Journal of Dental Sciences 19 (2024) 787–794

Available online at www.sciencedirect.com

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journal homepage: www.e-jds.com

Review article

Application of antimicrobial sonodynamic therapy as a potential treatment modality in dentistry: A literature review

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Received 6 November 2023; Final revision received 16 November 2023
Available online 22 November 2023

KEYWORDS
Antimicrobial photodynamic therapy;
Antimicrobial sonodynamic therapy;
Oral infections;
Sonosensitizer

Abstract The accumulation of dental plaque is a precursor to various dental infections, including lesions, inflammation around dental implants, and inflammation under dentures. Traditional cleaning methods involving physical removal and chemical agents often fall short of eliminating bacteria and their protective biofilms. These methods can also inadvertently lead to bacteria that resist drugs and upset the mouth's microbial harmony. To counter these issues, a new approach is needed that can target and clear away dental plaque, minimize biofilms and bacteria, and thus support sustained dental health. Enter antimicrobial sonodynamic therapy (aSDT), a supplementary treatment that uses gentle ultrasound waves to trigger a sonosensitizer compound, destroying bacterial cells. This process works by generating heat, mechanical pressure, initiating chemical reactions, and producing reactive oxygen species (ROS), offering a fresh tactic for managing dental plaque and biofilms. The study reviews how aSDT could serve as an innovative dental treatment option to enhance oral health.

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https://doi.org/10.1016/j.jds.2023.11.006

Introduction

Dental plaque is a biofilm that forms on the teeth, consisting of a complex community of over 500 bacterial species [1]. The colonization of plaque follows a specific pattern, starting with the adhesion of initial colonizers to the enamel surface, followed by secondary colonization through interbacterial adhesion [2]. Various treatments are available for removing dental biofilm, including mechanical removal through tooth brushing, the use of antiplaque or antimicrobial agents, and chemoprophylactic factors [3]. However, these approaches have limitations in completely eliminating microorganisms and preventing biofilm formation. Furthermore, they can contribute to the emergence of drug-resistant microorganisms and disrupt the normal bacterial flora in the oral cavity [4]. Therefore, there is a need for selective methods that can effectively remove dental plaque, reduce microbial biofilms, bacterial load, and maintain long-term oral health.

One promising approach is reactive oxygen species (ROS)-based antimicrobial strategies, which are based on the generation of ROS [5]. The oxidative stress pathway plays a crucial role in cellular damage, and ROS can interfere with bacterial growth and replication through various mechanisms, such as DNA damage and disruption of cellular metabolism [6,7]. Antimicrobial photodynamic therapy (aPDT) is ROS-based antimicrobial strategies [7]. It is a non-invasive treatment that utilizes harmless visible light-activated photosensitizers to generate ROS in the presence of oxygen, leading to the inactivation of microorganisms [8]. However, aPDT has a limitation in that it uses less penetrating light to induce a cytotoxic effect in sensitized tissues [9]. On the other hand, antimicrobial sonodynamic therapy (aSDT) is similar to aPDT but offers an advantage over it due to the significant depth that ultrasound waves can penetrate tissue. Ultrasound, being a mechanical wave, has a penetration depth of more than 10 cm in soft tissues and has been extensively studied for clinical diagnosis and treatment [9—11]. In aSDT, the target tissues are sensitized with a non-toxic sound-sensitizing chemical agent known as a sonosensitizer, which leads to the production of ROS [11,12].

Another difference between aSDT and aPDT is their mechanism of action. In addition to generating ROS, aSDT also applies mechanical pressure through the cavitation effect. Cavitation is a physical phenomenon that occurs when ultrasound waves induce mechanical stress on a target material or tissue. The synergistic combination of ROS and mechanical pressure in aSDT not only reduces the mitochondrial membrane potential, indicating the loss of mitochondrial function, but also visibly damages the cell membrane structure. In contrast, aPDT primarily affects the mitochondrial membrane potential without significant changes to the cell membrane structure. Therefore, aPDT targets the mitochondria as the main organelle, while aSDT targets both the membrane structure of the mitochondria and cells. The effectiveness of aSDT in killing target cells is achieved through a combination of inducing apoptosis with ROS and applying mechanical pressure through cavitation [11,13].

High safety, deep penetration and low cost, making aSDT as an antimicrobial therapeutic approach in dentistry [14]. In summary, this study aimed to provide a comprehensive review of the use of antimicrobial sonodynamic therapy as a potential treatment modality in dentistry. By harnessing the power of ROS, aSDT offers a novel strategy for combating dental plaque and associated microbial biofilms, with the goal of improving oral health outcomes.

Antimicrobial sonodynamic therapy

aSDT has emerged as a promising and innovative approach to fighting against microbes [15]. It employs low-intensity focused ultrasound (LIFU) to stimulate sonosensitizers, leading to the generation of cytotoxic reactive species that are detrimental to microbes [16]. Currently, sound waves with an ultrasonic energy density below 3 W/cm^2 are classified as low-energy sound. During high intensity focused ultrasound (HIFU) treatment, temperatures rise well above 80 °C. As a result, when the energy density at the focal point is high, it causes tissue damage. Therefore, it is recommended to use LIFU instead [17].

The schematic diagram of possible mechanisms of aSDT is presented in Fig. 1. When sonosensitizers are exposed to LIFU, they initiate a phenomenon known as acoustic cavitation. Acoustic cavitation involves the creation, growth, and sudden collapse of gas bubbles, which in turn results in three primary mechanisms that cause cell death.

1. *ROS-induced damage*: Acoustic cavitation can directly activate sonosensitizers, leading to the production of reactive oxygen species (ROS). These factors can disrupt the structural integrity of the cytoskeleton and cell membrane, ultimately leading to cell death [18].
2. *Sonomechanical damage*: The collapse of cavitation bubbles generates mechanical effects such as shear stress, shock waves, and localized high temperature (10,000 K) and pressure (81 MPa). These effects contribute to the demise of cells [19].
3. *Sonothermal damage*: The violent collapse of gas bubbles during cavitation generates extreme temperatures of up to 5000 K and pressures of 500 Pa. This release of energy causes the sonosensitizer to attach to the surface of pathogenic microorganisms. When ultrasonic waves irradiate the cells, the sonosensitizer is activated, and the energy released is transferred to oxygen, resulting in the generation of ROS. This process leads to the destruction of cell membranes, DNA damage, and ultimately cell death [20].

Another advantage of LIFU is its cost-effectiveness, enabling it to effectively target microbes deeply embedded in tissues and concentrate its effects in specific regions to activate the sensitizers [12]. As a result, aSDT has shown synergistic effects against diverse microorganisms, including bacteria, biofilm formations, and yeasts [12,14,21,22].

Ultrasound waves

In comparison to light irradiation in aPDT, irradiation of ultrasound waves in aSDT offers several advantages. It

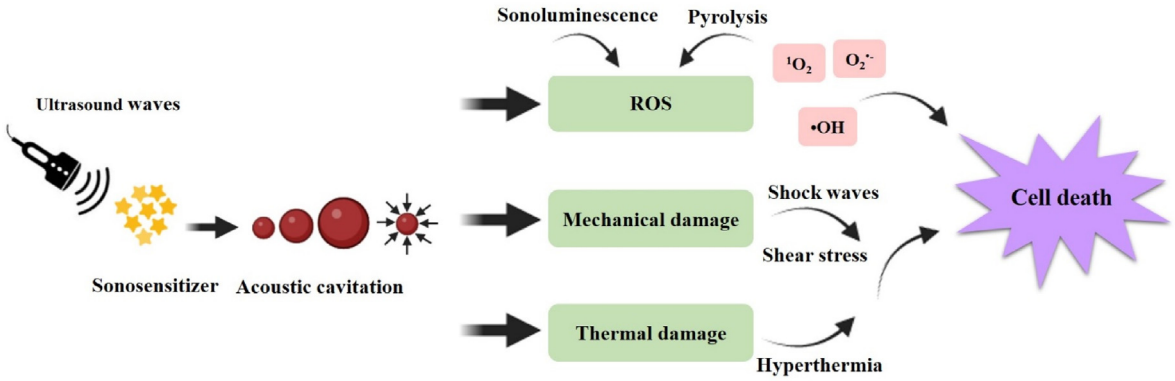

Figure 1 The schematic diagram of mechanism of aSDT (ROS, reactive oxygen species).

enables precise targeting of specific tissues during treatment, minimizing the impact on normal tissues [11]. Moreover, ultrasound waves surpass light irradiation in terms of its ability to penetrate deeper into the tissue. The depth of penetration for ultrasound waves, depending on the frequency applied (3 MHz and 1 MHz), ranges from 0.8 to 5 cm [23]. Ultrasound waves induce a phenomenon known as acoustic cavitation, which involves the formation, growth, and subsequent collapse of gas bubbles [20,24]. When these bubbles collapse, they release energy that is transferred to oxygen, resulting in the production of ROS. Consequently, cellular membranes are destroyed, DNA is damaged, and ultimately, cell death occurs [20]. The schematic diagram of aSDT mechanism is illustrated in Fig. 1.

Sonosensitizers

In aSDT, the selection of appropriate sonosensitizers plays a crucial role in determining the efficiency of the therapy. Several factors need to be considered when choosing the ideal sonosensitizer, including its ability to ROS when exposed to ultrasound waves, its capacity to target specific tissues, its water solubility, and its biocompatibility [25,26]. These factors collectively contribute to the overall effectiveness and safety of aSDT.

Inorganic sonosensitizers, such as titanium dioxide nanoparticles (TiO_2NPs), silicon nanoparticles, and zinc oxide nanoparticles (ZnONPs), have been shown to produce ROS when exposed to ultrasound waves. However, their efficiency in generating ROS is relatively low [27,28]. Additionally, these inorganic nanomaterials often have poor biocompatibility and are not easily degraded naturally, which limits their clinical applications [29].

Organic sonosensitizers, particularly those derived from photosensitizers like chitosan, offer distinct advantages over inorganic counterparts [30]. Firstly, organic sonosensitizers have well-defined molecular structures, allowing for easy synthesis in large quantities. Secondly, the relationship between the molecular structure of organic sonosensitizers and their therapeutic effects is well-understood, enabling precise control over ROS production induced by light and ultrasound waves. Thirdly, organic sonosensitizers demonstrate high efficiency in generating ROS under ultrasound waves, minimizing the risk of thermal and mechanical damage caused by ultrasound. Lastly, these organic compounds are relatively biodegradable and exhibit good biocompatibility, making them suitable for use in the body [31—33].

Despite these advantages, many organic sonosensitizers still face limitations that hinder their clinical use. One major challenge is their poor water solubility, which can cause aggregation during transportation in the body and impede their accumulation in tumor tissues. Moreover, some organic sonosensitizers can be highly toxic to the skin, leading to skin lesions. Additionally, their limited tumor-targeting ability affects their therapeutic effectiveness. Lastly, the efficiency of ROS generation by organic sonosensitizers under ultrasound excitation is generally lower compared to light excitation [34,35].

To address these limitations, there is a pressing need to develop new sonosensitizers that possess high sonotoxicity, low phototoxicity, excellent water solubility, biocompatibility, and strong targeting capabilities in the field of aSDT. Researchers are actively investigating novel organic compounds, improving their water solubility through various formulation strategies, and enhancing their targeting abilities by incorporating targeting ligands or nanocarriers.

Additionally, efforts are being made to optimize the molecular structure of organic sonosensitizers to improve their efficiency in generating ROS under ultrasound excitation. These advancements aim to overcome the current challenges and pave the way for the effective clinical application of organic sonosensitizers in aSDT [34].

Application of antimicrobial sonodynamic therapy in dentistry as a novel antimicrobial approach

Chlorhexidine (CHX) is a widely utilized mouthwash with strong antimicrobial properties that effectively combat oral diseases [36]. However, CHX treatment can lead to certain side effects, such as teeth and tongue discoloration, dry mouth, and a burning sensation [37]. In recent investigations, researchers have explored the antimicrobial potential of aSDT for oral infections caused by bacteria like *Streptococcus mutans* [38]. Previous studies have demonstrated that aSDT exhibits minimal cytotoxicity and apoptotic effects while displaying high cellular uptake, ROS

production, and antimicrobial activity, effectively inhibiting the growth of microorganisms [11,20,24].

Various sonosensitizers, including curcumin, curcumin-poly (lactic-co-glycolic acid) nanoparticles (Cur-PLGA-NPs), nanomicelle curcumin (NMCur), ZnONPs, and TiO_2NPs, have been employed in these studies and bacterial suspension directly exposed to sonosensitizers [20,24,28]. However, recent research has proposed the development of sonosensitive dental materials that incorporate sonosensitizers (Table 1 and Fig. 2). These materials can be activated by ultrasound waves and effectively combat cariogenic and periodontal pathogens by generating ROS.

Cariogenic pathogen

Pourhajibagher et al. investigated the physico-mechanical properties and anti-biofilm effects of resin-modified glass ionomer cement that incorporated nano-curcumin (n-Cur), nano-emodin (n-Emo), and nano-quercetin (n-Qct). These nanoparticles were activated using ultrasound waves [45]. The researchers aimed to evaluate the effectiveness of the modified cement in preventing biofilm formation by *S. mutans* around orthodontic bands. The results of their study demonstrated that the shear bond strength (SBS) of the modified glass ionomer cement decreased compared to the control group. Importantly, this decrease was dependent on the concentration of the nanoparticles. Among the various concentrations tested, 2% n-Qct, 5% n-Emo, and 5% n-Cur exhibited the highest levels of SBS. These concentrations showed no significant difference in performance compared to Transbond XT, commonly used orthodontic cement. As a result, these concentrations were considered suitable for clinical use.

It is worth noting that the addition of sonosensitizers to the glass ionomer cement did not compromise its ability to release fluoride. This is particularly important as fluoride release is a desirable property for materials used in orthodontic treatments. Furthermore, the incorporation of the nanoparticles, especially 5% n-Emo, led to a reduction in the setting time of the cement without any adverse effects on its clinical application. This suggests that the modified cement could offer advantages in terms of efficiency and convenience during orthodontic procedures.

In addition to the physico-mechanical properties, the researchers also evaluated the antimicrobial properties of the modified cements against *S. mutans* biofilms. The treatment of these biofilms with ultrasound waves in conjunction with the modified cements, especially those containing 5% n-Emo, resulted in improved antimicrobial efficacy. This finding suggests that the combination of ultrasound activation and the incorporation of sonosensitizers can enhance the antimicrobial activity of orthodontic cement, potentially improving the overall oral health outcomes of orthodontic patients.

Overall, the study by Pourhajibagher et al. highlights the potential of resin-modified glass ionomer cements containing ultrasound-activated nanoparticles for orthodontic applications [45]. These modified cements exhibited favorable antimicrobial effects against *S. mutans* biofilms while maintaining important properties such as fluoride release and setting time. Further research and clinical evaluations are warranted to validate these findings and explore the practical implementation of these modified cements in orthodontic treatments.

Opportunistic pathogen

Yasini et al. conducted a study to evaluate the effectiveness of n-Cur-mediated aSDT in combating biofilms formed by *Enterococcus faecalis* and *Candida albicans* in root canals [46]. The researchers discovered that the use of n-Cur, ultrasound waves, and aSDT resulted in a significantly lower colony count of *E. faecalis* compared to the control group, which utilized 5.25% sodium hypochlorite (NaOCl). Moreover, the colony count of *C. albicans* in the aSDT group was significantly lower than both the control group and the ultrasound waves group.

In addition to the colony count measurements, the mean thickness of the biofilm was also analyzed. The results demonstrated that the biofilm thickness in both the NaOCl and aSDT groups was considerably thinner compared to the other groups. Furthermore, the mean biofilm thickness in the aSDT group was significantly less than that in the ultrasound waves group.

To summarize, the study findings suggest that n-Cur-mediated aSDT exhibited a comparable efficacy to NaOCl, while surpassing the effectiveness of ultrasound waves and n-Cur alone in reducing the biofilms formed by *C. albicans* and *E. faecalis*. These results highlight the potential of aSDT as a promising treatment approach for combating biofilm-associated infections in root canals.

Periodontal pathogen

In a series of studies, researchers have explored the use of aSDT combined with different sonosensitizers to enhance the antibacterial effectiveness and bioactivity of dental implant surfaces. These studies highlight the potential of aSDT as a targeted and efficient approach for combating biofilms and implant-associated infections.

Bahrami et al. investigated aSDT against polymicrobial periopathogenic biofilms (*Porphyromonas gingivitis*, *Prevotella intermedia*, and *Aggregatibacter actinomycetemcomitans*) [40]. They coated miniscrews with ZnONPs and observed a significant reduction in biofilm count following aSDT treatment compared to the control group. Similarly, Pourhajibagher et al. explored ROS-based antimicrobial strategies using chitosan nanoparticles-indocyanine green (CNPs-ICG) and found that aSDT effectively targeted and reduced biofilms on dental implant surfaces [47].

Li et al. utilized gold-titanium dioxide ($Au—TiO_2$) as a sonosensitizer by coating an activatable $Au—TiO_2$ nanoplatform on implant surfaces. Under ultrasound waves, $Au—TiO_2$ generated oxygen, alleviating the hypoxic microenvironment of biofilms and enhancing the efficiency of aSDT [41]. It produced singlet oxygen and hydroxyl radicals, resulting in a potent antibacterial effect against pathogenic biofilms. *In vivo*, $Au—TiO_2$ exhibited excellent antibacterial ability, supporting the findings of Sun et al. who investigated the antimicrobial effect of ultrasound waves-enhanced $Au—TiO_2$ nanotubes against *P. gingivalis* [43].

Table 1 Application of antimicrobial sonodynamic therapy (aSDT) in dentistry.

Dental material			Sonosensitizer	Sonodynamic therapy		Microorganism	Pro-inflammatory cytokines	Additional test	Refs
	Category name	Type	Concentration	Frequency	Time				
Polymethyl methacrylate	Organic	Resveratrol	256 μg/mL 512 μg/mL 1024 μg/mL	1 MHz	1 min	*C. albicans* *S. aureus* *S. sobrinus* *A. naeslundii*	TNF-α IL-1β IL-6		[39]
Orthodontic miniscrew	Inorganic	Zinc oxide	0.1 g	30 kHz	1 min	*P. gingivitis* *P. intermedia*, *A. actinomyc etemcomitans*	TNF-α IL-1β IL-6		[40]
Dental implant	Inorganic	Gold—Titanium dioxide	N/A	1 MHz	5 min	*P. gingivalis* *F. nucleatum* *S. sanguinis*	TNF-α IL-1β	Biocompatibility	[41]
Dental implant	Inorganic	Black phosphorus nanosheets Polydopamine	1 mg/mL	1 MHz	20 min	*S. aureus*		Osseointegration Biocompatibility	[42]
Dental implant	Inorganic	Gold—Titanium dioxide	N/A	1 MHz	N/A	*P. gingivalis*		Cellular compatibility	[43]
Dental implant	Organic	Methylene blue-loaded poly (D,L-lactide-co-glycolide)	50 μg/mL	7 MHz	1 min	*P. gingivalis*		Flexural modulus Flexural strength Surface roughness	[44]
Glass ionomer	Organic	Emodin Quercetin Curcumin	2% 5% 10%	1 MHz	1 min	*S. mutans*		Shear bond strength Setting time Fluoride release	[45]
Root canal irrigation	Organic	Curcumin	10 uL	1 MHz	1 min	*E. faecalis* *C. albicans*			[46]
Decontamination solution	Organic	Chitosan nanoparticles-Indocyanine green	1000 μg/mL	1 MHz	1 min	*P. gingivitis* *P. intermedia*, *A. actinomycetemcomitans*			[47]

Abbreviations: *A. naeslundii*, *Actinomyces naeslundii*; *A. actinomycetemcomitans*, *Aggregatibacter actinomycetemcomitans*; *C. albicans*, *Candida albicans*; *E. faecalis*, *Enterococcus faecalis*; *F. nucleatum*, *Fusobacterium nucleatum*; IL, Interleukin; kHz, Kilohertz; MHz, Megahertz; N/A, Not applicable; *P. gingivitis*, *Porphyromonas gingivitis*; *P. intermedia*, *Prevotella intermedia*; *S. sanguinis*, *Streptococcus sanguinis*; *S. mutans*, *Streptococcus mutans*; *S. aureus*, *Staphylococcus aureus*; *S. sobrinus*, *Streptococcus sobrinus*; Refs, References; TNF-α, Tumor necrosis factor-α.

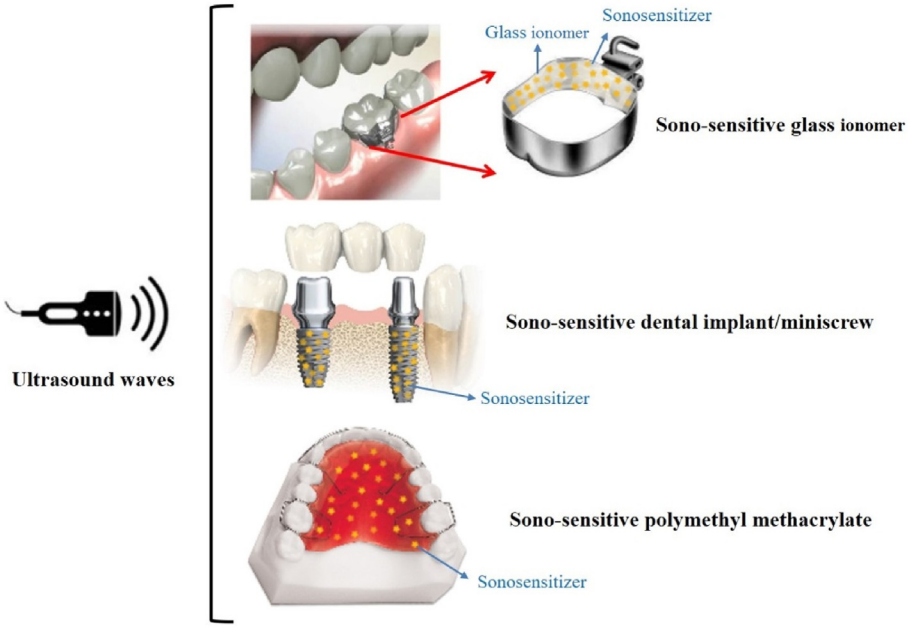

Figure 2 Sono-sensitive dental materials ("Sono-sensitive glass ionomer" refers to glass ionomer incorporating sonosensitizers. "Sono-sensitive dental implant/miniscrew" refers to dental implants or miniscrews coating with sonosensitizers. "Sono-sensitive polymethyl methacrylate" refers to polymethyl methacrylate containing sonosensitizers).

Aldegheishem et al. examined the mechanical properties and antibacterial efficacy of ROS based antimicrobial strategies using methylene blue-loaded poly (D,L-lactide-co-glycolide) nanoparticles (MB-loaded PLGA NPs) for peri-implantitis treatment [44]. By combining ultrasound waves with MB-loaded PLGA NPs, they achieved potent antibacterial activity against specific bacteria without compromising the mechanical properties and surface integrity of dental implants. Zeng et al. used black phosphorus nanosheets (BPNSs) and polydopamine (PDA) as a sonosensitizer for dental implant surfaces [42]. BPNSs generated ROS under ultrasound stimulation to combat implant-associated infections. The addition of PDA enhanced the stability of BPNSs and improved the coating's biocompatibility and photothermal performance. The resulting Ti/PDA/BP coating exhibited excellent biocompatibility, bioactivity, photothermal conversion, and sonodynamic conversion abilities. Through a synergistic effect, Ti/PDA/BP damaged bacteria's membrane and antioxidant system, resulting in high antibacterial activity against *Staphylococcus aureus* both *in vitro* and *in vivo*. Furthermore, the Ti/PDA/BP coating significantly promoted osteogenesis and bone-implant osseointegration.

In a study conducted by Pourhajibagher et al., they introduced a sono-sensitive acrylic resin [39]. They examined the effectiveness of aSDT against polymicrobial biofilms, including *C. albicans, S. aureus, S. sobrinus*, and *Actinomyces naeslundii*, formed on nano-resveratrol containing acrylic resin. The results of their study showed that the nano-resveratrol mediated aSDT significantly decreased the presence of multispecies microbial biofilms when compared to a control group that consisted of acrylic discs without nano-resveratrol, which were treated with PBS. Furthermore, this reduction was found to be dependent on the dosage of nano-resveratrol.

Effect of antimicrobial sonodynamic therapy on gene expression of pro-inflammatory cytokines

One possible concern when using ROS-based antimicrobial strategies is the potential toxicity they may have on neighboring cells. The interaction between inflammation and metabolism is complex, and ROS molecules can cause cellular damage by reacting with DNA, lipids, and proteins [48]. Various models of oxidative stress have been examined to understand how oxidant stress affects the nuclear factor-κB (NF-κB) signaling pathway. In response to inflammatory stimuli, ROS can activate NF-κB. NF-κB is a crucial transcription factor in M1 macrophages and is necessary for the activation of inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, IL-12, and cyclooxygenase [49].

Fortunately, a previous study showed that the expression of TNF-α and IL-6 genes in human gingival fibroblast (HGF) cells decreased to levels similar to those in untreated HGF cells after antimicrobial treatment [39]. This finding is consistent with the study by Bahrami et al., which demonstrated a significant decrease in the expression of TNF-α, IL-1β, and IL-6 genes following ROS-based antimicrobial strategies using ZnONPs as photo-sonosensitizers in aPDT, aSDT, and antimicrobial photo-sonodynamic therapy (aPSDT) [40].

On the contrary, the results of the study by Pourhajibagher et al. indicated that the expression levels of pro-inflammatory cytokines, such as TNF-α gene, increased after exposure to ROS-based antimicrobial strategies using Cur-PLGA-NPs [24].

However, they found that this increase did not have a significant impact on DNA fragmentation, cell survival, and apoptosis of the HGF cells. These conflicting outcomes may be attributed to differences in the properties of the photosonosensitizers used.

Limitations

SDT has been extensively studied for its potential in treating cancers due to its ability to penetrate tissues deeply [50]. In dentistry, aSDT has mainly been investigated as an antimicrobial method through laboratory studies. These studies have demonstrated the effectiveness of aSDT in reducing oral pathogens, including *S. mutans* [38]. However, the clinical application of this antimicrobial treatment and its impact on patient outcomes remain uncertain. The limited research in this field may be attributed to the novelty of the treatment method and a lack of understanding regarding its implementation in dentistry.

The present study focused on *in vitro* investigations that explored the antimicrobial properties of aSDT using sono-sensitive dental materials containing sonosensitizers. Oral infections and lesions such as denture stomatitis, peri-implantitis, and tooth decay can arise from poor oral hygiene practices. The reviewed studies demonstrated that the incorporation of sonosensitizers into dental materials, followed by ultrasound radiation, can reduce the pathogens associated with these oral conditions.

Furthermore, these studies indicated that aSDT with LIFU using sono-sensitive dental materials does not lead to irritation or inflammation of HGF. However, it is important to note that these investigations were conducted in laboratory settings and over short durations. To comprehensively evaluate the side effects and long-term impacts of this method, further clinical studies with extended follow-up periods are necessary. Additionally, exploring other clinical applications of this emerging technique for treating various oral microbial diseases is warranted. To optimize aSDT, future research should focus on developing new sonosensitizers and refining ultrasound delivery systems. These advances will contribute to enhancing the efficacy and safety of aSDT in dentistry.

Conclusion

The use of aSDT with sono-sensitize dental materials has demonstrated promising results in reducing proinflammatory biomarkers and microbial presence. This innovative approach appears to be both safe and effective in the adjuvant therapeutic of oral infection. However, it is important to acknowledge the limitations of the current review, such as the relatively small number of studies. Therefore, further research and investigations are warranted to validate these findings and fully explore the potential of aSDT using sono-sensitize dental materials in dentistry. By conducting additional studies, we can gain a more comprehensive understanding of this treatment modality and its implications for oral infection.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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