

**SEMECARPUS ANCARDIUM LINN. : A POTENT HERBAL  
IMMUNOMODULATOR****BALAJI PANIGRAHI AND MANISH VYAS\****Lovely School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, India***ABSTRACT**

Immunomodulation is a new area of interest to maintain health and sustainability. In order to boost immune system plants are more reliable source than synthetic and chemical agents because of less adverse effects. Therefore, extensive researches are being conducted on plants to get natural immunomodulators. Complementary and alternative medicine systems are renowned for using plant remedies for protection of health and eradicate diseases. Immunomodulation of these drugs are through not only by directly affecting the pathogen, but also by stimulating natural and adaptive defence mechanisms of the host. Ancient evidence and recent research suggest that single and compound formulations of *Semecarpus anacardium* Linn. can be a better alternate for conventional chemotherapy to treat various ailments. The aim of this review is to explore various researches carried out using *Semecarpus anacardium* Linn. for its immunomodulatory activity including its description, phytochemicals, pharmacological activities and therapeutic uses.

**KEYWORDS:** *Semecarpus anacardium* Linn., Immunomodulator, Immunostimulator, Immunosuppressant

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## INTRODUCTION

Immunomodulators are popular therapeutic agents across the globe as a natural health booster due to their role to maintain and protect the health by stabilizing the immune system<sup>1</sup>. An Immunomodulator is natural or synthetic substance which helps to regulate the immune system<sup>2</sup> and regulation is a stabilisation process by which an immunomodulator optimizes the response of immune system<sup>3</sup>. Immunomodulators are mainly classified as immunosuppressants (suppression of normal or excessive immune function) and immunostimulators (reconstitution of immune deficiency) on the basis of their effect on immune system<sup>4</sup>. There is not well understood or established mechanism of action of immunomodulators, however, some references have been described their ability to increase the production of messenger molecules in body, such as cytokines<sup>5</sup> and can also decrease the production of inflammatory cytokines such as biobran<sup>5</sup>. Alkylating agents, azathioprine, cinanserin, penicillamine, procarbazine, adjuvants and complementary copolymers are some popular synthetic drugs used as immunomodulators<sup>6</sup>. However, synthetic and chemical drugs are having several side effects<sup>7,8</sup>. Cyclosporine is reported for mainly renal failure/toxicity including hypertension, hepatotoxicity, hirsutism, gingival hyperplasia, gastrointestinal toxicity and neurotoxicity<sup>7,9</sup>. Azathioprine also affect rapidly growing cells, including bone marrow and gastrointestinal cells resulting in leucopenia, thrombocytopenia and gastrointestinal toxicity<sup>7</sup>. Few chemicals or synthetic drugs cause haemorrhagic cystitis and severe pancytopenia<sup>10</sup>. The major toxicities result from anti-thymocyte globulin (ATG) being recognized as a protein, leading to serum sickness and nephritis<sup>11</sup>. Fever, leucopenia, thrombocytopenia and skin rashes are common symptoms of the toxicity of chemical and synthetic agents<sup>12</sup>. Sometimes, infertility can be also caused by these drugs due to the destruction of testicular and ovarian cells<sup>13,14</sup>. Now a day, natural products are becoming mainstay of contemporary clinical practice. Various herbal plants effectively

investigated in a variety of pathophysiological states including immunomodulation<sup>15</sup>. Moreover, herbal drugs have less adverse effect in comparison to synthetic and chemical drugs. *Semecarpus anacardium* Linn. is well-known drug for its wide arrays of therapeutic properties including immunomodulation. Present review deals with the exploration of immunomodulatory activity of *Semecarpus anacardium* Linn.

### ***Semecarpus anacardium* Linn**

*Semecarpus anacardium* Linn. and its formulations have been used in complementary and alternative medicine system for the treatment of multiple diseases<sup>16</sup>. *Semecarpus anacardium* Linn. is a deciduous tree generally found in Sub-Himalayan region, east zone of the Beas, ascending to 1050 m in Assam (Khasia hills), Madhya Pradesh, Gujarat, Konkan, Kanara forests of Tamilnadu state<sup>17</sup>. It belongs to the family anacardiaceae. The height of tree is 15-25 m (Figure 1). Colour of bark is grey desquamating in rough flakes. Leaves are simple, alternate, obovate oblong, apex is rounded, coriaceous, glabrous above and more or less pubescent beneath, and main nerves are in 15-25 pairs (Figure 2). Flowers are greenish white in colour fasciculated in pubescent panicles<sup>18</sup>. Fruits are orange red in colour, smooth, fleshy, obliquely ovoid and 2.5 cm long. The taste of fruit is sweet and edible once ripe, shape is like thickened disc and calyx base is accrescent. The lower base consists of smooth, black, shining thick pericarp. It contains oblong cell filled with corrosive resinous juice between outer and inner laminae. Colour of juice is white when the fruit is immature and brownish or black when the fruit is ripe (Figure 3). Black corrosive juice is used for internal (dyspepsia, nervous debility, acute rheumatism, asthma and cough) as well as external purposes (inflammations, piles and skin disorders) throughout the India. White kernel found inside the nut which is protected by the hard shell. Kernel is sweet and nutritious like the kernel of almond or cashew<sup>19</sup>.

**Figure 1**  
***Tree of Semecarpus anacardium Linn***



**Figure 2**  
***Leaf and unripe fruit of Semecarpus anacardium Linn***



**Figure 3**  
**Dried fruit of *Semecarpus anacardium* Linn**



## PHYTOCHEMICAL PROFILE

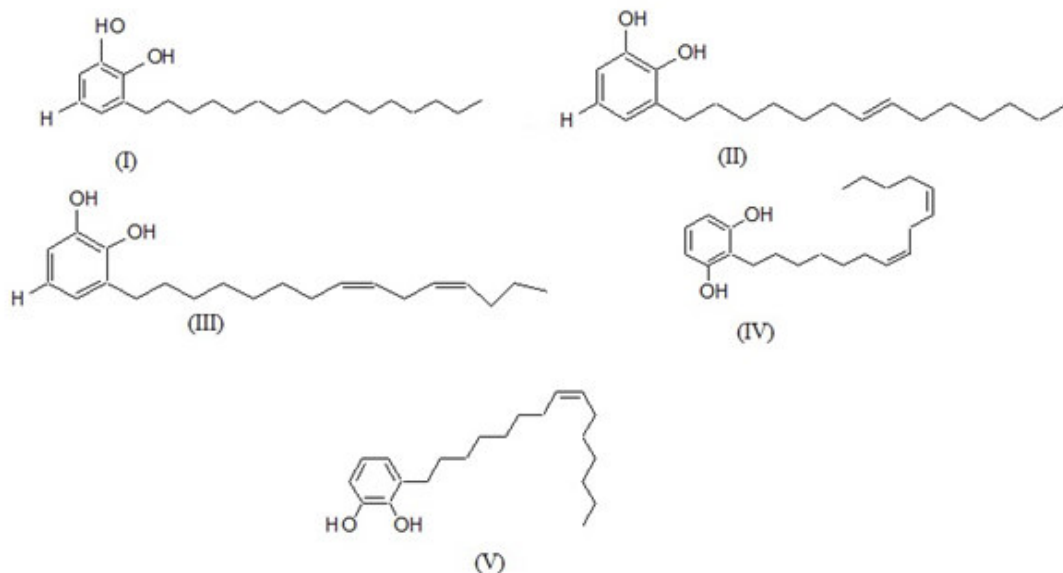
In traditional medicine, medicinal plants and their preparations have extensive use specially to treat the diseases. Nut extract preparations of *Semecarpus anacardium* Linn. are used to treat many diseases such as arthritis, tumours, infections<sup>20</sup> etc. Pharmacological activities of *Semecarpus anacardium* Linn. depend on the isolated compounds. Bhilawanols is a mixture of 3-pentadec(en)yl catechols unsaturated in the lipophilic side chain which is isolated from the nut shell. The major constituents of bhilawanol are the 8Z, 11Z-diene [Figure 4(I)] and 8 Z monoene [Figure 4(II)] with small quantity of saturated bhilawanol<sup>21</sup> [Figure 4(III)]. Investigations on methylated bhilawanol revealed that it contains more than seven components and two major compounds identified as dimethyl ethers of 1-pentadeca-8enyl-2, 3 dihydroxybenzene [Figure 4(V)] and 1-pentadeca- 7, 10 dienyl-1, 3 dihydroxybenzene<sup>22</sup> [Figure 4(IV)]. Further investigation suggested that bhilawanol contains two components 1, 2-dihydroxy-3 pentadecyl benzene [Figure 5(VI)] and its corresponding diene analogue<sup>23,24</sup> [Figure 5(VII)]. Three bi flavonoids extracted from the ethanolic fraction of the *Semecarpus anacardium* Linn. nut shells and characterized

as 1-4', 11-3', 4', 1-5, 11-5, 1-7-hexahydroxy [1-3, 11-8] biflavanone [Figure 5(VIII)A], 1-4', 11-4', 1-5, 11-5, 1-7, 11-7-hexahydroxy [1-3, 11-8] biflavanone (3', 8-binarigenin) [Figure 5(VIII)B] and 1-4', 11-4', 1-7, 11-7-tetrahexahydroxy [1-3, 11-8] biflavanone (3'8-billiquiritigenin)<sup>22</sup>[Figure 5(VIII)C]. The three other biflavonoids, jeediflavanone [Figure 6(IX)A], semecarpufavanone [Figure 6(IX)B], gallufavanone [Figure 6(IX)C] have also been extracted from the alcoholic extract of nut shells and characterized<sup>25,26,27,28,29</sup>. The two other new biflavonoids a dimeric flavonoid nallaflavanone [Figure 6(X)A], semecarpetin [Figure 6(X)B] and anacardoflavanone [Figure 6(XI)] have been isolated from the nut shells and characterized<sup>30</sup>. Ishratullai et al. (1977) isolated one more biflavonoid namely tetrahydrorobustaflavone [Figure 7(XII)] from the defatted nuts of the *Semecarpus anacardium* Linn. and structure characterized. The leaves of the *Semecarpus anacardium* Linn. contains amentoflavone [Figure 7(XIII)] as the sole compound<sup>31</sup>. The corrosive juice from the pericarp of the fruit found to contain catechol, fixed oil and anacardol (C<sub>18</sub>H<sub>13</sub>O<sub>3</sub>.COOH) to which the corrosive properties of the juice are due to two phenolic acids C<sub>16</sub>H<sub>15</sub>O<sub>3</sub>.COOH and C<sub>14</sub>H<sub>13</sub>O<sub>3</sub>.COOH<sup>18</sup>.

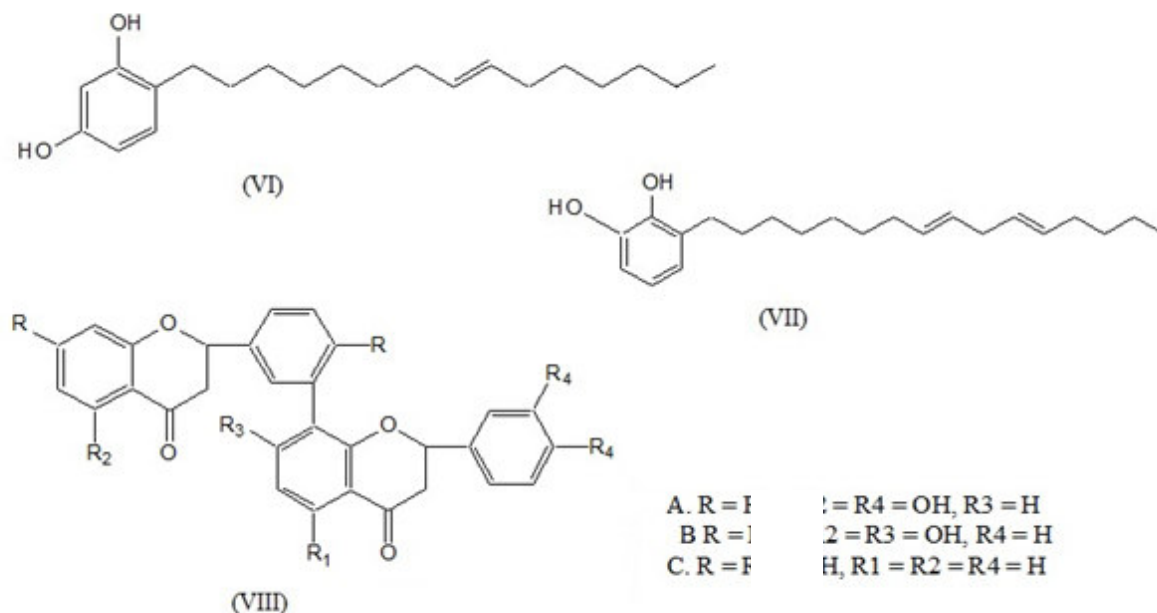
Anacardoside was isolated from the seeds of *Semecarpus anacardium* Linn. and Combination of NMR was used to elucidate its structure and configuration as-l-O-β-D-

glucopyranosyl- (1→6) - β -D- glucopyranosyloxy-3hydroxy-5-methylbenzene<sup>32</sup> [Figure 7(XIV)].

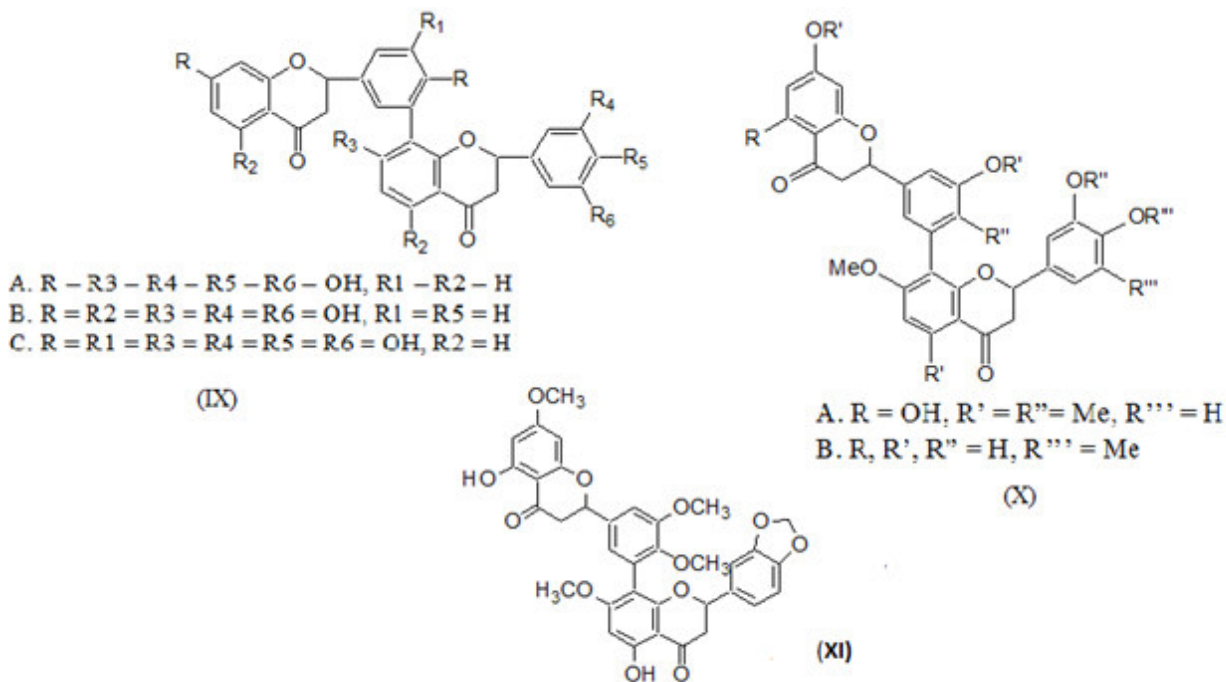
**Figure 4**  
**Chemical constituents *Semecarpus anacardium* Linn**



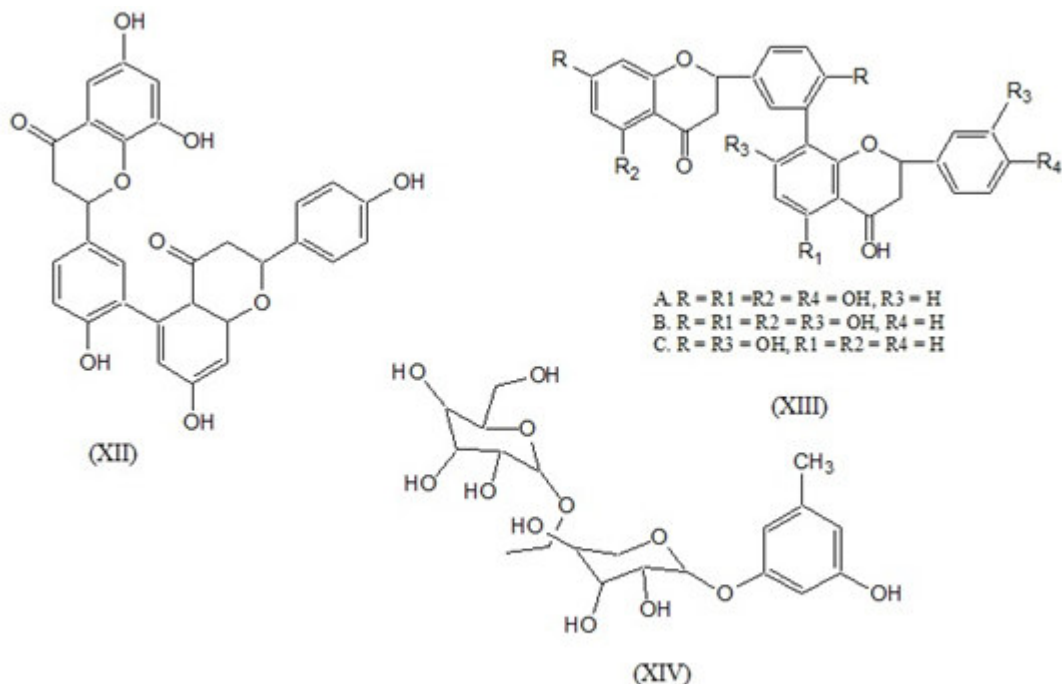
**Figure 5**  
**Chemical constituents *Semecarpus anacardium* Linn**



**Figure 6**  
**Chemical constituents *Semecarpus anacardium* Linn**



**Figure 7**  
**Chemical constituents *Semecarpus anacardium* Linn**



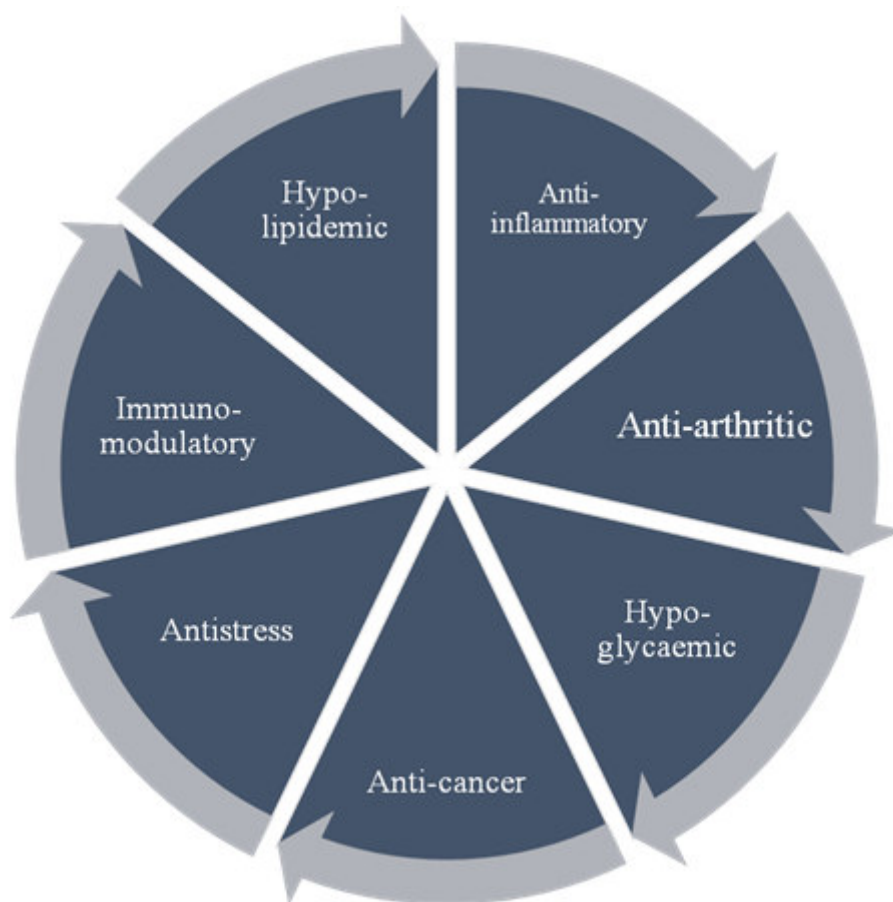
## PHARMACOLOGICAL ACTIVITIES

Recent studies suggested that single and compound formulations of *Semecarpus anacardium* Linn. has multiple

pharmacological activities such as anti-inflammatory activity<sup>33,34</sup>, anti-arthritis activity<sup>35,36</sup>, hypoglycaemic activity<sup>37,38</sup>, anti-

cancer activity<sup>39,40,41,42,43,44</sup>, contraceptive agent<sup>45,46</sup>, lipoxygenase inhibitory activity<sup>47</sup>, hypolipidemic activity & hypocholesterolemic

activity<sup>48,49</sup>, antimicrobial activity<sup>50,51,52,53</sup>, antistress activity<sup>54</sup> and immune modulatory activity<sup>55,56,57,58</sup> (Figure 8).



**Figure 8**  
**Main pharmacological activities of *Semecarpus anacardium* Linn.**

## IMMUNOMODULATORY ACTIVITY

The immunomodulatory activity of *Semecarpus anacardium* Linn. nut milk extract is reported by Balchandran Premalatha et al. (1998) in male Wistar rats bearing aflatoxin B<sub>1</sub>-induced hepatocellular carcinoma (HCC) was reported that immunomodulatory activity was assessed by measuring serum immunoglobulin (Ig) levels in control and experimental animals. Reduced IgG and elevated IgA and IgM in the hepatocellular carcinoma condition were found approximately normal. This significant modulation of immune response may be responsible for anti-carcinogenic activity. Male Wistar rats (100-200 gm) were used for this study. The rats were divided into four groups of six animals each. Group 1 was normal controls. Hepatocellular carcinoma was induced in groups 2 and 3. Single intraperitoneal injection of 2 mg kg<sup>-1</sup> aflatoxin

B1 was used to induce hepatocellular carcinoma. Group 3 was administered by 200 mg kg<sup>-1</sup> *Semecarpus anacardium* Linn. nut milk extract in sunflower oil from oral till 14 days. Group 4 was treated as a drug control and administered by same extract as group 3. Albumin and albumin-globulin ratio were decreased significantly (P < 0.001) in HCC-bearing in comparison to normal controls and globulin content was increased significantly (P < 0.001). Whereas, significant increase in albumin and albumin-globulin ratio and decrease in globulin content were found in *Semecarpus anacardium* Linn. nut milk extract treated group in comparison to HCC-bearing rats. No significant variation was not found in these parameters of drug control groups. Serum immunoglobulin levels in control and experimental animals. IgG levels were

decreased markedly ( $P < 0.001$ ) whereas IgA and IgM were elevated ( $P < 0.001$ ) in HCC-bearing rats. These were returned to near normal levels in the drug-treated group compared with HCC-bearing rats. Drug control animals did not show any significant variation in immunoglobulin levels compared with normal rats<sup>55</sup>. Immunomodulatory activity of *Semecarpus anacardium* Linn. extract in mononuclear cells of normal individuals and rheumatoid arthritis patients is revealed alcoholic extract of *Semecarpus anacardium* Linn. inhibited the spontaneous and LPS induced production of proinflammatory cytokines IL-1 $\beta$  and IL-12p40 but had no effect on TNF- $\alpha$  and IL-6 production, both at protein and mRNA level. The crude extract also suppressed LPS induced nuclear translocation of transcription factors, NF- $\kappa$ B and AP-1; the inhibition of NF- $\kappa$ B was through the inhibition of I $\kappa$ B $\alpha$  phosphorylation. The extract also suppressed LPS activated nitric oxide production in mouse macrophage cell line, RAW 264.7. Results of this study showed that *Semecarpus anacardium* Linn. extract can inhibit proinflammatory cytokine production and demonstrate its mechanism of action<sup>56</sup>. The effect of *Semecarpus anacardium* Linn. nut extract on the level of lipid peroxides (LPO) and the activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and reduced glutathione (GSH) in the lymphocytes and lymphoid organs, namely spleen and thymus of adjuvant induced arthritic rats, were investigated. The results were compared with normal and untreated arthritic rats. Evaluation of antioxidant effect of *Semecarpus anacardium* Linn. nut extract on the components of immune system in adjuvant arthritis revealed that *Semecarpus anacardium* Linn. nut extract significantly decreases the paw edema and arthritic score in arthritic rats on administration. However, significant edema in the hind paw was found in untreated arthritic rats. Levels of reactive oxygen species (ROS) i.e., hydroxy radical, superoxide radical, and H<sub>2</sub>O<sub>2</sub> were also measured in spleen, thymus, and lymphocytes of control and experimental animals. Biochemical markers of inflammation such as C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) were determined. Anti-arthritic profile was evaluated from the

changes in the paw edema and arthritic scores of arthritic and drug-treated rats. A significant increase in the level of LPO, ROS and decreased levels of antioxidant enzymes in arthritic rats were observed. On treatment with the drug, the above changes were reverted back to near normal levels. The significant increase in CRP level and ESR of arthritic animals were observed to be significantly restored in *Semecarpus anacardium* Linn. treated rats. No significant changes were found in sole drug-administered normal rats. In this study, adult male Wistar rats (120–130 g) were divided into 4 groups of 6 animals each. Group I was control and arthritis was induced in Group II [Freund's complete adjuvant containing 10 mg of heat-killed mycobacterium tuberculosis in 1 ml paraffin oil (0.1 ml) was injected into the left hind paw of the rat intradermally]. Whereas, Group III were treated with drug for 14 days (150 mg/kg body weight dissolved in 0.5 ml olive oil) after 14 days from the day of adjuvant injection. Besides, Group IV was drug-treated control (150 mg/kg body weight). The drug was administered for 14 days. The results of study showed that the levels of lipid peroxides in the lymphocytes, spleen, and thymus. Lipid peroxide level was found to be significantly increased ( $P < 0.05$ ) in lymphocytes, spleen, thymus of arthritis-induced animals when compared to control animals. After drug treatment for 14 days, the level was found to be significantly reduced in group III animals when compared to group II animals. There were no significant changes in group IV animals when compared with group I animals. Levels of enzymatic antioxidants (SOD, CAT, GPx) and non-enzymatic (GSH) antioxidants in lymphocytes, spleen and thymus, respectively. Both enzymatic and non-enzymatic antioxidants levels were found to be significantly decreased ( $P < 0.05$ ) in group II animals when compared with group I animals. The levels were reverted back to near-normal levels in group III animals when compared with group II animals. No significant changes were observed in group IV animals when compared with group I animals. Immunomodulatory effects of *Semecarpus anacardium* Linn<sup>57</sup>. Nut milk extract of *Semecarpus anacardium* Linn. was also investigated in adjuvant induced arthritis by studying the alterations in humoral and cell



mediated immune responses. Treatment by *Semecarpus anacardium* Linn. significantly restored variations in the humoral and cell mediated immunity up to normal level. In this study, adult male Wistar rats (120—130 g) were divided into 4 groups of 6 animals each. Group I was control animals. Whereas, Group II was arthritis induced [Freund's complete adjuvant containing 10 mg of heat killed mycobacterium tuberculosis in 1ml paraffin oil (0.1 ml) was injected into the left hind paw of the rat intradermally]. Group III: Drug treated [The drug (150 mg/kg body weight dissolved in 0.5 ml olive oil) was administered after 14<sup>th</sup> day from the day of adjuvant injection for 14<sup>th</sup> day by intubation]. Group IV: Drug treated control [The drug (150mg/kg body weight) was administered to normal animals for 14<sup>th</sup> day by intubation]. Results of this study revealed that effect of *Semecarpus anacardium* Linn. on the plaque forming cells (PFC) and antibody titre in control and arthritic animals, respectively. The increase in both plaque forming cells and antibody titre found in arthritic animals were significantly ( $p < 0.05$ ) reverted back on administration of the drug *Semecarpus anacardium* Linn. The levels of immunoglobulins (IgG, IgA, IgM) and serum soluble immune complex in control and experimental animals are shown in Table 2. In group II arthritic animals, the levels of the immunoglobulins were found to be significantly ( $p < 0.05$ ) increased when compared with that of control animals. On administration of *Semecarpus anacardium* Linn., these changes were significantly ( $p < 0.05$ ) recouped back to near normal levels. In drug control (group IV) animals, there were some variations in the above humoral immune parameters although they did not reached the significant ( $p < 0.05$ ) levels of lymphoid organs in control and arthritic animals. The weight and cellularity of spleen as well as the weights of popliteal lymph nodes were found to be increased but the thymic weight and cellularity were noticed to be decreased significantly in arthritic animals. These changes were reverted to near normal upon treatment with *Semecarpus anacardium* Linn. The effect of *Semecarpus anacardium* Linn. on the extent of leukocyte migration in control and arthritic animals were depicted. In group II arthritic animals, the migration of leukocytes was found to be significantly ( $p < 0.05$ ) elevated.

Whereas, in drug administered arthritic (group III) animals, these changes were brought back significantly ( $p < 0.05$ ) to near normal levels. No significant changes were observed in sole drug administered (group IV) animals although there were some alterations but not statistically significant when compared with that of control animals. Thereafter, it was found to decrease to some extent during the rest of the experimental period. *Semecarpus anacardium* Linn. treated (group III) animals showed a significant ( $p < 0.05$ ) decrease in the DTH response at 21<sup>st</sup> and 28<sup>th</sup> day of the experimental period when compared with the arthritic animals which shows the efficacy of the drug. Group IV drug control animals although showed altered levels, did not show any statistical significance when compared with that of control animals<sup>58</sup>.

## THERAPEUTIC USES

*Semecarpus anacardium* Linn. is extensively used as a single and compound form to treat a wide range of ailments since ancient time. Therefore, Ayurveda and siddha system of medicine consider it as a 'Panacea'. Ayurveda describes use of fruits and oil of *Semecarpus anacardium* Linn. in the treatment of neuritis<sup>59</sup> and helminthic infection<sup>53</sup>. It is extensively used in Indian medicine to treat gout and rheumatic pain<sup>60</sup>. It is also effective in heart, blood pressure, respiration and neurological disorders<sup>61,62,63</sup>. Leprosy, rheumatoid arthritis, piles, asthma, syphilis, gonorrhoea and leucoderma can be treated by using fruits of *Semecarpus anacardium* Linn.<sup>64,65</sup>. The nuts are also used for management of rheumatism, wound healing, diabetes and urinary diseases. *Semecarpus anacardium* Linn. is also used as aphrodisiac, nerve-tonic and as anabolic medicine in the Ayurveda<sup>66,67</sup>. Chloroform extract of whole nut has been reported in the treatment of oesophageal cancer and leukaemia<sup>68</sup>.

## CONCLUSION

In recent, natural or herbal products has gained attention due to the adverse effects of contemporary medicines. Moreover, single drug and formulations of complementary and alternative medicine systems are safe. Though

*Semecarpus anacardium* Linn. has various pharmacological activities including immunomodulatory activity, but it is the need of hour to investigate these activities at molecular level with help of various biotechnological tools

and techniques. Further studies should be conducted to reveal the molecular mechanism of interaction of *Semecarpus anacardium* Linn. with human body for immunomodulation and other activities.

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