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REVIEW ARTICLE

Photobiomodulation and salivary glands: a systematic review

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Abstract
To date, there is no compilation of evidence-based information associating photobiomodulation effect and salivary glands. This systematic review aims to assess photobiomodulation effect of low intensity laser on salivary glands in the presence of systemic diseases. MEDLINE databases were searched in duplicate through December 2018. In vivo studies and clinical trials were included if photobiomodulation was performed in salivary glands of animal (rat or mice) or human in the presence of systemic disease. The methodological quality was assessed in duplicate using the modified Newcastle-Ottawa scale (NOS). Search strategy identified 483 potentially eligible articles, and 449 were included. The Boolean search naturally leads to a high amount of works the majority of which were excluded because the analysis of the title and abstract demonstrated it was not focusing on PBM. Only 34 studies were selected for the full-text analysis, of which 5 were excluded due to non-use of photobiomodulation, 4 due to lack of control group, 2 because they were studies of cell cultures and 1 because they did not have the total of animals used. Thus, 21 papers were included for the critical evaluation of the impact of photobiomodulation on the major salivary glands; the studies used rats ($n = 10$) and humans ($n = 11$). Although studies reported an increase in the salivary rate, decrease in pain, and increase in quality of life after the PBM, the lack of standards for the application of light and reporting of the parameters, make it hard to reproduce the results. This topic is still in need for further research.

Keywords Photobiomodulation · Laser · Salivary glands · Review · Low-level laser

Introduction:

Saliva is a translucent liquid, relatively alkaline and of varying viscosity, produced in the salivary glands and secreted in the oral cavity for several functional attributions [24, 30]. Among them, saliva lubricates the mucosal surface, alkalinizes the pH, controls the microbiota, and begins the digestion of food and formation of the food bolus [30, 51]. About 99% of saliva is composed of water and the other components include electrolytes, immunoglobulins, digestive enzymes, and viscosity proteins, among other substances [5, 24, 30]. From a biochemical and functional point of view, saliva is classified as serous or mucosal. The first type is enzymatic and fluid, with the predominance of the amylase enzyme for the degradation of carbohydrates [5, 51]. The latter is characterized by a large amount of mucin and a consequent viscous appearance for agglutination of chewed foods before being swallowed [16, 30].

The salivary glands are structurally divided into major and minor. The major ones represent three pairs of glands called parotid, submandibular, and sublingual glands, while the smaller ones represent more than 500 units distributed in the following regions: lips, cheek, posterior half of hard palate, soft palate, oropharynx, and tongue. The parotid gland is almost exclusively serous, the submandibular is mixed (serous and mucous), while the sublingual and the minor are predominantly [30, 51]. The amount of saliva produced under normal conditions ranges from 1 to 1.5 l/day, with the submandibular gland accounting for 65% of that volume [24, 30, 51].

The parenchyma of the salivary glands is formed by acinus and the ductal system [23]. Acinus constitutes the saliva-producing units and are composed of acinar and myoepithelial cells [23]. These cells and the blood vessels of the glandular stroma are innervated by parasympathetic and sympathetic nerve fibers, which, respectively, have the function of stimulating and inhibiting salivary production and secretion [23,

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28]. After being produced in acinar cells, the saliva is pushed by the myoepithelial cells towards the ductal system and finally to the oral cavity [28, 51].

Saliva, in addition to its important functions in the oral cavity, is also a widely used fluid as a diagnostic medium for a variety of oral and systemic diseases, as it is a non-invasive, painless, easy to sample, and low-cost method [2].

Some local and systemic diseases or treatments, such as radiotherapy or diabetes may compromise the function of the glandular parenchyma, producing varying degrees of decrease in the salivary flow [2].

Several studies have been conducted to develop new approaches to prevent xerostomia; nevertheless, only limited progress was achieved. Subjects with dry mouth are often instructed to use mechanical stimulation (chewing gums), artificial saliva and/or lozenges as palliatives. Also, cholinergic secretagogues such as cevimeline or pilocarpine are also prescribed, but their side effects (such as excessive sweating) limits their chronical use [18].

Photobiomodulation (PBM) therapy, also known as low-level light therapy (LLLT), is a method in which the tissue is irradiated by a low power light (to avoid heating of the tissue; typically, 0.05 to 0.5 W at the source). Although the power is relatively low, the irradiance is usually 10 to 100 x (up to a few thousand mW/cm^2) higher than the one obtained from sunlight on the skin, which is about 33.6 mW/cm^2 at the near-infrared region.

PBM has proved to be effective for a variety of oral pathologies, such as temporomandibular disorder [37, 58], pain, edema and bite force [38], and impacted third molar extraction [56]. Although the mechanics of the PBM are still not fully understood, in this therapy, the photon is absorbed by the target tissue that converts it into useful energy that enhances the cell's biochemical and photochemical processes, increasing the ATP production and changing the cellular redoxstate [35, 48]. According to literature, the PBM provides photons on the mitochondria in cells; the photon energy will be absorbed by cytochrome C oxidase (Cox, the main chromophore for photobiomodulation), which is the last enzyme of the electron transportation chain, playing an essential role in mediating the electron transfer from the cytochrome c to the molecular oxygenation metabolism and production of ATP.

Some studies show the Cox absorbs photons in the red and near-infrared spectral regions. The more photons being absorbed by cytochrome c oxidase, the more oxidized (activated) state cytochrome c oxidase will be, leading to an increase in the oxygen consumption during the irradiation [20]. Such phenomena increase the mitochondrial membrane potential ($\Delta\psi m$), resulting in increased synthesis of ATP and leading to a modulation in the concentration of reactive oxygen species (ROS), Ca^{2+}, and NO [36]. Therefore, the accelerated oxygenation process and extra production of ATP will promote the regeneration of damaged cells and tissue.

Human trials also corroborate those findings Wang et al shows that irradiating the forearm of health subjects a dose-dependent increase in HbO, Hb, and CCO levels of the treated group [68]. Irradiating the brain also leads to similar results, with increase in the HbO, HbT, HbD, CCO levels and decrease in the HHb level [69]. Figure 1 shows the alterations reported by many authors attributed to the photobiomodulation of salivary glands (Table 1).

The correct choice of the light parameters depends on the application and the target tissue optical characteristics (mainly the scattering and absorption coefficients), but its optical characterization varies greatly from individual to individual and even within a single subject [14, 29, 63].[

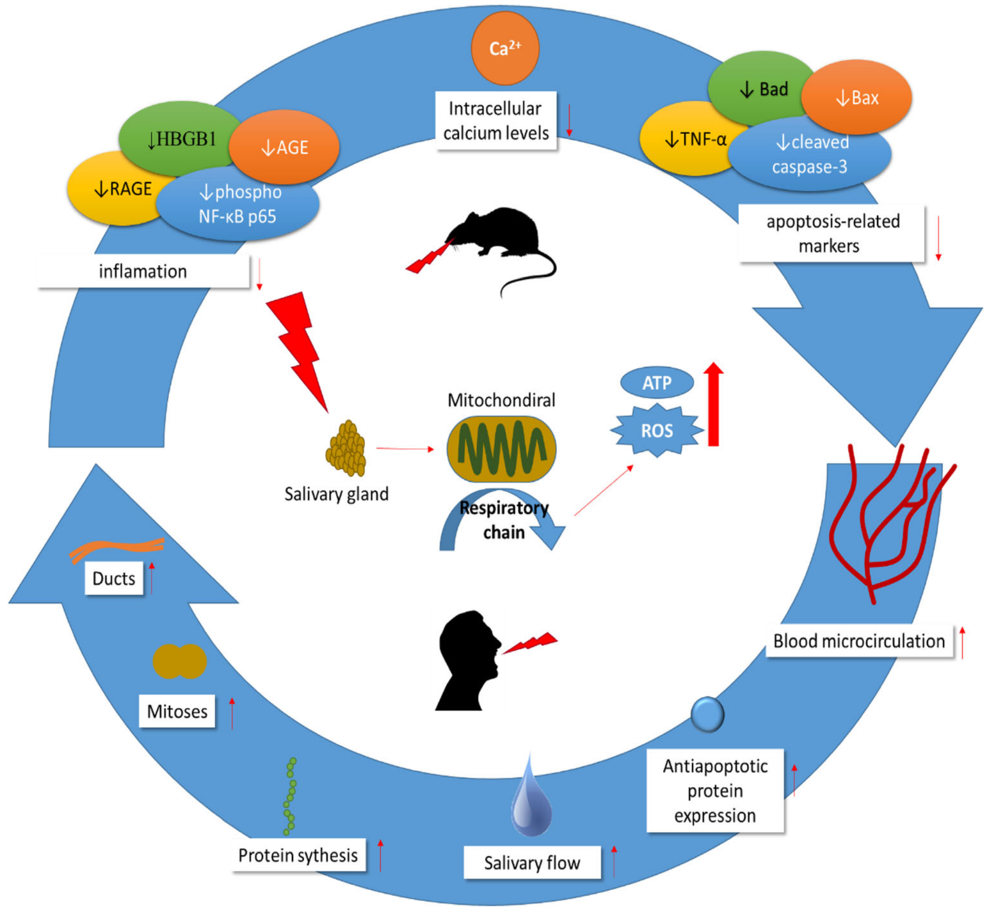
The photobiomodulation effect depends on the number of photons absorbed that is correlated to the wavelength, the rate at which the photons are delivered (power) and the correct selection of several temporal and spectral parameters [55]. When the target tissue is beneath the surface of the subject, it is also important to consider the main optical shield: the skin. The main chromophores of the skin are hemoglobin and melanin, which have high absorption bands at wavelengths shorter than 600 nm; therefore, most of the visible region of the spectrum and the ultra-violet light does not penetrate in the deeper tissue. On the other end of the spectrum, water considerably absorbs wavelengths greater than 1100 nm, leading to the so-called optical window of the tissue, ranging from the red (630 to 760 nm) to part of the near-infrared (760 to 1100 nm) wavelengths. PBM therapy usually requires light sources with wavelengths in the optical window, maximizing the penetration depth of the light [8, 47, 57].[.

Studies have shown that photobiomodulation has been widely used to improve the functionality of the larger salivary glands as well as the salivary flow. Different in vivo protocols react differently to light, depending on the various radiometric parameters and systemic condition [18, 21, 39].

Photobiomodulation therapy in larger salivary glands may result in improvement of oral complications and patients' quality of life. Also, several light parameters can be adjusted to obtain different results, such as irradiance, radiant power, radiant energy, radiant exposure (energy over the area), parameters of temporal irradiation, polarization, and wavelength. However, currently, the influence of these parameters on the impacts of photobiomodulation on larger salivary glands of humans and animal models is still unclear and not pacified in the literature, seeing as each author presents different parameters and analyses [18, 21, 39].

So far, it has been shown that PBM increases the numbers of ducts and epithelial cell mitosis and stimulates the protein synthesis in submandibular glands of rats [49, 62]. Also increased anti-apoptotic protein expression (along with decreased apoptosis-related markers) decreased inflation markers, and intracellular calcium levels have also been reported. The mitochondria stimulation also increases the

Fig. 1 Schematic diagram



availability of ATP, increases the glucose consumption (decreasing the bold glucose) by the cells, and promotes cell proliferation as well as increases blood microcirculation in the salivary glands [22, 35, 41, 42, 44], as shown in Fig. 1, Table 2.

This systematic review aims to assess the photobiomodulation effect of low-intensity laser on salivary glands in the presence of systemic diseases in animals and human.

Methods

Criteria for considering studies for this review

Type of studies

Our research question was based on photobiomodulation effect after LLLT irradiation; thus, the most adequate study design to answer this question was a systematic review of in vivo studies (animals) and clinical trials (human). Thus, we excluded case reports, review studies, protocol studies, case series, case-control, and cross-sectional and prospective cohort studies. To describe a standardized study and to reduce potential biases within the review process, this systematic review was prepared in accordance with the Review and Check checklist called Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Inclusion/exclusion criteria

The studies selected for analysis were included in the review when meeting the following criteria: (1) Studies involving photobiomodulation in salivary glands altered by systemic diseases. (2) Studies that described or allowed the calculation of the following radiometric parameters: wavelength; power; beam spot size; power density; energy density; repetition rate hertz (for pulsed light); pulse duration or duty cycle; exposure duration; and frequency of treatments; total radiant energy (joules). Absence or incomplete irradiation parameters were also excluded. (3) A minimum sample size of 10 patients (clinical trial). (4) The studies must have described at least two groups (treatment and control group).

Outcome measure

Salivary glands altered by some diagnosed systemic disease in human or animals treated by photobiomodulation procedure.

Table 1 Note: This data is mandatory. Please provide.

1st Author	Loncar [39]	Loncar [40]	Valenzuela [67]	Barbosa [6]
Motive	Xerostomia	Xerostomia	Burning mouth syndrome	Burning mouth syndrome
No. at treated	34	15/15	16/16 (2 groups)	15/15
No. at control	16		12	-
Design	Clinical trial	Clinical trial	Placebo controlled	Clinical trial
Laser source	Diode	Diode	Diode	Diode
Temporal regime	360 ns of duration/1 kHz	5.2 Hz	Cw	Cw
λ (nm)	904	685/830	815	660
Avg. power (mW)	6	30 35	1000	30
Target area (cm^2)	0.0244	0.0244	0.03	0.2826
Exposure p. site (s)	120	480/441	4/6	10
Energy p. site (J)	0.760	0.750	4/6	0.3
No. of sites	6	6	10	4
No. of sessions	10 consecutive days	10 consecutive days	4 weeks, once per week	4 weeks, once per week
Session energy (J)	4.32	14.4/14.4	40/60	--
Irradiated sites	Intraorally in noncontact mode to each salivary gland area, extra orally to the parotid and submandibular glands and intraorally to the sublingual gland	Bilaterally in noncontact mode to each salivary gland area, extra orally to the parotid and submandibular glands and intraorally to the sublingual gland	The laser was applied perpendicularly in contact with the mucosa in areas where the patient reported symptoms. Ten points spread over the area presenting symptoms were irradiated	The laser beam was directed at the areas affected by the burning sensation, with the laser fiber tip being in contact with the mucosa for 10 s. In patients with extensive burning areas, each site was irradiated for 10 s, with a distance of 1 cm between them
Outcome	↑ Salivary flow rate	↑ Salivary flow rate	↓ Pain; ↓ burning mouth syndrome score; ø salivary flow rate	↑ salivary flow rate; ↓ Burning mouth syndrome; ø TNF-α

Search strategy

Search strategies were performed in the PubMed/MEDLINE (Medical Literature Analysis and Retrieval System Online). MesH terms, keywords, and other free terms were used for searching, and Boolean operators were used in combining searches. Databases were searched through December 2018, with language restrictions (only English studies) from the studies that use laser in salivary glands, based on the following search strategy developed for MEDLINE (via PubMed): (salivary glands) OR hyposalivation) OR xerostomia) OR salivary flow) OR salivary glands) OR parotid glands)) AND (low-level laser) OR laser) OR lasers) OR photobiomodulation) OR low-level laser therapy) OR laser phototherapy). Reference lists of previous reviews and potential studies were examined (i.e., hand searching).

Assessment of validity, data extraction, and methodological quality in included studies

Two review authors (A.C.R.T.H. and A.M.D.) independently screened titles, abstracts, and full texts of the search results. Full text was obtained for all studies that appeared to meet the inclusion criteria or in instances where there was insufficient information from the title or abstract to make a clear decision. Disagreement was resolved by discussion with other review authors (R.A.P and S.K.B). Data was extracted and recorded in duplicate (A.C.R.T.H. and A.M.D.) using specially designed data-extraction forms: citation, publication status, year of publication; study location; characteristics of participants/animals; irradiation details (wavelength; power; beam spot size; power density; energy density; repetition rate hertz (for pulsed light); pulse duration or duty cycle; exposure duration; and frequency of treatments; total radiant energy (joules)); method used to assess the results; outcome measures; methodological quality of the study; and source of funding or conflicts of interest. Methodological quality was conducted using criteria for judging risk of bias in the "Risk of bias" assessment tool of Cochrane Handbook:

(1) Selection of study groups: sample size calculation, representativeness of the patients with systemic diseases, assessment of periodontal conditions, method used to

Table 2 Note: This data is mandatory. Please provide.

1st Author	Terlević Dabić [64]	Fidelix [18]
Motive	Drug-induced	Sjögren's syndrome
No. at treated	28	33
No. at control	15	33
Design	Clinical trial	Placebo controlled
Laser source	Diode	Diode
Temporal regime	5.2 Hz, 800 ms, 80% duty	Cw
λ (nm)	830	808
Avg. power (mW)	35	100
Target area (cm^2)	6.56	0.03
Exposure p. site (s)	300	40
Energy p. site (J)	10.5	4
No.. of sites	4	14
No.. of sessions	10	6 weeks; 2 per week
Session energy (J)	42	56
Irradiated sites	The laser irradiation was applied bilaterally in noncontact mode on parotid, submandibular glands, and intraorally to the sublingual gland	Extra orally at eight points in the parotid glands bilaterally, (four points in each gland), at four points in the submandibular glands (bilaterally, two points in each gland), and intraorally at two points in the sublingual glands (bilaterally, one point in each gland).
Outcome	↑ Salivary flow rate	ø Salivary flow rate; ø salivary sodium; ø salivary chlorine; ø salivary β2M; ø Sjögren's syndrome score

assess bacteremia, calibration of assessors of outcomes, and clear inclusion/exclusion criteria.

(2) Comparability of patients and management of confounders.

(3) Outcome of interest: criteria applied to evaluate bacteremia and assessment of outcomes.

(4) Statistical analysis: appropriateness and unit of analysis. If all criteria of methodological quality were fulfilled within the domains, points ("stars") were assigned to the study.

The Newcastle-Ottawa Scale was adapted for the purpose of this review, and each included study receives a maximum of 12 points. Studies with 9–12 points were considered as a high methodological quality, 6–8 points medium, and those with less than 6 points were considered to be of low methodological quality.

Data synthesis

Data were combined into evidence tables and grouped according to the type of study. A descriptive summary was performed to determine the quantity of the data by further evaluating study variations in terms of the study characteristics and outcomes.

Results

Thirty-four studies were selected for the full-text analysis, of which 5 were excluded due to non-use of photobiomodulation, 4 due to lack of control group, 2 because they were studies of cell cultures, and 1 because they did not have the total of animals used. Thus, 21 papers were included for the critical evaluation of the impact of photobiomodulation on the major salivary glands; the studies used rats (n = 10) and humans (n = 11) (Fig. 2, Tables 3, 4 and 5).

From these selected studies, one study employed a pulsed wave and 13 continuous wave (cw). Eight studies used radiation in the red region of the spectrum (660 to 685 nm) and eight in the infrared region (780 to 905 nm). Some studies have considered more than one light source to compare results and changes in larger salivary glands of humans and rats.

The visible light length varied between 660 and 685 nm, and the radiant energy varied from 4.32 to 60 J per session for human trials and 5.76 to 42 J per session for animal trials. The duration of the treatment also varied from a single session (animal) up to 12 weeks (24 sessions, human). Only two studies used pulsed light sources, while all the others used continuous wave.

Out of the 21 authors, 13 responded to the aspects of pain, xerostomia, oral mucositis, and saliva flow, while eight analyzed salivary biochemistry.

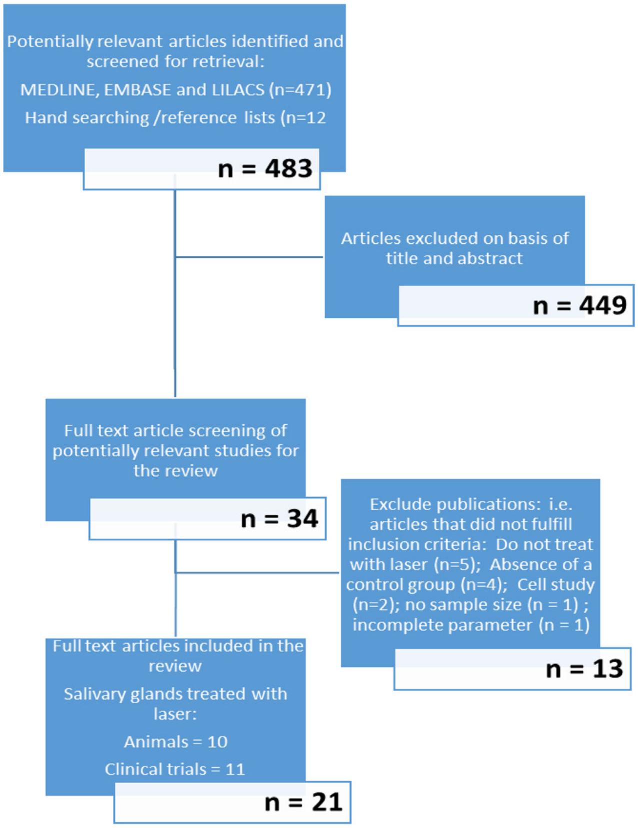


Fig. 2 Flowchart

The main reason for irradiating the salivary glands in clinical trials was head and neck cancer (4 studies) but the effects of the photobiomodulation on xerostomia, burning mouth syndrome, and Sjögren's syndrome were also evaluated. In the animal papers, three evaluated animals with diabetes, and one with hypothyroidisms.

Information is presented in this review in a summarized and systematic way, to allow the reader to easily identify the state of the art in this area as well as to observe the potent applications of PBM in the treatment of disorders in the salivary glands.

To achieve this goal, the authors divided the studies between those with animals and humans, and summarized each paper in tables containing the photometric parameters, methods of analysis, and main results.

The following tables summarize the primary results and radiometric parameters of all the studies on this review.

Discussion

In general, most authors observed a decrease in xerostomia, an increase in salivary flow, oral mucositis, and pain reduction, regardless of the wavelength used, as well as the time of irradiation and the amount of energy deposited in the tissues, which demonstrates the effectiveness of photobiomodulation [6, 9, 18, 22, 31, 39, 41, 42, 50, 52, 53, 64, 65]. The salivary biochemistry results showed a reduction in salivary glucose, calcium, and acinar fat; increase in IGF-1; decrease in T4 hormones; decrease in apoptosis and inflammation; and increase in protein [1, 3, 10, 13, 21, 22, 34, 52, 59].

PBM on salivary glands of healthy subjects

All the studies that report irradiation of the salivary glands of healthy subjects are in animal models [13, 21, 34]. Simões et al., using a λ = 808 nm laser, reported that the photobiomodulation did not affect at all the submandibular or the parotid gland of the healthy subjects [60]. These findings were similar to the results presented by Castro et al. using a red (λ = 660 nm) laser [11]. Nevertheless, an increase in total protein concentration in the parotid glands of the irradiated groups was observed, while the amylase activity in this gland showed a significant reduction. On the other hand, Fukouka et al. reported a lack of alterations in the total protein of the healthy group irradiated using a red laser (λ = 660 nm) laser [21]. Lack of change in the salivary flow is also reported for healthy irradiated subjects by Jesus et al [33].

Although the literature lacks studies presenting PBM of salivary glands on healthy volunteers, it is unlikely that there would be considerable side effects.

Salivary flow rate

From the eight studies that analyzed the salivary flow rate, six reported significant increase [26, 39, 45, 54] and two reported lack of difference [18, 67]; therefore, the usage of PBM to stimulate the salivary production by the glands is still not a consensus in the literature. However, the studies that reported lack of statistical differences were on burning mouth syndrome (in which the cause is still unknown) and Sjögren's syndrome (immune system, causes salivary gland swelling).

Loncar [39] and Loncar [40] used pulsed light sources but did not report any underlying reason for the xerostomia diagnosis of the patients. Although both studies reported increased salivary flow rate after the treatment, the authors reported that an infrared laser (830 nm) produced better results in comparison with red lasers (685 nm) under similar radiometric conditions. This is likely due to the deeper penetration depth of the infrared laser that results in the photobiomodulation of the deep glands and not only of the more superficial ones [39]. Studies on xerostomia induced by the treatment of head and neck cancer reported increased salivary flow rate because of the photobiomodulation therapy [45, 46, 54].

PBM increases the numbers of ducts and epithelial cell mitoses, stimulates the protein synthesis in submandibular glands of rats, decreases inflation markers, and increases blood microcirculation in the salivary glands. The mitochondria stimulation increases the availability of ATP allowing

Table 3 Note: This data is mandatory. Please provide.

1st Author	Palma [46]	González-Arriagada [27]	Oton-Leite [45]	Saleh [54]	Gonnelli [67]
Motive	Head and neck cancer	Head and neck cancer	Head and neck cancer	Head and neck cancer	Head and neck cancer
No.. at treated	29	108	30	12	17
No.. at control	0	108	30	11	10
Design	Clinical trial	Placebo controlled	Placebo controlled	Placebo controlled	Clinical trial
Laser source	Diode	Diode	Diode	Diode	Diode
Temporal regime	Cw	Cw	Cw	Cw	Cw
λ (nm)	808	660	685	830	660/780
Avg. power (mW)	30	100	35	100	40/15
Target area (cm^2)	0.04	0.028	0.028	0.028	0.04/0.04
Exposure p. site (s)	10	10	25	20	10/10
Energy p. site (J)	0.3	1	0.875	2	0.40/0.15
No. of sites	2ProI'	27	55	14	32/16
No. of sessions	12 weeks; 2 per week	3 weekly	5 consecutive days	6 weeks; 2 per week.	7 weeks; 3 per week
Session energy (J)	6.6	27	48	28	9.6/2.423
Irradiated sites	Major salivary glands were irradiated with the laser in contact. For this, 6 extra oral sites were illuminated on each parotid gland and 3 submandibular gland. 2 intraoral sites on each sublingual gland	3 sites in the upper labial mucosa, 3 lower labial mucosa, 3 soft palate, 3 bilateral buccal mucosa, 3 tongue's bilateral side, 3 tongue's ventral surface , 3 mouth's floor	Left and right buccal mucosa (8 on each side), upper and lower internal lip mucosa (3 sites), palatine folds (2 sites), tongue's lateral edge (10 on each side), tongue's dorsum (8 sites), soft palate (3 sites), mouth floor (2 sites), labial commissure (1 site).	Three points were applied to each parotid gland, two to each submandibular gland, and two to each sublingual gland	Extra orally at 780 nm: Six points on each parotid gland and two on each submandibular gland were illuminated Intraorally at 660 nm For sublingual glands, two points on the anterior region of the oral floor.
Outcome	↑ Salivay flow rate; ↑ pH; ↑quality of life	ø Mucositis, ø disgeusia; ↓ severity of mucositis; ↓ nasogastric tube nutrition; ↓ trismus; ↓ interruption of therapy due to mucositis	↓ Oral mucositis, ↓ pain e ↑ salivary flow rate	6th week: ø 12th week: ↑ salivary flow rate	↑ Salivary flow rate

conditions for increased production of saliva and restoring the overall oral health [22, 35, 41, 42, 44, 49, 62].

Although more research is still in need—especially in the case of burning mouth and Sjögren's syndrome—some works report that the regenerative effect on the salivary glands remains for a long period after the treatment [39].

Head and neck cancer

One of the main inductors of changes in the salivary glands is the radiotherapy applied to patients with head and neck cancer (HNC). One of the most common treatments for HNC is radiotherapy. Unfortunately, such approach is aggressive to the non-neoplastic tissue, which results in dose-dependent side effects [50, 53, 65]. The side effects of the treatment interferes with the patients' oral functions, ultimately affecting their overall life quality [13, 31, 34, 52]. The salivary glands are often irradiated during the treatment for HNC and, although the mechanism of radiation-induced damage of the salivary glands is still uncertain, acinar and atrophy degeneration are usually found in the histological analysis [3, 17, 32]. The degeneration of the tissue ultimately results in dry mouth (xerostomia), mucositis, decreased salivary flow rate, and quality of life [4]. Photobiomodulation of the salivary glands of HNC patients may be a good adjuvant treatment for the oral side effects of the radiotherapy.

All studies in this review reported increased salivary flow after the PBM treatment but the reason for such effect is still not fully understood [26, 45, 46, 54]. Nevertheless, the increase in anti-apoptotic protein expression and decrease in

Table 4 Note: This data is mandatory. Please provide.

1st Autor	Simões [61]	Jesus [33]	Fukuoka [22]	Fukuoka [21]	Castro [11]
Motive	-	Hypothyroidismis	Diabetes	Diabetes	Diabetes
Animal	Wistar male rats	Wistar male rats	Female Wistar rats	Female Wistar rats	Female Wistar rats
No.. of treated	11/11 (2 groups)	7/7/7 (3 groups)	10	10/8 (2 groups)	11/11/11/11 (4 groups)
No. of control	11	7	9/11 (2 groups)	10/7 (2 groups)	11/11 (2 groups)
Design	Controlled	Placebo controlled	Controlled	Controlled	Controlled
Laser source	Diode	Diode	Diode	Diode	Diode
Temporal regime	Cw	Cw	Cw	Cw	Cw
λ (nm)	808	660/780/780	660	660	660
Avg. power (mW)	500	40/40/70	70	70	90
Target area (cm^2)	1.8	0.04	0.028	0.028	0.017
Exposure p. site (s)	14/28	150/150/90	8	8	1/4
Energy p. site (J)	7/14	6/6/6.3	0.56	0.56	0.09/0.36
No. of sites	3	2	40	40	64
No. of sessions	2 consecutive days	2 weeks, every 2 days.	Single, 24 h before sacrifice	Single, 24 h before sacrifice	Single, 24 h before sacrifice
Session energy (J)	21/42	12/12/12.6	22.4	22.4	5.76/26.04
Irradiated sites	The laser was applied to each parotid gland separately and both submandibular glands together.	The irradiation mode was punctual and in contact, perpendicular to each submandibular gland	A trichotomy was performed in the area of the two submandibular glands then it was irradiated in 40 sites.	A trichotomy was performed in the area of the two submandibular glands then it was irradiated in 40 sites.	A total of 64 points of laser irradiation was applied and the irradiation delivery mode was punctual, transcutaneous, in contact and perpendicular to the skin surface.
Outcome	↓Amylase; ↑protein; ↓catalase; øperoxidase; øLDH	ø Salivary flow rate; ø glands weight; ø ductal and acinar cells	↓ HBGB1; ↓RAGE ↓AGE; ↓phospho NF-κB p65; ↓ TNF-α; ↓ Bad; ↓ Bax ; ↓ cleaved caspase-3	↓ Blood glucose; ↓ insulin resistance; ↑insulin sensitivity; ↑ β- cell function	↓ Blood glucose; ↓ intracellular calcium concentration; ↑ CalM protein; ↓lipid droplets

apoptosis-related markers (Bad, Bax, TNF-α, and cleaved caspase-3), in addition to the decrease in inflammatory markers (HBGB1, RAGE, AGE, and phosphor NF-kB p65) [22], enhances the reparation process of the salivary glands and might be related to the increase in the salivary flow rate.

Pain level and pH were also positively affected by the PBM [45, 46]. González-Arriagada et al reported lack of changes in the dysgeusia and incidence of mucositis but the PBM concomitant to the radiotherapy decreased the interruption of the cancer treatment due to severe mucositis and the usage of nasogastric tube nutrition [27]. Overall, PBM ultimately enhances the oral health and quality of life of patients with HNC undergoing radiotherapy [46].

In the rat study involving radiotherapy, the authors also reported the preservation of acinar structure and reduced occurrence of vacuolation allied to increased vascularization of the parotid glands. The tendency towards reduced cell apoptosis was likely due to the decrease in active caspase-3 [61].

It is important to mention that all studies report additional care to avoid applying the PBM directly on the tumor.

Diabetes

Diabetes mellitus is a metabolic syndrome of multiple origins. This chronic disease results from defects in insulin secretion or reduction of the biological function of this hormone, resulting in hyperglycemia [70]. Diabetes usually has concomitant oral manifestations that affect the overall dental health. Among other issues, diabetic patients have complained of xerostomia [19] and experience salivary gland dysfunction [12, 25, 43].

It is well known that the use of PBM in diabetic subjects can improve the healing of wounds [7, 15] but the effect of the application of PBM at the salivary glands of diabetic subjects is still not fully understood. To our knowledge, the literature lacks clinical trials (that meet the criteria for this review) about the effect of PBM on salivary glands of diabetic humans. However, three studies with animals were found [60, 61].

One of the most interesting findings in PBM therapy of salivary glands of diabetic rats is the decrease in the blood glucose and insulin resistance [21, 33]. This is partially

Table 5 Note: This data is mandatory. Please provide.

1st Author	Simões 2009 [60]	Simões [60]	Simões [61]	Uzêda-E-Silva [66]	Acauan [1]
Motive	Diabetes	Diabetes	Diabetes	Hypothyroidisms	Radiotherapy
Animal	Wistar female rats	Wistar female rats	Wistar female rats	Albino Wistar rats	Male Swiss mice
No. of treated	12/12/12 (2 groups)	15/15/15/ (2 groups)	15/15/15/ (2 groups)	7/7/7/7 (2 groups)	12/12 (2 groups)
No. of control	12/12	15/15	15/15	7/7 (2 groups)	5/6 (2 groups)
Design	Controlled	Controlled	Controlled	Controlled	Controlled
Laser source	Diode	Diode	Diode	Diode	Diode
Temporal regime	Cw	Cw	Cw	Cw	Cw
λ (nm)	660	660	660	660/780	830
Avg. power (mW)	100	100	100	40/40	100
Target area (cm^2)	0.017	0.017	0.017	1	0.014
Exposure p. site (s)	1/2/4	1/2/4	1/2/4	150/300	10/20
Energy p. site (J)	0.09/0.17/0.34	0.09/0.17/0.34	0.09/0.17/0.34	6/12	1/2
No. of sites	64	64	64	2	2
No. of sessions	1	1	1	8	1 before and 1 24 h after the radiotherapy
Session energy (J)	5.76/10.88/21.76	5.76/10.88/21.76	5.76/10.88/21.76	12/24	2/4
Irradiated sites	The hand-held wand, on skin contact mode, was positioned perpendicularly. Sixty-four points were necessary to cover evenly the entire parotid area	The hand-held wand, on skin contact mode, was positioned perpendicularly. Sixty-four points were necessary to cover evenly the entire parotid area	The hand-held wand, on skin contact mode, was positioned perpendicularly. Sixty-four points were necessary to cover evenly the entire parotid area	After the 2nd week of induction of hypothyroidism and repeated at intervals of 48 h for 2 weeks.	The spot tip was placed in contact with the mouse skin in the region corresponding to the parotid glands.
Outcome	↓Catalase activity; øperoxidase;	↓Sodium; ø phosporus, magnesion; ø photassium; ↑ calcium; ø zinc; ↓blood glucose	↓ Catalase activity; ø peroxidase activity	Myoepithelial cells: ↓@780 and ↑@660 for euthyroid rat; ø for hypothyroid rats	↓ Caspase-3; ↓ cell apoptosis; ↓ vacuolation; ↑vascularization; preservation of acinar structure

explained by the decrease in insulin resistance (HOMA-IR), the increase in insulin sensitivity (HOMA-IS), and better β-cells function (HOMA-β) observed in irradiated rats [33]. In addition, photobiomodulation is able to act directly on Ca^{2+} channels in a plasmatic membrane, increasing its concentration in the cell [11].

Diabetes also induces inflammation and enhances apoptotic cell death but PBM decreases such effects, reducing inflammation and apoptotic markers [22, 71].

Hypothyroidisms

The two studies on the effect of photobiomodulation on hypothyroidism were animal models [21, 33]. These studies show a limited impact of PBM on the salivary glands of rats with induced hypothyroidism. Jesus et al. reports a lack of alteration in the salivary flow rate, glands weight, and ductal and acinar cells [21, 33, 66]. They also report a lack of statistically significant differences between the control group and the photobiomodulation group of myoepithelial cells for the hypothyroidism-induced rats. Further research is in need before any conclusions are drawn for the effect of photobiomodulation on the salivary glands of subjects with hypothyroidisms.

Conclusion

PBM at the salivary glands is safe and well-tolerated. There are no reports of incidents or deleterious effects of the therapy. The preliminary data on this review suggests the efficacy of the PBM on the treatment of xerostomia, even when it is caused by an exogenous factor, such as radiotherapy. Regarding Sjögren's syndrome, studies reported an increase in the salivary flow rate after PBM. In addition, for patients undergoing radiotherapy, an increase in quality of life, decrease in pain, and a decrease in interruptions of the treatment due to oral complications were reported. A major issue with

PBM therapy in salivary glands is the lack of standards for the application of the light and reporting of the parameters, which makes it hard to reproduce the results. This topic is still in need of further research but the low cost of the light devices and the good preliminary results encourage more research in this promising field.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required, because it is a systematic review.

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