Medical Science Journal for Advance Research

Vol. 7, No. 3, September 2026
e-ISSN: 2774-4892

Application of Glucosamine to Rats with Rheumatoid Arthritis Further Enhances the Anti-inflammatory Effect of Salicylate

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ABSTRACT

Currently, steroidal anti-inflammatory drugs, nonsteroidal anti-inflammatory drugs, and immunosuppressive drugs are mainly used in the treatment of osteoarthritis, including rheumatoid arthritis, but all have their own advantages and disadvantages. Derivatives of salicylic acid, a traditional nonsteroidal anti-inflammatory drug, have antipyretic, analgesic, and anti-inflammatory effects, but have some side effects. Yet, they are known as the predominant drugs and widely used in the treatment of rheumatoid arthritis in the world. The mechanisms of glucosamine in the cartilage protection, in the anti-inflammatory function, and especially in the treatment of rheumatoid arthritis which is involved in immune response, have been elucidated. They are known to be effective in cartilage protection, anti-inflammation, and in the treatment of diseases such as rheumatoid arthritis, thrombosis, enteritis, and atherosclerosis. Hence, we established an adjuvant arthritis model and observed the effect of salicylic acid and glucosamine together on carrageenan foot edema. In this experiment, we found that carrageenan-induced foot edema was significantly suppressed and the peripheral white blood cell count and absolute lymphocyte count were significantly reduced compared to the control group.

Keywords: Glucosamine, Rheumatoid Arthritis, Anti-inflammatory, Salicylate.

Article Information
Received: June 6, 2026; Revised: July 24, 2026; Online: September 2026y

INTRODUCTION

The main symptom of osteoarthritis, including rheumatoid arthritis, is chronic progressive polyarthritis underlying immune disorders. If it reaches the end, several joints are broken and the stiffness changes occur. It is also a chronic inflammatory autoimmune disease with impaired whole-body organs and tissues, leading to disability and impaired daily living in humans. Effective prevention and treatment of this disease is of major public health importance. Worldwide, RA and OA account for 1% of the population. Despite the ever-increasing costs of treatment, disability has not decreased but has a rather increasing trend. In particular, the incidence of rheumatic diseases and osteoarthritis is increasing rapidly due to the sequela of COVID-19, a pandemic of recent times. Currently, the treatment of this disease is mainly based on steroidal anti-inflammatory drugs, nonsteroidal anti-inflammatory drugs, immunosuppressive agents, cartilage protectants, and viscosity supplements. A lot of traditional drugs have also been developed and widely used. However, corticosteroids, such as hydrocortisone, a typical drug as a steroidal anti-inflammatory drug, are effective in the acute phase, whereas long-term use has fatal disadvantages such as immune damage and cartilage destruction. In addition, nonsteroidal anti-inflammatory agents such as Voltaren with strong anti-inflammatory and analgesic

https://doi.org/10.46966/msjar.v7i3.437

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function, which are widely used in treating osteoarthritis, have been shown to be effective for a short period of time.

In contrast, they have limitations that they are not available for long periods of time due to certain side effects and therefore cannot be considered as a reasonable treatment option. Glucosamine is synthesized from glucose in the body. Glucose is converted into N-acetylglucosamine or N-acetylgalactosamine via several processes within the cell.

They are paired with uronic acid, such as glucuronic acid or diuronic acid (the constituent units of disaccharides), and form glycosaminoglycans such as heparin sulfate, hyaluronic acid, gelatin sulfate, concrotitin sulfate, and dermatan sulfate. These glycosaminoglycans are present in joints, articular cartilage, joint fluid or cornea, skin, etc. and have the potential to soften, moisturize and humidify tissues. Thus, glucosamine acts as a component of the body's glycosaminoglycans.

However, the biosynthesis of glycosaminoglycans decreases with age, and as such, it is necessary to supplement the glycosaminoglycans by ingestion as supplements. Recent data have shown that the therapeutic effects of glucosamine on the treatment of osteoarthritis, as well as the clinical studies of the effect of glucosamine on various diseases, are increasing.

It has been newly identified that its cartilage-protective, anti-inflammatory, and especially immunoreactive and anti-rheumatoid arthritis mechanisms have been verified and it is effective in cartilage-protection and anti-inflammation, and in treating the diseases such as rheumatoid arthritis, thrombosis, enteritis, and atherosclerosis.

Its mechanism is explained by suppression of activation of cells such as synovial cells, neutrophils, dendritic cells, lymphocytes, etc., and also by suppression of platelet activation. Salicylic acid was discovered from willow tree in the 1890s and has been used effectively for the treatment of various diseases with many research achievements up to now.

Recently, there have been many studies in China and other countries that have used salicylic acid in agriculture and livestock farming as well as in the medical field. Salicylic acid has a dermatogenic effect at low concentrations in medicine and a keratinolytic effect at higher concentrations.

In particular, aspirin (acetylsalicylic acid) as a salicylic acid derivative has some side effects, but it has antipyretic, analgesic and anti-inflammatory effects as the nonsteroidal anti-inflammatory drugs, and thus is still evaluated as the predominant drug worldwide.

However, the treatment by acetylsalicylic acid and sodium salicylate, which are widely used as salicylic acid derivatives, has been challenging because of their potential stimulatory effects on the gastrointestinal tract and their adverse effects on the kidney organs.

We conducted a study to evaluate the effect of glucosamine on the suppression of salicylate inflammation in RA rats.

METHODS

Experimental animals were administered intraperitoneally with a combination of glucosamine hydrochloride 25 mg/kg, magnesium salicylate 25 mg/kg, and isoalanamin hydrochloride 2 mg/kg.

Rats with adjuvant arthritis were prepared according to the literature.

After 7 days, we evaluated the effect on carrageenan-induced foot edema.

The edema rate and the edema control rate were calculated by the following formula :

$$\text{edema rate} = \frac{\text{volume of the foot after inflammation - volume of the foot before inflammation}}{\text{volume of the foot before inflammation}} \times 100(\%))$$

$$\text{edema suppression rate} = \frac{\text{mean edema rate of control group - mean edema rate of experiment group}}{\text{mean edema rate of control group}} \times 100(\%)$$

After 21 days, we evaluated the mass indices of the spleen and thymus, leukocyte count and the absolute lymphocyte count. We evaluated peripheral leukocyte counts and absolute lymphocyte counts by a comprehensive blood test.

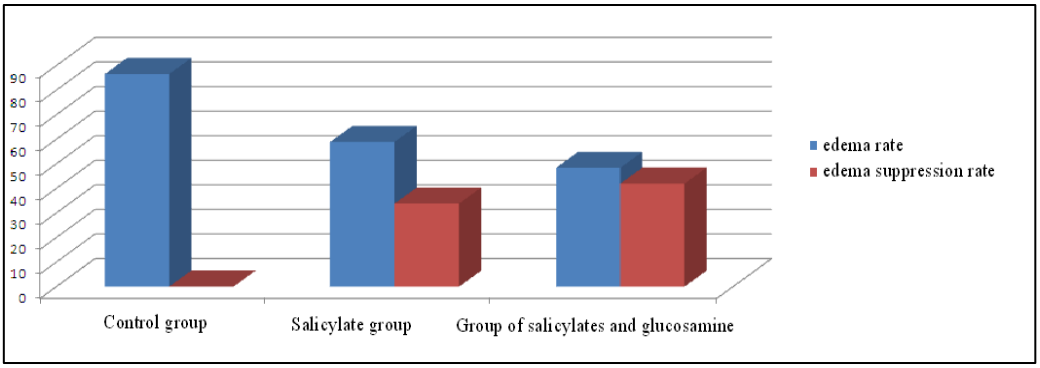
RESULTS

① Effect of the combination of salicylate and glucosamine on carrageenan foot edema

Table 1. Effect on carrageenan foot edema($\bar{X} \pm$ SE, n=10).

Category	Edema Rate (Percentage Of Edema Suppression)
Control group	86.5±3.2
Salicylate group	58.9±2.6*(33.8)
Group of salicylates and glucosamine	48.3±2.4*△(41.9)

**:p<0.05, **: p<0.01(Comparison with control group) , △:p<0.05(Comparison with salicylic acid group), ():suppression rate .*



Scheme 1. Effect on carrageenan foot edema.

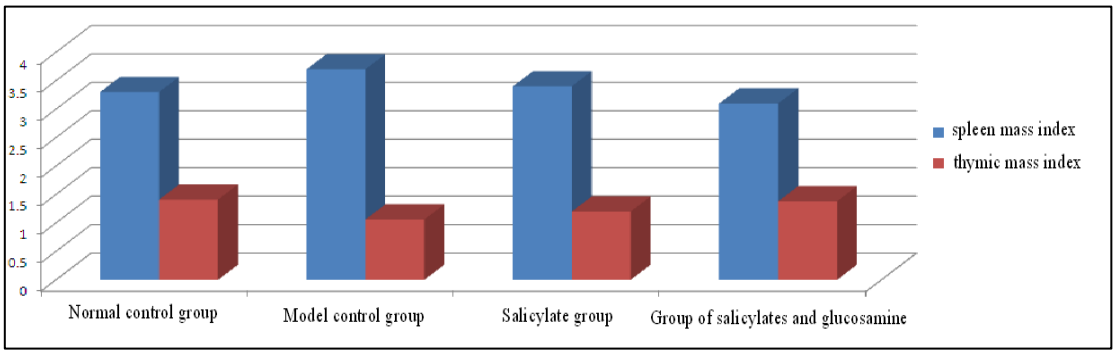
As shown in Table 1 and Scheme 1, edema was significantly suppressed in both salicylate group and group of salicylate and glucosamine compared to the control group. It was significantly more inhibited in the group of salicylate and glucosamine than in the salicylate group.

② Effect of the combination of salicylate and glucosamine on the mass indices of spleen and thymus in rats with adjuvant arthritis

Table 2. Effect on the mass indices of spleen and thymus($\bar{X}$ ±SE, n=10)

Category	Spleen Mass Index	Thymic Mass Index
Normal control group	3.3±0.04	1.41±0.016
Model control group	3.7±0.05	1.06±0.022
Salicylate group	3.4±0.05*	1.20±0.019*
Group of salicylates and glucosamine	3.1±0.04*△	1.38±0.015*△

**:p<0.05, **: p<0.01(Comparison with control group), △:p<0.05(Comparison with salicylic acid group).*



Scheme 2. Effect on the mass indices of spleen and thymus

As shown in Table 2 and Scheme 2, in both salicylate group and group of salicylate and glucosamine, spleen mass index was significantly decreased and thymic mass index was significantly increased compared to the control group.

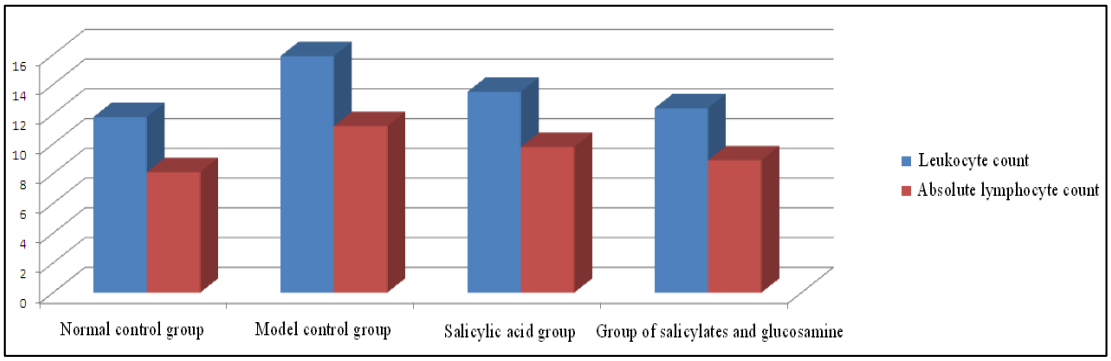
They were significantly more altered in the group of salicylate and glucosamine than in the salicylate group.

③ Effect of Glucal Injection on Peripheral Leukocyte Count and Absolute Lymphocyte Count in Rats with Adjuvant Arthritis

Table 3. Effect of peripheral leukocyte count and absolute lymphocyte count($\bar{X}$ ±SE, n=10)

Groups	Leukocyte count	Absolute lymphocyte count
Normal control group	11.8±0.2	8.1±0.2
Model control group	15.9±0.3	11.2±0.3
Salicylic acid group	13.5±0.3*	9.8±0.2*
Group of salicylates and glucosamine	12.4±0.2*△	8.9±0.2*△

**:p<0.05, **: p<0.01(Comparison with control group), △:p<0.05(Comparison with salicylic acid group).*



Scheme 3. Effect on Peripheral Leukocyte count and Absolute Lymphocyte count

As shown in Table 3 and Scheme 3, leukocyte count and absolute lymphocyte count were significantly reduced in both salicylate group and group of salicylate and glucosamine compared to the control group. They were significantly reduced in the group of salicylate and glucosamine than in the salicylate group.

DISCUSSION AND CONCLUSION

The anti-inflammatory and potent analgesic effects of glucosamine, together with the antipyretic, analgesic and anti-inflammatory effects of salicylic acid, were clearly demonstrated. The anti-inflammatory effects of isoalanamin were more effective.

Magnesium has an important role in enhancing the activity of adenosine triphosphatase (ATP) coenzyme in the balance of minerals, including sodium, potassium, calcium and magnesium, in vivo. In combination with these drugs, pharmacological trials of carrageenan foot edema have demonstrated marked suppression of foot edema.

In the model of adjuvant arthritis, leukocyte count and absolute lymphocyte count were significantly reduced compared to the control group. In addition, some biochemical tests of the liver and kidney showed no changes, and histopathological examination of solid organs (lungs, heart, liver, spleen, and kidney) showed no nutritional disturbances, congestion, or cellular infiltration.

Thus, glucorozamine further enhances the anti-inflammatory effect of magnesium salicylate on rheumatoid arthritis.

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