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Chemopreventive Efficacy of Medicinal Tea Compounds Against Hypoxia and Angiogenesis in Oral Tumors

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ABSTRACT

Hypoxia and aberrant angiogenesis are common features of oral cancers, which encourage growth and resistance to treatment. Rich in polyphenols, medicinal teas modulate inflammation, oxidative stress, and vascular signaling to provide chemopreventive benefits. The present research investigates the chemopreventive efficacy of selected medicinal tea compounds on hypoxia and angiogenesis markers in oral tumors. The primary aim is to evaluate whether regular administration of these compounds can attenuate hypoxic conditions and inhibit neovascularisation in preclinical oral tumor models. Data were gathered using laboratory-based cell culture models, where oral epithelial cells were exposed to conditions promoting hypoxia and angiogenesis to evaluate the effects of medicinal tea compounds (MTC). Bioactive tea compounds were administered at graded concentrations (low, medium, high) for defined time periods to assess dose-dependent responses. Analytical assessment involved dimensions of hypoxia-inducible factor-1 alpha (HIF-1α) expression, vascular endothelial growth factor (VEGF) levels, and related angiogenic markers using immunohistochemistry, ELISA, and quantitative PCR. Statistical analyses, including post hoc Tukey tests and ANOVA, were performed using IBM SPSS software to determine significance at $p < 0.05$. Results show that higher doses of medicinal tea compounds markedly reduced HIF-1α and VEGF expression compared to untreated controls. While apoptosis significantly increased with increasing drug concentration, a density of micro in tumor tissues reduced, suggesting that hypoxia and angiogenesis were effectively modulated. These results demonstrate the powerful chemopreventive effects of medicinal tea components in the development of oral cancers

Keywords: *Medicinal Tea Compounds, Oral Tumors, Chemoprevention, Hypoxia, Angiogenesis, Bioactive Metabolites*.

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1. INTRODUCTION

Uncontrolled cell proliferation in the tissues of the oral cavity is a hallmark of oral cancer, a common disease affecting the head and neck. It involves oral squamous cell carcinoma (OSCC) with mucosal variations. Chemotherapy is a systemic therapy, which can lead to pancytopenia, nausea and gastrointestinal effects [1]. Classifications of tumors could be subdivided and new entities could be included based on the evolving genetic, immunohistochemical and clinical information [2]. Cancer Stem Cells (CSCs) represents a small but important subpopulation within tumors and possesses the ability to self-renewal and differentiation into any type of cell [3]. This distinct group is a factor in the therapeutic resistance, recurrence, and metastatic development. In the management of oral cancer, a multidisciplinary approach is widely used, which involves surgical resection, chemotherapy, radiotherapy, and selective therapeutic agents like cetuximab to give an optimal result of treatment [4]. It is generally known regarding the associations between cancer and chronic inflammation. The pro-inflammatory mediators provoke inflammation to prevent or enhance the development and proliferation of tumors [5]. Traditional cancer therapies, such as radiotherapy, have significant side effects and disappointing results for patients with distant and localized tumor metastases [6]. Late identification of oral cancer could lead to increased morbidity and high mortality rates. The most prevalent causes of oral cancer are excessive smoking and drinking. Because a quarter of persons in low- or middle-income countries develop an oral lesion at a late stage, their chances of survival are low [7]. Oral cancer is among the most prevalent and deadly malignancies worldwide. According to the World Health Organization (WHO), there are around 177,757 fatalities and 377,713 new cases annually, showing a high rate of morbidity and mortality [8]. Since a delayed diagnosis lowers the effectiveness of therapy and the prognosis, early detection is essential for improved survival outcomes [9]. Around 90% of instances of oral cancer are oral OSCC, converting it into the neoplasm in the earth. OSCC is a complicated cancer with risk factors that are both inherited and acquired [10]. With a prevalence of about 90%, OSCC is the most prevalent and recurring of all cancerous epithelial tumors that develop in the oral cavity. The major treatments of OSCC still include surgery, radiation and chemotherapy. Tumor

recurrence and medication resistance have not contributed to a significant improvement in the 5-year survival rate. Platinum-based chemotherapeutic agents are potent anti-cancer drugs effective against various malignancies, including OSCC, and could serve as first-line agents in chemotherapy [11]. Oral tumor has existed as a significant global issue of public health and is among the most prevalent and deadly diseases. The head and neck cancer that is discovered in new cases worldwide each year is oral cancer [12]. With almost 85% of cases, carcinoma of the squamous cells of the oral cavity is the prevalent type of oral tumor. A dismal prognosis results from the majority of patients receiving an oral cancer diagnosis near the final stage of their illness, despite the importance of early detection [13].

1.1 Objective of Research

The chemopreventive potential of medicinal tea components is assessed in modifying hypoxia and angiogenesis, which are related to oral tumor growth. Eight experimental groups comprising 120 rodents were randomly assigned to the following groups: carcinogen control (4NQO), vehicle control, medium-dose MTE (3%), low-dose MTE (1%), high-dose MTE (5%), and pre- and post-treatment groups that combined MTE with carcinogen at 1%, 3%, and 5% doses. The investigation seeks to establish if regular exposure to bioactive tea metabolites can diminish HIF-1α and VEGF expression. The research also aims to determine how these chemicals affect microvessel density and apoptotic activity in oral tumor models. The research effort proposes to demonstrate a mechanistic relationship between medicinal tea polyphenols and the regulation of tumor-promoting pathways by investigating dose-dependent effects at the cellular and molecular levels. Finally, the aim is to emphasize medicinal tea ingredients as potential chemopreventive agents against oral carcinogenesis.

1.2 Research Organization

The research is organized as the following sections: Section 1 presents the Introduction; Section 2 explains Related Works; Section 3 depicts Materials and Methods; Section 4 discusses Results and Discussion; and Section 5 concludes the research and its Limitations.

2. RELATED WORK

Research trends and scientific features in 4-Nitroquinoline 1-oxide (4NQO) and 7, 12-Dimethylbenz[a] anthracene (DMBA) induced oral carcinogenesis was described [14]. The methods involved a scientometric analysis of publications in the field. Results revealed key contributors, research structure, and evolution, guiding future chemo preventive research. Limitations included reliance on published data and a lack of experimental validation. The chemo preventive and immunomodulatory effects of Antiretroviral Therapy (ART) and their combination were evaluated in oral leukoplakia [15]. The methods used a 4NQO-induced marine model with treatment interventions. Results showed RO delayed malignant transformation and enhanced apoptosis, while ART had an immunosuppressive effect. Limitations included variable efficacy of ART requiring optimization.

Apigenin's chemo preventive potential was assessed in oral leukoplakia [16]. Methods involved formulating 3D bio printed mucoadhesive films and testing in a 4NQO-induced rat model. Results demonstrated strong chemo preventive effects and structural stability of the films. Limitations included preclinical model use, requiring clinical trials for validation. Site-specific drug delivery was developed for oral cancer prevention [17]. Methods involved creating Janus nanoparticles with mucoadhesive and controlled-release layers loaded with tocilizumab. Results showed effective localized delivery, sustained release, and potential for chemoprevention. Limitations included the need for in vivo clinical evaluation to confirm efficacy.

The molecular objective was to investigate HIF-1α's role in tumor progression and evaluate strategies targeting its inhibition [18]. Literature on oxygen-dependent and independent regulation, oncogenic signaling, and tumor microenvironment effects was studied. Findings showed HIF-1α promoted invasion, angiogenesis, metabolic reprogramming, and cell survival, driving tumor growth. Limitations included reliance on preclinical studies, requiring further in vivo validation for clinical relevance. HIF-1α's role in breast cancer progression and its inhibition strategies were deliberate [19]. Hypoxia-induced activation of HIF-1α promoted apoptosis evasion, cell cycle progression, migration, EMT, metastasis, drug resistance, and immune evasion. Silencing or pharmacological inhibition reduced proliferation and enhanced therapy sensitivity. Limitations included reliance on preclinical and evaluation studies, highlighting the need for further clinical validation of therapeutic approaches.

The role of the hypoxia-induced lncRNA MIR210HG in Cervical Squamous Cell Carcinoma (CSCC) and its interaction with HIF-1α was investigated [20]. Functional assays assessed its effects on proliferation, migration, invasion, tumor growth, and metastasis. Results revealed a feedback loop between MIR210HG and HIF-1α, regulating PGK1 expression and promoting cervical carcinogenesis. Limitations included reliance on preclinical models, requiring further clinical validation. Noradrenaline NORAD, a hypoxia-induced lncRNA, and its interaction with HIF-1α and miR-495-3p were investigated in Colorectal Cancer (CRC) [21]. CRC cell assays assessed vasculogenic mimicry, chemoresistance, EMT, proliferation, and apoptosis under hypoxic conditions. Results showed upregulation promoted Vasculogenic Mimicry (VM) formation, 5-FU resistance, and EMT, while NORAD knockdown reversed these effects via the miR-495-3p/HIF-1α axis. Limitations included reliance on preclinical models, requiring further clinical validation.

The antiangiogenic effects of Efavirenz (EFV) on oral cancer were investigated by assessing Intratumoral Microvessel Density (MVD) [22]. Methods involved analyzing MVD as a potential factor in understanding EFV's impact on oral cancer cell proliferation and angiogenesis. Results showed EFV treatment did not significantly affect cancer cell viability ($F(6,20) = 0.7970$; $p = 0.5878$). Limitations included the need for further research to clarify MVD's role in EFV-mediated antiangiogenic effects. The antiangiogenic landscape in OSCC was assessed by evaluating MVD in the tumor center and invasion front of 71 patient specimens using CD31 immunostaining [23]. Results showed higher MVD at the invasion front, with high intratumoral MVD positively associated with disease-free survival ($p = 0.047$). Limitations included the need for further studies to clarify spatial microvascular heterogeneity's prognostic impact.

2.1 Research Gap

Despite extensive studies on oral carcinogenesis and hypoxia-driven tumor progression, several gaps remain. Scientometric analyses are limited to published data without experimental validation, restricting mechanistic insights [11]. Chemopreventive studies using ART, RO, and apigenin relied on preclinical models, limiting clinical translatability [12]. Investigations of HIF-1α and hypoxia-induced lncRNAs primarily focused on isolated molecular pathways, neglecting combined effects on hypoxia, angiogenesis, and apoptosis [15]. MVD-based antiangiogenic studies lacked integration with functional bioactive interventions [20]. The proposed analysis addresses these gaps by experimentally evaluating medicinal tea compounds on hypoxia and angiogenesis markers in oral tumor models, providing mechanistic insights with dose-dependent and multi-target assessment for improved translational relevance.

3. MATERIALS AND METHODS

The antioxidant impact of Medicinal Tea Extract (MTE) on angiogenesis and hypoxia in oral cancers was assessed in this study. To create tumors and hypoxic circumstances, a carcinogen was administered to experimental animals and oral epithelial cells. Graded concentrations of MTE were provided orally, and topical treatments of the vehicle or carcinogen were completed on a regular basis based on group assignments. Using PCR, ELISA, and Immunohistochemistry, hypoxia and angiogenesis indicators such as VEGF, HIF-1α, and microvessel density were measured. Standard tests were used to assess apoptosis.

3.2 Experimental Setup

The experimental animals were divided into eight groups to evaluate the effects of MTE on oral tumor development. The Vehicle Control (VC) group received plain drinking water along with a topical vehicle application, serving as a baseline for normal conditions without carcinogen or MTE exposure. The Carcinogen Control (C) group received plain drinking water but it was exposed to the carcinogen 4NQO, either in drinking water or topically, to induce oral tumors. The MTE preventive control (MTE-PC) groups were given graded concentrations of MTE in drinking water without carcinogen exposure to assess the baseline effects of MTE alone. Finally, the MTE preventive with carcinogen (MTE-P+C) groups received the same graded MTE doses along with 4NQO exposure to evaluate the chemopreventive potential of MTE against carcinogen-induced oral tumors. This design allowed for comparison of normal, carcinogen-induced, and MTE-mediated preventive effects on hypoxia, angiogenesis, and apoptosis in oral tissues, explained in Figure 1 and Table 1.

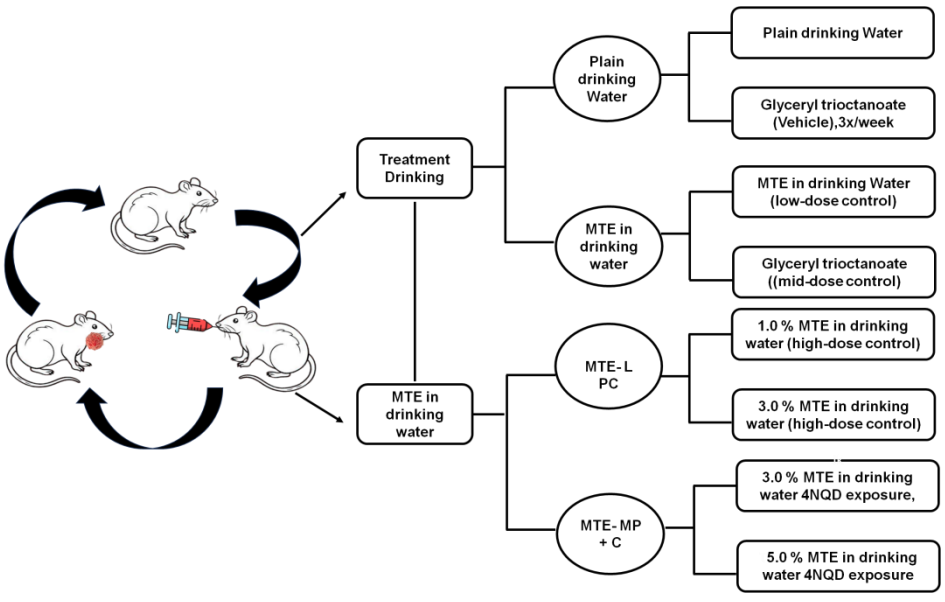

Figure 1 Experimental of rodent's buccal pouch oral cancer

Table 1: Experimental Group to Assess Medicinal Tea Extract's (MTE) Chemopreventive Impact on Oral Tumors

Group code	Treatment (drinking)	Topical / Carcinogen application
VC	Plain drinking water	Glyceryl trioctanoate (vehicle), 3×/week
C (Carcinogen)	Plain drinking water	4NQO in drinking water (or topical 3×/week, depending on protocol)
MTE-L PC	1.0% MTE in drinking water (low-dose control)	Glyceryl trioctanoate, 3×/week
MTE-M PC	3.0% MTE in drinking water (mid-dose control)	Glyceryl trioctanoate, 3×/week
MTE-H PC	5.0% MTE in drinking water (high-dose control)	Glyceryl trioctanoate, 3×/week
MTE-L P&C	1.0% MTE in drinking water	4NQO exposure, 3×/week
MTE-M P&C	3.0% MTE in drinking water	4NQO exposure, 3×/week
MTE-H P&C	5.0% MTE in drinking water	4NQO exposure, 3×/week

3.3 Cell Culture Models

Six to Nine-week-old male rodents were randomly assigned to normal housing with unlimited access to water and food. For 14 weeks, the rodents were provided with topical applications of 4-Nitroquinoline 1-oxide (4NQO) or vehicle control, as well as graded doses of medicinal tea extract in drinking water. They were split into four groups: vehicle control, carcinogen control, MTE preventative control, and MTE preventive with carcinogen. CO_2 inhalation was used to end the lives of the animals. Buccal pouches were evaluated for tumor burden, volume, and multiplicity. Tissue samples were either rapidly cryopreserved for subsequent molecular analyses or fixed and preserved for histopathological examination.

3.4 Compound Preparation and Administration

Medicinal tea compounds rich in polyphenols, such as Epi Gallo Catechin Gallate (EGCG), theaflavin, and catechin, were selected based on their reported antioxidant and antiangiogenic properties. Stock solutions were prepared in Phosphate-Buffered Saline (PBS) and sterilized using a 0.22 µm filter. Cells were divided into four treatment groups: control (untreated), low-dose (1 µM), medium-dose (3 µM), and high-dose (5 µM). Each treatment was administered under both normoxic and hypoxic conditions for 24-48 hours. Positive controls were treated with known antiangiogenic agents (e.g., bevacizumab). At the conclusion of the treatment period, rodents were mercifully slaughtered in accordance with institutional ethical requirements. Tissues from the buccal pouch were promptly gathered, meticulously removed, and prepared for histopathological, biochemical, and molecular examinations following sacrifice.

3.5 Assessment of Microscopic Tumor Parameters and Histopathology

For histological examination, tissues from the buccal pouch were paraffin-embedded, fixed in 10% buffered formalin, and stained. Tumor differentiation, hyperplasia, and aberrant cell growth were evaluated by a blinded pathologist. Calibrated microscopy and image analysis tools were used to quantify microscopic tumor parameters, such as tumor number and area. These analyses examined the impact of medicinal extracts from tea on the initiation and spread of tumors.

3.5.1 Hypoxia and Angiogenesis Markers

The expression levels of hypoxia-inducible factor-1 alpha (HIF-1α) and vascular endothelial growth factor (VEGF) were quantified using multiple analytical techniques:

Immunohistochemistry (IHC): Primary antibodies against VEGF and anti-HIF-1α were treated with fixed cell monolayers, and then HRP-conjugated secondary antibodies were added. A semi-quantitative score was assigned to the staining intensity.

Enzyme-Linked Immunosorbent Assay (ELISA): Using standard sandwich ELISA kits, the protein levels of VEGF and HIF-1α were determined from cell lysates and supernatants, and absorbance was determined at 450 nm.

Quantitative PCR (qPCR): TRIzol was used to extract the total RNA, which was then reverse transcribed into cDNA and

amplified using VEGF, HIF-1α, and GAPDH (housekeeping control) gene-specific primers. It used the 2-ΔΔCt technique to calculate expression levels.

The expression of indicators linked to angiogenesis and hypoxia in buccal pouch tissues was assessed using protein immunoblotting. Following the homogenization of snap-frozen tissues, the total protein has been extracted and measured. The identical quantities of protein were transferred to Polyvinylidene Fluoride (PVDF) membranes. After blocking the membranes, primary antibodies against VEGF, HIF-1α, and other pertinent markers were incubated, and HRP-conjugated secondary antibodies were added. To compare expression levels across treatment groups, chemiluminescence was used to visualize protein bands, and band intensity was measured. The molecular impact of medicinal tea extract on hypoxia of tumors and angiogenesis might be evaluated using this technique.

3.6 Immunohistochemical Analysis and Staining

Hypoxia and angiogenesis indicators in buccal pouch tissues were assessed by immunohistochemistry. After antigen retrieval, paraffin-embedded sections were treated with VEGF and HIF-1α antibodies, HRP-conjugated secondary antibodies, and 3,3′-Diaminobenzidine (DAB) formation. A blinded pathologist assigned a score (0–3+) to the staining intensity and the percentage of positive cells. To evaluate the dose-specific effects of medical tea extract on tumors, microvessel density was measured in hotspot areas. Carcinogen elevated MVD, VEGF, and HIF-1α (3) (12-15). VEGF (1), MTE-H P+C HIF-1α (1), and MVD (3-4) were all dose-dependently decreased by MTE, whereas PC groups stayed low, indicating baseline safety, as shown in Table 2.

Table 2: Effect of Medicinal Tea Extract in Oral Tumors

Group	HIF-1α Expression (Score)	VEGF Expression (Score)	Microvessel Density (MVD / HPF)
VC	0-1	0-1	2-3
C (Carcinogen)	3	3	12-15
MTE-L PC	1	1	3-4
MTE-M PC	1-2	1-2	4-5
MTE-H PC	2	2	5-6
MTE-L P+C	2	2	8-10
MTE-M P+C	1-2	1-2	5-7
MTE-H P+C	1	1	3-4

3.7 Analytical Assessments

The macroscopic tumor burden, volume, multiplicity, and incidence of oral tumor tissues were assessed. Immunohistochemistry (CD31) and histopathology evaluated angiogenesis. Apoptosis markers (Caspase-3) and VEGF and HIF-1α were measured by qPCR, ELISA, and Western blot. Apoptotic death was assessed using TUNEL assays and flow cytometry. To identify significance ($p < 0.05$), statistical analysis was conducted using Tukey's post hoc test and ANOVA.

Apoptosis Analysis used the TUNEL assay and flow cytometry to measure the percentage of apoptotic cells in oral tumor tissues, and the apoptotic consequences of MTE were assessed. Western blot and qPCR were used to examine the levels of apoptotic biomarkers (Caspase-3) and anti-apoptotic molecules Mcl-1. The results showed that apoptosis was induced in a dose-dependent manner and that the apoptotic index increased considerably at higher MTE concentrations as compared to cancer-only controls ($p < 0.05$).

3.8 Statistical Analysis

All quantitative data were expressed as mean ± Standard Deviation (SD). Statistical comparisons between groups were performed using one-way analysis of variance (ANOVA) followed by post hoc Tukey's tests to identify significant pairwise differences. Statistical significance was set at $p < 0.05$. Analyses were conducted using IBM SPSS software (version 26.0). Correlations between HIF-1α, VEGF, and MVD were determined using Pearson's correlation coefficient.

4. RESULTS

MTE treatment demonstrated its substantial molecular chemopreventive potential in oral carcinogenesis by increasing apoptosis and tissue preservation while dose-dependently lowering angiogenesis, hypoxia, inflammation, oxidative stress, and the growth of oral tumors.

4.1 Evaluation of MTE extract

The MTE extract evaluation demonstrated dose-dependent effects of tumor prevention. Its substantial protective activity was confirmed by the fact that high-dose MTE (5%) this concentration prevents the tumor growth prevented tumor growth, decreased tumor multiplicity, volume, and burden, and decreased oxidative stress. Table 3 shows that MTE efficiently and dose-dependently inhibits the growth of oral tumors. In addition to high tumor multiplicity (5.42 ± 1.25), volume (7.18 ± 3.89 mm^3), and burden (38.94 ± 18.73 mm^3), carcinogen-treated rodents (4NQO) also showed increased oxidative stress (MDA: 9.8 ± 0.7 nmol/mg protein). Both pre- and post-administration of MTE considerably decreased these parameters, with MDA dropping to 3.0 ± 0.3 and multiplicity in the medium- and high-dose groups being 1.42 ± 0.83 and 0.00 ± 0.00, respectively. MTE reduces multiplicity, volume, and burden by inhibiting tumor development in a dose-dependent manner.

Table 3: Medicinal tea extract's effects on rodent body weight, oxidative stress, and oral tumor growth

Group	N	Body Weight (g)		Rodents Buccal Pouch Tumors			Histopath. Grading Score	MDA (nmol/mg protein)	p-value
		Initial (Mean ± SD)	Final (Mean ± SD)	Multiplicity (Mean ± SD)	Volume (mm^3 ± SD)	Burden (mm^3 ± SD)			
VC	30	75.46 ± 9.82	114.27 ± 12.91	0	0	0	0.0 ± 0.0	2.1 ± 0.2	-
MTE-L PC (1.0%)	18	73.22 ± 11.13	111.08 ± 15.76	0	0	0	0.2 ± 0.1	2.4 ± 0.3	0.961
MTE-M PC (3.0%)	15	74.85 ± 8.27	112.35 ± 13.94	0	0	0	0.3 ± 0.1	2.5 ± 0.3	0.947
MTE-H PC (5.0%)	15	76.61 ± 8.92	116.42 ± 14.26	0	0	0	0.4 ± 0.1	2.7 ± 0.3	0.934
C (4NQO)	35	76.12 ± 9.15	113.76 ± 11.82	5.42 ± 1.25	7.18 ± 3.89	38.94 ± 18.73	3.9 ± 0.2	9.8 ± 0.7	< 0.001
MTE-L P+C (1.0%)	20	73.04 ± 10.67	106.21 ± 18.45	2.37 ± 1.01 *	1.28 ± 0.58 *	3.54 ± 2.41 *	2.6 ± 0.2	6.5 ± 0.5	0.004
MTE-M P+C (3.0%)	22	72.76 ± 11.48	109.92 ± 17.56	1.42 ± 0.83 *†	1.07 ± 0.47 *	1.93 ± 1.18 *†	1.9 ± 0.2	5.1 ± 0.4	0.002
MTE-H P+C (5.0%)	22	78.03 ± 9.82	121.87 ± 15.34	0.00 ± 0.00 *†‡	0.00 ± 0.00 *†‡	0.00 ± 0.00 *†‡	0.5 ± 0.1	3.0 ± 0.3	< 0.001

Note: * – Significantly distinct from the group that exclusively uses carcinogens (C), † – significantly separate from MTE-L P+C (1.0%) group, ‡ – Significantly separate from MTE-M P+C (3.0%) group

4.2 Analysis of both Microscopic and Macroscopic Buccal Pouch Lesions

The examination of buccal pouch lesions, both macroscopic and microscopic, shows that MTE successfully inhibits the growth of oral tumors. On a macroscopic level, MTE decreased tumor volume, multiplicity, and overall burden in a dose-dependent manner; at large doses, tumors were totally prevented. Histopathology under a microscope showed a reduction in dysplasia and hyperplasia, as well as a considerable suppression of angiogenesis and hypoxia indicators (HIF-1α, VEGF,

and MVD). Higher levels of Caspase-3 and lower levels of Mcl-1 showed an increase in apoptotic activity. These results demonstrate MTE's ability to stop oral carcinogenesis at the tissue and molecular levels by confirming that it has chemopreventive actions by concurrently inhibiting hypoxia, suppressing angiogenesis, and promoting apoptosis. Table 4 shows the exposure to carcinogens resulted in considerable hyperplasia (6.57 ± 0.25 μm²), hyperplasia (4.26 ± 0.13 μm²), and SCC (4.30 ± 0.18 μm²), along with high tumor multiplicity (5.64 ± 1.36), size (7.33 ± 4.04 mm³), and burden (39.77 ± 19.35 mm³). With 5% P+C totally suppressing cancers and lesions, MTE treatment dose-dependently decreased these parameters, demonstrating strong chemopreventive efficacy. With a significant decrease in hyperplasia, dysplasia, and SCC ($p < 0.001$), the 5% P+C group achieved total tumor prevention and demonstrated the strong, dose-dependent chemopreventive effectiveness of MTE in oral carcinogenesis.

Table 4: Post Hoc Tukey for Medicinal Tea Extract Decreases Histopathology and Tumor Growth Dose-Dependently

Group (n=3)	Tumor Multiplicity (Mean ± SD)	Tumor Volume (mm³ ± SD)	Tumor Burden (mm³ ± SD)	Hyperplasia (μm² ± SD)	p-value	Dysplasia (μm² ± SD)	p-value	SCC (μm² ± SD)	p-value
Carcinogen	5.64 ± 1.36	7.33 ± 4.04	39.77 ± 19.35	6.57 ± 0.25	-	4.26 ± 0.13	-	4.30 ± 0.18	-
1% P+C	2.58 ± 1.02	1.31 ± 0.63	3.62 ± 2.50	5.10 ± 0.06	0.016	3.30 ± 0.04	0.015	2.09 ± 0.07	0.015
3% P+C	1.71 ± 0.96	1.12 ± 0.53	1.97 ± 1.26	4.21 ± 0.22	0.004	2.10 ± 0.05	0.003	1.37 ± 0.49	0.005
5% P+C	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	2.91 ± 0.22	<0.001	0.52 ± 0.19	<0.001	0.00 ± 0.00	<0.001

Table 5 shows the ANOVA results, which show that all three forms of oral lesions—hyperplasia, dysplasia, and carcinoma of squamous cells (SCC) have significant differences across treatment groups. For hyperplasia, treatments had a significant impact on lesion development, as seen by the significantly higher between-group variation (SS = 12.48, F = 45.72, $p < 0.005$) than within-group variance. Treatment has a strong effect on both dysplasia (SS = 10.52, F = 52.41, $p < 0.005$) and SCC (SS = 14.18, F = 67.29, $p < 0.005$). When compared to carcinogen-only groups, these greatly significant F-values (***, $p < 0.005$) reveal that MTE treatment significantly reduced the severity of lesions by modulating their progression.

Table 5: ANOVA Statistical Evaluation of Oral Cancer Severity in Rodents by Treatment Group

Lesion Type	Source of Variation	Sum of Squares (SS)	df	Mean Square (MS)	F-value	P-value	Significance
Hyperplasia	Between Groups	12.48	3	4.16	45.72	<0.005	***
	Within Groups	1.08	8	0.135			
	Total	13.56	11				
Dysplasia	Between Groups	10.52	3	3.51	52.41	<0.005	***
	Within Groups	0.536	8	0.067			
	Total	11.056	11				
SCC	Between Groups	14.18	3	4.73	67.29	<0.005	***
	Within Groups	0.562	8	0.070			

	Total	14.742	11			

4.3 The administration of MTE did not cause any cytotoxicity to the tissue of the rodent's buccal pouch

When MTE was administered to animals, there was no visible tissue damage or negative buccal pouch consequences. In all MTE-treated groups, histopathological analysis showed normal epithelial architecture and no indications of cellular degeneration, inflammation, or necrosis. MTE preserved tissue integrity that was identical to the vehicle control, even at the maximum dosage. MTE's suitability for long-term chemopreventive usage against the development of oral tumors without endangering healthy oral tissues is supported by these findings, which show that it is non-toxic and biologically safe. Western blot and IHC molecular analysis revealed no discernible differences between the PBPs (1%, 3%, and 5% MTE) and vehicle control groups. In normal buccal tissues, MTE at test doses is safe and non-toxic, as evidenced by the unchanged levels of apoptotic indicators (Caspase-3, PARP), inflammation (TNF-α), proliferation (Ki-67, Cyclin E), and DNA damage (MDA).

4.4 Pre- and concurrent treatment with MTE

In the buccal pouch tissues of rodents, pre- and concurrent administration of Medicinal Tea Extract (MTE) greatly increased apoptosis while significantly reducing oxidative DNA damage, inflammation, and cellular proliferation caused by carcinogens. A dosage-dependent decrease in tumor characteristics, such as multiplicity, volume, and overall burden, was seen, with the highest MTE dose (5%) totally inhibiting tumor formation. Carcinogen-exposed tissues had markedly higher levels of molecular markers linked to DNA damage apoptotic indicators (Caspase-3, PARP), inflammation (TNF-α), proliferation (Ki-67, Cyclin E); however, these markers were successfully downregulated after MTE was administered. These results show that MTE is a powerful chemopreventive agent that can stop the growth of oral tumors and bring the cells back to normal.

4.4.1 MTE-enhanced carcinogen-induced apoptosis

MTE's chemopreventive potential was demonstrated by a significant increase in apoptosis observed the buccal pouch tissues of rodents exposed to carcinogens, both before and during treatment. Apoptotic indices were much lower in the carcinogen group, indicating a decrease in programmed cell death and an increase in tumor growth. The highest dose demonstrated maximal activation of apoptosis, and MTE therapy restored apoptotic metabolism in a dose-dependent manner. In addition to lower production of hypoxia and angiogenic markers, such as HIF-1α, VEGF, and vessel density, this effect was accompanied by decreases in tumor growth rate, volume, and burden. Histopathological analysis showed that groups treated with MTE had fewer hyperplastic, dysplastic, and SCC lesions, which were associated with increased apoptosis. Restoring apoptosis probably helped get rid of damaged or altered cells, which stopped precancerous lesions from turning into cancer. MTE demonstrated its protective, dose-dependent impact in preventing oral tumors and bolstered its potential as an organic chemopreventive drug by successfully counteracting carcinogen-induced apoptotic suppression.

4.4.2 MTE decreased carcinogen-induced inflammation, oxidative DNA damage, and proliferation

Expression of MDA, TNF-α, and Ki-67 was comparable among all vehicle control and MTE control groups (1%, 3%, and 5%). In the carcinogen (4NQO) group, expression of these markers was significantly higher than in vehicle controls. Pre- and concurrent treatment with MTE caused a dose-dependent decrease in MDA, TNF-α, and Ki-67, with the lowest expression observed in the 5% MTE+carcinogen group. Immunohistochemistry results for TNF-α and Ki-67 were consistent with Western blot analysis. These findings indicate that MTE effectively reduces carcinogen-induced oxidative DNA damage, inflammation, and proliferation, demonstrating its antioxidant, anti-inflammatory, and anti-proliferative chemopreventive potential in oral tumor development as shown in Figure (2 and 3).

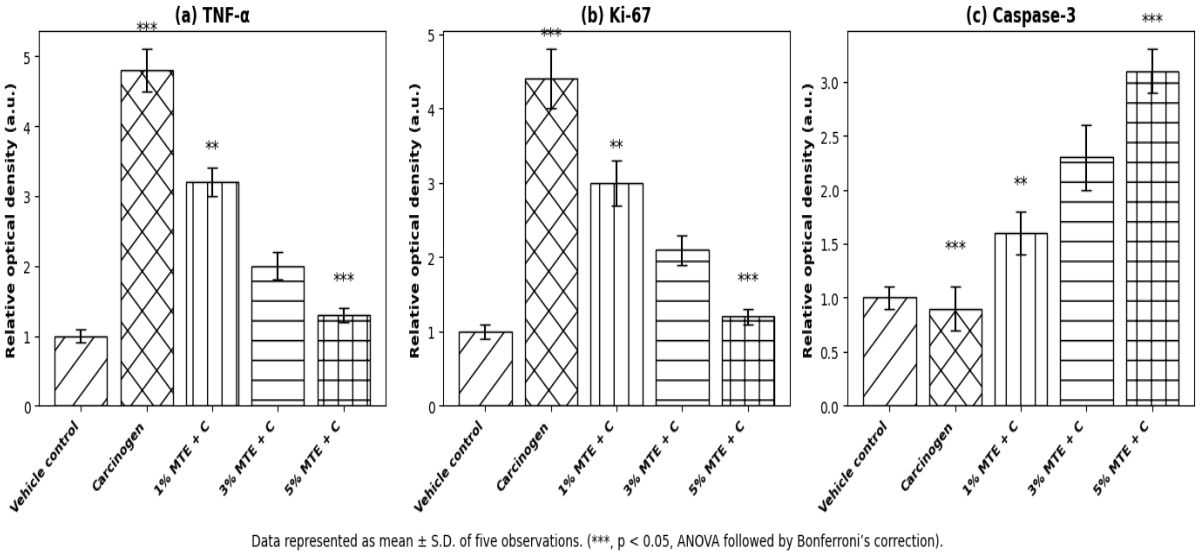

Figure 2: Error bar representation of average densitometry values among expserimental groups with biomarkers (a) TNF-α, (b) Ki-67, and (c) Caspase-3

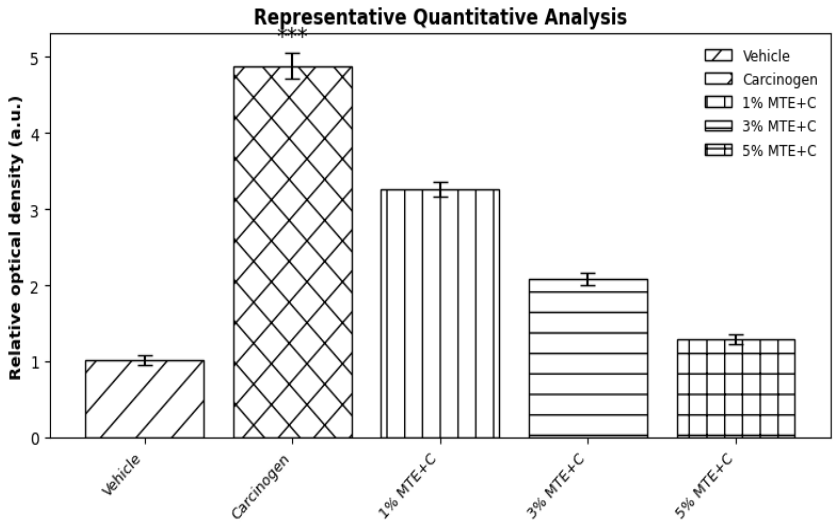

Figure 3: Effect of dose-dependent MTE on changes in optical density resulting from carcinogens

4.4.3 MTE increased carcinogen induced apoptosis

By increasing caspase-3 activation, encouraging programmed cell death, and decreasing the ability to survive of dysplastic and carcinogenic oral epithelium cells in treated groups, MTE accelerated carcinogen-induced apoptosis. Figure 4 shows that the graphs illustrate the relative optical densities of Caspase-3, Ki-67, and MDA among treatment groups. In contrast to the carcinogen group, which had significantly higher MDA levels due to enhanced lipid per oxidation, the polyphenolic-rich beverage treatment (1%, 3%, and 5%) dramatically decreased MDA levels ($p < 0.005$), demonstrating great antioxidant activity. As a result of treatment, the proliferation marker Ki-67 expression dramatically dropped, whereas Caspase-3 levels rose, indicating greater apoptosis. The polyphenol supplementation reduced oxidative stress, stopped cell division, and encouraged apoptosis in the development of oral cancer.

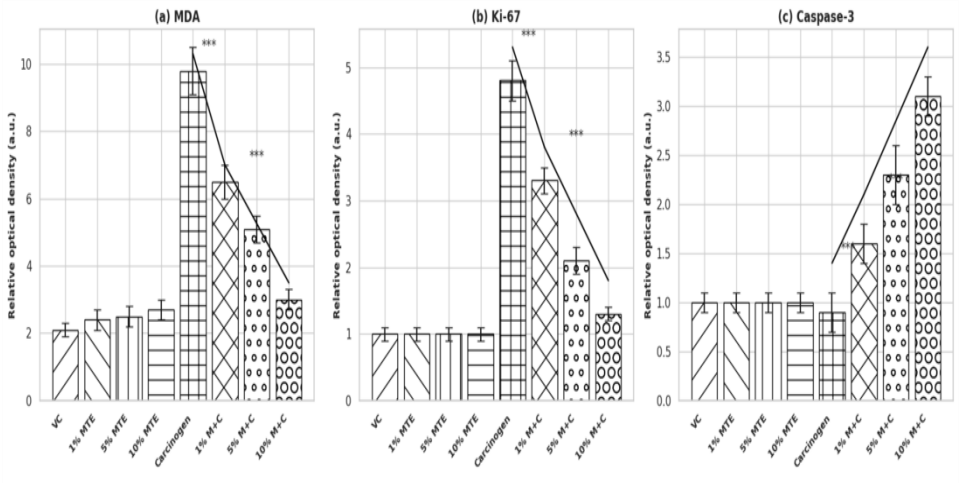

Figure 4: Immunohistochemical Impact of PC Therapies on Apoptosis and Oxidative Stress Indicators includes (a) MDA (b) Ki-67 (c) Caspase-3

4.5 Pre and concurrent MTE treatment, carcinogen-induced production of VEGF and HIF-1α was reduced.

HIF-1α and VEGF expression in Rodents Buccal Pouch (RBP) tissues was shown to be low and statistically non-significant in MTE control groups (1%, 3%, and 5%) compared to the vehicle control. The carcinogen-treated group demonstrated a strong and significant increase in VEGF and HIF-1α expression, suggesting increased angiogenesis and hypoxia. HIF-1α and VEGF expression were clearly down regulated in a dose-dependent manner both before and after treatment with MTE; the 5% MTE + carcinogen group showed the largest drop. Results from Western blotting further supported the anti-hypoxic and anti-angiogenic effects of MTE, emphasizing its capacity to prevent tumor vascularization and growth by suppressing the HIF-1α–VEGF. MTE inhibited hypoxia-driven vasculature and tumor growth by dramatically lowering carcinogen-induced HIF-1α expression. Through polyphenol-mediated regulation of oxidative damage and signaling pathways, high-dose MTE restored normal HIF-1α levels shown in Figure 5.

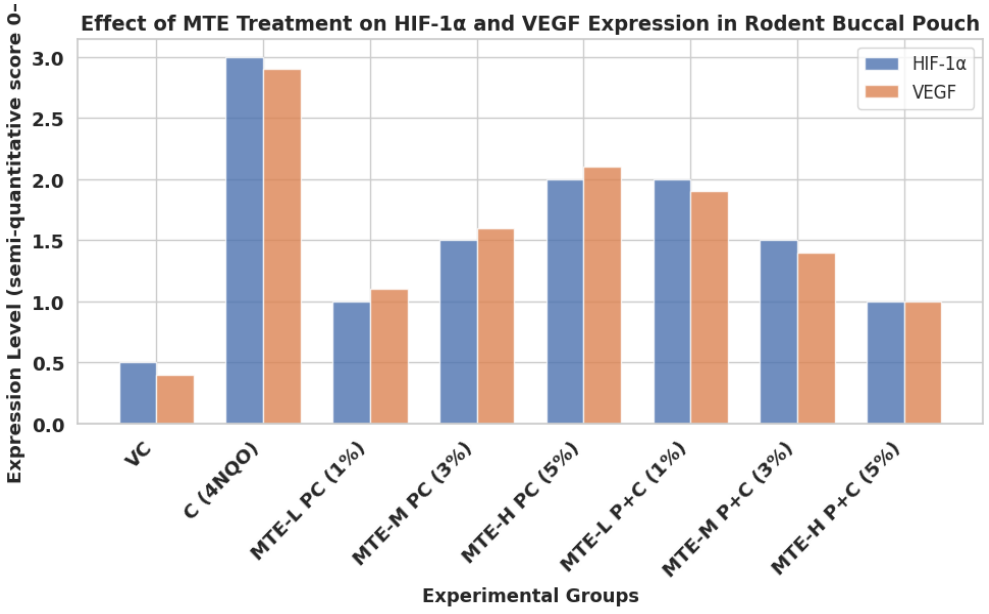

Figure 5: Effect of MTE treatment on HIF-1α and VEGF in Rodents Buccal Pouch

4.6 qPCR Examination of Inflammation, Proliferation, Angiogenesis, and Apoptosis Markers

The transcriptional alterations of important genes involved in angiogenesis, inflammation, proliferation, and apoptosis were assessed in rodent buccal pouch tissues using quantitative PCR (qPCR). SYBR Green chemistry was used for amplification after total RNA had been removed and reverse-transcribed into cDNA. Target genes included the pro-apoptotic Caspase-3, the anti-apoptotic Mcl-1, the proliferation-promoting Ki-67 and Cyclin E, the inflammatory TNF-α, and the angiogenesis-promoting HIF-1α and VEGF, with GAPDH acting as an internal regulator. Utilizing the 2^-ΔΔCt technique, relative levels of expression were determined. In contrast to apoptotic genes, carcinogen exposure markedly increased proliferative, inflammatory, and angiogenic genes. A dose-dependent reversal of these effects was observed upon pre- and concurrent administration of MTE, which increased pro-apoptotic gene expression while decreasing anti-apoptotic, inflammatory, and angiogenic protein production. By proving that MTE can restore normal cell equilibrium and stop the growth of oral tumors, these results support its molecular chemopreventive ability as shown in Figure 6

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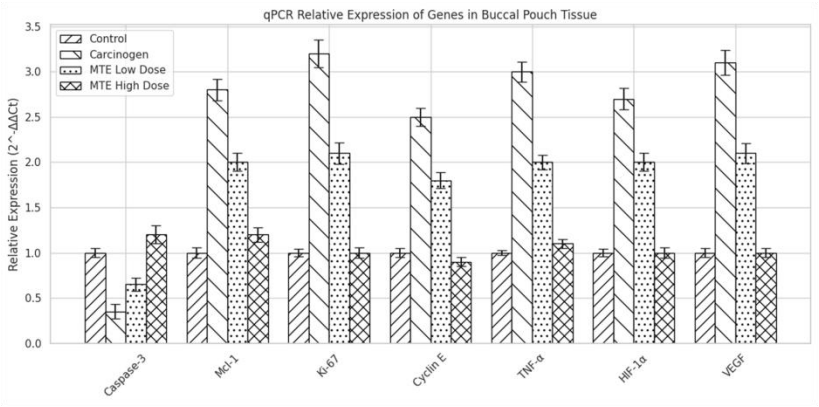

Figure 6: qPCR of Buccal Pouch Gene Expression Inflammation, Proliferation, Angiogenesis, and Apoptosis Markers

4.7 Analysis of correlations between various molecular markers implicated in the development of the rodent's buccal pouch oral cancer

Analysis of rodent buccal pouch tissues using Western blotting and immunohistochemistry revealed strong relationships between important molecular indicators of oral cancer. Pro-apoptotic Caspase-3 and anti-apoptotic Mcl-1 exhibited a substantial inverse association ($R = –0.91$, $p = 0.03$) in tissues treated with carcinogens, suggesting that apoptosis was suppressed. There was a strong positive correlation between the proliferation markers Ki-67 and Cyclin E ($R = 0.88$, $p = 0.02$), indicating increased cell proliferation. Hypoxia signaling and vascularization were linked by the substantial positive correlation ($R = 0.92$, $p = 0.01$) between the angiogenesis markers HIF-1α and VEGF. Proliferation and tumor measurements showed favorable correlations with oxidative stress (MDA) and inflammation (TNF-α) ($R = 0.85–0.9$, $p < 0.05$). The majority of indicators showed dose-dependent normalization across MTE-treated groups (1%, 3%, and 5% + carcinogen), while pro-apoptotic Caspase-3 showed an inverse correlation with angiogenesis, inflammation, and proliferation, underscoring the chemopreventive effect of MTE.

4.8 Discussion

Medicinal Tea Extracts (MTE) significantly modulated molecular markers associated with rodent buccal pouch oral cancer. Carcinogen exposure increased oxidative stress, inflammation (TNF-α), proliferation (Ki-67, Cyclin E), and hypoxia/angiogenesis markers (HIF-1α, VEGF), while suppressing apoptosis (Bax, Caspase-3). MTE dose-dependently reduced MDA, TNF-α, Ki-67, HIF-1α, VEGF, and Mcl-1, while enhancing Bax and Caspase-3, correlating with decreased tumor multiplicity, volume, burden, and histopathological lesions (hyperplasia, dysplasia, SCC). These results demonstrate strong positive correlations between oxidative stress, inflammation, hypoxia, and tumor progression, and negative correlations with apoptosis. MTE's multi-targeted effects prevent tumor development safely, highlighting its chemopreventive potential.

4.8.1 Prevention of Angiogenesis and Hypoxia

In solid tumors, hypoxia stimulates angiogenesis through VEGF and is fueled by HIF-1α. A hypoxic, angiogenic environment was confirmed in this research by the substantial elevation of HIF-1α and VEGF following 4NQO exposure.

MTE therapy, both before and after, reduced microvessel density (MVD) by dose-dependently downregulating VEGF and HIF-1α at the transcriptional and protein levels. Significantly, the 5% MTE+carcinogen group showed strong inhibition of hypoxia-induced angiogenesis by fully suppressing HIF-1α, VEGF, and MVD. This is in line with earlier findings that tea polyphenols alter angiogenic and hypoxic pathways in cancer models [12]. MTE's polyphenols promote the breakdown of HIF-1α, disrupting its stabilization. By hindering tumor vascularization and reducing the delivery of nutrients and oxygen, the concurrent decrease in VEGF limits the growth and evolution of tumors.

4.8.2 Effects of Antioxidants and Anti-Inflammatory

Oral carcinogenesis is caused by oxidative stress and chronic inflammation, while exposure to carcinogens raises MDA, TNF-α, Ki-67, and Cyclin E. These indicators were decreased by MTE in a dose-dependent manner, exhibiting anti-inflammatory, anti-proliferative, and antioxidant properties. MTE's multi-targeted chemopreventive potential is demonstrated by its capacity to preserve genomic stability, inhibit mutations, and stop tumor growth by scavenging reactive oxygen compounds and modifying signaling.

4.8.3 Safety and Tissue Integrity

The safety and specificity of chemopreventive drugs are crucial. As demonstrated by normal epithelial architecture and unchanged expression of apoptosis, proliferation, and DNA damage markers, MTE treatment in control mice (1%, 3%, and 5%) did not cause significant histological alterations or tissue damage. This supports MTE's potential translational application in the prevention of oral cancer by confirming that it is non-toxic and physiologically safe for long-term administration.

4.8.4 Effectiveness of Dose-Dependent Chemoprevention

MTE showed a definite dose-dependent effect on all evaluated parameters, including tumor burden, hypoxia, angiogenesis, apoptosis, oxidative stress, and inflammation. The maximum dosage (5%) restored apoptotic activity, normalized angiogenesis and hypoxia indicators, and totally prevented tumor development. This emphasizes how crucial dose optimization is to attaining the highest level of chemopreventive effectiveness while preserving safety.

4.8.5 Implications for Preventing Oral Cancer

The MTE is a potentially effective dietary or pharmaceutical intervention for high-risk individuals because it targets several hallmarks of oral carcinogenesis, including inflammation, oxidative stress, angiogenesis, apoptosis, and hypoxia. Due to its multi-targeted action, safety profile, and natural origin, it is a good choice for preventative measures and may even be able to supplement traditional treatments. Additionally, the correlation analysis provides a molecular basis for the chemopreventive activity of MTE by indicating that it not only slows tumor growth but also maintains normal cellular homeostasis.

4.8.6 Limitation of Previous Research

Earlier research on oral carcinogenesis has a number of drawbacks. Human translatability was limited by the fact that many chemopreventive studies, including those on apigenin or ART/RO, only used preclinical animals [16]. Mechanistic insight was limited by the lack of experimental validation in scientometric analysis [22,**29**]. Furthermore, natural bioactive substances were frequently not evaluated in antiangiogenic research based on microvessel density, which resulted in gaps in understanding of chemoprevention [19,**30**]. OSCC angiogenesis may not be fully understood due to a small sample size, inconsistent staining interpretation, and the lack of molecular angiogenic markers [**25]**. Self-reported data, a small sample size, and limited applicability to non-dental or larger student populations are some of the shortcomings [**24]**. Tea polyphenols' limited oral bioavailability (EGCG, for example) may limit systemic/tissue exposure, which would lower translational efficacy [**26]**. One drawback is the use of a humanized rat model, which might not accurately replicate the immune system reactions and metabolism of human NSCLC [**27]**. Effective clinical translation of polyphenolic drugs is hampered by their low solubility, restricted bioavailability, and poor stability [**28]**. The absence of comprehensive molecular mechanism analysis and in vivo validation for the effects of Jing-Si herbal tea is a limitation of the research [31]. Lack of dose-response analysis, long-term toxicity assessment, and use of a single animal model are limitations [32]. To overcome these limitations by combining molecular validation, dose-related analysis, and long-term risk assessment with both in vitro and in vivo models. It makes use of human-relevant models of oral carcinogenesis, evaluates angiogenesis, apoptosis, and inflammation and makes use of analytics and sophisticated imaging to enhance translational precision and mechanistic comprehension.

5. CONCLUSION

The growth of oral cancers is strongly chemo prevented by MTE, which is rich in polyphenolic compounds such as EGCG, theaflavin, and catechins. MTE considerably reduced the development of oral tumors caused by the carcinogen (4NQO) both before and after treatment, in a dose-dependent way. Tumor development was totally stopped by high-dose MTE (5%), which decreased the tumor burden from 38.94 ± 18.73 mm^3 to 0.00 mm^3, the tumor multiplicity from 5.42 ± 1.25 in the carcinogen group to 0.00 ± 0.00, and the tumor volume from 7.18 ± 3.89 mm^3 to 0.00 mm^3. Angiogenesis and hypoxia

were significantly suppressed, according to molecular analysis; microvessel density decreased from 12–15 to 3–4 vessels/HPF, and HIF-1α and VEGF expression scores dropped from 3 to 1. MTE also decreased oxidative stress (MDA: 9.8 ± 0.7 to 3.0 ± 0.3 nmol/mg protein) and the inflammatory marker TNF-α, while also restoring apoptotic activity, as shown by decreased Mcl-1 levels and increased Caspase-3 expression. Significant downregulation of the proliferative markers Cyclin E and Ki-67 supports the anti-proliferative effects. Crucially, MTE preserved normal epithelial architecture in control mice and did not exhibit any toxicity. These results demonstrate that MTE is a safe, efficient, and multi-targeted chemopreventive drug that has the potential to prevent oral cancer in humans by reducing oral carcinogenesis through the modulation of hypoxia, angiogenesis, apoptosis, inflammation, and oxidative stress.

It is limited by its dependence on preclinical cell culture and rodent models, which cannot accurately mimic human oral carcinogenesis. In addition to investigating synergistic effects with traditional medicines for increased translational potential, future research should concentrate on clinical studies to assess the safety, accessibility, and chemotherapy preventive effectiveness of medicinal tea ingredients in humans.

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