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EVALUATION OF SALVIA ROSMARINUS AND CORIANDRUM SATIVUM AS CHEMOPREVENTIVE AGENTS IN INDUCED ORAL SQUAMOUS CELL CARCINOMA (AN EXPERIMENTAL STUDY)

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ABSTRACT

INTRODUCTION: The most prevalent malignant tumor of the head and neck region is squamous cell carcinoma. The bad prognosis and low survival rate are mainly related to oral cancer patients. Developing chemopreventive techniques has been crucial to reduce the incidence of oral cancer. Chemoprevention with natural products has emerged as viable preventive options. Salvia rosmarinus and Coriandrum sativum have been studied and discovered to have powerful anticancer properties.

AIM OF THE STUDY: The present trial was proceeded to study the effects of salvia rosmarinus and coriandrum sativum during experimental hamster buccal pouch carcinoma induction; using PCNA as cancer proliferative cell marker.

MATERIAL AND METHODS: A total of 60 adult male hamsters were divided into 5 equal groups. Group I, biopsies of normal pouch mucosa were obtained as a negative control. All remaining groups were painted by DMBA as a carcinogenic agent. Group II, as a positive control group, was only painted by DMBA. Group III received topically salvia rosmarinus oil. Group IV received topically coriandrum sativum oil. Group V received both oils together. After 16, 24, and 32 weeks, 2 to 4 animals from every group had been sacrificed. Tissue lesions were prepared, and paraffin sections were stained with primary antibody for PCNA immunohistochemical evaluation.

RESULTS: The salvia rosmarinus and coriandrum sativum; either alone or in combination, significantly reduced the carcinogenic effect for DMBA-induced oral carcinogenesis.

CONCLUSION: Salvia rosmarinus and coriandrum sativum have a chemopreventive considerable action versus oral cancer development, and their synergetic action is considerably more effective.

KEYWORDS: Chemoprevention, Salvia Rosmarinus, Coriandrum Sativum, PCNA, Oral Squamous Cell Carcinoma.

RUNNING TITLE: Salvia Rosmarinus and Coriandrum Sativum Effects in OSCC.

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INTRODUCTION

Malignancy is one of the most important mortality causes all over the world; one death from six deaths is from this dangerous disease (1). Cancer in Egypt is the 2nd cause of death after cardiovascular illnesses (2). Oral cavity cancerous lesions are common in the human population, and oral squamous cell carcinoma (OSCC) accounts for 90% of malignancies of oral cavity (3). Hamster buccal pouch (HBP) malignant model has already identified various cancer phenotypes that are more resembling of human oral neoplasm development (4). Dimethylbenz[a]anthracene (DMBA) induced HBP carcinogenesis bears many similarities to human OSCC (5). A series of hyperplasia, dysplasia, and carcinoma are preceded by multistep carcinogenesis, which is known to be induced by the strong site-specific carcinogen DMBA. The HBP model has several advantages, such as an easy-to-access location for lesion monitoring and investigation, and a straightforward and predictable tumor induction process. Chemopreventive as well as chemotherapeutic drugs can be tested using this model (6). Understanding the molecular pathways behind oral cancer in humans has always been a priority. One promising course of management is chemoprevention. An appealing substitute that lessens the harmful effects is the topical and systemic application of

natural chemopreventive agents (7). Compounds with several uses in the domains of biochemistry, pharmacy, and medicine can be found in abundance in natural products (8). Chemoprevention is a new and exciting strategy that uses natural substances to regulate, restrict, or stop the growth of tumors (9). Many phytochemicals used by humans has antioxidant, anticarcinogenic and anti-cell proliferation activities (10).

Salvia rosmarinus, a mediterranean plant, contains a proprietary rosemary extract with a lot of polyphenolic compounds, including flavonoids, phenolic acids, diterpenes, triterpenic acids, lignans, 1-3hydroxybenzoic acid, hydroxycinnamic, and rosmarinic acid derivatives (11). Supercritical fluid extraction of rosemary extract significantly reduces malignancy growth and metastasis markers, including proliferation, migration, and invasion, thereby demonstrating antitumor efficacy. Rosemary extract has been found to have chemoprotective properties against hepatotoxicity, gastrointestinal ulcer-related illness, and cancer. It's anti-oxidant and anti-inflammatory properties have been shown in studies on colon, skin, breast, and ovarian cancers. It activates cell cycle arrest in G0/G1 and G1/S phases, as well as the mitochondrial pathway, and has antiproliferative and antiangiogenic properties against cancer cells (12).

Coriandrum sativum, a common herb in cooking and food seasoning, has been explored for its role in triggering apoptosis and its biochemical definition has been used in therapy detection (13). Numerous studies on coriander have revealed a variety of pharmacological benefits, including antibacterial, antioxidant, and anti-inflammatory characteristics. Coriander's antibacterial activity in addition to conventional antibiotics/antifungal drugs have been shown to synergistically impact. Besides its antitumorigenic qualities, coriander is a good addition to conventional therapy as it guards against the effects of colon cancer connected to lipid metabolism (14, 15). C. sativum can prevent oxidative stress-related illnesses and improve cancer treatment by preventing free radical production, oxidative stress, and degradation of vital components. Chemopreventive characteristics of C. sativum induce apoptosis via deat h receptor and mitochondrial pathways, hence increasing the activities of caspase-8, -9, and -3 in malignant cells (16).

The current research aimed to assess the efficacy of co riandrum sativum and salvia rosmarinus as chemoprev entive agents by comparing their individual and combi ned effects on experimentally developed OSCC.

MATERIAL AND METHODS

The research was done in the faculty of dentistry at Alexandria University with the agreement of the Animal Research Ethics Committee. It included 60 adult, gold, and pathogen-free Syrian hamsters that were 8 weeks old and weighed between 80 and 100 grammes each. These animals were received from the Theodor Bilharz Institute in Cairo, Egypt. They were housed in display polypropylene cages with regulated temperatures and 12-hour light/dark periods. They were fed a sterilized, 16%-protein meal free of soy and unlimited tap water access. This study used DMBA as a carcinogen (Sigma, USA), salvia rosmarinus oil, and coriandrum sativum oil as chemopreventive agents (Nawah Scientific Lab, Egypt). There is also an immunohistochemical (IHC) kit and a primary antibody for proliferating cell nuclear antigen (PCNA) (BioVision, Inc., USA).

The study's sample size was estimated using MedCalc Statistical Software version 19, with a minimum of 11 per group and an additional 12 to compensate for laboratory processing errors. Hamsters were divided into 5 groups of 12 each. The 1st group (I) acted as a regular control group, and normal buccal mucosa were excised. The second group (II) got solely the cancer-inducing substance and was classified as an active control group. The 3rd, 4th, and 5th groups got the carcinogenic agent in addition to salvia rosmarinus oil in group (III), coriandrum sativum oil in group (IV), or a combination of both oils in group (V). Drugs applied topically on the left buccal pouch with a number 4 paint brush three times per week in alternative days with the carcinogen.

After 16, 24, and 32 weeks of cancer induction and application of chemopreventive medicines, 2-4 animals from each group were slaughtered according to protocols of animal rights. Each hamster's left buccal pouch was opened longitudinally via the wall of skin and removed, then submerged in 10% formalin for a day.

The samples were then sliced, fixed in paraffin, and sectioned to a thickness of 4um. Then they were placed on slides, and hematoxylin and eosin (H&E) stain was applied. The histological sections from all groups were examined with a light microscope. Other successive sections, 3-4 um thick, were put on slides (super-frost plus-coated) and immunohistochemically stained with monoclonal PCNA antibody. Descriptive slides were deparaffinized, then rehydrated and stained using the peroxidase-antiperoxidase technique. An antigen-unmasking high-temperature approach was used in citrate buffer pH 6.0 in a microwave oven twice for 5 minutes each. The slices were treated with secondary antiserum after a rinse in phosphate-buffered saline. After that, they were rinsed in PBS, treated with avidine mixed biotine, and prepared in a peroxidase reaction with 0.01% H2O2 in PBS buffer (17). PCNA expression was examined, utilizing using an image analyzer with Image J software. Its staining was counted using a magnification of x400. A minimum of 10 sections of each hamster were haphazardly selected to determine the PCNA area percentage and optical density containing the most intensely immunostained tissues and the degree of immunoreactivity, respectively. The staining reaction

appeared as brown coloration, and its intensity was assessed as negative (0), weak (1), moderate (2), and strong (3).

Statistical Analysis

The collected data has been tabulated, and statistically analyzed with the SPSS system (version 11.0 software). The findings were presented as the mean Standard Deviation (± SD). The data was evaluated using a one-way ANOVA between the researched groups. One-way ANOVA was used to calculate average PCNA area percentage and optical density. It was applied to Post-hoc multiple comparisons with a last significant difference (LSD) of 0.05. All statistical results were ruled on significant at a P-value of <0.05.

RESULTS

This trial involved 60 Syrian golden hamsters. After retracting the skin of each hamster's buccal mucosa on the left side, the medial wall was meticulously examined to detect any pathological alterations and assess the clinical and histological conditions. The developing cancer happening varied throughout the research groups as showed in Table 1, and Figure 1. During the study period, no pathogenic alterations were found in **Group I.** On the other hand, **Group II** only got DMBA. During the trial, oral lesions ranging from carcinoma in situ to poorly differentiated OSCC occurred in 9 out of 12 animals (75%). Group I and group II had significantly different malignancy incidence rates ($p < 0.0001$). **In Group III**, DMBA and salvia rosmarinus oil were administered to the hamsters, 4 of the 12 animals (33.3%) in this trial exhibited OSCC, ranging in kind from initially invasive to moderately differentiated OSCC. The variance in the occurrence of malignancies between groups II and III was very statistically significant ($p < 0.0001$). Likewise, the same is true when assessing group I with group III. **Group IV** employed coriandrum sativum oil as a chemotherapeutic agent when painting the buccal pouches with DMBA. Throughout this study, 5 of the 12 animals (41.6%) had OSCC ranging from well to moderately differentiated. Group IV had a significantly higher reach of lesions ($p < 0.0001$) compared to prior groups I, II, and III. The animals in **Group V** were administered a combination of salvia rosmarinus oil and coriandrum sativum when painting the buccal mucosa with DMBA. Throughout the experiment, 3 out of 12 lesions (25%) developed OSCC that ranged from an early invasive type to a well-differentiated form. Group V had a significantly lower reach of lesions ($p < 0.0001$) compared to prior groups II, III, and IV. The histopathological variation between groups was evaluated via H&E slides to demonstrate an accurate diagnosis as shown in Figure 2.

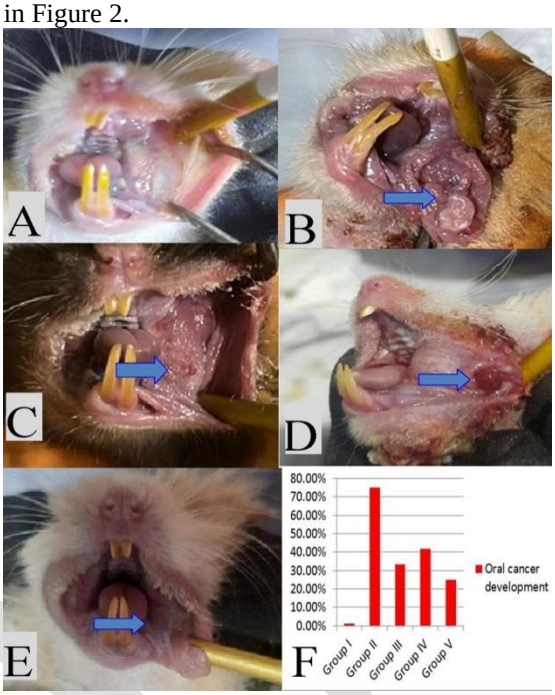

Figure 1: A Photomicrograph showing the Clinical Presentation for HBPs at 24 Weeks of the Trial; (A) Group I, Normal Presentation of HBP Mucosa. (B) Group II, Endophytic Ulcers with Necrotic Floors and Raised Borders. (C) Group III, Erythematous Papules. (D) Group IV, Tiny Exophytic Nodule. (E) Group V, Areas of White Patches. (F) The Percentage of Hamsters that Developed Oral Cancer among the Research Groups.

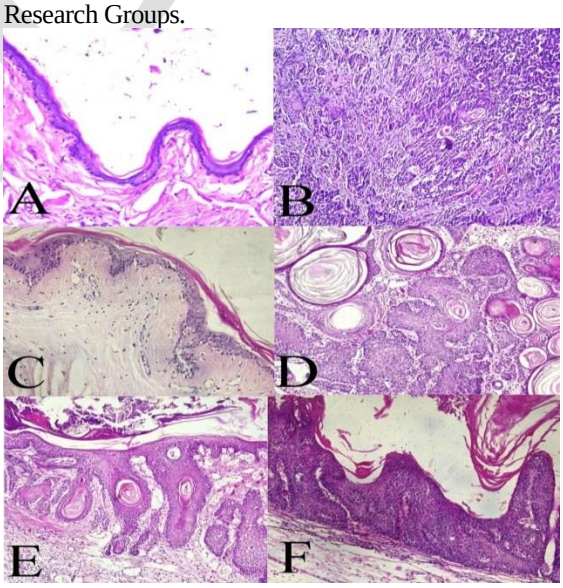

Figure 2: A Photomicrograph showing the Histopathological Examination for HBPs at 24 Weeks of the Trial: (A) Group I, Normal Histology of HBP Mucosa (X200). (B) Group II, Poorly Differentiation OSCC (X200). (C) Group III, Mild Epithelial Dysplasia (X200). (D) Group IV, Well Differentiation OSCC (X200). (E) Group V, Early invasive OSCC (X200). (F) Group V, Sever Epithelial Dysplasia (X200).

Immunohistochemical Evaluation

The proliferative marker, anti-PCNA antibody, was used to conduct an IHC evaluation among the study groups as demonstrated in Figure 3. Using an image analyzer computer system, the immunoreaction to anti-PCNA in the various experimental groups revealed differences in the means of the area percent and the optical density were showed at Table 2. The result revealed that **Group I** (the control group) had weak positive anti-PCNA antibody that was expressed in the basal and parabasal layers of epithelium. Anti-PCNA area percentage and optical density were the least values among study groups. **Group II** exhibited the highest mean anti-PCNA optical density and an anti-PCNA area percent. When relating group II and I, the variances in anti-PCNA area percent and optical density were extremely significant statistically ($p < 0.0001$). However, in **Group III,** the mean anti-PCNA area percent and the mean anti-PCNA optical density values were close to control group I. When comparing groups II and III, the variances in anti-PCNA area percent and optical density were extremely significant statistically ($p < 0.0001$).

In **Group IV**, there was a significant difference in anti-PCNA area percent ($p < 0.0001$) between groups II and IV. In both cases between groups IV and I and between groups IV and III, the variance in anti-PCNA area percent stayed not significant. Relating group IV to the preceding groups, I, II, and III, revealed statistically significant differences in anti-PCNA optical densities. **Group V** had a mean anti-PCNA area percentage and an average anti-PCNA optical density close to group III and group I. When comparing groups V and II, there was a considerable difference ($p < 0.0001$) in anti-PCNA area percentage and optical densities. When comparing groups I, III, IV and V, there was no statistically significant difference in anti-PCNA area percent.

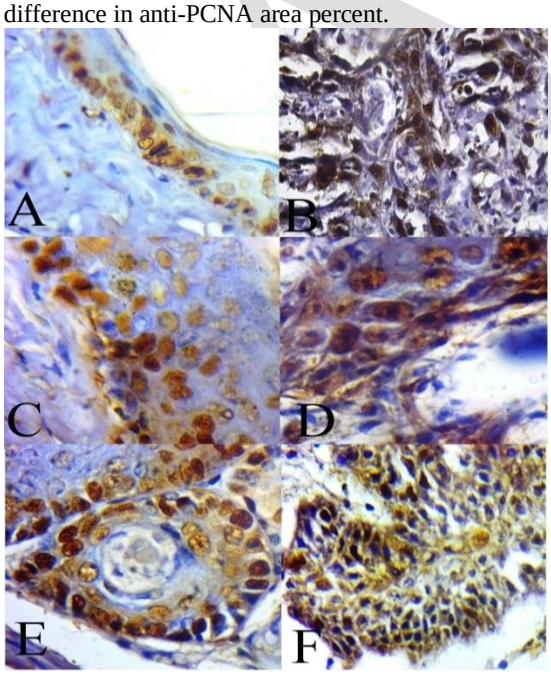

Figure 3: A Photomicrograph showing the PCNA Expression for HBPs at 24 Weeks of the Trial: (A) Group I, Normal HBP Epithelial Lining with Positive Expression in the Basal and Para basal layers. (X400). (B) Group II, Poorly Differentiation OSCC with Strong Positive Expression (X400). (C) Group III, Mild Epithelial Dysplasia with Weak Positive Expression (X400). (D) Group IV, Well Differentiation SCC with Moderate Positive Expression (X400). (E) Group V, Well Differentiation OSCC with Weak Positive Expression (X400). (F) Group IV, Moderate Differentiation OSCC with Moderate Positive Expression (X400).

Table (1): The Summary of the Histopathological Finding

No.	Weeks	Group I	Group II	Group III	Group IV	Group V
1.	16	No Pathological Changes	Focal Epithelial Thickening	No Pathological Changes	No Pathological Changes	No Pathological Changes
2.			Epithelial Dysplasia			
3.			Carcinoma In Situ			
4.			Early Invasive Carcinoma	Hyperkeratosis	Epithelial Dysplasia	
5.	24	No Pathological Changes	Well OSCC	No Pathological Changes	No Pathological Changes	No Pathological Changes
6.						
7.				Epithelial Dysplasia	Epithelial Dysplasia	
8.			Moderate OSCC		Well OSCC	Well OSCC
9.	32	No Pathological Changes	Moderate OSCC	Epithelial Dysplasia	No Pathological Changes	No Pathological Changes
10.		Epithelial Hyperkeratosis				
11.		Epithelial Hyperkeratosis	Poorly OSCC	Well OSCC	Moderate OSCC	Well OSCC
12.		Epithelial Hyperkeratosis		Moderate OSCC		

Table (2): It Shows the Relationship between the Examined Groups in Terms of PCNA Area Percentage and Optical Density.

Group	I	II	III	IV	V
PCNA Area Percent					
Min.	23	34	25.2	29	26
Max.	42	59.6	45	53.2	44
Mean	33.40	45.20	35.24	38.28	34.35
SD	6.57	7.77	6.36	8.22	6.44
PCNA Optical density					
Min.	39.6	43.1	39.2	41.7	34.7
Max.	58.7	94.2	73.2	73.4	65.8
Mean	47.2	68.78	48.80	53.16	48.42
SD	6.92	15.33	10.44	11.01	10.52

DISCUSSION

Chemoprevention developed a viable method of inhibiting, suppressing, or regulating the occurrence of carcinogenesis utilizing specific natural and synthetic chemicals (19). Coriandrum sativum and salvia rosmarinus are inspiring natural agents versus oral carcinogenesis because of their high polyphenol content, which limits cell proliferation by regulating the apoptotic transduction pathways (20).

Among the study groups, the second group, which received DMBA topically alone, had clearly evident lesions in their buccal pouches. The findings support those of *Manoharan et al*. as well as *Selvasundaram et al*.; they stated that a high percent tumor range occurred in all animals included in their studies that got DMBA carcinogen application (21, 22). This suggests that DMBA is a potent inducer for oral carcinomas. In contrast, only 80% of the hamsters in the *Osakabe et al.* work had buccal pouch masses, which may have been due to a distinct animal type (23). The animals received salvia rosmarinus oil supplemental to DMBA; the incidence of malignancy developed a rebate as compared to those given DMBA alone. This result is consistent with the findings of various studies testing the inhibitory impact of salvia rosmarinus via cancer development (24, 25). Further, *Osakabe et al*. *Anusuya et al.* and *Caceres et al*. were manifested the similar findings (23, 26, 27).

A lot of studies on different cell lines confirm the efficacy of rosmarinus oil on cancer prevention as: cervical cancer cell, breast lesions, and neoplasm T-cell leukemia cells. The antioxidant and antiproliferative actions versus many types of human malignant cells were investigated by *Elansary et al.* (28). Over that, *Cheung and Tai*, as well as *Cheng et al.*; found that the rosemary extract has cytotoxic activities on leukemia as well as cells of breast cancer (29, 30). The *Caceres et al.* concluded that hamsters treated with rosmarinic acid had a decreased extent of tumors, smaller carcinoma mass sizes, and much lower aggressiveness of neoplasms. The IHC manifestation of PCNA and p53 was dramatically changed during DMBA oral cancer induction. In contrast to the animals exposed to carcinogens without receiving any chemopreventive treatment. The hamsters in this research that had their buccal pouches painted with salvia rosmarinus oil concurrently with DMBA; experienced a reduction in lesion development. As well, *Osakabe et al.* stated that animals treated with rosmarinic acid resulted in a decline in the scope of HBP carcinogenesis generated by DMBA application, which lends support to the study findings (23).

The anticancer efficacy by coriandrum sativum oil against cancer cell line of oral cavity was evaluated by *Chouhan et al.* who conclude a lowering in malignant formation (31). Moreover, *Tang et al.* demonstrated that the herb showed antineoplastic activity in malignant breast cells. They also reported the existence of ascorbic acid in coriandrum sativum, a chemical familiar for its anticancer and antioxidant characteristics (32). In the current work, hamster buccal pouches painted with DMBA concurrently with applications of salvia rosmarinus and coriandrum sativum resulted in a lower incidence of tumors than those painted with DMBA concurrently with each oil alone.

Chemopreventive substances are known to cause apoptosis and inhibit the proliferation of cells. In this study, PCNA immunohistochemistry was used to cell proliferation assessment and compare the chemopreventive effects of salvia rosmarinus and coriandrum sativum on developed HBP malignant tumors. The current investigation found that PCNA expression played a significant effect in tumor severity. The PCNA area percent expression and optical density increased significantly in the tissues administered via DMBA in group II. They were extremely significant when compared to the examined samples of the control animal group I. In keeping with these running trial findings, *Caceres et al*. found decline in PCNA expression caused alleviation in tissue progression (27). The study done by *Poosarla et al*. was established that PCNA overexpression promoted aggressive cell behavior (33). Moreover, *Kato et al.* discovered that PCNA expression is higher in head and neck cancer than in other malignant kinds (34), which align with the findings of the current study. This corroborated the finding that the alterations in PCNA area percent and optical density were highly statistically significant once compared in groups II, III, and/or IV. In addition, the changes in PCNA manifestation values were extremely significant in statistical terms whenever relating group II to group V that received salvia rosmarinus oil with coriandrum sativum oil.

The findings suggest the antitumor chemopreventiv e activity of salvia rosmarinus oil and coriandrum s ativum oil during the DMBA-induced tumorigenesis processes in the HBPs employed in this study. Similar outcomes found by *Osakabe et al.* found that environmental phytochemicals resembling salvia rosmarinus may assist as a unique preventive agent for oral cancer because they inhibit malondialdehyde, chemokines, and arachidonic acid while protecting DNA from oxidative damage (23). Over the above, *Anusuya et al.* realized that flavonoids such as salvia rosmarinus stimulated the detoxification enzymes actions, improved antioxidants, and reduced the manifestations of p53 and bcl-2 through DMBA oral cancer induction (26). Additionally, *Caceres et al.* observed that salvia rosmarinus had a proper chemopreventive effect in dramatically lowering tumor intensity and aggression; immunoexpression of PCNA and p53 significantly changed during DMBA induced oral malignancy. This aligns with the findings of the current study.

The *Chouhan et al.* discovered that the oral cancer cell line showed a depression in cellular proliferation and induction of apoptosis when

treated with coriandrum sativum, which is consistent with the findings of ongoing research that confirmed the proper chemopreventive effect of coriandrum sativum in oral carcinomas (30). Also, *Marcucci et al.* concluded that coriandrum sativum inhibited cell proliferation and promoted cell death against neuroblastoma cells line (35). Further, *Chang et al.* demonstrated anticancer effects via cancer cells in rats, with a possibility to be used as anti-liver pathologies (36). In add to, *El Khatabi et al.* found that the coriandrum sativum has better colon rectal cancer preventive natural compound (37). On the other hand, *Singh et al.* resulted that the coriandrum sativum has lesser effect of malignant cells proliferation in setting of lung diseases (38), this shortening could be attributed to the wide range of malignancy grades and activities observed in prior clinical studies compared to the current experimental study.

CONCLUSION

The findings of the current research concluded that salvia rosmarinus and coriandrum sativum play a chemoprevention role in developing oral carcinomas. The combined act of the 2 agents was superior to either one alone. The PCNA expression provides information on the tumor's aggressiveness and the impact of anticancer treatments on oral malignancy activity, as well as evaluating the chemopreventive action of anticancer agents.

CONFLICT OF INTEREST

There is no conflict of interest that it has declared by authors.

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Ethical clearance

The research was done with the agreement of the Animal Research Ethics Committee at the faculty of dentistry, Alexandria University (IRB NO 0363-12/2021 IORG0008839)

REFERENCES

1- Smith Torres-Roman J, Julca-Marin D, Ticona-Tina D, Quispe-Vicuna C, Bazalar-Palacios J, De La Cruz-Ku G, et al. Trends in gastric cancer mortality 2005-2020 in Peru and its geographical areas: A joinpoint regression analysis. Cancer Epidemiol. 2023;87:102485.
2- Mohamed OAA, Tesen HS, Hany M, Sherif A, Abdelwahab MM, Elnaggar MH. The role of hypoxia on prostate cancer progression and metastasis. Mol Biol Rep. 2023;50:3873-84.
3- Rusanen P, Marttila E, Amatya SB, Hagstrom J, Uittamo J, Reunanen J, et al. Expression of toll-like receptors in oral squamous cell carcinoma. PLoS One. 2024;19:e0300437.
4- Azhamuthu T, Kathiresan S, Senkuttuvan I, Abulkalam Asath NA, Ravichandran P. Usnic acid attenuates 7,12-dimethylbenz[a] anthracene (DMBA) induced oral carcinogenesis through inhibiting oxidative stress, inflammation, and cell proliferation in male golden Syrian hamster model. J Biochem Mol Toxicol. 2024;38:e23553.
5- Arvindh S, Priyadarshini M, Baba AB, Veeravarmal V, Mishra R, Dash R, et al. The neem limonoid nimbolide modulates key components of the DNA damage response signalling in cellular and animal models of oral squamous cell carcinoma. Curr Pharm Biotechnol. 2024; 28:392-401.
6- Jadhav PA, Hole A, Ingle A, Govekar R, Noothalapati H, Krishna CM. Serum raman spectroscopy: evaluation of tumor load variations in experimental carcinogenesis. J Biophotonics. 2024;17:e202300424.
7- Russo GL, Spagnuolo C, Russo M. Reassessing the role of phytochemicals in cancer chemoprevention. Biochem Pharmacol. 2024;26:116165.
8- Gilad O, Muller C, Kupfer SS. Chemoprevention in inherited colorectal cancer syndromes. Clin Colon Rectal Surg. 2023;37:172-9.
9- Cecerska-Heryc E, Wiśniewska Z, Serwin N, Polikowska A, Goszka M, Engwert W, et al. Can compounds of natural origin be important in chemoprevention? Anticancer properties of quercetin, resveratrol, and curcumin-a comprehensive review. Int J Mol Sci. 2024;25:4505.
10- Jiang Q. Different roles of natural forms of vitamin E in chemoprevention and treatment of prostate cancer. Adv Nutr. 2024;10:100240.
11- Borges RS, Ortiz BLS, Pereira ACM, Keita H, Carvalho JCT. Rosmarinus officinalis essential oil: A review of its phytochemistry, anti-inflammatory activity, and mechanisms of action involved. J Ethnopharmacol. 2019;229:29-45.
12- Annemer S, Farah A, Stambouli H, Assouguem A, Almutairi MH, Sayed AA, et al. Chemometric investigation and antimicrobial activity of salvia rosmarinus spenn essential oils. Molecules. 2022;27:2914.
13- Al-Khayri JM, Banadka A, Nandhini M, Nagella P, Al-Mssallem MQ, Alessa FM. Essential oil from coriandrum sativum: a review on its phytochemistry and biological activity. Molecules. 2023;28:696.

14- Chithra V, Leelamma S. Coriandrum sativum-effect on lipid metabolism in 1,2-dimethyl hydrazine induced colon cancer. J Ethnopharmacol. 2000;71:457-63.
15- Gu L, Li M, Li CM, Haratipour P, Lingeman R, Jossart J, et al. Small molecule targeting of transcription-replication conflict for selective chemotherapy. Cell Chem Biol. 2023;30:1235-47.
16- Cs AS, Joseph TI, Girish KL, T P, Binu A, Mary J. Comparative analysis of cluster of differentiation 57 and proliferating cell nuclear antigen expression in different grades of oral squamous cell carcinoma: an immunohistochemical study. Cureus. 2023;15:e44779.
17- Zhang L, Liang B, Xu H, Gong Y, Hu W, Jin Z, et al. Cinobufagin induces FOXO1-regulated apoptosis, proliferation, migration, and invasion by inhibiting G9a in non-small-cell lung cancer A549 cells. J Ethnopharmacol. 2022;291:115095.
18- Badwelan M, Muaddi H, Ahmed A, Lee KT, Tran SD. Oral squamous cell carcinoma and concomitant primary tumors, what do we know? a review of the literature. Curr Oncol. 2023;30:3721-34.
19- Liao YH, Chou WY, Chang CW, Lin MC, Wang CP, Lou PJ, et al. Chemoprevention of oral cancer: A review and future perspectives. Head Neck. 2023;45:1045-59.
20- Sun W, Shahrajabian MH. Therapeutic potential of phenolic compounds in medicinal plants-natural health products for human health. Molecules. 2023;28:1845.
21- Manimaran A, Buddhan R, Manoharan S. Emodin downregulates cell proliferation markers during DMBA induced oral carcinogenesis in golden Syrian hamsters. African J Tradit Complement Alternat Med. 2017;14:83-91.
22- Selvasundaram R, Manoharan S, Buddhan R, Neelakandan M, Naidu RM. Chemopreventive potential of esculetin in 7, 12-dimethylbenz (a) anthracene-induced hamster buccal pouch carcinogenesis. Mol Cell Biochem. 2018;448:145-53.
23- Osakabe N, Yasuda A, Natsume M, Yoshikawa T. Rosmarinic acid inhibits epidermal inflammatory responses: anticarcinogenic effect of Perilla frutescens extract in the murine two-stage skin model. Carcinogenesis. 2004;25:549-57.
24- Horvathova E, Kozics K, Melusova M, Galova E, Sevcovicova A, Kusznierewicz B, et al. Chromatographic analyses of Lavandula angustifolia and Rosmarinus officinalis extracts and their biological effects in mammalian cells and cell-free systems. Neoplasma. 2017;64:856-68.
25- Al-Wahab A, Gobran HG, Dameer HA. Effect of rosmarinic acid as a chemopreventive modality on experimentally induced hamster buccal pouch carcinogenesis. Egypt Dent J. 2020;66:2411-21.
26- Anusuya C, Manoharan S. Antitumor initiating potential of rosmarinic acid in 7,12-dimethylbenz(a)anthracene-induced hamster buccal pouch carcinogenesis. J Environ Pathol Toxicol Oncol. 2011;30:199-211.
27- Baldasquin-Caceres B, Gomez-Garcia FJ, Lopez-Jornet P, Castillo-Sanchez J, Vicente-Ortega V. Chemopreventive potential of phenolic compounds in oral carcinogenesis. Arch Oral Biol. 2014;59:1101-7.
28- Elansary HO, Mahmoud EA. Egyptian herbal tea infusions' antioxidants and their antiproliferative and cytotoxic activities against cancer cells. Nat Prod Res. 2015;29:474-9.
29- Cheung S, Tai J. Anti-proliferative and antioxidant properties of rosemary Rosmarinus officinalis. Oncol Rep. 2007;17:1525-31.
30- Tai J, Cheung S, Wu M, Hasman D. Antiproliferation effect of Rosemary (Rosmarinus officinalis) on human ovarian cancer cells in vitro. Phytomedicine. 2012;19:436-43.
31- Chouhan S, Priya V, Gayathri R. Genotoxicity Analysis of coriandrum sativum on oral cancer cell line by DNA fragmentation. Int J Pharm Sci Rev Res. 2017;45:18-20.
32- Tang EL, Rajarajeswaran J, Fung SY, Kanthimathi MS. Antioxidant activity of coriandrum sativum and protection against DNA damage and cancer cell migration. BMC Complement Altern Med. 2013;13:347.
33- Poosarla C, Ramesh M, Ramesh K, Gudiseva S, Bala S, Sundar M. Proliferating cell nuclear antigen in premalignancy and oral squamous cell carcinoma. J Clin Diagn Res. 2015;9:ZC39-41.
34- Kato K, Kawashiri S, Yoshizawa K, Kitahara H, Okamune A, Sugiura S, et al. Expression form of p53 and PCNA at the invasive front in oral squamous cell carcinoma: correlation with clinicopathological features and prognosis. J Oral Pathol Med. 2011;40:693-8.
35- Marcucci MC, Oliveira CR, Spindola D, Antunes AA, Santana LYK, Cavalaro V, et al. Molecular dereplication and in vitro and in silico pharmacological evaluation of coriandrum sativum against neuroblastoma cells. Molecules. 2022;27:5389.
36- Chang M, Shi S, Liu H, Tu J, Yan Z, Ding S. Extraction, characterization, and in vivo antitumor activity of a novel polysaccharide from coriandrum sativum L. J Food Biochem. 2022 ;46:e14323.
37- El Khatabi K, Kumar S, El-Mernissi R, Singh AK, Ajana MA, Lakhlifi T, et al. Novel Eubacterium rectale inhibitor from coriandrum sativum L. for possible prevention of colorectal cancer: a computational approach. J Biomol Struct Dyn. 2023;41:8402-8416.