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# A REVIEW ON ANTI-CANCER ACTIVITY OF *AZADIRECTA INDICA* (NEEM) IN ORAL CANCER

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## ABSTRACT

*Azadirachta indica*, generally known as neem, is widely distributed in several semi-tropical and tropical nations, including India, Pakistan, and Bangladesh. For ages, the components derived from the neem plant have been utilized in traditional medicine to treat a variety of ailments, including cancer. The extracts of neem seeds, leaves, blossoms, and fruits have repeatedly demonstrated chemo preventive and antitumor activities in many forms of cancer. Azadirachtin and nimbolide are two of the few bioactive components of neem that have been thoroughly investigated, although more research on a wide range of other bioactive components is needed. The primary anticancer effects of neem components on malignant cells include cell growth inhibition, cell death induction, suppression of cancer angiogenesis, restoration of cellular reduction/oxidation (redox) balance, and stimulation of host immunological responses against tumor cells. Importantly, the anti-proliferative and apoptosis-inducing activities of neem components are tumor-specific, with no effect on normal cells. Furthermore, neem extracts make cancer cells more susceptible to immunotherapy and radiotherapy, as well as improve the efficacy of certain cancer

chemotherapeutic drugs. This review highlights the most recent research on the oral anticancer properties of neem components and their potential impact on cancer incidence and treatment management.

**KEYWORDS:** *Azadirachta indica*, Neem, Oral cancer, Chemoprevention, Anticancer.

## 1. INTRODUCTION

An evergreen tree called Azadirachta indica is widely planted throughout the Indian subcontinent. It is often known to as Indian Lilac or Indian Neem (Margosa tree). Because of its outstanding antibacterial action, neem (A. indica) has long been appreciated by Ayurveda as a remedy for a range of ailments. Neem has grown in popularity in modern medicine and is commonly used in Ayurvedic and homoeopathic treatments. The Sanskrit name of the neem tree, "Arishtha", translates to "Reliever of Sickness" in English. It is also known as "Sarba-roga-nibarini". India still refers to neem trees as "Village Dispensaries." Each component of the neem tree has a medical function, making its use profitable. The biological and therapeutic uses of neem have advanced significantly over the past fifty years. It is now acknowledged as a vital source of unique natural compounds, both for the manufacture of industrial goods and medications to treat a wide range of illnesses. What makes a medicinal plant therapeutically successful is the bio-chemical element that has a particular physiological impact on the human body. Salanin, nimbin, nimbolide, azadirachtin, guanine, and meliacin are some of the plant's bioactive isolates. The bitterness of neem seed oil is caused by meliacin. Tiglic acid (5-methyl-2-butanoic acid), which is produced from neem seeds, is responsible for the oil's odor. These chemicals are organic substances called terpenoids. Although the active ingredients are soluble in organic solvents such as hydrocarbons, alcohols, and other alcohols, they are primarily lipophilic and only sporadically hydrophilic. The utilization of medicinal plants for treating common ailments has grown in remarkable present significance over time due to the escalating side effects of chemical treatments. According to this viewpoint, there are currently many studies available on the biological functions of certain neem components, the pharmacological properties of neem extract, clinical investigations, and prospective medical uses for neem. For thousands of years, the main source of medicines has been substances derived from natural sources, primarily plant sources.[1,2]

**Fig. 1: Neem Components.**

### 1.1 Synonyms of Neem[3]

*Azadirachta Indicavar. Minor Valeton*

Azadirachta Indicavar. siamensis Valeton

Azadirachta Indicasubsp. vartakii Kothari, Londhe & N.P. Singh

Meliaazadirachta L.

Meliaindica (A. Juss.) Brandis

### 1.2 Taxonomical Classification[4]

Kingdom: Plantae

Subkingdom: Tracheobionta

Division: Magnoliophyta

Class: Eudicot

Subclass: Rutinae

Order: Rutales

Family: Meliaceae

Tribe: Melieae

Genus: Azadirachta

### 1.3 Therapeutic Role of Neem Plant[5]

Since the beginning of civilization, medicinal plants have played a crucial role in society's efforts to fight illness. Neem, which has been used medicinally for over 2000 years in India and its neighbors, has a wide variety of biological activities. Neem tree parts have long been used to cure inflammations, infections, fever, skin conditions, and dental issues due to its

tremendous medicinal potential. Neem tree parts include leaves, flowers, fruits, seeds, roots, and bark. The following list[8–9] includes some of the neem tree's medical characteristics.

**Seed**: Neem seeds are used to make neem oil and cake. Neem oil is used as a veterinary medicine, analgesic, anti-helminthic, anticholinergic, antihistaminic, antipyretic, antiviral, antiprotozoal, insecticide, bactericidal, insect repellant, and fungicide. Animal feed, soil fertilization, soil protection, and soil neutralization are all uses for neem cake.

**Leaves**: Neem leaves have antiemetic, antifungal, anticlotting, anti-helminthic, anti-tuberculosis, anti-tumor, antiseptic, and antiviral properties in addition to their ability to act as insecticides and nematicides as well as insect repellents. Twigs: Twigs are used as a pain remedy, mouth deodorant, and teeth cleanser.

**Bark**: Neem possesses antifungal, antiprotozoal, antiprotozoal, and antiemetic properties. Neem blossoms have stimulating and analgesic properties.

**Table 1: Neem Phytoconstituents & their Biological Activity.[6,7,8,9,10]**

| Neem compound | Source | Biological activity |
|---|---|---|
| Nimbidin | Seed oil | Anti-inflammatory, Antiarthritic, Antipyretic, Hypoglycaemic, Antigastric ulcer, Spermicidal Antifungal, Antibacterial, Diuretic. |
| Sodium nimbidate | | Anti-inflammatory. |
| Nimbin | Seed oil | Spermicidal. |
| Nimbolide | Seed oil | Antibacterial, Antimalarial |
| Gedunin | Seed oil | Antifungal, Antimalarial |
| Azadirachtin | Seed | Antimalarial |
| Mahmoodin | Seed oil | Antibacterial. |
| Gallic acid, (–) epicatechin and catechin | Bark | Anti-inflammatory, immunomodulatory. |
| Margolone , margolonone and isomargolonone | Bark | Antibacterial |
| Cyclic trisulphide and cyclic tetrasulphide | Leaf | Antifungal |
| Polysaccharides | | Anti-inflammatory |
| Polysaccharides GIa , GIb | Bark | Antitumour |
| Polysaccharides GIIa , GIIIa | Bark | Anti-inflammatory |
| NB-II peptidoglycan | Bark | Immunomodulatory |

## 2. ORAL CANCER

### 2.1 INTRODUCTION

Cancers of the mouth and the back of the throat are included in oral cancer.

Oral malignancies form under the tongue and on the gum and tissue lining of the mouth.

54,000 additional cases are expected in 2022.

Affects persons over the age of 40.

Most oral cancers are caused by the human papilloma virus (HPV), drinking alcohol, or using tobacco products.

One of the most prevalent tumors, oral cancer is a serious health issue, especially in underdeveloped nations. One of the main reasons of death is due to it. The two main risk factors for oral cancer appear to be smoking and drinking.

Pharyngeal cancer, which begins in the area of the throat right below the mouth, or oral cavity cancer, which begins in the mouth.

On the lower lip, oral malignant lesions predominate.

For dental surgeons in particular, oral cancer is a vitally relevant issue of worldwide public health. It is one of the top 10 tumors in terms of occurrence, and despite advances in research and treatment, survival rates have not increased noticeably in recent years, posing a persistent problem for biomedical science. In order to better comprehend the biological pathways of this malignancy, this publication integrated clinical, histological, and molecular ideas. This allowed the reader and researcher to create a map that could be used to position and integrate this growing body of knowledge. (Keys to preventing oral cancer).

Cancer that appears in the tissues of the mouth or throat is referred to as oral cancer. It is a part of the larger category of tumors known as head and neck cancers. The squamous cells in your mouth, tongue, and lips are where the majority grow.

In the United States, oral cancer affects more than 53,000 new cases a year, most of which affect persons over the age of 40. The majority of the time, oral cancers are only found after they have migrated to the neck lymph nodes. The key to surviving oral cancer is early identification. Find out what increases your risk, how it develops, and other details. [11, 12]

### 2.2 Types of Oral Cancers

Oral cancers include cancers of the:

Lips

Tongue

Inner lining of the cheek

Gums

Floor of the mouth

Hard and soft palate

Oral cancer symptoms are frequently initially identified by your dentist. By visiting the dentist every two years, you can keep your dentist informed about the condition of your mouth.

### 2.3 Risk factors for developing oral cancer

Use of tobacco is one of the main risk factors for mouth cancer. This involves chewing tobacco, using a pipe or cigarette, or smoking a cigar.

Particularly when both items are used frequently, people who regularly consume substantial amounts of alcohol and cigarettes are at even greater danger.

**Other risk factors include**

Human papillomavirus (HPV) infection

Chronic facial sun exposure

A previous diagnosis of oral cancer

A family history of oral or other types of cancer

A weakened immune system

Poor nutrition

Genetic syndromes

Being male

Men are twice as likely Trusted Source to get oral cancer as women are

### 2.4 Screening of oral cancer

Most oral cancer patients learn about it until it's too late. Visit your trusted dentist right away if you're worried you might have it.

Your dentist can do a screening during your appointment to see whether you exhibit any oral cancer symptoms.

Following are the steps your dentist will do during your oral cancer screening.

**The Oral Cancer Screening Process in 8 Steps**

Step 1: Examine the tissue and gums under your top lip.

Step 2: Feel your lip area to look for any suspicious areas.

Step 3: look for sores, mucus, and other warning signals on your tongue.

Step 4: Examine the gums and tissue just under the lower lip.

Step 5: Check the softness of your bottom palate by looking at it.

Step 6: Examine your tonsils and top palate for any abnormalities.

Steps 7 and 8 involve checking the area around the mouth's floor and the tongue's underside for any warning signs.

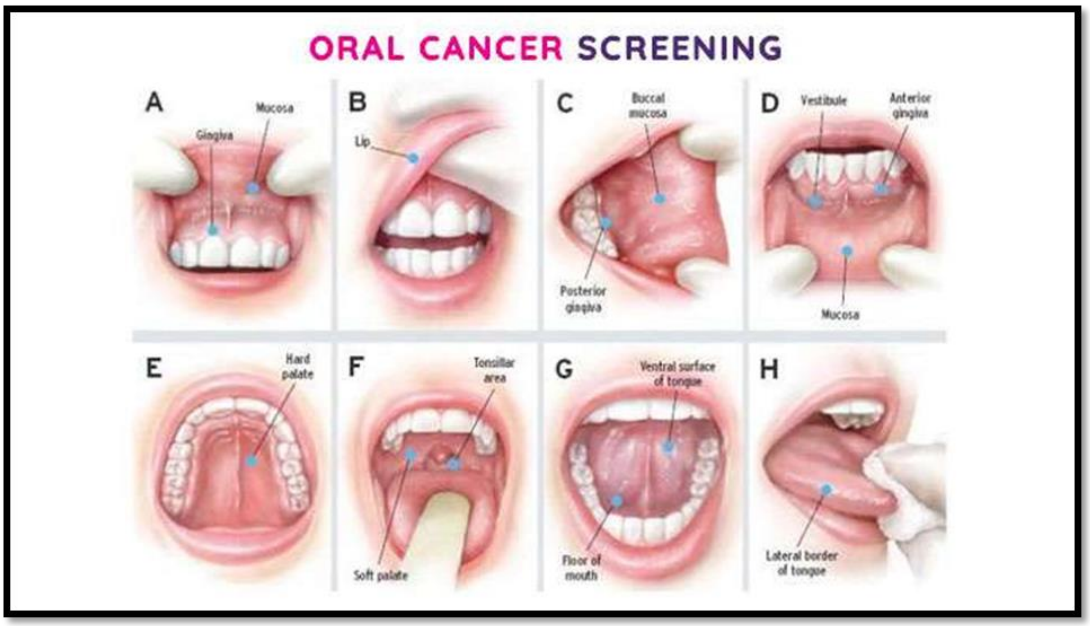


**Fig. 2: Oral Cancer Screening.**

### 2.5 Symptoms of Oral Cancer

Symptoms of oral cancer include

- You have a neck bump.
- Loss of teeth.
- A lip sore or swelling that won't go away.
- Painful or challenging swallowing.
- Speech changes.
- Mouth numbness or bleeding.
- Spots that are white or red on the gums, tongue, or mouth.

Some of these signs, such a sore throat or an earache, could be a sign of something else. Visit your dentist or doctor as soon as you can if you experience any of these symptoms, especially if they persist or you experience more than one at once. Discover the appearance of mouth cancer here.

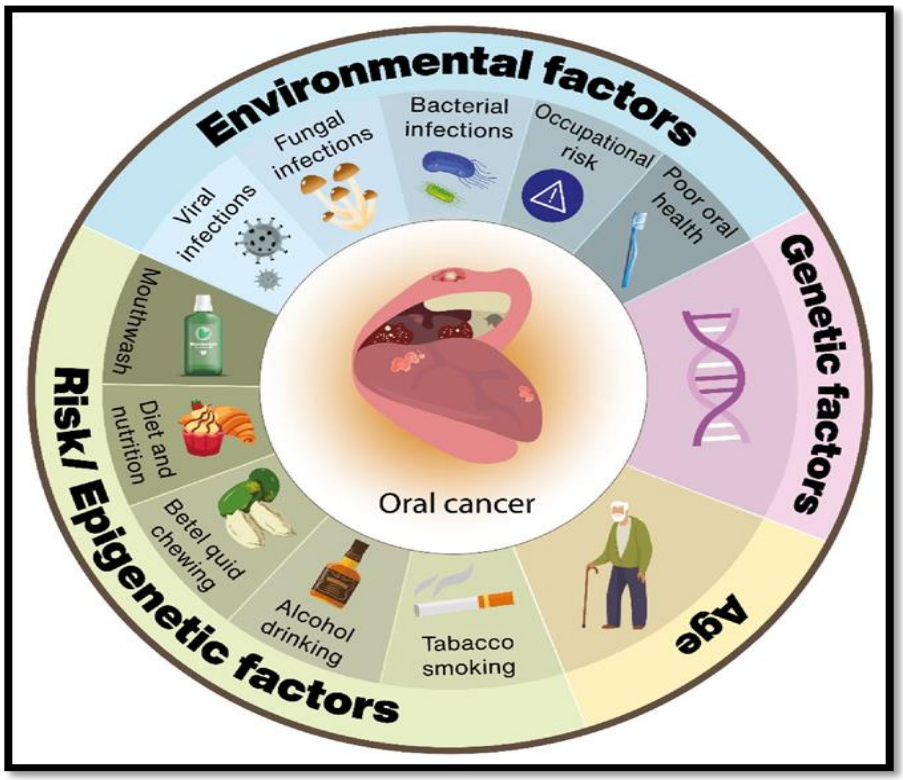


**Fig. 3: Risk Factors of Oral Cancer.**

### 2.6 Identification of Mouth Cancer

Your doctor or dentist will conduct a physical examination first. This entails carefully inspecting your tongue, cheeks, back of your throat, roof and floor of your mouth, as well as the lymph nodes in your neck. You can be referred to an ENT specialist if your doctor is unable to diagnose the cause of your symptoms.

Your doctor will conduct a brush biopsy or a tissue biopsy if they discover any tumors, growths, or suspicious lesions. A painless procedure called a brush biopsy gathers tumor cells by brushing them onto a slide. To check for malignant cells, a tissue biopsy involves removing a small portion of the tissue.

Your physician may furthermore carry out one or more of the following examinations:

X-rays to check for the presence of lung, chest, or jaw metastases of cancer

A CT scan to look for tumors in your neck, lungs, mouth, throat, or any other part of your body.

A PET scan is used to check for the spread of the cancer to the lymph nodes or other organs.

A head-and-neck MRI scan to produce a more precise image and assess the cancer's size or stage

An endoscopy to look into the trachea, windpipe, inner throat, sinuses, and nasal passages

### 2.7 Treatment of Oral Cancer

Depending on the kind, location, and stage of the cancer at diagnosis, many treatments are available for oral cancer.

#### 2.7.1 Surgery

Surgery to remove the tumor and malignant lymph nodes is frequently used as early stage treatment. Other tissue near the mouth and neck may also be removed.

#### 2.7.2 Radiation treatment

After surgery, radiation therapy is most frequently utilized to eliminate any cancer cells that might still be present in the oral cavity. Instead of surgery, doctors might advise radiation therapy if they believe it can eliminate an oral cancer tumor while still preserving patients' ability to chew, swallow, and speak.

#### 2.7.3 Chemotherapy

Chemotherapy, or radiation used concurrently with chemotherapy, frequently produces greater adverse effects but is also more effective than radiation administered alone.

The teeth and gums in this area of your body are susceptible to complications from radiation, so it's crucial to see a dentist before beginning treatment. Before beginning therapy, a dentist can ensure that your mouth is healthy. Before you begin radiation treatment, they might advise having certain problematic teeth extracted because they can increase your risk of infection. Your dentist can assist monitor for and treat any issues that might arise during and after treatment, such as infection or tooth and bone damage.

## 3. MECHANISM OF ACTION IN NEEM

*Azadirachta indica* has anti-cancer characteristics that alter tumor microenvironment, boost the cytotoxicity of white blood cells (monocytes), and slow the progression of tumors.

Neem leaf aqueous extract is reported to exert its chemo preventive function in the oral mucosa by controlling the enzymatic

Glutathione oxidation. Neem's anti-cancer activities are mediated by a variety of pathways.

According to the research, neem products like limuloids and leaf extracts had the following effects on oral cancer cells:

- Stops the development of malignant cells

- Induces apoptotic death, which kills cancer cells.
- Prevents the triggering of cancer cells
- Quickens the process of removing carcinogens
- Prevents invasion of malignant cells

## 4. RECOVERY

Many patients' oral cavity or pharyngeal cancers are successfully removed or destroyed by treatment. Treatment completion can be both anxious and exciting. Despite your relief upon finishing treatment, it might be difficult to stop worrying about the cancer returning. If you've had cancer, this happens frequently.

## 5. HERBAL PLANT OTHER THAN NEEM

Ayurvedic treatment for oral cancer includes the use of herbal drugs having anti-cancer properties. These plants boost the immune system, reduce swelling, and fight malignant cells. The following herbs are some of the ones usually used in Ayurvedic treatment for oral cancer:

- **Turmeric**: Used for centuries in Ayurvedic medicine, turmeric is a powerful anti-inflammatory and anti-cancer agent. Curcumin, which is present in it, has been demonstrated to suppress the development of cancer cells and lessen inflammation.
- **Amla**: Also known as Indian Gooseberry, Amla is a fruit that is high in antioxidants, vitamins C, and other nutrients that can help the body fight cancer cells and strengthen the immune system.
- **Guggulu**: This resin, which is derived from the Commiphora mukul tree, has anti-inflammatory and anti-cancer qualities. For thousands of years, it has been used to cure many cancers in Ayurvedic therapy.
- **Neem**: Neem is a potent herb that has antibacterial, antiviral, and anti-cancer effects. Oral cancer is just one of the cancer forms that it has been used to treat in Ayurvedic medicine.
- **Curcumin**: A component of turmeric known to possess anti-cancer effects is called curcumin. You can use it to cook with or as a supplement.
- **Ashwagandha**: As an adaptogenic herb, ashwagandha aids the body's ability to handle stress and anxiety. Additionally, it has anti-cancer qualities that may aid in reducing the proliferation of cancer cells.

**Table 2: Neem Components as Potential Agent for Cancer Prevention and Treatment.**

| Sr. No. | Plant Extract | Application | Targeted Cell | Model use | Reference |
|---|---|---|---|---|---|
| 1 | Neem leaf extract (NLE) | Proliferation inhibitory effect | Multiple cell cycle molecules | Prostate cancer cell | [18,19] |
| | | Induces apoptosis | Multiple apoptosis-modulating molecules | Prostate cancer cells, primary chronic lymphocytic leukemia cells | [19,28] |
| | | In vivo: proliferation inhibition | Proliferating cell nuclear antigen (PCNA) and cytokeratin | DMBA-induced HBP mouse model | [13,27] |
| | | In vivo: apoptosis induction | Bim, Bax, Apaf-1, caspases, and Bcl-2 | Breast cancer tissue, prostate cancer xenografts, and DMBA-induced HBP oral carcinogenesis model | [13,18,27,31,32] |
| | | Enhances immunity | Peripheral blood mononuclear cells (PBMCs), macrophages, natural killer (NK) cells, CD40–CD40L, interferon gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) | Murine Ehrlich carcinoma and B16 melanoma | [34,35] |
| | | Enhances immunity | Spleen and peripheral blood: macrophages, cytokines, and immune cells | Ehrlich's carcinoma cells, B16 melanoma, Lung sarcoma and lymphosarcoma in the Liver in Balb/c mouse model. | [33,36,37,38] |
| | | Increases the immunogenicity of vaccinations | Surface antigen of B16 melanoma cell (B16MelSAg), breast tumor associated antigen (BTAA), and carcinoembryonic antigen (CEA) | B16 melanoma tumor, breast cancer cells, and CEA + colorectal cancer cells | [37,39,40] |
| | | Alleviates mutagenicity of carcinogens | Likely drug metabolizing enzymes | In vivo bone marrow micronuclei test | [39,49,51] |
| | | Maintain cellular redox balance | Antioxidant phase II enzymes, glutathione level, protein oxidation, and lipid oxidation and peroxidation | Benzo(a)pyrene-induced stomach tumor model and DMBA-induced skin papilloma model, DMBA-induced rat mammary carcinogenesis model, MNNG-induced carcinogenesis | [52-56,58,60] |

| | | | | | |
|---|---|---|---|---|---|
| | | | | model, and DMBA-induced HBP oral carcinogenesis model | |
| | | Attenuates angiogenesis | Human umbilical vein endothelial cells (HUVECs), vascular endothelial growth factor (VEGF) | DMBA-induced HBP carcinogenesis model, chemical carcinogen-induced mammary tumorigenesis | [14,53,61] |
| 2 | Azadirachtin | Induces apoptosis | Bcl-2 family proteins, survivin and caspase-3, -8, and -9 | Cervical cancer cells | [21] |
| | | Cell cycle arrest | p53, p21, cyclin B, cyclin D1, and PCNA | Human cervical cancer (HeLa) cells | [21] |
| 3 | Nimbolide | Cell cycle arrest | Cyclins, CDKs, and CKIs, cell cycle checkpoint proteins are CHK2 and Rad17 | Colon carcinoma cells | [22,23] |
| | | Induces apoptosis | Bcl-2 family proteins, survivin, and caspase-3, -8, and -9. | Breast, prostate, hepatocarcinoma, cervical, choriocarcinoma, colon, lymphoma, leukemia, and melanoma | [20,21,24,25] |
| | | Disrupts cell cycle progression | Unclear | Breast, cervical, choriocarcinoma, lymphoma, leukemia cells HL-60, THP1, and melanoma cells | [20,21,24,25] |
| | | Retards tumor cell migration, invasion, and angiogenesis | Metalloproteinase-2/9 (MMP-2/9), VEGF, ERK1/2, NF-κB | Colon cancer cells | [23] |
| | | Inhibits cell growth | Unclear | Breast cancer cells | [20] |
| 4 | Gedunin | Inhibits cell proliferation | Bioinformatic analysis identifies 52 genes involved | Ovarian cancer cells | [26] |
| 5 | Neem leaf glycoprotein (NLGP) | Increases host immunity | Various immune cells in favor for type 1 immunity, maturation of dendritic cells | PBMC derived from HNSCC patients, myeloid derived dendritic cells | [41-45] |
| | | Relieves tumor immune suppression | Regulatory T cells (Tregs) | Mouse tumor model | [46] |
| | | Restores the impaired chemotactic | CXCR3-mediated axis, CCR5-mediated axis, CXCR4-mediated axis | PBMC derived from HNSCC patients | [47] |

| | | | | | |
|---|---|---|---|---|---|
| | | activity of PBMC | | | |
| | | Maturation of DCs and increased immunity against CEA | Maturation of dendritic cells, various immune cells | Swiss mice, peripheral blood from HNSCC patients | [42,43,48-50] |
| 6 | Mixture of neem limonoids and other components | Induces apoptosis | Intrinsic: cytochrome c, Bcl-2 family proteins Extrinsic: death receptors | Leukemia, prostate, cervical, colon, stomach, breast, choriocarcinoma, and hepatocarcinoma | [14,16,18,20,21, 28-30,62] |
| | | Induces caspase-independent cell death | Apoptosis-inducing factor (AIF) | Prostate | [30] |
| | | Induces autophagy | Unclear | Prostate and colon | [30] |
| | | Alleviates mutagenicity of carcinogens | Likely drug metabolizing enzymes | In vitro Ames test | [51] |
| | | Maintain cellular redox balance | Phase I reactions and phase II enzyme GST | Rat | [57,59] |

## 6. CONCLUSION

We concluded from this review that there is great potential for cancer prevention with neem tree extracts and chemicals. The regulation of cellular differentiation, proliferation, apoptosis, angiogenesis, and metastatic processes is part of the molecular mechanism of action. Numerous in vitro studies on cancer cell lines have been carried out thus far, but additional in vivo investigations are necessary to have a deeper comprehension of the potential positive and negative consequences that may arise from its application. By enabling lower chemotherapy dosages, this combined strategy can increase the effectiveness of conventional cancer treatments. Neem extracts have also shown promise in lowering the toxicity of chemotherapy medications. The usefulness of *Azadirecta indica* in treating and preventing oral cancer was demonstrated by this review, and we believe that a natural medicine with anti-cancer properties could be a huge benefit to medical professionals and patients alike. Furthermore, neem may have unexplored potential as a therapeutic vaccine in the future due to the immunomodulatory qualities of a few of its components. To fully understand the immense potential of neem and its compounds for cancer prevention and treatment, larger clinical trials are encouraged.

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