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# A Comprehensive Review on Pharmacological and Therapeutic Uses of *Azadirachta Indica* in the Treatment of Various Diseases

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***Abstract***

*In ancient medicine, the majority of illnesses were treated with plants and phyto-compounds. The most beneficial traditional medicinal plant is Azadirachta indica (Neem). In Ayurveda, it has several therapeutic effects. One of the most adaptable medicinal herbs, it exhibits a broad range of biological action. It possesses medicinal qualities, including anti-microbial, and high efficacy and safety agents. The biologically active components of this plant have a wide range of uses. The neem tree may be used inexpensively because each portion has some therapeutic value. These substances are a part of the class of natural products known as triterpenoids. The review contains all the information about various diseases that are being treated with the help of the neem plant. The therapeutic and potential uses of neem tree for future studies are discussed as well.*

**Keywords:** *Azadirachta indica*, Quercetin, anti-microbial, Newcastle disease, rheumatoid arthritis

## INTRODUCTION

Neem, Indian Lilac, Margosa, and Nimtree are other popular names for *Azadirachta indica* [1]. A member of the *Maliaceae* family, it is a tall, woody, evergreen plant [2]. The seeds, leaves, blossoms, and bark of this tree, which is native to tropical and semitropical regions of the world, are all utilized for a variety of therapeutic purposes [3]. Due to the presence of numerous phytochemicals in *Azadirachta indica* including limonoids, nimbin, and nimbolide, neem is able to effectively treat a variety of viral diseases [4]. It has a lot of bioactive substances with a range of medicinal functions. These bioactive compounds are known to exhibit biological actions, such as anti-pyorrheic, antiscabic, insecticidal, larvicidal, anti-implantation, and antiallergenic, anti-dermic, anti-feedent, anti-viral, anti-fungal, anti-inflammatory [5] anti-mutagenic, and anti-carcinogenic [6]. Additionally, it affects the central nervous system and possesses anti-pyretic, antimalarial, antitumor, antiulcer, anti-diabetic, and anti-fertility properties [7].

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## ORIGIN AND DISTRIBUTION

*Azadirachta* excels and *indica* have been identified as two distinct species [8]. India is the natural home of *Azadirachta indica* A. juss [5]. East Indian Subcontinent and Burma are where it first appeared. These days, it can be found in many Asian, African, Australian, and American nations. Neem is widely cultivated in many Asian countries, including India, Nepal, Thailand, Cambodia, Indonesia, Sri Lanka, Burma, Pakistan, Bangladesh, and Vietnam [9].

 

The number of trees in India is believed to be 25 million, with 5.5% of those being in Karnataka, which ranks third overall behind Uttar Pradesh (55.7% of the total) and Tamilnadu (17.8%). Additionally, neem trees may be found growing in these Indian states: Madhya Pradesh, Bihar, Delhi, Gujarat, Himachal Pradesh, Meghalaya, Orissa, Haryana, Punjab, Rajasthan, Kerala, Andhra Pradesh, West Bengal, Maharashtra as well as the Union Territory of the Andaman and Nicobar Islands. Neem seed production in India is the highest in the world, with an annual output of roughly 442, 300 tonnes, from which 88, 400 tonnes of neem oil and 353, 800 tonnes of neem cake are produced (Table 1) [5].

**Table 1.** Taxonomic position of *A. indica*.

| **Family** | ***Meliaceae*** |
|---|---|
| Class | *Dipsacales* |
| Division | *Magnoliophyta* |
| Order | *Rutales* |
| Suborder | *Rutinae* |
| Subfamily | *Melioideae* |
| Kingdom | *Plantae* |
| Species | *Indica* |
| Genus | *Azadirachta* |
| Latin | *Azadirachta indica* |

## Taxonomical Classification and Botanical Description

It is a tree that grows quickly, reaching a height of 20 to 23 m. Its straight trunk measures about 4–5 feet in diameter. Each of the complex, imparipinnate leaves have between 5 and 15 leaflets [10]. It blooms in the spring with a profusion of white flowers [3]. In the months of June through August, it yields green drupes that turn golden yellow as they ripen (Figure 1) [10].

**Figure 1.** *Azadirachta indica.*

## Active Phytochemical Constituents

*Azadirachta indica* is a valuable source of plant material since it has a variety of constituents that are excellent for managing both health and disease. A total of 135 distinct chemicals have been extracted from various neem parts [11]. The primary active ingredients include 6-desacetylnimbines, nimbandiol, nimbanene, ascorbic acid, n- hexacosanol, nimbolide, and amino acids [3]. 7-desacetyl-7-benzoylgeunin, Nimbin, 17-hydroxyazadiradione, and 7- desacetyl-7-benzoylazadiradione [10] and triterpenoids, Phenolic chemicals, carotenoids, alkaloids, flavonoids (Quercetin and ß-sitosterol are the first polyphenolic flavonoids), steroids, and ketones [12]. Meliantriol, salanin are two more [13]. These active chemicals all exhibit various biological and medicinal properties (Figure 2).

 

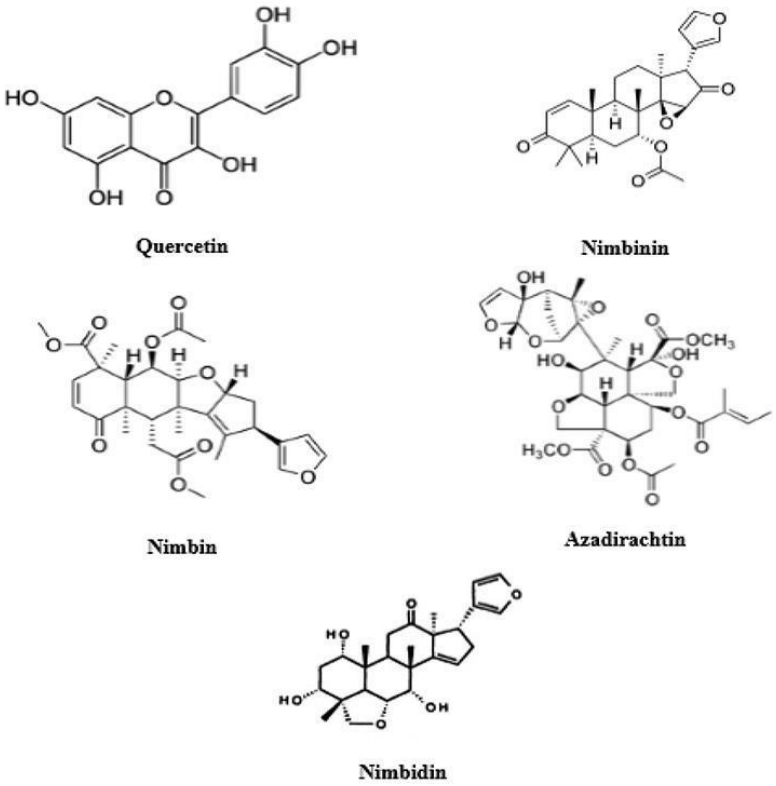


**Figure 2.** Chemical structure of major constitutent *Azadiracta indica*.

**Pharmacological and Biological Activity of *Azadirachta indica***

Neem's pharmacological and biological activities are investigated using extracts from several *Azadirachta indica.*

Components including leaves, bark, fruit, and roots [14] stem, flowers [13] (Figure 3) (Table 2).

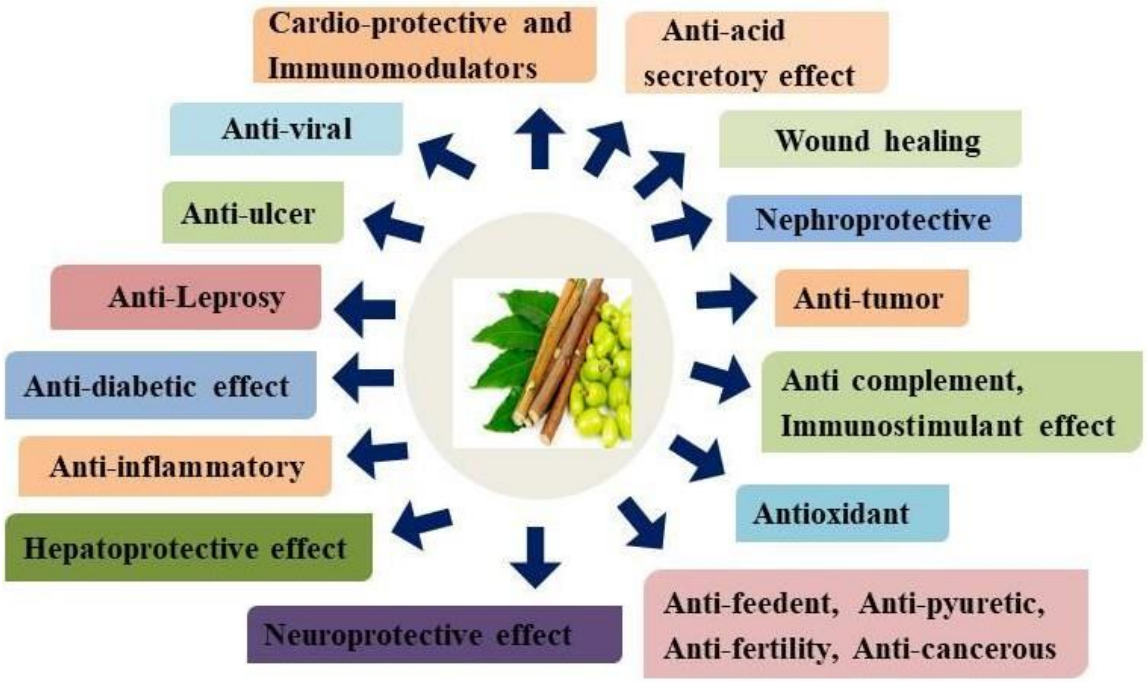


**Figure 3.** Pharmacological activity of *Azadirachta indica.*

 

**Table 2.** Biological Activity of *Azadirachta indica*.

| Parts of Plant | Biological Activity | Extracts | References |
|---|---|---|---|
| Leaves, flowers, stem, bark | Antioxidant | The antioxidant activity of leaf, flower, and stem bark extracts is higher. | [15] |
| Leaves | Anti-microbial activity | Neem leaf alcohol extract exhibits antibacterial activity and is effective in preventing the growth of the cancer-causing bacterium *S. sobrinus*. | [16] |
| Neem leaf | Anti-pyretic effect | Methanolic extract | [11] |
| Neem seed oil | Anti-bacterial, anti-inflammatory, analgesic activity | Aqueous, methanolic, and ethanolic extracts of neem leaves show antipyretic effects. | [13, 14] |

**Newcastle Disease**

The Newcastle disease virus (NDV) also known as the avian paramyxovirus serotype-1 (APMV-1), is the virus that causes extremely contagious sickness Newcastle disease (ND) [17]. The *Paramyxoviridae* family, which includes the *Paramyxovirinae* and the *Pneumovirinae*, is where Avian Paramyxovirus 1 is classified [18]. Most avian species and sensitive poultry are susceptible to NDV. It is an illness that spreads quickly to the neurological and respiratory systems and affects poultry species, such as guinea, hens, ducks, chickens, and turkeys [19]. This virus spreads via ingestion or inhalation and has infected 27 of 50 bird orders. NDV is an RNA virus with a spherical morphology that is bilayered, lipid-coated, and measures between 100 and 300 nm [20, 21]. RNA-guided RNA polymerase (L), hemagglutinin-neuraminidase (HN), fusion protein, matrix protein, phosphoprotein, and nucleoprotein (N) are among the six proteins that this 15 kb single-stranded, nonsegmented, negative-sense RNA virus codes for [22]. The HN and F glycoproteins on the viral surface of NDV attach to host cell surface proteins that contain Salic acid to start an infection [23]. The F protein undergoes a conformational change in response to this, which causes the viral envelope and cell plasma membrane to fuse [24]. The inactive polypeptide F0 is normally the first form of F, which is then degraded into the mature membrane anchored. The membrane-distal F2 domain and F1 domain form infectious viruses [21]. When the virus enters the cell, the P and L proteins form a polymerase complex when the M protein separates from the ribonucleotide protein complex in the cytoplasm. This polymerase complex starts the transcription of the viral RNA [25]. The whole NDV life cycle takes place in the cytoplasm [26]. Mild flu-like symptoms, laryngitis (an inflammation and swelling of the voice box and the surrounding area) or conjunctivitis (commonly known as pink eye) can all occur in NDV patients. NDV replicates itself by infecting cells (sometimes referred to as host cells), just like other viruses. Researchers are interested in NDV because it can harm the host cells and replicates more swiftly in human cancer cells than in most healthy human cells [27].

**Effect of *Azadirachta indica* on Newcastle Disease**

Neem bark extracts have shown encouraging effectiveness as an anti-viral medication and can be used as a potent antiviral replacement by lowering its cytotoxic effects. Neem bark extracts had significant antiviral activity [4]. *Azadirachta indica* is a layer flock vaccinated against Newcastle disease [28].

**Rheumatoid Arthritis**

The inflammatory condition known as rheumatoid arthritis (RA) is chronic, symmetrical, and autoimmune [29]. Synovium-inflamed joints, such as the large joints in the shoulders and knees and the tiny joints in the hands and feet, are first affected [30]. Women in their 30s to 50s are frequently affected [31]. Early RA is characterized as having symptoms that have remained for less than six months, as opposed to established RA, which is defined as having symptoms that have persisted for more than six months [32]. Clinical symptoms of symmetrical joint involvement include arthralgia, edema, redness, and even a limitation in range of motion [33]. In comparison to monozygotic twins (12–15%), non-twin siblings (2–4%), and the general population (less than 1%), 3–4% of dizygotic twins have RA [30].

 

With estimates of heritability ranging from 50% to 60% [34], RA has strong genetic roots. Several autoantibodies, such as anti-citrullinated protein antibodies (ACPAs) and anti-carbamoylated protein antibodies(anti-CarP) [35] and acetylation (AAPA) as well as the migration of T and B cells into the synovium [36] are involved in the pathophysiology of RA. The calcium-dependent enzyme peptidyl arginine-deiminase (PAD) performs the post-translational modification known as citrullination, which converts a positively charged arginine into a polar but neutral citrulline [33]. When compared to the ACPA-negative subset of RA, the ACPA-positive subset of RA exhibits a more aggressive clinical phenotype [37]. In addition to ACPA, RA has a role in the activation of macrophages and the stimulation of cytokine production [38]. There are many risk factors for RA, including systemic autoimmune causes, environmental risk factors, and genetic risk factors [39].

**Effect of *Azadirachta indica* on Rheumatoid Arthritis**

According to a research review, active phytochemical constituents of *A. indica*, such as Nimbin [40] and Nimbolide [41] show anti-inflammatory effects as determined by the mRNA expressions of inflammatory markers, TNF-α and MCP-1 [42]. From the oil of seeds kernels (*A.indica*), compounds called nimbin, and nimbolide are obtained [43]. According to recent research neem oil is used to treat and manage rheumatoid arthritis [40]. Neem oil is also used to treat numerous skin diseases [43]. Rheumatoid arthritis is effectively and protectively treated by extract of *A.indica* (nimbolide, nimbin) also lowers arthritic score and inflammatory cytokine levels [41].

**Sickel Cell Disease**

The majority of inherited hemophilia disorders are rare. However, sickle cell disease is one of them and it causes irreparable harm to many organs. Even though vaso-occlusion and sickling of the red blood cells are crucial to the pathogenesis of sickle cell disease [44]. The hemoglobin [Hb] b-chain's sixth position, where glutamic acid is replaced with valine [45]. Among the genetic causes of SCD are homozygosity for the rs334 mutation (HbSS, also known as SCA), compound heterozygosity between rs334 and mutations that either cause other structural variants of b-globin (like HbC, causing HbSC), or decreased levels of b-globin production (causing HbS/b-thalassemia), and homozygosity for the rs334 mutation [46]. A sickle cell crisis, which is an excruciatingly painful disorder, is caused when mutant hemoglobin (HbS) polymerizes into fibers that bend ("sickle") red blood cells and impede the flow of blood after providing oxygen to the tissues [47].

**Effect of *Azadirachta indica.* on Sickel Cell Disesase**

Recent research has demonstrated that *Azadirachta indica* extract and seed oil exhibit anti-sickling properties [48]. The ethanolic, methanolic, chloroform, and petroleum ether extracts of the leaf, fruit, and stem of the *Azadirachta indica* show antisickling activity [49]. The previous studies found that red blood cells treated with *Azadirachta indica* extracts and seed oil at various concentrations showed greater sickling inhibition rates [48].

**Cancer**

The most serious illness that may affect humans is cancer, which is a significant global health issue [50]. 277 or more different types of cancer disease are included in the term "cancer" in its broadest interpretation [51]. Cancer is a sizable category of disorders characterized by the unchecked cell development and spread of aberrant cells, according to preclinical research [52]. A succession of genetic changes that occur one after another and alter cell functioning are what cause cancer [51]. It is evident that chemical agents are the direct source of gene alterations and malignant cells. Smoking also contains a number of chemical components that are carcinogenic and cause lung cancer [53].

**Effect of *Azadirachta indica* on Cancer**

Since synthetic medications are hazardous, expensive, and change cell signaling pathways, current therapeutic modalities based on them have limited potential [50]. Ancient civilizations all throughout the world have gotten potential anticancer medications from herbal plants and plant-derived therapies, and modern civilization is increasingly utilizing them [54]. *Azadirachta indica* has a lot of applications

 

for treating cancer [16]. Numerous biologically active substances, including nimbin, nimbidin, nimbolide, and limonoids, are present in *A. indica* [10]. Through antitumor activity [55], antioxidant activity, and Cancer formation and treatment depend heavily on the control of cellular proliferation, tumor suppressor genes, and apoptosis, all of which play key roles in the growth suppression of malignant cells [56]. Numerous cancer cell types have been proven to be inhibited from proliferating when exposed to neem and its constituent parts. For instance, azadirachtin can prevent cervical cancer cells (HeLa) from proliferating by reducing levels of cyclin B and cyclin D1, which causes cell cycle arrest at the G0/G1 phase [57]. Nimbolide has been demonstrated to decrease the proliferation of oral squamous cell carcinoma cells is dose-dependent [58] and to stop the cell cycle in the G2/M phase to decrease cell proliferation in bladder cancer cells with an IC50 of 3 M (Figure 4) [59].

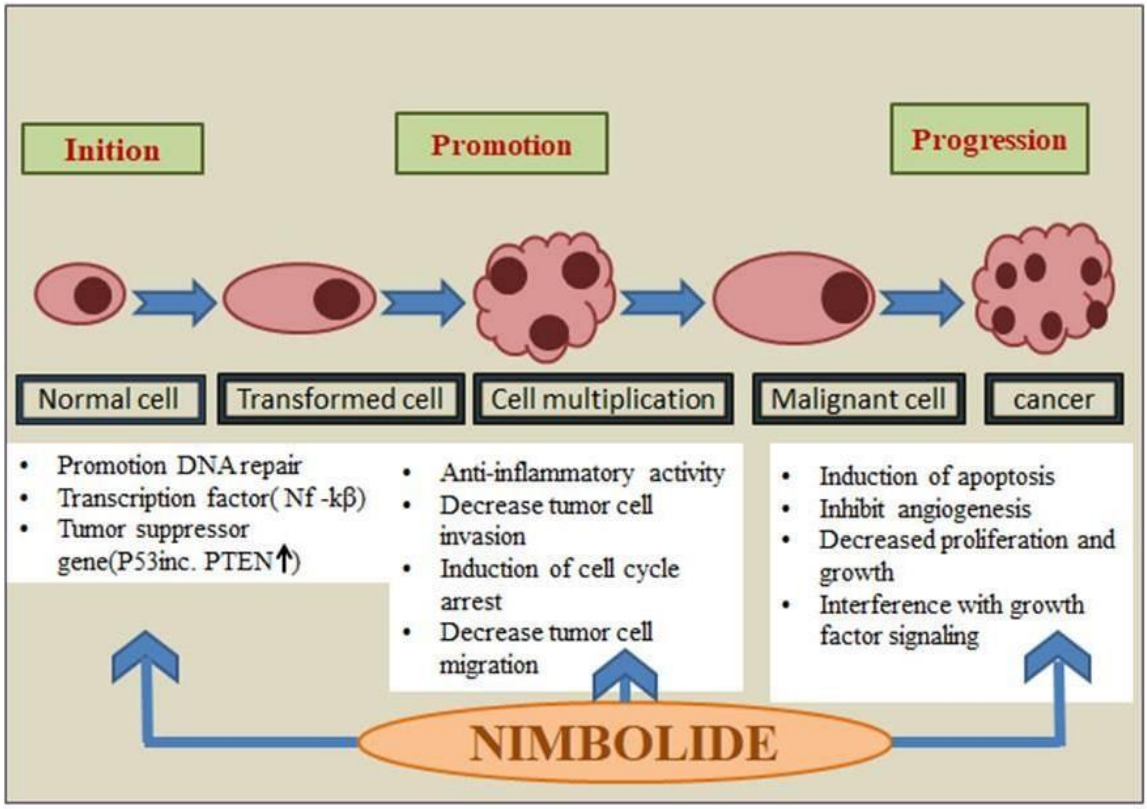


**Figure 4.** Nimbolide role in cancer prevention by inhibition of cancer stages.

**Syphilis**

The spirochete Treponema pallidum is the culprit behind the multisystem disease known as syphilis, which manifests clinically as a systemic, progressive, genital ulcerative, bacterial infection [60, 61]. Treponema pallidum is a member of the Spirochaetaceae family and the Treponema genus. It also contains at least six humans nonpathogens and four human diseases (T. *pallidum endemicum*, *T. pallidum pertenue, and T. pallidum carateum*) [62]. The three stages of infection are primary, secondary, and tertiary. A first lesion appears as a painless papule two to three weeks after the organism is infected, and it eventually ulcerates to produce a chancre [63]. The local host immunological response, adhesion, and transmission of primary syphilis [64]. 10 to 90 days after exposure to infections, a painless, indurated ulcer (chancre) at the site of the T. pallidum inoculation appears [65]. Any system or physiological part may be affected by a secondary syphilis infection, which might manifest itself 2 to 8 weeks after the chancre has disappeared. Systemic host immune response, systemic dissemination, and diagnosis are all aspects of secondary syphilis. T. pallidum propels itself using a mechanism resembling a corkscrew. Endoflagella can be found in the periplasm between the cytoplasmic membrane and its longitudinal axis, as well as between the outer membrane and the membrane [64, 65].

 

**Effect of *Azadirachta indica* on Syphilis**

Neem tree fruit and seeds have antimicrobial properties. The neem fruit is very efficient in treating syphilis because of its therapeutic and pesticidal qualities. Staphylococcus aureus, *E. coli*, and *Salmonella enteritidis* are three common bacterial species that an ethanol extract of neem seed oil is also effective against [66].

**Hypertension**

The hypertensive state, which may be defined as an increase in blood pressure above and beyond the usual range, denotes a deviation in the cardiovascular system's physiological state, which leads to the development of further disorders including myocardial infarction and stroke [67]. Due to its widespread prevalence around the world, hypertension is a significant public health issue [68]. Globally, there are at least 970 million people with hypertension, and by 2025, that number is expected to reach more than 1.5 billion [69]. Prior to the development of industrial society, blood pressure levels had small distributions, averages with age-related minor fluctuations, and averaged approximately 115/75mmHg12, which is likely the average (or optimal) blood pressure for humans. However, systolic blood pressure levels consistently increase with age in both men and women in most modern societies [70]. This pervasive learning may be explained by the fact that age serves as a substitute for the probability and duration of exposures to the many environmental variables that gradually raise blood pressure over time, such as excessive sodium intake, inadequate potassium intake, overweight and obesity, alcohol use, and physical inactivity [71]. Smoking, a sedentary lifestyle, and advanced age are other risk factors for high bp [67]. Unfavorable intrauterine conditions (such as prenatal hypertension or pre-eclampsia) or genetic vulnerability to high blood pressure are both linked to high blood pressure [72].

**Effect of *Azadirachta indica* on Hypertension**

Neem leaf extracts (alcoholic and aqueous) have been shown in numerous studies to reduce high blood pressure [73]. Neem lowers blood pressure by inhibiting calcium channels, boosting ERK 1/2 and Nrf2 gene expression, raising nitric oxide (NO) levels, and lowering oxidative stress indicators [74].

**Alzheimer's Disease**

The most prevalent neurodegenerative condition marked by gradual memory loss is Alzheimer's disease (AD) [75]. Neurodegenerative disease known as Alzheimer's dementia (AD) results in aberrant behavior amyloid and tau buildup in the brain and progressively worsening cognitive and functional deficits [76]. Alois Alzheimer was the first to document an instance of intellectual decline with histological evidence of senile plaques and neurofibrillary tangles in 1907 [77]. According to estimates, 4.5 million Americans have AD, and as the number of people over 65 continues to rise, that number might triple to 13.2 million by 2050. The problem seems to be becoming worse given that 14.2% of India's population, or 70% of the world's population aged 60 and over, is anticipated to reside in developing nations by the year 2020 [78]. Memory loss, poor decision-making judgment, a decline in effort and looseness, inability to communicate, repeating questions, increased language difficulty, issues with writing, reading, and using numbers, seizures, skin infections, difficulties swallowing, the inability to groaning, moaning or grunting, and increased tiredness are all symptoms of Alzheimer's disease [78, 79].

**Effect of *Azadirachta indica.* on Alzheimer's Disease**

In experimental AD models, oxidative stress, cognitive impairments, and neurobehavioral abnormalities can all be reversed with the help of *A. indica*, according to recent studies. Therefore, the effectiveness and safety of A. indica as a monotherapy or add-on medicine for preventive or symptomatic improvement (both cognitive and behavioral) in AD can be evaluated through randomized, multicentric clinical trials [80].

 

**Diabetes Mellitus**

Persistent hyperglycemia, which is caused by impairments in insulin secretion, insulin action, or both, characterizes the group of metabolic diseases known as diabetes mellitus. Protein, lipid, and glucose metabolism are erratic because of the anabolic properties of insulin [81]. Insufficient insulin levels to trigger sufficient response as well as insulin resistance of target tissues, primarily skeletal muscles, adipose tissue, and to a lesser extent, liver, at the level of insulin receptors, signal transduction system, and/or effector enzymes or genes, are what cause these metabolic abnormalities [82]. The current classification of diabetes was developed by the American Diabetes Association (ADA) in 1997 and includes type 1, type 2, other types, and gestational diabetes mellitus (GDM). ADA adopted this classification as the one that is currently most frequently used [83] Insulin resistance is a common feature of both types of diabetes, but they have different genetic causes [84].

**Effect of *Azadirachta indica* on Diabetes Mellitus**

Several studies have shown that medicinal plants are effective in the control and treatment of diabetes. Neem is the most widely used medicinal plant for managing and treating diabetes in several different parts of the world [85]. The enzyme dipeptidyl peptidase IV (DPP-IV) inactivates the hormone glucagon-like peptide-1 (GLP-1) which is essential for the release of insulin [86, 87]. Diabetes can be treated by inhibiting the peptidase DPP-IV [74]. DPP-IV transformed the starting material Gly-Pro-p-Nitroanilide (GPPN) into paranitroanilide (a product with a yellow color), and the absorbance was measured at 380 nm in this procedure. Neem leaves were tested using this method for their inhibitory action (35 l at various concentrations), and neem had a modest inhibitory effect (17%) on DPP- IV (Figure 5) [88].

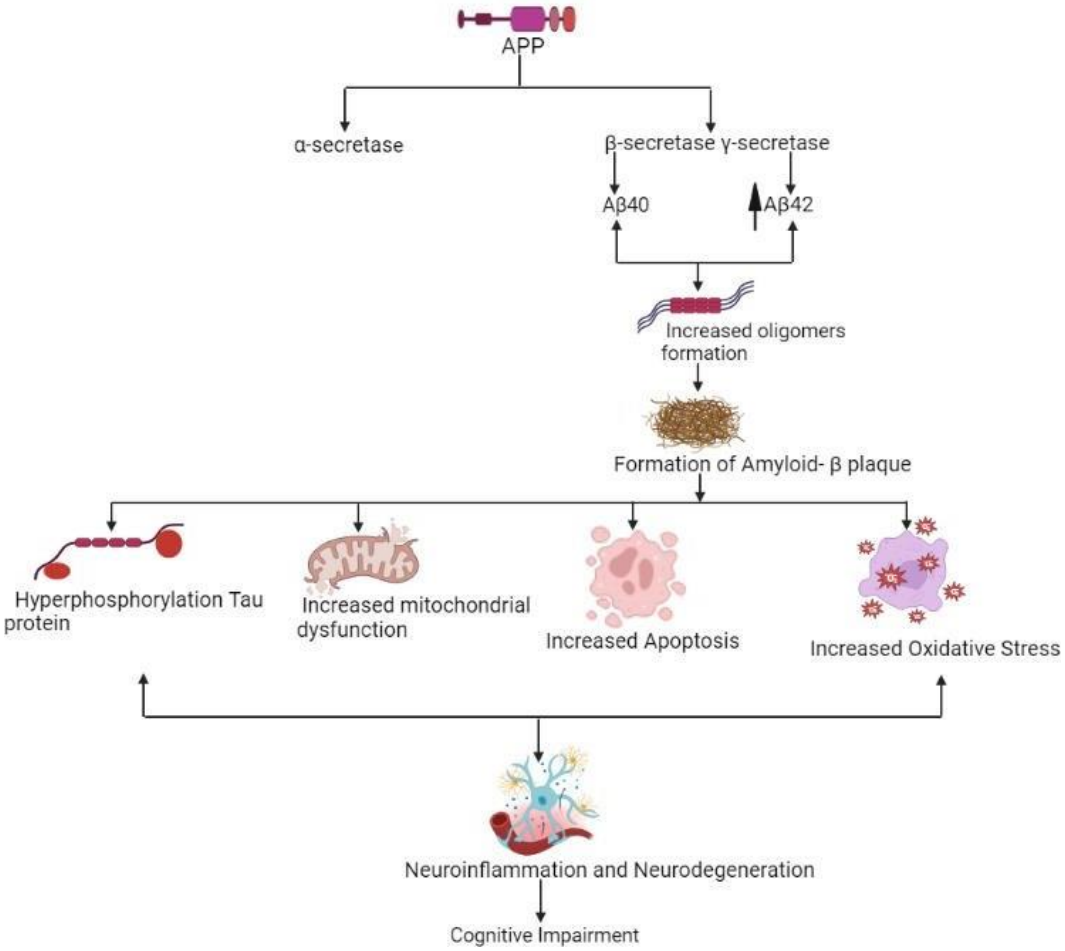


**Figure 5.** *Azadirachta indica* mechanistic activity and its several pathways of inhibition.

 

## CONCLUSIONS

*Azadirachta indica* also known as neem is an Indian herb. It possesses anti-bacterial, anti-fungal, anti-microbial, anti-cancer, anti-diabetes, anti-viral, anti-mutagenic, and anti-feedant properties. It has been previously used as a neuroprotective agent. Researchers are still exploring its various potentials and are using it to treat various diseases. Various parts of neem, such as roots, stems, leaves, bark, seeds, and fruit have different properties as they possess different chemical constituents. From the literature studies, we can conclude that *Azadirachta indica A.* can be formulated in different formulations for the treatment of various diseases.

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