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Review Article

## Medicinal Importance of *Azadirachta indica*: An Overview

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### Article Info:



#### Article History:

Received 07 April 2023

Reviewed 11 May 2023

Accepted 29 May 2023

Published 15 June 2023

### Cite this article as:

Devi J, Sharma RB, Medicinal Importance of *Azadirachta indica*: An Overview, Journal of Drug Delivery and Therapeutics. 2023; 13(6):159-165

DOI: <http://dx.doi.org/10.22270/jddt.v13i6.5892>

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### Abstract

**Background:** The neem tree has a long history of being referred to as a "wonder tree." Since the time of the Vedic civilization, neem has been used therapeutically in many different ways in India. The various components of the neem tree, including the stem, bark, roots, leaves, gum, seeds, fruits, and flowers, have a no. of chemical constituents and have been used as traditional medicines. The seeds, leaves, blossoms, and bark of this tree, are used for treating various diseases. Since ancient times, neem tree extracts have been widely employed in health management because they possess a number of health-promoting qualities. Some of the chemical constituents are named quercetin, azadirachtin, a number of limonoids, nimboterol, etc.

**Objective:** The aim of this review is to highlight the potential of *Azadirachta indica* in the treatment of various ailments and prospects associated with the delivery of *Azadirachta indica*.

**Methods:** We reviewed the literature from journal publication websites and electronic databases, such as Bentham, Springer, Science Direct, PubMed, Scopus, etc.

**Results:** The abundant availability of sources of *Azadirachta indica* makes a point in favor of exhaustive exploration of this plant. This plant has been used in the treatment of a number of ailments from ancient times by human beings and these are reported to be having anti-bacterial, anti-fungal, anti-viral, anti-inflammatory, anti-cancer, antihyperglycemic, and antioxidant potential.

**Conclusion:** There are a number of health benefits of *Azadirachta indica*. The neem tree (*Azadirachta indica*) is found to have various medicinal/pharmacological actions.

**Keywords:** *Azadirachta indica*, quercetin, carcinogenic, pharmacological effect, hepatoprotective, peroxidation.

## 1.0 INTRODUCTION

Since the earliest plant species, neem (*Azadirachta indica*) has been known for its medical benefits. In India, this tree has a long history of being referred to as a "wonder tree." Since the time of the Vedic civilization, neem has been used therapeutically in many different ways in India. Almost all tree components, including the stem, bark, roots, leaves, gum, seeds, fruits, and flowers, have been used as traditional medicines for domestic treatments for a variety of human illnesses from ancient times<sup>1</sup>. Neem is now widely used in medicine, and its extract includes a variety of chemical components, the two most sought-after of which are nimbinine, and nimbenol, *Azadirachta indica*, the neem tree's botanical name, is a resilient, evergreen plant native to tropical and subtropical regions that grow quickly. Neem's impact on the skin is one of its main benefits<sup>2</sup>. Because they are antibacterial, the tree's oils are used as a general antiseptic because they are antibacterial. Neem, also known as *Azadirachta indica*, is a plant that belongs to the Meliaceae family and has long been valued for its therapeutic benefits<sup>3</sup>. The seeds, leaves, blossoms, and bark of this tree, which is found in tropical and semitropical regions of the world, are

used for a variety of things. Since ancient times, neem tree extracts have been widely employed in health management because they possess a number of health-promoting qualities<sup>4</sup>. Neem's therapeutic effects in the treatment and prevention of numerous diseases are outlined in the review.



Figure 1: Leaves of *Azadirachta indica*



Figure 2: Neem Fruits and Leaves



Figure 3: Neem Seed

## 2.0 PLANT DESCRIPTION AND CLASSIFICATION

The neem tree grows fast that may grow up to 15-20 m tall and has tiny, brilliant green color leaves. It is abundant in tropical and semi-tropical areas. It blooms in the spring with a profusion of white flowers<sup>5</sup>. In locations with weak soils and 400-800 mm of yearly precipitation, they flourish. The neem tree was seen as so important and wonderful that it played a significant role in India<sup>6</sup>. It is categorized botanically as follows:

Table 1: Botanical Classification of Neem

Order	Rutales
Suborder	Rutinae
Family	Meliaceae
Subfamily	Melioideae
Tribe	Melieae
Genus	Azadirachta
Species	indica
Latin	<i>Azadirachta indica</i>

## 3.0 CHIEF INGREDIENTS AND THEIR STRUCTURE

Neem contains a variety of chemicals in various plant components, including quercetin, azadirachtin, a number of limonoids, and nimbosterol<sup>7</sup>. Nimbin, nimbolide, ascorbic acid, n-hexacosanol, and nimbolide are just a few of the substances that are found in leaves<sup>8</sup>. In addition, Nimbin, Nimbinin, Nimbinin, Zafaral, Salannin, and Azadirachtin are also present in this medicinal plant. The different chemical constituents of neem have different medicinal properties like, antibacterial, antifungal, anti-tumor, antifertility, hepatoprotective, antidiabetic, neuroprotective and nephroprotective. Some of these are discussed in this review article in detail. This review article provides information about the medicinal properties of neem which is also known as *Azadirachta indica*. According to reports, each of these components has a part in the control of diseases<sup>9</sup>. Figure 4 depicts the structure of the main neem components.

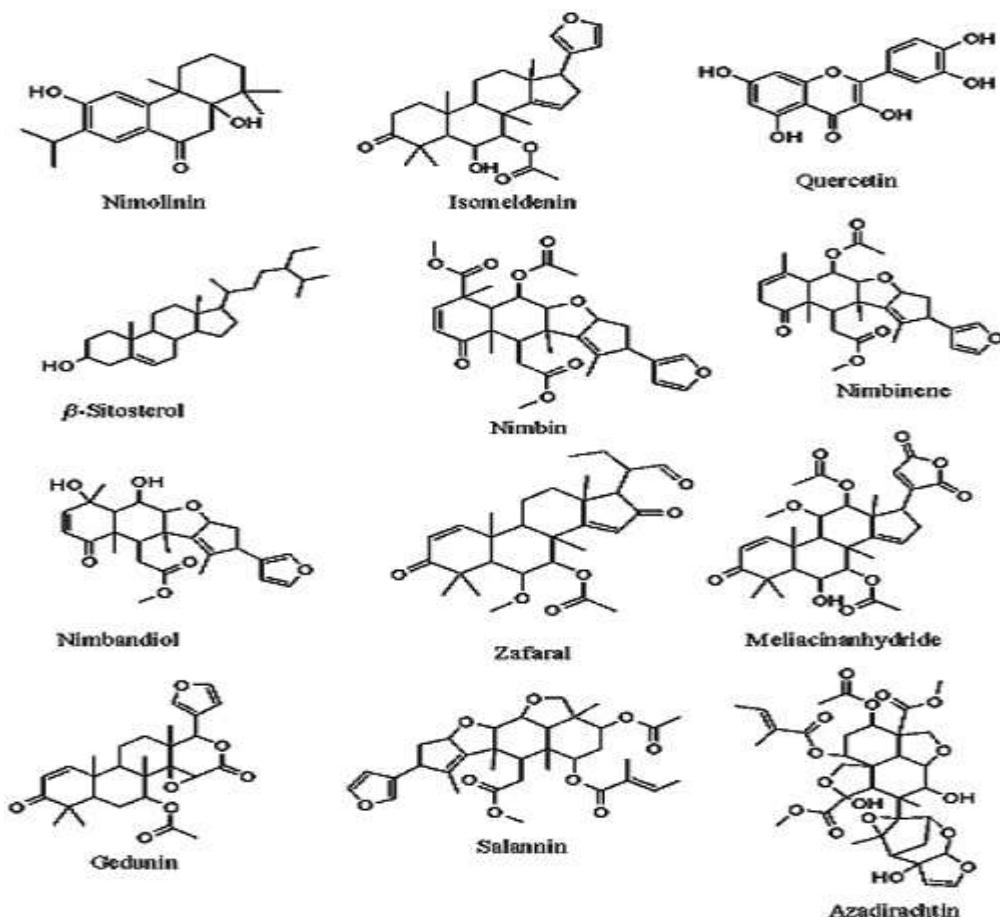


Figure 4: Chemical structures of Active constituents of Neem

#### 4.0 GEOGRAPHICAL DISTRIBUTION

Neem is a plant that originated on the Indian subcontinent and is now extensively cultivated, particularly in the drier (arid) tropical and subtropical regions of Asia, Africa, the Americas, Australia, and the South Pacific islands. It is readily available in several states of India. In the country's centre, Myanmar, it is quite prevalent<sup>10</sup>.

Neem is found on the Fiji Islands in the South Pacific. Neem is mostly found in Indonesia on the frier islands to the east (Bali, Lombok, and Sumbawa), as well as the low-lying northern and eastern regions of in the 1970s and 1980s of the previous century, it was first introduced in the Philippines<sup>11</sup>.

#### 5.0 MEDICINAL/PHARMACOLOGICAL ACTIVITIES OF NEEM

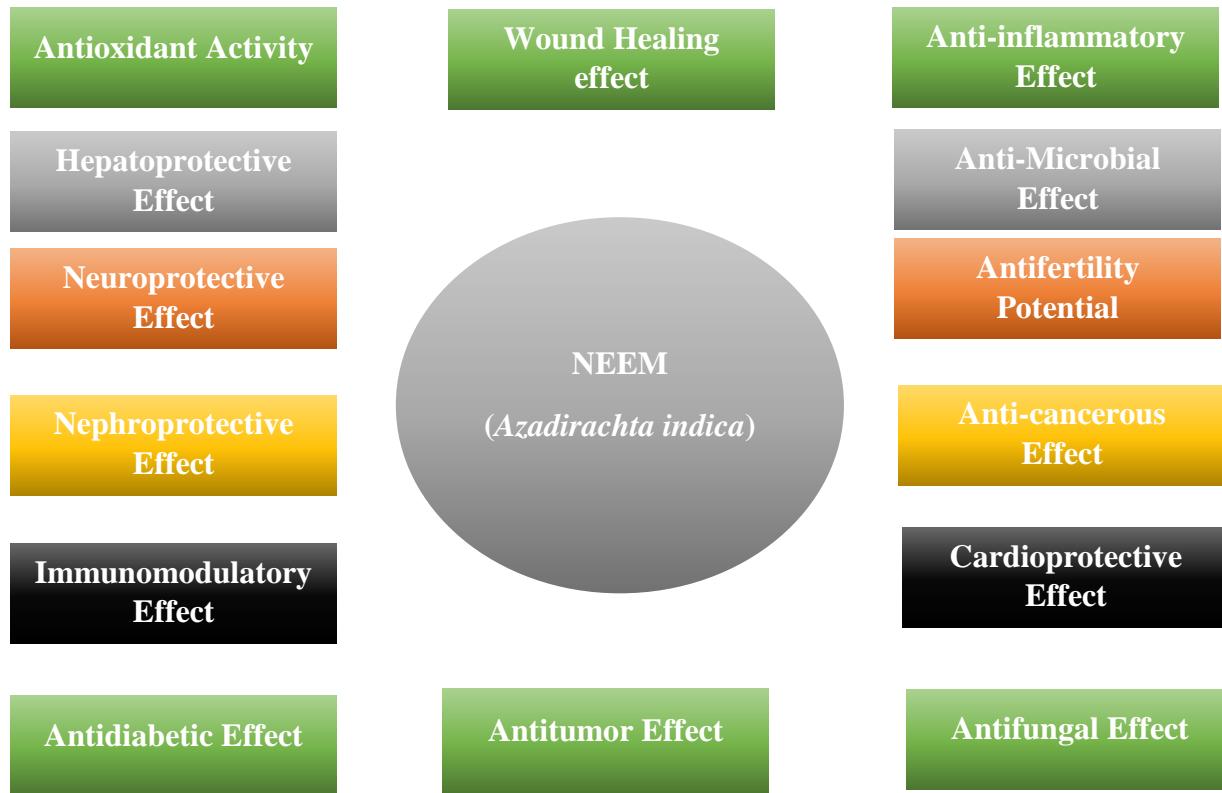


Figure 5: Pharmacological activities of neem and its ingredients

#### 5.1 ANTIOXIDANT ACTIVITY

The findings imply that leaf, blossom, and stem bark extracts have significant antioxidant activity<sup>8</sup>. In a different investigation, it was shown that ethanolic extracts of flowers and seed oil had superior free radical scavenging abilities. Additionally, it was shown in a comparative investigation that the bark had more complex phenolic contents than the leaves and had stronger antioxidant activity<sup>12</sup>. The evaluation of the methanolic extract of the roots' roots for the estimate of various flavonoids and their capacity to scavenge free radicals has also been conducted<sup>9</sup>.

#### 5.2 WOUND HEALING EFFECT

Neem oil's benefits on the treatment of chronic, nonhealing wounds were examined in one study, and the findings revealed that after 8 weeks of therapy, over 44% of patients had seen 50% wound healing<sup>13</sup>. A substantial decrease in the longest diameter wounds was seen in a study that employed the aqueous extract of neem leaves to monitor wound healing activities<sup>14</sup>.

#### 5.3 ANTI-INFLAMMATORY EFFECT

Numerous research have noted the anti-inflammatory properties of neem plants. Nimbidin from neem trees was utilised orally to test its anti-inflammatory effect in an experimental investigation using rat models. The inhibition of phagocytosis and the migration of macrophages were verified to the peritoneal cavities in response to inflammatory stimuli<sup>15</sup>.

#### 5.4 ANTIFUNGAL PROPERTIES

Numerous in vitro and in vivo investigations seem to support neem extracts' fungistatic and fungicidal activities. It has been discovered that neem extract has fungistatic and fungicidal effects on dermatophytes like *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and various other antifungal agents<sup>16</sup>. When taken as a whole, these studies strongly imply that neem products may be beneficial for the management and treatment of dermatophytes and fungal diseases in plants and animals, as well as for the biological control of biodeterioration of agricultural goods that have been kept<sup>17</sup>.

## 5.5 INSECT REPELLENT AND ANTFEEDANT PROPERTIES

Repulsion, antifeedant effects, or death are all methods for controlling important insects and other pests in medicine, veterinary medicine, and agriculture. Numerous studies seem to indicate that various neem compounds may be helpful in controlling insects and vectors by the methods said above<sup>18</sup>. Many components and products of neem are used to ward against mosquitoes. For instance, it has been discovered that the smoke of *A. indica* plant leaves can reduce mosquito populations by up to 70%. Neem oil may potentially have considerable insect-repellent properties<sup>19</sup>.

## 5.6 ANTI-ULCEROGENIC EFFECT

Utilizing several animal models, the hypoglycemic and anti-hyperglycemic effects of *A. indica* plant components have been studied. A lot of researchers have looked at how neem extracts affect gastric output and gastro-duodenal ulcers in normal and streptozotocin-induced diabetic mice<sup>18</sup>. When given intraperitoneally at a dose of 100-250 mg/kg or orally at a dose of 100-800 mg/kg, stem bark extracts of *A. indica* were reported to considerably reduce the stomach ulceration caused by indomethacin (40 mg/kg) in albino rats<sup>20</sup>. This activity was found to be accompanied by a dose-dependent reduction in total stomach acidity<sup>18</sup>. Thus *Azadirachta indica* also has an anti-ulcerogenic effect.

## 5.7 IMMUNOLOGICAL PROPERTIES

Utilizing several animal models, the hypoglycemic and anti-hyperglycemic effects of *A. indica* plant components have been studied. When streptozotocin was used to cause diabetes in mice, aqueous leaf extracts of Neem compounds may have a considerable modifying influence on the humoral and cell-mediated immune systems, according to a number of findings in the literature<sup>21</sup>. After giving mice a single intraperitoneal dosage of neem oil, researchers looked at the immunomodulatory effects. Neem oil raised the number of leukocytic cells, improved the phagocytic activity of peritoneal macrophages, increased the expression of MHC class II antigens, and stimulated the production of gamma interferon, according to their observations<sup>22</sup>. They came to the conclusion that neem oil functions as an immunostimulant that selectively stimulates the cell-mediated immune systems to generate an increased response to mitogenic stimuli.

## 5.8 ANTIOXIDANT AND ANTICARCINOGENIC ACTIVITY

When streptozotocin was used to cause diabetes in mice, aqueous leaf extracts of neem has been shown to have antioxidant properties in vivo during the germination of horse grain, which is characterized by low levels of lipid peroxides and lipo-oxygenase activity. In order to study the effects of nitrosamine N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), a carcinogenic nitrosamine, on lipid peroxidation and antioxidant status in male Wistar rats, researchers studied the effects of garlic and neem leaf extracts<sup>23</sup>. Before administering MNNG intraperitoneally, garlic and neem leaf extracts were given orally for five straight days. A considerable drop in glutathione (GSH) and lipid peroxidation in the stomach, liver, and blood of MNNG-treated rats was accompanied by increased lipid peroxidation<sup>24</sup>. In the stomach, which is the main target organ for MNNG, liver, and circulation, administration of garlic and neem-leaf extracts dramatically reduced the generation of lipid peroxides and increased the amounts of antioxidants and detoxifying enzymes<sup>12</sup>. The findings of their investigation imply that neem and garlic may exert their protective effects by boosting levels of GSH and GSH-dependent enzymes and by modifying lipid peroxidation. There are reports on the use of neem to treat patients with different types of cancer<sup>25</sup>. Neem leaf extract's chemopreventive properties have been investigated against oral

carcinogenesis brought on by 7,12-dimethylbenzanthracene (DMBA), as shown by a decreased incidence of neoplasm<sup>3</sup>. When treated effectively, a parotid tumor patient and an epidermal carcinoma patient responded successfully to neem seed oil<sup>26</sup>.

## 5.9 ANTIMALARIAL ACTIVITY

It has been discovered that neem possesses antimalarial properties. Neem seed extracts were tested for their impact on *Plasmodium falciparum*, the human malaria parasite, and the results were extremely significant<sup>27</sup>. It is interesting to note that neem components had an anti-plasmodial impact on parasites that had previously been found to be resistant to conventional antimalarial medications (chloroquine, pyrimethamine); this suggested a distinct method of action<sup>27</sup>. The fractions of neem seed are therefore effective against both the stages of the parasite that generate the clinical presentation and those that continue to transmit malaria. Fresh neem leaves were used to make the limonoids, which were discovered to exhibit antimalarial action against the chloroquine-resistant *P. falciparum* strain<sup>28</sup>.

## 5.10 DERMATOLOGICAL APPLICATIONS

Neem is particularly efficient in treating common skin conditions including ringworm, scabies, and acute and chronic eczema. When evaluated in vitro using the agar dilution method against 88 clinical isolates of dermatophytes, the ethanolic extract of *A. indica* leaves showed much greater anti-dermatophytic activity than the aqueous extract. The aqueous extract has an MIC<sub>90</sub> of 500 mg/mL, compared to the ethanolic extract's 100 mg/mL<sup>29</sup>. Numerous skin conditions have been reported to respond well to nimbidin. It was discovered that a herbal gel formulation made using *Centella asiatica*, Aloe vera, and *A. indica* extract as the foundation had outstanding pharmacological qualities<sup>30,31</sup>.

## 5.11 HEPATOPROTECTIVE ACTIVITY

Rats exposed to paracetamol-induced liver necrosis were shown to benefit from the use of aqueous neem leaf extract. On administration of the neem leaf aqueous extract, it was discovered that the increased levels of blood aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GGT) suggestive of liver injury were dramatically decreased<sup>32</sup>.

## 5.12 SPERMICIDAL AND CONTRACEPTIVE ACTIVITY

Numerous studies have looked at neem's spermicidal and contraceptive properties. According to recent research, albino rats treated with neem for 48 days had lower total sperm counts, sperm motility, and forward velocity<sup>33,34</sup>. While the fructose content of caudal sperm from the epididymis decreased, the proportion of aberrant sperm increased<sup>35</sup>. These findings point to the likelihood that these effects result from an androgen shortage brought on by the antiandrogenic characteristics of neem leaves, which in turn disrupt the physiological development of sperm<sup>36</sup>.

## 5.13 DIURETIC ACTIVITY

The stem bark and root bark's crude ethanolic extract exhibited hypotensive, spasmolytic, and diuretic properties. It was discovered that the chemical component sodium nimbidinate is a strong diuretic in dogs<sup>37,38</sup>. The drug's primary target was the renal tubules, where it delayed phenolsulfonphthalein excretion and led to the reabsorption of electrolytes and water. It was discovered that a greater oral dosage was efficient<sup>24</sup>. Nine patients with congestive heart failure and anasarca participated in a clinical experiment to examine sodium nimbidinate's diuretic properties<sup>39</sup>. Out of which, eight of the patients had a clear diuretic response<sup>40</sup>.

## 5.14 IN DENTISTRY

Mouthwash containing *Azadirachta indica* inhibits streptococcus mutants growth and contains chlorhexidine to inhibit lactobacillus development, both of which have been discovered to be especially efficacious against the caries-causing organisms that have the potential to prevent their growth<sup>41,42</sup>. Periodontal disease is also treated with neem oil. It is a remarkable option to systemic treatment for treating patients with periodontal disease<sup>43</sup>. In order to assess the effectiveness of 10% neem oil chips in treating periodontitis, a clinical microbiologist conducted the study<sup>44</sup>. The results showed improvements in the number of *P. gingivalis* strains that were decreased.

## 5.15 CVS

Neem extract exhibits a vasodilator effect, and this action is mediated through  $Ca^{2+}$  channel blockage and the nitric oxide route, demonstrating the potency of neem extract as a vasodilator that lowers blood pressure<sup>45,46</sup>.

## 5.16 INSECTICIDAL

When administered at the recommended amount for vegetable pests, *Azadirachta indica* seed has remarkable results as an insecticide in Sudan<sup>47</sup>. The third instar larvae of *Trogoderma granarium*, which is employed as a test insect, are used to extract oil from neem seeds, and the results have indicated that the oil is efficient against vegetable insects<sup>48,49</sup>.

## 5.17 ANTIBACTERIAL

Researchers used a bacterial pathogen in their study to examine the antibacterial activity of neem oil, and the results showed that streptococcus mutants had the largest inhibitory zone, measuring 27 mm in diameter<sup>48</sup>. The zones of inhibition for *lactobacillus acidophilus* and *Enterococcus faecalis* were found to be 24 mm and 18 mm, respectively<sup>50</sup>. Numerous studies have been done on the neem plant, *Azadirachta indica*, to determine its ability to fight against pathogens like *Staph aureus* and *E. coli*. Strains of *Staphylococcus aureus* react differently to the leaf's aqueous and methanol extracts<sup>50,51</sup>. On the *Staphylococcus aureus* strain, both dried and fresh leaves are employed, and comparisons are made based on the inhibitory zones that are discovered following incubation. The outcome demonstrates that fresh and dried neem bark and leaves both had a stronger antibacterial impact on these bacteria when combined with ethanol extract<sup>52</sup>.

## 5.18 ANTI-CANCER

Widespread anticancer usage has been reported for *Azadirachta indica*<sup>53</sup>. The start phase of cancer is suppressed by employing the *Azadirachta indica* extract in the research on aqueous neem leaf extract that is utilized to examine an in vivo murine system against 3H-B- $-P$  [54]. O-6-methylguanine-DNA methyl transferase (MGMT) is an enzyme that detoxifies O-6- alkyl guanines since it was recently discovered that they are carcinogenic while also attempting to preserve cell integrity<sup>55,56</sup>. Therefore, it was discovered in a recent study that neem aqueous and ethanolic extracts increase the activity of the MGMT enzyme. Neem also contains a molecule called Azadirachtin, Nimbolide, and Nimbidin that has anticancer properties<sup>57</sup>.

## 5.19 NEPHROPROTECTIVE EFFECT

In experimental animals, nephrotoxicity is induced using cisplatin. Due to the neem leaf extract's antioxidant, anti-inflammatory, and other free radical scavenging properties, it has demonstrated notable protective benefits against cisplatin-induced nephrotoxicity<sup>58</sup>.

## 5.20 IMMUNOMODULATION EFFECT

A non-specific immunostimulant is neem oil. In order to provide a stronger response to future mitogens, it also contributes to the activation of cell-mediated immune systems<sup>22</sup>.

## CONCLUSION

The neem plant has various phytochemical constituents having pharmacological activities against different diseases. This review basically describes the geographical conditions of neem, its chemical constituents, structures of chemical constituents, and medicinal activity of neem. The different chemical constituents of neem obtained from different parts of neem are effective and give pharmacological effects in the treatment of various diseases. Some of the medicinal activities of neem (*Azadirachta indica*) or we can say chemical constituents of neem are revised in this review from various previously published articles on neem.

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