th day**	**8th day**	**10th day**
	Increase in paw volume				
Arthritis positive control	0.658±0.073	0.758±0.072	0.950±0.082	1.138±0.087	1.540±0.203
Naproxen sodium (20mg/kg)	0.474±0.056ns (45.910%)	0.410±0.039 [b] (48.631%)	0.488±0.033 [a] (58.347%)	0.240±0.024 [a] (63.525%)	0.386±0.023 [a] (74.935%)
Nerolidol (200mg/kg)	0.352±0.031 [b] (46.504%)	0.246±0.028 [a] (67.546%)	0.364±0.024 [a] (68.014%)	0.246±00.023 [a] (74.105%)	0.362±0.008 [a] (76.493%)
Nerolidol (400mg/kg)	0.388±0.047 [c] (41.033%)	0.386±0.039 [a] (49.076%)	0.272±0.035 [a] (55.887%)	0.502±0.058 [a] (71.368%)	0.342±0.042 [a] (77.792%)
Nerolidol (800mg/kg)	0.424±0.098ns (35.562%)	0.384±0.056 [a] (49.340%)	0.478±0.045 [a] (57.996%)	0.296±0.034 [a] (68.842%)	0.290±0.032 [a] (81.168%)

Anti-arthritic efficacy of Nerolidol was also evaluated by using *in vivo* animal models. Arthritis was induced by formaldehyde in rats. Results are compared with the positive arthritic control group, which exhibited a subsequent upsurge in volume of the paw during the time of study. Evaluation was made on the last day of treatment, which showed that Nerolidol with (200, 400, 800mg/kg) doses considerably decrease the paw volume as shown in Figure 2 and percentages as follows: 76.493%, 77.792% and 81.168%, respectively, as compared to the arthritic control group. However, naproxen sodium on the 10th day exhibited a 74.935% decrease in the size of the paw.

Discussion

Using both in vitro and in vivo models, the current study shows that nerolidol has strong anti-arthritic potential in a dose-dependent way. Using the rat model of formaldehyde-induced arthritis and in vitro tests including egg albumin denaturation, BSA denaturation, and membrane stability of human red blood cells (HRBCs), nerolidol has continuously shown anti-inflammatory properties. Because it produces neo-antigens and activates immunological responses, protein denaturation plays a crucial role in the pathophysiology of autoimmune and inflammatory illnesses, including rheumatoid arthritis.[10] Therefore, one known target in anti-arthritic medication screening is the inhibition of protein denaturation. Nerolidol's ability to obstruct antigen production and subsequent inflammatory cascades is suggested by the considerable inhibition of protein denaturation seen in all in vitro tests.[11]

Stabilisation of HRBC membranes under hypotonic stress is considered an indirect marker for lysosomal membrane stability, which is crucial in preventing the release of inflammatory enzymes.[12] Nerolidol significantly reduced hemolysis, comparable to the standard drug diclofenac sodium.[13] This membrane-stabilising property may stem from its sesquiterpene alcohol structure, which enables interaction with membrane lipids, enhancing cellular resilience under stress.[14]

In vivo, the formaldehyde-induced arthritis model, which mimics human arthritis in terms of chronic inflammation and joint swelling, revealed nerolidol's ability to reduce paw oedema significantly at higher doses, particularly at 800 mg/kg.[15,16] This biphasic model involves an early neurogenic phase and a later inflammatory phase, both of which were effectively suppressed by nerolidol, indicating both peripheral and central anti-inflammatory effects.[17] The reduction of paw swelling indicates nerolidol's capacity to inhibit inflammatory mediators like prostaglandins, histamine, and cytokines.

Phytochemically, nerolidol is a sesquiterpene found in essential oils of several medicinal plants and has been recognised for its broad pharmacological activities, including anti-inflammatory, antioxidant, and neuroprotective effects. Its structure allows it to inhibit pro-inflammatory cytokines such as TNF-α and IL-1β and downregulate COX-2 expression, contributing to reduced joint inflammation and tissue damage.

Moreover, nerolidol's antioxidant properties may play a pivotal role in modulating oxidative stress-induced inflammation, which is central to the progression of arthritis. By activating endogenous defence systems and suppressing ROS-mediated damage, nerolidol offers both symptomatic relief and potential disease-modifying effects.[18]

Taken together, the anti-arthritic effects of nerolidol can be attributed to its multifactorial action: inhibition of protein denaturation, stabilisation of cellular membranes, suppression of inflammatory mediators, and modulation of oxidative stress. These findings support the therapeutic relevance of nerolidol in complementary and integrative medicine approaches to arthritis management.

Antioxidants and the neuroprotective effect of nerolidol also strengthen its effect against arthritis. Hence, it can be suggested that the anti-arthritic efficacy of Nerolidol might be due to the presence of sesquiterpenes and terpenes in it. The presence of these compounds in Nerolidol can powerfully support the anti-arthritic effect of Nerolidol in complementary and traditional medicine.

Conclusions

Nerolidol exhibits promising anti-arthritic activity through multiple mechanisms, including inhibition of protein denaturation, membrane stabilisation, and suppression of inflammatory mediators. Its phytoconstituents, particularly sesquiterpenes, contribute to its efficacy, suggesting that nerolidol holds potential as a complementary therapeutic agent in arthritis treatment. Nerolidol serves as an active anti-arthritic drug, and the result may be guessed due to the presence of phytoconstituents in it.

Author Information

1,5,6. Assistant Professor, Rawalpindi Medical University, Rawalpindi 2. Associate Professor, University of Sargodha, Sargodha 3. Biochemist, Rawalpindi Medical University 4. Lecturer, Allama Iqbal Open University.
Corresponding author: Dr. Shanila Akhter shanilaakhter105@gmail.com

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