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APPLICATION OF NEEM TREE IN AGRICULTURE, INDUSTRY, MEDICINE, AND ENVIRONMENT: A REVIEW

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Abstract

Background: The Neem tree (*Azadirachta indica* A. Juss.) is native to the South Asian countries, but its cultivation has already spread to countries in other continents, always with tropical climates. It is used in Traditional Medicine. The objective of this review was to consult and discuss the application of the Neem tree in agriculture, industry, Medicine, and the environment.
Materials and Methods: Literature retrieval was performed on four databases: OVID; PUBMED; EBSCOhost, and EMBASE, and in the ISI Web of Science. Key words for the search included Neem and *Azadirachta indica*.
Results: A series of studies have demonstrated that the Neem tree has been used medicinally since ancient times. The bark, leaves, fruit, flowers, and roots have been employed, each with very favorable applications. The bark of the Neem tree is cool, bitter, astringent, pungent, and refreshing. It is useful for oral diseases, cough, fever, neuromuscular pain, loss of appetite, fatigue, intestinal parasites, wound healing, as a laxative, as an anti-hemorrhoidal, as an emetic, for skin diseases, to calm excessive thirst, eliminate toxins, as an astringent, an expectorant, and it purifies the blood and prevents damage caused by free radicals to the body, neutralizing this damage. It is also used to treat snake bites and insect bites. The flowers are utilized to regulate body heat. The oil is removed from the seed for pharmaceuticals, paper, and food. Plants, vegetables, and herbs employed as food for humans, and currently in Traditional Medicine, have been accepted as an essential contribution to drug discovery and in chemotherapy in cancer prevention and development. This vegetable oil has physicochemical properties that allow its proposal as a potential raw material for the soap industry.
Conclusion: It was possible to know and discuss the variety of applications of the Neem tree, including the bark, leaves, fruit, flowers, and roots, each with very favorable applications in agriculture, industry, Medicine, and especially its use in the care environment.

Key words: Energizing, pharmacy, healing, purgative, pesticide.

Introduction

The Neem tree (*Azadirachta indica* A. Juss.), of the Meliaceae (mahogany) family, known as margosa or Indian lilac and originating in India, is one of the richest sources of secondary metabolites in nature. It has long been recognized for its properties both against insects and in improving human health. The Neem tree is an attractive, broad-leafed evergreen that can grow up to 30 m in height, with spreading branches extending some 10 m. It grows as a tree found in the temperate woodlands of southern West Africa. In the Traditional Medicine of the Ivory Coast, the leaf, bark, or seed is ground, and extracted with hot water, and left to cool. This same oily material is also employed as a cosmetic by women for treatment of their skin and hair (Gossé et al., 2005). The flowers and fruits are borne in axillary clusters and when ripe, the smooth, ellipsoidal drupes are greenish-yellow and comprise a sweet pulp enclosing a seed. The seed consists of a shell and 1–3 kernels, which contain azadirachtin and its homologues. Both the bark and the leaves also contain biologically active molecules, but not high levels of azadirachtin, which is found mainly in the seed kernels (Mordue and Nisbet, 2000).

A plant or a plant part is utilized for its therapeutic properties. Herbal medicines comprise one type of dietary supplement. They are sold as tablets, capsules, powders, teas, extracts, and fresh or dried plants. People use the plants as Traditional Medicine to maintain their health. The goals for the World Health Organization (WHO) Traditional Medicine Strategy 2014-2023 are to support Member States in: harnessing the potential contribution of Traditional & complementary medicine to the health, wellness and people-centered health care; promoting its safe and effective use through the regulation, evaluation and integration of Traditional & complementary medicine products, practices, and practitioners in health systems, as appropriate (WHO, 2013). One of these plants used in Traditional Medicine is the Neem.

The Neem tree is a tropical evergreen regulatory the Indian sub-continent. It has been used in Ayurvedic medicine for >4,000 years, due to its medicinal properties. The majority of the parts of the plant, such as fruits, seeds, seed kernels, leaves, bark, roots, and wood, contain compounds with antiseptic, antivirus-tested, antipyretic, antiulcer, anti-inflammatory, and antifungal properties. It has great potential in the fields of pest management, environmental protection, and Medicine (Ogbuewu et al., 2011).

Scientific research has confirmed that Neem seed oil is non-toxic to mammals and may be a very effective organic antiseptic, antifungal, dermatological, and dental agent. This oil has been employed for centuries in Traditional Indian Medicine to aid in the healing of tropical skin disorders, such as eczema, psoriasis, rashes, burns, and acne. It is rich in fatty acids and glycerides and, together with its healing properties, provides an excellent natural moisturizing base for skin care formulations (Gossé et al., 2005). Neem oil can be applied inside the vagina and will function as a spermicide. It cures vaginitis and prevents the transmission of sexual transmitted and infectious diseases, possibly including AIDS.

The Neem is the most studied tree in the world and is said to be the most promising tree for the XXI century. The tree has the ability to adapt to a wide range of climatic, soil, and typographical factors. It thrives in dry soils, shallow, rocky soils, and even in shallow, hard clay pots. The Neem tree requires little water and light. The tree grows naturally in areas where rainfall is within the range of 450–1,200 mm (**Figs. 1a and 1b**). However, even in areas where precipitation is as low as 150–250 mm, the Neem tree grows at altitudes of up to 1,500 m. It can grow well in the wide temperature range of 0–49°C. The pH range for Neem growth is 4–10. Neem trees have the ability to neutralize acidic soils (Ogbuewu et al., 2011).

Materials and Methods

The objective of this review was to become acquainted with and discuss the application of the Neem tree in agriculture, industry, Medicine, and the environment.

a

b

Figures 1a and 1b: **Neem tree.**

Neem Family

Neem is a member of the Mahogany family. It has similar properties to those of its close relative, *Melia azederach*. The term *Azadirachta* is derived from the Persian *azaddhirakt* ('noble tree'). The taxonomic positions of Neem are the following: Order: Rutales; Suborder: Rutinae; Family: Meliaceae; Subfamily: Melioideae; Tribe: Melieae; Genus: *Azadirachta*; Species: *indica*; Latin: *Azadirachta indica*; Indian: Holy tree, Indian lilac tree; Hindi: Neem, Nim; Sanskrit: Nimba; Hausa: Dogon yaro, and Igbo: Ogwu akuma (Ogbuewu et al., 2011).

Component of the Neem Tree

To know the components of the Neem tree, a mixture of free fatty acids was analyzed by gas chromatography of the fatty acids. The latter showed that it contained nine fatty acids. The most abundant are 43.1% of Δ^1-oleic acid, 19.4% of palmitic acid, 17.6% of Δ^2-linoleic acid, 16.4% of stearic acid, and 0.3% of arachidic acid; minor fatty acids include 0.6% of odeolidic acid, 0.3% of Δ^3–α-linoleic acid, 0.2% of margaric acid, 0.2% of behenic acid, 0.2% of lignoceric acid, and 0.1% of Δ^1–gadoleic acid (Gossé et al., 2005).
Azadirachtin, a complex tetranortriterpenoid limonoid from the Neem seed, is the main component responsible for both antifeedant and toxic effects in insects. Another limonoid and sulfur-containing compound with repellent, antiseptic, contraceptive, antipyretic, and antiparasitic properties are found elsewhere in the tree, e.g., leaves, flowers, bark, and roots (Mordue and Nisbet 2000). Limonoids, also denominated tetranortriterpenoids, are a group of highly oxygenated, heterocyclic compounds with alkoxy and hydroxyl groups, of which azadirachtin is the most well- known (Ospina-Salazár et al., 2015).

Developments

Due to high demand, concerted efforts to maximize production are being set in place and all factors affecting growth and crop development have become serious concerns for farmers (Egho and Ilondu, 2012). The poultry industry is an important part of agriculture in developing countries such as India. During the past two decades, India has experienced remarkable growth in poultry. Indian egg production was 2 million tons in 2002, and it has among the five egg- producing countries in the world.
The chicken meat production was 1.566 billion tons in the same year. Ascariasis remains a cause of economic losses in modern poultry farming. Among the closely related Coccidium parasites, *Ascaridia galli* (*A. galli*) infection in chickens is considered to be of great importance, as it can cause great economic losses in different ways, such as weight loss, meat production, egg production, and bird mortality.

However, due to the high cost of medicines, farmers are unable to afford to purchase anthelmintics. In addition, frequent use of these anthelmintics increases the population of resistant nematodes. Within this context, indigenous medicinal plants are employed as profitable. Some native plants, such as Neem, pineapple, and snuff, are reported to have anthelmintic properties and are utilized as herbal anthelmintics (Ali et al., 2011).

Despite recent advances in treatment, an estimated 192,370 new cases of invasive breast cancer are expected to occur among women in the U.S. during 2009, and about 1,910 new cases are expected in men. Adjuvant chemotherapy and hormonal therapy have been shown to improve survival in patients with breast cancer, but they possess potentially serious side effects and are expensive. Prognosis and traditional predictors are not sufficiently accurate. To improve indications for adjuvant treatment, other predictors and prognosis are therefore required. Many of these are directly or indirectly related with proliferation or apoptosis.

Apoptosis is a genetically controlled process and some mechanical aspects of apoptosis are at least partially conserved throughout evolution. The basic mechanism for the performance of apoptosis is (constitutively) present in all mammals; however, activation of apoptotic pathways is thought to be regulated by the balance between survival and many death signals. In many cell types, apoptosis is characterized by the generation of DNA fragments through the action of endogenous endonucleases. A large number of biochemical and other tests now exist for studying the process of apoptosis in cultured cells, including tests based on Neem leaf extract with regard to morphology changes as an apoptosis inducer, oligonucleosomal DNA fragmentation, distribution of the cell membrane, activation of caspase mitochondrial membrane phospholipids.

However, there has been a clear need among researchers of methods capable of detecting apoptosis in intact tissue samples (Othman et al., 2011). In industry, the Neem tree has proved to be the only source of numerous active ingredients such as insecticides, and the properties of zadirachtin (Satti et al., 2010) advantageously compete with synthetic insecticides. Extracts with high concentrations of this active agent may be a precursor of a new generation of insecticides, fungicides, miticides, and crop protection, without damage to the environment.

Potency/Activity of the Neem Tree

The Melon Fly, *Bactrocera cucurbitae* (Coquillett) (Diptera: Tephritidae) is widely distributed in the temperate zone of tropical and subtropical regions, causing damage to 81 host plants and comprising a major pest of cucurbit vegetables, with the magnitude of losses between 30 and 100%. Fruit flies lay eggs inside the fruit and, after hatching, the larvae begin to feed on the pulp, which renders the fruit unfit for human consumption. Once egg laying has begun, chemical eradication is difficult. Nearly all parts of the Neem tree possess some biological activity against many species of insect pests, such as flies in melon fruit (Yasmin et al., 2008).

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The rice moth, *Corcyra cephalonica* (Stainton), is a well-known pest found in stored grain and grain products in India, as well as in other tropical and subtropical regions. This moth was first identified and reported by Stainton (1866), who named it *Melissoblaptes cephalonica*. The only known species of this genus is *Cephalonica*. *Corcyra cephalonica* was first recorded in 1919.
Therefore, there is an urgent need for safety in order to create effective biodegradable pesticides with no toxic effects on organisms. Botanical insecticides are employed for broad- spectrum pest control, and many are safe in their application as a single action to eliminate pests and can be easily processed and used. The main advantage is that medicinal plants are readily produced by farmers and small-scale industries and are economical. In the previous study, the leaf powder of the Neem tree (*Azadirachta indica* A. Juss.) (**Figure 2**) was selected as a safe substitute for pest control in stored rice grain against the moth *Corcyra cephalonica* (Pathak and Tiwari, 2010).
Infections carried by snails are of great importance in the livestock industry in tropical and subtropical countries such as India. Snails act as intermediate hosts of various parasitic diseases of livestock and human, such as fascioliasis, paramphistomosis, and schistosomiasis, which are transmitted by *Lymnaea auricularia* var. *rufescens*, *Indoplanorbis exustus*, and *Lymnaea luteola*, respectively; thus, an experiment was conducted to attempt to eliminate snail vectors by the phytochemical method with methanol extracts from different parts of the Neem plant (Alam et al., 2010).

Figure 2: Powdered Neem tree leaves.

Farmers observed that the attack took place after 10–15 days of the occurrence of the pests; at this stage, it was too late to control the pest. In order to reduce the pest population and damage to plants, farmers prefer to apply synthetic insecticides. Physiological changes in the plant system favor reproduction of the pest. This inevitably leads to the implementation of the Integrated Pest Management (IPM) system (Vinodhini and Malaikozhundan 2011).

To sustain rice production under optimal conditions, improvement is made with respect to bio-rational practices, and implementation of the IPM system is useful against the emergence of pests. Both nymphs and adults suck sap from developing grains during growth; thus, they damage crops. An effective crop-protection schedule to improve and sustain rice yields through bio-rational practices comprises an essential component of the modern IPM system. About 128 species of insects have been reported to ravage rice paddy fields (Chakraborty, 2011). The commercial formulation of Nimbecidine (5%), Neem oil (2%), Neem seed-kernel extract (5%), Neem leaf extract (5%), Neem root extract (5%), and Neem bark extract (5%), in descending order, all resulted in the low incidence of chaffy grains. The oxidative status of the plants plays a key role in plant defense against stress (War et al., 2011).

Plant parasitic nematodes are important pathogens of all cultivated species, including sugar cane, a major agricultural crop grown in many countries with tropical and subtropical climates. The problems caused by phytonematodes are common (Mohan, 2011). In addition, the effect has been evaluated of Neem leaf extract on gastrointestinal nematodes in sheep, which produces a 100% decrease in *Strongyloides*, *Haemonchus*, *Ostertagia*, and *Trichostrongylus* (Dublin et al., 2012).

Damage caused by insects affects the quality, quantity, and commercial value of products. Many pests of stored products belong to the order Coleoptera, and one persistently destructive insect pest in stored products is the red flour beetle, *Tribolium castaneum* (Herbst). The indiscriminate use of broad-spectrum insecticides, far from resolving each situation arising in grain deterioration, has generated more problems than it has solved (Adarkwah et al., 2010).

The Commercial Neem extract (NeemAzal-T/S®) can be used as a safe sterility agent for the control of rodent pests, and the most effective dose for giving rise to this sterility and delayed reproduction is between 15 and 25 mg/kg (Morovati et al., 2007). Histopathological changes indicated disruption of spermatogenesis in some seminiferous tubules and reduced sperm counts. These changes included derangement of the first layer of spermatogonial cells and necrotic spermatocytes, which delayed reproduction in experimental animals.

In another, similar study, the authors attempted to observe the effect of the oral administration of neem seed oil and its various chromatographic fractions on the sperm dynamics and testicular cell-population dynamics of male albino rats for 60 days. Significant reduction in sperm density in testes and in cauda epididymis and sperm motility was observed. The Neem seed-oil fractions were shown to be the most potent contraceptive agents due to the arrest of spermatogenesis and inhibition luteinizing hormone and follicle-stimulating hormone gonadotropin secretion and steroidogenesis via the hypothalamohypophyseal gonadal axis. The absence of spermatids in the seminiferous tubules was conspicuous (Purohit et al., 2008).

At present, there is an increasingly interest on the isolation of natural compounds with antifungal activity, from which terpenoids have revealed the production of either fungistatic or fungicidal power in several pathogenic fungi (Ospina-Salazár et al., 2015). The toxicity and residual effect of a topically applied crude extract of Neem (N-9) and a pyrethroid against second-instar larva of *Musca domestica* L. (Holland strain) (Naqvi et al., 2007) was observed: 4.5 µg/larva (Coopex) and 12.5 µg/larva (N-9) caused 90 and 62% mortality, respectively. The residual effect was effective for 6 days with the higher tested dose, that is, 4.5 µg/larva, and caused 55% mortality in tested larvae. The teratomorphic effect of the adult *Musca domestica* did not completely emerge from puparium.

Both Neem leaves and Neem-seed oil extracts were capable of inhibiting the growth of *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Epidermophyton floccosum*, and *Microsporum canis*. The Neem leaf extract had the higher antifungal activity of the two, perhaps due to a higher concentration of terpenoids with low polarity, as its analysis by High Performance Liquid Chromatography (HPLC) profile revealed; consequently, there is a synergistic or additive effect of terpenoids in extracts from Neem. Also, supplementation of Neem leaf and bark in manure resulted in elimination of pathogenic *Escherichia coli* O157:H7 in <10 days. The active principle for inhibition of Neem leaves is localized in the organic extractable fraction. Neem supplementation in manure piles at dairies and feedlots, and also at produce fields, could comprise a novel strategy for on-site pathogen control (Ravva and Korn, 2015).

Plants, vegetables, and herbs employed as food for humans and, currently, in Traditional Medicine, have been accepted as an essential drug-discovery contribution, such as chemotherapy in cancer prevention and development. Despite the existence of a series of extracts from plants utilized against diseases in Traditional Medicine, few have been scientifically explored. *Azadirachta indica* (Meliaceae, Family name; common names: lilac, Neem tree, and Neem challenges, has been used successfully for centuries to shrink tumors by herbalists throughout Southeast Asia. Researchers in India, Europe, and Japan have now discovered that the polysaccharides and limonoids found in Neem bark, leaves, and seed oil (**Figure 3**) reduce cancerous tumors, and these have proven effective against lymphocytic leukemia. Neem has been reported to inhibit mitotic activity by means of the Neem leaf extract.

In vitro activity against ascites, sarcoma tumors, and bark polysaccharides are administered intraperitoneally (i.p.). The antiviral efficacy has been studied of the aqueous extract of Neem leaves against smallpox, chicken pox, polio, and measles, as assessed by inhibition assay. While the *Chikungunya* virus and measles were significantly inhibited by the vaccine, the extract has also been found active against Japanese encephalitis, West Nile virus, Dengue virus type 2, mumps, and the Parainfluenza virus. It has also been reported that the aqueous extract and Neem oil fraction (NIM-76) suppress HIV and the polio virus, respectively. Attempts have been made to detect the inhibitory capacity of Neem oil against Dengue virus type 2, but no degree of inhibition has been found to date (Amer et al., 2010). In addition, it has been determined that consumption of 5% of the Neem (*Azadirachta indica*)-leaf aqueous extract resulted in complete inhibition of chemically induced hepatocarcinogenesis in Sprague-Dawley rats (Manal et al., 2007). The Neem 5% aqueous extract decreased the level of alpha fetoprotein in animals treated with diethyl nitrosamine as hepatocarcinogenesis initiator, subsequently followed by 2-acetylaminofluorene as promoter of hepatocarcinogenesis. Serum concentration of alpha fetoprotein as liver tumor marker was measured.

It has been found that the combined extract may modulate protein breakdown in diabetes mellitus more effectively than the combination of *Azadirachta indica* (A. Juss.) with *Vernonia amygdalina* (Del.) (African Bitter Leaf), in which it was observed that a significant increase in albumin levels in *Azadirachta indica*-treated groups confirms its purported, most potent hepatoprotective effect, given that albumin is exclusively synthesized in the liver, whereas *Vernonia amygdalina* is most potent in the blood glucose reduction mechanism and *Azadirachta indica*, most potent in protecting the liver against damage in diabetic states. Only a combination of the two extracts provided the holistic efficacy desired in diabetes management (Ebong et al., 2008). This latter study was conducted in diabetic rats. Determination of hepatotoxicity markers in serum, including glutamic pyruvic transaminase and glutamic oxaloacetic transaminase activities, total protein, albumin, and urea, indicated that, of the four treatments, Neem provided best protection against hepatic dysfunction. The combined extracts of *Azadirachta indica* and *Vernonia amygdalina* comprise alternate, selective advantages that were expressed as positive synergy; hence, these were more beneficial than individual treatments. Polyherbal therapy is said to be a current pharmacological principle possessing the advantage of producing maximal therapeutic efficacy with minimal side effects.

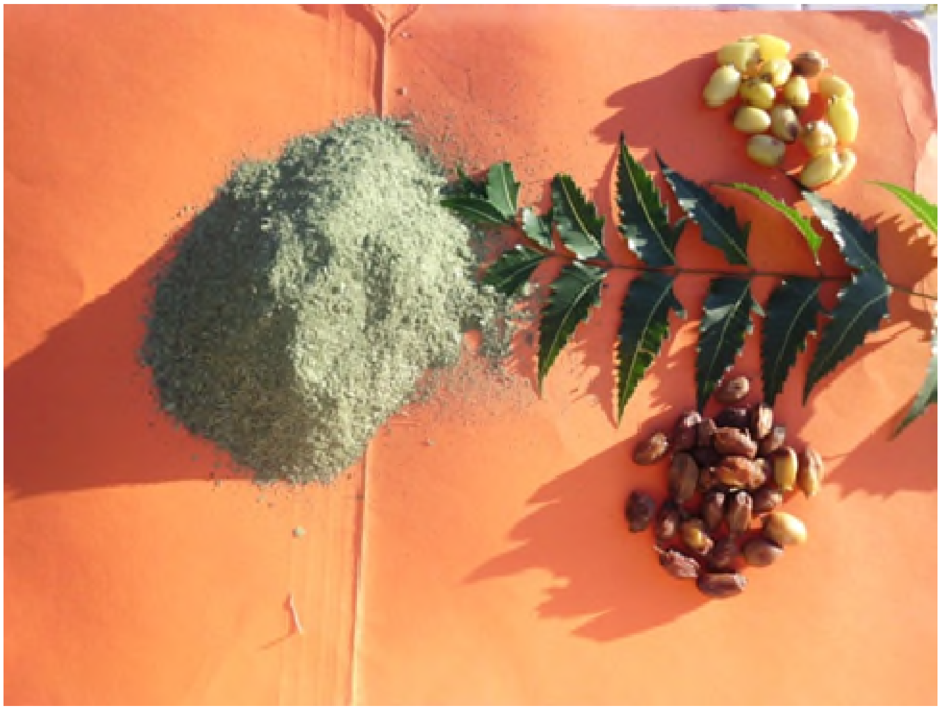

Figure 3: Leaves, leaf powder, seeds, and Neem seed kernels.

In addition, the effect has been demonstrated of oral treatment with the combined leaf extracts of Neem and Bitter Leaf on the prefrontal cortex of diabetic Wistar rats, which were randomized to one of the following treatment groups: control; diabetic group; streptozotocin+combined leaf extract; streptozotocin+metformin, and combined leaf extract only. These studies showed that the combined leaf extract of Neem and Bitter Leaf protected against diabetes-induced prefrontal Nissl substance deficit, these phytochemicals responsible for these effects (Akinola et al., 2011).

Additionally, *in vitro*, the antiviral, antitumor, and cytotoxic activities have been investigated of crude aqueous extracts of the seeds and leaves of the Neem plant. This acidic extract inhibited Ehrlich ascites carcinoma cell-line growth and exhibited anticancer activity (Amer et al., 2010). Thus, that result confirms the great potential of Neem aqueous extracts as powerful chemotherapeutic and antiviral agents. Microencapsulation of Neem seed oil was carried out by polyelectrolyte complexation of κ-carrageenan and chitosan, which could be utilized as an efficient matrix for Neem seed-oil encapsulation. The microcapsules were crosslinked by employing three different crosslinkings of the agents glutaraldehyde, genipin, and tannic acid. The release rate was found to be dependent on the nature and concentration of the crosslinkers utilized in the system. Glutaraldehyde was found to be most effective crosslinker, followed by genipin and tannic acid (Devi and Maji 2009).

Usability

Neem seed oil has been used in the industry in building materials and furniture, and as an adhesive for paints, lubricants, and insect repellent (Árias et al., 2009); this material possesses physicochemical properties that allow it to be proposed as raw material for the soap industry, lubricants, and waxes, and the extraction residue, for use as fertilizer. In the pharmaceutical industry, Neem oil is useful for treating the hair and for dry scalp: it is effective in counteracting hair loss and for treating seborrhea, dandruff, and psoriasis. Neem leaves acting as a hair conditioner prevents dryness and flaking.

Similarly, in the pharmaceutical industry and for personal hygiene, Neem bark and Neem oil are utilized for dental cleaning, for preventing and curing gum disease such as gingivitis, for bleeding gums, and for reducing bacterial plaque. It kills the bacteria that cause gum inflammation and is employed in tooth-powder manufacturing. It is also used for the production of antiseptics, as a binder, and as a tablet coater. In the cosmetics industry, it is utilized for facial masks; face powders, lotions, and sunscreen creams. In the paper industry, it is employed as an adhesive and as a paper strengthener, while in the textile industry; it is used in the dyeing and printing of tissue. In the food industry, it is used as a stabilizing agent, in gels, and as a thickener.

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Conclusion

It was possible to know and discuss the variety of applications of the Neem tree, including its bark, leaves, fruit, flowers, and roots, each with very favorable applications in agriculture, industry, Medicine, and especially, use in the care environment.

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