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Treatment of Oral Cancer by a Synthetic Analogue of Capsaicin & TRPV1 Antagonist: Capsazepine

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ABSTRACT

A synthesized homologue of the sensory neuron excitotoxin capsaicin is capsazepine. It was altered from capsaicin's chemical structure, which can act as a TRPV1 antagonist. It can interface with all of the monomer's residues of the TRPV1 channel's transmembrane domain and connect to the channel's pores. By inhibiting the TRPV1 channel and reducing the flow of Ca^{2+}, capsazepine can also have a number of other pharmacological properties. Capsazepine can have a variety of impacts on the survival and growth of cancer, including breast, ovarian, colon, oral, and osteosarcoma. It can also be used medically to treat other severe conditions such gastroenteritis, hepatitis, malaria, and seizures. According to reports, capsazepine shows pleiotropic anti-cancer activities against a variety of tumor cell lines.

Keywords: Oral cancer, capsazepine, TRPV1, signal transducer and activator of transcription (STAT), oral squamous cell cancer.

1. INTRODUCTION

Among the most prevalent forms of neck and head malignancies, oral cancer mostly affects the throat, paranasal sinuses, nasopharynx, hypopharynx, salivary glands, and oral cavity.[1] Except for certain regions of France, oral cancer is rare in the industrialized world. However, it is frequent in the developing world, notably in Southeast Asia and Brazil.[2] Based on the geographical location and the local population's lifestyle choices, different regions have different risk factors for oral cancer.

Oral cancer mainly affects men after midlife, while it is becoming more prevalent in younger individuals, smokers, and persons from poorer socioeconomic backgrounds. Oral cancer can also be caused by other things, such HPV infection.[3]

The aerodigestive tract may also develop new primary tumors. Up to 25% of those with oral cancer who've had it for more than three years and up to 40percent of the total of smokers will develop these lesions. The incidence of second primary oral malignancies is also present in lung cancer patients.[4] Some dysplastic leukoplakias, erythroplasias, submucous fibrosis, lichen planus, and chronic immunosuppression are examples of lesions or disorders that might be cancerous. Discoid lupus erythematosus, tertiary syphilis, Plummer-Vinson syndrome and dyskeratosis congenita are a few uncommon causes of oral cancer.[5]

The most of oral cancers, which have a prevalence rate of about 630,000 new cases globally, are squamous cell carcinomas. With over

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350,000 new cases and 177,000 fatalities annually, it is the tenth most prevalent cancer in the world.[6] Low- and middle-income countries (LMICs) account for two-thirds of the world's incidence, with South Asia accounting for half of those cases.[7] In contrast, if oral cancer is identified and treated at an early stage, namely stage I or stage II, the survival rate might surpass 80%. The survival rate of oral cancer is greatly increased by early discovery, which makes the illness easier to diagnose, cure, and monitor. The modern gold standard for identifying and identifying various forms of oral malignancies is biopsy of sample tissues accompanied by histological evaluation.[8]

Although few unambiguous controlled studies of various treatment options have been carried out, oral squamous cell carcinoma is currently treated surgically or with radiation. Chemotherapy and photodynamic treatment are occasionally used.[9] A tumor and its surrounding lymph nodes can be completely removed during surgery. This is preceded by a thorough histologic investigation for staging, which affects prognosis and determines if adjuvant radiation is necessary. Regular morphology and functioning are preserved with radiation, general anesthesia is not required, and salvage treatment is still an option in the event that radiotherapy is unsuccessful. Radiotherapy has drawbacks, including frequent side effects and riskier and more difficult after surgery. Prior to radiotherapy, dental care-both curative and preventive is crucial to reduce oral disease and the potential side effects of surgery.[10]

The prevalent pungent component in spicy chili peppers is called capsaicin (8-Methyl-N-vanillyl-trans-6-nonenamide). Capsaicin has the ability to open the transient receptor potential vanilloid type 1 (TRPV1) cation channel subfamily V member 1.[11] Capsazepine (N-[2-(4-Chlorophenyl) ethyl]-1, 3, 4, 5-tetrahydro-7, 8-dihydroxy-2H-2-benzazepine-2 carbothioamide) (Fig. 1) is a synthetic analog of the vanilloid receptor type 1 (VR-1) agonist capsaicin, was the first commercially available VR-1 receptor antagonist. The Sandoz made the initial discovery and characterization of it (now Novartis).[12]

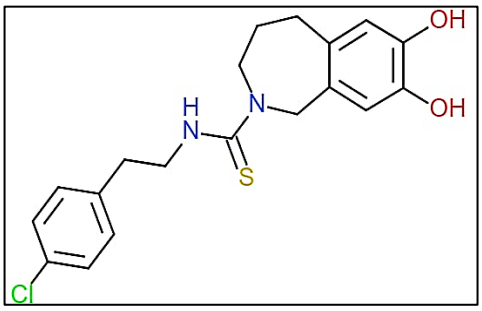

Fig. 1: Chemical structure of capsazepine

TRPV1 was initially discovered in sensory neurons like the dorsal root ganglia as a ligand-gated, non-selective, cation channel (DRG). Ca2+ is crucial for a number of signal transduction pathways, along with the release of neurotransmitters, brain stimulation, and cell death. Calcium (Ca^{2+}) ion uptake increases quickly once the TRPV1 channel is activated. It has also been claimed that capsazepine targets a number of additional receptors, particularly TRP channels like TRPV4 and TRPM8. In rats, it can also inhibit voltage-activated calcium channels and nicotinic acetylcholine receptors. It's significant to observe that capsazepine may block currents in HEK293 cells concentration-dependently and regulate human hyperpolarization-activated cyclic nucleotide-gated two and four channels.[12]

2. MECHANISM OF ACTION

Cell growth, survival, and metastasis are influenced by signal transducer and activator of transcription (STAT) protein activity in a variety of biological processes. In pathologic tissues recovered via prostatectomy, STAT3 activation is frequently dysregulated in malignant tissues and not in typical margin tissues.[13] Abdulghani et al. (2008) found that phospho-STAT3 expression was present in 67 percent of bone metastases and 77% of lymph node metastases in individuals with human prostate cancer, demonstrating the significance of STAT3 in the spread of metastatic disease. The both transmembrane (PTPε M) and cytoplasmic (PTPε C) forms of protein tyrosine phosphatase (PTP) ε are produced by using different promoters in the same gene.[14]

Capsazepine can influence the pathways for reactive oxygen species (ROS), Janus Activated Kinase (JAK), signal transducer and activator of transcription (STAT), intracellular Ca^{2+} concentration, and enhancer-binding protein homologous protein (CHOP). It has the ability to stop metastasis, stop cell growth, and start apoptosis. Capsazepine can reduce the amount of nuclear transcription factor kappa B (NF- κB) that is produced when lipopolysaccharide is present. It can also prevent the initiation of both TRPV1 and transient receptor potential cation channel, subfamily A and member 1 from occurring (TRPA1).[15]

The Janus activated kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, calcium ion influx, ROS-JNK-CHOP pathway, and regulation of other significant signal transduction pathways are some of the mechanisms behind the anti-cancer inhibitory effects. In tumor cells, STAT3 is typically overexpressed and controls the expression of oncogenic genes. By preventing STAT3 activity, capsazepine was found to significantly increase apoptosis in DU145 and PC-3 prostate cells.[12,16]

According to studies, capsazepine exhibits pleiotropic anti-cancer actions on a variety of tumor cell lines, including those from ovarian, breast, colon, mouth, and osteosarcoma cancers.[12,17] Based on data from clinical studies, the current research focuses on capsazepine's potential involvement in the treatment of oral cancer.

3. PHARMACOLOGICAL ACTION OF CAPSAZEPINE IN ORAL CANCER

Treatment with capsazepine was found to slow the progression of oral squamous cell carcinoma (OSCC). Tumor cells programmed cell death (apoptosis) due to the oxidative stress that capsazepine generates. When the drug capsazepine was used to treat oral cancer in humans, the tumor shrank significantly without causing any harm to the nearby tissues.[18]

Capsazepine's anti-cancer properties were shown in vivo by De La Chapa and colleagues in 2019. They created 30 new chemicals and tested them on cultivated HeLa cervical cancer cells for their ability to inhibit cell proliferation. Numerous compounds with IC_{50s} < 15 M and one molecule, 29 with an IC_{50} < 5 M, were found in cell viability experiments. This drug was six times more powerful than capsazepine. Using xenografts made from HeLa in athymic nude mice, they confirmed the anti-proliferative effectiveness of two lead compounds, 17 and 29, in vivo. By day 8, both analogs dramatically decreased tumor volumes when compared to mice receiving control treatment, with no noticeable side effects. According to calcium imaging, compound 17 stimulates TRPV1, but compound 29 neither stimulates nor suppresses TRPV1. This suggests that compound 17 has a distinct mode of action that does not include TRPV1 signaling. Both lead compounds were shown to be effective against every cancer type tested in cell viability assays using a panel of additional tumor types, along with oral squamous cell carcinoma, non-small cell lung cancer (NSCLC), breast cancer, and prostate cancer cell lines (HSC-3, H460, MDA-231, and PC-3, respectively). In HSC-3 and PC-3 cells, compound 29 had an IC_{50} of 1-2.5 μM. Accordingly, the study suggested that these new capsazepine analogs could be effective therapeutic agents for treating a variety of tumor types and that they should be further developed for use in clinical settings.[19]

De La Chapa et al., 2019 assessed TRPV1 associations using calcium imaging and a rat model of orofacial discomfort utilizing oral squamous cell cancer (OSCC) xenograft models. Cell cycle analysis and mitochondrial depolarization experiments were used to evaluate the anti-cancer mechanism(s) of action of capsazepine lead compounds. The most effective analog that showed appreciable anti-tumor activity in vivo was CIDD-99. TRPV1 activity is not implicated in the anti-cancer benefits of CIDD-99, according to calcium imaging experiments that showed the drug neither stimulates nor blocks the channel. Apoptosis, mitochondrial depolarization, and an S-phase block were all brought about by

the analogs. In cancers treated with these analogs, histological examinations showed enhanced apoptosis and decreased cell growth. Importantly, CIDD-99 exhibited the most anti-tumor effects, with 85% of tumors disappearing and only minuscule remnants of viable tissue remaining. It was determined that CIDD-99 was non-noxious and showed no signs of unfavorable effects.[20]

By using immunohistochemistry and qPCR analysis, Gonzales et al. (2014) showed that OSCC expresses the TRP vanilloid type 1 (TRPV1) receptor. Prototypical vanilloid agonist (capsaicin) and antagonist (capsazepine) were assessed for cytotoxic and anti-tumor actions in OSCC using cell proliferation assays, calcium imaging, and three animal xenograft models. Capsaicin-treated OSCC cell lines showed noticeably lower cell viability. Capsazepine pre-treatment was unable to remove these effects. Further evidence that the mechanism of action is unrelated to TRPV1 activation comes from the fact that capsazepine alone was extremely cytotoxic to tumor cells. Calcium imaging, which shows that TRPV1 channels are not functioning in the examined cell lines, further supported this. We next looked into whether the production of reactive oxygen species (ROS) and consequent apoptosis was the cause of the vanilloid cytotoxicity that was found.

Flow cytometry was used to confirm ROS generation, and co-treatment with the antioxidant N-acetyl-cysteine to stop it. FACS studies and the expression of c-PARP in treated cells showed that capsazepine therapy induces apoptosis in a dose-dependent manner. The study demonstrated that capsazepine injections intra-tumorally revealed great efficacy in inhibiting tumor development with no discernible effects. These trials proved that capsazepine has therapeutic promise for treating oral malignancies.[21]

4. FUTURE CONCERN

A polymodal cellular receptor, the TRPV1 ion channel may recognize many stimuli, process them, and then transform them into calcium-based signals. As a result, it serves as a crucial connection between the cellular response and the extracellular environment. TRPV1 is being studied more and more recently as a possible therapeutic target for a variety of conditions, including cancer, autoimmune illnesses, and inflammation. It is undeniable that TRPV1-based signaling may be involved in the control of cellular activities in both health and infection.

By stimulating capsazepine receptors or controlling other signaling pathways, capsazepine demonstrates potent anti-cancer activities in a variety of cancer types. Anti-proliferation, anti-angiogenesis, apoptosis, anti-metastasis and autophagy are the major anti-cancer mechanism of actions of capsazepine. It is important to note that capsazepine's concentration has a significant impact on how it performs biologically, and that various malignant tumors have significantly varying effective concentrations. Capsazepine has a wide range of clinical application prospects and may be used as a possible chemo-preventive or a new auxiliary therapeutic drug for cancer. Additionally, when used in conjunction with conventional chemotherapy drugs or radiotherapy, capsazepine can increase patients' sensitivity to chemo-radiotherapy, reduced doses, and improve patients' sensitivity. Capsazepine's anti-tumor activities show no negative impact on non-cancerous tissues in vivo.

However, the usage of capsazepine in clinical practice is quite restricted because of its hydrophobicity, poor affinity, and brief half-life. Capsazepine-loaded NPs may offer a very promising method of chemotherapy for malignant tumors. Recently, more and more effective carriers to lengthen the drug retention of capsazepine in the blood circulation and enable active targeting of specific cancer cells for improved, exact delivery, and target specificity have been established.

Although there has been significant progress in the study of capsazepine in tumors, additional well-controlled research is still required to evaluate the safety and effectiveness of capsazepine. Additional preclinical and clinical trials are required to fully understand the anti-

tumor effects of capsazepine when combined with other conventional medications or radiotherapy from cell biology tests, animal studies, and clinical trials demonstrating the drug's effectiveness in treating and preventing tumor.

5. CONCLUSION

It has become evident over the past few decades that cancer cells can develop multidrug resistance to traditional anticancer medicines, leading to tumor recurrence. Therefore, the search for novel, efficient anticancer medications is ongoing. Capsazepine has anti-inflammatory and therapeutic benefits on a variety of cancers. By altering the TRPV1 channel, it can prevent growth and metastasis, trigger apoptosis, and interact with all of the channel's monomer residues to have anti-tumor effects in oral cancer. In conclusion, capsazepine inhibits the multiplication of tumor cells without affecting healthy cells. As a result, it could provide a fresh therapeutic choice for the treatment of oral malignancies. Capsazepine has untapped potential, but more research is needed to fully understand it. This will help us learn more about its safety, toxicity, and proper mechanism of action in the body, which will help us conduct appropriate clinical settings.

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