



# A systematic review on Antiatherogenic Activity of sem.*Anacardium* nut extract

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## ABSTRACT :

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by joint inflammation, leading to pain, stiffness, and progressive joint damage. Despite advancements in pharmacotherapy, conventional treatments often exhibit limitations such as adverse effects and inadequate efficacy. Thus, there is a growing interest in exploring alternative therapeutic approaches derived from natural sources. *Semecarpus anacardium*, commonly known as the marking nut tree, has been traditionally employed in various indigenous medical systems for its purported anti-inflammatory and immunomodulatory properties. This review aims to consolidate the existing literature on the antiatherogenic potential of *Semecarpus anacardium* nut extract in the context of RA management. We comprehensively analyze in vitro and in vivo studies, as well as clinical trials, elucidating the mechanistic insights underlying its antiatherogenic effects, including its impact on oxidative stress, lipid metabolism, and inflammatory pathways. Furthermore, we discuss the safety profile and potential synergistic interactions of *Semecarpus anacardium* nut extract with conventional RA therapies. Our synthesis of evidence underscores the promising therapeutic value of *Semecarpus anacardium* nut extract as an adjunctive treatment for RA, with a particular focus on its antiatherogenic properties, thereby advocating for further research to validate its clinical efficacy and safety.

## KEYWORD :

*Semecarpus anacardium*, Bhallataka, Rheumatoid Arthritis, Medicinal plant, Arthritis, Antiatherogenic effect,

## INTRODUCTION :

The global acceptance of Indian herbal medicines is on the rise. In Ayurveda, nearly all medicinal preparations stem from plants, whether in their natural state or as refined extracts, mixtures, and other forms. Elsewhere in the world, the term Complementary and Alternative Medicine (CAM) encompasses various traditional remedies. CAM refers to any treatment used alongside or instead of standard medical approaches. In alternative medicine, medicinal plant preparations have gained widespread use, especially for diseases that modern methods struggle to treat.

*Semecarpus anacardium* Linn. (Family: Anacardiaceae) is distributed in the sub-Himalayan region, as well as in tropical and central parts of India. Commonly known as the 'marking nut' and referred to vernacularly as 'Bhallataka' or 'Bhilwa', it holds significant importance and applicability in indigenous systems of medicine. *Semecarpus anacardium* Linn. (Family: Anacardiaceae) is a plant renowned for its medicinal

value in Ayurvedic and Siddha systems of medicine. Chemical and phytochemical analyses of its nut reveal the presence of biflavonoids, phenolic compounds, bhilawanols, minerals, vitamins, and amino acids. Various nut extract preparations derived from this source exhibit effectiveness against numerous diseases, including arthritis, tumors, infections, and others. However, the elucidation of the active principle and the determination of the structure-function relationship could greatly enhance understanding of the pharmacological action of its nut <sup>1</sup>.

### Taxonomical classification <sup>1</sup>

Kingdom	Plantae
Subkingdom	Tracheobionta
Super division	Spermatophyta
Division	Magnoliopsida
Class	Magnoliopsida
Subclass	Rosidae
Order	Semecarpus
Family	Anacardiaceae
Genus	Semecarpus
Species	Anacardium

### Plant Description :

It is a moderate-sized deciduous tree found in the outer Himalayas and warmer regions of India up to 3500 ft. in height. The plant thrives in abundance in Assam, Bihar, Bengal, Orissa, Chittagong, central India, and the western part of the East Archipelago, Northern Australia. It is a medium-to-large-sized tree, reaching heights of 15-25 m, with dark bark shedding irregularly in small pieces. The leaves are simple, alternate, brick-elliptical, 30-60 cm long, and 12-30 cm wide, rounded at the apex, coriaceous, glabrous above, and more or less pubescent below. The flowers, greenish-white in panicles, appear with new leaves in May and June, easily identified by their large leaves and the red resinous exudate, which darkens upon exposure. The nut is approximately 2.5 cm long, ovoid, and smooth, golden-brown. It is commonly found in drier rather than damp areas. The fruit matures from December to March and is 2-3 cm wide. It does not exhibit specific soil preferences. It provides moderate shade and bears sideways ovoid or elongated drupes, 2.5 to 3.8 cm long, compressed, shiny black when ripe, situated on an orange-colored disc-shaped receptacle, at the base of the calyx and the tip of the peduncle. The bark is black and emits an irritating secretion when incised. The seed oil is primarily used for medicinal purposes. Seeds (1/4 or 1/2 piece) are typically boiled in milk and consumed <sup>2</sup>.

Botanical Name	<i>Semecarpus anacardium</i> Linn
Family	Anacardiaceae
English Name	Marking nut
Hindi Name	Bhilava
Useful parts	Fruit, gum and oil Sanskrita
Synonyms	Bhallataka, Arushkara, Agnika, Shophakrita, Agnimukha etc

### General description <sup>3</sup> :

#### Brief botanical description about Bhallataka (*Semecarpus anacardium*) :

It is a medium-sized deciduous tree with rough bark, yielding acrid juice. It is distributed throughout the hotter parts of the country, extending as far east as Assam and Gujarat, and found in the deciduous forests of all districts in Tamil Nadu. The leaves are large, clustered towards the ends of the branches, oblong or obovate-oblong, rounded at the apex, and cuneate at the base, coriaceous, and densely pubescent. Pedicels are equal to or shorter than the leaves. The flowers are small, greenish-white, sub-sessile, in fascicles on pubescent pedicels, with the female pedicels shorter than the male ones; pedicel short, with lanceolate, pilose bracts. The calyx is about 1 mm long, pilose outside, with 5-6 deciduous segments. The corolla petals are 4-5 mm long, ovate, acute, and imbricate. There are 5-6 stamens inserted at the base of the broad and annular disk. Filaments are subulate. The ovary is subglobose, densely pilose, crowned with 3 styles. It is 1-celled with ovules pendulous from a basal funicle. The drupe is kidney-shaped, obliquely ovoid, 2.35-5.88 cm long, smooth, shiny black when ripe, seated on a fleshy orange-red receptacle formed by the thickened disk and calyx base. The seeds are pendulous, with a coriaceous testa and somewhat fleshy inner coat. The tree becomes leafless between February and April, then blooms again in May. The fruit is a kidney-shaped drupaceous nut with a fleshy pear-shaped receptacle, 2.35 to 5.88 cm long, obliquely ovoid, smooth, shiny, and green. When ripe, the nut turns black, while the receptacle changes to orange. The pericarp is about 4-5 mm thick, containing a large elliptical ligneous oil cavity<sup>3</sup>.

#### Phytochemistry :

The most significant components of *S. anacardium* oil are phenolic compounds. When exposed to air, these compounds oxidize to form quinones. The oxidation process can be prevented by storing the oil under nitrogen. Two main phenolic compounds and a glucoside identified are bhilavanol A (monoene-pentadecyl catechol I), bhilavanol B (dienepentadecyl catechol II), and anacardoside (glucoside) (Goudgaon et al., 1984; Gil et al., 1995). Vesicant reactions of Bhallataka may be attributable to these phenolic compounds. Important biflavonoids such as semecarpufflavanone, jeediflavanone, gallufflavanone, nallaflavanone, semecarpetin, and anacardufflavanone have also been isolated (Murthy, 1985a, bn). The most significant components of *S. anacardium* Linn. are bhilwanols, phenolic compounds (Mathur and Agrawal, 1953), biflavonoids, sterols (Ishatulla et al., 1977), and glycosides (Rao et al., 1973a, b). Bhilwanol from fruits was shown to be a mixture of cis- and trans-isomers of ursulenol; this compound mainly consists of 1, 2-dihydroxy-3 (pentadecadienyl 8', 11') benzene and 1, 2-hydroxy-3 (pentadecadienyl 8') benzene (Indap et al., 1983). Other components isolated include anacardoside (Majumdar et al., 2008), semecarpetin, nallaflavanone, jeediflavanone, semecarpufflavanone, gallufflavanone, anacardufflavone mono-olefin I, diolefin II, bhilawanol-A, bhilawanol-B, amentoflavone, tetrahydroamentoflavone, semicarpol, anacardic acid, tetrahydrobustaflavone, O-trimethyl biflavanone A1(21), O-trimethyl biflavanone A2, O-tetramethyl biflavanone A1, O-hexamethyl bichalcone A, O-dimethyl biflavanone B, O-heptamethyl bichalcone B1, O-hexamethyl bichalcone B2, O-tetramethyl biflavanone C., and phenolics (Semalty et al., 2010a, b)<sup>4</sup>.

#### Arthritis :

Despite significant advances in both diagnosis and treatment, arthritis remains a disease as old as mankind and is globally the most common musculoskeletal disorder. The term "arthritis" is derived from the Greek word "arthron," meaning 'joint,' and the Latin word "itis," meaning 'inflammation of the joints.' Arthritis causes severe long-term pain and physical disability, affecting the psychosocial status of those affected and their families. The suffering is prolonged, inevitably impacting professional careers and independence, with indirect costs often exceeding direct costs for patients. Arthritis primarily results from damage and wear of cartilage, a flexible connective tissue found in the joints between bones

(Figure 45.1). Unlike bone, cartilage is not as hard and rigid, but it is stiffer and less flexible than muscle. It possesses resilient properties that help reduce mechanical pressure and friction effects <sup>5</sup>.

#### **Antiatherogenic effect :**

The imbalance between prooxidants and antioxidants is the main cause of the development of atherosclerosis. To prevent such conditions, antioxidant therapy is beneficial. *Semecarpus anacardium* exhibits antioxidant properties, with the capacity to scavenge superoxide and hydroxyl radicals at low concentrations. The process of atherogenesis, initiated by the peroxidation of lipids in low-density lipoproteins, is also found to be inhibited by *Semecarpus anacardium*. Sharma et al. demonstrated the cardiac activity of SA, as it generally reduces tissue and serum hyperlipidemia by inhibiting intestinal cholesterol absorption coupled with peripheral disposal, thus possessing anti-atherosclerotic activity. It is possible that the beneficial anti-atherogenic effect may be related to its antioxidant, anticoagulant, hypolipidemic, platelet anti-aggregation, and lipoprotein lipase-releasing properties. The mechanism of the hypotriglyceridemic effect has also been shown to be partly due to the stimulation of lipoprotein lipase activity <sup>6</sup>.

He demonstrated the anti-atherogenic potential of SA. Administration of *S. anacardium* nut shell extract to cholesterol-fed rabbits significantly reduced serum cholesterol (by 73.3%) and serum LDL-Chol. (by 80%). The extract feeding also prevented the accumulation of cholesterol/triglycerides in the liver, heart muscle, and aorta, and caused regression of plaques (by 75.3-83.5%). These results indicate that SA has a hypocholesterolemic action and prevents cholesterol-induced atheroma<sup>2</sup>.

The milk extract of *Semecarpus anacardium* nut was found to be effective against adjuvant-induced arthritis in albino Wistar rats at a dose level of 150mg/kg body weight, based on a dose-dependent study. This extract was observed to inhibit the acute tuberculin reaction in sensitized rats and the primary phase of adjuvant arthritis. Nut milk extract modulates reactive oxygen/nitrogen species levels and antioxidative systems in adjuvant arthritic rats. A significant decrease in the levels of lipid peroxides (LPOs), reactive oxygen species (ROS) such as superoxide radical, hydroxyl radical, H<sub>2</sub>O<sub>2</sub>, and myeloperoxidase, as well as reactive nitrogen species (RNS) like nitrate + nitrite, was observed in adjuvant arthritic animals upon administration of the drug at 150 mg/kg body weight per day. Treatment with SA restored the altered antioxidant defense components to near-normal levels. These findings suggest that SA preparations are mainly used for irregularities caused during arthritis and to treat arthritis. Additionally, *S. anacardium* also possesses the capability to modulate the accumulation of neutrophils and reduce the increased levels of lysosomal enzymes in adjuvant-induced arthritis rats. All these observations indicate that *Semecarpus anacardium* nut milk extract is a promising therapeutic agent for arthritis <sup>7</sup>.

#### **Clinical studies :**

At least 45 dissertations have been recorded for post-graduate studies in Ayurveda investigating various aspects of Bhallatak, with its role in rheumatoid arthritis emerging as the most common topic. Ayurvedic periodicals have also published clinical studies of Bhallatak in rheumatic diseases. Serial investigations conducted in rheumatic diseases have been interesting and have reported the role of *S. anacardium* in managing sciatica. In one study, Bhallatak ksheerpak was administered in a classical mode of vardhman prayog over a period of 3 weeks. Building on the positive findings from this clinical trial, patients with various rheumatic diseases, such as rheumatoid arthritis, ankylosing spondylitis, sciatica, periartthritis of the shoulder, and osteoarthritis, were studied in a controlled clinical trial. This 4-week study, again employing vardhman prayog, has shown positive responses in cases of periarticular arthritis of the shoulder, sciatic neuralgia, and early stages of rheumatoid arthritis and ankylosing spondylitis<sup>8</sup>.

#### **METHOD:**

##### **Adjuvant Arthritis in Rats:**

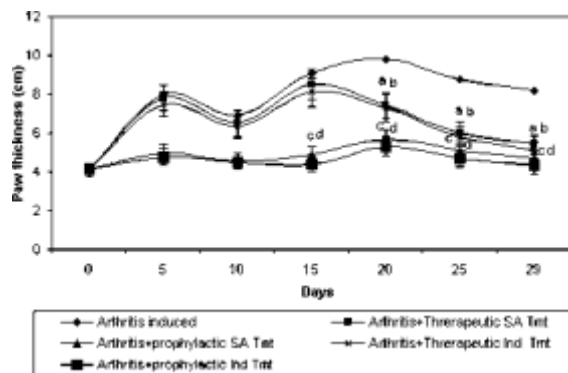
Two types of investigations were carried out: (a) The prophylactic effect was analyzed by dosing immediately before and during the development of arthritis, and (b) the therapeutic effect was analyzed by dosing after the development of arthritis<sup>10</sup>.

(a) Effect on Developing Adjuvant Arthritis: Three groups of albino rats (weighing 150–170 g), with six rats each, had the arthritic syndrome induced by subcutaneous injection into the plantar surface of the left hind paw using 0.1 ml of Complete Freund's Adjuvant (10 mg of heat-killed *Mycobacterium tuberculosis* per ml of paraffin oil). *Semecarpus anacardium* LINN. nut extract and indomethacin were administered daily in doses of 150 mg/kg body weight in olive oil and 10 mg/kg body weight, respectively, for 28 days from the day of induction. Control animals received the same volume of vehicle over the treatment period. The thickness of the injected foot was measured initially and daily, and changes in thickness over the course were employed as a measure of the degree of inflammation.

(b) Effect on Established Adjuvant Arthritis: Adjuvant arthritis was induced as described above, and the rats were left untreated until the 14th day. From day 14 onwards, they were treated daily until treatment was terminated on day 28. Paw thickness was measured daily, and the progress of inflammation was assessed<sup>11</sup>.

#### **RESULTS :**

Swelling and redness developed over a 24-hour period in the foot injected with adjuvant. This inflammatory reaction subsided slightly during the next 8 to 10 days and then increased when disseminated arthritis appeared (Fig. 2). In rats treated from the day of adjuvant injection, paw swelling was completely suppressed, and no secondary increase was seen. Drug treatment initiated 14 days after the adjuvant injection suppressed the secondary increase in swelling of the injected foot that occurred with the appearance of polyarthritis <sup>11</sup>.

**Figure 1** Anti-arthritic Effect of SA and Indomethacin on the Changes in Paw Edema of Control and Experimental Animals 12.

## CONCLUSION :

The present study's findings suggest that Bhallataka (*Semecarpus anacardium*) exhibits significant clinical efficacy in relieving joint pain, muscular pain, stiffness, and improving various associated symptoms. Notably, it demonstrates effectiveness in reducing pain, swelling, tenderness, and stiffness, making it a valuable candidate for managing these conditions. The plant's anti-inflammatory and pain-relieving properties contribute to its notable usefulness. Furthermore, the paper underscores the potential of Bhallataka (*Semecarpus anacardium*) in treating chronic and acute rheumatoid arthritis as well as immune suppressive diseases. While preliminary and preclinical studies have been conducted on this plant's extracts, its full potential as a phytopharmaceutical remains to be fully explored. It's imperative to note that Bhallataka is a poisonous plant and should only be used after undergoing a careful detoxification process. In conclusion, Bhallataka holds promise as a source of bioactive constituents for treating rheumatoid arthritis and immune suppressive diseases, but further research is needed to harness its full therapeutic potential.

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