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Effect of Aurum Metallicum on Adjuvant Induced Arthritis in Albino Rats

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ABSTRACT

Aurum metallicum is the homeopathic preparation of gold. The present study was done to evaluate whether Aurum metallicum is having any anti-rheumatic activity. Arthritis was induced by injecting 0.1ml of Complete Freund's Adjuvant in left paw of each rat. Aurum metallicum at three dilutions (6, 30 and 200 cH), distilled water and Diclofenac sodium (5mg/Kg) were given daily for 16 consecutive days to the treatment groups, control group and reference group respectively. Treatment started from day 8th day after Complete Freund's Adjuvant injection. Mean Paw volumes (Primary and Secondary), Thymus weight, Spleen weight and Total body weight were noted after 21 days of Complete Freund's adjuvant administration. Arthritis index was on 21st day post Complete Freund's adjuvant injection. The Aurum metallicum at the dilution of 6cH showed decrease in mean paw volume on 21st day post Complete Freund's Adjuvant administration ($P<0.01$). Aurum metallicum at dilution 6cH and 30 cH showed less weight gain in thymus gland and spleen compared to control ($P<0.01$, and $P<0.05$ respectively). Arthritis index was reduced Aurum metallicum at 6 cH. Aurum metallicum has anti-arthritic activity at dilution of 6cH as shown by various parameters discussed above.

Keywords: Knee, Complete Freund's Adjuant, Arthritis index, Nanoparticles, Gold, DMARDs.

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INTRODUCTION

"Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality. The disorder is much more common in women. Joint symptoms may include: Morning stiffness, which lasts more than 1 hour. Joints may feel warm, tender, and stiff when not used for an hour. Over time, joints may lose their range of motion and may become deformed. [1, 2] Treatment focuses on controlling symptoms and preventing joint damage. Historically, treatment for most people started with corticosteroids/non-steroidal anti-inflammatory drugs (NSAIDs), then slowly progressed for fewer people to non-biologic disease-modifying antirheumatic drugs (DMARDs) and finally progressed for even fewer people to biologic DMARDs if people had not responded to the previous drugs[3, 4]. Gold, which has been used for more than 75 years to treat rheumatoid arthritis (RA), is a Disease modifying Anti-Rheumatic Drugs (DMARD). These gold preparations are among the original medications targeting this form of arthritis. Gold not only decreases the pain and swelling of arthritis but also can prevent joint damage and disability. The use of gold compounds decreased since the 1990s because of numerous side effects like ulcerations of the mouth, skin changes (Chrysiasis), renal damage and bone marrow toxicity which require careful monitoring[5]. Aurum metallicum is the homeopathic preparation of gold. Homeopathic preparations are essentially nano medicines because they contain nano particles of parent compound as shown by Prashant chikramane et al[6]. Considering these points we decided to evaluate whether gold is having any antirheumatic activity at this low dose.

MATERIALS AND METHODS

Chemicals and Reagents: Freunds Adjuvant (from Sigma Aldrich) and Diclofenac (powder from Novartis India.

Animals used: Healthy wistar albino rats (150-200 gms) of either sex were taken for the study. All the animals were housed in standard laboratory conditions. These rats were given one daily dose of 0.1 ml of respective dilution with oral gavage tube. The animals were starved immediately before and after administration for at least 2 hours[7]. The study was approved by Institutional Animal Ethical Committee of Navodaya Medical College, Raichur, India, registered under CPCSEA, India (Registration No.671/CPCSEA).

Pharmacological Tests Models

CFA induced arthritis in rats: Arthritis was induced by injecting 0.1ml of CFA (Complete Freund's Adjuvant) in left paw of each rat. Aurum metallicum at three dilutions (6, 30 and 200

cH), distilled water and Diclofenac sodium (at 5mg/Kg) were given daily for 16 consecutive days to the treatment groups, control group and reference group respectively. Treatment started from day 8th day after CFA injecttion. Mean Paw volumes (Primary and Secondary), Thymus weight, Spleen weight and Total body weight were noted after 21 days of CFA administration. Arthritis index was assessed on 21st day post CFA injection.

Statistical analysis: Data was expressed as Mean ±SEM. The difference between groups was evaluated by one-way ANOVA followed by Dunnett's test. For scored data, Kruskal Wallis test followed by Dunn's multiple comparison tests was used. Data were considered statistically significant if $P< 0.05$.

RESULTS AND DISCUSSIONS

The mean paw volume in left and right paw taken on 7th and 21st day post administration of CFA is shown in table 1 (Primary and Secondary included). We can see that the mean paw volume was increased in both primary and secondary lesion post CFA administration. The Aurum metallicum at the dilution of 6cH showed decrease in mean paw volume on 21st day compared to that of control. Whereas higher dilutions of Aurum metallicum (30 and 200 cH) failed to show any decrease in mean paw volume as it is seen with diclofenac and 6cH dilution of Aurum metallicum. The changes in thymus, spleen and Total body weight on 21st day are shown in table 2. Diclofenac sodium, Aurum metallicum at dilution 6cH and 30 cH showed less weight gain in thymus gland compared to control. The spleen weight was not increased in all the groups compared to the control. With respect to the total body weight, the diclofenac group, Aurum metallicum (at dilution 6cH) showed a maximum weight gain than higher dilutions of Aurum metallicum (30 and 200 cH). Arthritis index score was calculated for each animal using parameter like nodules on the ears and tail, swelling of connective tissue in nose, inflammatory changes in forepaw and hindpaw. The Median Arthritis Index is shown in table 3. The arthritis score were reduced by Diclofenac sodium and Aurum met 6 cH when compared to control group. Aurothiomalate and aurothioglucose (IM preparations) contains 50% of elemental gold. Auranofin oral formulation of gold contains 29% elemental gold. Gold reduces chemotaxis, phagocytosis, macrophage and lysosomal activity, monocyte differentiation and inhibits cell mediated immunity. By an effect on synovial membrane and collagen, it prevents joint destruction and may induce healing of bony erosions. But all gold preparations have many adverse effects. Blood abnormalities like luekopenia, thrombocytopenia and pancytopenia, aplastic anemia (Rarely, which may be fatal). Other side effects are nephrotic syndrome,

enterocolitis, cholestatic jaundice, peripheral neuropathy, and pulmonary infiltrates and pruritic skin rashes. Many patients discontinue gold therapy within a year due to all side effects[8]. CFA induced arthritis is a chronic model of arthritis. In this model, the changes (paw volume changes, thymus, spleen weight changes, total body weight changes) seen is due chronic inflammation of joint and stimulation of immune system.[9] Danscher G, showed that on insertion of metallic gold beads, in vivo and in situ, gold ions are released from the implanted gold and diffuse out into the surrounding tissue. This phenomenon is similar to treatment with gold-containing drugs used for arthritic conditions[10]. Prashant Chikramane et al showed that the starting materials (e.g. gold in case of Aurum Metallicum) remnants can be detected in different dilutions of homeopathic preparations[6] Agnete Larsen et al in their experiment showed that gold particles (20-45 micrometer) injected directly into brain of mice showed antiinflammatory activity[11]. These studies suggest that gold can be used in very low doses to treat inflammatory conditions. In our study we used 6cH, 30cH, 200cH (lower to higher dilutions) of Aurum metallicum which is homeopathic preparation of gold.[12] In primary and secondary lesions, Diclofenac sodium decreased the paw volume significantly as compared to control ($P<0.001$). Aurum metallicum showed reduction in paw volume in primary and secondary lesions in various dilutions. It was significant ($P<0.01$) as compared to control with dilutions of 6 cH on 21st day. With 30 cH dilution Aurum metallicum was able to reduce paw volume in primary lesions but not in secondary lesions. We can say that, as the dilution of aurum metallicum was increased, the results were not consistent with that of Diclofenac sodium and Aurum metallicum 6cH. Weight gain of thymus was significantly reduced by diclofenac sodium and Aurum metallicum 6cH as compared to control ($P<0.01$). Also, weight gain of spleen was significantly reduced by diclofenac sodium and aurum metallicum at dilution 6 cH ($P<0.01$ and $P<0.05$ respectively). Significant body weight gain was seen with diclofenac sodium and Aurum metallicum 6cH ($P<0.05$). Arthritis index was reduced by Diclofenac sodium and Aurum metallicum 6 cH. These results shows that we found that Aurum met showed significant anti-inflammatory activity at less diluted formulation (6cH) ($P<0.05$) which is comparable to diclofenac sodium. Aurum metallicum has anti-inflammatory action in less diluted formulations. More diluted forms not showed anti-inflammatory activity. This may be due to less concentration of gold in them. Aurum metallicum has anti-arthritic activity at dilution of 6cH. Aurum metallicum can be used orally for chronic inflammatory conditions (Arthritis). In further studies we can inject preparations of Aurum metallicum locally at the affected site which may overcome the bioavailability problems and show enhanced anti-inflammatory activity even at higher dilutions.

Table 1: Effect of Aurum metallicum on CFA induced paw edema in rats

Groups	Left paw (µl)		Right Paw (µl)	
	7th Day	21st Day	7th Day	21st day
Control	79 ±1.4	144 ±3.8	31±2.3	68±2.3
Diclofenac sodium	33 ±1**	75 ±2.6**	8±0.61**	36±2**
Aurum met 6cH	42 ±1.5*	99±1.9*	11±0.77*	50±3.7*
Aurum met 30 cH	46 ±1.9	112±2.2	19± 1.6	64±3.1
Aurum met 200 cH	65±2.6	136 ±2.4	32±2.2	70±1.7

Values are Mean±SEM, * P< 0.01, **P<0.001

Table 2: Thymus weight, Spleen weight and Total body weight on 21st day post CFA administration

Groups	Thymus weight (g)	Spleen weight (g)	Initial Body weight (g)	Gain in body weight (g)
Control	0.18 ± 0.034	1.2±0.22	160 ± 2.99	9.0± 1.1
Diclofenac sodium	0.1 ± 0.0042**	0.69±0.085**	175 ± 5.1	22 ± 3.4*
Aurum met 6cH	0.12 ± 0.011**	0.76± 0.018*	181 ± 2.4	17 ± 1.8*
Aurum met 30 cH	0.16 ± 0.013	0.97 ± 0.055	167 ± 2.8	11 ± 1.3
Aurum met 200 cH	0.19± 0.010	1.00 ± 0.066	173 ± 4.2	7 ± 2.1

Values are Mean±SEM, *P<0.05, **P<0.01

Table 3: Arthritis score

Groups	Arthritis score
Control	4 (3,4)
Diclofenac sodium	2 (2,4) **
Aurum met 6C	3 (3,4) *
Aurum met 30 C	3 (3,4) *
Aurum met 200 C	3.5 (3,4)
Statistical analysis	Data represented as median (minimum, maximum)

∗P <0.05, ∗∗P < 0.01, compared with control group

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