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Therapeutic role of neem (*Azadirachta indica* Adr. Juss.) in different types of cancer: A systematic review

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Abstract

Azadirachta indica constituents exhibit potential therapeutic role to control cancer progression. The potential anti-cancerous activity of neem extracts reduces cell propagation, migration, inflammation, and invasion. The current review describes the importance and effectiveness of neem extracts in different solvents against various cancers. Studies performed in different geographic locations from 2001 to 2021 were searched in Google, PubMed, Google Scholar, and NCBI. The relevant information has been retrieved, including the type of extracts, solvents, year of publication, and type of cancers. A total of 125 relevant studies published in different journals have been screened, among which the most commonly used neem part was leaf (*n* = 79), followed by seed (*n* = 18), flower (*n* = 10), oil (*n* = 10), bark (*n* = 10), roots (*n* = 6), fruit (*n* = 6), gum (*n* = 5), limonoids (*n* = 5), nimbolide (*n* = 4), stem (*n* = 4), xylem (*n* = 1), and as herb (*n* = 1). Similarly, the most commonly investigated cancer to be treated with the neem extract was breast cancer (*n* = 23), followed by cancerous cell lines (*n* = 21), prostate cancer (*n* = 11), and leukemia (*n* = 8). Most of the studies applied ethanol (*n* = 40) as a solvent for neem extraction, followed by methanol (*n* = 25), distilled water (*n* = 17), ethyl acetate (*n* = 6), Gibco Dulbecco's Modified Eagle Medium (*n* = 4), 7,12-dimethylbenz[a]anthracene (*n* = 4), MTT assay (*n* = 3), acetone (*n* = 3), ether (*n* = 3), ethyl alcohol (*n* = 2), hexane (*n* = 2), glucose (*n* = 2), oxadiazol-2yl-benzothiazole (*n* = 2), and *N*-nitrosodiethylamine (*n* = 1). In conclusion, neem is an important medicinal plant with therapeutic potency against different types of cancer. However, its role has not been investigated widely in some cancers, including bone cancer, retinoblastoma, and oral cancer. Moreover, its potential role may be enhanced if nanocarriers are conjugated to prevent them from human enzymatic metabolism and for successful targeted delivery in cancer therapy.

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Introduction

According to the WHO report, cancer is one of the leading causes of socio-economic burden, posing clinical, economic, and social loads. The risk of developing cancer is 20.2% from 0-74 of age (Men = 22.4% and Women = 18.2%). About 18 million new cases were reported in 2018, among which lung cancer was at the top with 2.09 million breast cancer and 1.28 million prostate cancer (Sung et al., 2021). Based on mortality, cancer is the 2nd leading cause of death of 8.97 million people worldwide, but may likely seem 1st by coming 2060 with estimated death of 18.63 million. Three cancers, including lung, liver, and stomach are sex independent and most deadly among all cancers (Mattiuzzi and Lippi, 2019). Therapeutic efforts continue, and patients are interested in natural products to supplement their therapy for better prevention and less toxicity.

Pyhtomedicines have been recognized as potential therapeutic agents in numerous public health problems since time immemorial. These products are easily available and exhibit very less side effects when compared with synthetic drugs. Numerous drugs have been derived from natural resources which are pharmacologically active (Zong et al., 2012). Religious documents including Bible and Quran also highlighted the role of plants for good health and disease prevention. On the way to this, *Azadirachta indica* (neem), is commonly recognized as 'Divine Life-giving tree', which plays a significant role against many types of cancer (Alzohairy, 2016). Neem plant occurs in abundance in tropical and semitropical locations. The tree is in abundance in India, and many regions of Bangladesh, Nepal and Pakistan (Sharma et al., 2022). The fruits on the neem tree are green drupes that turn golden yellow when ripen during the months of June–August (Alzohairy, 2016). The neem extracts have been analyzed in different solvents for phytochemical screening tests. The plant constituents exhibit a potential antioxidant activity which is important for major health problem prevention and cure, as well as for modulation of genetic and molecular pathways.

Neem plant ingredients have been extensively applied in Unani, Ayurveda, Homeopathy, and also in modern medicine for curing various infectious and non-infectious diseases including metabolic disorders or cancer (Brahmachari, 2004). Plants and their constituents' preparation in various solvents got considerable interest in many countries for better disease management. In this regard, neem has numerous therapeutic implications in different types of disease cure and formulations to treat diseases with least side effects. *Azadirachta indica* contains various chemical constituents including nimbin, nimbolide, nimbidin, and limonoids, which play a very potential role in modulation of various biological pathways in disease management and other metabolic activities. Two important neem leaf polyphenolic flavonoids, quercetin and ß-sitosterol, are well known to have antifungal and antibacterial activities (Govindachari et al., 1998).

Although numerous pharmacological activities were reported such as anti-microbial and anti-inflammatory (Muhammad and Chandra, 2022), the earlier studies have confirmed the neem role as anti-inflammatory, anti-arthritic, anti-pyretic, anti-gastric ulcer, hypoglycemic, anti-fungal, anti-bacterial, and anti-tumor potentials (Bandyopadhyay et al., 2004; Paul et al., 2011). The most important active constituent is azadirachtin and some others are: nimbin, nimbolinin, nimbidol, nimbidin, sodium nimbinate, salannin, gedunin, and quercetin. Leaves comprise nimbanene, 6-desacetylnimbinene, nimbin, nimbolide, nimbandiol, ascorbic acid, amino acids, *n*-hexacosanol, 7-desacetyl-7-benzoylgedunin, 17-hydroxyazadiradione, 7-desacetyl-7-benzoylazadiradione, and nimbiol (Hossain et al., 2011) and seeds hold two important ingredients called gedunin and azadirachtin. The potential role of neem active constituents as chemopreventive effect were found in different types of tumor via inflection of various signaling pathways involved in various biological activities (Paul et al., 2011).

In the current systematic review, we intend to provide a fertile ground for better management of cancers in preventing, diagnosing, and treating cancers using *Azadirachta indica* phytomedicine. Moreover, integrating advanced technology and nanocarriers in targeting drug delivery may enhance therapeutic and diagnosis outcomes of global cancer prevention measures.

Therapeutic role of *Azadirachta indica* in different types of cancers

Lung cancer

According to the American Cancer Society's report in 2023, lung cancer has been the second most common, with 238,340 new cases. Chemotherapy has been extensively used, with more side-effects for good results. However, a few studies have been conducted on application of neem as a therapeutic agent in lung cancer. Phytochemicals are more effective with fewer side effects. Neem extracts have been applied for inducing apoptosis in different cancers, however, the extracts in different solvents demonstrated good anticancer potential, inhibiting cell growth. In a recent study, using neem gum extract Ag@C_{60} nanoparticles (NPs) exhibited promising cytotoxicity in lung cancer (Vinay, 2021).

Azadirachta indica constituents can effectively control cancer progression treated with ethanolic extract in different time spans, that showed an effective control of development of cells (Madhavan, 2021). ZnO NPs were also applied on lung cancer viability using 3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide (MTT) assay. Isolated components of neem have shown promising results in various cancer and animal models (Paul, 2011). Different parts and constituents of neem should be investigated in multiple solvents, and compared for effective nanocarrier targeted delivery for better future lung cancer therapy management.

Colorectal cancer (CRC)

Worldwide, CRC has been ranked 3rd most common in men and 2nd in women. According to the 2020 data, there were 1.9 million new cases of colorectal cancer globally. Phytochemicals have the potential to prevent the progression of CRC cell growth. Potential anti-cancerous activities of supercritical neem extract (SCNE) exhibited reduced cell propagation, migration, inflammation, and invasion in CRC. The cancer treated with neem extract in mice showed prominent control of malignance progression (Patel et al., 2018). Moreover, induced epigenetic modifications, treated with nimbolide, blocked the propagation of cancerous cells. The cell lines grown in the presence of neem leaf extract showed DNA methylation suppression and histone deacetylation suppression (Qiu et al., 2019). Colon cancer, malaria, malnutrition, and myeloma can be treated using neem extract (Arévalo-Híjar et al., 2018).

Numerous studies have been conducted on the applications of neem extracts for cancer prevention (Tables 1 and 2). However, a few studies have investigated the neem leaf extract's role in CRC (Table 2). More studies may be conducted with comparative analysis of different parts of neem in other solvents with targeted drug delivery techniques for better results against the CRC, a 3rd most common cancer worldwide.

Liver cancer

Liver cancer is the 6th most common cancer world-over. Neem gum-capped ZnO NPs could be exploited as nano-biomedical agents to develop novel medications. In 24-hour of *in vitro* investigation, the human liver cancer cell line (HepG2) showed that cell propagation was significantly slowed down at 100 g/mL (Vijayakumar et al., 2021). The ethanolic extract of neem leaf for herbal medication might be helpful in future studies. No abnormal changes were detected using reduced neem extract on the urea concentration in liver and kidney organs (Seriana et al., 2021). The nimbolide and neem leaf extract had no harmful effects on the liver and kidneys. They also showed significant histological protection for the liver and kidney (Zahran Mohamed et al., 2015).

Previous studies using ethanol extract of the neem leaf exhibited a reduced level of AST and ALT enzymes in a rat model with no side effects on liver (Zahran Mohamed et al., 2015). Haque et al. (2006) reported that leaf extract retained the AST and ALT enzymes at normal level in male rats. Bhanwra et al. (2000) also reported that neem leaf extract decreased the liver damage in paracetamol-induced rats during histopathological analysis. Dkhil et al. (2013) also reported a protective effect of neem leaf extract on rat liver. These studies demonstrated the significance of neem leaf extract containing antioxidant contents which acted as a hepatoprotective.

Dietary *A. indica* flower increased liver glutathione *S*-transferase (GST) activity. It may significantly reduce liver cancer. Furthermore, a variety of tumors were suppressed using *A. indica* extract (Tepsuwan et al., 2002a). Studies are limited on the applications of neem in liver cancer. However, the efficacy of liver cancer therapy may be enhanced if used in conjugation with nanocarriers to avoid any human enzymatic metabolism in targeted delivery.

Leukemia

According to the American Cancer Society report in 2023, the estimated cases of leukemia may exceed 59,610 with estimated 23,710 deaths. Acute state of leukemia needs rapid commencement of treatment. Chemotherapy damages the body's resistance to microbial infection. Heterogeneity of leukemias gives various exceptional challenges towards the initiation therapy. Although treatment possibilities exist, still most of the cases are incurable since they offer resistance to therapeutic agents. Novel phytomedicine-based techniques are crucial to improve the treatment outcomes. About half of anti-cancerous agents are natural products and their derivatives, commonly preferred in therapy. The diversity and unique chemical structures have been underexplored, which may have a potential biological activity (Lucas et al., 2010).

Absorption and temperature impact of leaf extract on Ag nanoparticle (NP) synthesis was investigated using the MTT assay, which revealed that the minimal inhibitory absorption was required against human acute lymphoblastic leukemia (ALL) cells in *in vitro* cytotoxicity inquiry of biosynthesized Ag NPs (Asimuddin et al., 2020). Based on previous investigations, it is evident that CLL (chronic

lymphocytic leukemia) is least grown-up leukemia and presently untreatable. In patient's primary CLL cells, ethanolic neem leaf extract (ENLE) shows anti-leukemic properties, establishing clinical effectiveness, thereby justifying further research as a probable therapy for CLL (Chitta et al., 2014). NLE reduces the CLL cell viability and shows good apoptosis results by 24 h. Biochemical analyses show that NLE demonstrates good anti-leukemic potency and also exhibits clinical efficacy, proving to be a potential therapy agent for CLL. However, studies are limited (Table 2) and further investigations are needed for better outcomes.

Skin cancer

Neem constituents have also been applied in skin cancer therapies and were found to be very useful. A study on Swiss albino mice showed that the chemo-preventive effect on induced DMBA skin tumor was recorded from stigmasterol isolated from neem. In a trial model of cancer, it can be inferred that stigmasterol has chemo-preventive action (Ali et al., 2015). It was shown that *Hypericum perforatum* and *A. indica* oil, both play an important role in controlling the skin cancer (Franco et al., 2014) by acting as an antioxidant. The neem extract has been used on a variety of tumor models in animals as the anti-cancerous agent (Arora et al., 2013).

In another report, the neem leaf extract was shown to prevent skin carcinogenesis by inducing pro-apoptotic proteins (Arora et al., 2011a, b). The increase in signal transducer and activator of transcription 1 (STAT1) and AP-1, as well as a decrease in NF-B (Inhibition of nuclear factor kappa B) expression, were associated with cancer inhibition in response to *A. indica* treatment. The results of this study suggest *A. indici*a's viability as a skin cancer chemopreventive agent (Arora et al., 2011a, b).

Gastric or stomach cancer

In vitro study, using neem compounds as a synthesis and capping agent to functionalize stomach cancer cells exhibited very high anticancer activity. *In vitro* apoptosis and antiproliferative properties were demonstrated using gastric cancer cells (Sironmani, 2016). During the pre-initiation stage stomach carcinogenesis in rats, the effects of aqueous extracts of neem on stomach carcinogenesis were investigated. Ethanolic leaf extract displayed its chemopreventive effects in the stomach, liver, and erythrocytes, and boosted antioxidant status (Arivazhagan et al., 2004). In another study, the neem leaf extracts exhibited antioxidant potential and modulation of lipid peroxidation showing an inhibitory role in the gastric cancer, as well as detoxification effect (Arivazhagan et al., 2001). However, this data is limited to accurately conclude the neem potential role in gastric cancer. Large scale studies are needed to explore the potential role of neem in gastric cancer.

Prostate cancer (PCa)

The PCa is the 4th leading cause of mortalities in males worldwide (Mattiuzzi and Lippi, 2019). A good number of patients are interested in natural products for PCa therapy. Neem leaves are known to have anticancer capabilities in melanoma malignancies interacting with cancer's hallmarks. After the mitochondrial membrane is damaged, the neem extract is found to be effective in controlling apoptosis in leukemia and colon cancer cells (Roma, 2015). The supercritical extract of neem leaves (SENL) possesses bioactive components which show that changes in androgen receptor, and the calreticulin levels could be at the root of the drug's anticancer efficacy (Wu et al., 2014).

The anticancer activity of ethanol extract is investigated *in vitro* as well as the efficacy *in vivo* cancer. Natural bioactive compounds containing ethanol extract of neem leaves (EENL) may have anticancer capabilities, and can modulate numerous cellular pathways in prostate cancer prevention, and this treatment may have pleiotropic effects (Mahapatra et al., 2011). An ethanolic extract of neem activated apoptosis in the prostate cancer cells (PC-3) and caused cell death. The neem extract seems very helpful in the treatment of prostate cancer (Kumar et al., 2006a). However, large scale studies are needed to evaluate the comparative role of neem different parts as anti-PCa for better management of public health issues.

Breast cancer

Breast cancer is one of the leading causes of death worldwide. There were 2.3 million breast cancer patients, and 685,000 deaths have been reported globally (WHO 2021; https:// www.who.int/news-room/fact-sheets/detail/breast-cancer). Botanical bioactive chemicals have the potential to be used as chemopreventive medication in cancer treatments. For example, epoxyazadiradione (EAD) is an anticancer limonoid derived from the neem plant. EAD is believed to inhibit triple-negative breast cancer (TNBC) growth by targeting several cellular processes, hence, it has the potential to become the best antineoplastic agent in the future (Lakshmi et al., 2021). If researchers could locate the proper plant, solvent, and fraction for the particular condition, they could treat cancer (Dehghan-Nayeri et al., 2020). The consistency and effectiveness of COCOGS-AuNPs in the creation of new anticancer drugs against

triple negative breast cancer cells (TNBC) are of dire need. The AuNPs may suppress the TNBC cell propagation and activate tumor cell digestion, leading to increased cellular death (Siddiq et al., 2019). More research is needed for successful cancer treatment (Trivedi et al., 2018).

By causing apoptosis and G_1 phase arrest, neem oil suppresses the development of human breast cancer cells. The nanoparticles were tested on MCF 7 breast cancer cell lines. The findings of anticancer activity investigations revealed that gold nanoparticles produced outcomes that were comparable to those of mainstream cancer medications (Kamala Priya and Iyer, 2015). N-methyl-n-nitrosourea (MNU)-induced breast tumor growth was reduced by treatment with ethanolic fraction of neem leaf (EFNL). By changing critical signaling pathways, EFNL has a substantial anticancer effect against breast carcinogenesis (Arumugam et al., 2014). Similarly, ENLE inhibited cancer cell proliferation by triggering apoptosis in MCF-7 (breast cancer), HeLa, and normal cells in a dose- and time-dependent manner, so showing that neem has the potential to be a therapeutic treatment for gynecological cancers (Sharma et al., 2014).

The bioactive compound (s) in the ethanol extract of *A. indica* may have induced MDA-MNB 231 cells to die by apoptosis, resulting in breast cancer. To fully comprehend the method by which this plant affects breast cancer cell lines, more research is required (Arisanty, 2013). The use of nimbolide in anticancer therapy has gained fresh hope (Elumalai et al., 2012b). Tumor formation was studied using a modified Xanthopoulos technique. Female BALB/c mice were divided into groups (one cancer control group and three malignant groups, each with 12 animals). In the presence of 500 mg/kg ethanolic neem leaf extract (ENLE), C-Myc was observed to be downregulated (Othman et al., 2012). The ENLE caused apoptosis in cells by suppressing signaling molecules and lowering cell growth, implying that it could be utilized to treat cancer (Elumalai et al., 2012a).

The apoptosis of 4T1 breast cancer cells is promoted by neem leaf extract (Othman et al., 2011). The expression of cancer-related genes was altered after being treated with 7,12-dimethylbenz[a] anthracene (DMBA). The ENLE exerts anticancer effects by inhibiting alterations in gene expression and histological lesions in the mammary tissues of female rats exposed to DMBA (Alakilli, 2010). The rise in antioxidants, inhibition in DNA damages, cell proliferation, hormone regulation, and protein oxidation have all been associated to chemoprevention by neem leaf fractions (Vinothini et al., 2009). Nineteen semisynthetic gedunin derivatives were synthesized and breast cancer cells SkBr3 were investigated to determine the mechanism of action. Despite the fact that no chemical was already proved to be more efficient than the natural product (Brandt et al., 2008a).

Cancer cell lines

Nimbolide offers a wide range of therapeutic applications due to its ability to overcome resistance. Nimbolide appears to modulate kinase-driven oncogenic signaling networks by decreasing the acquisition of cancer hallmarks (Nagini et al., 2021). In addition, an *in vitro* investigation on a human liver cancer showed that cell growth was successfully suppressed in 24 hours at 100 g/mL. Neem gum capped ZnO NPs are indicated as possible nano-biomedical agents for usage in novel pharmaceutical formulations (Vijayakumar et al., 2021). Ag@C60 NPs performed well in a cytotoxicity test. In bearing bores, TEM revealed quasi-spherical like structures. *In vitro*, the Ag@C60 NPs treated A549 cell line had dose-dependent lethal effects. The utilization of neem gum extract in microwave-assisted green production of Ag@C60 NPs is effective to control cancer (Vinay, 2021).

Azadirachta indica phytochemicals have been discovered to have anticancer and antibacterial effects. The coupling proficiency was completed using *in silico* procedures in the specified evaluation. By increasing the body's degrees of cell reinforcement particles, the plant reduces dangerous compound-induced injury. These particles improve the activity of cancer-prevention compounds, e.g., influence on glutathione. Approximately, 549 cells treated with *Azadirachta indica* ethanolic extract were isolated over a period of time (6, 12, 24 and 36 h). After 36 h, the cell development was halted. *Azadirachta indica* has regained interest in home-made therapies to prevent the negative effects of medicines (Madhavan, 2021). A limonoid contained in the leaves of the neem tree has been proven to suppress the growth of several human cancer cell lines. Using a microwave-assisted extraction (MAE) approach paired with a chromatographic technique, the nimbolide was isolated and purified from the leaves of the neem tree. From the neem leaves, the MAE was used to extract the highest concentration of nimbolide (Suttiarporn and Choommongkol, 2020). TLC chromatography, spectroscopic inspection, and GC-MS analysis were all performed on the final polysaccharide determination. The polysaccharide did not have antibacterial properties, but it did have antioxidant and cancer-fighting properties. The extracted polysaccharide was carboxymethylated and utilized to make a nanocarrier for the anticancer medication curcumin (Samrot et al., 2020).

An extract from neem leaves has cytogenotoxic potential in Swiss albino mice (Prakash and Chaurasia, 2020. The neem leaf extract was given to young weaning Swiss albino mice. In bone marrow

as well as primary spermatocytes, the extract strongly produced division disrupting chromosomal alterations (Prakash and Chaurasia, 2020). The extract selectively reduced the development of Hela cell lines The study found that, in addition to some of neem's primary ingredients having anticancer potential, its smaller metabolites might also hinder cancer cell development (Dong et al., 2019). The study discovered that nimbolide only caused apoptosis in cancer cells, but not in normal cells, and that activation of caspase signaling pathways is one of the apoptosis causing pathways. Thus, nimbolide has the potential to become a promising anticancer drug alternative in the future (Kashif et al., 2019).

The EENL may inhibit cell proliferation, reduce vascular endothelial growth factor (VEGF) stimulatory effects, and have antiangiogenic effects through regulating genes involved in cellular growth and cell death, so the treatment with EENL may be helpful in the treatment of cancer (Mahapatra et al., 2012).

In vitro, the well-known gedunin and azadirone, as well as the novel neem fruitin A, showed significant antiplasmodial activity, providing important information about the structure-antimalarial activity relationships in the limonoid class (Chianese et al., 2010). The chemical had strong DNA binding capabilities, as demonstrated by an increase in melting temperature and a change in the distinctive B-form in calf thymus DNA circular dichroism (CD) evidence; isothermal calorimetry was used to characterize the DNA binding, which demonstrated a primarily enthalpy-driven binding to CT DNA (Chatterjee et al., 2010a). The azadirachtin and nimbolide decrease cell cycle proliferation and elicit apoptosis in cell mechanisms. In comparison, nimbolide has been found to be a more effective antiproliferative and apoptosis-inducing drug, with the potential to be a multitargeted cancer prevention and treatment option (Harish Kumar et al., 2010). Surprisingly, it protects BDNF -/- pups against vestibular ganglion degeneration. In a TrkB-dependent manner, deoxygedunin also protects rat neurons against cell death. As a result, deoxygedunin replicates BDNF's biological capabilities by activating TrkB, making it an effective therapeutic tool for a number of neurological disorders (Jang et al., 2010a).

The outcomes of this study suggest that nimbolide has a lot of promise in therapy because of its antiproliferative properties (Harish Kumar et al., 2009). The extracts were eluted on a C18 column using a 60:40 water: acetonitrile mobile phase. The extracts were studied both against Gram-negative and Gram-positive bacteria, yeasts, and a fungus despite the absence of AZA spots or peaks on the extracts. To test if there was a dose-dependent connection between activity and concentration, the extracts were analyzed at various concentrations. Despite the lack of AZA, the ethanol extracts were effective against *Staphylococcus aureus* (Alves et al., 2009a).

Table 1. Detail of neem applications in different solvents against different cancer types

Neem extract	Solvent	Cancer type	References
Neem gum	Oxadiazol-2yl-benzothiazole	Human liver cancer cell line	(Vijayakumar et al., 2021)
Leaf nimbolide	DMBA	Myriad cancer cell lines	(Nagini et al., 2021)
Neem gum	Phytochemical oxadiazol-2yl-benzothiazole	Human liver cancer cell line	(Vijayakumar et al., 2021)
Neem gum	Fullerene, 4 aminothiophenol, silver nitrate, toluene, and diethyl ether	Lung cancer cell lines	(Vinay, 2021)
Azadiradione	Liposomes with improved bioavailability	Triple negative breast cancer	(El-Senduny et al., 2021)
Leaf phytochemicals	Ethanol	Human lung cancer cell line	(Madhavan, 2021)
Leaves and flowers	4',6-diamidino-2-phenylindole	T cell lymphoma cancer	(Jaiswara et al., 2021)
Leaves	Methanol	Human lung cancer cell lines	(Rani et al., 2021)
Limonoid	Ethanol	Triple-negative breast cancer cells	(Lakshmi et al., 2021)
Leaf	Ethanol	Liver and kidney damage leads to cancer in rats	(Seriana et al., 2021)
Bark, leaves, sap, fruit, seed,	Ethanol	Oral cancer	(Agrawal et al., 2020)
Aerial parts and dried plant powder	Ether, petroleum, methanol, hexane and water	MCF cell lines	(Jeba Malar et al., 2020)
Leaves	Ethyl acetate/hexane	Cancer cell lines	(Suttiarporn and Choommongkol, 2020)
Xylem	Xylose and glucuronic acid	Human colorectal cancer	(Jeba Malar et al., 2020)

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Neem extract	Solvent	Cancer type	References
Gum	Hydrogel matrix	Cancer	(Mankotia et al., 2020)
Gum	Glucose, idosan, allose, galactose, rRibose and xylose	MCF7 cancer cell line	(Samrot et al., 2020)
Leaf	Aqueous solution of $AgNO_3$	Human acute lymphoblastic leukemia	(Asimuddin et al., 2020)
Leaf	Ethanol	Albino mice cancer	(Prakash and Chaurasia, 2020)
Neem herb	Ethanol, methanol	Breast cancer cell lines	(Dehghan-Nayeri et al., 2020)
Leaf	Organic solvent	OSCC cell lines primary tongue tumors	(Qiu et al., 2019)
Neem gum	Fe_3O_4	Monocytic cell line cancer	(Asghar et al., 2019)
Limonoid	Nanoparticles	Pancreatic and breast cancer cell line	(Patra et al., 2019)
Bark	MTT assays	Lung cancer	(Zingue et al., 2019)
Dry seeds	Ethanol, ethyl acetate	Cancer	(Dong et al., 2019)
Leaf, seeds and aerial parts	DMSO	Colon cancer	(Qiu et al., 2019)
Nimbolide from leaf	Hoechst 33342 and propidium iodide	Cancer cell line	(Kashif et al., 2018)
Seed oil	Methanol and acetonitrile	THP-1	(Cesa et al., 2019)
Fruit	Hexadecyltrimethylammonium chloride (CTAC)	Breast cancer	(Siddiq et al., 2019)
Neem oil	DMBA	Breast cancer	(Zingue et al., 2019)
Leaf	Copper oxide and distilled water	Cancer cell apoptosis	(Dey et al., 2019)
Bark, leaves, flowers, seed oil	Methanol	Gynecological cancer	(Moga et al., 2018)
Cytotoxicity profile	Ethanol	Breast cancer	(Trivedi et al., 2018)
Young fresh leaves	15% TCA-acetone	Cancer	(Al Saiqali et al., 2018)
Neem leaf glycoprotein	Ethanol	Cancer	(Chaudhary et al., 2018)
Aerial parts and seeds	Organic solvent	Colorectal cancer	(Patel et al., 2018)
Limonoid	NF-KB signaling	Oral cancer cells	(Tanagala et al., 2018)
Nimbolide	Formic acid in water as mobile phase	Cancer cell line	(Baira et al., 2018)
Fresh leaf	Methanol	Colon cancer	(Arévalo-Híjar et al., 2018)
Leaf	ZnO NPs	Lung cancer A549 cells	(Rajeshkumar et al., 2018)
Leaf	Ethanol	Breast cancer cells	(Braga et al., 2018)
Oil	Methanol	Cancer cell line	(Kashif et al., 2018)
Seeds	Ethanol	Breast cancer cells	(Sharma et al., 2017)
Seeds	BCl_2	Human cervical cancer (HeLa) cells	(Shilpa et al., 2017)
Leaves, flowers	Ethanol, methanol, water	Cancer cell lines	(Alzohairy, 2016)
Leaf powder	Total phenolic content	Breast cancer	(Cheung et al., 2016)
Leaf	Reducing agents	Cellular apoptosis	(Kummara et al., 2016)
Leaf	*DMEM, *FBS	Gastric cancer	(Sironmani, 2016)
Roots	Methanol	Tumors	(Uppuluri et al., 2015)
Leaf	Ethanol	Liver and kidney tumors	(Mohamed et al., 2015)
Neem oil	Ethylenediaminetetraacetic acid (EDTA)	Human lymphocytes *in vitro*	(Jerobin et al., 2015)
Leaf powder	Ethanol	Pancreatic, prostate and melanoma cancers	(Roma, 2015)
Leaf	DMEM medium, Tamoxifen, Trypsin	MCF-7 breast cancer cell lines	(Kamala Priya and Iyer, 2015)
Leaf	Ethanol	Human cancer cells	(Roma et al., 2015)

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Neem extract	Solvent	Cancer type	References
Bark and leaves	Methanol and acetone	Skin cancer in mice	(Ali et al., 2015)
Leaves and flowers	MTT	Human renal cell carcinoma cells	(Hsieh et al., 2015)
Leaf	Dihydrotestosterone, prostate-specific antigen	Prostate cancer cells	(Wu et al., 2014)
Leaf	Ethanol	Breast cancer	(Arumugam et al., 2014)
Different parts	n-hexane: ethyl acetate: acetic acid and methanol–sulfuric acid	Human cancer cells	(Rout and Mishra, 2014)
Leaf	Ethanol	Breast and cervical cancer	(Sharma et al., 2014)
Neem oil	Methanol	Head and neck cancer	(Franco et al., 2014)
Non-toxic neem leaf glycoprotein	Methanol	Supraglottic laryngeal tumor	(Goswami et al., 2014)
Leaf	Ethanol and distilled water	B-chronic lymphocytic leukemia cells	(Chitta et al., 2014)
Seeds, leaves, flowers, and fruits	Ether, petroleum, and distilled water	Malignant cells and tumor cells	(Hao et al., 2014, p. 201)
Leaf	Nimbolide	Prostate cancer	(Wu et al., 2014)
Leaf and flower	Ethanol	Metastasis	(Bodduluru et al., 2014)
Leaf and flower	Ethanol	Cell proliferation and metastasis of cancer cells	(Elumalai and Arunakaran, 2014)
Leaf	Reducing and stabilizing agent	Breast cancer cells and breast carcinoma cell line	(Sathishkumar et al., 2014)
Mature leaves	Fetal bovine serum, and penicillin–streptomycin solution	Leukemia	(Yogesh et al., 2013)
Leaf	DMBA	Skin cancer	(Arora et al., 2013)
Leaf	Ethanol	Human breast cancer cells	(Arisanty, 2013)
Leaf	Ethanol	Cancer cell line	(Mahapatra et al., 2012)
Leaf and flower	Ethanol	Breast cancer	(Elumalai et al., 2012a)
Leaf	Ethanol	Breast Cancer	(Othman et al., 2012)
Stem and bark	Ethanol, distilled water	Cancer cell line	(Ashafa et al., 2012)
Leaf	Ethanol	Apoptosis leads to cancer	(Srivastava et al., 2012)
Leaf	Ethanol	Breast cancer	(Elumalai et al., 2012a)
Leaf	Ethyl acetate chloroform and methanol ethyl acetate	Apoptosis leads to cancer	(Manikandan et al., 2012)
Leaf	N-nitrosodiethylamine (NDEA)	Hepatic cancer	(Bharati et al., 2012)
Leaf	Ethanol	Prostate cancer	(Mahapatra et al., 2011)
Seed	Methanol	Cancer	(Kikuchi et al., 2011)
Leaf	Ethanol	Prostate cancer	(Gunadharini et al., 2011)
Fruit, oil, roots, and leaves	Ethanol	Colon and breast cancers	(Paul, 2011)
Leaf	DMBA	Skin tumor	(Bansal, et al., 2011)
Leaf	Ethanol	Pancreatic cancer	(Veeraraghavan et al., 2011)
Neem oil	Methanol	Tumor cells	(Aiello et al., 2011)
Leaf	Bovine serum	Murine tumor growth	(Chakraborty et al., 2011)
Leaf	Different reagents	Cervical cancer	(Roy et al., 2011)
Leaf	Ethanol	Breast cancer	(Othman et al., 2011)
Leaf	Ethanol	Murine skin cancer	(Koul et al., 2011)
Leaf	Ethanol	Prostate cancer	(Kumar et al., 2006b)
Fruit	Methanol	Cancer	(Chianese et al., 2010)
Leaf, seed, and stem	Water	Antiviral, antitumor	(Amer et al., 2010)
Leaf	Ethanol	Breast cancer	(Alakilli, 2010)

Table 1 continues on next page

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Neem extract	Solvent	Cancer type	References
Leaf	Ethanol	Cancer cell line	(Chatterjee et al., 2010b)
Leaf	Ethanol	Cancer cell line	(Harish Kumar et al., 2010)
Leaf	Ethanol,	Cancer cell line	(Jang et al., 2010b)
Leaf,	Ethanol and acetone	Cancer cell line	(Harish Kumar et al., 2009)
Leaf, seed oil, and stem	Methyl, alcohol	Cancer cell line	(Atawodi and Atawodi, 2009)
Leaf	Ethanol, methanol, and water	Cancer cell line	(Alves et al., 2009b)
Leaf	Ethanol	Breast cancer	(Vinothini et al., 2009)
Leaf and seed	Ethanol, methanol, and alcohol	Prostate cancer	(Girish and Shankara, 2008)
Oil	Ethyl acetate	Breast cancer	(Brandt et al., 2008b)
Leaf	Water, acetyl acetate, methanol	Breast cancer	(Brandt et al., 2008b)
Leaf	Ethyl alcohol, methanol, ethanol	Carcinogenesis	(Manikandan et al., 2008)
Nimbolide	Acetone, mesh silica gel, ethyl acetate	Cancer cell line	(Kumar et al., 2008)
Leaf	Ethyl acetate, methanol, water, alcohol	Cancer cell line	(Anitha et al., 2007)
Leaf	Ethanol, methanol	Tumor growth	(Roy et al., 2007)
Leaf	Ethyl acetate, methanol, water, alcohol	Cancer cell line	(Anitha et al., 2007)
Leaf	Ethyl alcohol	Carcinogenesis	(Subapriya et al., 2006)
Leaf	Ethanol, dimethyl sulfoxide, distilled water	Prostate Cancer	(Kumar et al., 2006b)
Limonoid	EtOAc, anhydrous THF, benzyl amine	Cancer cell line	(Sastry et al., 2006)
Whole tree	Indole butyric acid, benzyladenine, glucose, nitrate, phosphate, inoculum	Cancer cell line	(Prakash and Srivastava, 2006)
Bark, leaf and seed oil	Ethanol, water, hydro-alcoholic, distilled water, dimethyl sulfoxide	Prostate cancer	(Kumar et al., 2006b)
Leaf	Phosphate buffered saline, NLP	Carcinoma	(Haque and Baral, 2006)
Leaf	Ethanol	Cancer cell line	(Govindarajan et al., 2005)
Leaf flower, seed, roots and bark	Ethyl alcohol, distilled water	Anticarcinogenic	(Subapriya et al., 2005)
Leaf	Methanol, distilled water,	Gastric cancer	(Arivazhagan et al., 2004)
Leaf, bark, and seed	Methanol, water	Melanoma, carcinoma, and carcinogenesis	(Baral and Chattopadhyay, 2004)
Leaf, flower, seed, fruit, and roots	Ethyl alcohol	Stomach cancer	(Subapriya and Nagini, 2003)
Limonoids	Methyl and ethyl alcohol	Cancer cell line	(Nanduri et al., 2003)
Leaf	Methanol	Cancer cell line	(Reddy et al., 2003)
Bark, leaf, and flower	Ethanol	Skin carcinogenesis, prostate cancer	(Tepsuwan et al., 2002b)
Leaf, flower, and stem	Dimethyl ether	Liver cancer	(Tepsuwan et al., 2002a)
Seed	Methanol, water, phosphoric acid	Cancer cell line	(Kirakosyan and Kaufman, 2002)
Seed	Methanol	Carcinogenesis	(Nakagawa et al., 2001)

***** DMEM: Dulbecco's Modified Eagle Medium, FBS: Fetal Bovine Serum

Table 2. Summary of studies conducted on neem applications in different anti-cancerous activities

Type of neem part/components	No. of studies	Type of cancer	No. of studies
Leaf	79	Breast cancer	23
Seeds	18	Cancer cell line	21
Flower	10	Prostate cancer	11
Neem Oil	10	Leukemia	8
Bark	10	Liver cancer	6
Root	6	Lung cancer	5
Fruit	6	Carcinogenesis	5
Neem gum	5	Gastric cancer	2
Limonoids	5	Carcinoma	4
Nimbolide	4	Skin cancer	4
Stem	4	Colon cancer	3
Xylem	1	Pancreatic cancer	3
Neem herb	1	Cervical cancer	2
Type of Solvent	**No. of studies**	Oral cancer	2
Ethanol	40	Colorectal cancer	2
Methanol	25	Kidney cancer	2
Distilled water	17	Myriad cancer	1
Ethyl acetate	6		
Alcohol	5		
DMEM	4		
DMBA	4		
MTT	3		
Acetone	3		
Ether	3		
Ethyl alcohol	2		
Hexane	2		
Oxadiazol-2yl-benzothiazole	2		
Glucose	2		
N-nitrosodiethylamine (NDEA)	1		

The most commonly used neem part is leaf (*n* = 79 studies) followed by seed (*n* = 18), flower (*n* = 10), neem oil (*n* = 10), bark (*n* = 10), roots (*n* = 6), and fruit (*n* = 6) (Table 2). Similarly, the most commonly investigated cancer is breast cancer (23) followed by cancer cell line (21), prostate cancer (11), leukemia (8), liver cancer (6), lung cancer (5), carcinogenesis (5), gastric cancer (4), carcinoma (4), skin cancer (4), colon cancer (3), pancreatic cancer (3), cervical cancer (2), oral cancer (2), colorectal cancer (2), kidney cancer (2), and myriad cancer (1). In the same way, most commonly used extract is ethanol (40) followed by methanol (25), distilled water (17), ethyl acetate (6), alcohol (5), DMEM (4), DMBA (4), MTT (3), acetone (3), ether (3), ethyl alcohol (2), hexane (2), glucose (2), Oxadiazol-2yl-benzothiazole (2), and *N*-nitrosodiethylamine (NDEA) (1).

Conclusion and future prospects

In conclusion, neem has an excellent therapeutic potency against different types of cancer. However, its role has not been investigated in bone cancer, retinoblastoma, and oral cancer. Secondly, phytocompounds are mostly secondary metabolites whose size and polarity could not allow them to cross the human blood-brain barrier (BBB), mucosa, blood vessels, endothelial lining, and gastrointestinal tract. Therefore, conjugation and encapsulation of neem components with quantum dots and nanocarriers may be useful to increase their potency in BBB crossing, rate of absorption, and bioefficacy. The potential role of neem may be investigated with nano-conjugate constituents for successful targeted delivery in cancer therapy.

Future studies should investigate the possible role of individual components of neem plants along with and without nanocarriers for targeted delivery and the impact of nano-conjugation on the rate of metabolism and stability. Comparative studies on the role of neem components in different cancers and other infectious diseases using nanocarriers may be helpful for better management of public health issues.

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