ORIGINAL RESEARCH

Inhibition of Silver Diamine Fluoride-induced Tooth Discoloration by Using Natural Antioxidant: *In Vitro* Study

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Abstract

Aim: Silver diamine fluoride (SDF) is a well-known caries preventive aid capable of arresting carious lesions and preventing secondary caries formation. Despite having the caries prevention potential, the clinical use of SDF is limited due to the tooth discoloration caused by SDF. The objective of this study was to evaluate the efficiency of natural antioxidants to inhibit SDF-induced tooth discoloration.

Materials and methods: A total of 32 bovine teeth were polished to create a 6 mm circular window on the middle 1/3 (for enamel) or on the cervical 1/3 (for dentin) of the labial surface. Specimens were treated either with SDF alone or SDF followed by ascorbic acid (AA)/alpha lipoic acid (ALA)/7th generation bonding materials. The color parameters Lightness (L*), Chroma (C*), and Hue (H*) of the tooth window were measured at pretreatment, 1-hour, 1-week, and 1-month posttreatment using a digital color chromometer.

Results: Repeated measure ANOVA showed a significant tooth color alteration at 1-hour posttreatment. The L* and H* values dropped and C* value elevated significantly in 1-hour posttreatment measurement. All experimental groups showed significant tooth color alteration after treatment ($p < 0.05$) and were unable to reverse the discoloration even after 1-month period except the ALA group which did not show any significant ($p > 0.05$) color alteration compared with the pretreatment value.

Conclusions: Within the limitation of the *in vitro* model and according to the results of this study, it can be concluded that ALA has the potential to prevent SDF-induced tooth discoloration; however, AA was unable to prevent the discoloration.

Clinical significance: SDF induces discoloration of enamel and dentin can be reversed by applying Alpha lipoic acid immediacy after SDF application.

Keywords: Alpha lipoic acid; Antioxidant; Ascorbic acid; Bonding materials; Silver diamine fluoride; Tooth discoloration.

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Introduction

Dental caries is one of the most common infectious multifactorial oral diseases among all populations.[1] Enamel and dentin demineralization occur due to the effect of cariogenic bacteria and biofilm that produce acidic mineral-dissolving byproducts.[2] A caries lesion can be reversed or arrested if diagnosed early with the help of various re-mineralizing agents.[3] Secondary caries occurs on a tooth after the restorations have been used for a long period and are regarded as one of the most common reasons for the re-restoration of teeth. There have been several reports suggesting long-term consequences of amalgam and composite resin restoration replacement mainly due to secondary caries.[4] Considering the above problem lots of research has been carried out in developing new cariostatic dental materials.

Silver diamine fluoride (SDF) is an FDA-approved safe, noninvasive, caries-preventing, and arresting agent that can be applied topically in children and elderly patients. Silver diamine fluoride is a colorless alkaline solution consisting of silver and fluoride, these together in combination with ammonia form a complex which is more persistent than silver fluoride. Silver acts as an antimicrobial agent that simultaneously strengthens the underlying dentin. Fluoride is the active ingredient that stops dental caries and helps its prevention.[5] Silver diamine fluoride has also been reported to increase the mineral density of the carious enamel lesions and the microhardness of the carious dentin lesions.[6] In addition, annual or biannual application of SDF was proven to be more effective in the prevention and re-mineralization of carious lesions than the application of fluoride varnish quarterly.[7–9] Silver diamine fluoride has also been reported to have an inhibitory effect on proteolytic enzymes, such as matrix metalloproteinase (MMPs) and cathepsin which are involved in dentine collagen degradation and caries progression. Silver diamine fluoride application under glass-ionomer restorations has also been reported to exhibit pulpal response and increase the formation of reparative dentine. Moreover, preceding treatment of SDF to the margins of the cavity around the glass-ionomer restorations has been reported to resist

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Conflict of interest: None

the development of secondary caries. Besides its effective role in preventing caries, some laboratory-based studies also reported that the bond strength of restorations to dentine was not adversely affected by SDF using resin-based adhesives.[10]

In spite of its numerous benefits, one important drawback of SDF is the irreversible black staining on the teeth due to the formation of silver oxide which serves as an esthetic concern for many patients, especially when it is apparent in the anterior region, thus limiting its use clinically.[11,12] Dark discoloration forms after exposure of the silver part of SDF to reducing agents or sunlight.[13,14] Since the beginning of 2016, there has been some research conducted to find the potential ingredients or techniques that can be used to overcome SDF-induced discoloration. One of the methods reported to solve the issue of discoloration is the application of salt such as potassium iodide (KI) after SDF placement.[15] A recent review article on SDF-induced tooth discoloration summarized that KI and 20% glutathione (GSH) solution are the currently available option to overcome this issue.[16] Glutathione is an antioxidant in plants, animals, fungi, and some bacteria and archaea, and is capable of preventing damage to important cellular components caused by sources, such as reactive oxygen species, free radicals, peroxides, lipid peroxides, and heavy metals. Similar to GSH, ascorbic acid (AA), also known as vitamin C, has been found to have beneficial effects in dentistry. One of its primary roles is as an antioxidant, which can help protect against oxidative stress in the oral cavity. Overall, the use of ascorbic acid in dentistry holds promise for improving oral health outcomes. Alpha-lipoic acid (ALA) is a potent antioxidant that has been used in dentistry for its anti-inflammatory and regenerative properties. Alpha-lipoic acid has been shown to enhance wound healing, reduce oxidative stress, and improve cell viability in oral tissues. It has also been used in the treatment of oral diseases, such as periodontitis and oral lichen planus.

To overcome the tooth discoloration caused by SDF and in order to use it regularly in the clinics as dental caries preventive aid, extensive research is needed to eliminate SDF-induced tooth discoloration. The use of natural antioxidant such as AA and ALA can be considered more biocompatible and may overcome the negative effect of SDF. Considering the potential of antioxidant like GSH to reverse SDF-induced discoloration, this study is aimed to rule out whether the use of natural antioxidant such as AA and ALA following SDF application would reverse the SDF-induced discolorations effect compared with SDF application alone. Therefore, the objective of this study was to evaluate the efficacy of two natural antioxidant AA and ALA, and a synthetic resin (dental bonding) in reducing the discoloration after SDF application by comparing the color parameter alteration of enamel and dentin surface before and after application of tested materials. The null hypotheses tested in this study were (1) there are no differences in color alteration of enamel among the tested groups and (2) there are no differences in color alteration of dentin among the tested groups.

Materials and Methods

Specimen Preparation

This experimental study was conducted over 1 year in 2020–2021 using bovine tooth specimens under the ethical approval number RAKMHSU-REC-100-2019-UG-D. The minimum number of required specimen for each group (n) was determined by conducting a pilot study to evaluate data curation accuracy and statistical significance. For enamel specimens, the labial surface of 16 bovine incisors (n = 4) teeth free of cracks were successively ground flat using 600–2000-grit silicon carbide papers (SiC). For dentine specimens, the cervical dentine of 16 bovine incisors (n = 4) teeth was prepared following the same method. The specimens were immersed in demineralizing solution containing 2.2 mM/L $CaCl_2$, 50 mL acetic acid, and 2.2 mM/L KH_2PO_4 for 96 hours to create pre-lesion.[17] The pH of the demineralizing solution was adjusted to 4.5 using KCl. A 6 mm circular window was marked using a paper sticker. The color parameter Lightness (L*), Chroma (C*), and Hue (H*) of the marked window on enamel and dentine specimens were measured using a digital color chromo meter VITA Easyshade® Advance 4.0 (VITA Zahnfabrik, Bad Säckingen, Germany.). For accuracy, each specimen was measured three times. The specimens were randomly divided in to four groups according to the test materials.

Table 1: Group distribution, treatment protocol, and product detail of experimental groups

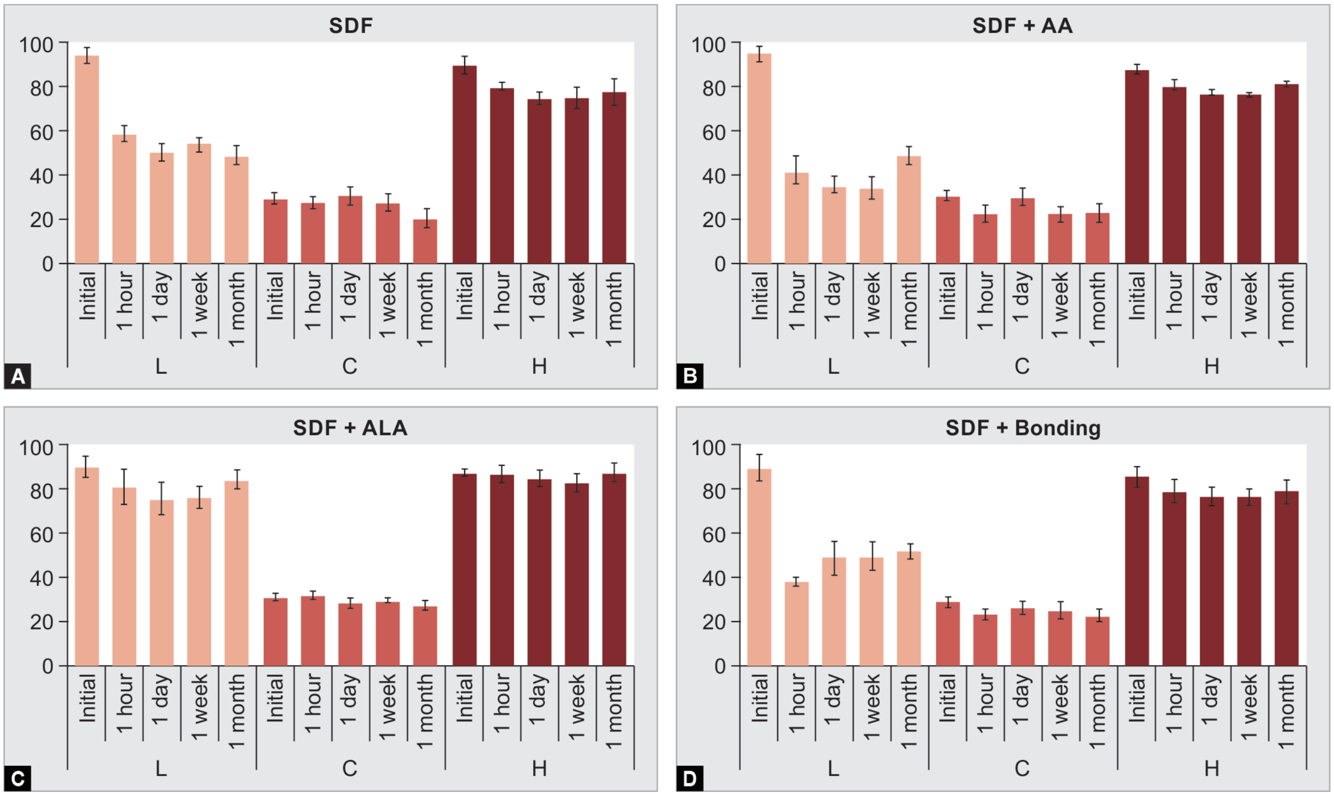
Groups	*Tested materials*	*Product details*
1	SDF only	Topamine Silver Diamine Fluoride complex, DentaLife Australia Pty. Ltd
2	SDF followed by AA	100% Vitamin C powder. MYPROTEIN, Manchester, UK
3	SDF followed by ALA	100% Alpha lipoic acid powder. MYPROTEIN, Manchester, UK
4	SDF followed by 7th generation bonding agent	Prelude One. Danville Material, San Ramon, CA, USA

Application of Test Materials

The solution of AA and ALA were prepared by mixing the powders with equal weight amount of deionized water. After recording of initial color parameter, the enamel and dentine specimens were treated with one of the test materials as mentioned in Table 1. In brief, SDF solution was poured in a light protective dental dampen dish and then applied on demineralized enamel and dentin surface using a dental micro-brush with agitating. The specimens were allowed to dry with addition of a gentle clean air spray for 1 minute. After that, for groups II and III, the test solutions were applied on SDF-treated surface using a clean microbrush and a gentle clean air spray for 1 minute was applied. The excess materials were rinsed off and the specimens were allowed to dry. For group IV, a 7th generation bonging materials were applied on SDF-treated surface following manufacturer instruction and polymerized using a curing light for 20 seconds. The specimens were immersed in an artificial saliva containing 0.7 mM $CaCl_2$, 0.2 mM $MgCl_2 \cdot 6H_2O$, 4.0 mM KH_2PO_4, 30 mM KCl, 0.3 mM NaN_3, and 20 mM HEPES.[18] The color parameters were re-evaluated after blot drying of the specimen window at 1-hour, 1-day, 1-week, and 1-month intervals.

Statistical Analysis

The raw data were analyzed using statistical software (SPSS 24.0, SPSS IBM, Armonk, NY, USA). The periodic color change of each group was compared using repeated measure ANOVA to determine whether the color changes were statistically significant over the time period. Multiple comparisons among the tested groups were analyzed using the Tukey's *post hoc* Test at a 95% confidence level to determine if there is a statistical significance in degree of staining prevention by the materials.



Figs 1A to D: Mean L*, C*, and H* values with a standard deviation of enamel specimens in different time period of experimental groups

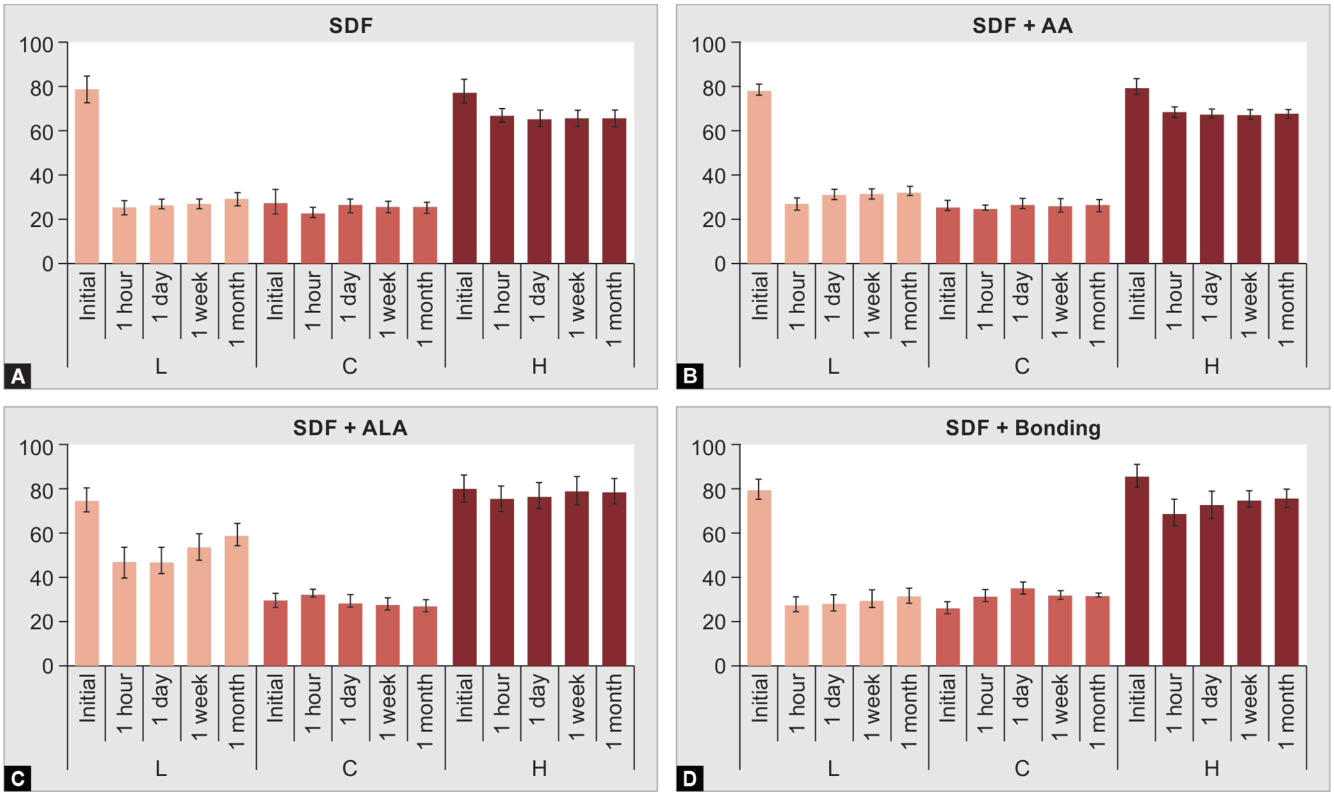
Result

The repeated measure ANOVA reveal that the tested materials have a significant effect on the L* ($p = 0.003$) and H* ($p = 0.001$) of the enamel surfaces; however, the effect on C* was statistically insignificant ($p = 0.257$). Group III (SDF followed by ALA-treated group) showed the highest L* and H* value which was statistically insignificant ($p > 0.05$) compared with the pretreatment value of the same. This indicates that the enamel color did not turn darker in this group. The L* and H* value of both groups II and group IV significantly decreased compared with the pretreatment value of the same. Group II and group IV showed a statistically insignificant value for L* ($p = 0.126$), C* ($p = 0.257$), and H* ($p = 0.815$) compared with Group I. This indicates that both the groups showed similar degree of enamel discoloration as SDF alone treated group. The L*, C*, and H* values of enamel in each group in each time interval are shown in Figure 1. In the case of dentine, the repeated measure ANOVA showed a significant effect on the L* ($p = 0.001$) and H* ($p = 0.001$); however, the effect on C* was statistically insignificant ($p = 0.142$). The L* value was significantly reduced in all four groups compared with the pretreatment value of the same indicates that the dentine turned dark after application of tested materials. Group III showed the highest posttreatment L* value among the tested groups. The L* value of the group III was statistically significant ($p = 0.001$) compare with other groups followed by group II ($p = 0.001$) and group IV ($p = 0.001$) and then group I in descending order. This indicates that although ALA could not stop the dark discoloration of demineralized dentin, the degree of discoloration can be significantly reduced by the application of ALA. The posttreatment H* value significantly decreased in all tested groups except the group III. The H* value was highest in group III followed by group II followed by group IV and group I in descending order. The L*, C*, and H* values of dentine in each group in each time interval are shown in Figure 2. The comparative mean L*, C*, and H* values of enamel and dentin surfaces of each experimental groups in pretreatment and during 1 month storage time are shown in Figures 3 and 4. Representative images of enamel and dentin specimens after 1-month incubation are shown in Figure 5, Flowchart 1.

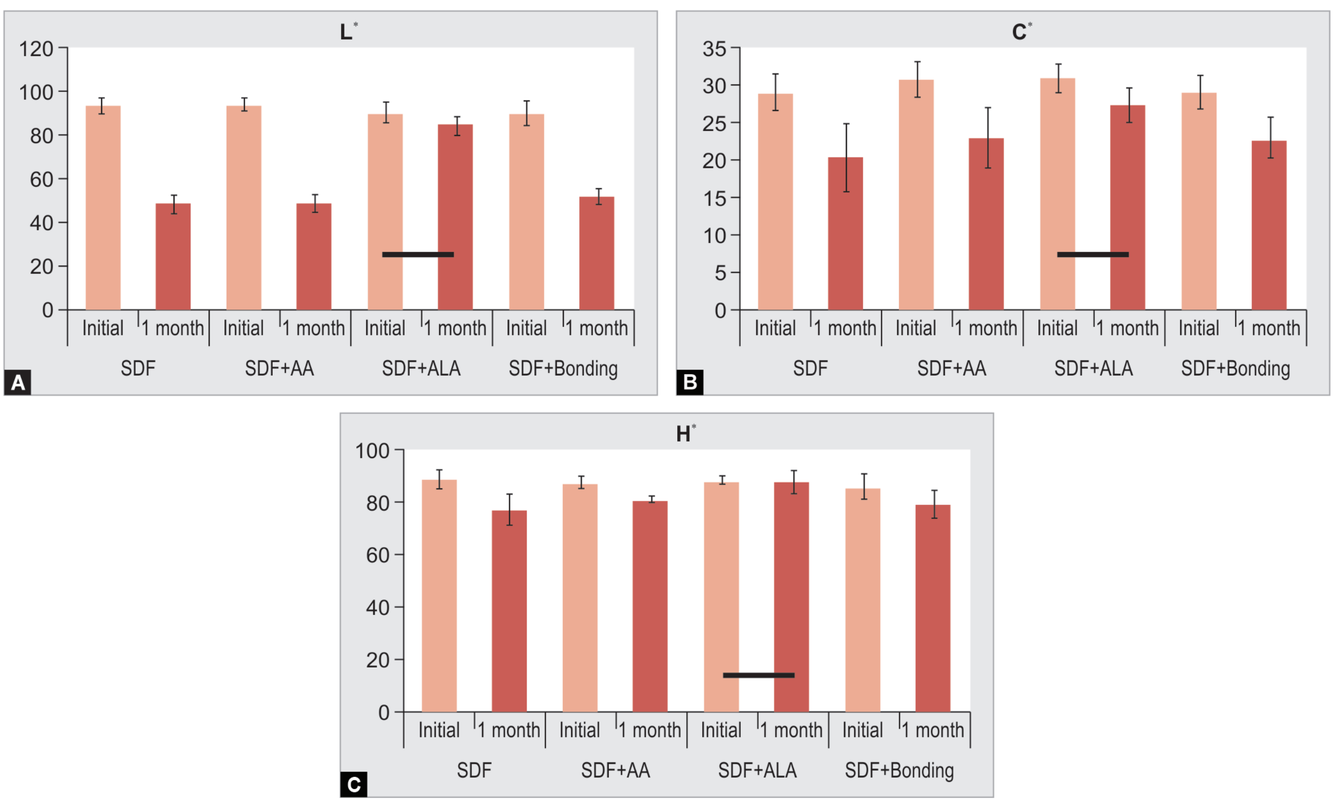
Discussion

This study was conducted to evaluate whether an immediate application of natural antioxidants such as AA and ALA and synthetic resin bonding can stop or reduce the SDF-induced discoloration of demineralized enamel and dentin. The color alteration of tested groups for enamel was significantly different compared with the control group, thus the 1st null hypothesis was rejected. The dentin specimens showed a similar tendency to enamel, thus the 2nd null hypothesis was also rejected.

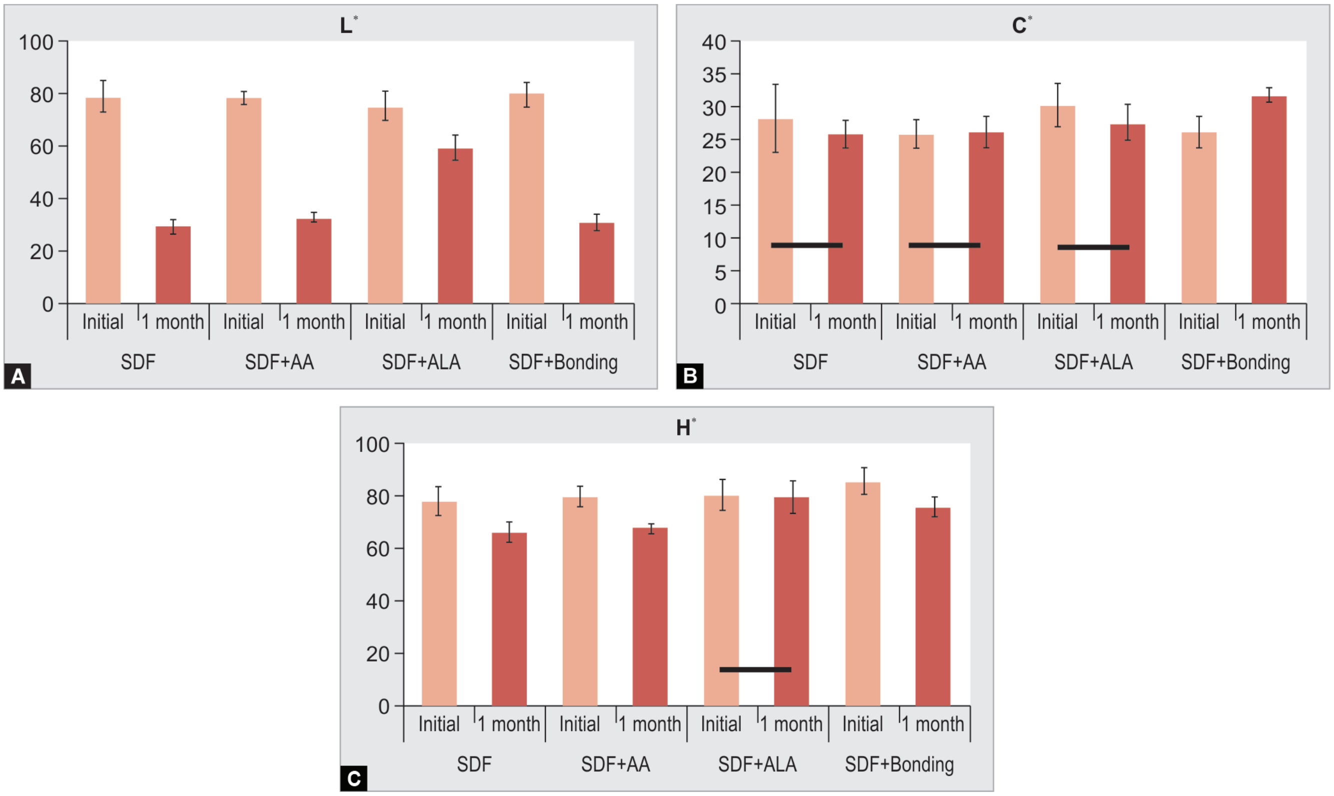
Bovine tooth is most commonly used *in vitro* experiments as an alternative to human tooth.[19] In the case of tooth color-related study, it is much more convenient than the extracted human incisor that widely varies in terms of age, ethnicity, food habit, and morphologically. SDF-induced tooth discoloration remains the main obstacle in gaining the popularity of SDF as a caries preventive aid in routine dental practice. This leads the researcher to investigate the exact mechanism of SDF-induced tooth discoloration and to find the remedy to overcome the obstacle. One of the mechanisms explained by Crystal YO, et al. (2017) is the precipitation of silver phosphate (Ag_3PO_4) after SDF application plays the major role in tooth discoloration.[20] Keeping this in mind, several previous studies attempted to prevent the precipitation of (Ag_3PO_4) by applying



Figs 2A to D: Mean L*, C*, and H* values with a standard deviation of dentin specimens in different time period of experimental groups



Figs 3A to C: Comparative mean L*, C*, and H* values with a standard deviation of enamel surfaces of each experimental group in pretreatment and one month storage time. Connected bar graph indicates no statistically significant difference



Figs 4A to C: Comparative mean L*, C*, and H* values with a standard deviation of dentin surfaces of each experimental group in pretreatment and 1-month storage time. The connected bar graph indicates no statistically significant difference

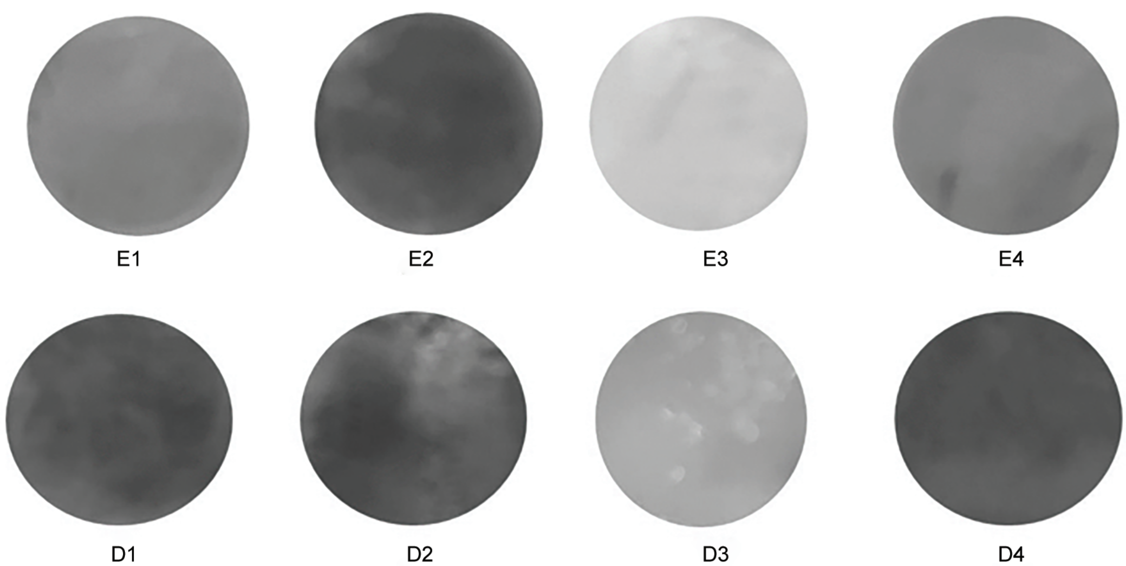
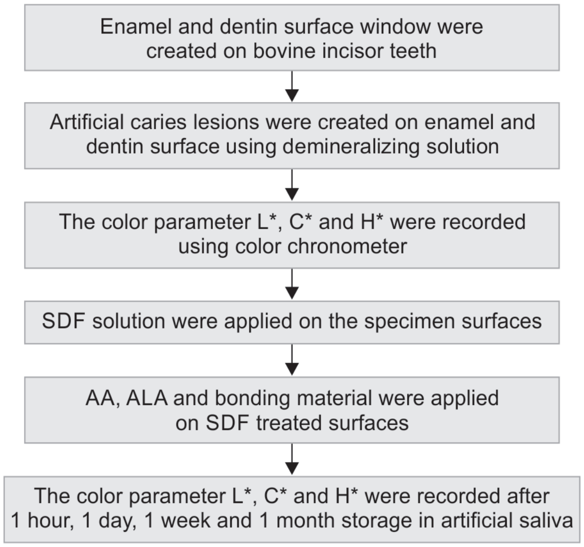


Fig. 5: Representative image of enamel and dentine specimens after 1-month storage following different treatment protocol. E = enamel, D = dentine. 1 = SDF only, 2 = SDF + AA, 3 = SDF + ALA, 4 = SDF + bonding

potassium iodide (KI) following SDF application. Potassium iodide can react with free silver ions and prevent the formation of Ag_3PO_4. The reaction between SDF and KI leads to the formation of a yellow colored silver iodide precipitate that prevents the black staining of teeth. Several studies have demonstrated the potential of KI to prevent SDF-induced tooth discoloration.[21–25] However, KI might not be applicable for the patient undergoing thyroid therapy or who has a known allergy to potassium or iodine. This limitation of KI keeps the necessity of finding a biocompatible material with the potential to prevent SDF-induced tooth discoloration.

Ascorbic acid (vitamin C) is a water-soluble chemical that the human body cannot store and contain no toxic effects.[26,27]

Flowchart 1: Flow diagram



This nutrient not only helps to avoid diseases like scurvy, which are caused by a lack of collagen but also helps to form tissues like skin, tendons, cartilage, and blood vessels. It also serves as a biological antioxidant and aids in wound healing.[26] There is not enough information on whether AA enhances or retards the degree of chromogen absorption by the enamel, a previous study by Bennett ZY et al. reveals that AA reduces tetracycline-induced discoloration. One of the speculations was the acidic pH of AA that reduces discoloration. In our study, the application of AA slightly increased the discoloration of both enamel and dentin specimens; however, there was no difference in the degree of discoloration after 1 month. Although the exact mechanism is not well understood, one possibility is the acidic nature of AA that might enhance the penetration of silver particles into enamel and dentin.[28,29]

Alpha-lipoic acid is a well-known antioxidant effective in scavenging hydroxyl radicals, singlet oxygen, and nitric oxide radicals due to its unique sulfur structure.[30] Alpha-lipoic acid is an effective reducing agent that can scavenge the superoxide radical as well as the hydroxyl and nitric oxide radicals.[31] Topical application of ALA provides protection against free radicals produced by exposure to ultraviolet radiation.[32] The possible application of ALA in dentistry is not well studied. A recent study by Aksoy U, et al. showed that the ALA treatment provided therapeutic effects on the inhibition of periapical bone loss by reducing the TNF-α, IL-1β, MMP-1, and MMP-2 levels.[33] In our study, the application of ALA following SDF showed the potential to prevent the discoloration of both enamel and dentin. Although the exact mechanism needs to be clarified further, several speculations can be made to explain the fact. One of the reasons could be the antioxidant or scavenging potential of ALA that can eliminate or subside the free radicals produced due to SDF–tooth interaction. Another possibility is due to the potential of ALA in preventing UV absorption which was found to be a contributing factor for SDF-induced tooth discoloration.

A recent study by Hamdy D et al. reported the potential of resin-based restorative materials in masking SDF-induced tooth discoloration.[34] However, in our study, the application of bonding material following SDF negatively affects tooth discoloration. One of the reasons could be the necessity of light-curing to polymerize the resin-based materials that enhance tooth discoloration by SDF.

This was the first-ever study reporting the potential of ALA to inhibit SDF-induced tooth discoloration. Due to the limitation of articles on ALA interaction with tooth, the exact mechanism of ALA preventing SDF-induced tooth discoloration was not completely understood and its interaction with SDF is needed to be explored further. A comparative evaluation of ALA with KI and other materials regarding tooth discoloration and caries inhibition should be studied in future research.

Conclusions

According to the results obtained in this *in vitro* study, it can be concluded that the natural antioxidant ALA might have the potential to prevent SDF-induced discoloration of enamel and dentin. Ascorbic acid was ineffective to prevent SDF-induced tooth discoloration. Masking with bonding material following SDF application was ineffective to prevent the discoloration of enamel and dentin. Alpha-lipoic acid could be the research of interest for future study related to SDF-induced tooth discoloration. Clinical application of ALA immediately after SDF may reduce the dark discoloration of enamel and dentin caused by SDF.

Clinical Significance

SDF-induced discoloration of enamel and dentin can be reversed by applying alpha lipoic acid immediately after SDF application.

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