

Phytochemistry and Therapeutic Potential of *Azadirachta indica* against Oral Cancer

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DOI: 10.18811/ijpen.v10i03.24

ABSTRACT

Alcohol utilization, tobacco use, and human papillomavirus infection are three separate or mixed hazard factors that could cause oral cancer (OC), a complex disease. This is an especially aggressive pathology that often has extreme effects and a low five-year survival price following surgery, chemotherapy, and /or radiotherapy. Natural merchandise possessing a variety of organic and molecular activities, in addition to chemopreventive and anticancer traits, are the source of drugs with the strongest antitumor impact. Frequently blanketed in a treatment method are hormone, immuno-targeted chemotherapy, and radiation treatments. However, those treatment options often have quite many negative quick-to-long-term destructive outcomes. Consequently, it is vital to create oral cancer therapy options with minimal facet outcomes or none in any respect. These days, many bioactive substances originating from distinct plants have won a hobby as potential healing techniques for the remedy of most cancers. Here in this evaluation, we've taken *Azadirachta indica* (neem), as the sizeable spectrum of biological activities and pharmacologic moves of the neem tree are well-established, and each portion of the tree has a few medicinal uses.

Highlights

- Neem components, such as neem leaf extracts and limonoids like azadirachtin and nimbolide, have dual active mechanisms against cancer-causing cells.
- Neem (*Azadirachta indica*) plant components have an antibacterial action by inhibiting microbial growth and the potential for cell wall disintegration.
- The important role of neem components in cancer prevention consists of the capacity to modulate the tumor environment through several actions, including decreasing angiogenesis and increasing the toxicity of the cell.
- Plants' anticancer properties are attributed to several bioactive compounds: like alkaloids, tannins, flavonoids, and phenols etc. which are crucial for the development of new medications.

Keywords: Neem, Cancer, Anti-inflammatory, Pharmacology, Phytochemicals

International Journal of Plant and Environment (2024);

ISSN: 2454-1117 (Print), 2455-202X (Online)

INTRODUCTION

Herbal or plant-based goods' medicinal houses are crucial for both coping with and stopping disease. Nowadays, many study is finished on the effectiveness of medicinal herbal and herbal medicine due to their brilliant characteristics and less terrible effects. Furthermore, vegetation is the supply of numerous pharmacologically lively medications. A few spiritual texts, like the Bible and the Quran, which encourage the use of herbs and culmination in the remedy of many illnesses, also spotlight the sizable position that herbs and medicinal flora play in the control of a huge variety of disorders (Moga *et al.*, 2018). One of the maximum common cancers impacting human beings worldwide is oral cancer. in step with the most estimates, at least 1.3% of males and 0.6% of girls will acquire a diagnosis of oral cancer. That percentage won't seem like a great deal, but when you remember the fact that there are 7 billion human beings on this planet, it provides up to a widespread quantity (Gupta *et al.*, 2017).

Neem, or *Azadirachta indica*, is a plant that is native to the Indian subcontinent and is a member of the Meliaceae circle of relatives. Because of all its biological advantages, the neem tree is likewise known as the village pharmacy. There are several programs for each part of the neem tree, such as its bark, leaves, sap, fruit, seeds, and twigs. They are typically used to deal with a spread of illnesses, consisting of pores

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How to cite this article: Lonhare, A., Verma, S., Ghosh, V., Naz, S. (2024). Phytochemistry and Therapeutic Potential of *Azadirachta indica* against Oral Cancer – A Review. *International Journal of Plant and Environment*. 10(3), 184-190.

Submitted: 06/06/2024 **Accepted:** 08/10/2024 **Published:** 30/11/2024

and skin situations. Neem's anticancer characteristics were investigated previously; these encompass its potential to alter the surroundings surrounding tumors, improve host monocytes' capacity for cytotoxicity, and inhibit tumor cellular growth (Agrawal *et al.*, 2020). Cancer, being a lifestyle-treating disease, is the second motive of loss of life universally. The developing threats of medication-resistant cancers suggest a crucial want for the improvement of more effective anticancer marketers. Herbal remedy offers a very reasonable exchange for trendy medicinal drugs in opposition to most cancers. In keeping with records from the international enterprise for research on most cancers, the predicted global prevalence of 36 cancers in 2020

is 29.8 million, with 19.3 million new cases and 10. Zero million cancer-related deaths. Presently, most cancers deal with the usage of a spread of therapeutic tactics, including radiation, surgical procedures, and/or chemotherapy drug treatments. Many anticancer drugs have poor side consequences, even while chemotherapeutic remedies can assist most cancer patients to stay longer and enjoy a temporary respite from their sickness. This has brought about greater emphasis on natural compounds as possible alternatives to anticancer capsules. Several investigations have shown the herbal bioactive chemical substances' anticancer effectiveness (Chandra *et al.*, 2023).

There's proof that a spread of plant additives, consisting of alkaloids, flavonoids, saponins, vitamins, minerals, and biomolecules, can successfully deal with cancer cells (Karati and Kumar, 2022). Herbal or plant-based total items' medicinal properties are essential for both coping with and stopping ailment. These days, numerous have look at is carried out on the effectiveness of medicinal herbs and natural products because of their remarkable features and less terrible consequences. Moreover, flora is the supply of numerous pharmacologically active medicines. Some spiritual texts, just as the Bible and the Quran, which encourage using herbs and culmination inside the treatment of many sicknesses, also spotlight the considerable position that herbs and medicinal flora play within the control of a wide variety of problems. Numerous biologically active substances, including limonoids, nimbin, nimbidin, and nimbolide, are present in *A. indica*. Quercetin and β -sitosterol were the first polyphenolic flavonoids identified from sparkling neem leaves. Because of their anticancer motion antioxidant activity and capability to modulate cellular proliferation, tumor suppressor genes, and apoptosis, all of these chemical compounds play vital roles in the genesis and control of most cancers (Moga *et al.*, 2018)

Many compounds located in neem (*A. indica*) leaves are crucial for the prognosis, treatment, and prevention of a wide variety of ailments. For a while, neem leaf has been used medicinally in almost every circle of relatives on the Indian subcontinent, but its large kind of programs have in general, been constrained to the ones living in rural regions. Several biological properties of neem leaf extracts were said, inclusive of antibacterial antifungal, and anti-tumorigenic homes. Neem leaf's numerous immunogenic traits have created new possibilities to investigate the plant's first-rate medicinal capability. Numerous studies have looked into the effectiveness of neem leaf extract as an anticancer agent (Chatterjee *et al.*, 2023).

The taxonomical classification of neem is given below in Table 1:

Table 1 : Classification of *A. indica* (Alzohairy *et al.*, 2016)

Order	Rutales
Suborder	Rutinae
Family	Meliaceae
Subfamily	Melioideae
Tribe	Melieae
Genus	<i>Azadiracta</i>
Species	<i>Indica</i>

Phytochemistry of *A. indica*

Neem oil is the most normally accessible *A. indica* product available on the market nowadays, in spite of the reality that almost every component of the plant has been used for classic medicinal functions in India. Neem oil production yields loads of hundreds of tons of neem cake, an abundant byproduct of neem oil manufacturing. This is employed in agriculture international at a rate of about 600 kilos in step with acre of farmland. India alone produces hundreds of lots of lots of neem oil annually. In step with Aneesa (2016), neem oil is a vegetable oil that is obtained via bloodless urgency of the plant's end result and seeds. Nevertheless, neem oil can be further processed by the use of specific solvents to provide a ramification of extracts which can be used for ensuing preclinical and scientific studies. A maximum of the compounds believed to be responsible for the organic sports of neem are discovered within the extracts, which can be commonly utilized in laboratories (e.g., water, ethanol, methanol, chloroform, and ether). However, distinctive solvents may be used to extract specific active additives from plant products. The most often applied extracts for antimicrobial checking out in currently launched literature are methanol and ethanol. Several secondary plant metabolites, which include isoprenoids (terpenoids with limonoid structures, as instance) and non-isoprenoids (tannins), have been connected to the general organic interest of the examined neem oil extracts (Wylie and Merrell 2022).

Various phytochemicals composition of *A. indica* are shown below in Table 2

Numerous phytochemicals, or hundreds of different molecules, have been proven to be bioactive and useful on their own in various contexts. Neem trees are rich in these compounds. Among the almost 300 distinct compounds found in neem trees, several of the more prevalent phytochemicals—such as gedunin, nimbolide, and azadirachtin—have previously been discovered as possible medications with a variety of biological actions (Saleem *et al.*, 2018). Limonoids, which make up one-third of the phytochemicals derived from the neem tree, are compounds that typically consist of four six-membered rings and one five-membered aromatic ring, (i.e., a furanolactone core). These compounds have been the subject of the most in-depth investigation for their individual antimicrobial properties thus far. This class of chemicals, which includes gedunin, azadirachtin, and the triterpenoids nimbolide, nimbin, and nimbidin, has also been investigated for its abundance of antioxidant capabilities. These and other chemicals obtained from neem seed oil have been examined for their previously demonstrated *in-vitro* properties, which vary from spermicidal and anti-psoriasis to anti-inflammatory and antiulcer (Wylie and Merrell 2022). The commonly beneficial properties of neem is given below in Fig. 1.

Recent Study of Neem against Oral Cancer

Neem extracts were shown to showcase anticancer residences in a selection of cancerous cell lines and preclinical animal fashions; those results were frequently ascribed to the plant's constituent limonoids. Neem limonoids have recently drawn quite a few interest from researchers as possible applicants for both most cancer remedies and prevention. Several limonoids protected in

Table 2: Phytochemical composition of *A. indica*

S. No.	Plant Part	Phytochemical composition of <i>A. indica</i>	References
1	Leaves extract	Phenolics, tannins, flavonoids, saponins, alkaloids	Hikaambo <i>et al.</i> , 2022
2	Leaves extract	terpenoids and fatty acid	Surhartono <i>et al.</i> , 2023
3	Leaves extract	Tannins	Mustafa 2016
4	Leaves extract	Flavonoids. Resin	Singh 2021
5	Seed extract	Terpenoids	Benisheikh <i>et al.</i> , 2019
6	Stem bark extract	Tannins, terpenoids, alkaloids	Meressa 2017
7	Leaves extract	saponins, alkaloids	Fatima <i>et al.</i> , 2020
8	Leaves extract	Saponins, tannins, terpenoids	Ogidi <i>et al.</i> , 2021
9	Root extract	phenolics, alkaloids, tannins	Momoh and Olaleye <i>et al.</i> , 2022
10	Leaves extract	tannins, glycosides and alkaloids	Kulkarni, Pandey and Patil 2017

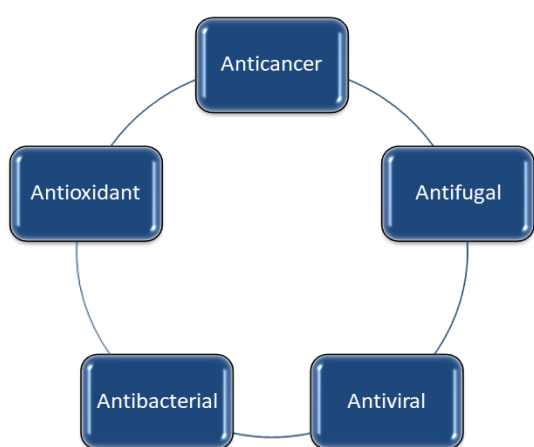


Fig. 1: Beneficial properties of neem (Moga *et al.*, 2018)

neem, which include nimbolide, gedunin, epoxyazadiradione, and azadirachtin, were thoroughly studied for their capability to deal with cancer. Strong biodegradable insecticide azadirachtin has a full-size antiproliferative impact with the aid of blocking off mobile division and mitotic spindle formation. It has been proven that gedunin’s antiproliferative motion is particularly mediated by inhibiting warmth shock protein 90 and its client proteins. To stop most cancers, epoxyazadiradione inhibits signaling pathways that might be pro-inflammatory and kinase-driven. In addition to modifying the epigenome, nimbolide, the most effective neem limonoid, inhibits the development of most cancer cells with the aid of controlling the phosphorylation of keystone kinases that force oncogenic signaling. A wealth of records shows that neem limonoids paintings in opposition to most cancers with the aid of preventing the improvement of traits that are indicative of the sickness, including angiogenesis, invasion, apoptosis evasion, irritation, and cell proliferation. Neem limonoids are treasured additions to the arsenal of naturally happening substances that block the initiation and unfolding of most cancers with the aid of specializing in aberrant oncogenic signaling (Pramanik *et al.*, 2018).

To investigate the impact on oral squamous cell carcinoma (OSCC) cell line cells using ethanolic neem leaf extract (ENLE). Materials and procedures: Following immunocytochemical

labeling, Ki67 and levels of caspase-3 were assessed in an oral squamous cell carcinoma cell line treated with three distinct ENLE doses for varying lengths of time. Statistical analysis was then conducted. Findings: The MTT Cytotoxicity Assay demonstrated a statistically significant increase in examining the cytotoxic effect of various ENLE concentrations at various durations. It also revealed a progressive decrease in the mean viability percentage in ENLE-treated SCC-15 cells as the ENLE concentration increased at both durations. When compared to control groups in both durations, Caspase-3 results demonstrated an increase in the number of apoptotic cells with increasing concentration and duration. When compared to control groups in both durations, Ki-67 data indicated a decrease in the number of viable cells with increasing concentration and duration. In summary, the evaluation of ENLE’s cytotoxicity on the SCC-15 cell line revealed that, in contrast to control cells, ENLE had a cytotoxic effect on the cells. The effect grew as the duration and concentration increased. An efficient and sensitive measure for both apoptosis and proliferation is immunocytochemistry (ICC) (Eldeeb *et al.*, 2022).

The therapeutic benefits of neem trees, including their insecticidal, antioxidant, antifungal, antitumor, and antibacterial qualities, are widely recognized. Research on various neem tree components, including neem leaf glycoprotein and the limonoids azadirachtin and nimbolide, showed that they have anticarcinogenic qualities against OSCC. The potential of gedunin alone or in combination with epalrestat (AR inhibitor) to suppress the downstream PI3K/Akt/mTOR/ERK/NF-κB signaling axis and aldose reductase (AR) in the oral cancer cell line SCC131 was investigated in an *in-vitro* investigation. In SCC131 cells, the administration of gedunin and epalrestat downregulated proangiogenic and pro-invasive proteins and prevented the production of ROS and ARase expression. Autophagy cell death after apoptosis is linked to G1/S phase cell cycle arrest. According to reports, aqueous neem leaf extract regulates the enzymatic breakdown of glutathione in the oral mucosa, hence having chemopreventive effects (Prakash *et al.*, 2021).

Nimbolide, a limonoid derived from the neem tree (*A. indica*), has drawn more and more interest from researchers because of its strong apoptosis-inducing and antiproliferative properties. The goal of the current investigation was to determine how

Table 3: Neem Plant part used for various other cancer cell line

S. No.	<i>A. indica</i> part	Types of cancer	Cell line	Solvent used	References
1	Leaf	Breast cancer cell line	MCF-7	Stabilizing and reducing agent	Sathishkumar <i>et al.</i> , 2014
2	Leaf	Apoptosis leads to cancer	-	methanol ethyl acetate and ethyl acetate chloroform	Manikandan <i>et al.</i> , 2012
3	Bark and leaf	Skin cancer	-	methanol and acetone	Ali <i>et al.</i> , 2015
4	Leaf	Breast cancer	MCF 10A, MCF7, and MDA-MB-231	Ethanol	Braga <i>et al.</i> , 2018
5	Aerial part and seeds	Colorectal cancer	HCT116 and HT29	Organic solvent	Patel <i>et al.</i> , 2018
6	Leaf, seed and aerial part	Colon cancer	HCT116 and HT29	DMSO	Qiu <i>et al.</i> , 2019
7	Leaf phytochemicals	Lung cancer	A549 cell line	Ethanol	Madhavan <i>et al.</i> , 2021
8	Azadiradione	Triple negative breast cancer	TNBC cell line (MDA-MB-231)	Liposomes with advanced bioavailability	El-Senduny <i>et al.</i> , 2021
9	Leaves and flower	Human renal cell carcinoma cell	786-O and A-498 cells	MTT	Hsieh <i>et al.</i> , 2015
10	Limonoid	Pancreatic and breast cancer cell line	AsPC-1 and MCF-7, MDA-MB-231	nanoparticle	Patra <i>et al.</i> , 2019
11	Oil	Cancer cell line	-	Methanol	Kashif <i>et al.</i> , 2018

nimbolide affected autophagy and when GSK-3 β and PI3K phosphorylation status determined whether SCC131 and SCC4 oral cancer cells would undergo autophagy or apoptosis. Furthermore, we examined alterations in the expression of proteins implicated in autophagy and apoptosis subsequent to nimbolide-based therapeutic intervention in a hamster model representing oral oncogenesis. Additionally, we show how the expression of important genes related to autophagy and apoptosis changed as hamsters and human OSCCs evolved step by step. Oral cancer cells treated with nimbolide had stereotyped alterations that included both autophagy and apoptosis. Time-course studies showed that nimbolide first triggers autophagy before transitioning to apoptosis. By suppressing PI3K/Akt signaling, nimbolide raises p-GSK-3 β Tyr216, the active form of GSK3 β that prevents autophagy. The inhibition of PI3K/Akt/GSK3 signaling by nimbolide may be largely attributed to the downregulation of HOTAIR, a competing endogenous RNA that sponges miR-126. An examination of important indicators of autophagy and apoptosis, together with p-AktSer473, during the successive development of hamster and human OSCC demonstrated a slow shift toward a pro-autophagic and antiapoptotic phenotype that may give tumors a survival advantage. In conclusion, the current study's findings provide light on the molecular processes by which nimbolide promotes apoptosis by nullifying the protective effects of cytoprotective autophagy by altering the phosphorylation state of HOTAIR, miR-126, and GSK-3 β , as well as Akt and GSK-3 β . It is crucial to develop phytochemicals, like nimbolide, that target the intricate relationship between proteins and non-coding RNAs (ncRNAs) that control the autophagy/apoptosis flux in order to prevent cancer and treat it (Sophia *et al.*, 2018).

One limonoid from the neem plant that has anticancer properties is called epoxyazadiradione (EAD). Here, we show that in TNBC cells (MDA-MB-231), EAD caused mitochondria-mediated apoptosis. Aside from this, it also induces G2/M phase arrest with downregulation of cyclin A2/cdk2, inhibits nuclear factor kappa-B (NF- κ B) nuclear translocation, inhibits colony formation, downregulates MMP-9 and fibronectin, and promotes antimigration. Furthermore, after receiving EAD, there is a noticeable decrease in the expression of EGFR in the nucleus and plasma membrane. Herein, we report for the first time the several cellular consequences caused by EAD, including the development of anoikis, metabolic interference, and downregulation of membrane/nuclear EGFR expression. In conclusion, EAD can be developed into the most effective antitumor drug in the future since it targets several cellular events to cause growth arrest in TNBC (Lakshmi *et al.*, 2021).

The phytochemicals in *A. indica* were shown to have antibacterial and robust anti-malignant increase traits. The usage of *in-silico* strategies and the coupling proficiency of five mixes observed in *A. indica* with all eleven proteins was finished within the precise exam. Plants cast off unfavorable compounds that motivate harm by increasing the frame's stages of mobile reinforcement particles. For example, they have an impact on glutathione levels and decorate the outcomes of substances that save you cancer. Around 549 cells had been subjected to ethanolic separation of *A. indica* over a number of time intervals (6, 12, 24, and 36 hours). The cells' development changed into under management after 36 hours. Homegrown drugs that can counteract the results of manufactured tablets have become more and more popular, *A. indica* L. A leaf's phytochemical content will increase, making an allowance for extra progressive

searching in addition to anticancer sports (Madhavan 2021).

The flavonoid found in neem plants has been shown to have anticancer properties. High flavonoid doses may lower the chance of developing cancer. The limonoids found in *A. indica* oil are effective in mitigating the mutagenic effects of 7,12-dimethylbenz(a)anthracene (Srivastava *et al.*, 2022).

Neem is used extensively in Ayurveda and has gained popularity in contemporary medicine. More precisely than any other part of the neem tree, the medicinal qualities of the neem leaf have been described. The conversation that follows will only address the pharmacological effects of neem leaves. Neem leaves are accessible all year round. Neem has been a common ingredient in both traditional and contemporary therapeutic formulations due to the ease with which the phytochemicals can be extracted. More than 200 substances have been found in the neem tree's various parts; more than 50 of these chemicals are found in the leaves. Fresh, young neem leaves are composed of minerals, calcium, phosphorus, protein, carbohydrates, and water. Numerous amino acids and fatty acids, including tyrosine, alanine, cysteine, glutamic acid, and glutamine, are abundant in the neem leaf. Antimicrobial and anticarcinogenic, antihyperglycemic, anti-inflammatory, antimutagenic, antioxidant, antiulcer cardioprotective, hepatoprotective, and immunomodulatory qualities are all present in neem leaf extracts and constituents (Maji and Modal *et al.*, 2021).

There are currently several oral cancer studies using neem as a cancer treatment. Scientists are now interested in limonoids from the neem tree (*A. indica*) for their cytotoxicity against human cancer cells. However, unfortunately, the anti-inflammatory and apoptosis inducing properties of azadirachtin have not been investigated in tumor models. An animal study evaluated the relative chemopreventive potential of neem lipids, azadirachtin and azadirachtin, in a hamster cheek pouch (HBP) carcinogenesis model. The results showed that nimolite was more anti-inflammatory and apoptotic than other drugs; This makes it a good choice for cancer prevention (Gupta *et al.*, 2017).

The plant part of the neem is not only beneficial for oral cancer as having various active components it is used for various other cancers which is as follows in Table 3.

Therapeutic properties of Neem component on oral disease

As a medicinal plant, neem plant components are used for various diseases. Neem tree components have demonstrated remarkable effectiveness in inhibiting cancer cells and enhancing the immune system's defense against the development of cancer. Some effects of neem are as follows (Naveed *et al.*, 2014).

Effects on cancer cell death

The ability of a cancer cell to proliferate uncontrollably and continuously is one of its defining characteristics. Consequently, one of the key components of anticancer therapy techniques is the capacity to stop cellular proliferation. The effects of neem oil components on the plasma membranes of HeLa cervical cancer cells demonstrate the potential benefits of employing neem extracts in reducing cancer cell multiplication, as demonstrated by previous studies. It has been demonstrated that components of neem effectively induce apoptosis and promote autophagy, which leads to the death of cancer cells. The enhanced apoptotic

effects of neem seed and leaf extracts have been investigated in a variety of human malignancies, including leukemia, prostate, cervical, and breast cancers. Neem extracts cause a series of molecular events in the oral cavity that correlate with the findings of increased apoptotic cell death, including an increase in the expression of Bim, Bax, Apaf-1, caspase 8, caspase 3, and PARP cleavage, according to studies of DMBA-induced hamster buccal pouch oral carcinogenesis models. Additionally, there is a simultaneous downregulation of Bcl-2 expression (Agrawal *et al.*, 2020).

Anti-inflammatory effect of neem

An important property of neem extracts is their ability to serve as anti-inflammatory agents. Inflammation is linked to a number of illnesses, such as diabetes and cancer, as well as physiological processes like eating and drinking alcohol. Currently, the main bioactive ingredient in neem is limonoid. The potential of limonoid, a furanolactone, to prevent the synthesis of inflammatory mediators is widely recognized. Due to its ability to stimulate endogenous opioid pathways, it is also utilized as a pain reliever. Studies on injured rat paws showed that limonoid from neem can stop fibrovascular tissue from growing and edema from forming. They found that this had a particular inhibitory effect over significant inflammatory molecules like interleukins and tumor necrosis factor and that it was most effective at a dosage of 120 mg/kg (Islas *et al.*, 2020). In their study, it is hypothesized that neem extract can be used as the basis of mouthwash in the treatment of periodontal disease and gum disease, as it significantly reduces plaque and gingivitis (Botelho *et al.*, 2008). In their study, it was hypothesized that mouthwash containing neem extract would have fewer longterm side effects and be more effective in treating plaque-induced gingivitis than mouthwash containing chlorhexidine (Chatterjee *et al.*, 2011).

Antifungal effect of neem

Neem leaves and oil have been shown to have antibacterial properties and reduce dental stomatitis caused by *Candida* (Casaroto and Lara 2010). To determine the effect of leaf extract on the *in-vitro* growth of *Aspergillus fumigatus*, *A. flavus*, *A. niger*, *A. terrestris*, *C. albicans* and *Microsporium gypsum*, Mahmoud *et al.* Research has been done. They found that alcohol containing juice has a good fungistatic effect and can be used as an antibacterial agent (Mahmoud *et al.*, 2011).

Antioxidant effect of neem

Neem extract has anti-inflammatory properties by preventing mucosal damage caused by hydroxyl and oxidative stress. Pandey and colleagues examined the antioxidant properties of neem phytochemicals. They found quercetin, lupeol, rutin, ellagic acid, ferulic acid and betasitosterol. The extract also shows significant free radical scavenging activity, recommending its use for a variety of oral, facial and skin conditions (Chaurasia *et al.*, 2016).

CONCLUSION

A. indica is a herb with many make use of, and the use of it medicinally will protect our society's various diseases. Researchers from all over the international have directed their

interest toward the management and prevention of oral cancer. There are numerous clinical therapy alternatives to be had, but they're all potentially very harmful, from time to time rendering the treatment unfeasible. The use of phytochemicals in this place offers many promises as an additional healing tool or while a stand-on my regimen for oral cancer prevention. Neem can be the best option for treating oral cancer, as this is an herbal source because it causes mild to less or no side effects all the treatments available till now is very costly, and not all can afford it. This will be a lost cost and every individual can afford it, as oral cancer is a global concern and neem can be beneficial for it.

CONFLICT OF INTEREST

The author has no conflict of interest.

ACKNOWLEDGMENT

I would like to express my profound gratitude to Shri Shankaracharya Professional University, Bhilai (C.G), and GD Rungta College of Science and Technology, Bhilai (C.G) for providing the necessary facilities to carry out the work.

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