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Review

The promise of low-intensity ultrasound: A review on sonosensitizers and sonocatalysts by ultrasonic activation for bacterial killing

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ABSTRACT

Antimicrobial resistance has become one of the main public health issues in modern society. Ultrasonic antimicrobial treatment (UAT) is expected to solve the problem of antimicrobial resistance since ultrasonic treatment does not cause drug resistance during inactivation. However, the ultrasonic application is hindered due to the high energy cost. To cast more lights on the ultrasound in tandem with catalysts as a superior strategy for bacterial inactivation, the present review focuses on the UAT with the assistant of continuous development of organic sonosensitizer and inorganic sonocatalyst. With the application of these nanomaterials, the ultrasonic parameters changed from low-frequency and high-power ultrasound to high-frequency and low-power ultrasound. The review also presents the composition of sonosensitizers/sonocatalysts including organic and inorganic nanoparticles and discusses the ultrasonic activation mechanisms triggered by these catalysts. Based on the synergistic effect of ultrasound and catalysts, we discuss the importance of extracellular oxidation and intracellular oxidation in the process of bacterial inactivation. Overall, UAT combined with catalysts appears to be an effective treatment strategy that can be successfully applied in the field of medicine, environmental treatment, and food industry.

1. Introduction

Bacterial resistance occurs when bacterial strains survive from bacterial killing agents through evolution, which becomes one of the major public health problems in modern society [1]. In recent decades, with the development of novel antibiotics in the medical market, more resistant bacterial species appear which may bring the antibacterial therapy back to the pre-antibiotic era [2]. Drug-resistant infections (DRIs) are estimated to cause 50,000 deaths each year in Europe and the United States [3]. By 2050, DRIs may cause 10 million deaths worldwide every year [4]. Besides, it cannot be ignored that resistant bacteria also appear frequently in the process of environmental treatment [5]. In this regard, actions should be taken to avoid this increasingly serious global healthcare crisis from bacterial resistance.

Unlike chemical or drug treatment on bacterial cells, physical treatment such as ultrasound and ultraviolet (UV) does not produce drug resistance, since these physical treatments do not rely on chemical reagents. However, UV inactivation is easily influenced by several factors, such as water quality, light scattering and absorption, cell shading, and organic fouling in UV lamps [6]. On the other hand, ultrasonic inactivation could conquer the above-mentioned limitations, due to its strong penetrating ability. Therefore, ultrasonic inactivation itself, or combined with UV irradiation, could be helpful in the fight against bacterial resistance [7].

Both physical and chemical effects from ultrasonic cavitation count for bacterial inactivation. During ultrasonic irradiation, collapsed microbubbles in water generate extremely high local temperatures and pressures in the critical region of ultrasound [8]. Moreover, mechanical effects, such as shock waves, shear forces, and micro-jets, lead to mechanical destruction and lysis of bacterial cell membranes [9-11]. However, the energy consumption by powerful ultrasound is highly concerned which limits the further application of ultrasonic inactivation of bacterial cells in water.

With the increase of ultrasonic frequency, the mechanical effect will gradually decrease and the chemical effect will gradually increase [12,13]. The collapse of the microbubbles produces H_2O_2 and reactive oxygen species (ROS), including hydroxyl radicals (•OH), hydroperoxyl radicals (•HO_2), and O_2, promoting the oxidation reaction [14-16]. •OH,

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$^{\bullet}HO_2$, or $^{\bullet}O$ are generated by the following reactions during US irradiation in water (reactions (1–4)) [16,17]. These oxidation reactions can damage biocompounds such as DNA, RNA, proteins, and lipids membranes [18,19], destroy the function and structure of bacteria, and finally induce cell death.

$$H_2O + \text{Ultrasonication} \rightarrow {}^{\bullet}OH + {}^{\bullet}H \quad (1)$$

$$^{\bullet}H + O_2 \rightarrow {}^{\bullet}HO_2 \quad (2)$$

$$^{\bullet}OH + {}^{\bullet}OH \rightarrow H_2O + {}^{\bullet}O \quad (3)$$

$$^{\bullet}O + {}^{\bullet}O \rightarrow O_2 \quad (4)$$

ROS are featured as that they will not produce other pollutants and have little harm to the environment. But due to their extremely short lifespan, the transfer of free radicals is limited [20-22]. In addition, ROS usually react with each other by the following reactions (reactions (5–7)). And these reactions inevitably reduce the oxidative inactivation performance via free radicals [17,23].

$$^{\bullet}OH + {}^{\bullet}H \rightarrow H_2O \quad (5)$$

$$^{\bullet}HO_2 + {}^{\bullet}H \rightarrow H_2O_2 \quad (6)$$

$$2H_2O_2 \rightarrow 2H_2O + O_2 \quad (7)$$

Alternatively, sonodynamic therapy is an effective method to induce bacterial death by using the combination of ultrasound and sonosensitizers to generate ROS for inactivation [24]. In fact, with the development of sonosensitizers, compared with ultrasonic treatment alone, sonosensitizers can increase the ROS yield, and also reduce energy cost.

This review is to cast more lights on the ultrasound in tandem with catalysts as a superior strategy to kill bacteria. Initially, fundamental aspects of ultrasonic cavitation and nano-sonocatalysts are discussed to prepare the ground for this work. We then focus on the composition of various sonosensitizers/sonocatalysts including organic and inorganic nanoparticles (NPs), giving a comprehensive understanding of how the catalysts contribute to ultrasonic cavitation. Furthermore, based on synergistic bioeffects from the combination of ultrasound and various catalysis, the inactivation mechanisms were also discussed. Moreover, we also highlighted the potential strategies using the combination of UV and ultrasonic antimicrobial treatment (UAT), which may further enhance the ROS yield for bacterial killing and reduce the energy cost. Therefore, in terms of bacterial inactivation, this work reviewed the combination of ultrasound and nanomaterials to amplify the yield of free radicals and the resulting killing pathway to determine the priority of future research.

2. Overall picture of ultrasonic antibacterial treatment

Cavitation effect refers to the change of microbubbles including rapid expansion, compression, and collapse in the liquid with the presence of sound pressure [10]. Cavitation could produce high temperature, pressure nearby the cavitation bubbles. Moreover, high shear forces and liquid jets could also be produced after the surface of cavitation bubbles [9-11]. Cavitation is also closely related to ROS generation. Cavitation bubbles could absorb sound energy, leading to the vibration of the bubbles to cause violent collapse, and generate high temperature (up to 10,000 K) and high pressure (81 MPa). Thereby a large amount of energy is released to induce hydrothermal dissociation to generate $^{\bullet}OH$ [17,25]. Acoustic cavitation does unique benefits, which can propagate into the deep area and also can be focused specifically on the target [11]. However, the energy consumption by powerful ultrasound is highly concerned which limits the further application of ultrasonic inactivation on bacterial cells [10].

To enhance the antibacterial effect of cavitation, additives can be added to an ultrasonic system [26]. These additives can simply be inert solids to increase the cavitation nucleus and lower the cavitation threshold or can have catalytic action in terms of degrading oxides and generating ROS [26]. It is worth noting that even though the catalytical additives, such as $FeSO_4$, can quickly degrade oxides, generate ROS, and enhance the inactivation efficiency of acoustic cavitation, the hydrogen peroxide produced by acoustic cavitation is insufficient for bacterial killing [26]. Alternatively, nano-sonosensitizers can not only lower the cavitation threshold as cavitation nucleus [27,28], increase the yield of ROS in the targeted area [29] but also further increase the ROS produced by acoustic cavitation through Fenton reactions [30]. Overall, nano-sonosensitizers can be added into the ultrasonic system as inert solids with catalytic action to enhance the antibacterial effect of cavitation. However, nano-sonosensitizers require a complicated process to be fabricated, and some nano-sonosensitizers are unstable and cytotoxic.

Ultrasound has been applied to microbial inactivation for many years. With the continuous development of nano-sonosensitizers and sonocatalysts, ultrasound/catalyst inactivation strategies have been reported since 2004 [31]. Relying on the library of web of science, we searched the relevant papers on ultrasonic / sonosensitizer for bacterial inactivation. To visually explain the effect of sonocatalysts on ultrasonic inactivation, Fig. 1 was produced. Sole ultrasonic inactivation is mainly reported from environment treatment and food hygiene, while medical treatment is relatively rare. Meanwhile, the ultrasonic parameters in these works are usually low-frequency (<100 kHz) high-power (>3W/cm^2) (Fig. 1a). With the addition of sonosensitizers and sonocatalysts, the ultrasonic parameters applied for UAT could be changed to high-frequency (>100 kHz) and low-power (<3W/cm^2) (Fig. 1a). The reduction of energy consumption is beneficial to promote the practical application of ultrasonic technologies. With the reduction of requirements for ultrasonic energy consumption, we hope that ultrasonic inactivation will also be well developed in the field of environment and food.

With the assistance of catalysts, ultrasound can inactivate Gram-positive and Gram-negative bacteria including *Staphylococcus aureus (S. aureus), Methicillin-resistant S. aureus (MRSA), Aggregatibacter actinomycetemcomitans, Listeria innocua, Bacillus cereus, Escherichia coli (E. coli), Extended-spectrum β-lactamase (ESBL)-producing E. coli, Porphyromonas gingivalis (P. gingivalis), Acinetobacter baumannii, Pseudomonas aeruginosa, and Legionella pneumophila* (Fig. 1b). Some of these bacteria are very difficult to be killed and prone to develop resistance. One of the best-known drug-resistant *S. aureus* is one major cause of hospital infections worldwide [32,33]. Disease-associated serotypes such as *E. coli* O157:H7, O121, and O104:H4 are capable of producing lethal toxins which have been found in water and soil [34-36]. In fact, due to the excessive use of antibiotics, many resistant bacteria have been found in water and soil. With the development of ultrasound / sonocatalyst, resistant bacteria in the environment are expected to be effectively controlled.

Some novel works reported that ultrasound could be used by the combination with catalyst and oxidant to kill bacterial cells [37]. Most studies using organic sonosensitizers tend to explore the inactivation path of bacteria rather than the number and types of free radicals from the aspect of sonochemistry (Fig. 1c). A typical example is the study of Xin et al. [38], maltohexaose-modified cholesterol and bacterial reactive lipid composition was used to establish a smart nanoliposome platform. This catalyst can specifically target the bacterial infection sites by activating bacterial specific maltose dextrin transport pathway. When different kinds of inorganic catalysts are applied, the types of free radicals become diverse. In addition to singlet oxygen ($^1O_2$), which was generated using organic sonosensitizers, other free radicals such as hydroxyl radical ($^{\bullet}OH$), superoxide radicals ($^{\bullet}O_2^-$), and $^{\bullet}HO_2$ were produced using ultrasound/inorganic sonocatalysts. These ROS have superior oxidation performance for bacterial inactivation. Interestingly, when organic sonosensitizers are combined with inorganic sonocatalysts, the main free radical produced is reported as $^1O_2$ and $^{\bullet}OH$. It is worth further study whether the organic/inorganic composite can improve the bacterial inactivation efficiency by producing a variety of

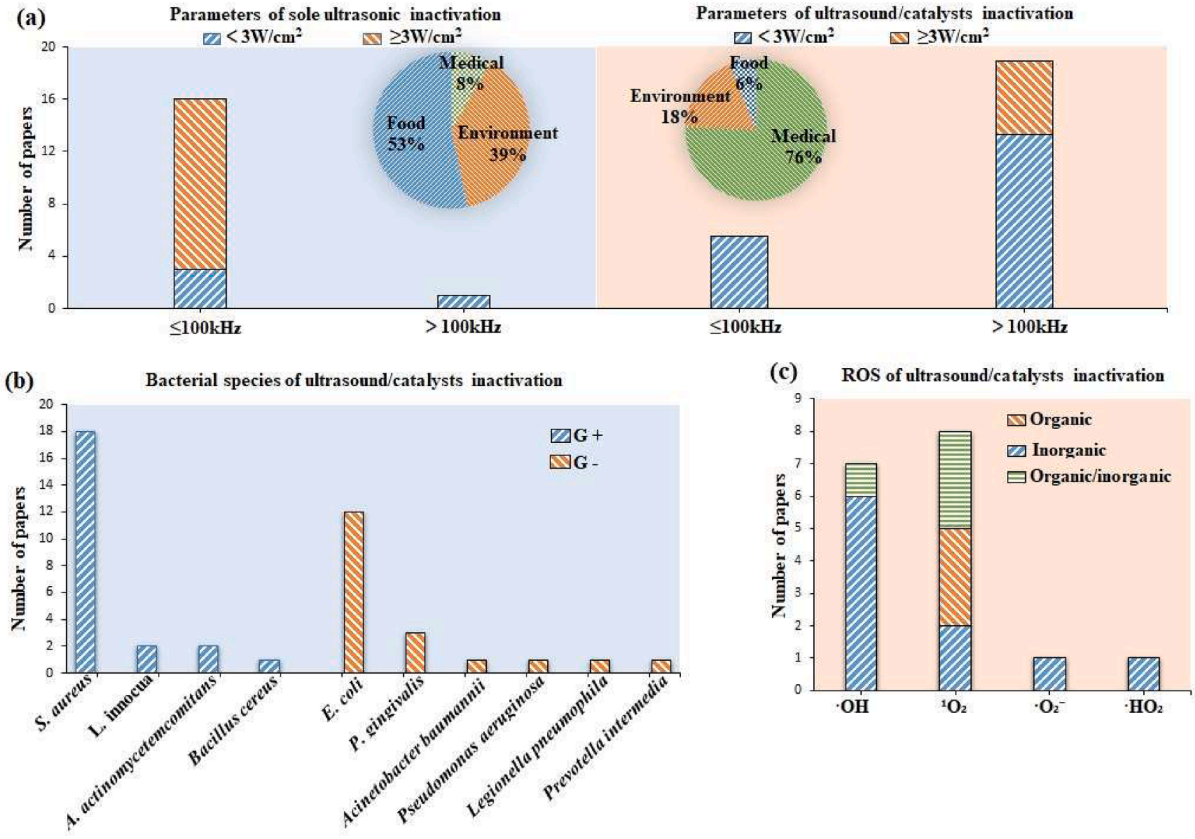

Fig. 1. Published reports on ultrasonic inactivation of bacterial cells with/without catalysts. (a) Parameters of ultrasound used for inactivation. (b) Inactivated bacterial species. (c) Generated ROS by ultrasound/catalysts.

free radicals in the ultrasonic field. In this regard, in the aspect of bacterial killing, we will discuss the ultrasonic activation mechanism of organic sonosensitizers and inorganic sonocatalysts, separately. We will then analyze the activation mechanism of the composite of organic/inorganic catalysts. It is hoped to help the design of ultrasonic inactivation catalysts.

3. Sonosensitizers/sonocatalysts for ultrasonic inactivation of bacterial cells

The cavitation effect refers to the process of rapid expansion, compression, and collapse of microbubbles in the liquid when sound pressure changes. It is one of the most important ultrasonic biological effects. According to different ultrasound parameters and organizational microenvironment, cavitation effects are divided into inertial cavitation and non-inertial cavitation. Inertial cavitation is closely related to ROS generation. Inertial cavitation bubbles absorb a large amount of sound energy, and the vibration of the bubbles causes violent collapse, generating high temperature (up to 10,000 K) and high pressure (81 MPa), thereby releasing a large amount of energy. So inertial cavitation can induce hydrothermal dissociation to generate •OH, •OH further reacts with other molecules to generate ROS and other oxidation reaction substrates [17,25].

At the same time, when the microbubbles collapse under inertial cavitation, the local rapid temperature rise is often accompanied by a luminescence phenomenon, which is called sonoluminescence. Studies showed that ultrasound could activate sonosensitizers from the ground state to the excited state through sonoluminescence [39,40]. Sonosensitizers directly react with surrounding oxygen molecules or other substrate molecules to form free radicals or release energy when returning to the ground state. The released energy interacts with the surroundings oxygen molecules, resulting in the production of $^1O_2$ [39,41,42]. Take inorganic sonocatalysts ZnO nanofluids as an example, after sonoluminescence excitation, the sonocatalyst with the gas nucleus and semiconductor property generate carriers, which separate and diffuse to the sonosensitizer surface. The electrons on the conduction band are captured by O_2 to generate a large amount of $^{\bullet}O_2^-$ (reaction 8) [24,43],

$$O_2 + e^- \rightarrow {}^{\bullet}O_2^- \quad (8)$$

the holes in the valence band may react with molecules in water to form •OH (reaction 9) [44],

$$H_2O + h^+ \rightarrow {}^{\bullet}OH + H^+ \quad (9)$$

at the same time, part of $^{\bullet}O_2^-$ can also be reduced to •OH and $^1O_2$ through electron induction (reactions (10,11)) [45,46].

$$^{\bullet}O_2^- + H_2O_2 \rightarrow {}^{\bullet}OH + OH^- + O_2 \quad (10)$$

$$2{}^{\bullet}O_2^- + 2H^+ \rightarrow {}^1O_2 + H_2O_2 \quad (11)$$

In this work, the sonosensitizers/sonocatalysts for ultrasonic inactivation are divided into organic sonosensitizers and inorganic sonocatalysts. Organic sonosensitizers are often derived from sonodynamic therapy for tumor treatment [47]. Inorganic catalysts, due to their semiconductor properties, show a variety of free radical generation mechanisms and good inactivation performance [48].

3.1. Organic sonosensitizers

Organic sonosensitizers used in UAT research mainly include porphyrin or its derivatives, xanthone, and the other organic sonosensitizers like curcumin (Cur) and hypocrellin B (Table 1). Porphyrin or

Table 1
Review of ultrasonic inactivation using sonosensitizers and sonocatalysts reported in the literature.

Types of sonosensitizers	Names of the sonosensitizers	Types of ROS	Parameters of ultrasound	Microorganism	Processing time	Highest inactivation efficiency[a]	Ref.
Porphyrin organic sonosensitizer	Hematoporphyrin monomethyl ether (HMME)	Not mentioned	1 MHz 100 Hz PRF 6 W/cm^2 30% cycle	*Staphylococcus aureus (S. aureus) (G +)*	30 min	95%	[51]
	HMME	Not mentioned	1 MHz 3 W/cm^2	*Porphyromonas gingivalis (P. gingivalis) (G-)*	10 min	99.997%[b]	[52]
	Fe@ upconversion nanoparticles (UCNP)-HMME	$^1O_2$	2 W/cm^2	*Methicillin-resistant S. aureus (MRSA) (G +)* *Extended-spectrum β-lactamase (ESBL)-producing Escherichia coli (E. coli) (G-)*	10 min	70% 60%	[65]
	Polymer-peptide-porphyrin conjugate (PPPC)	Not mentioned	1 MHz 1.5 W/cm^2	*MRSA (G +)*	0–9 min	100%	[53]
	Pd @ Pt-T790	Not mentioned	1 MHz 0.97 W/cm^2 50% cycle	*MRSA (G +)*	8 min	100%	[29]
Xanthones organic sonosensitizer	Rose Bengal (RB)	Not mentioned	28 kHz 0.84 W/cm^2	*S. aureus (G +)* *E. coli (G-)*	1 h	99.999% 99.998%	[55]
	RB	Not mentioned	1 MHz 2.5 W/cm^2	*Candida albicans (C. albicans)*	5 min	100%	[66]
	RB–antimicrobial peptide conjugate	Not mentioned	1 MHz 3 W/cm^2 50% cycle	*S. aureus (G +)* *Pseudomonas aeruginosa (G-)*	30 min	99.997% 99.999%	[56]
	erythrosin B	Not mentioned	20 kHz 0.86–0.90 W/mL	*Listeria innocua (G +)*	10 s	99.874%	[37]
Other organic sonosensitizer	Curcumin (Cur)	Not mentioned	1 MHz 1.56 W/cm^2	*MRSA (G +)*	5 min	99.999%	[60]
	Cur	Not mentioned	1 MHz 1.56 W/cm^2	*Bacillus cereus (G +)* *E. coli (G-)*	3 min 5 min	99.999% 99.000%	[61]
	Cur	Not mentioned	1 MHz 3 W/cm^2	*S. aureus (G +)*	32 min	99%	[67]
	Cur	Not mentioned	1 MHz 2 W/cm^2	*Aggregatibacter actinomycetemcomitans (G +)*	2 min	99.999%	[68]
	Propyl gallate	Not mentioned	40 kHz 0.092 W/mL	*Listeria innocua (G +)* *E. coli (G-)*	10–45 min 5–30 min	99.999%	[69]
	Nano-emodin	Not mentioned	1 MHz 100 Hz PRF 2 W/cm^2	*S. aureus (G +)* *P. gingivalis (G-)* *Acinetobacter baumannii (G-)*	5 min	99.999%	[63]
	Photodithazine	$^1O_2$	1 MHz 2.5 W/cm^2	*C. albicans*	5 min	100%	[66]
	Chlorin e6	Not mentioned	1 MHz 1.56 W/cm^2	*S. aureus (G +)* *E. coli (G-)*	5 min	99.999% 99.000%	[64]
	Hypocrellin B	Not mentioned	1 MHz 1.56 W/cm^2	*MRSA (G +)*	5 min	99.999%	[62]
	MLP18	$^1O_2$	1 MHz 0.97 W/cm^2	*MRSA(G +)* *ESBL-producing E. coli(G-)*	5 min	95% 80%	[38]
	Amphotericin B	Not mentioned	42 kHz 0.30 W/cm^2	*C. albicans*	15 min	99.65%	[70]
Inorganic sonocatalysts	TiO_2	Not mentioned	25 kHz 50 W	*E. coli(G-)*	60 min	95.6%	[31]
	TiO_2	•OH	36 kHz 300 W	*Legionella pneumophila (G-)*	30 min	99.8%	[71]
	TiO_2	Not mentioned	26 kHz 1.5 W/mL	*total coliforms (G-)* *faecal coliforms (G-)* *Pseudomonas spp (G-)* *faecal streptococci (G +)* *Clostridium perfringens species (G +)*	60 min	99.9% 99.9% 99.9% 72.8% 87.1%	[72]
	Non-woven TiO_2	•OH	36 kHz 0.28 W	*E. coli (G-)*	60 min	92.057%	[40]
	Ti-S-TiO_{2-x}	$^1O_2$ •OH	1 MHz 1.5 W/cm^2 50% cycle	*S. aureus (G +)*	15 min	99.995%	[73]
	ZnO nanofluids	$•O_2^-$ $•HO_2$ •OH	20 kHz 90 W/L	*E. coli (G-)*	10 s	83%	[17]
	ZnO_{ext}	•OH	20 kHz	*S. aureus (G +)* *E. coli (G-)*	Not mentioned	90%[b] 85%[b]	[74]
	Au@barium titanate	$^1O_2$ •OH	1 MHz 1.5 W/cm^2	*S. aureus (G +)* *E. coli (G-)*	4 min	99.23%	[24]
	UCNP@mSiO_2(RB)-Ag	$^1O_2$	2 W/cm^2	*MRSA (G +)*	10 min	98.94%	[75]

(*continued on next page*)

Table 1 (*continued*)

Types of sonosensitizers	Names of the sonosensitizers	Types of ROS	Parameters of ultrasound	Microorganism	Processing time	Highest inactivation efficiency[a]	Ref.
Organic sonosensitizer combined with inorganic sonocatalysts	UCNP@SiO_2- RB/HMME	$^1O_2$	2 W/cm^2	*MRSA (G +)* *ESBL-producing E. coli (G-)*	10 min	70%	[76]
	Chitosan Nanoparticles-Indocyanine green	Not mentioned	1 MHz 1.56 W/cm^2	*Aggregatibacter actinomycetemcomitans (G +)* *P. gingivalis (G-)* *Prevotella intermedia (G-)*	1 min	99.999%	[77]
	TiO_2-Sinoporphyrin sodium	$^1O_2$ •OH	1 MHz 1–5 W	*S. aureus (G +)*	60 s	92.41%	[78]
	Dextran-coated Si	Not mentioned	1 MHz 3 W/cm^2	*E. coli (G-)*	10 min	100%	[79]

a: Inactivation efficiency: defined as (1-N_T/N_0) *100%, where N_T refers to the number of CFU/mL after treatment and N_0 refers to the number of CFU/mL before treatment.

its derivatives is an effective sonosensitizer in sonodynamic therapy with a stable structure, lower toxicity, higher $^1O_2$ yield to induce cell apoptosis via the mitochondrial apoptotic pathway [49], and $^1O_2$ is generated by energy transfer between the triplet excited state sensitizer and O_2 [50]. Zhuang et al. [51] observed hematoporphyrin monomethyl ether (HMME) as a sonosensitizer for bacterial inactivation. When HMME was combined with ultrasound for inactivating *P. gingivalis* [52], the expression level of ROS in bacterial cells was significantly increased, suggesting that ROS could be the main cause of cell death. Sun et al. [29] bridged an organic sonosensitizer Meso-tetra (4-carboxyphenyl) porphyrin with Pd@Pt nanoplates. When the sonosensitizers were absorbed by cells, Pd@Pt promoted the decomposition of O_2 by endogenous H_2O_2 to increase the production of endogenous ROS. Wang et al. [53] modified porphyrin with the bacterial targeting peptide to improve the inactivation efficiency.

Xanthone compound Rose Bengal (RB) is not toxic [54], and under sonication, it could react with oxygen to produce $^1O_2$. When RB was applied as a sonosensitizer to inactivate *S. aureus* and *E. coli*, *E. coli* showed stronger resistance to UAT than that of *S. aureus* [55]. Since the special outer membrane of *E. coli* can effectively prevent RB from entering the cell, it reduces the yield of endogenous ROS and inactivation efficiency. To enhance the inactivation efficiency of RB, Costley et al. [56] coupled bacterial targeting peptides with RB to prepare RB-antimicrobial peptide conjugates, which effectively inactivate *Pseudomonas aeruginosa*.

Since Cur and hypocrellin B are natural pigments, Cur could be extracted from popular Indian spice turmeric and hyppcrellin B could be isolated from the parasitic fungus *Hypocrella bambusae*. Besides being used in clinical treatment, recent studies have found that they can also be used as sonosensitizers for ultrasonic inactivation [57-59]. Wang et al. [60,61] found that Cur has a good inactivation effect on *S. aureus, E. coli,* and *Bacillus cereus,* which does not depend on intracellular DNA damage. In addition, *E. coli,* as Gram-negative bacteria, has stronger resistance to Cur/ultrasound. It is probably due to its outer membrane effectively preventing Cur from entering the cell. Wang et al. [62] further investigated hypocrellin B combined with ultrasound for the inactivation of methicillin-resistant *S. aureus*. Interestingly, they found no DNA damage but the destruction of bacterial membranes which lead to the death of the bacteria.

In addition, there are some other organic sonosensitizers such as nano-emodin [63], chlorin e6 [64], chrysanthemum B [62] (table 1) used for ultrasonic inactivation, and they have achieved good bacterial removal effects. However, organic sonosensitizers have poor water solubility, short blood circulation time, and they are relatively unstable in the environment. To overcome the above shortcomings, researchers are developing inorganic nanomaterials as sonocatalysts.

3.2. Inorganic sonocatalysts

Inorganic sonosensitizers are featured as stable physical and chemical properties [80]. At present, regulating the physical and chemical structure of sonocatalysts to generate more free radicals under ultrasound irradiation is a hotpot. Traditional inorganic sonocatalysts such as titanium dioxide and gold nanoparticles have been found to effectively assist ultrasonic inactivation.

As a typical sonocatalyst, TiO_2 NPs have been applied to microbial inactivation [31,71,72,81,82]. Ultrasound can excite the electrons in TiO_2 NPs from the valence band to the conduction band which will form holes and makes some electron-hole pairs migrate to the surface of the nanoparticles and interact with the surrounding H_2O or O_2, and such interactions produce ROS such as •OH and $^1O_2$ [25,83,84]. However, due to the fast electron-hole recombination speed of TiO_2 NPs (50 ± 30 ns), the yield of ROS is not high [85]. Moreover, the agglomeration of NPs prevents the separation of electron-hole pairs from the energy band, resulting in a further decrease in ROS yield [86]. Changing the structure of TiO_2 NPs can also change their catalytic activity. Rahman et al. [40] synthesized a non-woven structure of TiO_2 NPs (Fig. 2) combining with ultrasound to effectively inactivate *E. coli.* The production of •OH significantly increased when non-woven TiO_2 NPs were activated by ultrasound. The authors suggested that non-woven TiO_2 NPs can provide more cavitation bubbles to enhance the cavitation bioeffects.

Due to its non-toxicity, Au NPs are widely used as nanocarriers for drug delivery [87,88]. Au NPs serve as nucleation sites, lower the cavitation threshold and further increase the cavitation rate [89]. Wu et al. [24] synthesized a piezoelectric nanocomposite material, barium titanate ($BaTiO_3$, BTO) nanocubes loaded with Au NPs (Au@BTO NPs), resulting in the separation and migration of electron-hole pairs, which in turn increases the yield of ROS (•OH, $^1O_2$) for inactivating *S. aureus* and *E. coli*. This work suggested that BTO has an excellent electromechanical conversion rate and high-voltage electrical coefficient. Au NPs are chemically reduced to loaded on the surface of BTO, forming a metal/semiconductor Schottky junction. This may bend the energy band of BTO and promote the mechanical deformation and piezoelectric effect of BTO caused by the low-intensity ultrasonic mechanical wave.

3.3. The combination of organic sonosensitizers and inorganic sonocatalysts

The combination of organic sonosensitizers and inorganic sonocatalysts can overcome the shortcomings of a single material and even endow the catalyst to realize multi-mechanism inactivation. For example, the electron holes produced by titanium oxide will recombine rapidly, resulting in the decrease of free radical production. To conquer this issue, Wang et al. [78] chemically modified TiO_2 NPs with organic substances to inactivate *S. aureus*. The hybrid catalyst can alleviate the agglomeration of TiO_2 NPs, promote the separation of electron-hole pairs from the energy band during ultrasonic activation, and thus increase the ROS yield. Zhao et al. [75] designed a new core–shell nanostructure upconversion nanoparticles@mSiO_2(RB)-Ag NPs. In this kind of NPs, RB, as a sonosensitizer, reacts with O_2 in water to produce $^1O_2$

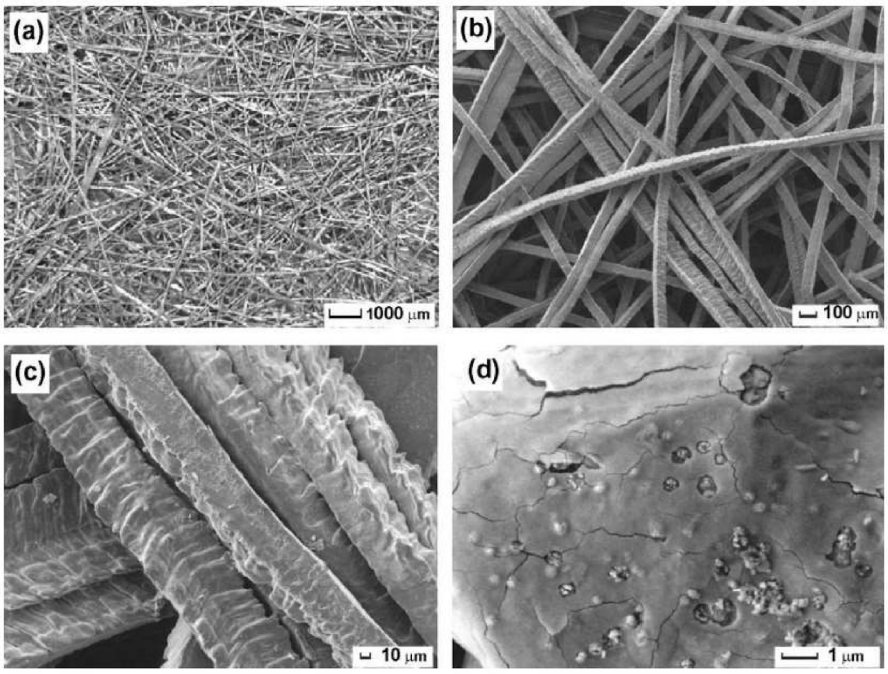

Fig. 2. Photograph of non-woven TiO_2 fabric (a), surface view of non-woven TiO_2 fabric by scanning electron microscopy with different magnifications (b–d).

after being activated by ultrasound. It is worth noting that Ag has a long-term inhibitory effect on bacteria. Compared with metal nanomaterials, Si NPs show lower cytotoxicity and have proved to be biodegradable [90-92]. Shevchenko et al. [79] synthesized Dextran-coated Si NPs to inactivate *E. coli*, and all bacteria were killed after 10 min ultrasound irradiation. In addition, iron-based nanomaterials have good Fenton catalytic activity, which expedites the decomposition of H_2O_2 into O_2 to provide a reaction substrate for ROS generation [93]. Following this idea, Wang et al. [65] synthesized Fe@UCNP-HMME NPs for the inactivation of *MRSA* and *ESBL-producing E. coli*.

Sonosensitizers/sonocatalysts are closely related to the ROS production efficiency of the cavitation effect. Organic sonosensitizers often catalyze to produce •OH and $^1O_2$. Due to the addition of inorganic sonocatalyst, there are more kinds of free radicals. By studying the physical and chemical structure of inorganic nanomaterials, the mechanism of ROS generation using ultrasound and inorganic sonocatalyst could list as below:

The separation and recombination of electrons and holes at the surface of semiconductors could be mediated to promote the generation of ROS under ultrasonic activation [94,95].
Inorganic nanoparticles with oxygen defect structures can also improve the yield of ROS by efficiently adsorbing H_2O_2 and O_2 in the microenvironment as reaction substrates to further raise ROS production [96,97].
It is also possible to promote the production of ROS by Fenton catalysts [30,98,99].
The combination of organic and inorganic sonocatalysts can produce a variety of free radicals.

4. Cellular Oxidation — Antibacterial Mechanism of ROS

The biological effects of ultrasound can be divided into extracellular oxidation and intracellular oxidation, the former damage the cell membrane through lipid peroxidation, and the latter causes gene and protein damage through oxidative stress (Table 2). It is worth exploring which kind of oxidation is more important in the bacterial inactivation process.

Table 2
Mechanisms of UAT in different works.

Sonosensitizers	Purpose	Mechanisms	Ref.
HMME	Medical	Increase in intracellular ROS	[52]
PPPC	Medical	Cell membrane damage	[53]
Fe@UCNP- HMME	Medical	Cell membrane damage	[65]
UCNP@SiO_2-RB/HMME	Medical	Cell membrane damage	[76]
Pd @ Pt-T790	Medical	Increase in intracellular ROS	[29]
Cur	Food	DNA damage[a]	[61]
Cur	Medical	DNA damage[a]	[60]
Cur	Medical	Downregulation in virulence genes	[68]
Cur	Medical	Cell membrane damage	[67]
Hypocrellin B	Medical	Cell membrane damage DNA damage[a]	[62]
Nano-emodin	Medical	Downregulation in virulence genes	[63]
Propyl gallate	Food	Lipid peroxidation	[69]
Amphotericin B	Medical	Increase in intracellular ROS	[70]
MLP18	Medical	Cell membrane damage Increase in intracellular ROS Drug delivery	[38]
TiO_2	Medical	Oxidative stress response	[71]
Non-woven TiO_2	Environment	Lipid peroxidation	[40]
Ti-S-TiO_{2-x}	Medical	Cell membrane damage	[73]
TiO_2-Sinoporphyrin sodium	Medical	Cell membrane damage Increase in intracellular ROS	[78]
ZnO nanofluids	Environment	Cell membrane damage Drug delivery	[17]
ZnO_{ext}	Medical	Cell membrane damage	[74]
Dextran-coated Si	Medical	Cell membrane damage	[79]
UCNP@mSiO_2(RB)-Ag	Medical	Cell membrane damage	[75]
Au@barium titanate	Medical	Lipid peroxidation	[24]

a: The authors conducted related research, but got negative results.

4.1. Extracellular oxidation — cell membrane damage and lipid peroxidation

For extracellular oxidation, the ROS produced by ultrasound or sonosensitizers can oxidize biological cell membranes [53], since ROS could react with phospholipids, enzymes related to the membrane, side chain of membrane receptor-associated polyunsaturated fatty and

nucleic acid to form lipid peroxidation products [100]. As a result, the fluidity and permeability of the cell membrane are changed, ultimately leading to changes in the structure and function of bacteria, and even cell death. This chain reaction is called lipid peroxidation. Moreover, it provides a continuous supply of ROS, and the newly generated ROS further react with other surrounding cells. This results in apoptosis or death, therefore improving the efficiency of inactivation. Rahman et al. [40] studied the effect of non-woven TiO_2 combined with ultrasound on lipid peroxidation of cell membranes and found that •OH produced by the reaction of non-woven TiO_2 significantly increased the lipid peroxidation level of bacteria membranes. Wu et al. [24] found that Au@BTO NPs combining with ultrasound had an excellent antibacterial efficiency against both Gram-negative *E. coli* and Gram-positive *S. aureus*, they deduced that the sonodynamic ROS generation induced lipid peroxidation in cytomembrane, which enhanced the permeability of cell membrane and finally led to the intracellular protein leakage and irreversible damage to bacteria. Martins et al. [101] got the same result in cancer cells, they studied the application of zinc phthalocyanine (ZnPc) as a sonosensitizer and discovered that the level of cellular lipid peroxidation increased three times after sonication.

Studies have shown that the outer membrane of the Gram-negative bacteria will also be oxidized and destroyed by ROS. By cutting the glycoside backbone to break the biopolymer, the composition and function of these cells are changed, which causes bacterial death [102,103]. But the highly organized bacterial outer membrane of Gram-negative bacteria may inhibit the absorption of sonosensitizers, resulting in a lower inactivation effect than that of Gram-positive bacteria [38].

4.2. Intracellular oxidation — cellular oxidative stress response

For intracellular oxidation, oxidative stress refers to the imbalance between the oxidation and anti-oxidation effects of biological cells. When the cells tend to be oxidized, the secretion of proteases increases, and a large amount of oxidative intermediate products are generated. Oxidative stress is a negative effect of oxygen free radicals intracellularly, which is closely related to cell apoptosis and death [104]. In the process of sonication, ultrasound and sonosensitizers produce a large amount of ROS, leading to cellular oxidative stress response, which is also one of the main antimicrobial mechanisms.

Studies have indicated that ROS produced in the cells can lead to the oxidation of intracellular proteins [105]. •OH attacks electron-rich sites, such as the double bond chain and main chain on the amino acid side [106,107]. So the specific function of the corresponding protein is inhibited, leading to dysfunction of the microbial cell and eventually death. In addition, •OH produced by microbial cells themselves can also damage intracellular nucleic acids, such as cutting the double helix structure of nucleic acids or modifying nucleic acids with nitrogen bases [108,109]. The normal physiological functions of microbial cells are interfered, causing cell death. Zhang et al. [52] used HMME combining with ultrasound to inactivate *P. gingivalis*, they found that UAT can increase the intracellular yield of ROS, and cause the death of bacteria. The same phenomenon was observed by Yang et al. [70], they synthesized amphotericin B-loaded nanoparticles combining with ultrasound to effectively inactivate *Candida albicans* by intracellular ROS produced by UAT. Pourhajibagher et al. further clarified that UAT can downregulate specific genes in cells. They found that the Curcumin-decorated nanophytosomes-mediated ultrasound could reduce the cell viability, metabolic activity, and biofilm growth in *Aggregatibacter actinomycetemcomitans* by downregulating the expression of rcpA, qseB, and qseC genes [68]. Meanwhile, nano-emodin-mediated ultrasound could significantly downregulate the expression levels of lasI, agrA, and abaI as the virulence genes in *Pseudomonas aeruginosa*, *S. aureus*, and *Acinetobacter baumannii*, causing the reduction of the formation of bacterial biofilms and the viability of bacteria [63].

To visually explain the importance of extracellular/intracellular oxidation on ultrasonic inactivation in different works, Fig. 3 was produced according to the studies listed in table 2. When inorganic sonosensitizers are used alone or in combination, Researchers pay more attention to extracellular oxidation (Fig. 3a), only a few studies include both extracellular oxidation and intracellular oxidation. Meanwhile, medical-related studies focus more on the oxidation effect on cells (Fig. 3b).

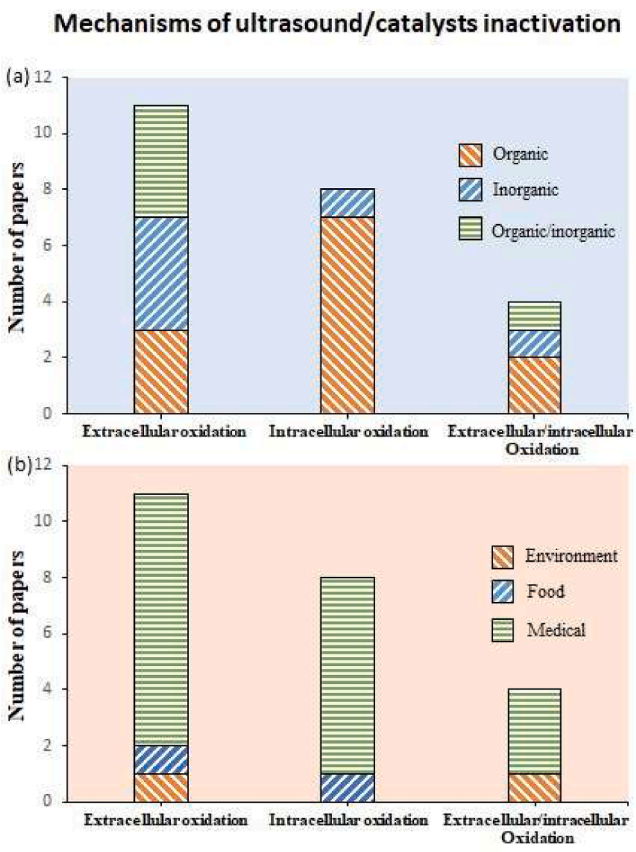

Fig. 3. Published reports on ultrasonic inactivation of bacterial cells with catalysts. (a) Mechanisms of different catalysts. (b) Mechanisms of different applications.

Both extracellular and intracellular oxidation may play a very important role in the ultrasonic inactivation process. However, there are still disputes. For example, Wang et al. [61] clarified that ultrasound/Cur did not damage the DNA of *E. coli*, while the outer membrane significantly affects the antimicrobial effect of UAT. Thus, it seems that intracellular and extracellular oxidation does not necessarily exist at the same time.

5. Conclusion

With the development of functional nanomaterials, ultrasonic inactivation technology is gradually combined with nanomaterial technology, which has brought about significant changes in this field. To cast more lights on the ultrasound in tandem with catalysts for bacterial killing, the key findings are summaries as below:

(1) For bacterial inactivation, low-frequency high-power ultrasound is gradually replaced by high-frequency low-power ultrasound.
(2) Organic sonosensitizers show the advantage of low biological toxicity and produce highly active singlet oxygen. However, the manufacturing cost of these organic sonosensitizers is high and its application field is narrowed in medical application.
(3) With the development of inorganic sonocatalysts, the combination of ultrasound and inorganic sonocatalysts can be better used

in the field of environment and food. Particularly, semiconductor catalysts produce free radicals through hole electron separation in the sound field, which is an interesting mechanism and opens the way for the design of unique inorganic catalysts.

(4) Lipid peroxidation and oxidative stress may not exist at the same time during UAT. In different strategies of ultrasonic inactivation, intracellular and extracellular oxidation may work separately. So far, it is unclear how to accurately regulate intracellular and extracellular oxidation.

In summary, oxidation is the key to ultrasonic inactivation using low-intensity ultrasound. Sonocatalysts can promote the application of UAT from the perspective of increasing the yield of ROS and reducing energy consumption, but it is essential to develop high-efficiency nano-sonosensitizers and/or sonocatalysts to increase the yield of ROS and clarify the relationship between ROS generation and the regulation of intracellular and extracellular oxidation. The review could be helpful for the development of a controllable, efficient, and safe ultrasonic antimicrobial technology.

CRediT authorship contribution statement

Gongdao Wang: Writing – original draft, Formal analysis. **Wei Wu:** Conceptualization, Funding acquisition, Writing – review & editing. **Jun-Jie Zhu:** Conceptualization, Writing – review & editing. **Danhong Peng:** Writing – review & editing.

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.

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