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# Original article: Prevalence of Diffused Oral Mucosal Pigmentation and Its Associated Factors in Northern Iran

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## ABSTRACT

**Introduction:** Understanding the prevalence of such pigmentation is crucial for clinical diagnosis and informed treatment planning. This study aimed to evaluate the prevalence of diffused oral mucosal pigmentation and identify its associated factors among patients visiting the Dental School of Rasht in 2023.

**Materials and Methods:** This analytical cross-sectional study was conducted on 243 patients aged 12 years and older who attended the Dental School of Rasht in 2023. Participants were selected through non-random sampling. After obtaining informed consent, demographic and medical history information was recorded for all participants. Subsequently, a thorough oral examination was performed, and relevant findings were documented using a structured checklist. Data analysis was conducted at a significance level of 0.05.

**Results:** Among the 243 patients examined, 95 (39.1%) exhibited diffused oral mucosal pigmentation. The severity of pigmentation was categorized as mild in 67.4% of cases, moderate in 20%, and severe in 12.6%. The gingiva was identified as the most commonly affected site. Statistically significant associations were observed between oral mucosal pigmentation and factors such as alcohol consumption (P=0.001), smoking (P<0.001), the presence of cutaneous hyperpigmentation (P=0.035), and the use of thyroid medications (P=0.012) and antihypertensive drugs (P=0.028). Furthermore, the severity of pigmentation showed a significant relationship with gender and smoking.

**Conclusion:** The gingiva demonstrated the highest prevalence of diffused oral mucosal pigmentation. Given the associations with systemic diseases, particularly hypertension, and the use of specific medications, such as antihypertensive drugs, thorough examination of oral soft tissues for discoloration is essential.

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## 1. Introduction

Oral pigmentation presents in various patterns, including focal, multifocal, or diffuse manifestations. This condition arises from the deposition, production, increased synthesis, or accumulation of pigments of endogenous or exogenous origin within the oral tissues, leading to mucosal discoloration in shades of brown, gray-blue, or black. These pigmentations can be classified as either physiological, commonly observed in individuals with darker skin tones, or pathological, resulting from various systemic or local conditions (1).

Among endogenous pigments, melanin is one of the most prominent contributors to oral mucosal discoloration, alongside hemoglobin and hemosiderin. The diffuse or multifocal increase in melanin production can result from genetic predisposition, particularly in cases of physiological pigmentation, as well as hormonal fluctuations, systemic disorders such as Addison's disease and Cushing's syndrome, or external factors like medication use and smoking (1-3). Due to the diverse range of potential causes, accurately identifying the etiology of oral pigmentation poses a diagnostic challenge.

A comprehensive diagnostic approach requires detailed patient history, encompassing medical, dental, familial, and social aspects, along with thorough intraoral and extraoral examinations. These evaluations are crucial to detect concurrent systemic signs, such as cutaneous hyperpigmentation. When clinical findings are inconclusive, additional diagnostic measures—including laboratory tests, radiographic imaging, and other specialized investigations—are necessary to ascertain the underlying cause of pigmentation (1). Key elements of patient history that facilitate the diagnosis of pigmented lesions include assessing the lesion’s color, duration, location, distribution, number, size, and shape (4).

Population-based studies are instrumental in enabling timely prevention and treatment strategies through early diagnosis. Given the geographic and temporal variations in the prevalence of oral lesions and associated conditions, conducting such studies helps to update healthcare providers' knowledge, minimize diagnostic and therapeutic errors, and ultimately improve patient outcomes (5).

Therefore, this study aimed to assess the prevalence of diffused oral mucosal pigmentation and its associated factors among patients attending the Dental School of Rasht.

## 2. Materials and Methods

Patients who visited the Dentistry Faculty of Rasht, Iran, in 2023. Participants were selected using a non-probability convenience this analytical cross-sectional study was conducted on 243 sampling method. Inclusion criteria comprised all patients aged 12 years and older referred to the Department of Oral and Maxillofacial Diseases in 2023. Patients who withdrew from the study at any stage or had incomplete data recorded on their checklists were excluded.

The required sample size was calculated based on an estimated prevalence of diffused oral mucosal pigmentation (28.4%) from previous studies (6), with a confidence level of $\alpha$=0.05, margin of error (d)= 0.0568, and standard deviation (SD). This yielded a minimum sample size of 243 participants.

Participants were provided with detailed explanations about the study objectives and procedures before giving written informed consent. A pre-prepared checklist was used to gather demographic data (age, gender, and occupation), medical history (including systemic diseases such as Addison’s disease, Cushing’s syndrome, Peutz-Jeghers syndrome, autoimmune hyperthyroidism [Graves' disease], Laugier-Hunziker syndrome, hemochromatosis, vitamin B12 deficiency, HIV/AIDS (Human immunodeficiency virus (HIV) / Acquired immunodeficiency syndrome (AIDS)), primary biliary cirrhosis, and inflammatory diseases such as lichen planus), pregnancy or lactation status, medication use, alcohol consumption, smoking habits, and the presence of cutaneous hyperpigmentation. Systemic disease information was obtained through patient interviews and self-reported data.

Following data collection, all participants underwent a thorough intraoral soft tissue examination under adequate lighting conditions. Examinations were performed by a trained final-year dental student under the supervision of an oral and maxillofacial specialist. Single-use instruments, including mirrors and tongue depressors, were employed to assess the soft tissues, including the hard and soft palates, floor of the mouth,

dorsal and ventral surfaces of the tongue, gingiva, buccal mucosa, labial mucosa, and the vermilion borders of the lips. Observations regarding the presence, location, and number of areas affected by diffused oral mucosal pigmentation were meticulously recorded.

The diagnosis of pigmented lesions was based on clinical characteristics, including the number, distribution pattern, intensity, color, and location of the lesions. Diffused oral mucosal pigmentation was defined as flat brown or black melanin pigmentation affecting more than one site of the oral mucosa. The severity of pigmentation was categorized into three groups based on the number of affected areas: mild (one area), moderate (two areas), and severe (more than two areas) (7).

Data analysis was conducted using SPSS version 28 at a significant level below 0.05. Descriptive statistics were presented as frequencies and percentages for qualitative variables and as mean ± standard deviation for quantitative variables. The normality of quantitative data was assessed using the Shapiro-Wilk test and skewness/kurtosis indices, while homogeneity of variances was evaluated with Levene's test. Depending on the nature of the data and statistical assumptions, independent t-tests and chi-square tests were used for comparisons. When assumptions of normality or homogeneity were violated, non-parametric tests, such as the Mann-Whitney U test and Fisher's exact test, were applied.

## 3. Results

Among the 243 participants in this study, 148 individuals (60.9%)—101 males (41.5%) and 142 females (58.5%)—did not exhibit oral mucosal pigmentation, with a mean age of 39.39±15.65 years. Conversely, 95 individuals (39.1%)—40 males (39.6%) and 55 females (38.7%)—presented with pigmentation, with a mean age of 39.36 ± 14.36 years. The severity of pigmentation was categorized as mild in 64 patients (67.4%), moderate in 19 patients (20%), and severe in 12 patients (12.6%). There were no significant differences between the pigmented and non-pigmented groups concerning age (P = 0.988) or gender (P=0.891). Similarly, within the pigmented group, the frequency of pigmentation did not significantly differ between males and females (P=0.891).

Table 1 illustrates the frequency distribution of diffused oral mucosal pigmentation based on the affected locations. The gingiva was the most commonly affected site, with 85 cases (89.5%).

Among the participants, 2 individuals (0.8%) were pregnant. of these, one exhibited mucosal pigmentation, and the other did not. The difference in pigmentation prevalence between pregnant and non-pregnant participants was not statistically significant (Fisher's Exact Test, P=0.999).

Table 2 compares the prevalence of diffused oral mucosal pigmentation among patients based on their systemic disease history. No significant differences in pigmentation prevalence were observed across the systemic diseases examined.

Although pigmentation prevalence did not significantly differ between individuals taking medications and those who were not (P=0.141), significant associations were observed among individuals using thyroid medications (P=0.012) and antihypertensive drugs (P=0.028), with higher pigmentation prevalence noted in these groups (Table 3).

**Table 1.** Frequency of diffuse pigmentations of the oral mucosa

| Place of pigmentation | Presence of pigmentation | |
|---|---|---|
| | Yes n (%) | No n (%) |
| Vermilion of lips | 21 (22.1) | 74 (77.9) |
| Hard and soft palate | 16 (16.8) | 79 (83.2) |
| Floor of the mouth | 3(3.2) | 92 (96.8) |
| Dorsal and ventral surfaces of the tongue | 3 (3.2) | 92 (96.8) |
| Buccal mucosa | 15 (15.8) | 80 (84.2) |
| Gingiva | 85 (89.5) | 10 (10.5) |

**Table 2.** Frequency comparison of diffuse pigmentation of the oral mucosa in patients referred to the Faculty of Dentistry, Rasht, Iran, according to systemic disease records.

| History of systemic diseases | Special conditions/ considered systemic disease | Presence of pigmentation | | | P-value |
|---|---|---|---|---|---|
| | | Total n (%) | Yes n(%) | No n (%) | |
| Hypothyroidism a | Yes | 14 (5.7) | 8 (57.1) | 6 (42.9) | 0.154 |
| | No | 229 (94.3) | 87 (38) | 142 (62) | |
| Hypothyroidism b | Yes | 2 (0.8) | 0 (0) | 2 (11) | 0.522 |
| | No | 241 (99.2) | 95 (39.4) | 146 (60.6) | |
| Thalassemiab | Yes | 5 (2.05) | 2 (40) | 3 (60) | 0.999 |
| | No | 238 (97.95) | 93 (39.1) | 145 (60.9) | |
| Diabetes a | Yes | 16 (6.5) | 8 (80) | 8 (50) | 0.355 |
| | No | 227 (93.5) | 87 (38.3) | 140 (61.7) | |
| Hypertensiona | Yes | 24 (9.8) | 10 (41.7) | 14 (58.3) | 0.786 |
| | No | 219 (90.2) | 85 (38.8) | 134 (61.2) | |
| Cardiovascular disease b | Yes | 8 (3.2) | 4 (50) | 4 (50) | 0.715 |
| | No | 235 (96.8) | 91 (38.7) | 144 (61.3) | |
| Kidney disease b | Yes | 4 (1.6) | 2 (50) | 2 (50) | 0.645 |
| | No | 239 (98.4) | 93 (38.9) | 146 (61.1) | |
| Rheumatism b | Yes | 1 (0.4) | 0 (0) | 1 (100) | 0.999 |
| | No | 242 (99.6) | 95 (39.3) | 147 (60.7) | |
| Cancer b | Yes | 1 (0.4) | 0 (0) | 1 (100) | 0.999 |
| | No | 242 (99.6) | 95 (39.3) | 147 (60.7) | |
| Neurological diseases b | Yes | 3 (1.2) | 0 (0) | 3 (100) | 0.283 |
| | No | 240 (98.8) | 95 (39.6) | 147 (60.4) | |
| Lung disease b | Yes | 2 (0.8) | 1 (50) | 1 (50) | 0.999 |
| | No | 241 (99.2) | 94 (39) | 147 (61) | |
| Hemophilia b | Yes | 1 (0.4) | 1 (100) | 0 (0) | 0.391 |
| | No | 242 (99.6) | 94 (38.8) | 148 (61.2) | |
| Blood lipids b | Yes | 1 (0.4) | 0 (0) | 1 (100) | 0.999 |
| | No | 242 (99.6) | 95 (39.3) | 147 (60.7) | |
| Multiple Sclerosis b | Yes | 1 (0.4) | 1 (100) | 0 (0) | 0.391 |
| | No | 242 (99.6) | 94 (38.8) | 148 (61.2) | |

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a. Pearson Chi-Square, b. Fisher's exact test

**Table 3.** Comparison of the frequency of diffuse pigmentation of the oral mucosa in patients referring to the Dentistry Faculty of Rasht based on drug use

| Type of drug | Medicine use | Presence of pigmentation | | | P-value |
|---|---|---|---|---|---|
| | | Total n (%) | Yes n(%) | No n (%) | |
| NSAID[b] | Yes | 7 (7.6) | 3 (42.8) | 4 (57.2) | 0.999 |
| | No | 84 (92.4) | 92 (38.9) | 144 (61.1) | |
| Thyroid medications [a] | Yes | 16 (17.5) | 11 (69) | 5 (31) | 0.012 |
| | No | 75 (82.5) | 84 (37) | 143 (63) | |

| | | | | | |
|---|---|---|---|---|---|
| Diabetes medication [a] | Yes | 16 (17.5) | 8 (50) | 8 (50) | 0.355 |
| | No | 75 (82.5) | 84 (38.3) | 140 (61.7) | |
| Anti-hypertensive drugs [a] | Yes | 36 (39.5) | 20 (55.5) | 16 (445) | 0.028 |
| | No | 55 (60.5) | 75 (36.2) | 132 (63.8) | |
| Thalassemia medication [b] | Yes | 5 (5.4) | 2 (40) | 3 (60) | 0.999 |
| | No | 86 (94.6) | 93 (39) | 145 (61) | |
| Contraceptive drugs [b] | Yes | 2 (12) | 0 (0) | 2 (100) | 0.522 |
| | No | 89 (97.9) | 95 (39.4) | 146 (60.6) | |
| Calcium [b] | Yes | 6 (6.5) | 4 (66.6) | 2 (33.4) | 0.213 |
| | No | 85 (93.5) | 91 (38.3) | 146 (61.7) | |
| Iron[b] | Yes | 8 (7.8) | 2 (25) | 6 (75) | 0.487 |
| | No | 83 (91.3) | 93 (39.5) | 142 (60.5) | |
| Vitamin [b] | Yes | 7 (7.6) | 3 (42.8) | 4 (57.2) | 0.999 |
| | No | 84 (92.4) | 92 (38.9) | 144 (61.1) | |
| Anticoagulant drugs [b] | Yes | 4 (4.3) | 2 (50) | 2 (50) | 0.645 |
| | No | 87 (95.7) | 93 (38.9) | 146 (61.1) | |
| Psychiatric drugs [b] | Yes | 8 (8.7) | 4 (50) | 4 (50) | 0.715 |
| | No | 83 (91.3) | 91 (38.7) | 144 (61.3) | |
| Anti-anxiety drugs [b] | Yes | 10 (10.9) | 6 (60) | 4 (40) | 0.195 |
| | No | 81 (89.1) | 89 (38.1) | 144 (61.9) | |
| Antihyperlipidemic drugs [b] | Yes | 4 (4.3) | 2 (50) | 2 (50) | 0.645 |
| | No | 87 (95.7) | 93 (38.9) | 146 (61.1) | |
| Anticonvulsant drug [b] | Yes | 4 (3.4) | 1 (25) | 3 (75) | 0.999 |
| | No | 87 (95.7) | 94 (39.3) | 145 (60.7) | |
| Corticosteroids [b] | Yes | 1(1) | 0 (0) | 1 (100) | 0.999 |
| | No | 90 (99) | 95 (39.2) | 147 (60.8) | |
| Gastrointestinal Medications [b] | Yes | 3 (3.2) | 2 (66.6) | 1 (33.4) | 0.562 |
| | No | 88 (96.8) | 93 (38.7) | 147 (61.3) | |
| Antineoplastics medications [b] | Yes | 2 (2.1) | 0 (0) | 2 (100) | 0.522 |
| | No | 89 (97.9) | 95 (39.4) | 146 (60.6) | |
| Methadone [b] | Yes | 2 (2.1) | 2 (100) | 0 (0) | 0.154 |
| | No | 89 (97.9) | 93 (38.9) | 146 (61.1) | |

a. Pearson Chi-Square, b. Fisher's Exact Test

Additionally, pigmentation prevalence was significantly higher among individuals who smoked (P<0.001), consumed alcohol (P=0.001), or had hyperpigmented skin (P=0.035). Logistic regression analysis using the forward stepwise method revealed that smoking (P<0.001) and the presence of hyperpigmented skin (P=0.047) significantly influenced the likelihood of diffused oral mucosal pigmentation. Smokers were 4.39 times more likely to exhibit pigmentation than non-smokers, while individuals with hyperpigmented skin were 2.29 times more likely to present with pigmentation compared to those without skin hyperpigmentation.

Ordinal regression analysis assessing the simultaneous effects of variables on the severity of oral mucosal pigmentation indicated that gender (P=0.007) and smoking (P=0.037) significantly influenced pigmentation severity. Males and smokers were at a higher risk of severe pigmentation compared to females and non-smokers.

## 4. Discussion

This study aimed to determine the prevalence of diffused oral mucosal pigmentation among patients attending the Dental School of Rasht. Results indicated that 95 out of 243 participants (39.1%) exhibited diffused pigmentation. This prevalence aligns closely with the findings of Rabiei et al., who reported a similar frequency of 43.47% (100 out of 230 patients) in their study (8).

Conversely, the studies by Barkian et al. and Mirzaei et al. reported lower prevalence rates of 24.8% and 27.94%, respectively (6, 7). These discrepancies may stem from differences in genetic predispositions, environmental factors, and the diverse ethnic and racial composition of populations across various regions of Iran—a country known for its geographical and cultural diversity. Variations in sample size and study methodology may also contribute to these differences.

In this study, the mean age of individuals with oral mucosal pigmentation was 39.36±14.36 years, while those without pigmentation had a mean age of 39.39 ± 15.65 years. No significant association was found between age and pigmentation prevalence. Similar findings were reported by Rabiei et al. and Masilana et al., who also observed no significant relationship between age and pigmentation prevalence (8, 9). However, Ghanai et al. found a significant association, reporting a higher prevalence of pigmentation in younger individuals (10). Additionally, studies by Salehi et al. and Janiani et al. demonstrated a significant relationship between age and pigmentation severity, noting an increase in severity with advancing age (11, 12).

The observed differences in these studies may be attributed to variations in the age ranges of study populations and differing methodologies. It has been suggested that pigment intensity increases during childhood and adolescence, peaking around 15 years of age due to physiological growth and hormonal changes during puberty (13). In our study, the low proportion of participants under 18 years of age may explain the lack of a significant relationship between age and pigmentation.

Regarding gender, 38.7% of females and 39.6% of males exhibited diffused oral pigmentation, with no statistically significant difference in prevalence. These findings align with those of Eaturi et al., Salehi et al., and Maybodi et al., who also found no significant gender-based differences in pigmentation prevalence (12, 14, 15). However, gender significantly influenced pigmentation severity, with males showing a higher risk of more severe pigmentation. This result corroborates the findings of Salehi et al., who reported higher pigmentation severity in males (12). One possible explanation is that smoking—a known stimulant of melanin production—is more prevalent among men, thereby contributing to increased pigmentation severity in this group.

In this study, the severity of pigmentation was categorized as mild in 67.4% of cases, moderate in 20%, and severe in 12.6%. Salehi et al. reported a different distribution, with 58% mild, 14% moderate, and 28% severe cases (12). Similarly, Mirzaei et al. observed mild pigmentation in 54.9%, moderate in 16.5%, and severe in 28.6% of cases (7). Compared to these studies, the prevalence of mild pigmentation was higher in our findings.

The gingiva was the most commonly affected site of pigmentation in the present study, with a prevalence of 89.5%, followed by the vermilion of the lips, soft and hard palates, buccal mucosa, floor of the mouth, and dorsal and ventral surfaces of the tongue. These findings are consistent with Mirzaei et al., who identified the anterior upper gingiva as the most frequent site, followed by the anterior lower gingiva (7). Similarly, Salehi et al. reported the labial gingiva as the most commonly affected site, followed by the buccal gingiva, lips, lingual gingiva, and cheeks, although no pigmentation was observed in the tongue and palate within their study population (12). Barkian et al. also found the gingiva to be the most frequently pigmented site, followed by the buccal mucosa, lips, and tongue, with the hard palate being the least common location (6).

The higher prevalence of pigmentation in the gingiva and anterior oral regions can be attributed to the greater density of melanocytes in these areas compared to the posterior regions.

In the present study, 39.1% of patients had systemic diseases, of which 45.2% exhibited oral pigmentation. The most prevalent systemic conditions were hypertension, diabetes, and hypothyroidism. However, no significant association was identified between the type of systemic disease and the prevalence of

pigmentation, a finding consistent with Barkian et al. (6). In contrast, Hassona et al. reported a significant association between systemic diseases, such as Addison's disease and lichen planus, and focal pigmentation (16). Salehi et al. also identified systemic diseases as a significant factor influencing oral pigmentation prevalence, a result that differs from our findings (12).

The established relationship between certain systemic diseases, such as Addison's disease, and mucosal hyperpigmentation (17) suggests that variations in study populations and systemic conditions under investigation may explain the differences across studies. Notably, none of the participants in the present study had systemic diseases commonly linked to oral pigmentation, such as Addison's disease or Cushing's syndrome. Additionally, the relatively small number of patients with conditions like hypothyroidism in this study limits the generalizability of these findings. Future research with larger sample sizes and diverse systemic conditions is necessary to explore the potential relationships between common systemic diseases and oral mucosal hyperpigmentation.

Regarding medication use, 37.4% of participants were on medication, of which 45.1% exhibited oral pigmentation. Antihypertensive drugs (39.5%) were the most commonly used, followed by thyroid medications and antidiabetic drugs (17.5% each). A significant association was observed between antihypertensive and thyroid medications and the prevalence of oral pigmentation, whereas other medications did not show such a relationship. Specifically, individuals using antihypertensive or thyroid medications were more likely to exhibit pigmentation.

These findings emphasize the importance of considering medication use as a contributing factor in the diagnosis of oral pigmentation. Further studies should investigate the mechanisms underlying these associations and evaluate the potential impact of other less-studied medications on oral mucosal pigmentation.

In agreement with the present study, García et al. identified a significant relationship between the use of antihypertensive drugs and the prevalence of oral pigmentation (18). Conversely, Binmadi et al. reported significant associations between pigmentation prevalence and the use of antimalarial drugs, antibiotics, and anticancer medications, but found no significant link with antihypertensive medications (19). This discrepancy may stem from the relatively small number of patients on antihypertensive medications in their study.

Similarly, Khattiabi et al. observed no significant association between medication use and oral pigmentation, which might be attributed to their specific study population—dental students—a group characterized by low rates of medication use and systemic diseases (20).

Overall, pigmentation can be diffused an adverse effect of certain medications, including anticancer drugs, specific antihypertensive medications, and others. The mechanisms underlying drug-induced pigmentation include the deposition of drug metabolites, stimulation of melanin production (with or without an increase in melanocyte numbers), and other unknown factors. Since the clinical presentation of drug-induced and non-drug-induced pigmentation often appears similar, obtaining a detailed medical history and conducting a thorough clinical examination are essential for an accurate differential diagnosis (21).

Regarding lifestyle factors, this study found that 78.1% of participants who consumed alcohol exhibited oral pigmentation, suggesting a higher prevalence of pigmentation among alcohol consumers. Consistent with this finding, Collins et al. also reported a significant association between alcohol consumption and oral lesions, including pigmentation (22). However, Hassona et al. observed no significant relationship between alcohol use and oral pigmentation (16).

The discrepancies among these studies might be explained by the co-occurrence of alcohol and tobacco use among participants with oral pigmentation. In the present study, 13 out of 19 alcohol consumers were also smokers, 11 of whom had oral hyperpigmentation. This overlap indicates a potential combined effect of alcohol and smoking on pigmentation prevalence, warranting further investigation to elucidate their individual and synergistic impacts on oral mucosal pigmentation.

It is plausible that melanin in the oral mucosa interacts with toxic substances in smoke, alcohol, or other drugs, which are capable of penetrating tissues. This interaction may provide a protective effect on the oral mucosa, contributing to the

observed hyperpigmentation. In this study, 27 participants (11.1%) were smokers, and 19 of these smokers (70.4%) exhibited oral pigmentation, revealing a significant association between smoking and the prevalence of oral pigmentation. These findings are consistent with studies by Multani et al. and Ghapanchi et al. (23, 24).

Similarly, Marakoglu et al. found a significant relationship between smoking and oral pigmentation, with smoking 5 to 9 cigarettes per day being sufficient to induce pigmentation (25). In the present study, the severity of pigmentation correlated with the amount of cigarette consumption, with heavier smokers displaying more severe oral pigmentation. This observation aligns with Darwis et al., who noted that longer smoking duration is associated with increased severity of oral pigmentation (26). In a longitudinal study by Araki et al., which tracked the relationship between cigarette consumption and pigmentation in a Japanese population over two phases with a 4-year gap, the prevalence of pigmentation was significantly higher among individuals who smoked more than 10 cigarettes per day. Moreover, after 4 years, pigmentation prevalence further increased in these individuals (27).

Oral hyperpigmentation caused by smoking is believed to result from the presence of polycyclic amines, such as nicotine and benzopyrene, which particularly affect melanocytes in the gingiva. This occurs through two mechanisms: a direct impact on the oral mucosa or via saliva, and an indirect effect through the increased entry of nicotine into the bloodstream (28, 29).

In this study, 5% of patients exhibited cutaneous hyperpigmentation, and of these, 57.1% also showed concurrent diffused oral hyperpigmentation. A significant association was found between the presence of cutaneous hyperpigmentation and oral pigmentation. Specifically, individuals with cutaneous hyperpigmentation were 2.29 times more likely to exhibit diffused oral pigmentation compared to those without cutaneous hyperpigmentation. This finding may be explained by the shared origin of both cutaneous and oral hyperpigmentation, with melanin being the common factor.

Although this study provides a comprehensive view of the prevalence and associated factors of diffuse oral mucosal pigmentation, it has certain limitations. The use of non-random sampling and geographic limitation of the study to a specific region may reduce the generalizability of the findings to other populations. Furthermore, relying on clinical examination-based diagnostic methods increases the potential for error in identifying underlying causes. Future studies could benefit from incorporating advanced imaging techniques or biopsies and examining the relationship between systemic factors and pigmentation in larger and more diverse populations.

## 5. Conclusion

Diffused oral mucosal pigmentation has a relatively high prevalence, with the highest frequency observed in the gingiva. The study found significant associations between oral mucosal pigmentation and factors such as systemic diseases, particularly hypertension, as well as the use of specific medications, including antihypertensive and thyroid medications. Therefore, a thorough clinical examination of the oral soft tissues is crucial for detecting color changes and investigating their underlying causes, particularly in relation to smoking, alcohol consumption, and medication use.

## Ethical Considerations

The study protocol was approved by the Ethics Committee of Gilan University of Medical Sciences (Ethics Code: IR.GUMS.REC.1402.134)

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None

## Authors' Contributions

**Mohammad Samami:** Conceptualization, Supervision, Visualization, Methodology, Writing-review & editing **Mohammad Ebrahim Ghafari:** Formal analysis, Software, Writing-review & editing **Zahra Hemmati:** Investigation, Data curation, Writing-review & editing **Fereshteh Najar-karimi**, Investigation, Project administration, Writing-Original draft, Writing-review & editing

## Conflict of Interests

None

## Availability of data and material

Not applicable

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