Journal of Oral Biology and Craniofacial Research 12 (2022) 469–480

Contents lists available at ScienceDirect

Journal of Oral Biology and Craniofacial Research

journal homepage: www.elsevier.com/locate/jobcr

Impact of photobiomodulation on external root resorption during orthodontic tooth movement in humans – A systematic review and meta-analysis

Nida Nayyer, Tulika Tripathi *, Gayatri Ganesh, Priyank Rai

Department of Orthodontics & Dentofacial Orthopaedics, Maulana Azad Institute of Dental Sciences, MAMC Complex, Bahadur Shah Zafar Marg, New Delhi, 110002, India

ARTICLE INFO

Keywords:
Photobiomodulation
Root resorption
Systematic review
Meta-analysis
Low-level laser therapy

ABSTRACT

Background: Photobiomodulation has been gaining traction as a plausible therapy to control orthodontically induced root resorption.

Aim: The aim of the present review was to systematically appraise randomized controlled trials conducted to study the influence of photobiomodulation on external root resorption during orthodontic movement in humans.

Method: ology - A systematic search was carried out employing keywords in various electronic databases namely MEDLINE (Pubmed), Cochrane Library, Google Scholar, Semantic Scholar, ScienceDirect and Opengrey.eu for studies up to March 2020. Pre-defined inclusion and exclusion criteria were used to select the studies. Data extraction was carried out and the risk of bias was assessed using Cochrane Risk of Bias tool. Meta-analysis was conducted using random effects model for selected studies. Subgroup analysis was conducted for resorption on each axial surface of the tooth root viz. mesial, buccal, distal and palatal as well as for vertical thirds viz. cervical, middle and apical third. Summary of Findings was formulated according to GRADE Profile.

Results: The search retrieved 1509 results out of which six studies were included for the systematic review. Two studies showed low overall risk of bias and the remaining four showed unclear risk of bias. The meta-analysis was conducted for three studies with an overall sample size of 120 teeth which showed a pooled mean difference of 0.08 (95% CI 0.15 – (−0.02) to 1.96, p=<0.0001) in favour of photobiomodulation group with respect to mean total resorption per tooth. I^2 index revealed 88% heterogeneity.

Conclusion: It is concluded that there is moderate grade of evidence to suggest beneficial effect of photobiomodulation on root resorption. Further high-quality randomized controlled trials with standardized intervention parameters are recommended.

Registration: PROSPERO registration number - CRD42020167291.

1. Background

One of the commonly associated iatrogenic effects of fixed orthodontic treatment is the occurrence of orthodontically induced inflammatory root resorption (OIIRR).[1] It is described as the loss of root structure manifesting as root length reduction or outward defects which decrease root volume.[2] A prospective study showed that 94% of the patients undertaking orthodontic treatment displayed root resorption of more than 1 mm.[3] Root resorption may jeopardize the functional ability of teeth by introducing mobility, especially when superimposed with periodontal disease.[4,5] Consequently, countering iatrogenic root resorption has become one of the prime objectives of researchers around the globe. Various methods such as shortening of the treatment duration, controlled mechanics or awareness of factors of individual susceptibility such as systemic disorders, genetics, previous trauma or age have been known to display reduced occurrence of OIIRR.[6] Newer non-invasive techniques such as low-level laser, light-emitting diodes and low intensity pulsed ultrasound (LIPUS) are also being investigated for the same lately.[7,8]

Photobiomodulation (PBM) therapy entails exposure of biologic cells or tissues to low levels of red and near-infrared light. The devices consist of semiconductors such as arsenic, aluminium, gallium or indium which

* Corresponding author.
E-mail addresses: drnidanayyer@outlook.com (N. Nayyer), drtulikatripathi@yahoo.com (T. Tripathi), gayatri2ganesh@gmail.com (G. Ganesh), priyankraibraces@hotmail.com (P. Rai).

https://doi.org/10.1016/j.jobcr.2022.05.014
Received 25 May 2021; Received in revised form 19 May 2022; Accepted 23 May 2022
Available online 31 May 2022

convert electrical energy to light energy.[9] The energy thus generated acts on cellular and molecular levels to influence bone and cementum remodeling mechanisms. The core mechanisms involve stimulation of mitochondrial activity and ATP production, activation of ion channels and subsequent modulation of the inflammatory process.[10] It was formerly believed that photobiomodulation required the usage of coherent laser light, however, of late, light-emitting diodes (LEDs) have also been serving as a cheaper alternative. The basic tenet of operation for LEDs and diode lasers is the same and termed as the PIN (positive-intrinsic-negative) semiconductor diode.[11] Currently, photobiomodulation is being tested extensively in orthodontics for pain management and accelerating tooth movement during fixed mechanotherapy, wound healing, bone regeneration after rapid maxillary expansion, root resorption control and post-treatment retention.[8,12–15]

Although the effect of photobiomodulation on root resorption has been described by various trials, there continues to exist, a discrepancy in the correlation between OIIRR and photobiomodulation. In view of this background, the present systematic review and meta-analysis was conducted to assess the influence of photobiomodulation on root resorption during orthodontic tooth movement in human subjects enrolled in randomized controlled trials.

2. Materials and methods

2.1. Protocol and registration

The systematic review was registered in PROSPERO on 28th April 2020 (CRD42020167291). It was conducted and reported according to the Cochrane Handbook[16] of systematic reviews and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[17,18]

2.2. Eligibility criteria

The PICOS (Participants, Intervention, Control, Outcome and Study design) scheme was utilized to assess the eligibility.

2.3. Inclusion criteria-

P – Human teeth subjected to orthodontic force application in any direction.
I – Photobiomodulation therapy using either low-level laser or light-emitting diode.
C – Human teeth subjected to orthodontic force application without any intervention (photobiomodulation).
O – Studies reporting quantitative measurements of root resorption.
S - Randomized controlled trials conducted on humans.

2.4. Exclusion criteria-

1. Non-randomized clinical trials
2. In-vitro studies or animal studies
3. Studies without a control/comparison group.
4. Studies conducted on replanted teeth, teeth with periodontal and/or periapical pathologies or primary teeth.
5. Review articles, case reports, case series, letters to editor.
6. Studies available only in languages other than English.

2.5. Sources of information and research strategy

The search was carried out by two review authors in several electronic bibliographic databases namely MEDLINE via Pubmed, Cochrane Library (Cochrane database of systematic reviews, Cochrane central register of controlled trials (CENTRAL), Google Scholar, Semantic Scholar, ScienceDirect and Opengrey.eu for studies up to March 2020. Reference lists of eligible studies and review articles were also explored.

Table 1
Search strategies employed for various databases and results retrieved.

SNo.	Database	Search strategy	Results retrieved	
1	Cochrane Library	#1- laser #2 - photobiomodulation #3 = #1 OR #2 #4 - resorption #5 = #3 AND #4	19071 441 19289 4248 63	
			Cochrane Database of Systematic Reviews	Cochrane CENTRAL Register of Controlled Trials
			11	52
2	Pubmed	((((((tooth movement) OR movement) OR (orthodontic[All Fields] OR orthodontically[All Fields])) OR force)) AND ((((((((((lasers) OR low-level light therapy) OR semiconductor lasers) OR laser) OR phototherapy) OR photobiomodulation) OR diode) OR biostimulation) OR LLLT) OR "PBM") OR "PBT")) AND (((((root resorption) OR tooth resorption) OR cementum) OR cementoclast*) OR (odontoclast[All Fields] OR odontoclastic[All Fields] OR odontoclastogenesis[All Fields] OR odontoclasts [All Fields])) (Filters- Human studies)	33	
3	Google Scholar	"low level laser" OR “photobiomodulation” "root resorption" (searched on 20.1.20) Filters applied – Exclude ‘patents and citations’ Year range- 1990–2000.	988	
4	ScienceDirect	("laser" OR "light" OR "photobiomodulation" OR "biostimulation" OR "phototherapy" OR "diode") ("cementum" OR "resorption" OR "cemental" OR "cementoclast" OR “odontoclast”) ("tooth movement") (Filter applied – Research articles)	47	
5	Semantic Scholar	Root resorption laser Root resorption photobiomodulation Root resorption light (Filters applied – Journal article, Clinical Trial) Total	173 69 136 378	
6	Opengrey.eu	("laser" OR "light" OR "photobiomodulation" OR "biostimulation" OR "phototherapy" OR "diode") ("cementum" OR "resorption" OR "cemental" OR "cementoclast" OR “odontclast”) ("tooth movement")	0	
	Total		1509	

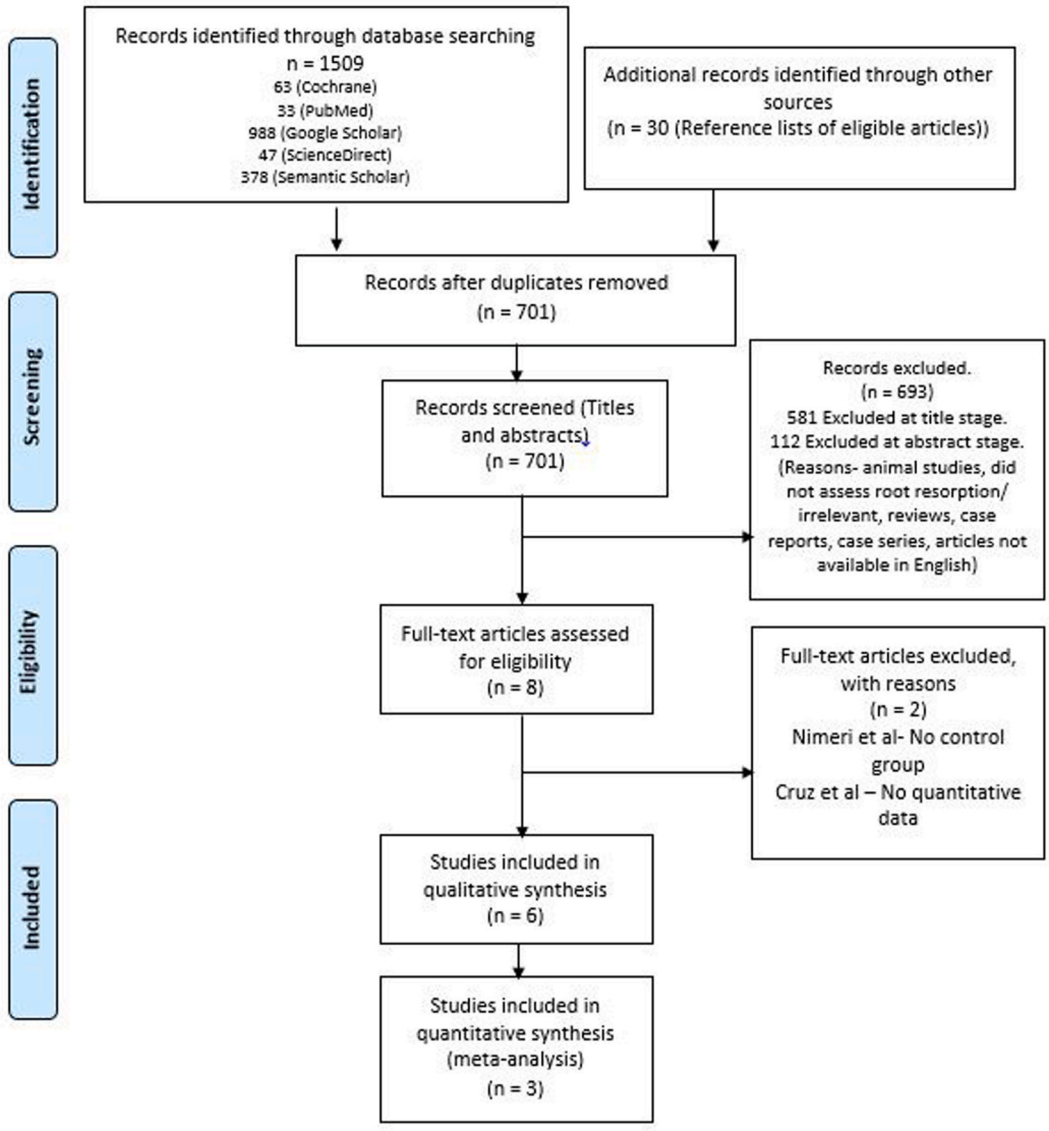

Fig. 1. PRISMA flow chart depicting study selection.

All articles and manuscripts published in English or with English translations available were incorporated in the search.

The search strategy devised included the terms relating to or describing the intervention using MeSH (medical subject headings) terms and subsequently was adapted for use according to different databases.

The search strategies employed for various databases are listed in Table 1-.

2.6. Study selection

Two authors screened the titles and/or abstracts of studies obtained from the search results to shortlist articles that potentially met the inclusion criteria. The full text of these studies were then read and independently assessed for eligibility by the same review team members. A third author opined in case of any disagreements.

2.7. Data items and collection

Data extraction was executed and tabulated under the headings: a) author, year, b) general study characteristics, c) patient demographics, d) details on intervention e) outcome details.

2.8. Risk of bias of individual studies

The risk of bias of included studies was evaluated according to Cochrane guidelines for RoB 2.0 tool for randomized trials. The assessment of risk for individual studies was carried out by two authors independently followed by resolution of discrepancies after discussion with the third author. The studies were categorized as low, high or unclear risk of bias referring to Cochrane Handbook where a low risk of bias was assigned where all the categories were judged as low risk, high risk if a majority of the categories were at high risk and unclear risk if the data was insufficient to formulate a decision.

2.9. Summary measures, data synthesis and assessment of heterogeneity

A narrative synthesis of the data extracted from the included studies concerning the type of their intervention, target population characteristics, type of outcome and intervention content was completed. Absolute anticipated effect was calculated and the summary of evidence using GRADE (Grading of Recommendations, Assessment, Development and Evaluation) Evidence Profile was formulated with mean difference as the effect estimate.[19]

The level of heterogeneity in the outcome measures of the studies

Table 2
General characteristics of included studies.

S. No	Author/Year	Study Subjects	Number of Teeth	Mean Age and Gender	Study Groups	Study Design	Study Duration	Method of Evaluation
1	Goymen et al. 2019[27]	30	30 teeth	14 males; 16 females Mean age 16.27 ± 0.87 years	Group 1–10 teeth LLLT and OIRR; Group 2–10 teeth LED and OIRR; Group 3–10 teeth Placebo and OIRR	Randomized controlled trial	4 weeks	Micro-computed tomography (micro-CT) 3D Quantitative
2	Fernandes et al. 2019[26]	30	30 teeth	Age range- 35–65 years.	G1 Control (n = 10) - Without orthodontic movement and without premature contact; G2 (n = 10) - Orthodontic movement only; G3 (n = 10) - Orthodontic movement plus laser irradiation (LLLT)	Randomized clinical trial (?)	90 days	Conventional computed tomography 3D Quantitative
3	Khaw et al. 2018[25]	20	40 teeth	8 males; 12 females Mean age – 15 years 9 months	Group 1–20 teeth LLLT and OIRR; Group 2 - 20 teeth Sham and OIRR	Double blind, split mouth randomized controlled trial	6 weeks	Micro-computed tomography (micro-CT).
4	Okla et al. 2018[24]	Initial – 38 Dropouts – 12 Final sample – 26	52 teeth	Mean age: Experimental group-16.7 ± 6.75 years. Control group-13.2 ± 0.99 years.	Experimental group (n-12) – LLLT (Orthopulse) and OIRR; Control Group (n-11) - Placebo and OIRR	Randomized controlled trial (?)	6 months	Digital periapical radiographs, 2D Quantitative
5	Ng et al. 2017[23]	20	40 teeth	10 males - 16.4 ± 1.3years 10 females - 16.7 ± 1.1 years	Group 1–20 teeth LLLT and OIRR; Group 2 - 20 teeth Placebo and OIRR	Double blind, split mouth randomized controlled trial	28 days	Micro-computed tomography, 3D Quantitative
6	Sousa et al. 2007[21]	10	26 teeth	6 female and 4 male patients Mean age of 13.1 years	Laser Group (LG) - 13 teeth LLLT and OTM with OIRR; Control Group (CG) – 13 teeth Placebo and OTM with OIRR	Randomized controlled trial (?)	4 months	Periapical radiographs, 2D Quantitative

was determined using I^2 index with significance indicated by p value < 0.05 and the pooled mean difference was calculated. Sub-group analysis was also done to assess root resorption of different axial surfaces and vertical thirds of the root. The heterogeneity for the same was calculated using I^2 index. Forest plots were plotted for both mean total root resorption as well as mean resorption volumes on individual axial surfaces and vertical thirds. Funnel plot was plotted for mean total root resorption.

3. Results

3.1. Study selection

The electronic search retrieved 1509 results from all the databases. Seven hundred and one results remained after removal of duplicates which were then screened by titles and abstracts. Full texts of eight articles were downloaded to be tested for eligibility out of which two were excluded.[20–27] The study by Cruz et al. was excluded due to missing quantitative data and Nimeri et al. was excluded because of missing control group.[20,22] The level of agreement between the two authors screening the titles, abstracts and full texts were 0.81, 0.89 and 0.91 as assessed by Kappa's calculation method. Clinical and statistical heterogeneity across the six studies was gauged, on the basis of which three (Ng et al., Ang-Khaw et al. and Goymen et al.) were selected for quantitative analysis.[23,25,27] The results retrieved from the search along with reasons behind exclusion have been depicted in the *PRISMA Flowchart* (*Fig. 1*) and Table 1.

3.2. General characteristics of included studies

We included six studies for qualitative analysis. The general characteristics of the studies are reported in Table 2. The studies by Ang-Khaw et al. (2018) and Ng et al. (2017) conducted on 20 patients each were double-blind, randomized controlled trials having split-mouth designs and requiring bilateral maxillary first premolar (MFP) extractions for orthodontic treatment.[23,25] Ang-Khaw et al. study comprised 8 males and 12 females and the study of Ng et al. had an equal number patients in both the genders while the mean age of the patients were 16.4 ± 1.3 years and 16.7 ± 1.1 years respectively. Both the studies had a test group and a placebo group. However, the root resorption was assessed after a duration of 70 and 28 days by Ang-Khaw et al. and Ng et al. respectively. Goymen et al. conducted their randomized controlled trial in three different groups of 10 patients each - LLLT group, LED group and control group.[27] Fernandes et al. equally divided their total sample of 30 patients into Control group, only 'Orthodontic Force' group and 'Orthodontic Force and PBM' group.[26] The mean age of subjects in Goymen's study was 16.27 ± 0.87 years with 14 males and 16 females; the data was not reported by Fernandes et al. The study by Sousa et al. comprised 10 subjects (6 female and 4 male) involved in a split-mouth design while Okla et al. studied 26 patients who were divided into two groups namely, LLLT and control.[21,24] Both the studies were of six months duration. Out of the six studies, four studies (Ng et al., Ang-Khaw et al., Goymen et al. and Fernandes et al.) assessed root resorption three-dimensionally subsequent to photobiomodulation.[23,25–27] Three studies used micro-CT for resorption measurement (Ng et al., Ang-Khaw et al., Goymen et al.) while Fernandes et al. employed conventional computed tomography. The remaining two studies by Okla et al. and Sousa et al. assessed root resorption two-dimensionally by using intra-oral periapical radiographs subsequent to the clinical procedure.[21,24]

3.3. Characteristics of the interventions

The type of orthodontic movement carried out varied across the studies. Ng et al., Ang-Khaw et al., and Goymen et al., exerted 150g of buccal tipping force on maxillary first premolars. Sousa et al. applied 150g retractive force on canines using NiTi coil spring, Okla et al. studied maxillary central incisors undergoing non-specific decrowding,

Table 3
Details of intervention (photobiomodulation).

S. No	Author	Laser type	Wavelength	Model (Manufacturer)	Output power (mW)	Fluence/ Energy density (J/ cm^2)	Total dose per tooth	Site of application	Duration and frequency
1	Goymen et al. 2019[27]	GaAlAs laser device LED application according to the manufacturer's instructions with an 850-nm wavelength	Laser - 810-nm LED – 850 nm	Cheese dental laser; Wuhan Gigaa Optronics Technology Co. Ltd., Wuhan, China OrthoPulse, Biolux Research Ltd., Vancouver, BC, Canada	Not reported	Laser - 8 J/ cm^2 LED - 20 mW/cm^2		10 points total	Laser - 0, 3, 7, 14, 21 and 28 days LED -10 min per day
2	Fernandes et al. 2019[26]	Diode laser	808 nm	Laser Duo, MMOptics, São Carlos, SP, Brazil	100 mW	Beam area = 0.04 cm^2 Energy density - 25 J/cm^2		10 points on the gingival tissue (five points per vestibular and five per palatine region): two points on the cervical third (one mesial and one distal gingiva), two points on the apical third (one mesial and one distal), and one point in the middle third (root center)	10 s per point Three different moments: immediately after force application (T0), after 3 (T1) and 7 days (T2), as well as, whenever a new elastic chain was placed to activate the intrusion, during a total of 3 months
3	Khaw et al. 2018[25]	Aluminum-gallium-indium-phosphorus laser	660 nm	Thor Photomedicine, Buckinghamshire, United Kingdom	75-mW	Power density of 0.245 W/cm^2 Fluence of 3.6 J/cm^2 $1/e^2$ spot size - 0.260 cm^2, $1/e^2$ power density - 0.245 W/cm^2	Total energy - 7.6 J	4 points buccally and 4 palatally 2 points at the cervical portion (mesial and distal), 1 at midroot, and 1 at the apex of the tooth per buccal and lingual sides	15 s per point LLLT regimen was performed at weekly sessions over a period of 6 weeks
4	Okla et al. 2018[24]		850 nm	OrthoPulse® Biolux Research Ltd., Vancouver, BC, Canada	Not reported	Continuous wave, 0.065 J/cm^2		Complete arch	5 min per arch per day
5	Ng et al. 2017[23]	AlGaAs Aluminum-gallium-Arsenic	808 nm	Klas, Konftec Corporation, Taiwan	Continuous mode- 180 mW Pulsed mode- 360 mW at 20 Hz	Beam area of 0.5 cm^2 Total irradiated surface area was 4 cm^2	1.6 J per point	4 buccal, 4 palatal points Apex, Middle third (centre of the root), Cervical third (mesial) and Cervical third (distal)	Continuous laser - 9 s per point Pulsed laser - 4.5 s per point Days 0,1,2,3, 7, 14, 21.
6	Sousa et al. 2011[21]	Aluminum-gallium-arsenide (AsGaAl)	780 nm	Twin Laser (MM Optics Ltda, São Carlos, São Paulo, Brazil)	20 mW	5 J/cm^2 Irradiated area of about - 0.04 cm^2	0.2 J of energy per point Total – 2J		10 s per point Day 0, 3, 7, 30 and 60

and Fernandes et al. exerted intrusive force on maxillary molars.[21,23,25–27] Details of the intervention (PBM), namely, the laser type, wavelength, manufacturer, output power, fluence/energy density, total dose per tooth, site of irradiation and duration and frequency were recorded (Table 3). Goymen et al., Ng et al. and Sousa et al. employed Gallium Aluminium Arsenic laser at a wavelength of 810 nm (LLLT group), 808 nm and 780 nm respectively.[21,23,27] Ang-Khaw et al. used Aluminium-Gallium–Indium–Phosphorus (AlGaInP) at 660 nm.[25] Fernandes et al. used an 808 nm diode but the semiconductor has not been specified.[26] The powers used by the authors were 100 mW by Fernandes et al., 75 mW by Ang-Khaw et al., 20 mW by Sousa et al. and 180 mW (continuous delivery group) and 360 mW (pulsed delivery group) by Ng et al.[21,25,26] The other two studies did not specify the power used.[24,27] Goymen et al. used LED at 850 nm for their second test group.[27] Okla et el reported to have used the OrthoPulse® device kit (Biolux Research Ltd.,Vancouver, BC, Canada) for photobiomodulation (850 nm wavelength) and Biolux devices as a placebo (24). In the trials by Ang-Khaw et al. & Ng et al., PBM was applied on 4 buccal and 4 palatal points around the roots of the MFP and Fernandes et al. applied it around 5 buccal and 5 palatal points.[23,25,26] Sousa et al. did not specify the details of the points of irradiation while Okla et al. exposed the entire arch. Goymen et al. irradiated 10 points in total. In all the studies except the study by Okla et al., the laser tip was in direct contact with the tissue surface.

3.4. Characteristics of the study outcomes

Ng et al., Ang-Khaw et al. and Goymen et al. assessed of the total amount of root resorption in a three-dimensional manner by measuring the volume of root surface craters using micro-CT images. Although

Table 4
Characteristics of the study outcomes.

S. No	Author/ Year	Outcome (Mean ± SD)			Difference	Results	Conclusion
		LLLT	LED	Placebo/Sham			
1	Goymen et al. 2019[27]	Mean Crater Volume −0.42 ± 0.07 mm^3	Mean Crater Volume −0.25 ± 0.03 mm^3	Mean Crater Volume −0.4 ± 0.06 mm^3	LLLT versus Placebo- 0.016 mm^3 less mean resorption in placebo group. LED versus Placebo- 0.154 mm^3 less mean resorption in LED group. p value - 0.099	There is a tendency for Group 2 (LED group) to have few resorption values especially on the buccal side and in total.	Within the limitations of the study, no significant difference in root resorption with application of LLLT or LED.
2	Fernandes et al. 2019[26]	-	-	-	Only graphical representation provided. p value > 0.05	Between G2 (orthodontic force only) and G3 (orthodontic force with PBM), shortening of MB and DB roots was greater in G2. No difference in the shortening of palatal root between groups G2 and G3 noted.	No comments made on root resorption.
3	Khaw et al. 2018[25]	Mean Crater Volume −0.746 ± 0.41 mm^3	-	Mean Crater Volume −0.779 ± 0.374 mm^3	0.033 mm^3 less in the test group p value - 0.71	Greater resorption of crater volume in the sham group compared with the laser group that was not statistically significant	No statistically or clinically significant difference was found in root resorption crater volumes between the control group and the LLLT group when laser was applied weekly for 6 weeks.
4	Okla et al. 2018[24]	Mean Root Length - 19.63 mm	-	Mean Root Length - 20.85 mm	p value – 0.021	Mean root length at the 6-month time interval was significantly shorter for the experimental group compared to the control group	Photobimodulation using Orthopluse did not reduce root resorption.
5	Ng et al. 2017[23]	Mean Crater Volume 0.381 ± mm^3	-	Mean Crater Volume 0.495 mm^3	114 mm^3 less and 23% less mean resorption in Test group p value - 0.026	LLLT treatment produces an average 0.114 mm^3 (23%) less root resorption than the placebo.	LLLT seems promising in preventing or reducing orthodontic root resorption during the initial stages of orthodontic force application.
5	Sousa et al. 2007[21]	Mean resorption according to Levander and Malmgren Index – 0.08	-	Mean resorption according to Levander and Malmgren Index – 0.15	0.07 (Levander Malmgren Index) p value - 0.592	No statistically significant difference was found in the resorption of either root between the laser-irradiated and non-irradiated groups	No comments made on root resorption.

Fernandes et al. employed CT for resorption measurement, resorption data was presented as root length loss (millimeters).[23,25–27] Out of these, three studies (Ang-Khaw et al., Ng et al. and Goymen et al.) have further described the distribution of the resorption on four axial surfaces and three vertical thirds for each tooth with mean and standard deviations or standard errors.[23,25,27] Fernandes et al. provided a graphical representation of root length changes in the mesiobuccal, distobuccal and palatal roots.[26] The remaining two studies by Okla et al. and Sousa et al. evaluated the amount of the root resorption two-dimensionally by measuring the differences in the root length directly or by using the Levander and Malmgren Index on periapical radiographs respectively.[21,24] The details have been elucidated in Table 4.

3.5. Risk of bias of included studies

The risk of bias of all the included studies was ascertained within the specified domains of the Cochrane Risk of bias 2.0 tool. Out of the six studies, two clinical studies (Ng et al., Ang-Khaw et al.) had a low risk of bias across the various domains of Selection bias, Performance bias, Detection bias, Attrition Bias and Reporting bias as the studies conformed to the guidelines and reported the data in detail.[23,25] The remaining four studies were placed in the category of overall unclear risk of bias as the information provided in the studies was insufficient to allot them to a high risk or a low risk category.[21,24,26,27] Three studies namely Fernandes et al., Sousa et al. and Okla et al. failed to provide three-dimensional quantitative resorption data to be included in the meta-analysis, hence have been marked as a high risk of attrition bias.[21,24,26] Performance of various trials in specific domains of the Cochrane Risk of bias tool is depicted in Table 5 along with pictorial representations generated in Revman software (version 5.4) in Figs. 2 and 3. The Kappa statistic for inter-observer agreement for overall risk of bias categorization was 0.85.

3.6. Results of individual studies, synthesis of results and additional analyses

Based on the magnitude of homogeneity in the methodologies and study outcomes, the number of studies included in the meta-analysis was three out of six (Ng et al., Ang-Khaw et al. and Goymen et al.)[23,25,27] These studies were split-mouth randomized controlled trials applying 150g buccal tipping on maxillary first premolars and used micro-CT for volumetric analysis. The study by Ng et al. showed an average 0.114 mm^3 less root resorption than the placebo which had statistical significance ($P = 0.026$). In the study by Ang Khaw et al., there was a mean difference of 0.033 mm^3 greater resorption crater volume in the sham group compared with the intervention group which statistically insignificant ($P = 0.71$).[25] For the purpose of synthesizing the results, the three study groups of Goymen et al. were arranged into two sets – first, the laser versus placebo group and second, the LED versus placebo group. In their study, there was a non-significant increase of 0.016 mm^3 in resorption in laser group vis-à-vis placebo group and a non-significant decrease in resorption of 0.154 mm^3 in LED group compared to control group.[27]

The overall sample size of the meta-analysis of the 4 groups extracted out of 3 studies consisted of 60 teeth in the photobiomodulation (Laser/ LED) arm and 60 teeth in the placebo arm. Mean difference was used to determine the association and random effect model was applied for meta-analysis. There was high heterogeneity in the included studies as determined by I^2 index (88%) with appreciable variation in the confidence intervals. The pooled mean difference for overall total root

Table 5
Risk of Bias Assessment of included studies.

S. No	Author	Selection Bias		Performance Bias (Blinding of personnel)	Detection Bias (Blinding of outcome assessment)	Incomplete Outcome Data (Attrition Bias)	Reporting Bias (Selective reporting)
		Random Sequence Generation	Allocation Concealment				
1	Goymen et al. 2019[27]	Unclear Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk Individuals included were randomly divided into three groups.	Unclear Insufficient information to permit judgement of 'Low risk' or 'High risk'.	Unclear Insufficient information to permit judgement of 'Low risk' or 'High risk'.	Unclear Insufficient information to permit judgement of 'Low risk' or 'High risk'	Low No missing outcome data	Unclear Trial number not available
2	Fernandes et al. 2019[26]	Unclear Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk	Unclear Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk	Unclear Insufficient information to permit judgement of 'Low risk' or 'High risk'	Unclear Insufficient information to permit judgement of 'Low risk' or 'High risk'	High One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;	Unclear Trial number not available
3	Khaw et al. 2018[25]	Low The randomization scheme was generated by using www.randomization.com. Block sizes of 4, 6, 6, and 4 were used to maintain equal numbers of laser and sham treated sites between the left and right sides of the patients.	Low Participants and investigators enrolling participants could not foresee assignment because a web based sequence was used to conceal allotment	Low Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken	Low Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken. The outcome assessor was only unblinded after the teeth were scanned, root resorption craters counted, and the data had been collected and verified.	Low No dropouts, the outcome assessment was completed on all	Unclear Not available on the site
4	Okla et al. 2018[24]	Unclear Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk	Unclear Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk	Unclear Insufficient information to permit judgement of 'Low risk' or 'High risk'	Unclear Insufficient information to permit judgement of 'Low risk' or 'High risk'	High One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis	Unclear Trial number not available
5	Ng et al. 2017[23]	Low The investigators describe a random component in the sequence generation process using a remote computerized random number generator.	Low Participants and investigators enrolling participants could not foresee assignment because of the use of random permuted blocks with allocation concealed in sequentially numbered, opaque, sealed envelopes.	Low Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. It was a double-blind trial, both the experimental laser and the placebo-laser beams were invisible to the naked eye, and at 808 nm there was negligible glow from the laser; hence, both the participants and operator were blinded during this trial.	Low Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken. The outcome assessor was only unblinded after the teeth were scanned, root resorptions craters counted, and the data had been collected and verified.	Low No dropouts, the outcome assessment was completed on all	Low The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
6	Sousa et al. 2011[21]	Unclear Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk	Unclear Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk.	Unclear Insufficient information to permit judgement of 'Low risk' or 'High risk'	Unclear Insufficient information to permit judgement of 'Low risk' or 'High risk'	High One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;	Unclear Trial number not available

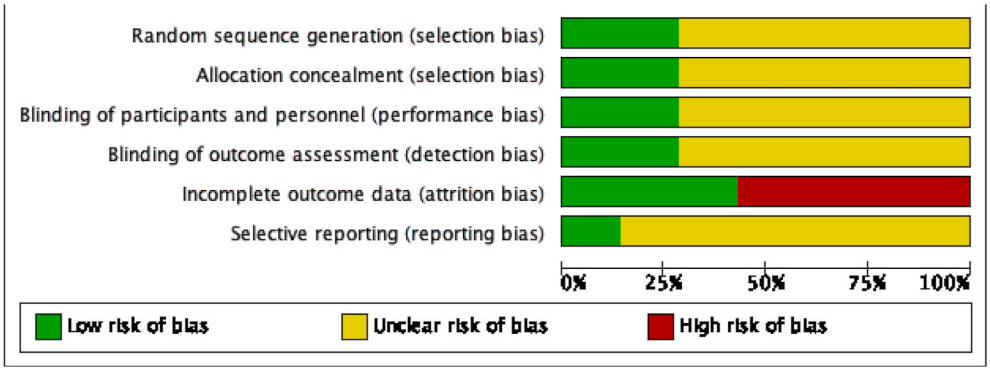

Fig. 2. Risk of bias of studies in specific domains of Cochrane Risk of Bias tool.

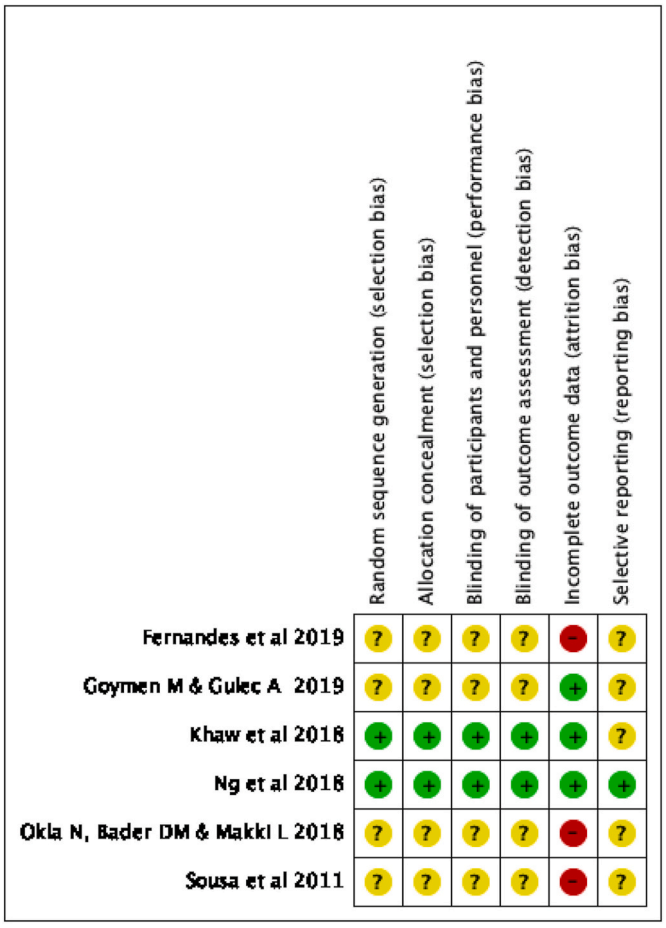

Fig. 3. Risk of bias of individual studies in each domain of Cochrane Risk of Bias tool.

resorption was 0.08 (95% CI 0.15 – (−0.02) to 1.96, p=<0.0001) in favour of photobiomodulation group i.e. significantly lesser total root resorption was seen in the photobiomodulation group (Fig. 4).

Subgroup analysis (Fig. 5) was done to determine the root resorption on different axial surfaces. I^2 test revealed high heterogeneity in the included studies for resorption data for the buccal (94%, $p < 0.01$) and distal (91%, $p < 0.01$) surfaces while it was lower for palatal surface (43%, $p = 0.15$) and the least for mesial surface resorption values (0%, $p = 0.44$). The pooled mean differences obtained in root resorption between the photobiomodulation groups and control groups were 0.03, −0.02, −0.04, −0.03 for buccal, palatal, mesial and distal surfaces respectively.

Furthermore, subgroup analysis (Fig. 6) was conducted for resorption volumes on three vertical divisions of a premolar root viz. cervical, middle and apical third. I^2 testing showed high heterogeneity and non-significant pooled mean differences between test and control groups with respect to cervical and apical thirds. The pooled mean difference for the middle third was 0.08 in favour of photobiomodulation ($p < 0.00001$). The funnel plot is depicted in Fig. 7.

4. Discussion

The present systematic review applied the selection criteria so as to restrict the review to human trials aiming to scrutinize the impact of photobiomodulation on orthodontic root resorption. A systematic review by Michelogiannikis in 2019 included both animal and human studies and concluded that photobiomodulation effects on root resorption were debatable.[8] There is skepticism about the extrapolation of conclusions of animal research onto man since there is a considerable difference between the tooth size of rats and humans.[12] To avoid incoherence in drawing conclusions, the participants included in the present systematic review were limited to human teeth.

The criterion of intervention in this review was selected as photobiomodulation in the form of low-level diode laser or light-emitting diode. In the present study, the final data which was synthesized for meta-analysis included three groups with LLLT and one with LED as intervention group.

The focus of the method of outcome assessment in the current

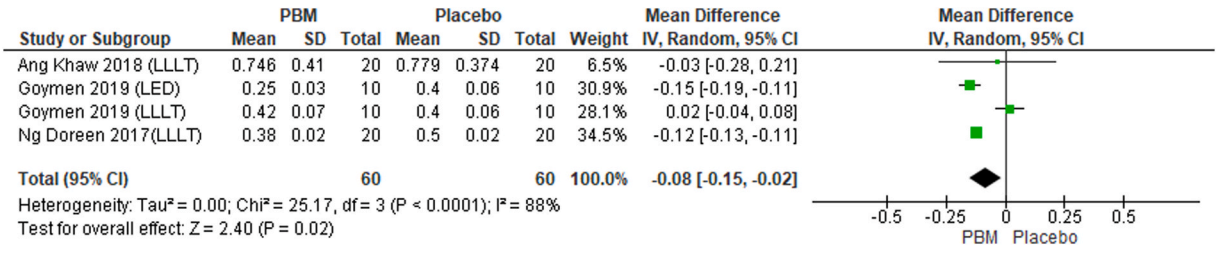

Fig. 4. Forest plot of mean total root resorption.

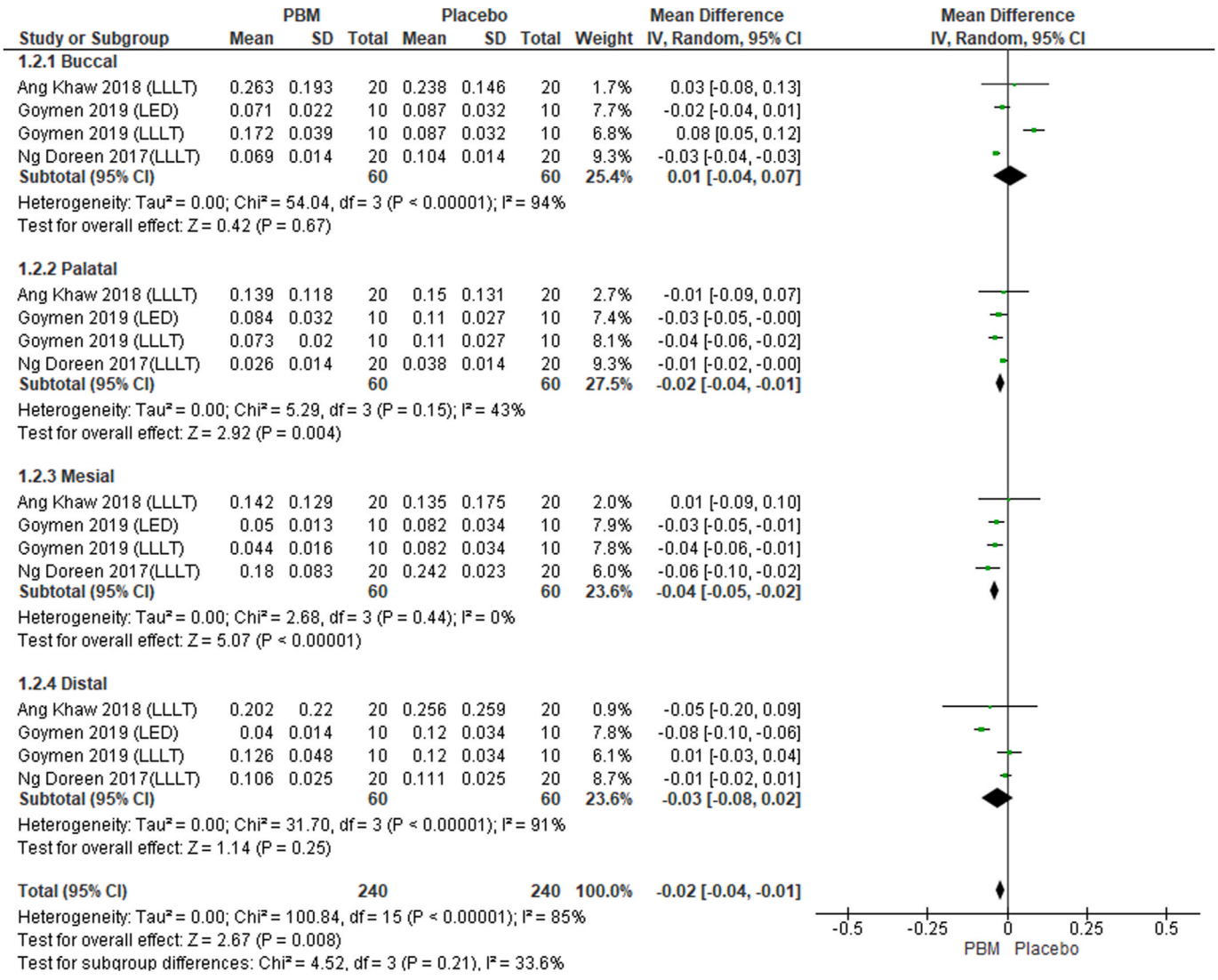

Fig. 5. Forest plot of mean resorption on each axial surface of root i.e. buccal, palatal, mesial and distal surface.

systematic review was laid on quantification of the root resorption so as to enable decisive interpretation of the magnitude of effect of the intervention. Out of the six studies, two studies employed periapical radiographs (Sousa et al., Okla et al.) while the remaining used three-dimensional computed tomography. The validities of 2D radiographic analyses can be questionable as demonstrated by Chan et al. owing to parallax errors and surface material denudation while preparing specimens for the same.[28] Furthermore, owing to the meagre methodological homogeneity amongst the 6 studies, trials with two-dimensional resorption data were excluded from the meta-analysis (Sousa et al., Okla et al.).[21,24] Although Fernandes et al. employed conventional computed tomography for resorption measurement, data was presented as root length shortening (millimeters), permitting the study to be excluded from the meta-analysis.[26] Consequently, three studies, Ng et al., Ang-Khaw et al. and Goymen et al. qualified and were selected for the meta-analysis.[23,25,27] Mean difference was the calculated summary effect as the outcome was a continuous variable and the random effects model was used due to the heterogeneity amongst the selected studies. The risk of bias assessment using Cochrane's RoB tool revealed that two out three studies chosen for meta-analysis carried 'low' overall risk of bias (Ng et al. and Ang-Khaw et al.) and one study carried 'unclear' risk of bias (Goymen et al.).

The meta-analysis demonstrated a positive effect of photobiomodulation with regards to mean total root resorption per tooth although it depicts considerable statistical heterogeneity and the evidence for the same is strong ($p < 0.05$). The sub-group analyses of axial surfaces show decrease in root resorption in the irradiated teeth on their mesial, distal and palatal surfaces but there is statistically significant heterogeneity for buccal and distal surfaces ($I^2 = 94\%$ and 91% respectively). Further, the low and moderate heterogeneities of mesial and palatal surface resorptions are based on weak statistical evidence. Similarly, in terms of vertical thirds, photobiomodulation groups tended to demonstrate lower resorption per vertical third but only the middle third showed overlapping confidence intervals and insignificant heterogeneity ($I^2 = 0\%$). The Summary of Findings (SoF) table formulated according to GRADE Pro in order to appraise the quality of evidence showed a moderate overall quality of evidence. Risk of bias was not serious as the potential limitations in study design were unlikely to lower the confidence in the estimate of the effect. Inconsistency was graded as serious owing to the considerable heterogeneity in the outcome. Indirectness and imprecision were not serious and hence the certainty of evidence was moderate (Table 6). The funnel plot generated to evaluate publication bias shows asymmetry but the interpretation derived from it should not be relied upon as the number of studies in considerably low.

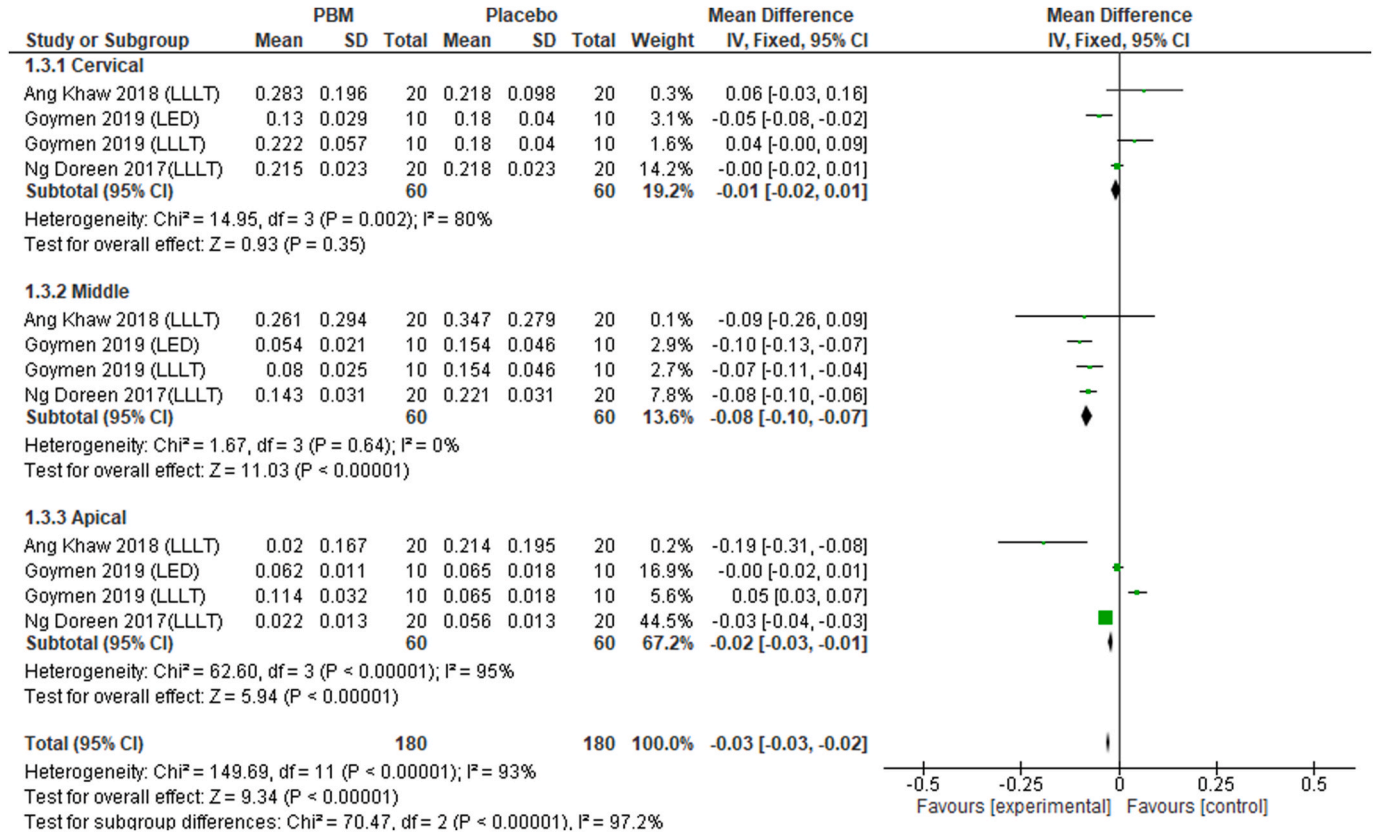

Fig. 6. Forest plot of mean resorption on each vertical third of root surface i.e. coronal, middle and apical third.

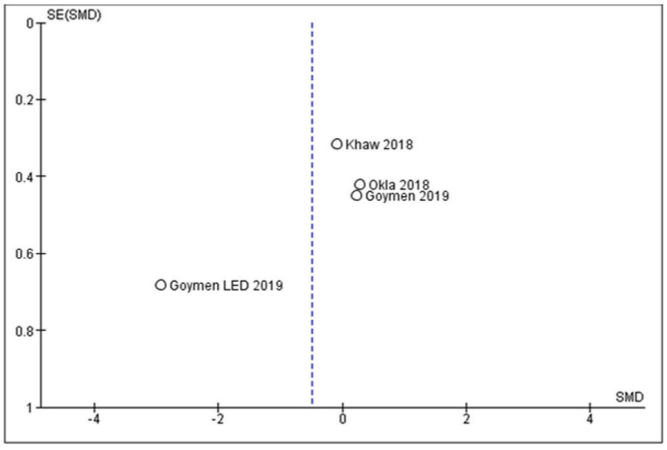

Fig. 7. Funnet plot.

4.1. Limitations and recommendations

A limitation of the present systematic review is the low number of randomized controlled trials conducting quantitative analysis of root resorption using comparable measurement methods. There is also a probability for different biological reactions being elicited by different wavelengths of photobiomodulation lights.[29,30] Even though there may not be significant therapeutic differences between LLLT and LED, the evidence for the same has yet to be established. Furthermore, orthodontic force factors have a bearing on the magnitude and distribution of root resorption along with the duration of study and outcome assessment method which were found to be variable.[31] In view of this knowledge, the results of the meta-analysis must be interpreted with caution. It is strongly recommended that high-quality trials with more uniformity in intervention methodology be executed.

5. Conclusions

The following conclusions may be drawn from the present review:

1. There is moderate grade of evidence to suggest that photobiomodulation has a beneficial effect on root resorption.
2. More high-quality randomized controlled trials with similarity in intervention methods are required for better strength of evidence regarding the influence of PBM on root resorption related to orthodontic tooth movement.

Ethics approval and participation consent

Not applicable.

Consent for publication

The authors give consent for publication.

Funding

The study is self-funded.

Availability of supporting data

The data can be shared on request.

Declaration of competing interest

None.

Table 6
Summary of Findings according to GRADE Assessment Profile.

Author(s): Goymen M et al [27] , Ng D et al [23], Ang Khaw et al [25]

Question: Photobiomodulation therapy compared to sham therapy in orthodontic tooth movement

Setting: various

Bibliography:

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	photobiomodulation therapy	sham therapy	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
External Root Resorption (follow up: mean 4 weeks)												
4	randomised trials	not serious	serious [a]	not serious	not serious	none	60	60	-	MD **0.08 lower** (0.15 lower to 0.02 lower)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. There were considerable heterogeneity in terms of the outcome across studies since the value of I square was 80%.

Summary of findings:

Photobiomodulation therapy compared to sham therapy in orthodontic tooth movement

Patient or population: human teeth undergoing orthodontic tooth movement

Setting: various

Intervention: photobiomodulation therapy

Comparison: sham therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sham therapy	Risk with photobiomodulation therapy				
External Root Resorption follow up: mean 4 weeks	The mean external Root Resorption was **0**	MD **0.08 lower** (0.15 lower to 0.02 lower)	-	120 (4 RCTs)	⊕⊕⊕◯ MODERATE [a]	

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. There were considerable heterogeneity in terms of the outcome across studies since the value of I square was 80%.

ABBREVIATIONS

PBM Photobiomodulation
OIIRR Orthodontically induced inflammatory root resorption
ATP – Adenosine Triphosphate
microCT micro-computed tomography
LLLT Low-level laser therapy
LED Light-emitting diode
μm^3 – cubic micrometer
mm^3 cubic millimeter

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jobcr.2022.05.014.

References

1 Weltman B, Vig KWL, Fields HW, Shanker S, Kaizar EE. Root resorption associated with orthodontic tooth movement: a systematic review. *Am J Orthod Dentofacial Orthop*. 2010;137(4):462–476. https://doi.org/10.1016/j.ajodo.2009.06.021. Available from:.

2 Brezniak N, Wasserstein A. Orthodontically induced inflammatory root resorption . Part I : the basic science aspects. *Angle Orthod*. 2002;72(2):175–179. https://doi.org/10.1043/0003-3219(2002)072<0175:OIIRRP>2.0.CO;2. Available from:.

3 Lund H, Grondahl K, Hansen K, Grondahl H. Apical root resorption during orthodontic treatment A prospective study using cone beam CT. *Angle Orthod*. 2012; 82:480–487. https://doi.org/10.2319/061311-390.1. Available from:.

4 Jönsson A, Malmgren O, Levander E. Long-term follow-up of tooth mobility in maxillary incisors with orthodontically induced apical root resorption. *Eur J Orthod*. 2007;29(5):482–487. https://doi.org/10.1093/ejo/cjm047. Available from:.

5 Sondeijker CFW, Lamberts AA, Beckmann SH, et al. Development of a clinical practice guideline for orthodontically induced external apical root resorption. *Eur J Orthod*. 2020;42(2):115–124. https://doi.org/10.1093/ejo/cjz034. Available from:.

6 Brezniak N, Wasserstein A. Orthodontically induced inflammatory root resorption . Part II : the clinical aspects. *Angle Orthod*. 2002;72(2):180–184. https://doi.org/10.1043/0003-3219(2002)072<0180:OIIRRP>2.0.CO;2. Available from:.

7 Raza H, Major PW, Dederich D, El-Bialy T. Effect of low-intensity pulsed ultrasound on orthodontically induced root resorption caused by torque: a prospective, double-blind, controlled clinical trial. *Angle Orthod*. 2016;86(4):550–557. https://doi.org/10.2319/081915-554.1. Available from:.

8 Michelogiannakis D, Al-shammery D, Akram Z, Rossouw PE, Javed F, Romanos GESC. *Arch Oral Biol*. 2019;100:1–13. https://doi.org/10.1016/j.archoralbio.2019.01.017. Available from:.

9 Chung H, Dai T, Sharma SK, Huang Y-Y, Carroll JD, Hamblin MR. The nuts and bolts of low-level laser (light) therapy. *Ann Biomed Eng*. 2012;40(2):516–533. Available from: http://link.springer.com/10.1007/s10439-011-0454-7.

10 Zein R, Selting W, Hamblin MR. Review of light parameters and photobiomodulation efficacy: dive into complexity. *J Biomed Opt*. 2018;23(12):1–17. https://doi.org/10.1117/1.JBO.23.12.120901. Available from:.

11 Heiskanen V, Hamblin MR, Diseases M, Hospital MG. Photobiomodulation : lasers vs light emitting diodes. *Photochem Photobiol Sci*. 2019;17(8):1003–1017. https://doi.org/10.1039/c8pp00176f. Available from:.

12 Seifi M, Vahid-Dastjerdi E. Tooth movement alterations by different low level laser protocols: a literature review. *J Laser Med Sci*. 2015;6(1):1–5.

13 Deana NF, Zaror C, Sandoval P, Alves N. Effectiveness of low-level laser therapy in reducing orthodontic pain: a systematic review and meta-analysis. *Pain Res Manag*. 2017;2017, 8560652. https://doi.org/10.1155/2017/8560652. Available from:.

14 Cepera F, Torres FC, Scanavini MA, et al. Effect of a low-level laser on bone regeneration after rapid maxillary expansion. *Am J Orthod Dentofacial Orthop*. 2012 Apr;141(4):444–450. https://doi.org/10.1016/j.ajodo.2011.10.023. Available from: .

15 Mcgrath C, Gu M. Effects of Low-Level Laser Therapy as an Adjunct for Orthodontic Retention : A Systematic Review of Human and Animal Studies. Pre-screen. Available from: https://doi.org/10.21203/rs.3.rs-28836/v1.

16 Atrium T, Gate S, Road TC, Collaboration TC, Kingdom U. *Cochrane Handbook for Systematic Reviews of Interventions*. 2011.

17 PRISMA checklist. Available from: http://prisma-statement.org/prismastatement/Checklist.aspx. Accessed November , 2019.

18 Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions : explanation and elaboration. *J Clin Epidemiol*. 2009;62. https://doi.org/10.1371/journal.pmed.1000100. e1–34. Available from:.

19 Guyatt GH, Oxman AD, Santesso N, et al. GRADE guidelines : 12 . Preparing Summary of Findings tables - binary outcomes. *J Clin Epidemiol*. 2013;66(2): 158–172. https://doi.org/10.1016/j.jclinepi.2012.01.012. Available from:.

20 Cruz DR, Kohara EK, Ribeiro MS, Wetter NU. Effects of low-intensity laser therapy on the orthodontic movement velocity of human teeth: a preliminary study. *Laser Surg Med*. 2004;35(2):117–120. https://doi.org/10.1002/lsm.20076. Available from:.

21 da Silva Sousa MV, Scanavini MA, Sannomiya EK, Velasco LG, Angelieri F. Influence of low-level laser on the speed of orthodontic movement. *Photomed Laser Surg*. 2011; 29(3):191–196. Available from: https://www.liebertpub.com/doi/10.1089/pho.2009.2652.

22 Nimeri G, Kau CH, Corona R, Shelly J. The effect of photobiomodulation on root resorption during orthodontic treatment. *Clin Cosmet Invest Dent*. 2014;6:1–8. https://doi.org/10.2147/CCIDE.S49489. Available from:.

23 Ng D, Chan AK, Papadopoulou AK, Dalci O, Petocz P, Darendeliler MA. The effect of low-level laser therapy on orthodontically induced root resorption: a pilot double blind randomized controlled trial. *Eur J Orthod [Internet]*. 2017:1–9. https://doi.org/10.1093/ejo/cjx065. Available from:.

24 Okla N, Bader D, Makki L. Effect ofphotobiomodulation on maxillary decrowding and root resorption: a randomized clinical trial. *APOS Trends Orthod*. 2018;8:86–91. https://doi.org/10.4103/apos.

25 Ang Khaw CM, Dalci O, Foley M, Petocz P, Darendeliler MA, Papadopoulou AK. Physical properties of root cementum: Part 27. Effect of low-level laser therapy on the repair of orthodontically induced inflammatory root resorption: a double-blind, split-mouth, randomized controlled clinical trial. *Am J Orthod Dentofacial Orthop*. 2018;154(3):326–336. https://doi.org/10.1016/j.ajodo.2018.04. 022. Available from:.

26 Fernandes MRU, Suzuki SS, Suzuki H, Martinez EF, Garcez AS. Photobiomodulation increases intrusion tooth movement and modulates IL-6, IL-8 and IL-1β expression during orthodontically bone remodeling. *J Biophot*. 2019;12(10), e201800311. https://doi.org/10.1002/jbio.201800311.

27 Goymen M, Gulec A. Effect of photobiomodulation therapies on the root resorption associated with orthodontic forces: a pilot study using micro computed tomography. *Clin Oral Invest*. 2020;24(4):1431–1438. https://doi.org/10.1007/s00784-019-03155-w.

28 Chan EKM, Darendeliler MA. Exploring the third dimension in root resorption. *Orthod Craniofac Res*. 2004;7(2):64–70.

29 Wang Y, Huang Y, Wang Y, Lyu P, Hamblin MR. Biochimica et Biophysica Acta Photobiomodulation of human adipose-derived stem cells using 810 nm and 980 nm lasers operates via different mechanisms of action. *BBA - Gen Subj*. 2017;1861(2): 441–449. https://doi.org/10.1016/j.bbagen.2016.10.008. Available from:.

30 Santana-blank L, Rodrı E, Santana-rodrı K. Theoretic , experimental , clinical bases of the water oscillator hypothesis in near-infrared photobiomodulation. *2010; Photomed Laser Surg*. 2010 Aug;28(Suppl 1):S41–S52. https://doi.org/10.1089/pho.2009.2647.

31 Nayyer N, Tripathi T, Gopal R. Effect of photobiomodulation on external root resorption during orthodontic tooth movement—a scoping review. *Laser Dent Sci*. 2019;3(4):219–226. https://doi.org/10.1007/s41547-019-00072-9.