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Evaluation of the Effect of Chitosan and Titanium Dioxide Nanoparticles Mixed with Orthodontic Primer on Shear Bond Strength: A Systematic Review and Meta-analysis

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ABSTRACT

Background and aim: Orthodontic adhesives, commonly used to bond brackets, can significantly enhance bacterial biofilm. Nanoparticles have strong antimicrobial properties without compromising bond strength. Therefore, the aim of the present study was to evaluate the effect of chitosan and TiO₂ NPs mixed with orthodontic primer on shear bond strength.

Material and methods: For this systematic review and meta-analysis study, international databases such as MEDLINE (PubMed and Ovid), Web of Science, and Scopus were searched until October 2024 using keywords relevant to the study objectives. STATA/MP. v17 software was used to analyze data.

Results: The present study included twelve in-vitro studies with a total sample size of 684 human premolars. The mean difference in SBS score between the 1% and 5% chitosan NPs group and control group was -1.11 MPa (MD, -1.11 MPa; 95% CI, -2.27, 0.04; p=0.16) and 5.08 MPa (MD, -5.08 MPa; 95% CI, -7.80, -2.35; p=0.09), respectively. there were no statistically significant differences after comparing the mean SBS differences between the 1% TiO₂ NPs group and control group (MD, -0.43 MPa; 95% CI, -0.99, 0.12; p=0.13).

Conclusions: According to the results of the present meta-analysis, 1% and 5% chitosan NPs and 1% TiO₂ have potential as promising adjuncts in dental adhesive formulations, improving antimicrobial activity without compromising adhesive properties.

1. Introduction

White spot lesions (WSLs) are sites of enamel demineralization that develop along the contour of the bracket base and are caused by treatment with fixed orthodontic appliances.^[1] Although this varies depending on the detection criteria and the individual risk of caries, the prevalence is usually 25 to 30 percent. After 12 months of orthodontic treatment, the rate is high and does not differ by gender or group.^[2] Various materials and treatments are used to reduce bacterial colonization and improve remineralization. However, their use is limited due to side effects.^[3] Numerous scientists have investigated the use of fluoride in adhesives to promote remineralization.^[4] Unfortunately, the effects of these additives can only last a few weeks, increasing the likelihood of adhesive failure.^[5] Studies investigated the addition of metal nanoparticles (NPs) to adhesives to optimize nanotechnological properties. However, these changes can weaken the shear bond strength,^[6] and adding

some metal NPs to the orthodontic resin can lead to undesirable changes in tooth enamel color.^[7] Due to reduced shear bond strength (SBS) during orthodontic treatment, the likelihood of bracket detachment can increase, increasing treatment time and patient dissatisfaction.^[8] Furthermore, cytotoxicity increases when using metal NPs.^[9] Chitosan, a naturally occurring biopolymer, is produced by deacetylation of chitin.^[10] Chitosan and its derivatives have attracted the interest of researchers due to their ability to inhibit fungi, Streptococcus Mutans, and Streptococcus sanguinis.^[11, 12] This polysaccharide-based polymer is non-toxic, biodegradable, and biocompatible, which can overcome the limitations of metal NPs.^[13] Cement and orthodontic adhesives have been coated with various NPs, including silicon dioxide, hydroxyapatite, copper, silver, gold, zinc oxide, and titanium dioxide (TiO₂).^[14] In contrast to other NPs, TiO₂ NPs have been proposed to

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have superior optical properties, including high reflectance index, chemical stability, and the absence of color changes in the resin composites surrounding the brackets. In addition to improving mechanical properties such as flexural strength, microhardness, and elastic modulus, adding TiO₂ NPs to dental composites resulted in SBS values equal to or even higher than those of composites without NPs.^[15] In addition, several studies have shown that resins containing TiO₂ NPs have strong antimicrobial properties without compromising bond strength and may be a good way to stop WSLs and enamel demineralization.^[16-18] The present study evaluated the effect of chitosan and TiO₂ NPs mixed with an orthodontic primer on shear bond strength.

2. Material and methods

Search strategy and Information sources

To assess how combining TiO₂ NPs and chitosan NPs with orthodontic primer affects the SBS, the international databases Cochrane, Embase, and MEDLINE (PubMed and Ovid) were searched for relevant keywords until October 2024 (Table 1). Google Scholar was used with Web of Science, EBSCO, ISI, Elsevier, the Cochrane Central Register of Controlled Trials, and the Scopus Wiley Online Library. The present study is based on the 27-point checklist for PRISMA 2020.^[19]

Table 1. The search strategy used for each database.

| NO. | Search Terms |
|--|--|
| The search strategy used in MEDLINE (via PubMed) | |
| 1 | (("Orthodontic"[Mesh] OR "Orthodontic treatment"[Mesh]) OR ("Orthodontic Adhesive"[Mesh] OR ("Orthodontic Cement"[Mesh] OR "Orthodontic Bracket"[Mesh])) |
| 2 | ("Nanoparticle"[Mesh] AND "Titanium dioxide"[Mesh]) AND ("chitosan "[Mesh]). |
| 3 | ("Shear Bond Strength"[Mesh]). |
| The search strategy used in Cochrane | |
| 1 | " Orthodontic treatment " OR " Orthodontic Bracket " OR " Orthodontic Cement" OR " Orthodontic Adhesive" |
| 2 | " Nanoparticle" AND " Titanium dioxide " AND " chitosan ". |
| The search strategy used by Embase | |
| 1 | (Orthodontic treatment) OR (Orthodontic Adhesive) OR (Orthodontic Bracket) OR (Orthodontic Cement): ab, ti, kw. |
| 2 | Nanoparticle AND Titanium dioxide AND chitosan: ab, ti, kw. |
| 3 | Shear Bond Strength: ab, ti, kw |
| 4 | chapter' OR 'conference abstract' OR 'conference paper' OR 'conference review' OR 'editorial' OR 'erratum' OR 'letter' OR 'note' OR 'preprint' OR 'short survey'/it (Filter) |

Selection criteria

English-language publications met the inclusion requirements for this study. The answers to the questions in the current study were based on the PICO strategy; Population (P): orthodontic adhesives; Intervention (I): TiO₂ NPs and chitosan NPs (C): without additives; Outcome (O): shear bond strength. Review studies and books, qualitative studies, animal studies, studies without comprehensive and relevant data, and Data not reported shear bond strength were excluded from the study.

The process of selection and data collection

Two researchers used a previously developed standard data collection form to reduce reporting, data collection errors, and omissions in individual subject data collection. The original form prepared by the research team included information such as the author's name, year of publication, study design, sample size, sample type, experimental groups, and control group.

Heterogeneity and publication bias

The heterogeneity across studies was examined using the Chi-square (χ^2) test and quantified by the I^2 statistic. According to the I^2 value, heterogeneity was classified as low (less than 50%), between 50 and 74% means moderate heterogeneity, and above 75% is considered high heterogeneity.

Methodological quality

The following 10 methodological points were examined to assess the risk of bias in each in-vitro study (20, 21): (1) Reporting teeth storage medium after extraction. (2) Teeth randomization. (3) Screening for caries and cracks on teeth. (4) Previous enamel polishing. (5) Standardization of force applied on brackets during bonding. (6) Materials used according to manufacturer's instructions. (7) Reporting storage medium after bonding. (8) Time of teeth storage before testing SBS (before debonding). (9) Reporting chisel type. (10) Crosshead speed of test. After collecting these items, the number of unreported items was used to classify studies into high, medium, or low-risk bias studies. Investigations that did not report seven or more elements were classified as high risk, investigations that did not report 4-6 elements were classified as moderate risk, and investigations that did not report three or fewer elements were classified as low risk.

Data analysis

Mean SBS scores were calculated by examining mean differences with 95% confidence intervals. The results were reported based on a fixed-effects model with the Inverse variance method. The data were analyzed at a significance level 0.05 using Stata software (version 17).

3. Results

Description of studies

A total of 359 results were retrieved from databases. The number of articles was reduced to 296 after eliminating duplicates, records marked as

ineligible by automation tools, and other reasons. After reviewing abstracts and titles, 53 articles were selected from the citations. As a result of the final search, 12 studies were found suitable for inclusion in the current systematic review and meta-analysis.

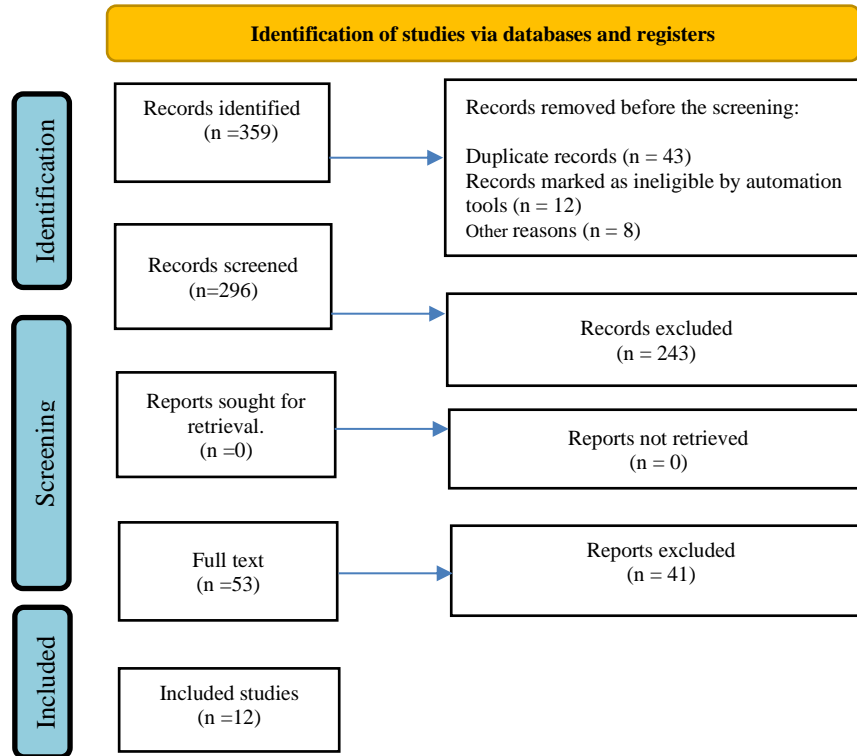


Fig. 1. PRISMA 2020 Checklist.

Study characteristics

All included studies used in-vitro designs. The sample size was variable among studies; the total sample size was 684 teeth. Human premolars were used in most of the studies, except for the study of Almeshal et al., 2024,^[23] which used human lower central incisors, and Mirhashemi et al., 2021,^[28] which did not specify the type of sample size. The concentration of TiO₂ NPs

and chitosan NPs was different between studies. A summary of study characteristics is provided in Table 2.

Bias assessments

Table 3 demonstrates the evaluation of the methodological risk of bias. The individual risk of bias of all studies was classified as low risk of bias.

Table 2. Summary of characteristics of the included studies.

| Study. Years | Study Design | Sample Size | Sample Type | Experimental Groups | Control Group |
|---|--------------|-------------|---------------------------------|--|-------------------|
| Mahendra et al., 2022 ^[4] | In-vitro | 40 | Human premolars | 1% TiO ₂ NPs | Without additives |
| Behnaz et al., 2018 ^[17] | In-vitro | 120 | Human premolars | 1% TiO ₂ NPs | Without additives |
| EL-Awady et al., 2023 ^[18] | In-vitro | 80 | Human premolars | 1% TiO ₂ NPs | Without additives |
| Harsha et al., 2024 ^[22] | In-vitro | 20 | Human maxillary first premolars | 1% TiO ₂ NPs | Without additives |
| Almeshal et al., 2024 ^[23] | In-vitro | 24 | Human lower central incisors | 5% and 10% chitosan NPs | Without additives |
| Mohammed et al., 2023 ^[24] | In-vitro | 48 | Human upper premolar teeth | 1%, 5% and 10% chitosan NPs | Without additives |
| Duvvuri et al., 2023 ^[25] | In-vitro | 40 | Human premolars | 1%, 5.0%, and 10.0% TiO ₂ NPs | Without additives |
| Firouzmanesh et al., 2023 ^[26] | In-vitro | 50 | Human premolars | 1% TiO ₂ NPs | Without additives |

| | | | | | |
|---|----------|----|-----------------|---------------------------------|-------------------|
| Akel et al., 2022 ^[27] | In-vitro | 60 | Human premolars | 1% TiO ₂ NPs | Without additives |
| Mirhashemi et al., 2021 ^[28] | In-vitro | 40 | NR | 1%, 5%, and 10% chitosan NPs | Without additives |
| Farzanegan et al., 2021 ^[29] | In-vitro | 72 | Human premolars | 0.5% , 1% and 1.5% chitosan NPs | Without additives |
| Assery et al., 2019 ^[30] | In-vitro | 90 | Human premolars | 1% and 3% TiO ₂ NPs | Without additives |

NPs: nanoparticles; NR: not reported.

Table 3. Methodological risk of bias assessment.

| Study. Years | Teeth Storage Medium after Extraction | Teeth Randomization | Screening for Caries and Cracks on Teeth | Previous Enamel Polishing | Force Standardized Applied on Brackets during Bonding. | Using Materials According to the Manufacturer' s Instructions | Storage Medium after Bonding | Storage Time before Debonding | Chisel Type | Crosshead Speed | Score |
|---|---------------------------------------|---------------------|--|---------------------------|--|---|------------------------------|-------------------------------|-------------|-----------------|----------|
| Mahendra et al., 2022 ^[4] | + | + | + | + | + | + | + | + | + | + | Low risk |
| Behnaz et al., 2018 ^[17] | + | + | - | + | + | + | + | + | + | + | Low risk |
| EL-Awady et al., 2023 ^[18] | + | + | + | + | + | - | + | + | + | + | Low risk |
| Harsha et al., 2024 ^[22] | + | + | + | + | + | + | + | + | + | + | Low risk |
| Almeshal et al., 2024 ^[23] | + | + | + | + | + | + | + | + | + | + | Low risk |
| Mohammed et al., 2023 ^[24] | + | + | - | + | + | + | + | + | + | + | Low risk |
| Duvvuri et al., 2023 ^[25] | + | + | + | + | - | + | + | + | + | + | Low risk |
| Firouzmanesh et al., 2023 ^[26] | + | + | + | + | + | + | + | - | + | + | Low risk |
| Akel et al., 2022 ^[27] | + | + | + | + | + | + | + | + | + | + | Low risk |
| Mirhashemi et al., 2021 ^[28] | + | + | + | + | + | - | + | + | + | + | Low risk |
| Farzanegan et al., 2021 ^[29] | + | + | + | + | - | + | + | + | + | + | Low risk |
| Assery et al., 2019 ^[30] | + | + | + | + | - | - | + | + | + | + | Low risk |

Effect 1% chitosan NPs on SBS

The mean difference in SBS score between the 1% chitosan NPs group and the control group was -1.11 MPa (MD, -1.11 MPa; 95% CI, -2.27, 0.04; p=0.16). The heterogeneity between studies was low ($I^2 = 47.85\%$, $p = 0.15$) (Fig. 2). There were no statistically significant differences after comparing the mean SBS differences between the 1% chitosan group and the control group.

Effect 5% chitosan NPs on SBS

The mean difference in SBS score between the 5% chitosan NPs group and the control group was -5.08 MPa (MD, -5.08 MPa; 95% CI, -7.80, -2.35; p=0.09). The heterogeneity between studies was high ($I^2 = 95.36\%$, $p = 0.00$) (Fig. 3). There were no statistically significant differences after comparing the mean SBS differences between the 5% chitosan group and the control group.

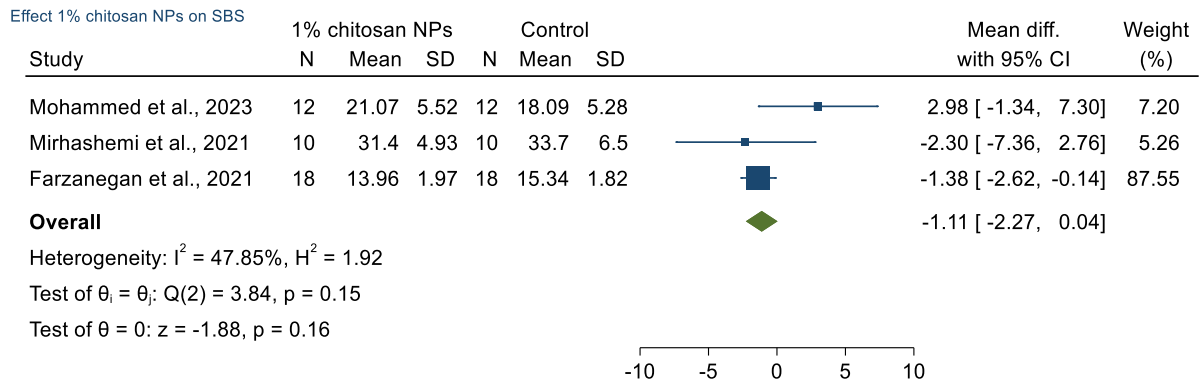
Effect 10% chitosan NPs on SBS

The mean difference in SBS score between the 10% chitosan NPs group and the control group was -7.94 MPa (MD, -7.94 MPa; 95% CI, -10.66, -5.22; p=0.04). The heterogeneity between studies was high ($I^2 = 93.45\%$, $p = 0.00$) (Fig. 4). There were statistically significant differences after comparing the mean SBS differences between the 10% chitosan group and the control group.

According to Figs 2, 3, and 4, the 1% chitosan NPs had the highest mean SBS value, followed by the 5% and 10% chitosan NPs.

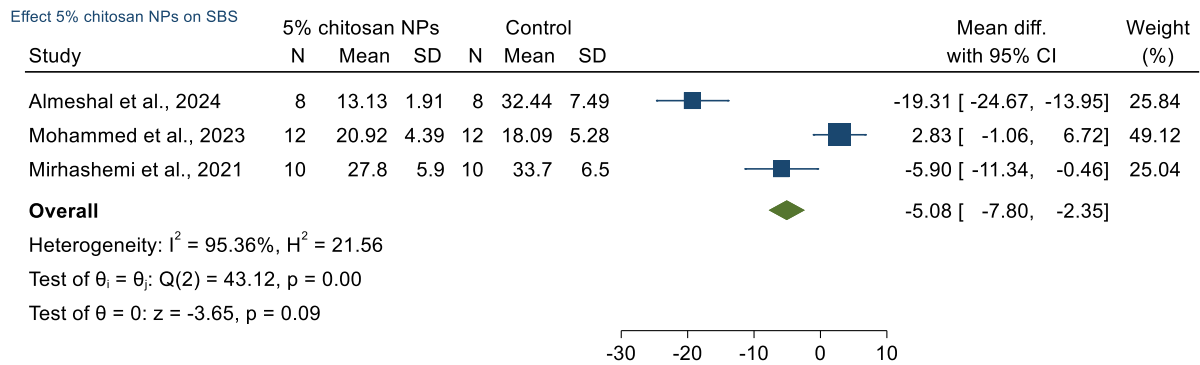
Effect of 1% TiO₂ NPs on SBS

The mean difference in SBS score between the 1% TiO₂ NPs group and the control group was -0.43 MPa (MD, -0.43 MPa; 95% CI, -0.99, 0.12; p=0.13). The heterogeneity between studies was moderate ($I^2 = 68.99\%$, $p = 0.00$) (Fig. 5). There were no statistically significant differences after comparing the mean SBS differences between the 1% TiO₂ NPs group and the control group.



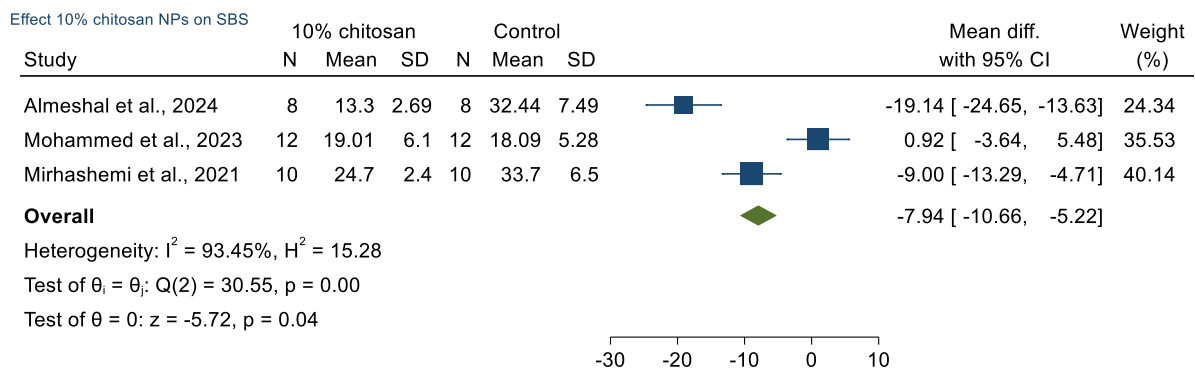
Fixed-effects inverse-variance model

Fig. 2. The forest plot showed an effect of 1% chitosan NPs on SBS.



Fixed-effects inverse-variance model

Fig. 3. The forest plot showed an effect of 5% chitosan NPs on SBS.



Fixed-effects inverse-variance model

Fig. 4. Forest plot showed an effect of 10% chitosan NPs on SBS.

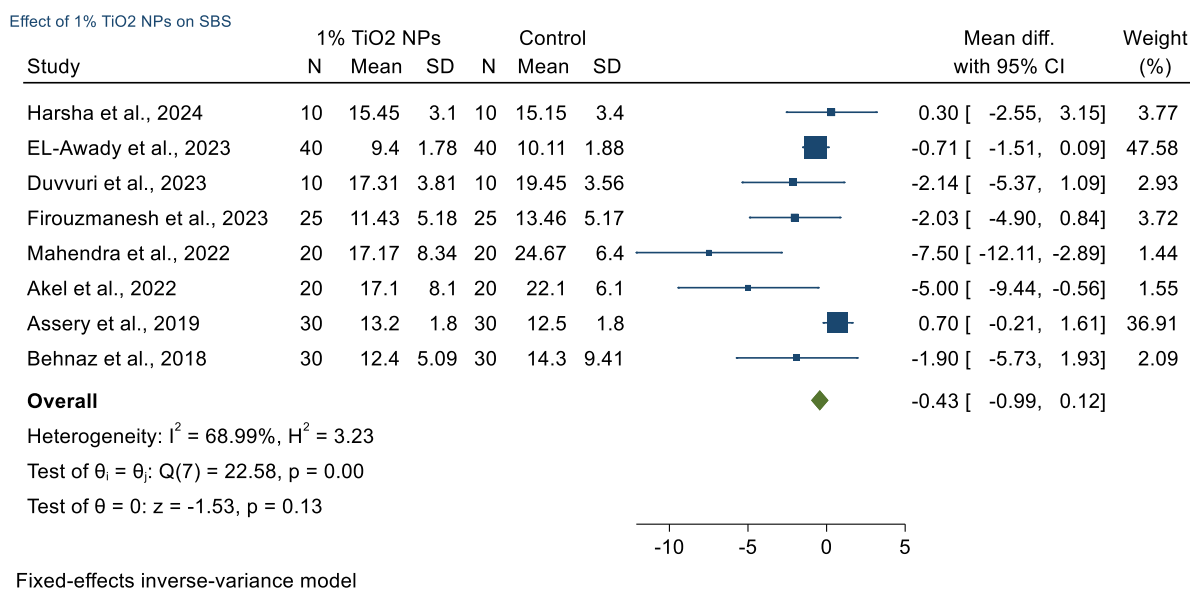


Fig. 5. Forest plot showed the effect of 1% TiO₂ NPs on SBS.

4. Discussion

White spot lesions (WSLs), a typical lesion in orthodontic treatment, weakens tooth enamel, persists for a long time, and is difficult to restore completely through natural remineralization.^[31] Numerous studies have shown that primers containing nanoparticles are effective in reducing the level of demineralization in the first six months after bracket bonding.^[32] Chitosan NPs have shown potential in significantly inhibiting the growth of *S. mutans*, a bacterium often associated with dental caries.^[33] The present study examines the SBS of an orthodontic primer incorporating chitosan NPs. The antibacterial activity, availability, chemical stability, and biocompatibility of chitosan nanoparticles led to their selection.^[34] According to the present meta-analysis, there were no statistically significant differences in the mean SBS values between the 1% and 5% chitosan NPs in the control group. However, adding 1% chitosan NPs increases the orthodontic SBS, while adding more than 1% NPs decreases the SBS. As a result, the SBS of 1% chitosan NPs containing a primer increased, showing that the NPs function as stress-absorbing materials that reinforce structures; 1% chitosan NPs help to reduce the interfacial tension concentration in the adhesion-resin complex. No change in mechanical properties was noticeable compared to the control group, even at concentrations of 5% chitosan NPs. A possible explanation for the result is that the small size of the nanomaterial allows for easier distribution within the low-viscosity primer. Research agrees that orthodontic adhesives enriched with TiO₂ nanoparticles exhibit increased antimicrobial activity when tested *in vitro*.^[35] The present study examines the SBS of an orthodontic primer incorporating TiO₂ NPs. According to the present meta-analysis, there were no statistically significant differences in the mean SBS values between the 1% TiO₂ NPs and the control group. It is still unclear how the addition of 1% TiO₂ NPs to orthodontic adhesives can reduce WSLs and caries around bonded orthodontic brackets; the currently available information is limited and, to our knowledge, there is no systematic review or meta-analysis linking the features of this modification and its outcomes. This highlights the need for programs to produce orthodontic adhesives with antimicrobial nanoparticles on a standardized commercial scale due to the WSLs.^[36] This is especially important when oral hygiene is poor, as it reduces tooth decay rates, maintains oral health, and has a low risk of

complications after treatment. Consistent with the results of the present study, Sodagar et al., 2017(15) reported that the SBS value of orthodontic composites containing 1% TiO₂ NPs was higher than those containing 3% and 5%.

Furthermore, Poosti et al., 2013 have shown no significant differences in SBS values between orthodontic composites with and without TiO₂ NP infiltration.^[37] Studies showed a decrease in SBS as the concentration of TiO₂ NPs increased.^[25, 29] present study reported that the addition of TiO₂ NPs decreased the SBS compared to the control groups. The present study had some limitations; different concentrations of TiO₂ were used in the studies, and due to high dispersion, only one percent of TiO₂ was included in the meta-analysis. The diameter and thickness of the test discs were not clearly described in all studies. High heterogeneity between studies was observed, so the results of the current study should be interpreted with caution. More studies with a higher sample size and similar methodology are needed to confirm the current evidence. SBS was implicated in some studies, as the compact nature of the adhesive may disrupt the adhesive matrix. This may also be due to methodological differences in the type of nanoparticles, concentration, size, and methods of adding nanoparticles.

5. Conclusion

According to meta-analysis, the combination of 1% and 5% chitosan NPs had no effect on the shear bond strength (SBS) of orthodontic adhesive. In other words, orthodontic primers containing different concentrations of chitosan NPs (1%, 5%) demonstrated appropriate SBS, with no interesting findings at 10% concentration. 1% TiO₂ NPs into orthodontic adhesive during bonding procedures does not adversely affect their shear bond strength. 1% and 5% chitosan NPs and 1% TiO₂ have potential as a promising adjunct in dental adhesive formulations, improving antimicrobial activity without compromising adhesive properties.

Conflict of Interest

The authors declared that there is no conflict of interest.

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