Research Article

Journal of Environmental Nanotechnology

Therapeutic Potential of Spice-derived Phytochemicals in Oral Cancer Innovations in Nano-delivery for Medicine and Drug Development

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Received: 12.09.2024 Accepted: 28.11.2024 Published: 30.12.2024
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ABSTRACT

Oral cancer remains one of the leading global health challenges, with alcohol and tobacco consumption being major risk factors. Despite advancements in medical research, conventional treatments like surgery, radiotherapy, and chemotherapy for oral cancer are often accompanied by severe side effects, including toxicity, deformity, and compromised functionality. While effective in reducing tumor size, these treatments frequently impact patients' quality of life. Recent interest has shifted towards natural bioactive compounds found in Indian spices, renowned for their therapeutic properties rooted in ancient medicinal traditions. Studies have shown that compounds from spices such as turmeric, clove, black pepper, chili, and cumin exhibit significant anticancer activity, specifically inhibiting oral cancer. These bioactive molecules effectively induce programmed cell death, inhibit cell proliferation, reduce metastasis, and suppress angiogenesis in various oral cancer cell lines, including KB, L292, HEp-2, HSC-4, Ca-9-22, and ORL-48. This review aims to provide a comprehensive overview of the therapeutic potential of spice-derived compounds, emphasizing their mechanisms of action and efficacy against diverse oral cancer cell lines, and highlighting their promise for innovative treatment strategies in environmental and therapeutic nanotechnology.

Keywords: Oral cancer; Bioactive compounds; Indian spices; Phytotherapy; Tumor inhibition; Cell Proliferation; Angiogenesis.

1. INTRODUCTION

Oral cancer is a major global medical issue that ranks sixth overall, although it is the worldwide sixth major cause of death related to cancer. The annual prevalence of new cases of oral cancer was estimated to be 187,000, and as of the year 2020, oral cancer accounted for 377,173 fatalities that were publicly acknowledged (Sung *et al.* 2021; Sun *et al.* 2023; Kumari *et al.* 2024) An extensive variety of cancers that manifest themselves within the oral cavity are collectively referred to as oral cancer. This category encompasses a range of cancers that can develop in various parts of the oral cavity and surrounding areas. It includes cancers that may affect the cheeks, tongue, lips, and the floor of the mouth, as well as the soft palate, hard palate, and sinuses. Additionally, these cancers can impact the pharynx, which is the part of the throat behind the mouth and nasal cavity. Due to their location, these cancers can significantly impair essential functions such as speaking, chewing, swallowing, and breathing, and they often require complex treatment approaches involving surgery, radiation, or chemotherapy to manage their spread and impact on the patient's quality of life (Chi *et al.* 2015). These cancers, if not diagnosed and treated early, can be life-threatening, with a survival rate of less than 60% (Jansen *et al.* 2018; Aires *et al.* 2017). Oral cancer like any other type of cancer has more than one cause, but the most important cause is tobacco products. Smokeless tobacco products include naswar and gutka, while tobacco smoking products include cigarettes, cigars, and pipes all of which deposit several carcinogenic products into the human system. Benzopyrene, polonium, formaldehyde, cadmium, and lead are some of the compounds that can be found in tobacco smoke. Tobacco smoke also contains several other compounds, including tobacco-specific nitrosamines (TSNAs). Other compounds that can be found in tobacco smoke include formaldehyde. It is well-established that all of these toxins are known to cause oral cancer (Lakshmi *et al.*

2017; Janbaz *et al.* 2014; Grasso and Mann, 1998). Furthermore, the incidence is also elevated when people habitually use products such as chewing betel quid which are known to contain carcinogens (Norton, 1998). The risk is boosted by alcohol when taken with tobacco as it opens up the conduits for carcinogens and thus results in DNA damage through acetaldehyde. Oral cancer is well understood to be caused by many factors (Fig. 1) including bacterial and viral; however, HPV, especially HPV 16 and HPV 18, are definite causes of oral cancers. Infections with HPV can cause a series of persistent physiological changes in the cells resulting to cause malignant transformation (Paver *et al.* 2020; Hubbers and Akgul, 2015). Furthermore, cancers caused by inflammation from bacterial and viral infections, in addition to exposure to toxic substances such as formaldehyde and asbestos fibers are linked to an increased risk of oral cancer by researchers (Kumar *et al.* 2016).

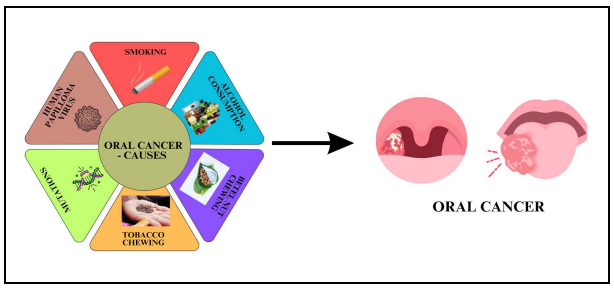

Fig. 1: Oral cancer causes

As for the primary therapies applied in the case of oral cancer, one can distinguish between surgery, radiotherapy, as well as chemotherapy. While these treatments can bring down the tumor size and control the direction of the disease, the side effects are often severe and the treatment, specifically in the later stages, is relatively unfruitful (Deivayanai *et al.* 2024). Surgical interventions, although sometimes necessary, can lead to significant disfigurement, impaired functionality, and a profound impact on the patient's quality of life. Radiotherapy, while effective in targeting cancerous tissues, can cause salivary gland damage, mucositis, loss of taste, and other complications (Beumer *et al.* 1979; Vissink *et al.* 2003).

Chemotherapeutic agents, such as 5-Fluorouracil (5-FU), Cisplatin, Cetuximab, Docetaxel, Erlotinib, Nivolumab, Methotrexate, Imatinib, Paclitaxel, and Carboplatin, although widely used, are associated with a range of adverse effects including acute renal toxicity, neurotoxicity, nephrotoxicity, cardiotoxicity, hypomagnesemia, pulmonary toxicity, myelosuppression, hair loss, reduced blood cell counts, xerostomia, dysgeusia, and dry lips (Bostan *et al.* 2021; Tsvetkova and Ivanova, 2022; Gold and Raja, 2023; Andreadis *et al.* 2003; García-Chías *et al.* 2019). Due to the restrictions and adverse reactions linked to traditional treatments, there has been an increasing fascination with alternative therapeutic methods. An encouraging approach to explore is the utilization of phytomedicine, which refers to medicinal substances obtained from plants. Phytomedicine, which has been utilized in traditional medicine systems for centuries, is now being supported by recent scientists, confirming their effectiveness in treating a diverse array of diseases.

Spices have garnered attention for their potential anti-cancer properties. These spices contain bioactive compounds that have been shown to exhibit significant anti-cancer, anti-inflammatory, and antioxidant activities (Juana *et al.* 2012). Some of the most extensively studied spices include turmeric, clove, black pepper, chilli, and cumin. These spices are not only the ones valued for Indian cuisine but are also credited to the traditional systems of medicine such as Ayurveda.

Turmeric, obtained from the root of the *Curcuma longa* plant, contains curcumin, a polyphenolic pigment known for its potent anti-cancer effects. Turmeric is a botanical ingredient employed in traditional medicinal practices. Curcumin has been shown to impede angiogenesis, the physiological process responsible for the formation of new blood vessels that provide blood to tumors (Thamarai *et al.* 2024). Additionally, it can trigger apoptosis, a type of programmed cell death, in cancer cells; both of these effects have been empirically proven. Another advantage of curcumin is its demonstrated ability to inhibit the metastasis of cancer to other anatomical sites. The aforementioned analyses were authored by (Kim *et al.* 2012; Mosaddad *et al.* 2021; Shin *et al.* 2009). Thus, the inhibitory effect on the synthesis of COX-2 and other inflammatory mediators is a contributing factor to its anti-cancer characteristics. Another spice that has been found to possess a great anti-cancer compound is clove (*Syzygium aromaticum*). The bioactive compound known as eugenol that is found in cloves was used as the material by demonstrating that it possesses anti-oral cancer cells. Eugenol causes cell death, and cell growth suppression, and exhibits anti-inflammatory activity and, therefore, has the potential of being used in treating cancer (Prakash *et al.* 2021; Sanikop *et al.* 2021).

Nigella sativa or black seed is a plant that has the substance thymoquinone in it. Almatroodi *et al.* 2020 have reported experimental evidence of its usefulness in suppressing the proliferation of several types of cancer cells, including oral cancer cells. Thymoquinone can induce cancer cell apoptosis and suppress cancer cell growth and proliferation. In addition, studies have confirmed that it contains characteristics that assist in the inhibition of inflammation (Rooney and Ryan, 2005, Chu *et al.* 2014). Further, it has also been established that the black seed extract is capable of decreasing the survival of head and neck squamous cell carcinoma cells based on the concentration and the time factor (Alaufi *et al.* 2017).

Numerous research findings have proved that *Cinnamomum zeylanicum*, also known as Cinnamon, contains cinnamaldehyde, an active compound that has potential anti-cancer characteristics against oral cancer cells. The repellent cinnamaldehyde stimulates apoptosis and the NF-κB pathway and reduces the viability of tumor cells (Yang *et al*. 2016; Nazhvani *et al*. 2020; Ahmed and Ghani, 2022).

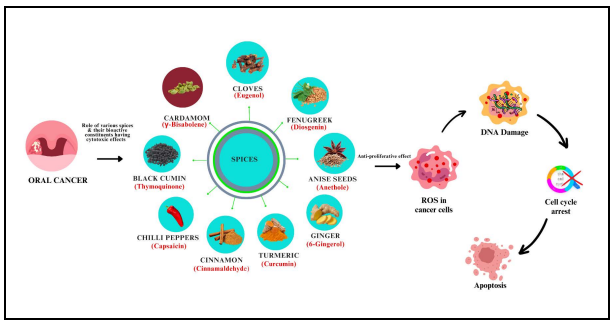

Fig. 2: Spices and their potential anti-cancer properties

Chilli peppers (*Capsicum annuum)* are known to contain capsaicin which according to the report has a pro-apoptotic effect on cancer cells. Capsaicin leads to the alteration of the mitochondrial-dependent signaling that enhances ROS generation which in turn activates apoptotic pathways and causes cancer cell death (Lin *et al.* 2013; Ip *et al.* 2010). Kamaruddin *et al.* 2019) have also pointed out that the c- sure capsaicin can inhibit the growth of oral cancer cells in a concentration and time-dependent manner. Besides, cardamom, scientifically referred to as *Elettaria cardamomum* has also been studied as another anti-cancer agent. As per (Jou *et al.* 2015; Zaki *et al.* 2024) it has been found that the aqueous extract of cardamom and one of its active compounds γ-bisabolene has a suppressive effect against oral cancer cell lines. These effects are obtained due to caspases-3/9 activation and a decrease in the mitochondrial membrane's establishment of the potential. A study by (Al-Oqail *et al.* 2013) revealed that the seeds from Trigonella *foenum-graecum*, more commonly known as fenugreek, have anti-inflammatory activity as well as the ability to inhibit the growth of human laryngeal carcinoma cells. Ginger, scientifically referred to as *Zingiber officinale*, is credited for the existence of a bioactive compound known as 6-gingerol with the natural potential to suppress the growth of oral cancer cells. The studies carried out by (Kapoor *et al.* 2016; Zhang *et al.* 2021; Saravanan *et al.* 2022) have demonstrated that ginger extract is armed with potential anticancer properties as it has the potential to suppress the growth viability of oral cancer cell lines and trigger apoptosis.Positive outcomes from the studies bring hope to another potential fact that bioactive spices found in spices could be used as either an adjunct therapy for oral cancer or even a complete replacement therapy (Butnariu *et al.* 2022). These compounds also inhibit the growth and multiplication of cancer cells, inhibit the formation of new blood vessels, restrict cancer, and cause cancer cells to die in a predetermined manner. Another reason for the curative effect of such substances are due to the properties of anti-inflammatory and antioxidant activities, as illustrated in Fig. 2.

While the therapeutic potential of these phytochemicals is well-documented, a major challenge in their clinical application is their limited bioavailability. Many of these compounds have low solubility and rapid metabolism, resulting in poor absorption and distribution within the body. Consequently, high doses are often required to achieve therapeutic effects, which can limit their practicality and effectiveness as standalone treatments (Jamuna *et al.* 2023). To overcome these limitations, nanotechnology has emerged as a powerful tool for enhancing the bioavailability, stability, and targeted delivery of spice-derived phytochemicals. Nano-delivery systems, including nanoparticles, liposomes, and nano-emulsions, can encapsulate these bioactive compounds, protecting them from degradation and facilitating their controlled release at specific cancer sites (Saravanan *et al.* 2020). This targeted delivery not only enhances therapeutic efficacy but also reduces the need for high doses, minimizing potential side effects. The integration of nanotechnology with spice-derived phytochemicals presents a promising avenue for oral cancer treatment, offering a novel approach that combines natural anticancer agents with advanced drug delivery methods. These nano-delivery systems can be engineered to bypass biological barriers, ensuring that the active compounds reach the cancer cells directly, thus enhancing treatment precision and potency. Additionally, nano-formulations can be modified to improve cellular uptake and extend the circulation time of phytochemicals in the body, further increasing their therapeutic potential. This review explores the advancements in nano-delivery systems for spice-derived phytochemicals in oral cancer treatment, examining how these innovative technologies can optimize the therapeutic effects of natural compounds. By highlighting recent research on nano-engineered phytochemicals, this study aims to provide insights into the potential of these integrative approaches to address the limitations of traditional cancer therapies. The development of nano-formulations for spice phytochemicals represents a significant step forward in medicine and drug development, offering a safer, more effective, and patient-friendly alternative for oral cancer management.

2. ROLE OF PHYTOCHEMICALS IN CANCER

T There are different types of phytochemicals in spices that have shown efficacy in the prevention and control of oral cancer. Investigators have found that some spices may help prevent the formation and growth of cancer by regulating numerous biological pathways. The health benefits of curcumin are numerous and include reduction in inflammation and oxidative stress, induction

of apoptosis, inhibition of growth and proliferation of oral cancer cells, amongst others. The bioactive component of black pepper, piperine, is an anti-cancer agent and is known to enhance the bioavailability of curcumin (Hatcher *et al.* 2008). Allicin which is derived from garlic possesses the features of an antioxidant agent and can check the proliferation of cancer cells and thus possesses the potential to prevent oral cancer risk (Shukla and Kalra, 2007). Gingerol which is obtained from ginger has been well proven to possess anti-cancer components (Kapoor *et al.* 2016). This is done by the promotion of apoptosis on oral cancer cell lines and the suppression of inflammation (Fig. 3).

Since there has been no discernible progress made in the treatment of oral cancer in recent years, these spices have the potential to be utilized as additional treatments for the treatment of this disease. There is a list of spices and their phytochemicals in Table 1 that pertains to the prevention of oral cancer.

Table 1. Spices and their phytochemicals in oral cancer prevention

Spice	Phytochemical	Mechanism of Action	Evidence in Oral Cancer
Turmeric	Curcumin	Reduces inflammation, inhibits cell proliferation, induces apoptosis	Inhibits oral cancer cell growth, and reduces tumor size in animal studies
Black Pepper	Piperine	Enhances bioavailability of curcumin, induces apoptosis	Potentiates anti-cancer effects of curcumin in oral cancer models
Garlic	Allicin	Antioxidant inhibits tumor growth, modulates apoptosis	Shows potential in reducing oral cancer risk and cell proliferation
Ginger	Gingerol	Reduces inflammation, induces apoptosis, inhibits cell growth	Reduces oral cancer cell proliferation and induces apoptosis in preclinical studies
Clove	Eugenol	Antioxidant induces apoptosis, inhibits cell growth	Exhibits anti-cancer effects in oral cancer cell lines

3. THERAPEUTIC POTENTIAL OF DIFFERENT SPECIES AGAINST ORAL CANCER

3.1 Anise Seed (*Pimpinella anisum*)

A solvent extract from anise seeds has been reported to exhibit dose-dependent cytotoxicity against KB oral cancer cell lines, with higher concentrations of the extract (100 µg/ml) reducing cell viability by approximately 32%. This sensitization resulted in a 19% reduction in cell viability, with an average IC50 achieved at 48 hours. (Mukunda *et al.* 2020) were able to detect effective concentrations of 0.35 µg/ml and 0.705 µg/ml.

3.2 Black Cumin (*Nigella sativa*)

The bioactive compound known as thymoquinone (TQ) is extracted from the seeds of black cumin. An antiproliferative effect against cancer cells, including those that have been linked with oral cancer, has been exhibited by it (Rooney and Ryan, 2005a; Chu *et al.* 2014; Alaufi *et al.* 2017) have investigated and reported the impact of black cumin extract (TQ) on squamous cell carcinoma of the head and neck cells (UMSCC-14C). By inhibiting UMSCC-14 oral cells in a concentration-dependent and time-dependent manner, the TQ extract exhibits an IC50 value of 8.6±0.4 µM at 24 hours, subsequently followed by 7.0±2.3 µM at 48 hours, and finally 7.0±0.7 µM at 72 hours. Both of these values are significant. (Rooney and Ryan, 2005) investigated and reported the black cumin bioactive compounds such as alpha hederin and thymoquinone on human laryngeal carcinoma cells (Hep2 cell lines). Alpha-hederin inhibited cellular viability in a time-dependent manner with an IC_{50} value of 21.6±1.4 µM at 24 h and 13.1±1.9 µM at 48 h followed by 11.3±0.4 µM at 72 h. Thymoquinone hederin inhibited cellular viability in a time-dependent manner with an IC_{50} value of 51.6±3.0 µM at 24 h and 28.5±2.7 µM at 48 h followed by 22.9±1.1 µM at 72 h.

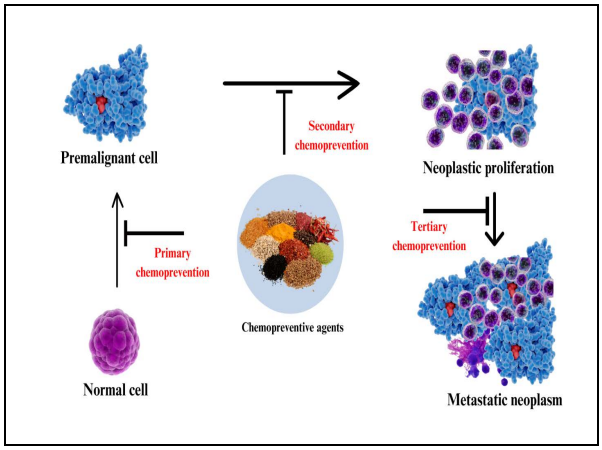

Fig. 3: Common phytochemicals and their mechanisms in cancer prevention

3.3 Cinnamon (*Cinnamomum zeylanicum* Breyn.)

Cinnamaldehyde, a bioactive compound sourced from cinnamon bark has been found to exhibit anti-cancer effects against oral cancer (Yang *et al.* 2016 Nazhvani *et al.* 2020) investigated and reported the cytotoxicity of Cinnamon extract having potential anticancer activity on KB oral cell lines. Cinnamon

exhibited anticancer activity at 5 mg/ml concentration. It showed 80% inhibition at 10 mg/ml in 24 h and 100% at 40 mg/ml at 48 h. IC30 value is 3.3 mg/ml. (Ahmed and Ghani, 2022) investigated and reported that cinnamon extract inhibits the activity of NF-κB and AP-1, both of which are involved in promoting the survival and proliferation of cancer cells. The study also documented that cinnamon oil induces mitochondria-mediated apoptosis in cancer cells. Additionally, the research revealed the cytotoxic effectiveness of cinnamon oil extract against OSCC cell lines, with an IC50 of 90.40 µg/ml after 24 hours and 42.95 µg/ml after 48 hours.

3.4 Chilli Peppers (*Capsicum annuum*)

Capsaicin, a bioactive component included in chilli peppers, has attracted considerable interest due to its potential to inhibit oral cancer (Lin *et al.* 2013; Ip *et al.* 2010) Through the inhibition of a wide variety of signal transduction pathways, including NF-kB and AP-1, it achieves this goal. According to the findings of the research, capsaicin is responsible for the disruption of these activities by interfering with the processes that occur within mitochondria, increasing the formation of reactive oxygen species (ROS), and activating several apoptotic pathways that are present within cells. Caspase-3, caspase-7, and caspase-9 are the enzymes that are responsible for bringing about apoptosis, also known as programmed cell death, in cancer cells. This ensures the removal of malignant cells completely from the body (Ip *et al.* 2010; Kamaruddin *et al.* 2019) examined and reported the viability and growth of ORL-48 cells incubated under the effect of various capsaicin doses and treatment durations. The viability of cells went down gradually with a rise time in incubation, as IC50 (the amount of capsicum that suppresses cell growth by 50%) reached 200 µM after 48 hours. Capsaicin showed cytotoxicity as evidenced by decreased cell viability at increasing concentrations. The presence of capsaicin, however, stopped ORL-48 cell growth in such a way that depended on both concentration and duration. Optical density values declined in line with this inhibition. (Lin *et al.* 2013) evaluated and reported the proliferation and viability of the KB cells treated with capsaicin at different concentrations. The IC50 value of the Capsaicin was 150 µM at 48 h.

3.5 Cloves (*Syzygium aromaticum*)

Clove spice contains bioactive compounds such as eugenol, which has shown the potential to inhibit oral cancer (Prakash *et al.* 2021; Sanikop *et al.* 2021) investigated the ethanolic extract of cloves on KB oral cancer cells. The ethanolic extract significantly inhibited the KB oral cells with an IC50 value of 224.3 µg/ml.

3.6 Cardamom (*Elettaria cardamom* (L.) Maton.)

It has been reported that the aqueous extract of cardamom demonstrates cytotoxic effects against oral cancer cell lines (Ca9-22 and SAS) in a manner that is dependent on the concentration, with the cytotoxic concentration (CC50) being observed at 81.2 µg/ml (Jou *et al.* 2015). Additionally, the same study has brought to light that γ-bisabolene, a bioactive compound found in cardamom, exhibited a powerful cytotoxic effect against the development of these cell lines. The IC50 was achieved at an extremely low concentration of 5.15 µg/ml, and it was found to be 29.5 µg/ml against these cell lines when compared to the aqueous extract. This effect was attributed to the activation of caspases-3/9 and a reduction in the potential of the mitochondrial membrane. (Zaki *et al.* 2024) conducted research on cardamom extract, which resulted in a decrease in the percentage of viable cells. This finding suggests that cardamom extract may have the ability to exert cytotoxic impacts on laryngeal cancer cells (Hep-2 cells). The IC50 value for cardamom extract was reported as 186 µg/ml.

3.7 Fenugreek (*Trigonella foenum-graecum* L.)

(Liu *et al.* 2012) have demonstrated that fenugreek seeds possess notable anti-inflammatory properties, making them a subject of interest in various medicinal and therapeutic studies. Specifically, in the context of cancer research, these seeds have shown promising effects against certain types of oral cancer. For example, when tested on human laryngeal carcinoma cells (Hep2 cell lines), the aqueous extract of fenugreek seeds exhibited significant cytotoxicity. According to a study by (Al-Oqail *et al.* 2013), treating these cancer cells with the extract at a concentration of 1000 µg/ml for 24 hours resulted in a reduction of cell viability to 55%. This finding suggests that fenugreek seed extract could potentially serve as a natural therapeutic agent with anticancer properties, particularly against laryngeal carcinoma cells.

3.8 Ginger (*Zingiber officinale*)

Ginger has been documented to possess 6-gingerol as a bioactive constituent for exhibiting anti-proliferative effects against oral cancer (Kapoor *et al.* 2016). Methanolic extract of ginger has demonstrated an in-vitro cytotoxic effect against SCC4 and KB oral cancer cell lines with IC50 values achieved at 480 µM for the former and 500 µM for the latter cell lines, respectively (Kapoor *et al.* 2016). Another in-vitro study has authenticated the potent inhibitory effect of 6-gingerol against cancerous cells with inhibitory concentration (IC50) observed at very low concentrations- 64.38 µM against Ca9-22 and 79.46 µM for YD10B cells at 72 h (Zhang *et al.* 2021).

3.9 Turmeric (*Curcuma longa*)

Curcumin is the polyphenol or bioactive compound extracted from the turmeric. It can inhibit the overly proliferated cancer cells by programmed cell death, thereby inhibiting angiogenesis. Curcumin stands out as a promising therapeutic agent to inhibit the growth and progression of head and neck cancer (Kim *et al.* 2012; Mosaddad *et al*. 2021; Shin *et al.* 2009; Shin *et al.* 2009) investigated and reported that the cytotoxicity of the curcumin extract has potential anticancer activity on YD10b oral cell lines extracted from the human tongue. Curcumin extract inhibited 50% growth of YD10b oral cell lines at 8.37 ± 1.13 µM in 24 h. (Kim *et al.* 2012) investigated and reported that the cytotoxicity of the curcumin extract has potential anticancer activity on YD10b oral cell lines extracted from the human tongue. Curcumin extract suppressed the growth of YD10b cells in a concentration-dependent manner with 40% viability at 20 µM and 20% viability at 40 µM in 24 h. (Nazhvani *et al*. 2020) investigated and reported that the cytotoxicity of the curcumin extract has potential anticancer activity on KB oral cell lines extracted from epidermal carcinoma of the mouth. Cinnamon exhibited an anticancer activity impact at 5 mg/ml concentration; it showed 50% cell viability at 145 mg/ml in 24 hours followed by 48 hours reaching a maximum efficacy of 80% at 2.2 mg/ml concentration. The IC50 value was 145 mg/ml. The study conducted by (Ohnishi *et al.* 2020) on HCS- 4 and Ca9-22 oral cell lines treated with curcumin extract at different concentrations of 10µM – 20µM; 15µM showed the (IC50) inhibition of 50% viability of the cells. The curcumin inhibited HGF-induced activation of MET/ ERK pathway and migration of HSC-4 oral cells and suppressed HGF-induced epithelial-mesenchymal transition (EMT) in HSC -4 and Ca9-22 oral cell lines.

Table 2: Therapeutic potential of different species against oral cancer

Name of the spice	Type of oral cancer cell line tested in vitro	IC_{50} values reported	Reference	Possible bioactive constituent responsible for anti-proliferative effect	Reference
Anise seed (*Pimpinella anisum*)	Epidermal carcinoma of mouth (Kb)	48.0705 µg/ml	Mukunda *et al.* (2020)	-	Mukunda *et al.* (2020)
Black Cumin *(Nigella sativa)*	Head and neck squamous cell carcinoma cells (UMSCC-14)	8.6±0.4 µM at 24 h 7.0±2.3 µM at 48 h 7.0±0.7 µM at 72 h	Alaufi *et al.* (2017)	Thymoquinone (TQ)	Rooney and Ryan, 2005; Chu *et al.* 2014
	Human laryngeal carcinoma cells (Hep-2 cell lines)	21.6±1.4 µM at 24 h 13.1±1.9 µM at 48h 11.3±0.4 µM in 72 h	Rooney and Ryan, (2005)	Alpha-hederin	Rooney and Ryan, 2005
	Human laryngeal carcinoma cells (Hep-2 cell lines)		Rooney and Ryan, (2005)	Thymoquinone	Rooney and Ryan, 2005; Chu *et al.* 2014
Chillis *(Capsicum)*	Oral cavity (ORL-48 Cell lines)	200 µM after 48 h	Kamaruddin *et al.* (2019)	Capsaicin	Lin *et al.* 2013; Ip *et al.* 2010
Cloves *(Syzygium aromaticum)*	Epidermal carcinoma of mouth (KB Cell lines)	800 µg after 48 h	Sanikop *et al.* (2021)	Eugenol	Prakash *et al.* (2021)
Cinnamon (*Cinnamomum zeylanicum* Breyn.)	Mucosal epithelium of oral cavity (SCC25)	90.40 µg/ml after 24 h 42.95 µg/ml after 48 h	Ahmed & Ghani, (2022)	Cinnamaldehyde	Yang *et al.* (2016)
	Epidermal carcinoma of mouth (KB cell line)	80% inhibited at 10 mg/ml in 24 h 100% at 40 mg/ml in 48 h	Nazhvani *et al.* (2020)	Cinnamaldehyde	Yang *et al.* (2016)
Cardamom (*Elettaria cardamom* (L.) Maton.)	Human laryngeal carcinoma cells (Hep-2 cell lines)	186 µg/ml	Zaki *et al.* (2024)	Aqueous extract	Jou *et al.* (2015)
	Human gingival (Ca9-22)	81.2 µM	Jou *et al.* (2015)	γ-bisabolene	Jou *et al.* (2015)
	Human gingival (Ca9-22)	5.15µM	Jou *et al.* (2015)	γ-bisabolene	Jou *et al.* (2015)
	Human tongue squamous cell (SAS)	29.5 µM	Jou *et al.* (2015)	γ-bisabolene	Jou *et al.* (2015)
Fenugreek (*Trigonella foenum-graecum* L.)	Human laryngeal carcinoma cells (Hep-2 cell lines)	55% at 1000 µg/ml	Al-Oqail *et al.* (2013)		Al-Oqail *et al.* (2013)
Ginger (Zingiber officinale)	Tongue squamous cell carcinoma (SCC4)	480 µM	Kapoor *et al.* (2016)	6-gingerol	Kapoor *et al.* (2016)
	Epidermal carcinoma of mouth (KB oral)	500 µM	Kapoor *et al.* (2016)	6-gingerol	Kapoor *et al.* (2016)
	Human gingival (Ca9-22)	64.38 µM	Zhang *et al.* (2021)	6-gingerol	Kapoor *et al.* (2016)
	Human tongue (YD10B cells)	79.46 µM	Zhang *et al.* (2021)	6-gingerol	Kapoor *et al.* (2016)

Turmeric (*Curcuma longa)*	Human tongue YD10b	Inhibited 50% cells at 8.37 ± 1.13 µM in 24 h	Shin *et al.* (2009)	Curcumin	(Kim *et al.* 2012; Mosaddad *et al.* 2021; Shin *et al.* 2009)
		40% viability at 20 µM and 20% viability at 40 µM.	Kim *et al.* (2012)	Curcumin	(Kim *et al.* 2012; Mosaddad *et al.* 2021; Shin *et al.* 2009)
	Human tongue squamous cell HSC-4	15 µM after 24 h	Ohnishi *et al.* (2020)	Curcumin	(Kim *et al.* 2012; Mosaddad *et al.* 2021; Shin *et al.* 2009)
	Human gingival (gum) squamous cell Ca9-22	15 µM after 24 h	Ohnishi *et al.* (2020)	Curcumin	(Kim *et al.* 2012; Mosaddad *et al.* 2021; Shin *et al.* 2009)
	Epidermal carcinoma of mouth KB	145 mg/ml in 24 h	Nazhvani *et al.* (2020)	Curcumin	(Kim *et al.* 2012; Mosaddad *et al.* 2021; Shin *et al.* 2009)

4. CONCLUSION

Oral cancer, recognized as one of the most common types of cancer globally, can be managed with several treatment options, including chemotherapy and radiotherapy. However, these treatments are more likely to result in adverse effects as a consequence. There has been a significant amount of research conducted to discover a treatment that is effective for oral cancer. Recently, medicinal phytochemicals extracted from natural spices have grabbed attention due to their efficacy in treating oral cancer due to their anticancer activity. By incorporating natural spices into one's daily routine, one can lessen the likelihood of developing prostate cancer. Nanotechnology has emerged as a solution to these challenges, offering advanced nano-delivery systems that enhance the absorption, targeted delivery, and controlled release of spice-derived compounds. Nano-formulations such as nanoparticles, liposomes, and nano-emulsions enable these bioactive agents to reach cancerous tissues more effectively, reducing the required dosage and minimizing side effects. This integration of natural phytochemicals with nanotechnology presents an innovative approach, combining the strengths of both natural therapies and cutting-edge medical advancements. Scientists have been conducting research on natural remedies for the treatment of cancer, as well as combinations of natural phytochemicals and chemotherapeutic drugs, in oral cancer cell lines over the past few years.

FUNDING

There is no funding source.

CONFLICT OF INTEREST

The authors declared no conflict of interest in this manuscript regarding publication.

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