



Evaluation of the Cytotoxicity of Different Teething Gels on Human Gingival Fibroblast Cells and Their Effects on In Vitro Wound Healing

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ABSTRACT

Objectives: This study aims to compare the cytotoxicity of teething gels with different compositions and their impact on in vitro wound healing.

Materials and Methods: The viability of human gingival fibroblast cells treated with teething gels was evaluated, and the gels' cytotoxicity and effects on wound healing were investigated using a scratch test.

Results: The cytotoxicity of five different teething gels on human gingival fibroblast cells, as well as their effects on in vitro wound healing after 24 and 48 hours, were compared. Among the teething gels, the lidocaine hydrochloride + cetylpyridinium chloride-based gel group had the most cytotoxic effect on human gingival fibroblast cells.

Conclusions: In light of the results of this study, the necessity of using teething gels during the eruption period is questionable.

Keywords: Wound healing, fibroblasts, tooth eruption

Farklı Diş Çıkarma Jellerinin İnsan Dişeti Fibroblast Hücreleri Üzerindeki Sitotoksitesinin ve In Vitro Yara İyileşmesi Üzerindeki Etkilerinin Değerlendirilmesi

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ÖZ

Amaç: Bu çalışmanın amacı, farklı içeriklere sahip diş çıkarma jellerinin sitotoksitesini ve in vitro yara iyileşmesi üzerindeki etkilerini karşılaştırmaktır.

Gereç ve Yöntemler: İnsan gingival fibroblast hücreleri üzerine uygulanan diş çıkarma jellerinin canlılık değerleri değerlendirildi ve sitotoksitesileri ve yara iyileşmesi üzerine etkileri çizik testi ile araştırıldı.

Bulgular: Beş farklı diş çıkarma jelinin insan dişeti fibroblast hücreleri üzerindeki sitotoksitesisi ile 24 ve 48. saatlerde in-vitro yara iyileşmesi üzerindeki etkileri karşılaştırıldı. Lidokain hidroklorür + setilpridinyum klorür bazlı jel grubu, diş çıkarma jelleri arasında insan gingival fibroblast hücreleri üzerinde en fazla sitotoksik etkiye sahipti.

Sonuçlar: Çalışmamızın sonuçları göz önüne alındığında, diş çıkarma jellerinin erüpsiyon döneminde kullanılmasının gerekliliği tartışmalıdır.

Anahtar Kelimeler: Diş sürmesi, fibroblastlar, yara iyileşmesi

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Introduction

Several non-pharmacological and pharmacological treatment methods are used to manage symptoms during the eruption period. Teething gels, one of the pharmacological methods, are frequently used by parents and healthcare professionals.¹⁻³ In the literature, it was found that 4.4%- 73.4% of the parents in various countries use teething gels or topical drugs.⁴⁻⁶ Wake et al. showed that teething gels were frequently advised by dentists, pharmacists, nurses, and paediatricians during the eruption period of primary teeth.⁷ According to the study by Reeve et al.,⁸ teething gels were prescribed by paediatric dentists

at a rate of 23.7 %. Teething gels can be also used in to treat of oral aphthae and scratched areas in the oral region to promote wound healing during the postoperative period.^{8,9}

Teething gels are also available without a prescription in the light of current advertising campaigns, as well as the advice of healthcare professionals. When the prospectuses of teething gels are examined, it is seen that there is no clear statement about the usage dose and possible side effects. Therefore, it cannot be foreseen what problems may be caused by unconscious repetitive use of these gels. Although teething gels with different contents have been used frequently from the past to present, their

effectiveness and possible side effects are still controversial. There are limited studies on the fact that teething gels provide anti-inflammatory effects in periodontal diseases and accelerate wound healing in oral aphthae and postoperative period.⁹⁻¹¹ There are more published reports about the side effects of using teething gels, especially in young children. Tooth decay, developmental problems, paresthesia, hypotension, bradycardia, Stevens-Johnson syndrome, metabolic acidosis, seizure, and cardiac arrest were among the reported side effects of teething gels.¹²⁻¹⁷ Best of authors' knowledge, there are no studies in the accessible literature comparing the cytotoxic effect of teething gels or their effects on wound healing.

Due to the ethical and methodological problems of clinical studies, especially in children, various effects of dental materials are evaluated on different cell cultures. Cell culture tests are frequently used to evaluate the biocompatibility of dental materials. These tests have many advantages, such as they can be repeated under standard conditions, standard measurements can be made by direct observation on cells, experimental stages can be kept under control, easily repeated and not affected by individual factors.^{18,19} The MTT method, recommended by international standards such as the ISO 10993 series, has been frequently used to assess cytotoxicity of dental materials on cell culture.²⁰

The median lethal dose (LD₅₀) is one way to measure the short-term poisoning potential (acute toxicity) of a material. LD₅₀ values have been used to compare relative acute hazards of materials, especially when no other toxicology data is available for the chemicals. When comparing the two materials, the material with a low LD₅₀ value is considered a more toxic material than the material with a high LD₅₀ value.^{21,22}

The proper function of fibroblasts plays a pivotal role in the maintenance of periodontal tissue homeostasis and the facilitation of effective wound healing. It has been well established that cellular activities such as proliferation, growth, and extracellular matrix synthesis are key contributors to periodontal tissue regeneration and repair processes.^{24,25} However, the presence of adverse effects associated with certain dental materials may compromise these cellular mechanisms, potentially leading to impaired wound healing outcomes.

This study aims to evaluate the LD₅₀ value of five different teething gels on human gingival fibroblast cells and their effects on *in vitro* wound healing.

Materials and Methods

Ethical Consideration

The ethics committee's approval of the study was obtained from Afyonkarahisar University Clinical Research Ethics Committee (Decision No. 2020/473).

Cell Culture and Sample Preparation

Human gingival fibroblast cells (HGF-1), obtained from the American Type Culture Collection (ATCC®, Virginia, USA), were utilized in this study. Upon delivery in dry ice within a styrofoam container, the cells were stored at

-150 °C until further use. For cultivation, cells were maintained in Dulbecco's Modified Eagle Medium (DMEM; Capricorn, Ebsdorfergrund, Germany) containing stable glutamine, supplemented with 10% fetal bovine serum (FBS; Capricorn), 1% penicillin-streptomycin (Capricorn), and 1% sodium pyruvate (BI Biological Industries, Beit-Haemek, Israel). Cultures were incubated at 37 °C in a humidified atmosphere with 5% CO₂. Subculturing was performed until an adequate number of cells was reached, and cells at passage six were employed in the experimental procedures.

Cytotoxicity Test

Cell viability was tested using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay. The HGF-1 cells were placed in 96-well micro plates and allowed to adhere to the bottom of the wells.

In the study, five different teething gels were evaluated (Figure 1). Group 1: Hyaluronic acid-based gel (HAG), Group 2: Lidocaine hydrochloride and cetylpyridinium chloride-based gel (LCG), Group 3: Choline salicylate-based gel (CG), Group 4: Lidocaine hydrochloride-based gel (LG), Group 5: Herbal-based gel (HG). The cells with DMEM were selected as a control group. The content information of the teething gels was shown in Table 1.

For determination of the median lethal dose (LD₅₀) of teething gels, 1 gram (gr) of each teething gel was taken into falcon tubes with a precision scale to standardize the amounts of gels used. 1 milliliter (ml) of medium solution was added to the gels and the main stock was prepared. The stock gel was mixed homogeneously with the vortex device. The teething gels were diluted at various dilutions (1:2, 1:4, 1:8, 1:16, 1:32, 1:64, 1:128, 1:256, 1:512, 1:1024) and applied to the wells. The micro plates were incubated for 24 hours. Then a MTT reagent (Sigma Aldrich®, Darmstadt, Germany) was applied, and the micro plates were incubated for 4 hours. The MTT solution was then removed from the wells, and dimethyl sulfoxide solution (DMSO, Sigma Aldrich®, Darmstadt, Germany) was added to the wells to dissolve the formed formazan crystals (100 µl/well). The absorbance value was measured using a spectrophotometer (570-nm wavelength, ELx800; Epoch, Bio-Tek Instruments, Winooski, VT, USA) after the formazan crystals were dissolved. Triple repeated measurements of each groups were performed by a single experienced, blinded, calibrated researcher. The following formula was used to calculate the percentage of vitality value;

$$\text{Vitality value (\%)} = \frac{\text{Optical density value of the well}}{\text{Optical density value of the control group}} \times 100$$

Since the consistency and densities of the materials selected for the study were variable the dilutions that killed 50% (± 2) of the cells for each preparation (LD₅₀ value) were determined in terms of standardization. The median lethal dose (LD₅₀) was defined as the extract concentration that reduced cell viability by 50%, calculated using a four-parameter logistic regression model.

$$LD^{50} = \frac{(50 - V1)(C2 - C1)}{(V2 - V1)} + C1$$

*C1: The lower concentration where cell viability is still above 50%

*C2: The next higher concentration where cell viability has dropped below 50%

*V1: The cell viability (%) measured at C1

*V2: The cell viability (%) measured at C2

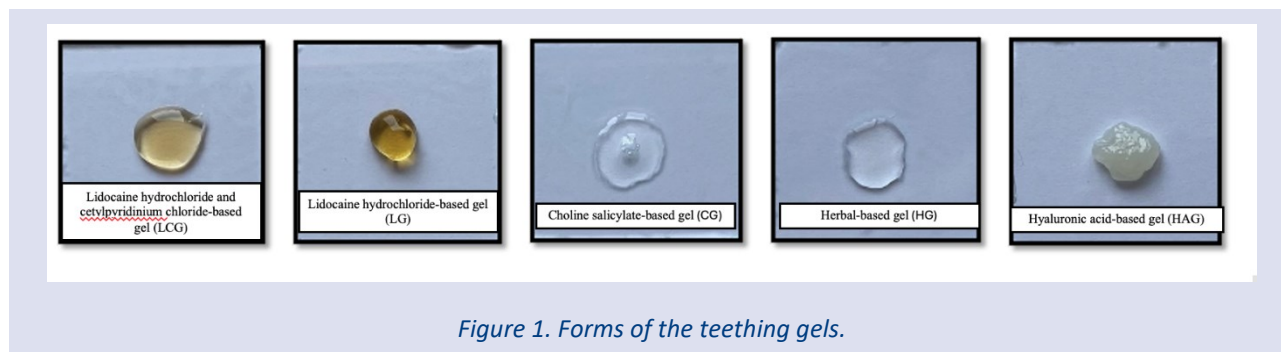


Figure 1. Forms of the teething gels.

Table 1. Teething gels that were used in the study

Group	Teething gel	Content	Company	LOT Number
1- Hyaluronic-acid based gel (HAG)	Aftamed*	<u>Main ingredient:</u> Hyaluronic acid (240 mg/100 mg). <u>Sub-ingredients:</u> Water, PEG 400, xylitol, polyvinyl alcohol, cellulose gum, PEG 40, hydrogenated castor oil, PVP, PVM/MA copolymer, VP eicocene copolymer, glyceryl, laurate, polycarbophil, sodium saccharinate, sodium phosphate, flavor, choline alfosterate, trisodium phosphate, dodecahydrate, edta, lactic acid, sodium hydroxide.	Bioplax Pharma (Wallington, United Kingdom)	1902253019
2-Lidocaine hydrochloride+cetylpridinium chloride based gel (LCG)	Calgel*	<u>Main ingredient:</u> Lidocaine hydrochloride, cetylpyridinium chloride. <u>Side ingredients:</u> Sorbitol, xylitol, alcohol, sodium saccharin, menthol, sweetener, caramel.	GlaxoSmithKline (Brenthford, United Kingdom)	21G018
3-Choline salicylate-based gel (CG)	Dencol*	<u>Main ingredient:</u> Choline salicylate <u>Side ingredients:</u> Chlorhexidine gluconate, glycerin, sorbitol, povidone K90, PEG 40 hydrogenated castor oil, citric acid monohydrate and deionized water.	Berko Pharma (Istanbul, Turkey)	2001209
4-Lidocaine hydrochloride-based gel (LG)	Dentinox*	<u>Main ingredient:</u> Lidocaine hydrochloride, hydroxypolyethoxy dodecane, camomil tincture. <u>Side ingredients:</u> Xylitol, sorbitol, propylene glycol, carbomer 934 P, 10% sodium hydroxide solution, polysorbate 20, sodium saccharin, menthol, distilled water.	Abdi İbrahim (Istanbul, Turkey)	19L017
5-Herbal-based gel (HG)	Jack N' Jill*	<u>Main ingredient:</u> Calendula extract, chamomile extract <u>Side ingredients:</u> Water, glycerin, hydroxyethyl cellulose, xylitol, potassium sorbate, vanilla flavor, citric acid.	Jack N'Jill (Melbourne, Australia)	B70649A

In Vitro Scratch Assay

An in vitro scratch assay, a conventional and cost-effective method frequently employed to assess wound healing and cell migration, was performed in accordance with previously established protocols.²⁵ Cells were seeded into six-well plates, and following adequate adherence, uniform linear scratches were created using sterile 20 µL pipette tips. Subsequently, wells were rinsed with phosphate-buffered saline (PBS) to eliminate cell debris, and fresh culture medium was immediately added.

Visualization of the scratch regions was carried out using an inverted microscope (Leica®, Wetzlar, Germany) prior to the application of test preparations. Gel dilutions corresponding to the determined LD₅₀ values were introduced into the wells, followed by incubation for 24 hours. Assessments were conducted at 24 and 48 hours post-application.

Quantification of the scratch area was performed using ImageJ software (National Institutes of Health, New York, USA), based on the average of three independent replicates (15 measurement points per group). Images of

the scratch sites were captured at baseline (0 hours), and at 24 and 48 hours. The percentage of wound closure was calculated using the following formula.²⁶

$$\text{Scratch - healing percentage (\%)} = \frac{\text{First scratch area} - \text{last scratch area}}{\text{First scratch area}} \times 100$$

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics software (version 26; IBM Corp., Chicago, IL, USA). Descriptive statistics, including mean, median, standard deviation, as well as minimum and maximum values, were calculated. The normality of data distribution was assessed using the Shapiro–Wilk test, which indicated

that the variables were not normally distributed. Consequently, the Kruskal–Wallis test was employed for comparisons of scratch healing across groups. For pairwise comparisons, the Dunn post hoc test was applied. A p-value less than 0.05 was considered indicative of statistical significance.

Results

The Figure 2 demonstrates the cell viability of tested teething gels at different dilutions. The dilutions that provided LD50 value of the teething gels were found as 1:2 for HG, 1:16 for CG, 1:64 for HAG and LG, and 1:128 for LCG. The LCG group had the most cytotoxic effect on HGF-1 cells among teething gels.

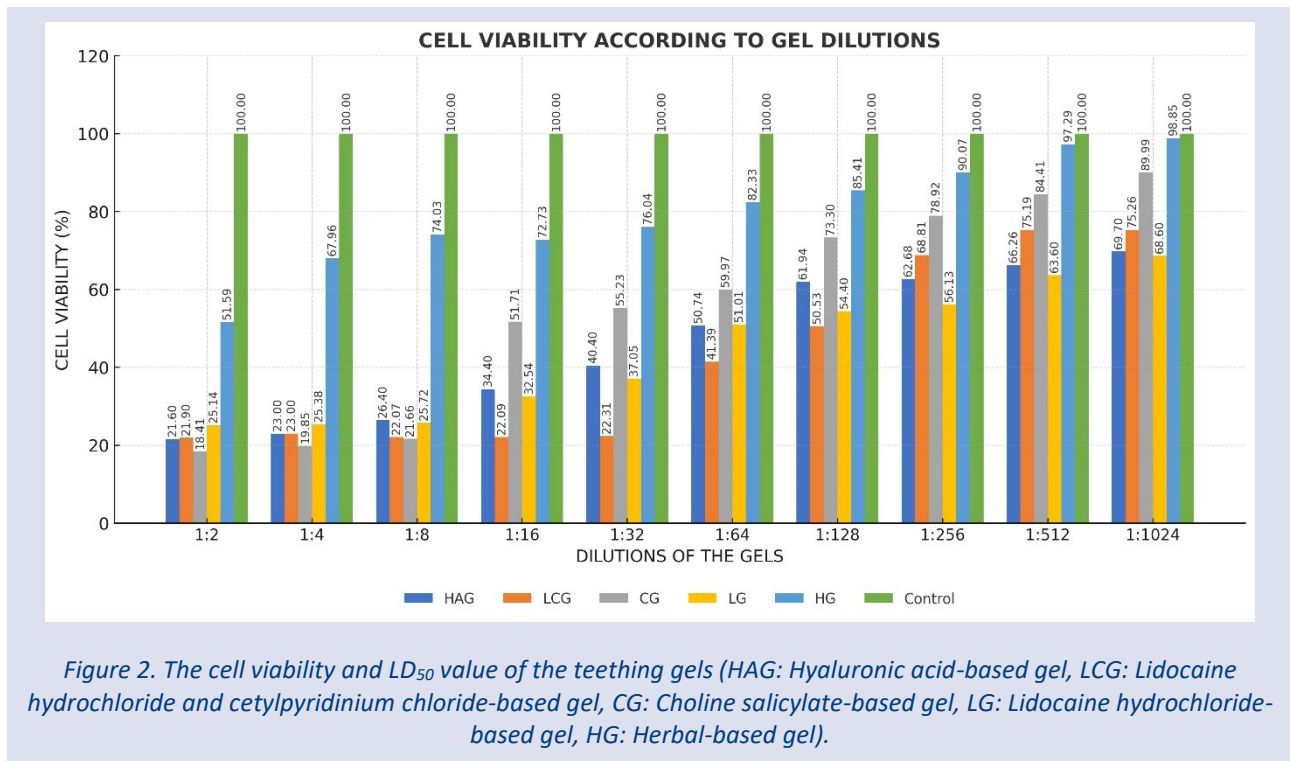


Figure 2. The cell viability and LD₅₀ value of the teething gels (HAG: Hyaluronic acid-based gel, LCG: Lidocaine hydrochloride and cetylpyridinium chloride-based gel, CG: Choline salicylate-based gel, LG: Lidocaine hydrochloride-based gel, HG: Herbal-based gel).

Figure 3 demonstrates the images of the scratch assays at initial hour, 24-hour and 48-hour intervals. The LCG group had the lowest scratch-healing percentage among all groups at 24 hours (3.49%). Differences between LCG with CG (25.4%), LG (22.1%) and HG (30.46%) were found statistically significant at 24 hours (p = 0.004; p = 0.005; p = 0.007).

In the control group, the median of scratch-healing was 51.44% and the percentage of healing was statistically higher than LCG (24.84%) and CG (26.67%) at 48 hours (p = 0.003, p = 0.025). The results of scratch-healing percentages of the groups at 24 and 48 hours are shown in Table 2.

In this present study, it was found that the scratch-healing percentage of any teething gel was not statistically better than the control group at 24 and 48-hours (p > 0.05).

Discussion

Teething gels are frequently preferred by both parents and health professionals for especially teething symptoms

despite insufficient scientific evidence to support their efficacy.^{2,27} The American Academy of Paediatric Dentistry and the American Food and Drug Administration have warned parents and healthcare professionals about the unconscious use of teething gels and the potential side effects of them.^{28,29} But, when the prospectuses of most of the teething gels were reviewed, it was seen that there was no clear explanation about the dosage and possible side effects. Although it is widely used, especially in young children, no study has been found to evaluate the cytotoxicity of these products or their effects on scratch-healing. Since this study will be a first, it may also be a steppingstone for future studies.

Since the consistency and densities of the materials selected for the study were variable the dilutions that killed 50% of the cells for each preparation (LD₅₀ value) were determined in terms of standardization and LCG was found to have the highest cytotoxicity on HGF-1 cells. Also, it was found that none of the teething gels were not statistically better than the control group in regarding of scratch

healing. Two different teething gels containing lidocaine hydrochloride were used in the current study. LCG, which contains alcohol with the main active ingredients of lidocaine hydrochloride and cetylpyridinium chloride, provided the LD50 value at a dilution of 1:128 and was the teething gel with the highest cytotoxicity on HGF-1 cells. In the previous studies, cell viability was found to be statistically significantly lower in the groups that were treated with lidocaine solution, which is consistent with the present findings.^{30,31} The cytotoxicity difference between

the lidocaine hydrochloride preparations in the study may be due to the cetylpyridinium chloride and alcohol in the LCG. According to the literature, cetylpyridinium chloride is cytotoxic to mouse fibroblast and human keratinocyte cells. Furthermore, when the cytotoxic effect of the alcohol was examined on various cell lines, it was found that it had a cytotoxic effect at varying rates depending on the concentration and application time.³²⁻³⁴ However, there is no clear conclusion regarding the alcohol derivative in the LCG' content.

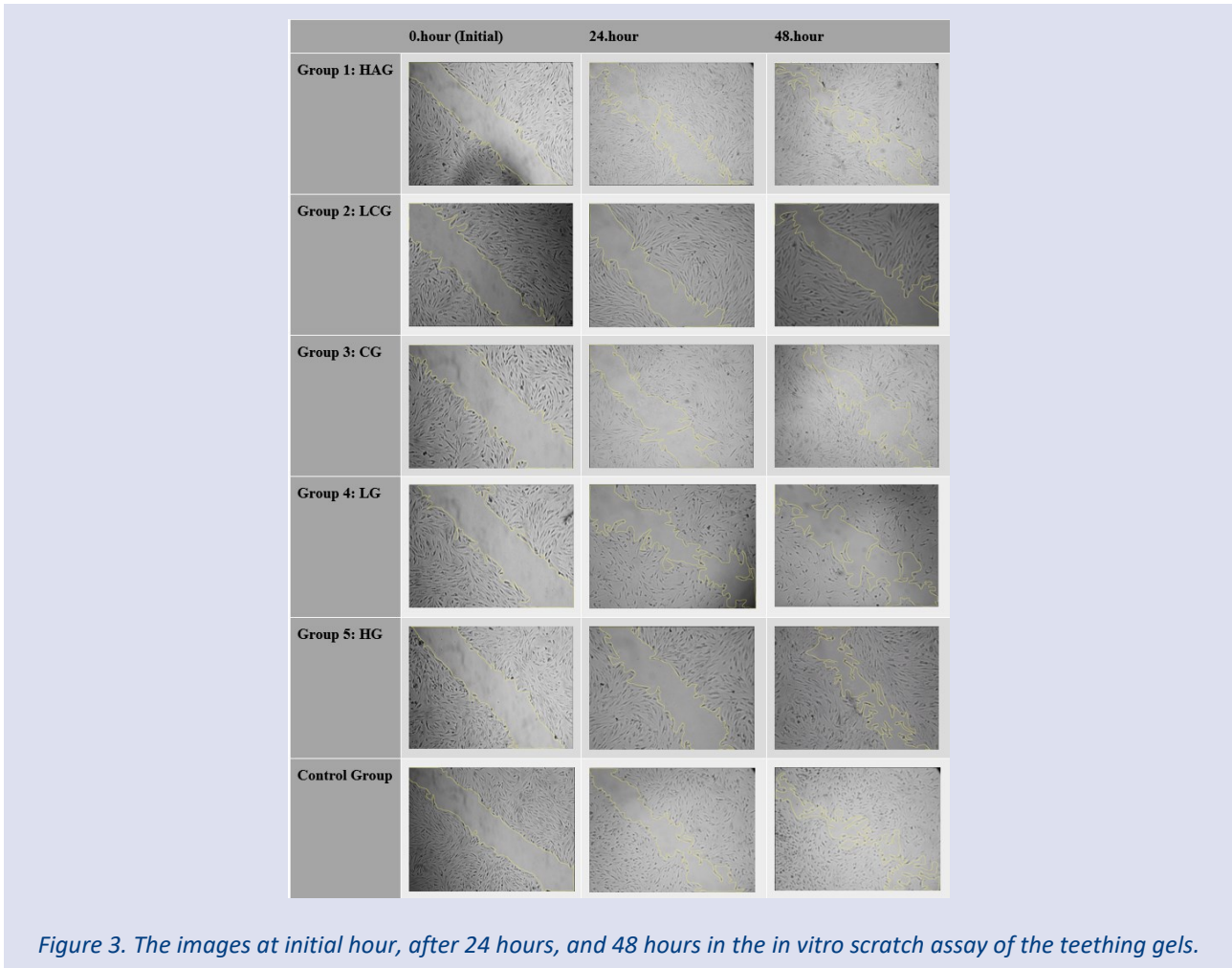


Figure 3. The images at initial hour, after 24 hours, and 48 hours in the in vitro scratch assay of the teething gels.

Table 2. The scratch-healing percentages of the teething gels at 24 and 48 hours

		Scratch-healing percentage at 24 hours (%)	Scratch-healing percentage at 48 hours (%)
Group 1: HAG	Mean ± SD	17.8 ± 6.25	40 ± 4.89
	Median (Min–Max)	19.05 (9.26–24.27) ^{ab}	39.32 (34.92–50.73) ^{ab}
Group 2: LCG	Mean ± SD	4.68 ± 3.98	28.53 ± 13.14
	Median (Min–Max)	3.49 (1.02–13.4) ^b	24.84 (17.33–48.72) ^a
Group 3: CG	Mean ± SD	24.5 ± 2.21	27.44 ± 3.25
	Median (Min–Max)	25.41 (20.92–26.25) ^a	26.67 (23.55–31.43) ^a
Group 4: LG	Mean ± SD	26.4 ± 11.44	45.43 ± 10.61
	Median (Min–Max)	22.12 (6.6–39.82) ^a	46.65 (34.32–63.92) ^{ab}
Group 5: HG	Mean ± SD	24.9 ± 15.1	43.4 ± 16.29
	Median (Min–Max)	30.46 (3.79–43.23) ^a	50.36 (14.69–66.45) ^{ab}
Control Group	Mean ± SD	17.7 ± 8.11	51.53 ± 8.46
	Median (Min–Max)	18.45 (8.08–32.35) ^{ab}	51.44 (39.67–64.77) ^b

SD: Standard deviation, Min: Minimum, Max: Maximum, ^{a-b}: There is no difference between median of percentages with the same letter, HAG: Hyaluronic acid-based gel, LCG: Lidocaine hydrochloride and cetylpyridinium chloride-based gel, CG: Choline salicylate-based gel, LG: Lidocaine hydrochloride-based gel, HG: Herbal-based gel.

Besides its cytotoxic properties, the LCG group showed the lowest scratch-healing percentage at 24 (3.5%) and 48 hours (24.8%). No study regarding the effect of this teething gel on scratch healing was found in the available literature, so the results were associated with the studies on the main active ingredients. Several studies on the effect of lidocaine hydrochloride on scratch healing found that groups that were treated with lidocaine had lower collagen production and scratch rupture strength and impaired scratch healing.^{35,36} In another study, it was emphasized that cetylpyridinium chloride has negative properties, such as variable pH level and strong cytotoxic effects which may limit scratch healing.³⁷ Additionally, studies on the effect of alcohol on scratch healing have found that it has a negative impact on the inflammatory and proliferation phases of scratch healing and inhibits endothelial function.^{38,39} The results of previous studies evaluating the active ingredients of LCG agree with the present results in terms of cytotoxicity and scratch healing. However, comprehensive studies involving all components are needed to obtain more precise results.

Choline salicylate, which is an active ingredient in the carboxylic acid derivatives group of NSAIDs, is preferred in teething gels because of its analgesic and anti-inflammatory properties.⁹ Cytotoxicity studies of choline salicylate in the literature focused on the use of choline salicylate in eye drops. Eye drops containing choline salicylate applied to the rabbit corneal cell line in the studies, and no statistically significant cytotoxic effect was found during five or ten minutes.^{40,41} In the present study, cytotoxicity of CG was found lower compared to most of the other gels but, especially scratch-healing was statistically lowest than control group after 48 hours. To date, no studies have been reported examining the impact of choline salicylate on scratch assay-based wound healing. In a case report, multiple peptic ulcer areas were detected in the stomach and duodenum of a patient who used a gel containing choline salicylate regularly, and healing was observed in the ulceration areas when the patient was called for control three months after the use of the gel was discontinued.⁴² Considering the previous studies also reporting its adverse effects, it is hoped that the present study will raise awareness about unconscious use of choline salicylate, especially in children.

Hyaluronic acid, which is a glycosaminoglycan, is found naturally in several body tissues. It has anti-inflammatory and anti-edema properties so, hyaluronic acid based teething gels have been frequently preferred in the field of dentistry in recent years. In clinical studies on hyaluronic acid, it has been reported that it reduces gingival bleeding, decreases periodontal pocket depth, causes more bone formation when applied to tooth extraction sockets, and contributes to healing in recurrent aphthous ulcers.^{9-11,43} In the study, a high-molecular-weight hyaluronic acid-based gel was evaluated and the LD50 values was found similar with LG, the results of scratch assay healing were similar with control group at 24 and 48 hours. The difference of this in vitro study between previous clinical studies can be attributed to polycarbophil

in HAG, a protein that attaches to wet mucosa and provides direct mechanical protection on the wound.⁴⁴

Among the gels in the present study, the least cytotoxic group was HG group, which provided the LD50 value at 1:2 dilution. The scratch-healing percentage of the gel was similar to control group at 24 and 48 hours. As no studies evaluating the hydrogel (HG) were identified in the available literature, the results were interpreted in the context of the reported positive healing effects of German chamomile and pot marigold extracts, which constitute the main components of the gel.⁴⁵⁻⁴⁷ However, further studies evaluating the effects of the by-products in the gel are required to provide more precise results.

The present study has several limitations. One of them is that the chemical formulations and doses of the products used in the study are not known exactly. Therefore, results are often associated only with known contents. The other limitation was the tests have been done on healthy cells, but future studies also need to evaluate their effects on inflamed cells. Also, the effects of the gels in the oral environment cannot be examined, so the tissue response cannot be observed. Since there is no information in the literature about the absorption times or swallowing amounts of these gels in the mouth, it is recommended to diversify the application times in future studies.

Conclusions

In the present study, the cytotoxicity of teething gels varies according to ingredients and dilutions, and it was found that none of the teething gels were not statistically better than the control group in regarding of wound healing. Considering the results, the necessity of clinical application of teething gel is controversial. The teething process is a physiological process. It is recommended to manage this process using more conservative non-pharmacological methods, such as cold application or hug therapy before treatment with various pharmacological products. Despite the limitations, the current study will make suggestions regarding the possible cytotoxic effects that may occur because of the unintentional use of these products. The results of the study can be a starting point for future studies on this topic.

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Conflicts of Interest Statement

The authors declare no conflict of interest.

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