

# Botanical Briefs: Neem Oil (*Azadirachta indica*)

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## PRACTICE POINTS

- Neem is a traditional herb with various bioactivities, such as melanogenesis-inhibitory activity, toxicity against pests, antimalarial activity, and antioxidant activity.
- Neem should be used with caution as a remedy because of its skin-lightening properties, which are attributed to melanogenesis-inhibitory activity via tyrosinase inhibition.
- Chemical leukoderma should be included in the differential diagnosis when a patient presents with a hypopigmented rash after topical use of neem products.

*Azadirachta indica*, commonly known as neem, has many uses as a natural remedy. We review and discuss the pharmacologic, biologic, and medicinal properties of neem in disease management. We also report a rare clinical case of a 77-year-old man who presented with a hypopigmented rash on the lower back, bilateral flanks, and buttocks after 6 months of repeated application of neem oil to treat persistent arthritis and lower back pain.

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Commonly known as neem or nimba, *Azadirachta indica* traditionally has been used as an oil or poultice to lighten skin pigment and reduce joint inflammation. Neem is a drought-resistant evergreen tree with thin serrated leaves, white fragrant flowers, and olivelike fruit (Figure 1). This plant is indigenous to India but also is readily found within tropical and semitropical

environments throughout the Middle East, Southeast Asia, North Africa, and Australia.

## Traditional Uses

For more than 4000 years, neem leaves, bark, fruit, and seeds have been used in food, insecticide, and herbal medicine cross-culturally in Indian Ayurvedic medicine and across Southeast Asia, particularly in Cambodia, Laos, Thailand, Myanmar, and Vietnam.<sup>1-3</sup> Because of its many essential nutrients—oleic acid, palmitic acid, stearic acid, linoleic acid, behenic acid, arachidic acid, and palmitoleic acid—and readily available nature, some ethnic groups include neem in their diet.<sup>4</sup> Neem commonly is used as a seasoning in soups and rice, eaten as a cooked vegetable, infused into teas and tonics, and pickled with other spices.<sup>5</sup>

All parts of the neem tree—both externally and internally—have been utilized in traditional medicine for the treatment of various diseases and ailments. The flowers have been used to treat eye diseases and dyspepsia, the fruit has been employed as an anthelmintic, the seeds and leaves have been used for malaria treatment and insecticide, the stem bark has been used for the treatment of diarrhea, and the root bark has been used for skin diseases and inflammation.<sup>6</sup> Neem oil is a yellow-brown bitter substance that often is utilized to treat skin diseases such as psoriasis, eczema, fungal infections, and abscesses.

**Case Report**—A 77-year-old man presented with a diffuse rash across the lower back. He reported that he had been using topical neem oil to alleviate lower back pain and arthritis for the last 6 months with noted relief and improvement of back pain. After roughly 3 to

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4 months of using neem oil, he noted a rash on the lower back, bilateral flanks, and buttocks (Figure 2). The rash was asymptomatic, and he denied any pruritus, scaling, pain, or burning. The patient was referred to dermatology and received a diagnosis of chemical leukoderma secondary to contact with *A indica*. The patient was advised to stop using the topical neem oil, and the rash was simply monitored, as it was asymptomatic.

## Bioactivity

Research has elucidated multiple bioactivity mechanisms of neem, including melanogenesis-inhibitory activity, toxicity against pests, antimalarial activity, and antioxidant activity.<sup>1,7-9</sup> Literature on the diverse phytochemical components of *A indica* indicate high levels of limonoids, flavonoids, and triterpenoids that are responsible for much of its antioxidant, anti-inflammatory, and insecticide properties.<sup>1,10</sup>

**Melanogenesis-Inhibitory Activity**—To date, neem has been added to a number of cosmetic products used in Ayurvedic medicine. One study of isolated compounds in *A indica* showed superior inhibitory activities against melanogenesis with minimal toxicity to cells (86.5%–105.1% cell viability). Western blot analysis of samples extracted and isolated from neem root and bark showed melanogenesis-inhibitory activities in B16 melanoma cells through the inhibition of microphthalmia-associated transcription factor expression and decreased expression of tyrosinase, as well as tyrosinase-related proteins 1 and 2, which are largely responsible for melanin synthesis.<sup>11</sup> In another study, *A indica* flowers and their extracted constituents—6-deacetylnimbin and kaempferide—suggest melanogenesis-inhibitory activities in B16 melanoma cells with little to no toxicity to the cells (81.0%–111.7% cell viability).<sup>1</sup> In an evaluation of *A indica* seed extracts, some of the isolated limonoids

and diterpenoids exhibited a marked melanogenesis-inhibitory effect (74%–91% reduction of melanin content) with no toxicity to the cell.<sup>5</sup> All of these studies indicate that active compounds in neem root, bark, flowers, and seeds may be potential skin-lightening agents.

**Toxicity Against Pests**—Neem seeds have phytochemicals that convey some insecticidal properties. The seeds often are ground into a powder, combined with water, and sprayed onto crops to act as an insecticide. As a natural method of nonpesticidal management, *A indica* acts as an antifeedant, insect repellent, and egg-laying deterrent that protects crops from damage. Studies of *A indica* have noted effective nonpesticidal management against arthropod pests such as armyworm, termites, and the oriental fruit fly.<sup>7,12,13</sup>

**Antimalarial Activity**—One study indicated that nimbolide, a limonoid from the neem plant, demonstrated antimalarial activity against *Plasmodium falciparum*. In separate cultures of asexual parasites and mature gametocytes, parasite numbers were less than 50% of the number in control cultures (8.0% vs 8.5% parasitemia, respectively).<sup>14</sup> Thus, the lower parasite numbers indicated by this study highlight the antimalarial utility of nimbolide and neem oil.

**Antioxidant and Anti-inflammatory Activity**—Neem bark has been reported to have considerable antioxidant activity due to its high phenolic content.<sup>15</sup> One study showed that azadirachtin and nimbolide in neem exhibited concentration-dependent antiradical scavenging activity and antioxidant properties.<sup>16</sup>



**FIGURE 1.** Leaves of a neem plant (*Azadirachta indica*).



**FIGURE 2.** Hypopigmentation on the lower back, bilateral flanks, and buttocks due to neem oil–induced chemical leukoderma.

The anti-inflammatory potential for neem may occur via the inhibition of the nuclear factor- $\kappa$ B signaling pathway, which is linked to cancer, inflammation, and apoptosis.<sup>17</sup> It also has been observed that nimbidin within neem extracts—such as leaves, bark, and seed extract—suppresses the function of macrophages and neutrophils relevant to inflammation.<sup>16</sup> Another study indicated neem's anti-inflammatory activity due to the regulation of proinflammatory enzymes such as cyclooxygenase and lipoxigenase.<sup>18</sup>

### Safety, Toxicity, and Risks

**Ingestion**—Although neem is safe to use in the general population, neem oil poisoning has been reported, particularly in young children. Ingesting large quantities of neem has resulted in vomiting, hepatic toxicity, metabolic acidosis, late neurologic sequelae, and encephalopathy in young children.<sup>19</sup> The diagnosis of neem oil poisoning is based on patient history, clinical examination, and imaging findings. Poisoning can manifest as drowsiness, tachypnea, and generalized seizures.<sup>20</sup>

**Topical Application**—Topical use of neem appears to be safe if the substance is diluted with other ingredients. However, direct application to the skin is not advised, as it may cause leukoderma and could induce allergic contact dermatitis and other allergic reactions.<sup>4</sup>

### Final Thoughts

The use of neem extract for disease prevention and treatment has been prevalent around the world since ancient times. Neem has been documented to possess melanogenesis-inhibitory activity, toxicity against pests, antimalarial activity, and antioxidant activity by means of tyrosinase inhibition, phytochemical production, limonoid expression, and nuclear factor- $\kappa$ B regulation, respectively. However, topical use of neem may trigger a cutaneous response, highlighting the importance of considering a diagnosis of neem oil-induced chemical leukoderma when patients present with a hypopigmented rash and relevant history.

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