Original article

To evaluate the effects of Low-level laser therapy (LLLT) on wound healing of extraction socket: A systematic review

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Abstract:

Background: Low power laser therapy or low-level laser therapy (LLLT) is relatively novel and has demonstrated tremendous advantages in dentistry which includes reduction in post-surgical pain as well as swelling and also accelerates wound healing and helps in bone regeneration etc. ***Objective:*** This systematic review aimed to find out whether low-level laser therapy promotes tooth extraction wound healing. ***Materials and Methods:*** Literature was searched from January 2010 till 31 December 2020 using PubMed, Scopus, and Web of science. Further findings were done from gray literature google scholar, and Research Gate using Low-level laser therapy, photobiomodulation, wound healing, extraction socket healing, cold laser, biostimulation, low-level laser irradiation, and phototherapy. Any article that reported effects of low-level laser therapy on wound healing was included. 19 studies fulfilled the criteria and were included for this systematic review. Quality assessment was done for each article using Joanna Briggs Institute (JBI) checklist for analytical cross-sectional studies. ***Results and Discussion:*** Throughout the search, approximately 22,808 relevant articles were found. Out of which 50 articles fulfilled the selection criteria. 31 articles were excluded because that did not fulfill inclusion criteria. 19 articles were included for this systematic review that compared the effects of low level-laser therapy on wound healing after extraction of a tooth. ***Conclusion:*** Overall, this systematic review concluded that low-level laser therapy enhanced the process of wound healing after extraction of teeth but most of the research was conducted on animals. Further research is needed to investigate the biostimulatory effects of low-level irradiation on wound healing after extraction of a tooth.

Keywords: Low-level laser therapy, photobiomodulation, wound healing, extraction socket healing, cold laser, biostimulation, low-level laser irradiation, and phototherapy

Bangladesh Journal of Medical Science Vol. 22 No. 03 July'23 Page : 585-597
DOI: https://doi.org/10.3329/bjms.v22i3.65328

Introduction:

Currently, the use of lasers in dental practices is common [1]. LLLT has made its way in dentistry and is being used for the prevention of inflammatory signs and symptoms post-surgically and also gaining popularity for its ability to heal wounds faster and helps in bone regeneration [2]. LLLT is non-surgical and also have positive outcomes [3]. LLLT have also been suggested for accelerating orthodontic tooth moments and reducing the time [4]. Low level lasers are unlike other lasers which are used for cutting or ablation or coagulation of the tissues because

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it consumes light at lower energy level that is red and near infrared (NIR) light and produces bio-stimulatory effects [5]. The term laser is short form of 'Light Amplification by the Stimulated Emission of Radiation' [6].

Historically, soon after the creation of ruby laser in 1960, LLLT which is also referred to as photobiomodulation came into existence in its contemporary form followed by invention of helium neon laser (HeNe) in 1961 [5]. Since 1960 after the development of therapeutic laser system for medical and cosmetics purposes, positive effects of low powered irradiation were seen on wound healing and pain relief [7]. After the invention of first working laser in 1967 in Semmelweis University, Budapest, Hungary, Dr. Endre Mester wanted to check the effects of LLLTon cancerous cells in mice. He divided the mice into 2 groups and shaved their backs. One group was exposed to ruby laser with the power of 694-nm. Surprisingly, group that was exposed to laser did not get cancer cell destruction but the hair on their back started to grew faster when compared with untreated group [8]. This experiment showed the first biostimulatory effect of laser therapy [8]. As soon as Mester found this effect of LLLT he tried these discoveries on patients with non-healing skin ulcer and found very positive results [9] [5].

There are three main properties of lasers, which are being used by the medical community monochromatic emission, collimation and coherence [10]. The light produced from a laser is *monochromatic*, specifically; it is of one wavelength (color) [6]. On the contrary, light emitted from a bulb is a mixture of numerous different wavelengths (colors). This is the 2nd important property that can differentiate lasers from conventional light. Laser produces light that is extremely *collimated.* [10]. This advocates that there is a probability of accomplishing enormous power concentrations into a thin stream of light [11]. Coherence is one of the fundamental characteristic of lasers [12]. The waves of light rays discharged have the same relative level. This property is also called as 'pencil beam' because laser concentrates at a spot which is of very low divergence in order to achieve the results of their energies at great distances[5].

Once radiations reaches to the target tissue, four distinct interactions can occur that is absorption, scattering, transmission and reflection [6]. Light rays are absorbed by molecules recognized as chromophores. The exact mechanism that produces therapeutic action of LLLT is still not very well-known but it seems that LLLT effects are of the broader range at the cellular, molecular and tissue levels [5]. LLLT

As mentioned in earlier researches, laser energy has both inhibitory and excitatory outcome on the progression of wound healing [13]. However, exact mechanism is unknown due to the lack of knowledge concerning best healing parameters, doses of laser radiation required and its mode of action [14]. Medrado et al, (2003) found that laser energy proliferated collagen deposition, decreased inflammatory reaction and improved deposition of myofibroblasts on cutaneous wounds. It had been advised that the doses of laser radiation at 8J/cm² were more effective than 4J/cm² [15]. Various researchers observed, at molecular level, when HeNe lasers were applied at higher doses of i.e. 10 J/cm² it produced harmful effects but the same laser at lower doses i.e. 5 J/cm² speeded up the wound healing by their action on mitochondria which stimulated cell proliferation and also speeded up the migration of fibroblasts at the site of wound [16] [17]. Whereas, GaAs laser produced excitatory effects on fibroblasts at 3J/cm² [18]. Er:YAG lasers showed their best effects at dose of 3.37J/cm² [19].

In former researches, it was established that light entered to a depth of 0.5-50 mm and that occurred at the wavelength of 630-780 nm and revealed outstanding potentials for wound healing [20] [21]. According to Karu et al (1993) the wavelength of 660nm is being most effective [22]. Many researches had been published stating that laser therapy at wavelength of 660 nm improvised wound healing superficially for example acne or skin conditions [13]. The optical window for electromagnetic spectrum that causes effective penetration lies in the range of red and NIR wavelengths (600-1070nm), maximum effects are observed in this range. The ranges of 600-700 nm wavelengths are preferred for the treatment of superficial tissues whereas, the ranges of 780-950 nm wavelengths penetrate extra, and are choice of treatment for deeper-seated tissues. It is well known that if the irradiation application is not adequate or time of application is also less then there won't be any response. Abergel et al., established that the 632.8 nm HeNe laser did not show any result on cellular proliferation of fibroblasts. On the other hand, other researchers observed that with the exposure of 904nm GaAs laser there was increase in proliferation of human fibroblasts [5]. With one dose of diode laser therapy, instant, dramatic, continuous pain-relieving effects were produced on recurrent aphthous stomatitis (RAS) lesions [23]. High power laser such as a 940nm laser is used to ablate or cut, and coagulate soft tissues, in a contact mode to achieve accuracy in surgery. Pulsed modes have also been created through which variety of soft tissues surgeries can be accomplished without local anesthesia. Interestingly, when high power diode lasers are in defocused mode, they work as low power laser [23] . The benefit of this version of laser is that the same device can be used as high or low power laser. Diode laser in defocused mode works on physical limits that only produce biostimulatory effect without damaging the tissue. With the application of defocused diode laser, analgesic effects were produced and it also accelerated wound healing [24]. Diode lasers with wavelengths of 940–980 nm are effective in improving wound healing, reducing postoperative inflammation and accelerating regeneration [25]. LLLT can be effective in enhancing wound healing by improving the levels of intercellular mediators[26].

It was suggested that the range of 600-700nm wavelength of laser light was preferred to treat superficial tissues whereas 780-950nm wavelength penetrated deeper and preferred choice for treating deeper seated tissues, but the evidence was not strong. Further investigation was needed because the current available evidence was not very clear. Therefore, this review article summarized which parameter of laser had the most beneficial effect on wound healing after tooth extraction. The aim of this systematic review was also to evaluate the effects of LLLT on wound healing of extraction sockets. The study hypothesis was that LLLT had photobiostimulatory effect on extraction sockets and it accelerated wound healing.

Methods amd Materials:

The aim of this systematic review was to evaluate the effects of LLLT on wound healing of extraction sockets. The specific questions that needed to be answered for this review were following the format approach as recommended in PRISMA checklist guideline 2020. Literature was searched in multiple databases. PICO framework was used to include studies for this systematic review. The Population for current systematic review was either animals or human who had extraction; Intervention was LLLT after tooth extraction; Comparison of irradiated extraction socket with control group and the outcome was to assess the impact of LLLT on wound healing after tooth extraction. Components of PICO format is described in table 1. The key words that were used were Low-level laser therapy, photobiomodulation, wound healing, extraction socket healing, cold laser, biostimulation, low-level laser irradiation, and phototherapy. The research subject was "whether low level laser therapy affected wound healing after extraction of a tooth?"

Table 1: ***Describes the component of PICO***

Pico component	
P	Animals or human who had extraction
I	LLLT after tooth extraction
C	Irradiated extraction socket was compared with control group
O	Analysis of impact LLLT on wound healing after extraction of a tooth

Search Strategy

A comprehensive search of electronic database was carried out for literature in English January 2010 till December 2020 primarily from PubMed, Scopus, and Web of science. The following MESH keywords were used Low-level laser therapy, photobiomodulation, wound healing, extraction socket healing, cold laser, biostimulation, low-level laser irradiation, and phototherapy. Further findings were done from gray literature google scholar, and ResearchGate. Apart from all search engines reference lists of shortlisted articles were also reviewed for further relevant research.

Eligibility Criteria

Articles which were used for this systematic review consisted of publications from past ten years (January 2010 till December 2020) Eligibility criteria for insertion in this research were authentic in vivo studies on the effects of LLLT on wound healing of extraction socket. The inclusion and exclusion criteria can be seen in table 2.

Table 2: ***Inclusion and Exclusion criteria for this systematic review***

Inclusion criteria	Exclusion criteria
In vivo studies on the effect of low level-laser therapy on wound healing after extraction within the last 10 years. Research must have compared the effects of LLLT on wound healing on placebo and experimental groups after extraction.	Studies in which wound healing was not examined. Studies in language other than English. Studies with insufficient data. Studies that didn't compare the data. Studies with less than 10 subjects.

Study Selection

The sum of all articles found was 22,808 that include from PubMed (n=16), Scopus(n=5380) Web of science (n=12). The further studies identified via other sources such as gray literature google scholar, and ResearchGate (n=17,400). All the research was primarily added to a software EndNote(X8) and same research were removed (n=9195). Further records excluded because of irrelevant data were 8155. The remaining records were further screened, and 19 studies were selected for this systematic review. All the headings and summaries were scrutinized and selected according to eligibility criteria. Figure 1 is the flow diagram indicating the process of data extraction.

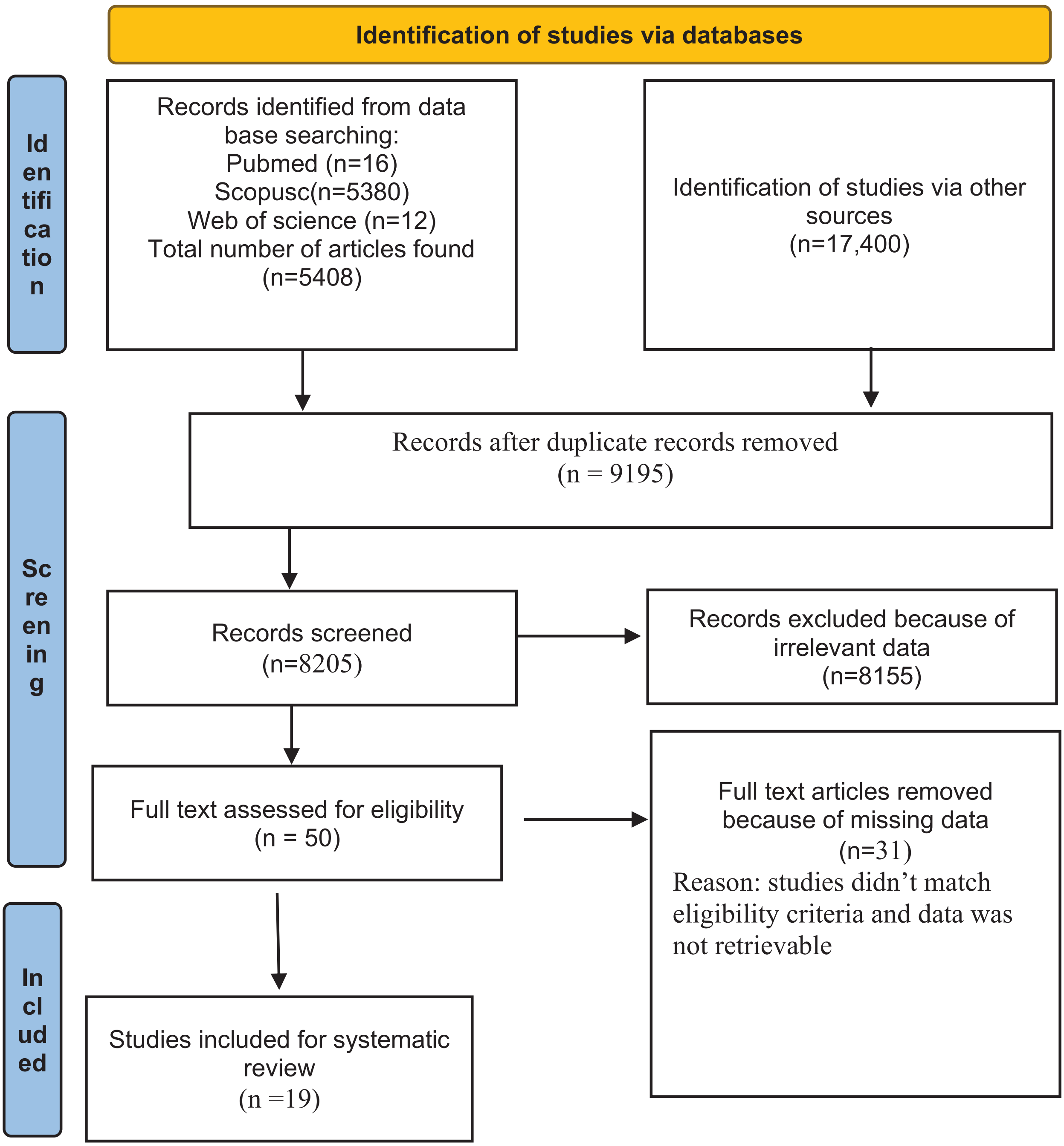

Figure1 : Flowchart showing selection of studies. Total number of studies found were 9083 that include from PubMed (n=16), Scopus (n=5380) and Web of science (n=12). The additional studies found through other sources were (n=17,400). The Reference Management Software Package (Endnote X8) was used to check the duplication and 9195 studies were removed. Studies (n=8155) were excluded because of irrelevant data. The remaining (n=50) was further screened and finally (n=19) studies were selected for full text read.

Data abstraction

Once the initial search was done articles were explored by all the authors for appropriateness whether the article fulfills the criteria of our research question. Two Feld based experts (M.K. and I.Q.) worked independently on abstraction and duplication from each study using a standardized form. The information relating effects of low-level laser therapy on wound healing after extraction of a tooth was recorded. Out of those 19 articles, 9 studies were based on rats, 7 were based on humans and 3 were based on rabbits as subject. Table 3 summarizes the list of selected studies, the year it was published, sample characteristic; number of subjects enrolled for the studies and the country the study was done.

Quality assessment

The quality of all the included articles was assessed by two independents researchers (M.K. and I.Q.). Joanna Briggs Institute (JBI) critical appraisal checklist for analytical cross-sectional studies was used to establish risk of biasness in included article (Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies report- ing prevalence and cumulative incidence data. Int J Evid Based Healthc. 2015;13(3):147–53.). JBI appraisal checklist for analytical cross-sectional studies is based on 8 questions and each of them is analyzed by giving score 1 or 0 (yes=1), (no=0), and (unclear or not applicable=0). The over-all score for individual article was presented as percentages and article was

Table 3: ***Risk of biasness in current study***

Risk of biasness according to JBI Checklist											
S.no.		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**OVERALL**	**WEIGHT (%)**
	Göl, Özkan et al., [27]	1	1	1	1	0	0	1	1	+	75 %
	Ribeiro, Monteiro et al., [28]	1	1	1	0	0	0	1	1	-	62.5%
	John, Mohanty et al., [29]	0	1	0	0	0	0	0	1	X	25%
	Khalil and Noureldin [30]	1	1	1	0	0	0	1	1	-	62.5%
	Çırak, Özyurt et al., [31]	1	1	1	1	0	0	1	1	+	75%
	Comunian, Custódio et al., [32]	1	1	1	1	0	0	1	1	+	75%
	Noda, Aoki et al., [33]	1	1	1	1	0	0	1	1	+	75%
	Hamad, Naif et al., [34]	1	1	1	1	0	0	1	1	+	75%
	Mergoni, Vescovi et al., [35]	1	1	1	1	0	0	1	1	+	75%
	Romão, Marques et al., [36]	1	1	1	1	0	0	1	1	+	75%
	Batinjan, Zore et al., [37]	1	1	1	0	0	0	0	1	-	50%
	Halon, Donizy et al., [38]	1	0	0	1	0	0	1	1	-	50%
	Park, Ahn et al .[39]	1	1	1	1	0	0	1	1	+	75%
	Park and Kang [40]	1	1	1	1	0	0	1	1	+	75%
	Korany, Mehanni et al., [41]	1	1	1	1	0	0	1	1	+	75%
	Paschoal and Santos-Pinto [42]	1	1	1	0	0	0	0	1	-	50%
	Fukuoka, H., et al [43]	1	1	1	1	0	0	1	1	+	75%
	Mozzati, Martinasso et al., [44]	1	0	1	1	0	0	1	1	-	62.5%
	Mozzati, Martinasso et al [45](hepatic failure)	1	0	1	1	0	0	1	1	-	62.5%

Risk of Bias legends:

1. Were the criteria for inclusion in the sample clearly defined?
2. Were the study subjects and the setting described in detail?
3. Was the exposure measured in a valid and reliable way?
4. Were objective, standard criteria used for measurement of the condition?
5. Were confounding factors identified?
6. Were strategies to deal with confounding factors stated?
7. Were the outcomes measured in a valid and reliable way?
8. Was appropriate statistical analysis used?

+ Low Risk
- Moderate Risk
x High risk characterized according to different degrees of risk of bias (high risk of bias if 20–50% items scored yes, moderate risk of bias if 50–80% items scored yes, and low risk of bias if 80–100% items scored yes as per JBI checklist) as shown in Table 3 and Fig. 2.

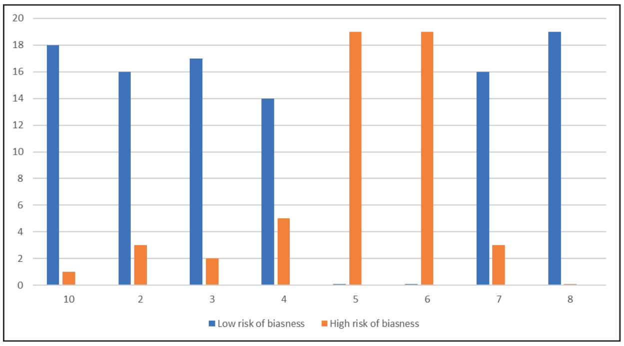

Figure 2: Items of JBI Critical Appraisal Checklist of involved articles. JBI appraisal checklist for analytical cross-sectional studies is based on 8 items and each question is judged by scoring (yes=1), (no=0), and (unclear or not applicable=0). The overall score for each individual question of all the studies is presented in this chart.

Laser parameters in the selected studies varied considerably in terms of their wavelength, power, mode and dosages. Variation in laser types were also observed. The majority of the research was done with diode lasers. Table 4 denotes a list of selected studies for this systematic review.

Ethical clearance:

No ethical clearance was required for this systematic review article.

Results:

A total of 19 studies were included in this systematic review. Table 4 and table 5 summarize all the research, duration of low-level laser application, number of sittings done and clinical outcome of the laser therapy. Out of those 19 studies 2 studies are from Turkey, 4 from Brazil, 1 from India, 2 from Egypt, 2 from Japan, 1 from Iraq, 3 from Italy, 1 from Croatia, 1 from Poland and 2 from Korea. Mostly all the research was done with diode laser of different wavelengths and power and dose. Table 6 summarizes the sessions of low-level laser application and their clinical outcome.

Table 4: ***Summary the list of selected studies, year of publish, subjects and their quantity on which this study was done and country.***

Author	*Year*	*Sample characteristics*	*No. of subjects*	*Country*
Göl, Özkan et al., [27]	2020	Wistar-Albino rats (Bisphosphonate Treatment)	33	Turkey
Ribeiro, Monteiro et al., [28]	2020	Male Wistar rats (Exposed to cigarette smoke)	60	Brazil
John, Mohanty et al., [29]	2020	Human (healthy)	62	India
Khalil and Noureldin [30]	2019	Rabbits (healthy)	36	Egypt
Çırak, Özyurt et al., [31]	2018	Albino Wistar rats (healthy)	30	Turkey
Comunian, Custódio et al., [32]	2017	Rabbits (healthy)	18	Brazil
Noda, Aoki et al., [33]	2016	Sprague Dawley rats (healthy	27	Japan
Hamad, Naif et al., [34]	2015	Rabbits (healthy)	20	Iraq
Mergoni, Vescovi et al., [35]	2015	Sprague–Dawley rats (infused with intraperitoneal zoledronic acid)	30	Italy
Romão, Marques et al., [36]	2015	Human (healthy)	20	Brazil
Batinjan, Zore et al., [37]	2013	Human (healthy)	150	Zagreb, Croatia
Halon, Donizy et al., [38]	2013	Human (HIV infected)	27	Poland
Park, Ahn et al.,[39]	2013	Sprague-Dawley rats (healthy)	24	Korea
Park and Kang [40]	2012	Sprague-Dawley rats (Diabetic)	48	Korea
Korany, Mehanni et al., [41]	2012	Swiss Albino rats (exposed to 6 Gy gamma radiations)	30	Egypt
Paschoal and Santos-Pinto [42]	2012	Human (healthy)	14	Brazil
[43]	2011	Healthy Wistar Rats (healthy)	42	Japan
Mozzati, Martinasso et al., [44]	2011	Human (healthy)	10	Italy
Mozzati, Martinasso et al [45](hepatic failure)	2011	Human (hepatic failure)	12	Italy

Table 5. Parameters of lasers used by various researchers for their studies.

Author	*Year*	*Type of laser*	*Company*	*Wavelength*	*Power*	*Mode*	*Dose*
Göl, Özkan et al[27]	2020	GaAlAs diode laser	Cheese; Wuhan Gigaa Optronics Technology Co., Ltd, Wuhan, China	810 nm	0.4W	Not mentioned	16 J/cm2
Ribeiro, Monteiro et al.,[28]	2020	GaAIAs diode laser	Photon Laser, DMC Equipaments, São Carlos, SP, Brazil	980 nm	0.03W	Not mentioned	54 J/cm
John, Mohanty et al.,[29]	2020	Soft tissue diode laser	Photon Plus Series	980 nm	0.1W	NR	7.5J/cm2
Khalil and Noureldin [30]	2019	Diode laser	Lambda SpA, Brendola, Italy	980 nm	0.5W	Continuous	Not mentioned
Çırak, Özyurt et al.,[31]	2018	He_Ne laser GaAlAs diode laser	LABpen MED 30; Therapielaser, Graz, Austria (BTL Laser, 2000; BTL Industries Ltd, Hertfordshire, UK)	HeNe: 655nm GaAlAs: 830nm	HeNe: 0.03W GaAlAs: 0.1W	Continuous Continuous	HeNe: 6 J/cm2, and 10 J/cm2 GaAlAs: 6 J/cm2, and 10 J/cm2
Comunian, Custódio et al.,[32]	2017	light emitting diode (LED) GaAlAs diode laser	MMOptics, São Paulo-SP, Brazil	infrared 830 nm 780 nm	Not mentioned	Not mentioned	30 J/cm2 30 J/cm2
Noda, Aoki et al [33]	2016	GaAlAs diode laser	Lumix 2TM HFPL, Fisioline s.r.l., Verduno, Cuneo, Italy	904–910-nm	1.02 W	Pulsed	61.2 J/cm2
Hamad, Naif et al.,[34]	2015	GaAlAs diode laser	A.R.C. laser GmbH, Germany	808 nm	0.9 W	Continuous	1459 J/cm2
Mergoni, Vescovi et al [35]	2015	Nd:YAG Laser	Fidelis®, Fotona, Slovenia	1064nm	1.25 W	Pulsed	14.37 J/ cm2
Romão, Marques et al.,[36]	2015	GaAlAs diode laser	Twin Flex; MMOptics Ltda, Sa˜o Carlos, SP, Brazil	808 nm	0.1W	Continuous	75 J/cm2
Batinjan, Zore et al [37]	2013	Diode Laser HF	Hager and Werken GmbH and Co. Duisburg, Germany, 2009	660 nm	0.05W	Not mentioned	Not mentioned
Halon, Donizy et al., [38]	2013	GaAlAs diode laser	Doris CTL 1106 MX Laser, Warsaw, Poland	820 nm	0.2W	Continuous	6 J/cm2
Park, Ahn et al., [46]	2013	GaAlAs diode laser	Diobeauty30®; Diotech, Busan, Korea	980 nm	0.01W	Continuous	13.95J/cm2
Park and Kang [47]	2012	GaAlAs diode laser	Diobeauty-30®, Diotech, Busan, Korea	980 nm	0.01W	Continuous	13.95 J/cm2
Korany, Mehanni et al., [41]	2012	GaAlAs diode laser	Not mentioned	830 nm	0.075W	Continuous	Not mentioned
Paschoal and Santos-Pinto [42]	2012	GaAlAs diode laser	Thera Lase; DMC São Carlos, SP, Brazil	830 nm	0.1 W	Not reported	60 J/cm2
Fukuoka, Daigo et al [43]	2011	CO2 Laser HLLT (high level laser therapy) LLLT (low level laser therapy)	PanalasCO5S; Panasonic Shikoku Electronics Co., Ltd., Osaka, Japan	10.6 μm 10.6 μm	1.0 W 1.0 W	Continuous Pulsed (Σ-mode)	152 J/cm2 40 J/cm2
Mozzati, Martinasso et al [48]	2011	GaAs laser diode laser	Lumix 2 HFPL; Fisioline, Cuneo, Italy	904-910nm	0.2W	Super Pulsed	180 J/cm2
Mozzati, Martinasso et al [45] (Hepatic failure)	2011	GaAs laser diode laser	Lumix 2 HFPL; Fisioline, Cuneo, Italy	904-910nm	0.2W	Super Pulsed	180 J/cm2

Table 6: Summary of all the research, duration of low-level laser application, number of sittings done and clinical outcome of the laser therapy.

Author	*Laser applied for duration in seconds*	*No. of sessions in days*	*Clinical outcome*
Göl, Özkan et al.,[27]	91 seconds	2nd, 4th, 6th, 8th, 10th 12th, 14th	Increased in the levels of CD31, promoted wound healing.
Ribeiro, Monteiro et al.,[28]	0.42 s	1st, 2nd, 3rd, 4th	Increased level of bone biomarker RANKL, RANK and OPG, but cigarette smokes had negative effects.
John, Mohanty et al [29]	200 seconds	1st	Extraction socket healed faster in laser-irradiated group compared to cryotherapy group.
Khalil and Noureldin. [30]	60 seconds	SL: 1st day ML: 1st, 3rd, 6th, 9th, 12th	SL and ML both has bone stimulatory effects on wound healing after extraction.
Çırak, Özyurt et al., [31]	Group B1= 200 seconds Group B2= 333 seconds Group C1= 60 seconds Group C2= 100 seconds	1st, 2nd, 3rd, 4th, 5th, 6th,7th	Both the laser group showed faster healing but C2 group showed extensive systematized bone formation at energy dose of 10 J/cm2
Comunian, Custódio et al [32]	Group 1= 150 seconds Group 2= 50 seconds	2nd, 4th, 6th, 8th, 10th, 12th, 14th, 16th, 18th	photobiomodulation was observed in both the groups treated with lasers and LED.
Noda, Aoki et al., [49],	60 seconds	1st, 2nd, 3rd, 4th, 5th	Epithelialization and bone repair was improved.
Hamad, Naif et al., [50]	300 seconds	1st, 4th, 7th, 10th, 12th	Large number of mature bones, thick collagen fibers, and number of blood vessels were prominent in irradiated sockets compared to controlled.
Mergoni, Vescovi et al., [35]	300 seconds	1st , 2nd, 4th, 6th	Irradiated sockets showed greater number of octeocalcin protein which is responsible for improvised bone healing.
Romão, Marques et al., [36]	150 seconds	1st, 2nd, 3rd and 4th	Low level laser phototherapy can be useful in bone repair.
Batinjan, Zore et al.,[37]	180 seconds	1st	Post-surgical complications were reduced and improved wound healing
Halon, Donizy et al [51]	Not reported	1st, 2nd, 3rd, 4th and 5th	Patients infected with HIV virus demonstrated new blood vessels formation hence speeded up wound healing.
Park, Ahn et al., [46]	300 seconds	3rd and 7th day	Increased duration of irradiation is directly proportional to bone formation and mineralization.
(Park and Kang [47]	60 seconds	1st, 3rd, 5th, 7th and 14th	Improvised wound healing in extraction socket of both diabetic and healthy rats.
Korany, Mehanni et al., [41]	Not reported	Not reported	LLLTaccelerated wound healing, increased bone trabeculae, mature collagen fibers were found.
Paschoal and Santos-Pinto [42]	51 seconds	1st, 2nd, 3rd	Visually no significant difference was found. No histological analysis was done.
Fukuoka, Daigo et al., [43]	HLLT: 30 seconds LLLT: 15 seconds	1st (HLLT), 2nd (LLLT)	Bone repairs were comparatively better in laser irradiated group; alveolar bone height was more in laser irradiated group.
Mozzati, Martinasso et al., [48]	900 seconds	1st, 3rd, and 5th	Increased in collagen I and collagen III, decreased post-operative pain, swelling and trismus.
Mozzati, Martinasso et al., [52] (hepatic failure)	900 seconds	1st, 3rd, and 5th	Increased collagen III was found on day 7 after extraction suggesting increased osteogenic process.

Discussion:

Since 1960, LLLT with parameters have made its way in diverse medical and dental world [53]. Another name for LLLT is photobiomodulation or biostimulation [54]. This involves the utilization of low levels of red and near infrared light for the purpose of treatment of many ailments [30]. LLLT does not raise the temperature of the targeted tissue above 1□C. That's why it is also referred as cold laser [54]. The possible mechanism of action reported by various authors, that produces biological effect is the action of low level of lasers on cell's mitochrondia [50]. Mitochrondial stimulation causes increase in adenosine triphosphate (ATP) production [47]. It is assumed that this increased adenosine triphosphate (ATP) increases the cellular activity [50]. Thus, resulting in stimulation of transcription factors and also increases the growth factors [29]. These transcription factors activate protein production resulting in cellular proliferation and migration [54]. This cellular proliferation and migration promotes collagen metabolism resulting in enhanced fibroblastic and osteoblastic activities resulting in improved granulation tissue formation and promotes the process of wound healing [47 55].

The outcome of LLLT depends on various elements, for example its type, wavelength, power, duration, and dose. Initially HeNe laser showed the stimulatory effect but now semi-conductor diode lasers have gained the fame [5]. Out of 19 articles, which were reviewed in this study, 14 were based on diode lasers to see the effects of LLLT on wound healing after tooth extraction.

Göl, Özkan et al., [27] experimented on forty male Wistar-Albino rats, which were first treated with zoledronic acid that is the most common choice of drug in treating cancer. The side effect of this drug is biphosphonate-related osteonecrosis of the jaw (BRONJ) and may result in impaired wound healing after oral surgery. The first molar tooth was extracted under general anesthesia and LLLT was applied after 48 hours of surgery. These irradiations were repeated after every 48 hours for 15 days. Rats were sacrificed on the 4th and 8th week with overdose of sodium pentobarbital. Immunohistochemical analysis was done to check the levels of CD31 and matrix metalloproteinase-2 (MMP-2) It was observed that LLLT increases the levels of CD31 in groups of rats that were at risk of BRONJ as compared to controlled groups. In her study LLLT showed positive outcome on wound healing [27].

Ribeiro, Monteiro et al., [28] used 60 male Wistar rats for her experiment to see the effect of LLLT on alveolar sockets of rats that were exposed to cigarette after tooth extraction. Cigarette smoke has nicotine with toxic effects, which may cause impairment in healing process. In their study they observed the levels of bone biomarkers that are receptor activator of nuclear factor-kappa B (RANK), RANK ligand (RANKL), and osteoprotegerin (OPG). Quantitative polymerase chain reaction (Q-PCR) and reverse transcription (RT) analysis were done to check the levels of these bone biomarkers. 60 rats were divided into 4 groups, Experimental I, Experimental II, Experimental III and Controlled group. Each group was subdivided into 3 groups that consisted of 5 rats. Atraumatic extraction of the maxillary right first molar was done under general anesthesia. After controlling the blood from extraction socket, low level laser irradiation was applied to experimental I and experimental III groups. Laser parameters are described in table 4. Irradiation was applied every day for 3 days. The subdivided groups were euthanized on the 3rd, 7th and 14th day following tooth extraction for Q-PCR and RT analysis. It was observed that bone biomarkers RANKL, RANK and OPG were increased in irradiated group as compared to controlled group. However, cigarette smokes inhalation had negative effects on overall healing [28].

John, Mohanty et al [29] compared the effects of LLLT and cryotherapy on pain and wound healing in 62 healthy humans undergoing premolar extractions for orthodontic treatment. Subjects were divided into 2 groups and each group consisted of 31 participants. Laser irradiations were applied on group 1b and group 1a as controlled sites. Single session of LLLT was done for 200 seconds on 5 points that was distal, mesial buccal, palatal/lingual and at the center of the socket. Wound healing was assessed on day 4th, day 7th and day 14th. It was observed that LLLT had positive effects on both pain and wound healing [29].

Khalil and Noureldin [30] compared the effects of single dose and multiple doses of LLLT on 36 rabbits which were divided in 3 subgroups: C group (control), SL group (single laser) and ML group (multiple laser). Laser was applied 60 seconds immediately after extraction in SL group and ML group received irradiation immediately after extraction followed by every 72 hours for 12 days. Histological analysis of bone was done in the 3rd week and 6th week. They observed that single session of laser irradiation was as effective as multiple sessions on bone forming cells [30].

Çırak, Özyurt et al., [31] compared the effects of gallium-aluminum arsenide lasers and helium-neon lasers after tooth extractions. Experiments were done on 30 rats and their incisors were extracted. Rats were divided into 5 subgroups. Group A was controlled group, whereas Group B was exposed to helium-neon lasers. Group B was subdivided into B1 and B2. Group B1 received 6 J/cm2 and Group B2 received 10 J/cm2 for 7 days. Similarly Group C was exposed

to GaAlAs laser which further divided in Group C1, which was also exposed to 6 J/cm2 and group C2 that was exposed to 10 J/cm2 for 7 days. At the end of the 30th days, all the animals were sacrificed for histological evaluation. It was concluded that LLLT was an effective technique for increasing wound healing after tooth extraction. Doses of 10 j/cm2 in both types of lasers had a better outcome. Since gallium-aluminum arsenide lasers penetrate more compared to helium-neon lasers it is assumed that gallium-aluminum arsenide lasers can show much successful results in a month [31].

Comunian, Custódio et al., [32] compared the effects of low-level lasers with LED. For this experiment 18 rabbits were divided into 3 groups. Rabbits in group 1 were treated with LED after 48 hours of premolar extraction. Whereas rabbits in group 2 were exposed to low level laser radiation after 48 hours of extractions. Rabbits in group 3 were untreated controlled group. Surgical extraction of the first lower right premolar was done. Both the groups received 9 sessions of irradiation respectively after each 48 hours. Irradiation with laser and LED both were effective in photobiomodulation, whereas, only LED showed favorable effect on bone repair [32].

Noda, Aoki et al., [49], used HiFP for evaluation of wound healing after extractions. Rats were treated with HiFP low level diode laser for 1 minute after immediate extractions. Clinical analysis was done on 0, 3rd and 7th day and histological analysis was done on 3rd day and 7th day. It was concluded that HiFP LLLT stimulated epithelialization and osteogenesis in sockets after tooth extraction. The study indicated that HiFP low-level diode laser irradiation promotes epithelialization and bone formation in tooth extraction sockets, possibly through activation of both cell proliferation and differentiation. HiFP LLLT may improve early stage wound healing of tooth extraction sockets [49].

Hamad, Naif et al.,[50], Mergoni, Vescovi et al., [53], and Romão, Marques et al., [36] studied the effects of different kind of LLLT on different subjects for example rabbits, rats and human. They examined the wound healing of socket after extraction of a tooth. Different parameters of lasers were used for their studies but all of them concluded that LLLT had positive effects on wound healing after extraction of teeth [50 53 36].

Batinjan, Zore et al., [37] and Halon, Donizy et al., [38] did their studies on human. [38] checked the effects of LLLT on extraction sockets of patients who were infected with human immunodeficiency virus. It was observed that LLLT augmented new blood vessels formation and accelerated wound healing. Batinjan, Zore et al [37] also concluded that LLLT reduced post-surgical problems such as pain, swelling and halitosis significantly. Wound healing was without any complication as compared to controlled group [37, 38].

Park and Kang [40] checked the effects of diode laser on extraction socket of diabetic rats. The extraction sockets of diabetic rats and normal rats were irradiated multiple time post surgically. Histological analysis showed improvement in wound healing of extraction socket and more new alveolar bone was formed [40]. Batinjan, Zore et al [46] used the same diode laser and experimented on rats to check the time related to expression of genes and protein. In their experiment, they irradiated the extraction socket for 300 seconds for 3 or 7 days. They concluded that increased duration of irradiation is directly proportional to bone formation and mineralization.

Other studies also concluded that low level of laser therapy increases wound healing. Paschoal and Santos-Pinto [42] assessed wound healing visually and no apparent changes were observed [42]. Table 6 summarizes the details of all the studies with the observations each author concluded.

Conclusion:

This systematic review concludes that LLLT can enhance wound healing after tooth extraction. Different parameters of lasers was part of this systematic review and almost all of them showed positive impact on wound healing. The biological effect of laser depends on its wavelengths. LLLT used by researchers were in the range of 780-950nm. However, most of the studies were done on animals, therefore more clinical studies on humans are needed to prove the concept. Once proven to be effective on humans, LLLT can be a good choice for patients to fasten wound healing after extraction especially in patients with systemic conditions that affect natural healing. In addition, low level laser can also be beneficial to replace analgesic post extraction.

Conflict interests

The author states that there is no conflict of interest.

Funding

The author states that they do not have a source of funding.

Author's contribution

All authors contributed to the writing of this systematic review article

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