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## Neem (*Azadirachta indica*): Prehistory to contemporary medicinal uses to humankind

Venugopalan Santhosh Kumar<sup>1\*</sup>, Visweswaran Navaratnam<sup>1,2</sup><sup>1</sup>Centre for Drug Research, Universiti Sains Malaysia, 11800 Penang, Malaysia<sup>2</sup>Drugs for Neglected Diseases Initiative (DNDi), 1 Place St Gervais, CH-1201 Geneva, Switzerland

## PEER REVIEW

## Peer reviewer

Dr. V. Ravichandran, M.Pharm., P.h.D., senior associate professor, Faculty of Pharmacy, Aimst University, Semeling – 08100, Badaong, Kedah, Malaysia.

Tel: 006-044298000 Ext: 1029

Fax: 006-044298009

E-mail: [sameshyaravi@gmail.com](mailto:sameshyaravi@gmail.com); [phravi75@rediffmail.com](mailto:phravi75@rediffmail.com)

## Comments

The paper is convincing and is based on the diversified application of neem tree. The article has been highlighted with the historical links of neem tree with the ancient medicines. It also gives a detailed description of the existing historical evidences of neem tree with the mankind and in medicine. It has provided a new insight into the exploration and utilization of neem tree as a source for development of new therapeutic molecules.

Details on Page 512

## ABSTRACT

The divine tree neem (*Azadirachta indica*) is mainly cultivated in the Indian subcontinent. Neem has been used extensively by humankind to treat various ailments before the availability of written records which recorded the beginning of history. The world health organization estimates that 80% of the population living in the developing countries relies exclusively on traditional medicine for their primary health care. More than half of the world's population still relies entirely on plants for medicines, and plants supply the active ingredients of most traditional medical products. The review shows the neem has been used by humankind to treat various ailments from prehistory to contemporary.

## KEYWORDS

*Azadirachta indica*, Palm leaf manuscripts, Prehistory

### 1. Introduction

Neem is an omnipotent tree and a sacred gift of nature. Neem tree is mainly cultivated in the Indian subcontinent. Neem is a member of the mahogany family, Meliaceae. Today it is known by the botanical name *Azadirachta indica* (*A. indica*) A. Juss. Neem has been used extensively by humankind to treat various ailments before the availability of written records which recorded the beginning of history.

Since prehistoric times, neem has been used by humankind.

The latinized name of neem, *Azadirachta indica*, is derived from the Persian. Azad means “free”; dirakht means “tree”; i-Hind means “of Indian origin”. Hence it literally means “the free tree of India”[1]. The neem tree is an incredible plant that has been declared the “Tree of the 21st century” by the United Nations[2]. The US National Academy of Science published a report in 1992 entitled “Neem: A tree for solving global problems”[3].

\*Corresponding author: Venugopalan Santhosh Kumar, Centre for Drug Research, Universiti Sains Malaysia, 11800 Penang, Malaysia.

Tel: +91-944-5305819

E-mail: [natu\\_sea@hotmail.com](mailto:natu_sea@hotmail.com)

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**2. Neem during prehistoric times**

The age of the earth is (4.54±0.05) billion years. Plants from the supercontinent spread onto the land 475 million years ago. Anatomically modern humans inhabited 200 000 years ago[4]. Pangaea was a supercontinent that existed during the late Paleozoic and early Mesozoic eras, forming about 300 million years ago. The name Pangaea is derived from ancient Greek pan meaning “entire”, and Gaia meaning “earth”. The single global ocean which surrounded Pangaea is accordingly named Panthalassa[5].

Pangaea broke into two pieces, one in the north, and the other in the south (Figure 1)[5]. Scientists called the two new continents Laurasia (the continent in the north), and Gondwanaland (the continent in the south).



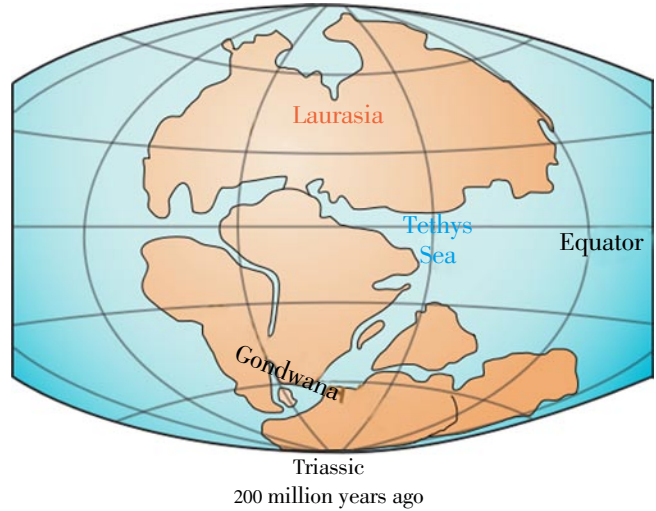
**Figure 1.** Pangaea continents.

The concept of Lemuria was born in the 1860s when certain British geologists noted the striking similarity between rock formations and fossils found in India and Africa. Maps of the lost land were produced taking the idea from the palaeo-continent of Gondwana that existed from approximately 510 to 180 million years ago (Figure 2)[6].

It separated from Laurasia 200–180 million years ago during the breakup of Pangaea. Two hundred million years ago, the continents of Antarctica, South America, Africa, India and Australia were joined together as a single supercontinent known as Gondwana, or Gondwanaland[6].

In the research of Joseph, the existence of a land is called Lemuria, which is one of the world’s oldest civilizations about 2.0 lakhs years ago[7]. Due to tsunami, people regularly moved from the Island Mu to Atlantis in Mexican Sea and

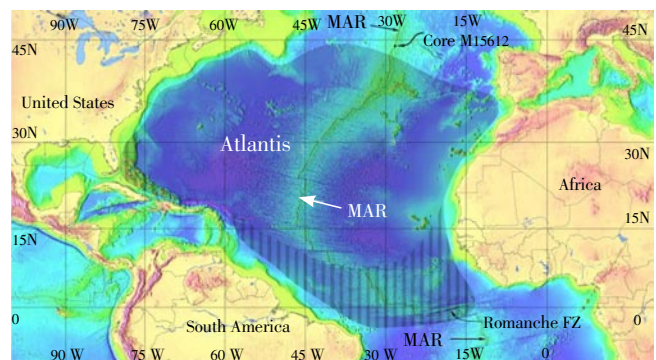
Kumari Kandam in Indian Ocean about 100 000 years ago (Figures 3–5)[8–10].



**Figure 2.** Laurasia–Gondwana continents.



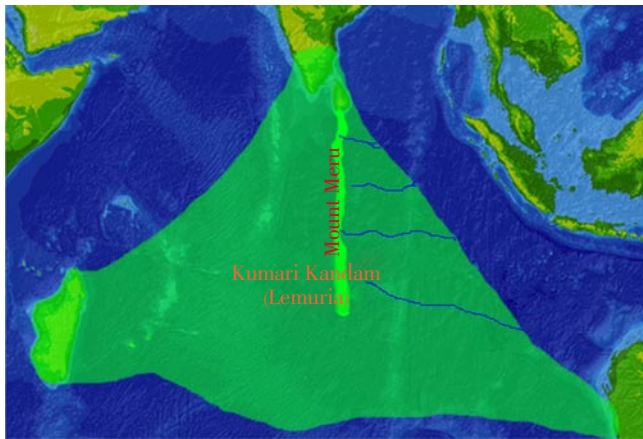
**Figure 3.** Mu – Lost continent.



**Figure 4.** Atlantis – Lost continent.

Kumari Kandam is said to have been located in the Indian Ocean, to the south of present day Kanyakumari district, Tamil Nadu at the southern tip of India[10]. There are certain references in Tamil Sangam (Sangam literature) classics to a landmass where people lived and which was swallowed

up by the sea. The literary references of the lost land were about three Tamil Sangams (Academy of poets). The other meaning of Sangams is assemblies of siddhars.



**Figure 5.** Kumari Kandam – Lost continent.

First two Sangams taking place in a sunken land mass was called Kumari Kandam. The first Tamil Sangam located in Thenmadurai, had 4449 poets and 549 members including the father of Siddha medicine Agathiyar and lasted for 4440 years. The head of Sangam was Agathiyar (Figure 6)<sup>[11]</sup>.



**Figure 6.** The great sage Agathiyar father of Siddha medicine.

Agathiyar specialized in medicine, language, alchemy and spirituality. Siddhars were the great scientists of ancient days. After the sea swallowed Thenmadurai, the capital was shifted to Kaptapuram. The second Sangam functioned for 3700 years and had 59 members, with 3700 poets

participating. This city was also submerged in the sea. The capital was shifted to the present Madurai. Here the third Sangam was established and functioned for 1850 years. The academy had 49 members, and 449 poets were described as having participated in the Sangam<sup>[12]</sup>. The Tamil Sangam classics refer to a populated land Kumari Kandam, which was submerged in the sea.

Siddha medicine is one of the oldest medical systems known to mankind<sup>[13]</sup>. Its origin goes back to 10000 B.C to 4000 B.C. As per the textual and archeological evidences which indicated the remote antiquity of the Dravidian civilization of the erstwhile submerged land Kumari Kandam, situated in the Indian Ocean. Kumari Kandam civilization went back to 50000 B.C. The Siddha system of medicine (traditional Tamil system of medicine), which has been prevalent in the ancient Tamil land, is the foremost of all other medical systems in the world.

In the annals of the ancient Siddha system of medicine, the first medicinal plant mentioned as well as found a place, in ancient Tamil literature is neem or margosa. Neem has been used by humankind from time immemorial as a deterrent for smallpox and other infectious diseases and is also considered to possess powers to ward off evil spirits. The earliest mention about the uses of medicinal plants were found in Thirumular Thirumantiram–Ennayiram, Tholkappiam and the ancient Tamil works of Sangam literature, which were believed to have been written thousands of years ago<sup>[14]</sup>.

The roots of Siddha medical system, which has been practiced in South India, go far beyond the historical boundaries. It has existed as a separate system of medicine thousands of years before the dawn of history.

### 3. Siddha mission to China and transmigration

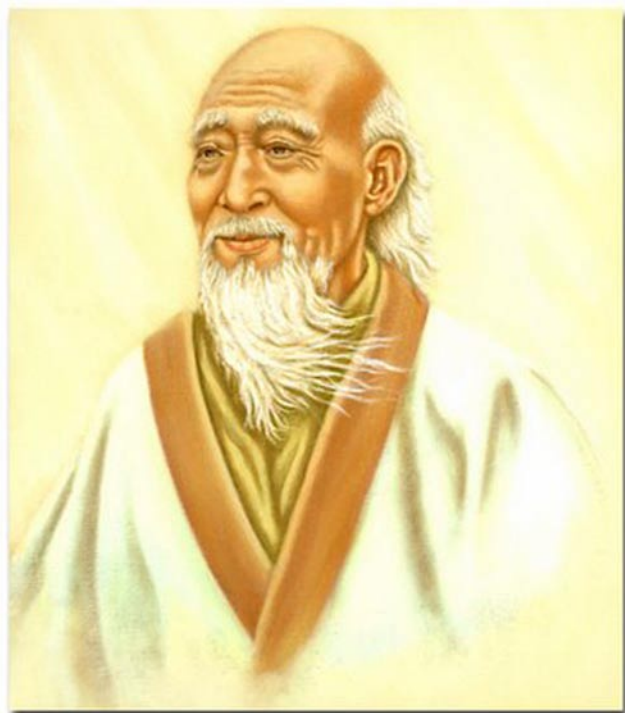
Bhogar Siddhar proceeded to China to spread the knowledge of Siddha sciences as per the last wishes of his guru Kalangi Nathar who belongs to China (Figure 7)<sup>[15]</sup>. In his palm leaf manuscripts, Bhogar claims to have flown to China at one point in a sort of airplane which he built and he held discussions with Chinese Siddhas before returning to India. Kalangi Nathar made China the center of his teaching activities. Kalangi Nathar decided to enter into samadhi in seclusion for 3000 years. In China, Bhogar was instructed by Kalangi Nathar in all aspects of the Siddha sciences. These included the preparation and use of the kaya kalpa herbal formulae to promote longevity. After Kalangi Nathar entered into trance, Bhogar assumed his teaching mission to the Chinese. To facilitate this, he transmigrated and thereafter went by the name “Bo–Yang”. “Bo” is a derivation of the word “Bhogam” which means bliss, material and spiritual<sup>[16]</sup>.

This bliss, for which he was named “Bo–Yang” is experienced when the Kundalini shakti, the feminine

primordial yin energy awakens, passes up to the crown of the head, the masculine yang pole, in the Sahasra cakra (Sanskrit word) at the summit of the head and unites with it. Many natural dualities (such as female and male, dark and light, low and high, cold and hot, water and fire, life and death and so on) are thought of as physical manifestations of the yin-yang concept.



**Figure 7.** Bhogar Siddhar.



**Figure 8.** Lao-Tzu.

After this incident with the Chinese disciples, Bo-Yang became also known as Lao-Tzu ("Old Master"), and was accessible for nearly 200 years, and trained hundreds of Chinese disciples. The courtesy name of Lao Tze was Bo-yang (Figure 8)<sup>[17]</sup>.

In the fifth century B.C, Confucius met Lao-Tzu and afterwards said of him: "I know a bird can fly, a fish can swim, and an animal can run. For that which runs, a net can be fashioned; for that which swims, a line can be strung. But the ascent of a Dragon on the wind into heaven is something which is beyond my knowledge. Today I have met Lao-Tzu, who is perhaps like a dragon". Bo-Yang's leading disciple was Yu (whom he also gave the Indian name Pulipani).

At the end of his mission to China, about 400 B.C, Bo-Yang, with his disciple Yu and other close disciples, left China by the land route. As recorded in the Taoist literature, at the request of the gatekeeper at the Han Ku mountain pass Lao-Tzu crystallized his teachings. He did so in two books, the Tao Ching, with 37 verses, and the Te Ching with 42 verses.

Upon Bhogar return to Tamil Nadu, India, he submitted his 7000 verse manuscript for evaluation to his guru, Agathiyar at Courtrallam and to an academy of Siddhas there. It was endorsed by all of them as a great work.

Later, after the period of the Six Dynasties (220 to 590 A.D), Bhogar returned with some Tamil disciples to China as a second mission to China. He left his mission in Tamil Nadu with Pulipani (Yu), the Chinese Siddha.

The emergence of Lao Tze with his theory of duality of matter and the journey of Bhogar to China seem to have taken place at same time and it is even possible Bhogar himself transmigrated as Lao Tze in China, like another Siddhar Sri Ramadevar, who was known as Yacob in Arabia.

According to the traditions of Southern India, there are 18 siddhars in particular who attained perfection, which included their spiritual, intellectual, mental, vital and physical bodies. The names of these 18 siddhars vary according to different sources. Siddhars travel across the world. Ramadevar Siddhar travelled to India and Arabia. In Arabia, he was known as Yacob. Pulasityar Siddhar belongs to Sri Lanka. Punnaikannar Siddhar belongs to Egypt. As Bhogar had close connection with China, it was said to be that Roma Rishi Siddhar had connection with Rome. Hence he was called Roma Rishi.

Bhogar visiting to South America has been confirmed by accounts left by the Muecas of Chile "Bocha, who gave laws to Muecas, was a white, bearded man, wearing long robes, who regulated the calendar, established festivals, and vanished in time like others (other remarkable teachers who had come across the Pacific according to numerous legends of Incas, Aztecs and Mayans)".

#### 4. Neem in Siddha

All parts of neem tree are commonly used in traditional

Indian medicine for household remedy against various human diseases<sup>[18]</sup>. The definition of Siddha medicine is conquest of death: “that which ensures preventive against mortality”. This statement is attributed to Tirumular, a revered Siddha whose treatise called Tirumantiram<sup>[19]</sup>. This system of medicine originated from Tamil Nadu, South India. The system was very popular in ancient India. Believed to be more than 10000 years old, the Siddha system of medicine is considered to be one of the most antiquated traditional medical systems. The Siddha system of medicine is prevalent in the southern states of India, Sri Lanka, Malaysia, and Singapore. The first medicinal plant mentioned in the Siddha medical system is neem.

The uniqueness of Siddha system is evident by its continuous service to the humanity for more than 5000 years in combating diseases and also in maintaining its physical, mental and moral health while many of its contemporaries had become extinct long ago<sup>[20]</sup>.

Siddhars were spiritual adepts who possessed the Ashta Siddhis, or the eight supernatural powers. The word Siddha came from the word siddhi, which means the perfection of heavenly bliss. Sage Agathiyar is considered the guru of all Sidhars, and the Siddha system is believed to have been handed over to him by Lord Muruga.

Typically siddhars were saints, doctors, alchemists and mysticists all at once. They wrote their findings, in the form of poems in Tamil language, on palm leaves which are collected and stored in what are known today as palm leaf manuscript, today still owned by private families in Tamil Nadu and handed down through the generations, as well as public institutions such as universities all over the world (India, Germany, Great Britain and USA).

## 5. Palm leaf manuscript

Palm leaf manuscript is one of the oldest medium of writing in India especially in Southern India. It is also the major source for writing and painting in South and Southeast Asian countries. Digital enhancement of palm leaf manuscripts images using normalization techniques was carried out in the State University of New York. In 1997, the United Nations Educational Scientific and Cultural Organization (UNESCO) recognized the Tamil Medical Manuscript Collection as part of the Memory of the World Register<sup>[21]</sup>. A very good example of usage of palm leaf manuscripts to store the history is a Tamil grammar book named Tolkappiyam, which was written during the 4th century B.C. A global digitalization project

led by the Tamil Heritage Foundation collects, preserves, digitizes and makes ancient palm leaf manuscript documents available to users via the internet.

The Memory of the World Register is a compendium of documents, manuscripts, oral traditions, audio-visual materials, library, and archival holdings of universal value. The Institute of Asian Studies, Chennai serves as Asian regional training centre for UNESCO’s Memory of the World project to conserve and digitalize thousands of Asian palm leaf manuscripts, starting with the Tamil Medical Manuscript Collection of the Institute of Asian Studies and other manuscript repositories in South India. Palm leaf manuscripts are also conserved in McCain Library, the University of Southern Mississippi.

Most Tamil medical manuscripts preserved at the Institute of Asian Studies reflect the ancient system of medicine. This system explains the methods of obtaining medicines from herbs, herbal roots, leaves, flowers, barks and fruits. The proportions of the ingredients as well as the specific processes are explained in detail<sup>[22]</sup>.

Three hundred and fifty years old palm leaf manuscript conserved in the Centre for Traditional Medicine and Research (CTMR), Chennai, India, reveals the medicinal uses of neem trees (Figure 9).

The above palm leaf manuscript reveals the therapeutic uses of neem and explicit that neem flower will be used to prevent and treat bile disorders; neem leaf will be used to prevent and treat ulcers; and neem bark will be used to prevent and treat CNS disorders, paralysis and psychiatric disorders. This palm leaf manuscript is 350 years old. This particular palm leaf manuscript was called Agathiyar Gunavagadam. Originally Agathiyar Gunavagadam which was written by the great Siddhar Agathiyar in the 6th century B.C and it was carried generations to generations by siddhars.

The siddhars wrote their knowledge in palm leaf manuscripts. They also propagated Siddha system of medicine in Arabia, Persia, Turkey, China and other places. Siddha is the science which takes human and nature as part of closed system. The basis of Siddha science is understanding that earth, air, water, fire and ether correspond to five senses of human body are fundamentals to all living things. All created or evolved matters in the world, whether animal or vegetable or mineral, all fall under these categories. The human anatomy and physiology, causative factors of diseases, materials for the treatment and cure of the disease, also fall in the five elemental categories. These give rise to three doshas or humors. This knowledge has been passed from one generation to another through written



**Figure 9.** Three hundred and fifty years old palm leaf manuscript conserved in the Centre for Traditional Medicine and Research (CTMR) library highlights the therapeutic uses of neem tree in the 3rd and 4th line.

medium mostly in palm leaf parchments.

Perhaps they were aware of the germicidal action and the medicinal properties of the margosa. Tirumular, the great Siddha is said to have been in deep penance for several thousands of years in eternal bliss under a sacred papal tree.

The neem tree has been widely used in the traditional systems of medicine. It is of immense use in a number of medicines and personal products. Its curative power is being used on a large scale to manufacture medicines for skin diseases including leprosy, ulcers, gastro intestinal problems, oral care, urinary track problems, hair problems, diabetes, blood Pressure and cholesterol.

## 6. Neem in Indus Valley civilization

On the Indian subcontinent, the neem tree has been used for more than 4500 years. The earliest documentation of neem mentioned the fruit, seeds, oil, leaves, roots and bark for their advantageous medicinal properties.

The first recorded indication that neem was being used in the medical treatment was about 4500 years ago. This was the high point of the Indian Harappa culture, one of the great civilizations in the ancient world. There is evidence found from excavations at Harappa and Mohenjo-Daro in Northwestern and Western India, in which several therapeutic compounds including neem leaves, were gathered in the ruins.

In 1922, British archaeologists began to excavate the sites of Harappa and Mohenjo-Daro. They uncovered the remains of long-forgotten cities. British archaeologists discovered the 5000 year-old Indus Valley civilization. They were amazed to discover two cities – Mohenjo-Daro and Harappa. These cities were so advanced that they could practically compete with cities today in areas of architecture, engineering and construction. The streets were designed in a grid system that was well planned and organized. There was an underground sewer system with stone manhole covers for access. A sophisticated water supply and drainage system with waterproof brickwork ran throughout the city. The houses were spacious in the upper class sections containing modern amenities like lavatory facilities.

They also found skulls upon which cranial surgery had been performed, and clay pots, which contained medicinal herbs. One of the most prominent medicinal herbs they found was *A. indica*, which is also known as neem. It shows the first evidence of an advanced medical system that includes both surgery and phytopharmacology in one of the world's most ancient and developed civilizations[23].

## 7. Distribution of neem

At the beginning of this century, the neem tree was still highly esteemed by Indian emigrants who took it along to the places where they settled. Thus, the neem tree was introduced in places such as Australia, East and sub-

Sahelian Africa, South East Asia, and South America. Today, the neem is well established in at least 30 countries worldwide, in Asia, Africa and Central and South America. Some small scale plantations are also reportedly successful in Europe and United States of America.

Neem trees are fast growers, and in three years may grow to 20 feet in height from seed planting. It will grow where rainfall is only 18 inches per year and it thrives in areas of extreme heat up to 120 degrees. It is estimated that a neem tree has a productive life span of 150 – 200 years. It is estimated that there are around 18 millions neem trees in India.

Neem tree is found all over in Malaysia. It exists mainly in Kedah, Penang, Langkawi and Perlis. Neem tree is found widely in Sungai Petani, Kedah, Malaysia.

Neem trees were also introduced in Pan Zhi Hua, Sichuan province, China[24]. There are over 400000 neems in Yunnan province that make Yunnan the biggest artificial area of neem planting globally and the raw material center of neem products in China. In 1995, the researcher of Chinese Academy of Forestry introduced the neem in India to the hot river valley areas in Yunnan and the neem grows well there. The research group has introduced the neem from South Asia, Southeast Asia and Africa to China since 1997. In 1998, the demonstration of industrial neem planting was started out in China. Because of the advantages on climate and terrain, the neem planting was popularized and promoted in Yunnan rapidly. Yunnan has had the largest area of neem plantation. Chinese Academy of Forestry plays an important role in cultivating technology of neem[25].

In the last two decades, research on neem has been intensified and many of the agricultural and medical properties of neem were rediscovered. Today, neem plays a major role in the rural industry of India, and projects for the commercial use of neem have been successfully introduced in the places like Kenya[26].

Earlier this century, people somehow managed to introduce this Indian tree to West Africa, where it has since grown well. They probably expected neem to be useful only as a source of shade and medicinal especially for malaria. But in Ghana, it has become the leading producer of firewood for the densely populated Accra Plains, and from Somalia to Mauritania, it is a leading candidate for helping halt the southward spread of the Sahara Desert. *A. indica* is an extensively popular tree in Nigeria and is commonly referred to as Neem (English), “Dogon Yaro” (Hausa) and “Akun shorop” (Igbo). Senegal Neem Foundation (SNF) was created by Dr. D. D. Faye, as a crucial part of Africa Bound Corporation. Africa considers neem as a green gold. In Senegal, neem tree is known as the “Independence Tree”[27].

The world's largest neem plantations are 10 sq km in the plains of Arafat, Saudi Arabia. A Saudi philanthropist planted 50000 neem trees to shade and comforts the two million pilgrims[28]. In the last decade, neem has been introduced into the Caribbean, where it is being used to help reforest several nations. Neem is already a major tree species in Haiti.

## 8. Drugs from nature

The world health organization (WHO) estimates that 80% of the population living in the developing countries relies exclusively on traditional medicine for their primary health care. More than half of the world's population still relies entirely on plants for medicines, and plants supply the active ingredients of most traditional medical products. Researchers generally agree that natural products from plants and other organisms have been the most consistently successful source for ideas for new drugs. Drug discovery scientists often refer to these ideas as "leads," and chemicals that have desirable properties in lab tests are called lead compounds<sup>[29]</sup>. Plants became the basis of traditional medicine system throughout the world for thousands of years and continue to provide mankind with new remedies. The plant based indigenous knowledge was passed down from generation to generation in various parts of the world, especially in the Indian sub-continent and has significantly contributed to the development of different traditional systems of medicines<sup>[30]</sup>.

## 9. Contemporary medicinal uses of neem in humankind

Neem (*A. indica*) is a divine tree mainly cultivated in Indian subcontinent and it is commonly known as neem<sup>[31,32]</sup>. All the parts of *A. indica* tree is commonly used in traditional Indian medicine for household remedy against various human diseases<sup>[33]</sup>. Indian people have long revered the neem tree (*A. indica*). For centuries, millions have cleaned their teeth with neem twigs, smeared skin disorders with neem leaf juice, taken neem tea as a tonic, and placed neem leaves in their beds, books, grain bins, cupboards, and closets to keep away troublesome bugs. The tree has relieved so many different pains, fevers, infections, and other complaints so that it has been called "the village pharmacy." In rural India, peoples often used water decoction of neem leaves for the prevention and treatment of various ailments. Research undertaken in the University of Nigeria showed the medicinal properties of fractionated acetone/water neem leaf extract<sup>[34]</sup>. Tests conducted at the King Institute of Preventive Medicine, Chennai in December 2012 found that the Siddha neem preparation brought down symptoms and speeded up the recovery of patients affected by dengue<sup>[35]</sup>.

To those millions in India, neem has miraculous powers, and now scientists around the world are beginning to think they may be right. Two decades of researches have revealed promising results in so many disciplines that this obscure species may be of enormous benefit to countries both poor and rich. Even some of the most cautious researchers are saying that "Neem deserves to be called a wonder plant".

### 9.1. Antibacterial activity

Recent research shows the isolation and identification

of the antibacterial active compound from petroleum ether extract of neem oil<sup>[36]</sup>. The study of Zhong *et al.* showed an antibacterial activity of 9–octadecanoic acid–hexadecanoic acid–tetrahydrofuran–3,4–diyl ester from neem oil<sup>[37]</sup>. Elavarasu *et al.* studied *in vitro* anti–plaque microbial activity of neem oil<sup>[38]</sup>.

### 9.2. Antiviral

Galhardi *et al.* studied the *in vitro* antiviral property of *Azadirachta indica* polysaccharides for poliovirus<sup>[39]</sup>. The study of Saha *et al.* showed water extracted polysaccharides from *A. indica* leaves with anti–bovine herpes virus type 1 (BoHV–1) activity<sup>[40]</sup>. The research of Xu *et al.* showed the *in vitro* antiviral activity of neem seed kernel extracts against duck plague virus<sup>[41]</sup>. Tiwari *et al.* showed the *in vitro* antiviral activity of neem (*A. indica* L.) bark extract against herpes simplex virus type–1 infection<sup>[42]</sup>.

### 9.3. Sexually transmitted disease

Few researchers have focused on neem efficacy in treating sexually transmitted diseases. The reports that have been completed are overwhelmingly positive. Recent research of Shokeen *et al.* showed the evaluation of the activity of 16 medicinal plants against *Neisseria gonorrhoeae*<sup>[43]</sup>.

### 9.4. Neem and the immune system

Thoh *et al.* studied that azadirachtin interacts with the tumor necrosis factor (TNF) binding domain of its receptors and inhibits TNF induced biological responses<sup>[44]</sup>.

### 9.5. Anti–inflammatory activity

The study of Alam *et al.* showed the anti–inflammatory activity of epoxyazadiradione against macrophage migration inhibitory factor<sup>[45]</sup>. Thoh *et al.* found that azadirachtin interacts with retinoic acid receptors and inhibits retinoic acid–mediated biological responses<sup>[46]</sup>.

### 9.6. Antioxidant effect

Manikandan *et al.* researched that antioxidant and protective effects of active neem leaf fractions against hydrogen peroxide induced oxidative damage to pBR322 DNA and red blood cells<sup>[47]</sup>.

### 9.7. Anticarcinogenic activity

Chatterjee *et al.* showed that identification of a sulfon oquinovosyldiacylglyceride from *A. indica* and studies on its cytotoxic activity and DNA binding properties<sup>[48]</sup>. Perumal *et al.* studied ethanolic neem (*A. indica* A. Juss) leaf extract induced apoptosis and inhibits the IGF signaling pathway in breast cancer cell lines<sup>[49]</sup>. Aravindan *et al.* showed that molecular basis of 'hypoxic' breast cancer

cell radio-sensitization with phytochemicals<sup>[50]</sup>. Induction of apoptosis in human breast cancer cells by nimbolide were carried out by Elumalai *et al*<sup>[51]</sup>. Srivastava *et al.* showed that neem oil limonoids induces p53-independent apoptosis and autophagy<sup>[52]</sup>. A review of the anticancer biology of *Azadirachta indica* was carried out by Paul *et al*<sup>[53]</sup>. Research of Veeraraghavan *et al.* showed the effect of neem leaf extract on rel protein-regulated cell death/radiosensitization in pancreatic cancer cells<sup>[54]</sup>. Mahapatra *et al.* showed novel molecular targets of *Azadirachta indica* associated with inhibition of tumor growth in prostate cancer<sup>[55]</sup>.

### 9.8. Skin diseases

Neem has a remarkable effect on chronic skin conditions. Acne, psoriasis, eczema, ringworm and even stubborn warts are among the conditions that can clear up easily when high quality, organic neem oil is used. Neem oil and leaves has been used in Siddha medicine for the treatment of skin diseases<sup>[56]</sup>. In addition, neem oil can be used as an excellent component of cosmetics to help clear, beautify and rejuvenate the skin.

### 9.9. Antisnake venom activity

Ashis *et al.* studied a snake venom phospholipase A2 (PLA2) inhibitor (AIPLAI) was isolated from leaves of *A. indica* (neem) and the mechanism of PLA2 inhibition by AIPLAI *in vitro* condition was also studied<sup>[57]</sup>.

### 9.10. Digestive disorders

Neem is generally accepted in the ayurvedic medical tradition as a therapy for ulcers and other types of gastric discomfort. Neem promotes a healthy digestive system by protecting the stomach, aiding in elimination and removing toxins and harmful bacteria. Bandyopadhyay *et al.* studied the neem bark extract of gastroprotective effect<sup>[58]</sup>.

### 9.11. Parasitic diseases

Historically, neem has been used to rid the body of all forms of parasites. Neem quickly kills external and internal parasites. Neem extracts have hormone mimics that interfere with the life cycle of parasites, inhibit their ability to feed and prevent the eggs from hatching. Abdel *et al.* studied the efficacy of a single treatment of head lice with a neem seed extract<sup>[59]</sup>. Luong *et al.* found that neem leaf slurry is a sustainable, natural product and anopheline larvicide in west African Villages<sup>[60]</sup>.

## 10. Conclusion

This article clearly shows that neem (*A. indica*) has been used by humankind to treat various ailments from

prehistory to contemporary.

### Conflict of interest statement

We declare that we have no conflict of interest.

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### Comments

#### Background

A majority of the world population in developing and low income countries relies on traditional medicine for their primary health care. In this context, neem tree is a promising prospect for the alleviation of common health problems in the developing world. The manuscript emphasizes the historical links of neem tree with ancient medicines systems around the globe and its role in health care systems in the ancient medicine. It also stresses the need for its further exploration and its incorporation into modern medicine.

#### Research frontiers

The authors had highlighted the biodiversified applications of neem tree in the ancient health care system with well supported literature. The historical links of neem tree with human evolution and its application in health care management have been widely discussed. It also calls for further exploration of the biopotential of neem tree in its utilization in modern medicine.

#### Related reports

The authors had presented the manuscript in a well organized manner and the literature support for the claims and postulations had been correlating well.

#### Innovations and breakthroughs

The manuscript provides a detailed description of the existing historical evidences of neem tree with the mankind and its application in health care systems from ancient times to the modern medicine. It portrays a clear description of neem tree and its broad biopotential activity.

#### Applications

The recommendation of the present studies emphasizes on exploration of neem tree as a major source for development



of more therapeutic molecules and creation of more scientific evidences for its various medicinal applications.

### Peer review

The manuscript is convincing and is based on the diversified application of neem tree. The article has been highlighted with the historical links of neem tree with the ancient medicines. It also gives a detailed description of the existing historical evidences of neem tree with the mankind and in medicine. It has provided a new insight into the exploration and utilization of neem tree as a source for development of new therapeutic molecules.

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