Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 17s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Therapeutic Prospects Of Ocimum Sanctum And Piper Betel Leaves In Cancer Management: A Review

K. Hemanth[1], S. Gejalakshmi[*2]

[*1]Department of Pharmacognosy, Dr.M.G.R. Educational and Research Institute, Velappanchavadi, Chennai-77, India

[2]Department of pharmaceutical chemistry, Faculty of Pharmaceutical Sciences, Dr.M.G.R Educational and Research Institute, Velappanchavadi, Chennai-77, India

***Corresponding author:**

S. Gejalakshmi

Email ID: gejampharm@gmail.com

Cite this paper as: K. Hemanth, S. Gejalakshmi, (2025) Therapeutic Prospects Of Ocimum Sanctum And Piper Betel Leaves In Cancer Management: A Review. *Journal of Neonatal Surgery*, 14 (17s), 929-938.

ABSTRACT

The present review is on the potential therapeutic uses of the main phytoconstituents of Ocimum sanctum species and Piper betel leaves, as an anticancer drugs for a range of cancer forms. Tulsi and betel leaves have been more widely recognized in recent years because of its anticancer qualities. Many plant components from these plants are being tested for possible anticancer benefits in ongoing clinical trials. It was found to be active against some of the cancer cell lines that include those from OSCC (oral squamous cell carcinoma), Ehrlich ascites carcinoma, breast cancer, hepatocellular carcinoma, human ovarian carcinoma (SKOV-3) cancer, human gastric adenocarcinoma (AGS), and human gastric cancer cell lines by various assay methods. The naturally-extracted phytochemicals from both plants exhibit the anticancer activity as well as effects on other forms of cancer cell lines.

Keywords: *Ocimum sanctum, Piper betel, Tulsi, Cancer cell lines*

1. INTRODUCTION

The complex set of disorders referred to as cancer can be defined by uncontrolled cell development and the ability for the disease to invade or spread to additional body parts. (metastasis). It arises due to genetic mutations, environmental factors, and lifestyle choices. Colorectal, prostate, lung, breast, and skin cancers comprise some of the common varieties of cancer. Despite advances in modern medicine, cancer continues to be the primary cause of death rates globally. Surgery, radiation therapy, chemotherapy, immunotherapy, and targeted therapy comprise some of the most common cancer therapies. While these methods have improved survival rates, they often come with significant side effects and limitations, such as drug resistance and damage to healthy tissues. Rising appreciation for complementary and alternative therapies, such as using the benefits of traditional medicinal plants is the outcome [1].

Plant-based traditional medicine has been employed for centuries to treat various ailments, including cancer. These kinds of plants possess a great deal of biologically active molecules which that exhibit anticancer properties via a range of techniques, including antioxidant activity, altered cell signaling pathways, apoptosis activation, and prevention of metastasis and angiogenesis. Some of the traditional plants includes Ocimum sanctum and Piper betle[2].

Ocimum sanctum is an aromatic herb of the Lamiaceae family, frequently referred to as holy basil or tulsi. It originates in India and have been revered for its medicinal properties in Ayurvedic medicine. O. sanctum has properties that are anti-inflammatory, antibacterial, anti-tumor, antidiabetic, hepatoprotective, arthritis activities etc. Present review explores the potential anticancer properties of Ocimum sanctum, focusing on its bioactive compounds, mechanisms of action, and anticancer studies [3].

Piper betle, commonly known as betel leaf, is a plant that is a member of the family Piperaceae.. Betel leaf has long been consumed for its stimulant and digestive advantages. It is widely used in Southeast Asia for therapeutic reasons. Antioxidant, anti-inflammatory, antibacterial, anticancer, antiulcer, antidiabetic, hepatoprotective, and immunomodulatory properties have been shown by this plant [4]. Recent scientific research has highlighted its potential anticancer properties, making it a subject of interest in cancer research.

1.1. Plant Profile-

a. Ocimum sanctum

Family- Lamiaceae

Genus- Ocimum

Species- Ocimum sanctum Linn.

Common Names- Holy Basil, Tulsi Plant

Description: Ocimum sanctum is a small, aromatic perennial herb or shrub that can grow up to 1 meter in height mentioned in **Figure 1a**. The plant has quadrangular, purplish or green stems with simple, opposite leaves that are ovate and slightly toothed. The flowers are small, purple or white, and arranged in racemes [5].

Geographical Distribution- Native to India, holy basil is grown extensively throughout Southeast Asia, the Middle East, and some parts of Africa. It thrives in tropical and subtropical climates and can be found in gardens and wild habitats in these regions.

Chemical constituents- Bioactive Constituents in Ocimum sanctum includes eugenol (a potential therapeutic agent against various types of cancers), ursolic acid, rosmarinic acid, apigenin and luteolin, ocimumosides and ocimarin mentioned in **Figure 2a**. The anticancer effects of Ocimum sanctum are attributed to several mechanisms.

Brief about common Ocimum species

Around the world, traditional medical systems incorporate ocimum, a highly significant medicinal plant. Though it is known as "Tulsi" in India, it is frequently referred to as "basil." Basil is significant in both religion and medicine. As a member of the Nepetoideae subfamily, Ocimum is a member of the Lamiaceae family, which also includes plants that have powerful aroma and essential oils that contain monoterpenes, sesquiterpenes, and phenylpropanoids. Their leaves have properties that include being delicious, ophthalmic, fragrant, thermogenic, acrid, antiviral, and insecticidal. The descriptions of a few common Ocimum species are shown here, along with their Indian names [6].

(a) **(b)**

Figure 1. a) Ocimum sanctum plant and leaves, b) Piper betle plant and leaves

Ocimum sanctum (Rama Tulsi): The plant resists winters better than other varieties and has leaves that are a pure green color. More fertilizer and irrigation are also necessary. An aromatic herb of great repute, the Queen of Herbs is a common sight in nearly every surrounding of Indian houses. Location: Under bright sun outside. Watering: daily, except throughout the winter. 15 to 40º C is the temperature range.

Ocimum tenuiflorum (Krishna Tulsi): The plant has purple stems with strongly aromatic leaves and purple-fringed leaves, making it more advantageous medicinally than other species. These are the following growth tendencies: Location: Outside in full sun light. With the exception of the winter. The range of temperatures is 20 to 45 ºC. Every day, watering is done.

Ocimum basilicum (Ban tulsi): It will reach a maximum height of 12 to 51 inches, or 30 to 130 cm. Its smooth, light-green leaves have a length of 3 to 11 cm and a width of 1 to 6 cm. The tiny white flowers are clustered in a spike at the end of the

stem. Basil grows best in hot, dry regions because it is a cold-sensitive plant. When there's a chance of frost, it functions as an annual.

Ocimum tenuiflorum (Amrita Tulsi): This fragrant perennial kind of holy basil is grown less commonly in India. The following growth tendencies are listed: Location: outside in the open, in between 15 and 40 ºC with light to full sun. Watering every day, except in the winter.

Ocimum gratissimum (Vana Tulsi): Native to India, holy basil is a woody, aromatic perennial herb. The following are its growth tendencies: With full sun and temperatures ranging from 15 to 40 °C, Place: Outside, Watering is done every day, except in the winter [7].

b. Piper betle

Family: Piperaceae

Genus: Piper

Species: Piper betle Linn.

Common Names: Betel leaf, Paan

Description: Piper betle is a perennial, dioecious, and semi-woody climber that can grow to a height of up to 15 meters when supported by a tree or other structures. The plant has heart-shaped, glossy green leaves that are alternately arranged on the stem. The leaves are aromatic and have a distinct pungent taste illustrated in **Figure 1b**.

Geographical Distribution- Most of Southeast Asia's tropical and subtropical regions—including Bangladesh, India, Sri Lanka, Thailand, and Malaysia—are home to piper betle cultivation. It prefers hot and humid climates and grows well in well-drained, fertile soils[8].

Chemical constituents- The leaves of piper betle contain a range of substances that are bioactive that contribute to its medicinal properties are phenols (hydroxychavicol, eugenol, chavibetol) alkaloids (arecoline, guvacoline) flavonoids (catechin, quercetin), tannins (tannic acid) and essential oils (chavicol, chavibetol, eugenol) mentioned in **Figure 2b** [9].

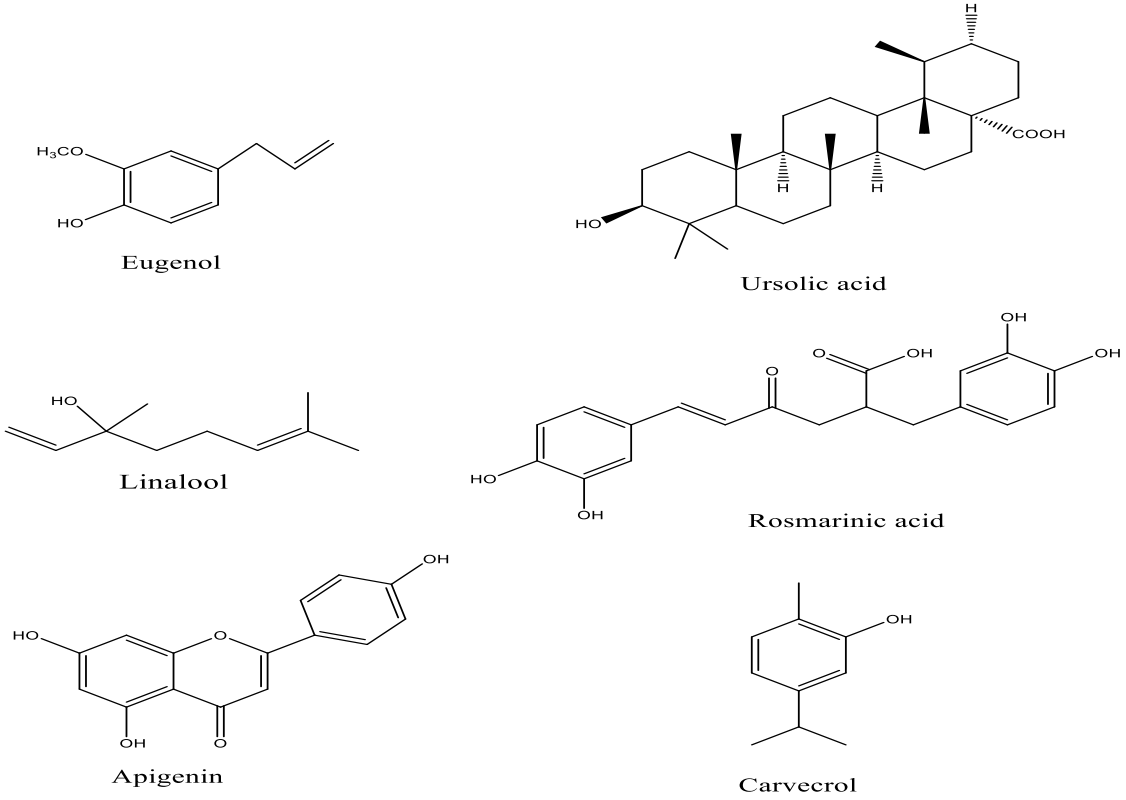

Figure 2a. Chemical structures of phytoconstituents of *Ocimum sanctum*

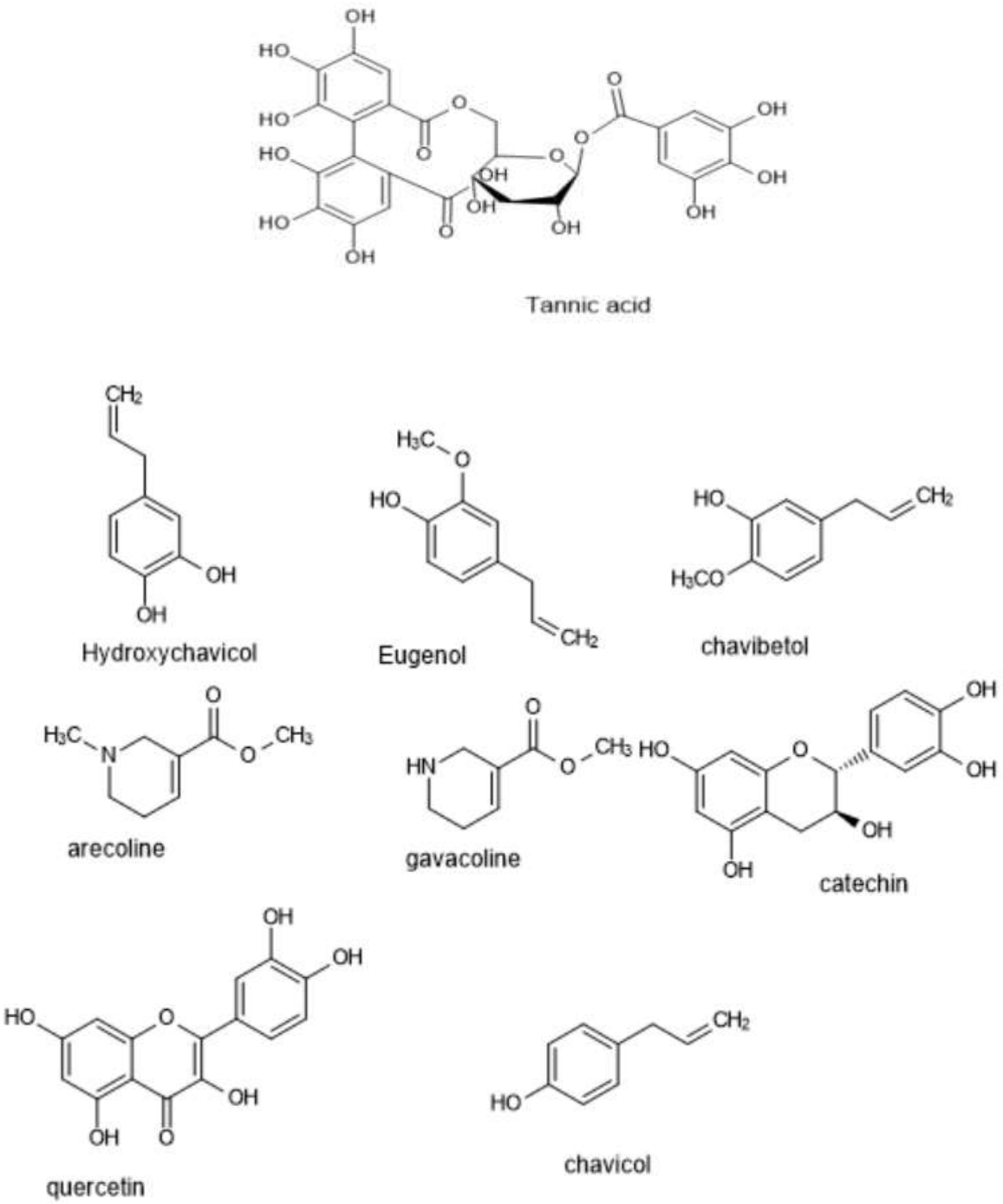

Figure 2b. Chemical structures of phytoconstituents of *Piper betle*

2. ANTICANCER EFFECTS OF OCIMUM SPECIES

2.1. Ocimum sanctum

Prachi Shivpuje et al., 2021 using both dark (Krishna Tulsi) and light (Rama Tulsi) leaf extracts, the antiproliferative and cytotoxic effects on oral cancer cell lines (KB cells) were assessed using the MTT assay. The MTT Assay was utilized to determine the cell survival of the KB mouth cell line that was subjected to both dry and watery extracts that included five different doses of Tulsi leaves. The IC50 values for both extracts were calculated. The optimized IC50 values of the extract in KB oral cancer cells are 20 µg/ml for group III (aqueous extract with light leaves) and 10 µg/ml for group IV (aqueous extract with dark leaves) for a 48-hour period. Of the four extracts that were examined, two showed encouraging activity, as

shown by IC_{50} values that were less than 50 µg/ml. The aqueous extract exhibited the most cytotoxic effect, lysing groups of light and dark leaves with an IC_{50} value of 10 and 20 µg/ml. When compared to the dry extract, it was discovered that the aqueous solution of Tulsi (both the light and dark leaves) is highly beneficial. The highest efficacious dosage involved 20 µg/ml of light leaf aqueous extract and 10 µg/ml of dark leaf aqueous extract [10].

Kusumawadee Utispan et al., (2023) carried out synthesizing the Ocimum sanctum leaf ethanolic extract (EEOS). HNSCC cell lines that were isogenic primary (HN18/HN30) and metastatic (HN17/HN31) were utilized. The cytotoxic doses were determined using the MTT test on HNSCC cell lines following a 72-hour exposure to varying concentrations (0.1–0.8 mg/ml) of EEOS. A fluorometric approach was employed to ascertain the quantities of malondialdehyde and reactive oxygen species (ROS) in order to assess the impact of EEOS on HNSCC cells. Using flow cytometry, the effects of EEOS on apoptosis, DNA damage, and the cell cycle in HNSCC cells were evaluated. Caspases-3 and -9 were quantified by ELISA in the HNSCC cells treated with EEOS. The chemical components of EEOS were identified by mass spectrometry, time of flight mass spectrometry, electrospray ionization, and high-performance liquid chromatography. The EEOS cytotoxicity was found to be susceptible to the HN18, HN17, HN30, and HN31 cells at low dosages of 0.1, 0.3, 0.2, and 0.2 mg/ml respectively. The HN18 and HN17 cells' ROS levels significantly increased after receiving EEOS treatment. Moreover, EEOS significantly elevated malondialdehyde levels in HN18 and HN31 cells. Moreover, EEOS interrupted the cell cycle in HN30 and HN31 cells and significantly enhanced DNA damage and mortality in HN18, HN30, and HN31 cells. In HN18 cells, EEOS preferentially elevated caspase-9. On the other hand, in the HN17 cells treated with EEOS, caspase 3 was triggered without apoptosis. Based on the total data, it was shown that the type of HNSCC cell impacted by EEOS produced distinct effects[11].

A.M. Luke et al., (2021) carried out the impact of Ocimum sanctum leaf extract, both moist and dry, on the oral squamous cell carcinoma (OSCC) cell line Ca9-22. For this, the Ca9-22 cell line was grown and maintained. After a day, Ocimum sanctum plant extract, both dry and watery, was applied to the cells. The malignant cells' vitality was evaluated using the 3-(4, 5-dimethythiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) assay and the neutral red uptake (NRU) assay. The lethal concentration50 (LC50), lethal concentration25 (LC25), minimum inhibitory concentrations (MIC), and highest permissive concentration (HPC) were all calculated using the probit computational technique. The plant extract in the experiment had a MIC of 5 mg/L and an HPC of 30 mg/L in an aqueous environment. The HPC for the MTT and NRU assays was 35 mg/L, while the MIC for the dry extract was 5 mg/L. The LC values for the dry extract in the MTT assay are 12.58 (LC25), 20.89 (LC50), and 29.51 mg/L (LC75), whereas for the aqueous extract they are 7.41 (LC25), 14.79 (LC50), and 26.91 mg/L (LC75). The plant's LC values for the aqueous extract were 10.23 (LC25), 14.79 (LC50), and 20.89 mg/L (LC75), and for the dry extract they were 16.59 (LC25), 23.44 (LC50), and 30.19 mg/L (LC75). A prior study established that ocimum sanctum have anti-cancerous potential [12].

2.2. Ocimum basilicum

Hanan Anwar Aly TAIE et al. (2010) isolated essential oils by hydro-distillation and phytochemicals from ethanolic extract of Ocimum basilicum. Ehrlich ascites carcinoma cell lines are utilized, and female Swiss albino mice weighing 22–25 g and aged 8–10 weeks are injected with ethanolic extracts containing 1250, 1500, 1750, or 2000 ppm and oil extracted from them (0.04, 0.06, 0.08, and 0.10 mg). Ehrlich Carcinoma Cells are contrasted with untreated cells. The quantity of dead cells rose together with the amounts of oil and (OEE). The largest percentage of dead cells with ethanolic extract (59.83% and 59.37%, respectively) were found in treatments with 50% compost and bio and 75% compost and bio. Ocimum oil had a greater reducing effect on viability, and the same two treatments showed the greatest viability inhibition. The percentage of dead cells was 81.05% with an IC50 of 0.0616 ppm for 50% compost plus biofertilizer and 77.89% with an IC50 of 0.0642 ppm for 75% compost plus biofertilizer, respectively [13].

T. A. Aburjai et al., (2019) extracted essential oils from Ocimum basilicum "Cinnamon" by hydrodistillation. Gas chromatography-mass spectroscopy had been employed for the analysis and identification of the chemical components. There were 31 components found, accounting for 97-80% of the essential oil. The principal compounds found in the main chemical components were hinesol, trans-α-bergamotene, eucalyptol, linalool, and eugenolThree distinct cancer cell lines: MCF7 (breast cancer), MDA-MB-231 (triple-negative breast cancer cell line), and U-87 MG (glioblastoma). The MTT assay was used to determine whether any viable cells remained after the cells were exposed to several doses of essential oil for a duration of 72 hours. To calculate the inhibitory concentrations 50 (IC50), three independent trials were conducted and the percentage of viable cells that survived were used. The IC50 values on MDA-MB-231 were 432.3±32.2 µg/ml, 320.4±23.2 µg/ml on MCF7, and 431.2±15.3 µg/ml on U-87 MG. Linalool, eugenol, and eucalyptol, three essential oils from Ocimum basilicum, exhibited potent anticancer action against a various forms of cancerous cell [14].

Doguer et al., (2021) reported that Aqueous extract from dried leaves of Ocimum basilicum, or purple basil (PB), was blended to sirkencubin syrup (SC), a traditional Turkish beverage. Studies were carried out on human colon cancer cells (Caco-2). Using the Cell Counting Kit-8 (CCK-8) assay, the effects of SC, PBS, and UT-PBS (ultrasound-treated PBS) on the viability of human colon cancer cells (Caco-2) were evaluated. The cells were treated by adding varying amounts of SC, PBS, and UT-PBS (15–40 µL) to 100 µL of fresh medium each well. The results revealed that the IC50 values for SC, PBS, and UT-PBS were, respectively, 288.1, 239.8, and 276.6 µl/ml. When it came to anticancer action against (Caco-2) PBS demonstrated

superior results. The conclusion is that functional beverages could become a useful treatment tool to slow the spread of some diseases[15].

Hanachi et al., (2021) carried the Two herbal extracts were tested using the MTT test on human gastric adenocarcinoma (AGS) and human ovarian carcinoma (SKOV-3) cancer cell lines to determine their anticancer properties. Ocimum basilicum, or sweet basil, and Impatiens walleriana, or busy Lizzie, are the names of the extracts. The results of the investigation indicated that O. basilicum was effective against SKOV-3 at a dosage of 5 mg/mL. 91% of the growth was observed to be considerably inhibited and 63.58% more cell death occurred at the half-maximal inhibitory dose (IC50) of 0.91 ± 0.11 mg/mL. On the other hand, 5 mg/mL of I. walleriana boosted the growth inhibition of AGS by 89% and increased cell death by 93.29%, with an IC50 of 2.5 ± 0.21 mg/mL. A flow cytometry analysis revealed that the main reason both extracts caused apoptosis was the presence of bioactive substances like caffeic acid. Strong anticancer agent caffeic acid is known to prevent DNA synthesis. Furthermore, both extracts contain significant amounts of carotenoids and anthocyanins, with I. More anthocyanins are found in walleriana. These plant extracts, Ocimum basilicum being a more popular option, offer extensive therapeutic effects in medicine [16].

2.3. Ocimum gratissimum

Nangia-Makker et al., (2013) reported the growth of the tumor was slowed down when MCF10ADCIS.com cells put into female nude mice were treated with an aqueous extract of O. gratissimum, often known as holy basil. The delayed growth of the tumor was hypothesized by the authors to be caused by suppression of chemotaxis, chemoinvasion, and MMP-2 and MMP-9 enzymatic activity. It is significant to remember that MMP-2/-9 action entails encouraging cell invasion, angiogenesis, and proliferation; as a result, altering its enzyme activity will alter how cells behavior. Considering that carcinoma is characterized by in situ basement membrane production, which exhibits a delay in creation, allows one to evaluate MMP-2/-9 activity. This implies that by suppressing tumor growth, the O. gratissimum extract may change it. It is concluded that one of the anticipated effects of Ocimum species is the reduction of cancer cell proliferation [17].

2.4. Ocimum tenuiflorum

Wongwarut Boonyanugomol et al., 2021 examined by employing a hydro-distillation process, the anti-cancer activity of Ocimum tenuiflorum essential oil (OTEO) from leaves in a human gastric cancer cell line (AGS). Following OTEO therapy, AGS cell viability was evaluated using an MTT assay and the inhibition of metastasis was measured using cell invasion and migration assays. The expression of genes associated with apoptosis in treated AGS cells was measured by qRT-PCR. Results: In a dose-dependent manner, OTEO significantly reduced AGS cell viability and successfully stopped cell migration and invasion (IC50 163.42 µg/mL). Morphological research revealed that OTEO produced the morphologies of cell shrinkage, chromatin condensation, and fragmentation, which are frequently linked to apoptotic cell death. Pro-apoptotic genes (TP53, BAX, and BAK) were up-regulated during OTEO therapy, whereas anti-apoptotic genes (BCL-2 and BCL-xL) significantly down-regulated. Moreover, OTEO-exposed AGS cells showed a notable increase of CASP8, CASP9, and CASP3 gene expression. Using GC-MS analysis, it was demonstrated that caryophyllene (25.85%) and α-pinene (11.66%) were the two primary components of OTEO. According to the results of this in vitro investigation, OTEO may have significant anti-gastric cancer activity and may trigger apoptosis in AGS cells for the first time via both intrinsic and extrinsic mechanisms [18].

Indrayudha et al., 2021 has carried out a study to ascertain the T47D cancer cells-killing potential of an ethanolic extract mixture combining Ocimum tenuiflorum Linn. and Cinnamomum burmannii. The basil leaves and the bark of the cinnamon tree were extracted using ethylene 96%. Whereas cinnamon bark was extracted by sonication, basil leaves were extracted by maceration. The cinnamon bark was qualitatively examined in test tubes, and the basil leaves were analyzed using thin layer chromatography with silica gel GF254 serving as the stationary phase and n-hexane: ethyl acetate (7.5: 2.5) serving as the mobile phase. An MTT assay was used for the cytotoxicity test. The results of the qualitative tests showed that cinnamon bark contains phenols, quinones, and saponins, whereas basil leaves include alkaloids, flavonoids, phenols, and terpenoids. The IC50 value of Ocimum tenuiflorum Linn. was reported to be 267.88 µg/mL, but the IC50 value of Cinnamomum burmannii was found to be 465.21 µg/mL. The combinational cytotoxic test findings were assessed using the combination index (CI) value. The ethanolic extracts of Cinnamomum (500 µg/mL) and Ocimum (500 and 50 µg/mL) combined had synergistic effects, according to the results of the combinational cytotoxic test [19].

Sharma et al. 2016 reported that a high ratio of terpenes and phenylpropanoids, as well as a few minor flavonoids with proven antioxidant and anticancer properties including orientin and vicenin, make up the volatile oil's extremely complex chemical makeup. Because of its anti-proliferative effect on the human liver cancer cell line HepG2, orphanin has been described as a possible anticancer drug; nevertheless, the exact mechanism of action of orphanin remains unclear. In order to identify potential anticancer agents, an in-silico structure-activity relationship study on orientin was conducted. Additionally, a pharmacophore mapping and QSAR model were constructed to screen out structurally similar analogues from the Discovery Studio (DSv3.5, Accelrys, USA) chemical database. For in vitro testing, fenofibryl glucuronide was chosen as the equivalent. The binding affinity and mode of action of orientin and its counterpart were investigated by means of molecular docking studies on quinone oxidoreductase, a possible flavonoid target. Contrary to expectations, in vitro data showed only 41% cell

death at 202.389 µM concentration (at 96 hours). As a result, it was found that fenofibryl glucuronide, the selected orientin analogue, was non-cytotoxic/non-anti-carcinogenic in HepG2 human cancer cells after exposure for up to 96 hours at dosages of up to 100 µg/ml (202.389 µM). It was determined that pure molecules of orientin and its analog fenofibryl glucuronide exhibited extremely low cytotoxicity or no effect on the HepG2 liver cancer cell line [20].

3. ANTICANCER EFFECT OF PIPER BETLE

Ananda Guha Majumdara et al., 2019 investigated the way Hydroxychavicol (HC), an abundantly available, naturally occurring allylarene found in Piper betle leaves, affected pancreatic cancer cells. According to the research, HC prevents pancreatic cancer cells from proliferating and from going through the epithelial-mesenchymal transition (EMT). As demonstrated by H2AX, 53BP1 induction, and comet test, hydroxychavicol causes DNA damage that ultimately leads to apoptosis and a catastrophic mitotic event. Apoptosis caused by hydroxychavicol is caspase-mediated and JNK pathway-dependent. In healthy cells, cyclin B1 and CDC2 work cooperatively to overcome the G2/M checkpoint, and as a result of their suppression, HC induces a severe G2/M cell cycle arrest. By broadly suppressing genes involved in epithelial-mesenchymal transition, HC also prevents pancreatic cancer cells from migrating and invading. At least 14 distinct genes were found to express differently in pancreatic cancer cells after HC therapy, according to a quantitative real-time PCR-based array. These results highlight HC's enormous potential as a pancreatic cancer anticancer medication [21].

Pei-Fang Wu et al., 2014 examined the utilization of p53 null Hep3B cells (hepatocellular carcinoma) in the xenograft model and the cell model to evaluate the anti-tumor efficacy of Piper betle leaves (PBLs). The results showed a dose- and time-dependent increase in cell toxicity caused by PBLs (0.1 to 1 mg mL−1). Using flow cytometry and western blot analysis, the basic processes were illustrated. It was found that PBLs elevated the expressions of ATM, cAbl, and p73 along with the JNK and p38 pathways, resulting in cell cycle arrest and mitochondria-dependent apoptosis. Furthermore, by triggering the MAPK-p73 pathway, PBLs stopped tumors from growing in rats carrying the Hep3B gene. By demonstrating their anti-tumor activity in vitro and in vivo by targeting the p73 pathway, the research findings indicated the application of PBLs as a novel chemopreventive medication for the treatment of human hepatocellular carcinoma (HCC) in the future [22].

Sadiya R Veettil et al., 2020 assessed the piper betle aqueous extract for anti-cancer properties on KB-cancer cell lines. Piper betle leaf extract was added to the cancer cell lines at progressively higher concentrations (6.25, 12, 25, 50 and 100µg/ml). The cytotoxic effect of the extract on the cells was examined by verifying for any discernible changes in the morphology of the cells under an inverted phase contrast microscope and by calculating the percentage of viable cells using the MTT test method. The extract treatment caused the cancer cells to undergo significant morphological alterations that were suggestive of apoptosis and cell cytotoxicity. The results of the MTT experiment demonstrated that when the concentration of the extract rose, the proportion of viable cancer cells decreased. At the highest concentration of 100µg/ml of Piper betle leaf extract, the percentage of live cells was measured at 43.42%, suggesting that the extract exhibits anticancer effects. Chemotherapeutic drugs could be made using piper betle leaf's cytotoxic potential; however, more in-depth research on the leaf's anticancer properties and the extraction of its constituent components are required to validate the leaf's value in cancer therapy [23].

Muskan Tamboli et al., 2024 studied the aqueous extract of Piper betle leaves' anticancer properties in vitro against the human oral cell line SCC 29B. The Brine Shrimp Lethality assay model was used to test for anti-cancer activities because it is rapid, inexpensive, and simple to use. Piper betel L. extracts revealed LC50 values of 10g/ml, 20g/ml, 30g/ml, 40g/ml, and 50g/ml, which indicated their effectiveness against brine shrimp. In the Brine Shrimp experiment, the hydroalcoholic extract of Piper betel L. leaves showed an LC50 value of 24 µg/ml, while the standard group with 5-FU showed an LC50 value of 54 µg/ml [24].

V. Radhalakshmi et al., 2024 investigated how HT29 human colorectal cancer cells were influenced by betel leaf (Piper betel) ethyl alcohol extract. Strong antioxidants and antibacterial agents, flavonoids and phenolic chemicals make up the extract. Following exposure to an 80% ethyl alcohol extract, human colon cancer cells underwent apoptotic cell death, fragmentation, upregulation of p53 and downregulation of Bcl-XL expression. The results demonstrated a dose-dependent decrease in cell proliferation. The findings demonstrate how treatment with ethanolic betel leaf extracts activates the mitochondrial apoptotic pathway. Treatment-induced DNA damage resulted in Apoptosis and stoppage of the G1 cell cycle. The low cytotoxicity and anticarcinogenic qualities of betel leaf ethyl alcohol extracts on HT29 indicate its efficacy as a functional food or food supplement and suggest a different strategy for treating human colon cancer (combination treatment) [25].

Supavadee Boontha et al., 2019 developed transdermal patches incorporating the extract and investigating the piper betle leaf extract's anticancer and antioxidant qualities in MCF-7 human breast cancer cells. The 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay was performed to quantify the antioxidant ability of the macerated P. betle leaf extract. Sulforhodamine B (SRB) and wound healing tests were used to determine the cytotoxicity and reduction of cell migration, respectively, in order to assess the anticancer activity of MCF-7 cells. Transdermal patches were made via casting, and the mechanical properties and external appearance of the patches were evaluated before to and following a stability test. The study's findings indicate that P. betle leaf extract may have anti-breast cancer effects. It is possible to effectively develop a transdermal patch that contains 0.03 percent of the extract to treat breast cancer. With a half-maximal inhibitory concentration

(IC50) of 30.0 ± 0.1 µg/mL, the extract showed antioxidant activity. Additionally, at a dose of 25 µg/mL, it strongly inhibited the migration of MCF-7 cells and demonstrated cytotoxicity with an IC50 of 114.3 ± 14.9 µg/mL. Patch base formulations with 4.2% pectin, 0.4% hydroxyl propyl methylcellulose (HPMC), 0.4% polyvinyl pyrrolidine K-90 (PVP-K90), and 3% propylene glycol (PG) were chosen for integration into the extract based on these desired qualities [26].

Aiysvariyah Rajedadram et al., 2021 studied the antiproliferative mechanism of hydroxychavicol (HC, an extract from Piper betle). The effects on the cell cycle, apoptosis, and expression of c-Jun N-terminal kinase (JNK) and P38 mitogen-activated protein kinase (MAPK) in HT-29 colon cancer cells were examined. The separation of HC from Piper betle leaf (PBL) was verified by nuclear magnetic resonance (NMR), gas chromatography-mass spectrometry (GC-MS), and high-performance liquid chromatography (HPLC). The cytotoxic effects of 5-fluorouracil (5-FU), PBL water extract, and HC were evaluated on HT-29 cells after 24, 48, and 72 hours of therapy. For a maximum of thirty hours, the effects of 5-FU and HC treatments on apoptosis and the cell cycle were investigated. The expression of phosphorylated JNK (pJNK) and P38 (pP38) MAPKs varied for up to eighteen hours. PBL aqueous extract (380 µg/mL) and HC (30 µg/mL) attained their half maximum inhibitory concentration (IC50) values in 24 hours, whereas 5-FU (50 µmol/L) took 72 hours to reach its IC50 value. Cell cycle arrest at the G0/G1 phase was seen in HC-treated cells beginning at 12 hours. When comparing HC-treated cells to 5-FU-treated cells, there was a statistically significant increase in apoptotic cell death ($P<0.05$). pJNK and pP38 MAPK were produced in large amounts by HC-treated cells at 12 hours, but not by 5-FU-treated HT-29 cells ($P<0.05$). It is shown that HC induces HT-29 cells to go through apoptosis and enter cell cycle arrest; P38 MAPK and JNK could potentially be involved in these mechanisms [27].

Sushma Reddy Gundala et al., 2014 carried out a study by increasing the levels of ROS in cancer cells above the lethal threshold, dietary phytochemicals, which are good ROS-modulating agents, have been shown to preferentially kill cancer cells while sparing healthy cells. Here, we demonstrate how the production of reactive oxygen species during the extraction and purification of hydroxychavicol (HC) from Piper betel leaves significantly inhibits the growth and multiplication of human prostate cancer cells, or PC-3 cells. HC impacted the dynamics and development of the cell cycle, reduced clonogenicity, and mediated cytotoxicity by inducing DNA damage from ROS that activated numerous pro-apoptotic markers. Moreover, the introduction of acidic vesicular organelles and increased expression of beclin-1 and LC3-IIb, two autophagic markers, suggested a novel autophagic response brought on by HC treatment. Surprisingly, quenching ROS with the antioxidant tiron dramatically prevented caspase-3 downregulation and HC-induced suppression of cell growth, demonstrating the crucial role ROS play in causing cell death. The collapse of mitochondrial transmembrane potential in PC-3 cells caused by HC further illustrated the link between ROS generation and the stimulation of caspase-mediated apoptosis. Using quantitative tumor volume measurements and non-invasive real-time bioluminescent imaging, we found that oral therapy with 150 mg/kg bw HC every day resulted in a notable 72% suppression of prostate tumor xenografts. HC employing quantitative tumor volume measurements with non-invasive, real-time bioluminescent imaging. HC was well tolerated and did not exhibit any toxicity at this dosage. This is the first study to demonstrate the in vivo and in vitro efficacy of HC against prostate cancer. Its specific prooxidant activity, which destroys cancer cells, could be the cause of this. In any case, it provides compelling evidence for more preclinical studies to validate HC's possible benefits in the management of prostate cancer [28].

4. CONCLUSION

Ocimum sanctum and Piper betel are the traditional plants that their leaves extract contains various chemical constituents that exhibits the anticancer properties and show effects on various forms of cancereous cell lines. This review led to the conclusion that its extracts specifically prevented growth of Oral cell lines, Oral squamous cell carcinoma (OSCC), Human gastric adenocarcinoma (AGS) and human ovarian carcinoma (SKOV-3) cancers, Ehrlich ascites carcinoma, hepatocellular carcinoma, human gastric cancer cell line, and pancreatic cell lines. The phytochemicals extracted naturally from both the plants show this anticancer effect and they may also have effect on other types of cancers which were never researched before. This can be demonstrated by further investigation.

REFERENCES

[1] Baliga, M. S., & Rao, S. (2010). Radioprotective potential of Ocimum sanctum Linn. and its phytochemicals. Pharmacological Research, 62(3), 322-330.

[2] Prakash, P., & Gupta, N. (2005). Therapeutic uses of Ocimum sanctum Linn (Tulsi) with a note on eugenol and its pharmacological actions: A short review. Indian Journal of Physiology and Pharmacology, 49(2), 125-131.

[3] 3.Mondal, S., Mirdha, B. R., & Mahapatra, S. C. (2009). The science behind sacredness of Tulsi (Ocimum sanctum Linn.). Indian Journal of Physiology and Pharmacology, 53(4), 291-306.

[4] Badwaik, R., Biswas, D., & Haldar, P. K. (2021). Cytotoxicity and apoptotic induction in breast cancer cells by Ocimum sanctum Linn. leaf extract. *Journal of Cancer Research and Therapeutics, 17*(1), 146-153.

[5] Sharma, P., Yadav, S., & Rai, V. K. (2021). Anticancer potential of Ocimum sanctum and its bioactive

constituents: In vitro and in vivo studies. *Journal of Ethnopharmacology, 271*, 113-119.

[6] Gupta, S., & Chauhan, R. (2022). Anti-metastatic effect of Ocimum sanctum in murine lung cancer model. *Journal of Experimental Therapeutics and Oncology, 14*(2), 101-110.

[7] Singh, N., & Sharma, V. (2021). Quality of life improvement in advanced cancer patients treated with Ocimum sanctum: A pilot study. *Integrative Cancer Therapies, 20*, 1-9.

[8] Verma, P., & Kumar, A. (2021). Synergistic effects of Ocimum sanctum and conventional chemotherapy in cancer treatment: A clinical perspective. *Cancer Medicine, 10*(15), 5213-5223.

[9] Pattanayak, P., Behera, P., Das, D., & Panda, S. K. (2010). Ocimum sanctum Linn. A reservoir plant for therapeutic applications: An overview. Pharmacognosy Reviews, 4(7), 95-105.

[10] Prachi Shivpuje, Renuka Ammanangi, Kishore Bhat, Sandeep Katt. Effect of Ocimum sanctum on Oral Cancer Cell Line: An in vitro Study, The Journal of Contemporary Dental Practice, September 2015;16(9):709-714.

[11] Kusumawadee Utispan, Sittichai Koontongkaew, Nattisa Niyomtham, Boon-ek Yingyongnarongkul. Ethanolic extract of Ocimum sanctum leaf modulates oxidative stress, cell cycle and apoptosis in head and neck cancer cell lines, Heliyon 9 (2023) e15518.

[12] A.M. Luke, R. Patnaik, S.T. Kuriadom, M. Jaber , S. Mathew. An in vitro study of Ocimum sanctum as a chemotherapeutic agent on oral cancer cell-line, Saudi Journal of Biological Sciences, 28 (2021) 887–890.

[13] Taie, H.A.A.; Salama, Z.A.-E.R.; Radwan, S. Potential Activity of Basil Plants as a Source of Antioxidants and Anticancer Agents as Affected by Organic and Bio-organic Fertilization. Not. Bot. Horti Agrobot. Cluj Napoca 2010, 38, 119–127.

[14] Aburjai, T.A.; Mansi, K.; Azzam, H.; Alqudah, D.A.; Alshaer, W.; Abuirjei, M. Chemical Compositions and Anticancer Potential of Essential Oil from Greenhouse-Cultivated Ocimum basilicum Leaves. Indian J. Pharm. Sci. 2020, 82, 179–184.

[15] Doguer, C.; Yıkmı¸s, S.; Levent, O.; Turkol, M. Anticancer effects of enrichment in the bioactive components of the functional beverage of Turkish gastronomy by supplementation with purple basil (Ocimum basilicum L.) and the ultrasound treatment. J. Food Process. Preserv. 2021, 45, e15436.

[16] Hanachi, P.; Fakhrnezhad, F.R.; Zarringhalami, R.; Orhan, I.E. Cytotoxicity of Ocimum basilicum and Impatiens walleriana Extracts on AGS and SKOV-3 Cancer Cell Lines by Flow Cytometry Analysis. Int. J. Cancer Manag. 2021, 14, e102610

[17] Nangia-Makker, P.; Raz, T.; Tait, L.; Shekhar, M.P.V.; Li, H.; Balan, V.; Makker, H.; Fridman, R.; Maddipati, K.; Raz, A. Ocimum gratissimum retards breast cancer growth and progression and is a natural inhibitor of matrix metalloproteases. Cancer Biol. Ther. 2013, 14, 417–427.

[18] Boonyanugomol, W.; Rukseree, K.; Prapatpong, P.; Reamtong, O.; Baik, S.-C.; Jung, M.; Shin, M.-K.; Kang, H.-L.; Lee, W.-K. An In Vitro Anti-Cancer Activity of Ocimum tenuiflorum Essential Oil by Inducing Apoptosis in Human Gastric Cancer Cell Line. Medicina 2021, 57, 784.

[19] Indrayudha, P.; Hapsari, H.S. Cytotoxic activity of combined ethanolic extract of Cinnamomum burmannii and Ocimum tenuiflorum Linn against T47D cancer cells. Arch. Venez. Farmacol. Ter. 2021, 40, 114–120.

[20] Sharma, P.; Prakash, O.; Shukla, A.; Singh Rajpurohit, C.; Vasudev, P.G.; Luqman, S.; Kumar Srivastava, S.; Bhushan Pant, A.; Khan, F. Structure-Activity Relationship Studies on Holy Basil (Ocimum sanctum L.) Based Flavonoid Orientin and Its Analogue for Cytotoxic Activity in Liver Cancer Cell Line HepG2. Comb. Chem. High Throughput Screen. 2016, 19, 656–666.

[21] Ananda Guha Majumdara , Mahesh Subramaniana. Hydroxychavicol from Piper betle induces apoptosis, cell cycle arrest, and inhibits epithelial-mesenchymal transition in pancreatic cancer cells. Biochemical Pharmacology, 2019, 166, 274–291.

[22] Pei-Fang Wu, Hsien-Chun Tseng, Charng-Cherng Chyau, Jing-Hsien Chen and Fen-Pi Chou. Piper betle leaf extracts induced human hepatocellular carcinoma Hep3B cell death via MAPKs regulating the p73 pathway in vitro and in vivo. Food and Function, 2014, 5, 3320–3328.

[23] Sadiya R Veettil, E Anuradha Sunil, Archana Mukunda, Arun Mohan, Shanly John, Meera K Pynadath. Anticancer effect of Piper betle leaf extract on KB cell lines – an in vitro study. Oral and Maxillofacial Pathology Journal, 2022, 13(1) 28-31.

[24] Muskan Tamboli, Naziya Tamboli. Exploration of in-vitro anti-cancer activity of Piper betel linn. Oral and Maxillofacial Pathology Journal.2021, 11(2), 157-165.

[25] V. Radhalakshmi, Maya Raman, Minnu Rose Joy. Protective benefits of ethyl alcohol extract of Piper betel L. to prevent colon carcinogenesis. Pharmacological Research - Natural Products. 2024, 100024.

[26] Supavadee Boontha, Jirapon Taowkaen, Thanaporn Phakwan, Teerapong Worauaichai, Piyarat Kamonnate, Benjaporn Buranrat, Tasana Pitaksuteepong. Evaluation of antioxidant and anticancer effects of Piper betle L (Piperaceae) leaf extract on MCF-7 cells, and preparation of transdermal patches of the extract, Tropical Journal of Pharmaceutical Research June 2019, 18 (6): 1265-1272.

[27] Rajedadram A, Pin KY, Ling SK, Yan SW and Looi ML. Hydroxychavicol, a polyphenol from Piper betle leaf extract, induces cell cycle arrest and apoptosis in TP53-resistant HT-29 colon cancer cells. J Zhejiang Univ Sci B. 2021, 22:112–122.

[28] Gundala SR, Yang C, Mukkavilli R, Paranjpe R, Brahmbhatt M, Pannu V, Cheng A, Reid MD and Aneja R: Hydroxychavicol, a betel leaf component, inhibits prostate cancer through ROS-driven DNA damage and apoptosis. Toxicol Appl Pharmacol. 2014, 280:86–96.