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SHORT COMMUNICATIONS

Unveiling the Anticarcinogenic Efficacy of Nirgundi with Emphasis on Oral Cancer: A Comprehensive Review

Ashwini Ravi, Vasanthi V, Vinitha K B, Gopikrishna Padmanabhan, Shruthi Venkatkumar, Rajkumar K

Department of Oral Pathology, SRM Dental College, Bharathi Salai, Chennai, Tamil Nadu, India.

Abstract

India contributes one-third to the global cancer burden, which may be attributed to the fact that the diagnosis is usually made in the advanced stage. Oral cancer is the most common cancer, predominantly caused by the use of tobacco in middle-aged males in India. The concept of chemotherapy initially emerged after systemic mustard gas poisoning damaged the bone marrow and lymphatic tissues. Traditional medicine has been proven to have medicinal value with fewer side effects as compared to allopathic drugs. Phytochemicals have been reported to exert anticancer effects by modulating the immune response and targeting the molecular mechanisms. Few studies have demonstrated that the traditional herbs exert antitumor efficacy by inducing cytotoxicity, promoting apoptosis, regulating epigenetic modifications, inhibiting metastasis along with their antioxidant and anti-inflammatory activity. Nirgundi (Vitex negundo) in various composition has been used in producing commercial pharmaceutical products for the management of both oral health and general health. The present review focuses on the antitumorigenic efficacy of Nirgundi in various cancers, with an emphasis on oral cancer.

Keywords: Nirgundi- Vitex- anticarcinogenic- phytochemical- oral cancer

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Introduction

Cancer is the prime cause of mortality in recent days. Research has documented that genetic and epigenetic changes can cause cancer [1]. Oral cancer is the most common cancer, predominantly caused by the use of tobacco in middle-aged males in India. Oropharyngeal cancer is reported in patients with Human Papilloma virus infection. India contributes one-third to the global cancer burden, which may be attributed to the fact that the diagnosis is usually made in the advanced stage. West Bengal is leading with the highest number of oral cancer cases, and the lowest number of cases are reported from Kerala [2].

Chemotherapeutic drugs either target the enzymes within the cell or change the metabolism of cells. The concept of chemotherapy initially emerged after systemic mustard gas poisoning damaged the bone marrow and lymphatic tissues. Following this, an animal study using nitrogen mustard to target lymphoma was conducted in mice to prove this hypothesis. Later, nitrogen mustard was administered to a 48-year-old patient at Yale University to treat lymphosarcoma, which paved the way for the chemotherapy regimen. Numerous side effects have been reported from the duration and dosage as they harm the healthy cells amidst the cancer cells. Bone marrow suppression and hematologic toxicity are a few major adverse effects of chemotherapy [3].

Vitex negundo, also known as Nirgundi, is a large shrub, and it belongs to the family of Verbenaceae. All the parts of the plant have medicinal uses and are recommended for the treatment purposes of various diseases [4]. According to the literature, only 16 of the 36 species of Vitex namely, V. agnus-castus, V. negundo, V. rotundifolia, V. trifolia, V. gardneriana, V. ferrugenia, V. cannabifolia, V. doniana, V. polygama, V. leucoxylon, V. pinnata, V. scabra, and V. mollis have been evaluated in studies [5]. The chemical composition of different Vitex

Corresponding Author:
Dr. Vasanthi V
Assistant Professor, Department of Oral Pathology, SRM Dental College, Bharathi Salai, Chennai, Tamil Nadu, India.
Email: drvasanthivinoth@gmail.com

species varies, which results in the production of various phytochemicals. Vitex negundo in various composition has been used in producing commercial pharmaceutical products for the management of both oral health and general health. From leaves, seeds, and roots, a number of bioactive substances have been extracted in the form of volatile oils, flavonoids, lignans, iridoids, terpenes, and steroids. Anti-inflammatory, antioxidant, antidiabetic, anticancer, and antibacterial properties are displayed by these bioactive substances. The present review focuses on the antitumorigenic efficacy of Nirgundi in various cancers, with an emphasis on oral cancer.

Cytotoxic and apoptotic efficacy of Nirgundi (Figure 1)

Multiple molecular pathways control the cell cycle, with cyclin dependent kinase (CDK) and cyclin proteins playing a critical role [6]. In HepG2 cells, an ethanolic extract of Vitex has antioxidant and antiproliferative properties [7]. Vitex root extract contains alkaloids, saponins, and flavonoids, which have an anti-filarial effect on Brugia malayi microfilariae [8]. Casticin, a polymethoxy flavone, induces apoptotic cell death through Forkhead box class (FOXO3a) activation. Casticin lowers the levels of expression of FoxM1, survivin, and polo-like kinase 1 (PLK1) while increasing the expression of p27. Casticin used small interfering RNA (siRNA) to silence FOXO3a expression, which increased FoxM1 expression and thus slowed apoptosis [9]. Nishindanol, an isolated diterpene, exhibits cytotoxicity against cancer cell lines by targeting the Hedgehog (Hh) signaling pathway. Vitetrifolin D inhibits Hh-related protein production (PTCH and BCL2). Glioma-associated oncogene (GLI1) binding on its DNA binding domain was disrupted by vitetrifolin D in an electrophoresis mobility shift assay [10]. Cannabifolins A-F, six new polyoxygenated triterpenoids isolated from the leaves of V. negundo var. cannabifolia, were discovered to have anti-inflammatory properties [11]. The anticancer effect of Lignan mixture EVn-50 and pure compound VB1 was studied in cancer cells using an expression-based study of various proteins involved in the cell cycle. Treatment with EVn-50 or VB1 causes G2/M arrest and also increases histone phosphorylation. This study demonstrates a broad-spectrum cytotoxic effect by arresting the cancer cell cycle, which then induces apoptosis [12].

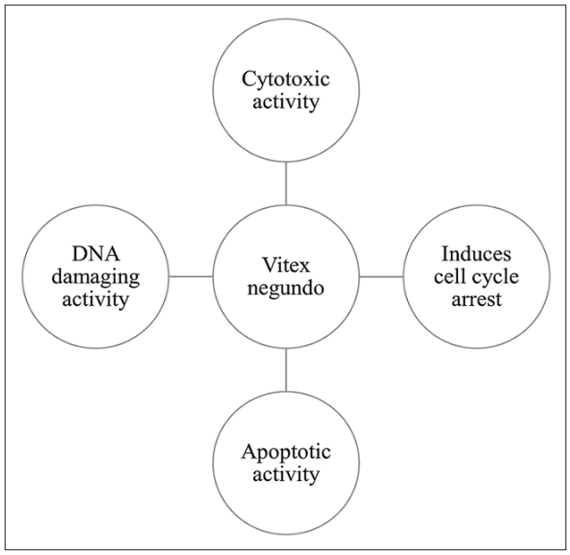

Figure 1. Cytotoxic and apoptotic efficacy of Nirgundi

Hepatocellular cancer

Vitexin derived from the seed of V. negundo shows promise in the treatment of hepatocellular carcinoma. Vitexin inhibits HepG2, Hep3B, and Huh-7 cell proliferation as well as anchorage-dependent and independent HepG2 cell growth by arresting the cell cycle at G1/G0. Vitexin also inhibits the formation of endothelial tubes by decreasing VEGF secretion. In HepG2 cells, vitexin treatment decreased phosphorylation of Akt and FOXO3a. Furthermore, siRNA-mediated Akt1 knockdown increased growth inhibition, whereas siRNA-mediated FOXO3a knockdown decreased expression [13].

Lung cancer

The chloroform-soluble extract of V. negundo leaves isolated the flavone vitexicarpin, which has anticancer properties [14]. 5,3′-Dihydroxy-6,7,4′-trimethoxyflavanone (DHTMF), a constituent of V. rotundifolia, inhibited growth and induced apoptosis by decreasing Bcl-2 expression and increasing Bax level, and cleavage of caspase-3 was found to be dose-dependent in lung carcinoma cells. DHTMF treatment reduced the phosphorylation of Akt and mTOR, vascular endothelial growth factor (VEGF), and hypoxia-inducible factor (HIF-1), all of which are important proteins in angiogenesis. DHTMF also decreased CD34 expression, tube formation, and migration in human umbilical vein endothelial cells (HUVECs). This study emphasizes the role of DHTMF in angiogenesis inhibition as well as apoptosis via the Serine-threonine kinase/mammalian target of Rapamycin (Akt/mTOR) pathway [15].

Choriocarcinoma

Similarly, vitexin compound 2 (VB2) inhibits proliferation and apoptosis in human choriocarcinoma JEG-3 cell lines by suppressing mTOR and 4E-BP1 expression [16]. Evn-50 inhibits cell growth and induces apoptosis in Michigan Cancer Foundation/Tumor-associated Macrophages (MCF-7/TAM) cells by decreasing ERK1/2 phosphorylation in the Mitogen Activated Protein Kinase (MAPK) and Akt signal pathways [17]. Casticin inhibits cyclooxygenase (COX-2) and iNOS expression while targeting and suppressing Nuclear Factor-B (NF-B) and MAPK signaling in lipopolysaccharide-stimulated mouse macrophages. Casticin from V. rotundifolia fruits inhibits nitric oxide and prostaglandin E2 (PGE2), lowers the levels of interleukin (IL-6), and tumor necrosis factor, and thus induces apoptosis. Casticin also inhibits the expression of iNOS and COX-2 while increasing the production of Nuclear factor erythropoietin-2-related factor 2/heme oxygenase 1 (Nrf2/HO-1). Casticin also inhibited NF-B subunit p65 proteins in the nucleus and decreased Akt and MAPK activation [18].

Breast cancer

Studies conducted by Arularasu et al. on induction of apoptosis by the aqueous and ethanolic leaf extract of Vitex negundo L in MCF-7 human breast cancer cells showed that the crude extract of V. negundo possesses anticancer properties, growth inhibition, and apoptosis in cancer cells. The cytotoxic efficacy of V. negundo was determined with the MTT (3-(4, 5-dimethylthiazol-2-yl)-2-5-diphenyltetrazolium bromide) assay. They observed 49.39% growth inhibitory effects on MCF-7 human breast cancer cell at 300 g/ml of aqueous extract and 200 g/ml in case of ethanol extract [19]. The study conducted by Salleh et al. aimed to get preliminary information regarding the anti-proliferative capabilities of cancer cell lines. The study of the proximate analysis on the leaves of Vitex negundo L. (VN) was conducted on six different types of cancer-originating and normal cells, including hormone-dependent breast cancer cell line (MCF-7), non-hormone-dependent breast cancer cell line (MDA-MB-231), ovarian cancer cell line (Caov-3), cervical cancer cell line (HeLa), liver cancer cell line (HepG2), and human foreskin fibroblast cell line, aqueous and organic extracts of the leaves of VN were used to determine its cytotoxic effect (Hs27). Through the use of the colorimetric MTT assay over intervals of 24, 48, and 72 hours, the anti-proliferation properties of these extracts were examined. According to preliminary findings, the methanol extracts significantly affected (p 0.05), and cell lines were more effectively inhibited by the methanol extract on MDA-MB-231 cell lines with an IC50 of 65.38 g/mL [20].

Cervical cancer

Gong et al. isolated rotundifuran from the fruits of V. trifolia and found that the proliferation of cervical cancer cells was suppressed by induction of apoptosis. The study also evaluated the molecular mechanisms associated with the development of cervical cancer. Cyr61 was identified as a potential target as the relative gene expression was 2.963. The study concluded that rotundifuran could upregulate Cyr61 expression and can be considered as a potential therapeutic herb in the management of cervical cancer [21].

Colon cancer

The study conducted by Prabhu et al. demonstrated the efficacy of silver nanoparticles (AgNPs), which are biosynthesized from leaf extracts of V. negundo L. and showed an antitumor effect on the human colon cancer cell line HCT15. The UV-visible spectrum was used to determine the synthesis of the AgNPs, and it was then further examined using energy-dispersive spectroscopy, transmission electron microscopy, X-ray diffraction, and Fourier transform infrared spectroscopy (FTIR). Changes in cell morphology, cell viability, nuclear fragmentation, cell cycle, and comet assay were used to assess the toxicity. Using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) test, the proportion of viable cells was calculated. Findings of the study proved that human colon cancer cell line HCT15 proliferation was suppressed by biosynthesized silver nanoparticles with an IC50 of 20 g/ml during 48 h incubation [22].

Oral cancer

Oncogenic pathways, namely the Mitogen Activated Protein Kinase (MAPK) pathway, the Epidermal Growth Factor Receptor (EGFR) pathway, the Phosphatidyl Inositol 3 Kinase/Mammalian Target of Rapamycin (PI3K/mTOR) pathway, the Janus-kinase/signal transducer and activator of transcription (JAK/STAT) pathway, and suppressor pathways such as the p53/p16/Retinoblastoma pathway are dysregulated in oral carcinogenesis [23-25]. Species of Vitex have been documented to target the PI3K/Akt pathway, JAK/STAT pathway, Wnt/β-catenin pathway, MAPK pathway, and NF-κB pathway. The extracts were also stated to activate caspases, activate pro-apoptotic proteins, inhibit anti-apoptotic proteins, upregulate Cytochrome C, downregulate Matrix Metalloproteinase (MMP-9), induce cell cycle arrest, induce apoptosis, inhibit viability of cells, inhibit epithelial mesenchymal transition, prevent invasion, and prevent migration. Vitexicarpin/Casticin from VN has been proven through in-vitro studies to exert an antitumorigenic effect on breast cancer, bladder cancer, cervical cancer, colon cancer, hepatocellular cancer, leukemia, esophageal cancer, lung cancer, ovarian cancer, prostate cancer, and melanoma [26–27].

The study conducted by Badgujar et al. showed the cytotoxic effect of methanol extracts against the KB oral cancer cell line using an MTT assay. This study examined the effects of methanol extracts of Vitex negundo, Lantana camara, Bauhinia variegata, and Bauhinia racemosa on phytochemicals, antioxidants, and cytotoxic properties. Medicinal plants (V. negundo, L. camara, B. variegata, and B. racemosa) were extracted in methanol using various extraction techniques, and their antioxidant activity was assessed using the 2,2-diphenylpicrylhydrazyl method, the superoxide scavenging method, the chelation of metal ions, and the MTT assay on human cancer cell lines. The hot extraction approach produced the highest yield among the various extraction techniques. The methanol extract of V. negundo has larger amounts of total phenolic and flavonoid compounds. Maximum IC50 values for V. negundo leaves are 350.12 and 73.27 g/ml, respectively [28].

In conclusion, Asian, African, Arabic, Native American, Oceanic, Central, and South American, and other cultures have also developed traditional medicine systems throughout history. A thorough investigation in this area could yield previously unknown medicinal applications for Nirgundi. Ethnobotanical studies open many doors to previously undocumented knowledge. Such surveys have been carried out and reported from various parts of the Indian subcontinent. Nirgundi is mentioned in each of them in a different way in terms of its medicinal use. Similar expeditions in other parts of India and countries where the plant is known to occur would bring to light the unknown aspects of this plant and other such plants that remain unknown to the world's

scientific community.

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