



## Review Article

# Effect of titanium dioxide nanoparticle reinforcement on flexural strength of denture base resin: A systematic review and meta-analysis

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## SUMMARY

The study was designed to assess the change in flexural strength of unmodified heat cure denture base polymer resin on reinforcement with titanium dioxide nanoparticles in different concentrations. In vitro, randomized control trials reporting flexural strength of titanium dioxide nanoparticle reinforced resin were selected. The review was formulated based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses- Protocol (PRISMA-P) guidelines. Quality assessment was performed according to Consolidated Standards Of Reporting Trials (CONSORT) guidelines and risk of bias Cochrane tool. Six articles in the category of 1%, 3%, 5% weight fractions of titanium dioxide nanoparticles were subjected to a meta-analysis. A meta-analysis was performed using random-effects at a 95% confidence interval. Within the limitations of the study, it can be assumed that there is no precise conformity on the ideal titanium dioxide nanoparticle concentration required to improve the flexural strength of the polymer. Stringent use of standard ISO guidelines may help in obtaining consistent results.

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## 1. Introduction

A healthy dentition plays a vital role in the welfare of an individual of all age groups. Regardless of notable development in different fields of dentistry, edentulism is of significant concern universally. A study stated edentulism to be a permanent debilitating disorder and an 'ultimate indicator of disease load' [1]. Another study detailed that though complete edentulism is on an all-time low since the last decade, it persists as one of the crucial oral conditions in the geriatric age group. Allied researches have shown that denture usage is on a high due to the rise in the elderly population, and a vast range of them still depend on removable dentures for restoring form and function [2,3].

Denture base resins have evolved a long way since its inception. The most common resin since the 1930s and still in use is polymethylmethacrylate (PMMA). This is attributed to its properties of durability because of adequate mechanical properties, dimensional stability, biocompatibility, cost-effectiveness, aesthetics, and ease of fabrication compared to metallic dentures. Despite the accept-

able features, it is easily susceptible to breakage during service because of factors such as dynamic masticatory load and handling practices among denture wearers [4].

A study analyzed various modifications in the form of chemical changes, additives/reinforcements (fibers, fillers, nanoparticles) [5], and different curing techniques to counteract the vulnerability of PMMA based dentures. Recently, Wang W et al. described the impact of incorporating nanoparticles into denture resin to improve its mechanical properties [6]. The literature reports various tried and tested nanoparticles [5–7]. Amid them, nanoscale titanium dioxide/titanium dioxide nanoparticles (TiO<sub>2</sub> NPs) have been of importance with the investigators because it possesses exceptional properties.

TiO<sub>2</sub> NPs remains one of the preferred alternatives because of their ease of availability, low toxicity, chemical stability, robust physical properties, antibacterial activity, and cost-effectiveness [8]. An array of biomedical applications has been reported, including photosensitizing agents in photodynamic malignancy treatment, in the drug distribution system, in vivo cell imaging techniques, as biosensors to analyze biological molecules, and gene therapy [9]. TiO<sub>2</sub> NPs have paved their way into dentistry based on its excellent biocompatibility property and are applied to a variety of resin and polymers to improve their characteristics. Dental products like resin-based adhesives, composite resins, denture polymers, stereolithographic printing of dentures, and maxillofacial silicones have been reinforced with TiO<sub>2</sub> NPs to study their

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resultant effect [6,10–13]. Several studies can be cited in the literature assessing the mechanical properties of TiO<sub>2</sub> NPs reinforced into PMMA in different fraction weight, to modify its mechanical and biological properties. Amongst them, flexural strength tests are relevant to the loading characteristics of a denture base in oral conditions and are regarded as a prime mode of clinical fracture [14,15].

Recently, researchers have provided consideration to several test conditions and their corresponding effects on the outcome. While in vitro laboratory-based mechanical tests do not replicate an intra-oral dynamic environment, they extend a precise atmosphere for planning and investigating the samples. This allows a comparison between the variables considered in the study. In-vitro studies use standardized methods for assessment of any mechanical parameter related to the material. The test conditions exercised hinder the evaluation of the outcome. Examples of such conditions include but not restricted to the temperature of the testing environment, standardization of equipment, the internal structure of the tested samples, and load and force employed. A clarification for the diverse results amongst in-vitro mechanical strength studies might relate to variation in testing standards, errors in interpretation, and comparison. The flexural load is a combination of stresses, occurring most commonly in the oral condition under pressure. Thus, it is substantial for defining the characteristic values of thermoplastic and thermosetting polymers. At present, there are no reviewed data on the flexural strength of TiO<sub>2</sub> NPs reinforced heat polymerization denture base resin, from which we can draw inferences. Because of the lack of standardization procedures, only independent assessment of the literature on in vitro studies published is possible.

The objective of this study is to review and analyze the literature related to heat cure denture base resins/polymethylmethacrylate (PMMA), which is reinforced with TiO<sub>2</sub> NPs of different concentrations/ weight fractions tested for flexural strength according to ADA/ISO standards. The null hypothesis is that the TiO<sub>2</sub> NPs reinforcement did not change the flexural strength of the resin in comparison to the unmodified heat cure resin (control group). The alternate hypothesis is that the TiO<sub>2</sub> NPs reinforcement changed the flexural strength of the resin in comparison to the unmodified heat cure resin (control group).

## 2. Materials and methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines were applied to perform the meta-analysis (Table A1 in Supplementary material) [16]. A non-registered protocol was prepared to precede the literature search, using the PICOS strategy as follows: Population (P): polymethylmethacrylate, denture base resin, heat cure acrylic resin, mechanical properties of acrylic resin; Intervention (I): titanium dioxide nanoparticles; Comparison (C): titanium dioxide nanoparticle in different weight fractions; Outcome (O): change in flexural strength; Study design (S): in vitro randomized control trials.

### 2.1. Eligibility criteria

The inclusion criteria were in vitro randomized control trials that investigated the flexural strength property as one of the parameters, TiO<sub>2</sub> NPs reinforcement in any concentration, and heat cured polymethylmethacrylate denture base resin. The other inclusion criteria were conformity with ADA specification number 12 and ISO 1567 or revised ISO 20795-1 regulations, with specimens conditioned under distilled water before testing, and a standardized universal testing machine employed for a 3-point bend test; stating the means and standard deviations for all the groups.

The authors excluded articles not related to the field of dentistry to eliminate the bias of testing and reporting methods. Articles testing flexure strength by other methods than 3-point bend tested were omitted. Studies performed on auto polymerizing, light cure resin, and microwave cure resin did not qualify for the review and analysis. Studies not reporting TiO<sub>2</sub> NPs and flexural strength were left out. Research papers not in English and review articles were excluded from the study.

### 2.2. Search strategy

The authors performed an extensive bibliographic search using PubMed, Web of Science (core collection), google scholar, and Scopus databases to recognize relevant full-text articles in English published until January 2019, with no limitations to the commencement year. Hand searching of reference sections belonging to the individual study did not yield additional articles. Based on the PICOS questionnaire, keywords were employed for search in all selected databases, split by the Boolean operator OR, later combined by the Boolean operator AND. A typical search performed in PubMed using PICOS strategy is as follows: (polymethyl methacrylate[MeSH Terms] OR (polymethyl[All Fields] AND methacrylate[All Fields]) OR polymethyl methacrylate[All Fields] OR polymethylmethacrylate[All Fields]) OR (polymethyl methacrylate[MeSH Terms] OR (polymethyl[All Fields] AND methacrylate[All Fields]) OR polymethyl methacrylate[All Fields] OR pmma[All Fields]) OR denture base resin[All Fields] OR acrylic resin[All Fields] AND mechanical properties[All Fields] OR flexural\* strength[All Fields] AND nanoparticles[All Fields].

A similar strategy was used to perform a sensitive document search in Scopus and Web of Science databases. Web of science did not yield any search results on advanced search with key terms.

### 2.3. Data management, screening, and selection

To begin with, the authors (MKB and RK) independently screened only titles and abstracts. After excluding duplicates and irrelevant articles, full-length articles were scrutinized. The mandate of all the authors was considered to include the article in the final review. Any conflict regarding inclusion and exclusion criteria was mutually resolved with final judgment from the third author (RN).

All the authors gauged the data extraction procedure. The data obtained from the articles categorized under inclusion criteria were tabulated using a systematized arrangement in electronic format (Office Excel- Home and student 2016 software, Microsoft Corporation, One Microsoft Way, Redmond, WA 98052-6399, USA). The authors categorized the information based on Author/year, type of study, standard specimen size, curing cycle, testing condition, crosshead speed of tester, TiO<sub>2</sub> NPs size, the method used for dispersing nanoparticles, concentration, number of samples used and results (mean and standard deviation) and conclusion.

The outcome of flexural strength analysis in a TiO<sub>2</sub> NPs reinforced heat cure denture base resin was prioritized. Any additional data related to result present in the articles were considered only for descriptive review and not for meta-analysis as it did not justify the study objective.

### 2.4. Assessment of risk of bias

Consolidated Standards of Reporting Trials (CONSORT) guidelines adapted from an article [17] was applied to assess the quality of the articles [Table A2 in Supplementary material]. After evaluating the individual article, the parameters were reported as yes or no [Table 1].

**Table 1**  
Methodological characteristics of in-vitro studies based on modified CONSORT criteria.

Author/year	Item grade														
	1	2a	2b	3	4	5	6	7	8	9	10	11	12	13	14
Nazirkar G et al. (2014)	Yes	Yes	Yes	No	Yes	No	No	No	No	No	Yes	Yes	Yes	No	No
Harini P et al. (2014)	Yes	Yes	Yes	No	Yes	No	No	No	No	No	Yes	Yes	Yes	Yes	No
Hamouda IM et al. (2014)	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	No	Yes	No	No
Ahmed MA et al. (2016)	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	No	No	Yes	No
Tandra E et al. (2018)	Yes	Yes	Yes	No	Yes	No	No	No	No	No	Yes	No	No	No	No
Karci M et al. (2018)	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No	No	Yes	No

(1) Structured summary of trial design, methods, results and conclusions, (2a) scientific background and explanation of rationale, (2b) specific objectives and/or hypothesis, (3) the intervention of each group, including how and when it was administered, with sufficient detail to enable replication, (4) completely defined, pre-specified primary and secondary measured of outcome, including how and when they were assessed, (5) how the sample size was determined, (6) method used to generate the random allocation sequence, (7) mechanism used to implement the random allocation sequence, (8) who generated the random allocation, (9) who was blinded after assignment to intervention, (10) statistical methods used to compare groups, (11) results for each group and estimated size of effect and its precision, (12) trial limitations, addressing sources of potential bias, imprecision, and, if relevant multiplicity of analysis, (13) sources of funding and other support, (14) where to full trial protocol can be accessed [11].

The authors adapted and modified the Cochrane risk of bias tool to achieve the specified objective of the study [18]. The risk of bias was evaluated based on the following criteria: an explanation of sample size calculation, sample allocation, and concealment, blinding of the operator, whether the analysis methods were at par with ISO/ ADA standards employed or not, and selective outcome reported. If the criteria described in the article was clear, it obtained a score of 0. If a specific approach was testified, but inadequately or vaguely, the score was established at 1, and if a specific setting was undisclosed, the score was set as 2. Articles which obtained count amid 0 and 3 were graded as low risk of bias, counts between 4 to 7 as moderate, and between 8 to 10 as high-risk [19]. The assessment was performed individually by two authors, and the third author resolved any uncertainty between them after a valid debate.

### 2.5. Data analysis

The meta-analysis was carried out using a random-effects model in Review Manager (RevMan; [Computer program] Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.) Meta-analyses were performed for flexural strength analysis only as per the objective of the study. 0.5% and 2% TiO<sub>2</sub> NPs group was not subjected to meta-analysis due to the lack of comparative outcome.

Heterogeneity was calculated by the Q test (for  $p < 0.1$ ). As variability among studies is inevitable, the Inconsistency  $I^2$  test was also employed.  $I^2$  values above 50% were considered indicative of substantial heterogeneity. Forest plots were created with a 95% confidence interval (Z test). A funnel plot was not presented as the number of studies included in the analyses is less than 10.

## 3. Results

### 3.1. Data selection

Fig. 1 represents the selection summary of the articles involved in the meta-analysis. The initial database searches resulted in 181 studies, out of which 3 were duplicates. 175 other studies that were unsuccessful in complying with the inclusion criteria were disregarded. The remaining 12 studies were examined using full texts, and another 6 articles were excluded, which did not conform with the inclusion norms. After applying the CONSORT guidelines, 6 studies were retained for both qualitative and quantitative analysis.

### 3.2. Risk of bias

Table 2 presents the risk of bias for the included studies. The articles involved in the meta-analysis showed a moderate risk of bias. The risks of bias generated were primarily attributed to the

sample size estimation, allocation concealment of specimens, and blinding of the machinist [Figs. A1 and A2 in Supplementary material]. None of the articles reported on whether or not blinding of the operator was performed during testing. All 6 studies failed to explain the concealment technique and allocation method used to distribute samples into different groups. Of 6 articles, 5 reported on sample size estimation.

### 3.3. Meta-analyses

Six studies met the requirements for quantitative analysis. Three meta-analyses were performed from the flexural strength data for respective fraction weights of TiO<sub>2</sub> NPs by generating forest plots.

It can be observed from the forest plot Fig. 2 that 1% TiO<sub>2</sub> NPs reinforcement did not have significant influence in improving the flexural strength of the conventional group (Mean Difference (MD) 2.22, 95% Confidence Interval (CI) -9.81 to 14.26; participants = 92; studies = 5; Inconsistency test ( $I^2$ ) = 90%). The studies involved showed high statistical heterogeneity.

Fig. 3 is a forest plot representing 3% TiO<sub>2</sub> NPs reinforcement group resin (MD 1.86, 95% CI -3.74 to 7.45; participants = 32; studies = 2;  $I^2$  = 59%) presented no significant improvement in the flexural strength over the control group. The studies included showed substantial statistical heterogeneity.

Fig. 4 represents 5% TiO<sub>2</sub> NPs reinforcement group (MD) 9.03, 95% CI -8.55–26.61; participants = 64; studies = 4;  $I^2$  = 81% favoured the experimental group. The included studies presented high heterogeneity.

The study involving 0.5% TiO<sub>2</sub> NPs reinforcement presented with values MD = 11.51, 95% CI 2.88–20.15, favored the experimental group. The study involving 2% TiO<sub>2</sub> NPs reinforcement presented with values MD = -28.69, 95% CI -63.10 to 5.72, favored the control group. Forest plots were not generated for the 0.5% and 2% categories due to the lack of a comparative outcome.

## 4. Discussion

The current systematic review was performed to assess the variations in the methodology used to perform a test and to analyze the effects of different test conditions on the results obtained. Based on our analysis, we state that the study question of whether the incorporation of TiO<sub>2</sub> NPs into denture base resin brought no significant changes in the flexural strength values when compared to the unmodified resin (control group) used in the study. The variations in the test standards, sample size, curing cycle, test conditions, crosshead speed of tester, TiO<sub>2</sub> NPs size, the concentration of TiO<sub>2</sub> NPs, and the dispersion technique can be observed in Table 3.

The forest plot (Fig. 2) generated for the 1% TiO<sub>2</sub> NPs reinforcement showed a positive effect on the resin based on the

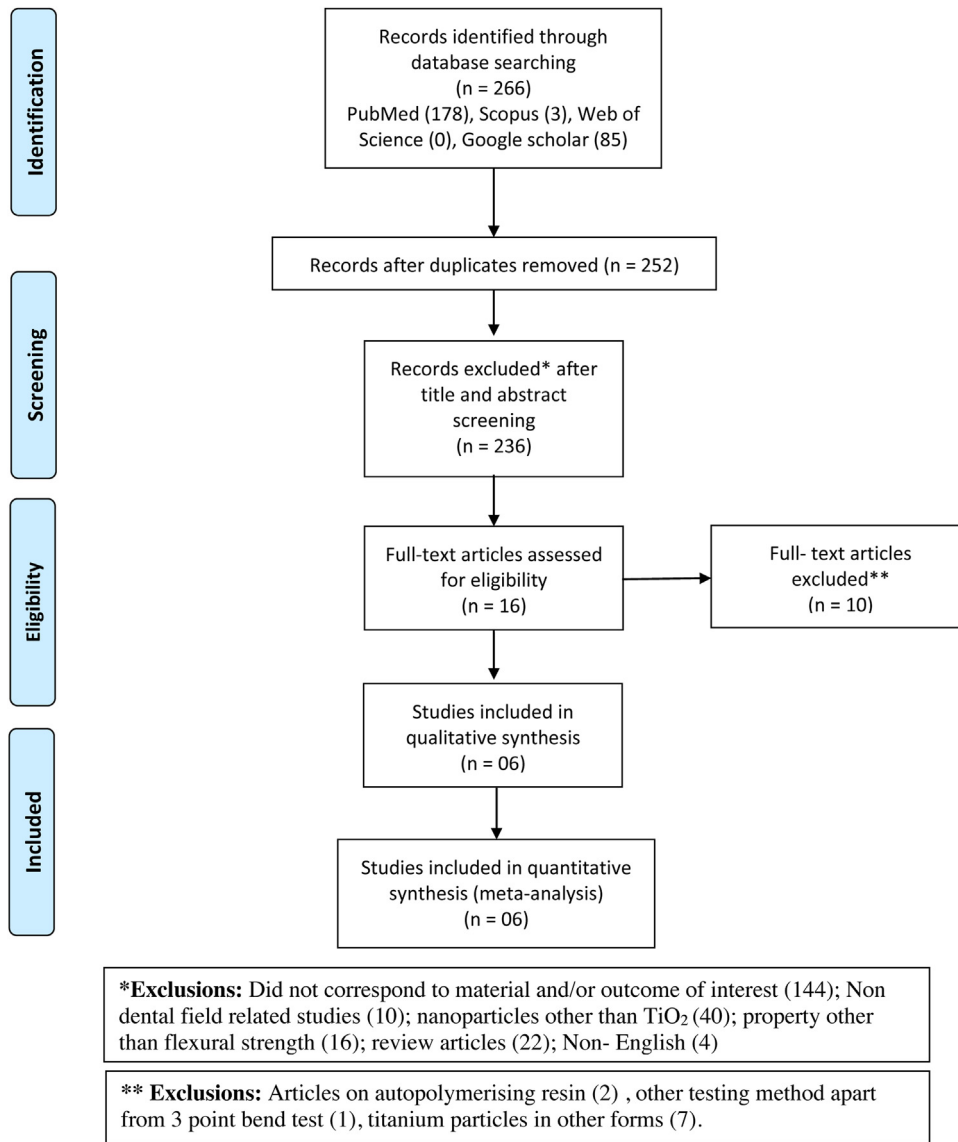


Fig. 1. PRISMA flow chart of study selection.

**Table 2**  
Risk of bias tool (adapted and modified from Cochrane risk of bias tool).

Author/year	Allocation concealment	Sample size	Blinding	Assessment methods	Selective outcome reporting	Risk of bias
Nazirkar G et al. (2014)	1	2	2	0	1	Moderate
Harini P et al. (2014)	1	2	2	1	1	Moderate
Hamouda IM et al. (2014)	1	2	2	1	0	Moderate
Ahmed MA et al. (2016)	1	2	2	1	0	Moderate
Tandra E et al. (2018)	1	2	2	1	1	Moderate
Karci M et al. (2018)	1	0	2	0	1	Moderate

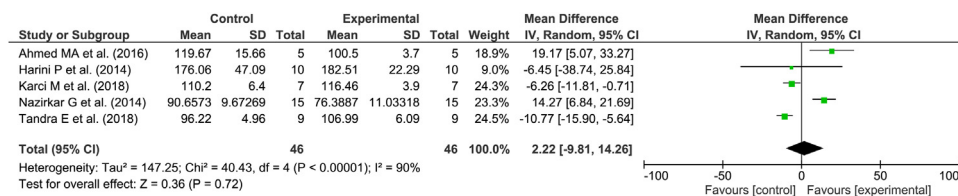


Fig. 2. Forest plot for flexural strength analysis of 1% TiO2 NPs reinforcement.

**Table 3**  
Summary of the observed data from the included studies.

Study	Nazirkar et al. (2014)		Harini et al. (2014)			Hamouda et al. (2014)	Ahmed et al. (2016)		Tandra et al. (2018)		Karci et al. (2018)		
Test Standard	ADA12		ISO 1567			ADA 12	ADA 12 and ISO 20795-1 (2008)		ADA 12		ISO 1567		
Type of resin	Heat cure acrylic resin, Dental products of India, Mumbai		Clear heat polymerizing acrylic resin (Brand: undisclosed)			Acrostone conventional heat-cured acrylic resin (Acrostone, WHN, England)	Heat-polymerized acrylic resin (Vertex-Dental by J.V. oldenbarneveltin 62 3705 HJ Zeist, Netherlands)		Heat cure acrylic resin (QC 20-Densply)		Heat cure acrylic resin (Meliodent, Heraeus Kulzer, Newbury Berkshire, UK)		
Specimen size	65 × 10 × 3.3 mm		65 × 10 × 3 mm			65 × 10 × 2.5 mm	50 × 10 (±0.2) × 3 (±0.2) mm		65 × 10 × 2.5 mm		65 × 10 × 3 mm		
Curing cycle	N/S		N/S			Gradual rise to 73 ± 1 °C for 90 mins, and then boil at 100 °C for 30 min	Water bath curing for 2 h at 95 °C and 150 bar		N/S		Immersed in a water bath and were kept at 74 ± 1 °C in a water-bath for 8 h and subsequently boiled for 2 h		
Storage	At 37 °C distilled water for 50 ± 2 h		Wet condition at 37 °C for 50 h			Stored in water at room temperature for 24 h	N/S		Aquadest for 48 h at 37 °C		Distilled water for 30 days		
Cross head speed	5 mm/min		1.50 mm/min			2 mm/min	5 mm/min		N/S		5 mm/min		
TiO <sub>2</sub> NPs details	7 nm of amorphous anatase TiO <sub>2</sub> NPs		N/S			21 nm	46 nm		Silanized TiO <sub>2</sub> (size: N/S)		99.5% purity, 13 nm, 60 m <sup>2</sup> /g specific surface area, 4.1 g/cm <sup>3</sup> intensity, white color		
TiO <sub>2</sub> NPs brand	Sisco Research Laboratory, Mumbai, India		Reinste Nano Ventures Pvt. Ltd.			Sigma-Aldrich (Batch number: MKBC-4174)	Nano technology center (Beni-Suef-University, Beni-Suef city, Egypt)		NPs from Sigma-Aldrich; Silane from Ultradent-Fondaco		Nanografi, Ankara, Turkey		
NPs Dispersion Method	Added to monomer and sonicated for 1 h		Ultrasonic dispersion of TiO <sub>2</sub> NP into monomer			Hand mixing (manually stirring) of TiO <sub>2</sub> NP into resin powder	N/S		Unclear		Ball Milling (Pulverisette-5; Fritsch International, Idar-Oberstein, Germany)		
Wt. (%)	0.5	1	1	2	5	5	1	5	1	3	1	3	5
n	15	15	10	10	10	10	5	5	9	9	7	7	7
Mean (MPa) (±SD)	79.1433 (±14.06463)	76.3887 (±11.03318)	182.51 (±22.29)	204.75 (±29.42)	223.43 (±49.27)	113.5 (±16.9)	100.5 (± 3.7)	90.1 (± 5.1)	106.99 (±6.09)	91.64 (±5.38)	116.46 (± 3.9)	111.34 (± 3.4)	104.06 (± 7.3)
FS of TiO <sub>2</sub> NPs group vs. control group in the study	↓	↓	↑	↑	↑	↓	↓	↓	↑	↓	↑	↓	↓
Other property tested	None		None			Monomer release and toughness	Impact strength and microhardness		None		None		

Abbreviations: N/S = not stated; NPs = nanoparticles; wt. % = fraction weight in percentage; n = number of samples; SD = standard deviation; ↓ = reduced; ↑ = increased; FS = flexural strength.



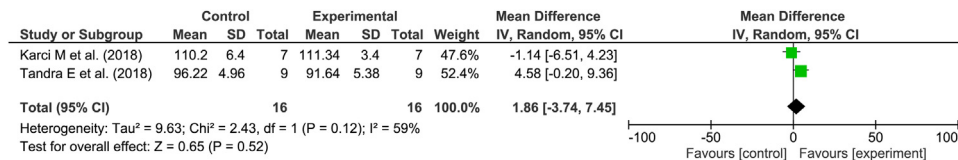


Fig. 3. Forest plot for flexural strength analysis of 3% TiO<sub>2</sub> NPs reinforcement.

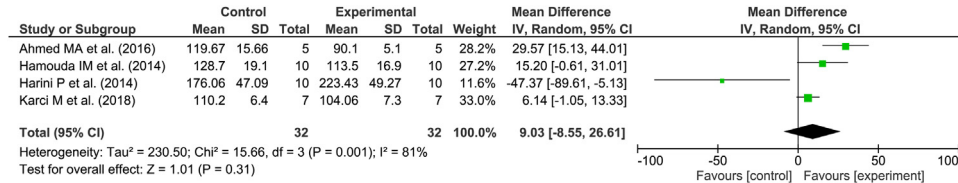


Fig. 4. Forest plot for flexural strength analysis of 5% TiO<sub>2</sub> NPs reinforcement.

pooled estimate. A increase of 2.22 MPa in flexural strength value is observed in the effect estimate. Also, the meta-analytic effect is statistically insignificant based on the CI. Hence for the 1% TiO<sub>2</sub> NPs group, the null hypothesis is accepted, and the alternate hypothesis stating that there is a change in flexure strength on the addition of TiO<sub>2</sub> NPs is rejected. The forest plot (Fig. 3) generated for the 3% TiO<sub>2</sub> NPs reinforcement showed a positive effect on the resin based on the pooled estimate. An increase of 1.86 MPa in flexural strength value is observed in the effect estimate. However, the meta-analytic effect is statistically insignificant based on the CI. Hence for the 3% TiO<sub>2</sub> NPs group, the null hypothesis is accepted, and the alternate hypothesis is rejected. The forest plot (Fig. 4) generated for the 5% TiO<sub>2</sub> NPs reinforcement presented a positive effect on the resin based on the pooled estimate. An increase of 9.03 MPa in flexural strength value is noticed in the effect estimate. The meta-analytic effect is statistically insignificant, based on CI. Hence for the 5% TiO<sub>2</sub> NPs group, the null hypothesis is accepted, and the alternate hypothesis is rejected. The heterogeneity amongst the studies was substantial, ranging between 59% to 91% based on the I<sup>2</sup> values. As the studies analyzed were sufficiently homogeneous in terms of interventions and outcomes, the heterogeneity obtained can be attributed to the methodological diversity between them.

High biocompatibility, outstanding physical properties, inexpensive, antibacterial activity are amongst the desirable features which mark it as a promising reinforcer for denture base resins [8]. Hence, TiO<sub>2</sub> NPs have been employed rigorously as an additive to enhance the physical properties of polymethylmethacrylate resins used for the fabrication of dentures. Several studies can be cited in the literature assessing the mechanical properties of TiO<sub>2</sub> NPs reinforced into PMMA in different fraction weight, to modify its mechanical and biological properties. Amongst them, flexural strength tests are relevant to the loading characteristics of a denture base in oral conditions and are regarded as a prime mode of clinical fracture [14,15].

Harini et al. (2014) reported an increase in flexural strength values at all the concentrations of TiO<sub>2</sub> NPs tested (1%, 2%, and 5%). They inferred that the enhanced flexural strength was due to the reduction in filler size, which binds to the polymer matrix improving the property [20]. Tandra et al. (2018) witness an increase in flexural strength value at 1 wt.% category in relation to the control group. The authors stated that the silanization of TiO<sub>2</sub> NPs increased its surface energy, enhanced the intermolecular force of attraction, increased cross-linking resulted in an improved bond between the resin matrix and the NPs [21]. Karci et al. (2018) observed an increase in flexural strength value at 1 wt.% concentration when compared to the control group and related it to non-agglomeration of the nanoparticles at that percentage. The authors termed 1 wt.%

of unmodified TiO<sub>2</sub> NPs to be the best concentration, dispersed with the mechanical techniques, for reinforcement of denture base resin [22].

Nazirkar et al. (2014) reported a reduction in flexural strength values when compared to the conventional unmodified resin. The authors explained that the reinforced TiO<sub>2</sub> NPs act as an impurity and intervenes with the polymerization process. They also stated that the TiO<sub>2</sub> NPs additives also increases the level of residual monomer by acting as a plasticizer reducing the strength of the resin [23]. Hamouda et al. (2014) stated that 5% TiO<sub>2</sub> NPs reinforcement showed the lowest flexural strength values compared to conventional resin, glass fiber reinforced, and high impact resin. However, the authors failed to explain the influence of TiO<sub>2</sub> NPs reinforcement on flexural strength [24]. Ahmed et al. (2016) reported a reduction in flexural strength values at 1% and 5% concentration compared to the conventional resin. The authors stated that the TiO<sub>2</sub> NPs reinforcers act as impurities. They concluded that flexural strength values are also dependent on the type of resin and concentration of the nanoparticles [25]. Tandra et al. (2018) observed reduced flexural strength values with a 3 wt.% category compared to conventional resin. The authors related it to an agglomeration of TiO<sub>2</sub> NPs at high levels, which interferes with the polymerization reaction [21]. Karci et al. (2018) attributed the reduced flexural strength value at 3 wt.% and 5 wt.% TiO<sub>2</sub> NPs reinforcements with inhomogeneous distribution of the particles leading to agglomeration [22].

The variations obtained in the flexural strength on reinforcing with different concentrations of TiO<sub>2</sub> NPs can be attributed to its concentration. As the nanoparticles bear very high surface area to volume ratios, only a small quantity of it is required to alter the polymer properties [26,27]. When TiO<sub>2</sub> NPs enter the matrix, it reduces the mobility of the polymer chain due to strong interfacial interactions between the filler and the matrix. This phenomenon probably results in improved strength of the resin caused due to the reduced segmental motion of polymer, inherent modulus of TiO<sub>2</sub> NPs, and a strong interfacial bond between at filler-matrix interface [28]. On the contrary, when the concentration of TiO<sub>2</sub> NPs fillers increases beyond a certain level (generally above 5% fraction weight), it acts as an impurity, thereby disrupting the polymer chains. The high concentration of fillers will further reduce the mobility of the polymer chains leading to brittle behavior and early failure [29,30]. TiO<sub>2</sub> NPs can behave as a plasticizer at high concentration. The plasticizing effect leads to a reduction in monomer conversion rate and high levels of residual monomer, resulting in decreased flexure strength [30,31].

The principle behind the usage of a differently sized nanoparticle is that alteration of filler size is considered responsible for the

performance of the material (PMMA). Reinforcements with high-volume fractions of nanoparticles have superior flexural strength. It is attributed to the large surface area of the fillers, low atomistic defects, and high surface energy at the filler-matrix interface [32]. Overall it is well comprehended that as the size of the particle used for reinforcing the material matrix reduces, structural integrity improves. It eventually results in better properties of polymer/composite as the magnitudes approach atomic or molecular levels [33]. In contrast, as the size of the reinforcers reduces, the internal surface area increases resulting in agglomeration of the particles instead of homogenous dispersion [34]. These agglomerated regions can act as areas of stress concentrations, thereby adversely affecting the mechanical property of the resin [35]. Agglomerations restrict molecular motion in the polymer under load-bearing applications, causing deformation [36]. Moreover, there is repulsion between the PMMA matrix and the TiO<sub>2</sub> NPs, due to the hydrophobic nature of PMMA, creating increased molecular mobility and reduced strength [37]. Many authors have tried to prevent agglomeration by functionalizing the surface of TiO<sub>2</sub> NPs by modifiers like surfactants, proteins, and different acids [38–41]. Such treatments will lower the surface energy of the nanoparticles and prevent cluster formation [42].

Various dispersion techniques have been tried and tested for incorporating TiO<sub>2</sub> NPs into PMMA resin. It is difficult to achieve uniform dispersion due to the Van der Waal's forces between the TiO<sub>2</sub> NPs leading to agglomeration. The incorporations were done either to polymer powder or to the monomer liquid to attain homogenous dispersion. Few techniques tried to break the resultant agglomerations and to achieve uniform distribution of the nanoparticles were ultrasonic mixers/ultrasonic dispersions, mortar and pestle technique, high-energy ball millers, silanization of nanoparticles, amalgamators, the twin-screw extraction process, manual hand mixing, and sonication. Amongst these techniques, ball milling appeared more promising for achieving uniform dispersion of the particles in the matrix [43]. However, studies have reported that simple manual blending will create inherent defects due to weak bonding between the nanoparticles and the resin matrix [44,45]. The properties of the achieved matrix accordingly depend on the interaction between the polymer and the reinforced nanoparticle. Based on the reasons stated in different studies on the addition of TiO<sub>2</sub> NPs into either powder/liquid, we can substantiate that the effect on the resultant property is ultimately dependent on the prevention of formation of agglomerates and achieving a homogenous distribution of TiO<sub>2</sub> NPs in the dispersed phase. Hence the difference in outcome in the reported studies can be related to the type of resin, type of nanoparticle, surface modification of the nanoparticles, mode of incorporation, and concentration of reinforcement.

The current revised ISO guidelines stay at ISO 20795-1(2008) with a revision of the 2013 version in progress. This ISO guideline corresponds with ADA specification number 12 for denture based polymers and hence been interchangeably used in many articles. ISO guidelines for denture base polymers states that the flexural strength should be measured after immersion of the specimen in distilled water at 37 °C for 50 ± 2 h before testing, placed 50 mm apart, with crosshead speed of 5 mm/min, bearing dimension of 65 × 10 × 3 mm, to simulate oral environment [46,47]. The ISO advocate's use of brass metallic dies for the fabrication of a sample. The manufacturer instructions should be followed for processing the specimen unless specified. All the studies reported in the analyses stated the application of ADA/ISO criteria.

A critical feature that directs the polymerization cycle is the release of free radicals from benzoyl peroxide, and the temperature principally regulates the rate. The extent of polymerization achieved is a function of time and the temperature within the resin. The following polymerization cycles are recommended [15],

though ISO supports curing cycle provided by the manufacturer: controlled water bath at 74 °C for 8 h or longer, with no terminal boiling; 74 °C water bath for 8 h and later raising the temperature to 100 °C for 1 h; 74 °C for approximately 2 h followed by curing at 100 °C for 1 h. Three out of six studies involved in the analysis stated that conventional or standard curing cycles were employed, but failed to explain the time and temperature used for polymerization.

The mechanical property of a reinforced denture polymer is influenced by the bulk, type of reinforcement, and on the bond between resin matrix and reinforcer interface. On immersion in water-soluble components from the denture polymer will leach out [48–50]. Water molecules subsequently fill up the resultant voids by inward diffusion. These developments are time-dependent. As a result, the quantity of these components contained in the resin alters over time till equilibrium is attained. Plasticizers and unreacted monomers influence the strength of the resin in several ways by enabling the movement of the polymer chains to a certain extent. Therefore, subsequent immersion in water affects the strength of a denture base resin due to the presence of the soluble constituents in variable amounts [48]. All the studies used in the analyses, except one which did not state the storage criteria, employed wet conditioning of the specimen before proceeding with flexural strength testing as per the ADA/ISO guidelines as summarized in Table 3.

Under the flexural load, the ratio of deformation components to total deformation is influenced by particular polymer and loading conditions, which includes temperature and test speed. Structural inaccuracies in the specimens may give rise to unusual fractures during a three-point bend test. The estimates are still acceptable if fracture lies within the middle third of the specimen. Hence, great care must be advocated while placing the samples in the load line. If not, the values obtained may be skewed or affected by a torsional moment [51]. Three studies used crosshead speed in compliance with the ADA/ISO criteria, while two other studies used different speeds. Tandra et al. (2018), did not report the crosshead speed of the tester used (Table 3).

The current review undertaken presents certain limitations. At present, there is no authenticated or an established guideline for analyzing and grading the methodological quality and risk of bias of an *in vitro* study. Hence CONSORT criteria and the Cochrane risk-of-bias tool adapted from different articles were modified for use in the present study [17–19]. This review considered *in vitro* articles reporting flexural strength values of denture base resin reinforced with titanium dioxide nanoparticles only. There are various other parameters than flexural strength that may portray the difference in results due to variations in study methodology, which has not been reported in this study. One type of nanoparticle, i.e., TiO<sub>2</sub> NPs were considered in this review and analysis. The current review is restricted to heat cure PMMA resin and does not report auto polymerizing resins, light cure resin, microwave cure resin, or any other structurally/chemically-modified denture polymers. The reports may vary for an *in vivo* study because of oral conditions, which are considerably different from a sustained laboratory environment. The review was limited to articles in the English language and refrained using unpublished data or conference proceedings. Hence publication bias is expected. Confidence in cumulative evidence was not reported due to the unavailability of a standard protocol for preclinical studies.

## 5. Conclusions

From the systematic review, we infer that the properties of nanoparticles reinforced polymers depend in general on the nanoparticles type, geometry, dimension, concentration, and interaction with the resin matrix. The difference in testing conditions/techniques and standardization, disparities in polymerization

cycles, and manipulation methods are other factors which influence the properties of the polymer. There exists no standard registered protocol for reporting and grading a systematic review of in vitro randomized control trials in the literature. Based on the available evidence, mixed opinions and reports were observed. No particular TiO<sub>2</sub> NPs concentration can be termed as most or least effective as a reinforcement.

It would be worthwhile to perform in vitro tests with sufficient sample size calculated via statistical techniques, follow standard criteria specified by ISO/ADA, and with blinded and calibrated analyzing apparatuses to enhance the standard of impending articles. It is also essential to report laboratory procedure employed stepwise and methodically, to avoid ambiguity between different studies addressing similar outcomes.

### Conflicts of interest

None.

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### Data availability statement

All the data associated with the study are presented within the manuscript.

### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.jdsr.2020.01.001>.

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