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Genotoxic and Cytotoxic Effects Induced by Orthodontic Appliances on the Buccal Mucosal Cells: A Systematic Review

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ABSTRACT

Background: *Orthodontic appliances are widely used for the correction of malocclusion and improvement of oral function and aesthetics. These appliances are fabricated from various metallic and polymeric materials that remain in prolonged contact with oral tissues, raising concerns regarding potential genotoxic and cytotoxic effects on oral epithelial cells due to ion release, corrosion, and material degradation in the oral environment.* ***Objective****: To systematically evaluate the available in vivo human evidence on the genotoxic and cytotoxic effects induced by orthodontic appliances on buccal mucosal cells.* ***Methods****: A systematic literature search was conducted using PubMed, Scopus, Google Scholar, and ProQuest databases following PRISMA guidelines. Clinical in vivo studies assessing genotoxicity and/or cytotoxicity of fixed or removable orthodontic appliances using micronucleus testing, Comet assay, or cell viability-related methods were included. Data extraction and quality assessment were performed independently by two reviewers using Joanna Briggs Institute criteria, and findings were synthesized narratively due to methodological heterogeneity.* ***Results****: Five clinical studies involving 185 participants were included. Two studies reported increased DNA damage and reduced cell viability following prolonged exposure to fixed orthodontic appliances. Other studies demonstrated no significant increase in micronuclei frequency in buccal mucosal cells, while one study reported localized genotoxic effects in palatal cells associated with removable acrylic appliances. Overall findings were inconsistent and influenced by appliance type, material composition, exposure duration, and tissue site assessed.* ***Conclusion****: Orthodontic appliances may induce mild and inconsistent genotoxic or cytotoxic effects on oral epithelial cells, which appear to be transient in most cases. Further well-designed longitudinal studies with standardized biomonitoring protocols are required to clarify clinical relevance and support the development of highly biocompatible orthodontic materials.*

Keywords
Orthodontic Appliances; Genotoxicity; Cytotoxicity; Buccal Mucosal Cells; Micronucleus Test; Comet Assay

INTRODUCTION

Orthodontic treatment is widely used to correct malocclusion and improve oral function and facial aesthetics, and its demand continues to grow across age groups in both clinical and educational settings (1). Contemporary fixed and removable systems incorporate multiple metallic and polymeric components—brackets, tubes, bands, archwires, ligatures, and bonding composites—most commonly manufactured from stainless steel and nickel–titanium alloys, while removable appliances frequently rely on acrylic resins (2,3). Although these materials are generally considered suitable for intraoral use, their prolonged contact with oral tissues has raised concern regarding local biological effects, particularly when corrosion, wear, and degradation occur during routine mastication, oral hygiene practices, and orthodontic activation (3,5).

The oral cavity presents a chemically dynamic environment in which fluctuations in pH, temperature, salivary composition, and microbial activity can influence the stability of orthodontic biomaterials (3,5). Under such conditions, metallic appliances may release ions such as nickel and chromium, and resin-based components may leach residual monomers or additives, potentially interacting with epithelial cells and inducing cellular stress (3,5). From a toxicological standpoint, genotoxicity refers to injury to genetic material (e.g., DNA strand breaks or chromosomal alterations) that may manifest as increased DNA migration or micronuclei formation, whereas cytotoxicity reflects compromised cellular integrity and function through mechanisms such as oxidative stress, apoptosis, necrosis, and reduced viability (4,6). Accordingly, human biomonitoring studies have employed validated assays—including the Comet assay for DNA strand breaks, the micronucleus test for chromosomal damage, and cell viability-related approaches for cytotoxic outcomes—to evaluate mucosal responses during orthodontic therapy (6,9–11).

Buccal epithelial cells are frequently selected for in vivo monitoring because sampling is non-invasive, repeatable, and the tissue is directly exposed to appliance-related contact and salivary constituents (9,10). Nevertheless, the published clinical evidence remains inconsistent. Several longitudinal or prospective investigations have reported increases in DNA damage and/or micronuclei frequencies following appliance insertion, with some attributing effects to ion release and oxidative pathways (6,9,11,25). In contrast, other studies have found no significant increase in

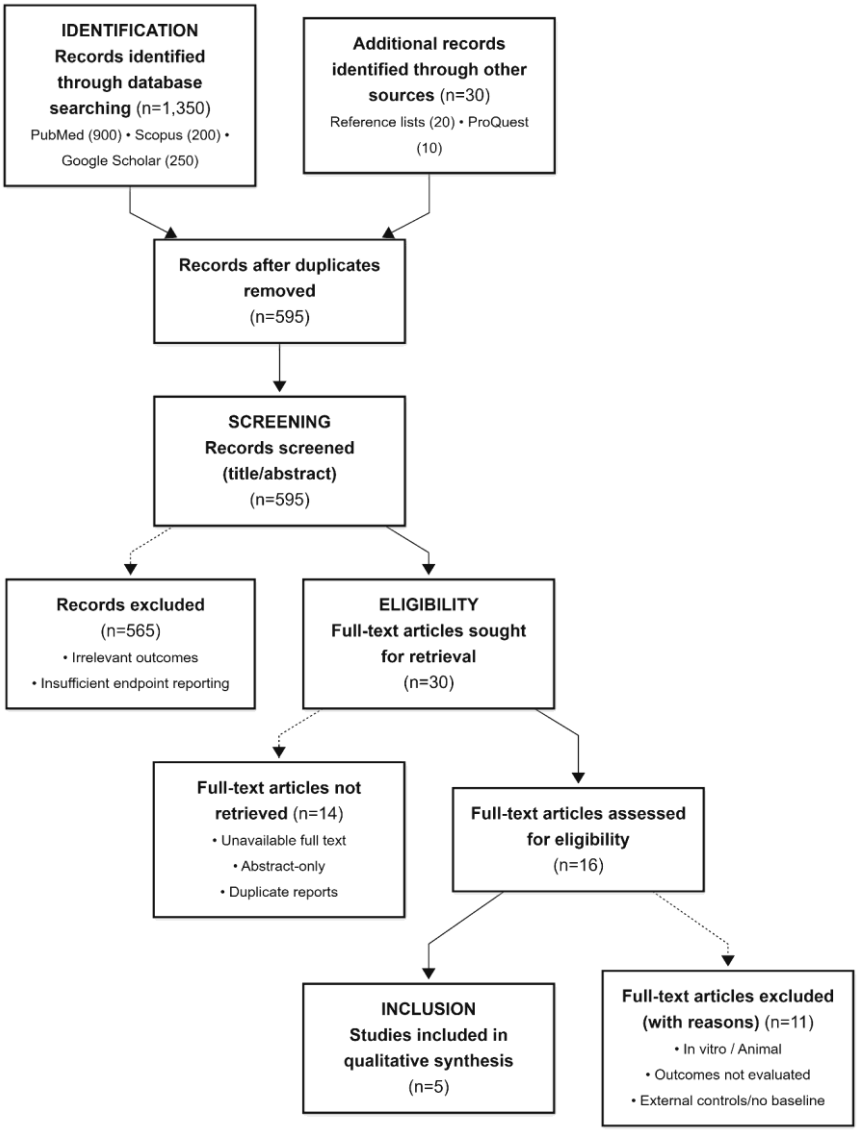
micronuclei or have suggested that any observed alterations are transient and compatible with rapid epithelial turnover and repair capacity (8,12,14). Additional complexity arises from heterogeneity in appliance type (fixed versus removable), material composition (stainless steel, nickel–titanium, acrylic resin), exposure duration, and outcome selection, which collectively hinder clear clinical interpretation (2,7,20,34). Given the widespread use of orthodontic appliances and the mixed direction of findings across human studies, a systematic synthesis that focuses specifically on in vivo buccal (and where relevant, palatal) epithelial outcomes is warranted to clarify the extent, direction, and consistency of reported genotoxic and cytotoxic effects.

Therefore, the objective of this systematic review was to assess the genotoxic and cytotoxic effects induced by orthodontic appliances on buccal mucosal cells, using evidence from clinical human studies that evaluated outcomes through Comet assay, micronucleus testing, and/or cell viability-related methods (9–14).

MATERIALS AND METHODS

Data Sources and Search Strategy

A comprehensive literature search was conducted across PubMed, Scopus, and Google Scholar to identify relevant published studies, while ProQuest was used to retrieve grey literature. The search strategy combined Medical Subject Headings (MeSH) and free-text keywords related to orthodontic treatment and cellular toxicity. The primary search terms included “genotoxic effect,” “cytotoxic effect,” “orthodontic treatment,” “Comet assay,” “micronucleus test,” “cell viability test,” “DNA damage,” “orthodontic brackets,” “orthodontic tubes,” and “archwires.” Boolean operators (“AND” “OR”) were applied to refine the search combinations. No restrictions were imposed with respect to language, age, sex, ethnicity, or geographical location. In addition to electronic database searching, manual screening of reference lists from eligible studies and relevant review articles was performed to ensure completeness. The literature search and screening process was conducted independently by two reviewers to minimize selection bias. Any disagreements were resolved through discussion and consensus. The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the study selection process is illustrated using a PRISMA flow diagram (Figure 1).



Study Selection

The study selection process involved a two-stage screening approach. Initially, titles and abstracts retrieved from the database search were screened to exclude clearly irrelevant studies. Full-text articles of potentially eligible studies were then assessed in detail against predefined inclusion and exclusion criteria. Only studies meeting all inclusion criteria were retained for qualitative synthesis and quality appraisal.

Inclusion Criteria

Studies were included if they met the following criteria: Involved human participants undergoing orthodontic treatment with fixed or removable appliances. Evaluated genotoxic and/or cytotoxic effects of orthodontic appliances on buccal or palatal mucosal epithelial cells. Employed in vivo biomonitoring assays, including the micronucleus test, Comet assay, and/or cell viability-related methods. Included baseline (pre-treatment) evaluation with subsequent post-treatment assessment in the same participants.

Exclusion Criteria

Studies were excluded if they: Were conducted in vitro or involved animal models, Did not evaluate genotoxic or cytotoxic outcomes, Lacked baseline assessment prior to orthodontic appliance placement, Included external control groups without longitudinal intra-individual comparison (baseline versus post-treatment).

Data Extraction

Data extraction was independently performed by the two reviewers using a standardized extraction form. Information retrieved from each included study comprised: author(s), year of publication, study design, sample size, type of orthodontic appliance (fixed or removable), material composition, duration of exposure, genotoxic and/or cytotoxic assays employed, timing of baseline and follow-up assessments, and principal findings. Any discrepancies in extracted data were resolved by consensus.

Quality Assessment

The methodological quality of the included studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist for observational and clinical studies. Each study was evaluated based on participant selection, exposure measurement, identification and handling of confounding factors, outcome validity and reliability, completeness of follow-up, and appropriateness of statistical analysis. Studies were categorized as low quality (score <4), moderate quality (score 4.0–5.9), good quality (score 6.0–7.4), or high quality (score 7.5–8.0). Quality appraisal was conducted independently by both reviewers, with discrepancies resolved through discussion.

Data Synthesis

Given the heterogeneity in study designs, orthodontic appliance types, materials, exposure durations, and outcome measures, quantitative meta-analysis was not considered appropriate. Therefore, a qualitative narrative synthesis was performed. The findings were summarized and compared based on diagnostic assays used, type and material of orthodontic appliances, and direction of observed genotoxic or cytotoxic effects.

Study Selection

The electronic and manual literature search yielded a total of relevant records after removal of duplicates. Following title and abstract screening, full-text assessment was conducted for potentially eligible articles. Based on the predefined inclusion and exclusion criteria, five clinical in vivo studies were included in the final qualitative synthesis. Studies were excluded primarily due to in vitro design, use of animal models, lack of baseline assessment, or absence of genotoxic or cytotoxic outcome evaluation. The study selection process is summarized in the PRISMA flow diagram (Figure 1), and excluded studies with reasons are presented in Table 3.

Quality Assessment of Included Studies

Methodological quality assessment using the Joanna Briggs Institute (JBI) criteria revealed variability among the included studies (Table 1). Two studies were rated as high quality, demonstrating robust methodology, low risk of bias, clear exposure measurement, and appropriate statistical analysis (9,11). Two studies were categorized as good quality, primarily due to incomplete handling of confounding factors or follow-up limitations (12,14). One study was assessed as moderate quality, reflecting limited outcome measurement consistency and incomplete follow-up (13). No studies were classified as low quality.

RESULTS

The five included studies were published between 2008 and 2021 and collectively evaluated 185 participants undergoing orthodontic treatment (Table 2). All studies employed a prospective or longitudinal clinical design. Four studies evaluated patients treated with fixed orthodontic appliances, while one study focused on removable acrylic appliances. Stainless steel brackets and archwires were the most commonly assessed materials, with nickel–titanium archwires and acrylic resins also represented.

Buccal mucosal epithelial cells were assessed in all studies, while one study additionally evaluated palatal mucosal cells due to the nature of the removable appliance (13). Baseline assessments were performed prior to appliance placement in all included studies, followed by post-treatment evaluations at varying intervals ranging from 10 days to 20 months.

Table 1. Methodological Quality Assessment of Included Studies Using Joanna Briggs Institute (JBI) Criteria

Study	Clear Definition of	Clear Definition &	Identification of	Handling of	Validity & Reliabil	Consistent Outcome	Complete	Appropriate Statistica	Total Sco	Overall	Reference

	Participants	Measurement of Exposure	Confounders	Confounders	ity of Outcomes	Measurement	Follow-up	l Analysis	re (0–8)	Quality	
Kapadia et al. (2018)	1	1	1	1	1	1	1	1	8	High	(11)
Heravi et al. (2013)	1	1	0	0	1	1	1	1	6	Good	(12)
Cruz et al. (2021)	1	1	0	0	1	0	0	1	4	Moderate	(13)
Toy et al. (2014)	1	1	1	1	1	1	1	1	8	High	(14)
Westphalen et al. (2008)	1	1	1	0	1	1	0	1	6	Good	(9)

Table 2. Characteristics and Key Findings of Included Studies Evaluating Genotoxic and Cytotoxic Effects of Orthodontic Appliances

Author, Year	Study Design	Sample Size (n)	Appliance Type	Material Composition	Genotoxic Assay	Cytotoxic Assay	Assessment Time Points	Key Findings
Kapadia et al. (2018)	Longitudinal	80	Fixed	Stainless steel brackets and archwires	Comet assay	Cell viability test	Baseline; 5, 10, 15, and 20 months post-insertion	↑ DNA strand breaks; ↓ cell viability over time
Heravi et al. (2013)	Prospective clinical	25	Fixed	Stainless steel brackets; NiTi and stainless steel wires	Micronucleus test	Not assessed	Baseline; 9 months post-insertion	No significant change in micronuclei frequency
Cruz et al. (2021)	Prospective clinical	30	Removable	Acrylic resin	Micronucleus test	Not assessed	Baseline; 15–21 days post-insertion	No change in buccal cells; ↑ micronuclei and degenerative changes in palatal cells
Toy et al. (2014)	Prospective clinical	30	Fixed	Stainless steel brackets, tubes, ligatures; NiTi archwires; light-cured composites	Micronucleus test	Not assessed	Baseline; 1, 3, and 6 months post-insertion	No increase in micronuclei; ↑ binucleated epithelial cells
Westphalen et al. (2008)	Prospective clinical	20	Fixed	Stainless steel brackets	Comet assay; Micronucleus test	Not assessed	Baseline; 10–30 days post-insertion	↑ micronuclei at 30 days; no significant comet assay changes

Table 3. Excluded Studies and Reasons for Exclusion

No.	Study (Year)	Reason for Exclusion	Reference
1	Karandish et al. (2025)	In vitro study	(15)
2	Ahuja et al. (2024)	In vitro study	(16)
3	Omidkhoda et al. (2022)	Did not evaluate genotoxic or cytotoxic outcomes	(17)
4	Shiva et al. (2023)	Did not evaluate genotoxic or cytotoxic outcomes	(18)
5	Hafez et al. (2011)	Included external control group without intra-individual baseline comparison	(6)
6	Sodor et al. (2015)	In vitro study	(19)
7	Martín-Cameán et al. (2015)	In vitro study	(20)
8	Santos et al. (2010)	Animal study	(21)
9	Retamoso et al. (2012)	Animal study	(22)
10	Duraisamy et al. (2024)	Animal study	(23)
11	Grimsdottir et al. (1992)	Animal study	(24)

Genotoxic Effects of Orthodontic Appliances

Genotoxic outcomes were evaluated using the Comet assay and/or the micronucleus test. Two studies employing the Comet assay reported evidence of increased DNA damage following orthodontic appliance insertion (9,11). Kapadia et al. observed a significant increase in DNA strand breakage over extended follow-up periods up to 20 months, indicating sustained genotoxic stress (11). In contrast, Westphalen et al. did not detect significant Comet assay alterations but reported a significant increase in micronuclei frequency after 30 days of exposure, suggesting chromosomal damage rather than direct strand breaks (9).

Three studies utilized the micronucleus test exclusively. Two studies involving fixed appliances found no significant increase in micronuclei frequency in buccal epithelial cells after treatment (12,14). However, Toy et al. reported an increase in binucleated cells, indicating altered cellular division without overt chromosomal damage (14). In the study involving removable acrylic appliances, Cruz et al. reported no increase in micronuclei in buccal cells but demonstrated a significant rise in micronuclei frequency and degenerative nuclear changes in palatal epithelial cells, highlighting site-specific genotoxic responses (13).

Cytotoxic Effects of Orthodontic Appliances

Cytotoxicity was directly assessed in one included study using a cell viability test. Kapadia et al. demonstrated a reduction in cell viability over time following placement of fixed orthodontic appliances, indicating cytotoxic effects in buccal mucosal cells alongside genotoxic changes (11). Other studies did not employ direct cytotoxicity assays but reported surrogate markers such as increased binucleation or nuclear degenerative changes, which may reflect subclinical cytotoxic stress (13,14).

Overall, the findings indicate heterogeneous genotoxic and cytotoxic responses associated with orthodontic appliance use. Evidence of increased DNA damage and reduced cell viability was observed in some longitudinal studies, particularly with prolonged exposure to fixed appliances (9,11). Conversely, several studies reported no significant increase in micronuclei frequency, suggesting either transient effects or effective cellular repair mechanisms (12,14). Localized genotoxic effects were more apparent in palatal mucosa exposed to removable acrylic appliances, emphasizing the influence of appliance type and tissue contact (13).

DISCUSSION

This systematic review synthesized the available in vivo human evidence on the genotoxic and cytotoxic effects of orthodontic appliances on buccal mucosal cells using validated biomonitoring assays. The findings demonstrate heterogeneous biological responses, with some studies reporting measurable DNA damage or reduced cell viability, while others observed no significant or only transient cellular alterations. These discrepancies appear to be influenced by appliance type, material composition, exposure duration, tissue site assessed, and methodological differences across studies.

Studies employing the Comet assay provided evidence of increased DNA strand breaks following orthodontic treatment, particularly with prolonged exposure to fixed appliances (9,11). Kapadia et al. reported sustained DNA damage accompanied by reduced cell viability over follow-up extending to 20 months, suggesting cumulative biological stress associated with long-term appliance wear (11). In contrast, Westphalen et al. observed an increase in micronuclei frequency without corresponding Comet assay changes, indicating that chromosomal alterations may occur independently of detectable strand breaks and underscoring the complementary nature of these assays (9). Such findings support the use of multiple biomarkers when evaluating genotoxicity in clinical settings.

Conversely, several studies using the micronucleus test alone did not demonstrate a significant increase in micronuclei frequency in buccal epithelial cells after orthodontic treatment (12,14). These observations are consistent with reports suggesting that oral mucosal epithelium possesses high regenerative and DNA repair capacity, which may counterbalance transient genotoxic insults (10,31). The increase in binucleated cells reported by Toy et al. may reflect altered cell division dynamics rather than overt chromosomal damage, emphasizing the need for cautious interpretation of isolated cytological findings (14).

The study by Cruz et al. provided important insight into site-specific effects, demonstrating increased micronuclei frequency and degenerative nuclear changes in palatal cells, while buccal cells remained unaffected (32). This localized response is biologically plausible, given the prolonged and direct contact of acrylic removable appliances with palatal mucosa. Similar observations have been reported in other investigations evaluating acrylic materials, suggesting that tissue exposure patterns may be as relevant as material composition in determining cytogenetic outcomes (28).

Material characteristics also appear to modulate biological effects. Nickel-containing alloys, particularly nickel–titanium wires, have been implicated in ion release and oxidative stress, which may contribute to DNA damage under certain conditions (25,26). However, the majority of included studies suggest that stainless steel, nickel–titanium, and acrylic materials exert limited or reversible effects on oral epithelial cells when used clinically (12,14,31). This aligns with evidence indicating that corrosion-related ion release is generally low and often remains within biocompatible thresholds

Despite these insights, the evidence base remains constrained by small sample sizes, variability in follow-up duration, inconsistent outcome measures, and limited control for confounding factors. Additionally, only one included study directly assessed cytotoxicity using a cell viability assay, highlighting a gap in comprehensive evaluation of cellular function alongside genotoxic markers (11). Future studies would benefit from standardized biomonitoring protocols, longer follow-up periods, inclusion of oxidative stress biomarkers, and stratification by appliance material and exposure duration.

CONCLUSION

This systematic review indicates that orthodontic appliances may induce genotoxic and cytotoxic changes in oral epithelial cells in certain clinical contexts, as evidenced by increased DNA damage, micronuclei formation, or reduced cell viability in some studies. However, the overall evidence suggests that these effects are inconsistent, often mild, and frequently transient, with several studies reporting no significant cytogenetic alterations following treatment. The regenerative capacity of oral mucosa and variability in appliance materials and exposure patterns likely contribute to these divergent findings. While current evidence does not conclusively demonstrate persistent or clinically significant toxicity associated with orthodontic appliance use, the findings underscore the importance of ongoing biomonitoring, particularly in long-term treatments and in appliances

with prolonged tissue contact. Further well-designed longitudinal clinical studies are required to clarify the biological relevance of observed cellular changes and to support the development and optimization of highly biocompatible orthodontic materials.

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