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Rare-earth ions as antibacterial agents for woven wool fabric

Shota Akioka[1] · Shinji Hirai[1] · Kenta Iijima[1] · Akihiro Hirai[2] · Mohammed Abdullah Hamad Alharbi[1]

Abstract

Woven fabrics were bestowed with antibacterial property by the simple adsorption of rare-earth metal ions, and the underlying mechanism was investigated using electron spin resonance (ESR) spectroscopy. The adsorption of Ce^{3+} ions on wool, silk, and cotton fabrics resulted in significant inhibition of *Staphylococcus aureus* (a gram-positive bacterium), with maximum antibacterial activities (viable bacterial count compared to the reference) of 4.7, 5.8, and 5.2, respectively. Even after 50 wash cycles, the values remained at 3.9, 2.9, and 4.8, respectively. The adsorption of La^{3+} and Gd^{3+} ions on wool fabrics also resulted in antibacterial activities of 5.8 and 5.9, respectively. In addition, wool adsorbed with Ce^{3+} exhibits a satisfactory antibacterial activity of 6.2 against *Escherichia coli* (a gram-negative bacterium). Such bacterial inhibition is attributed to Fenton reactions between the adsorbed rare-earth ions and hydrogen peroxide (H_2O_2) produced during bacterial metabolism, as determined from the ESR spectra collected using the spin trap method in the presence of H_2O_2. The safety of cerium nitrate was also investigated, and no significant issues arose, indicating that it was a safe antibacterial agent. This facile method of imparting antibacterial properties to natural fabrics may be useful for preventing infections in humans.

Keywords Rare-earth ions · Wool · Cerium · Antibacterial activity · Adsorption · Fabric treatment

Introduction

Existing antibacterial/deodorizing finishing agents used in fabrics include quaternary ammonium salts (i.e., cationic surfactants as the main component of invert soap), organic compounds such as triclosan, and inorganic compounds, including silver ions supported on zeolite, titanium oxide, and zinc oxide (Bekrani et al. 2020; Espitia et al. 2012; Galal et al. 2011; Ghiasi et al. 2021; Lu et al. 2007; Zhang et al. 2009). For example, silver is often used as an antibacterial substance, although it may have genotoxicity and its carcinogenic potential is needed to assess additionally (Hadrup et al. 2018; Wen et al. 2017). Inorganic antibacterial agents exhibit excellent thermal stability and good durability; however, they are more expensive than organic compounds (Yamamoto and Sawai 2002).

The antibacterial activity of silver ions is attributed to the strong binding of the eluted silver ions onto the thiol group (–SH) of cysteine in bacteria (Yuan et al. 2013), which facilitates the formation of a silver complex. Silver may be excreted extracellularly as a soluble or sparingly soluble compound (e.g., stable silver sulfate or metallic silver) or through sequestration in proteins containing large numbers of –SH groups (Russell and Hugo 1994) and nitrogen groups (–N–) (Izatt et al. 1971). Moreover, silver ions can kill bacteria by interfering with their metabolic system, demonstrating bactericidal activity (Yamamoto 1999).

The antibacterial property of woven wool fabric increases slightly after immersion in an aqueous solution of silver nitrate ($AgNO_3$). However, wool contains ~ 85% keratin (Bradbury 1973; Kulkarni and Baumann 1980), which includes 10.5 mol% air-oxidized cysteine (Bradbury 1973). The sulfur therein can react with silver to produce Ag_2S and cause fabric discoloration (Tsukada 2004). Therefore, silver compounds are not suitable antibacterial agents for wool products. However, the alternatives of ZnO and TiO_2 are activated under UV irradiation, but the amount of UV exposure fluctuates widely during the course of the day (Gaya and Abdullah 2008; Eren et al. 2015).

✉ Shota Akioka
19096001@mmm.muroran-it.ac.jp

1 Research Center of Environmentally Friendly Materials Engineering, Muroran Institute of Technology, 27-1 Mizumoto-cho, Muroran, Hokkaido 050-8585, Japan

2 NTT Medical Center Tokyo, 5 Chome-9-22 Higashigotanda, Shinagawa City, Tokyo 141-8625, Japan

The demand for rare-earth elements in Japan has decreased to approximately one-third of the peak value due to various factors such as a sharply reduced need for abrasives (Japan Oil, Gas and Metals National Corporation (JOGMEC) 2015; Morimoto and Seo 2014). Despite growing demand for certain elements (especially praseodymium, neodymium, dysprosium, and terbium for magnets), light rare-earth elements such as yttrium, lanthanum, and cerium are now in excess due to the balance of rare-earth ore composition. Rare-earth ions can be obtained in the form of sulfates from waste treatment using sulfation and in the form of acid salts from the leaching stage (Ren et al. 2018). Thus, the development of effective applications of these ions, especially in the form of nitrides, is valuable. Furthermore, cerium nitrate is present in the spent nuclear fuel from nuclear power plants (Sanpei et al. 2002), and its effective use can help reduce the environmental pollution caused by such effluents. Therefore, we believe that this technology can be environmentally friendly in terms of process, energy saving, and the effective use of waste materials.

Several studies have demonstrated the use of light rare-earth elements as antibacterial agents, especially the relatively more abundant cerium (Lin et al. 2007; Liu 2007; Manikandan et al. 2017; Nose and Okabe 2012; Pourkhorsandi et al. 2021; Shah et al. 2012). Recently, the complex oxide $La_2Mo_2O_9$ (LMO) was found to have hydrophobic properties and antibacterial effects against gram-negative and gram-positive bacteria. It also inhibited non-enveloped (bacteriophage Qβ) and enveloped (bacteriophage Φ6) viruses (Matsumoto 2019). Φ6 resembles and can be used as a surrogate for influenza viruses and SARS-CoV-2 (the pathogen causing COVID-19) (Ito et al. 2021; Wang et al. 2020). Matsumoto et al. (2020) reported that the activity of LMO against bacteriophage Φ6 can be improved by substituting lanthanum with cerium. Moreover, γ-$Ce_2Mo_3O_{13}$ exhibited high activity against both Φ6 and SARS-CoV-2, possibly due to the valence fluctuation of cerium (Ito et al. 2021). Cerium has two stable ionic forms, namely Ce^{3+} and Ce^{4+}. Ce^{3+} has one 4f electron that is nearly the same as the outer 5d and 6s electrons that are lost upon ionization; thus, cerium can also form Ce^{4+}, which is unique among rare-earth metals. Heckert et al. (2008) attributed such a high activity to a "Fenton-like reaction" through the valence fluctuation of cerium. The hydroxyl radical (·OH) has high antibacterial activity owing to the strong oxidizing property, as indicated by its very positive standard electrode potential among reactive oxygen species. It damages not only the cell walls but also the entire microbe. Iron is a strong redox cycling metal and is known to react with hydrogen peroxide (H_2O_2) to produce ·OH via the Fenton reaction (Heckert et al. 2008; Imlay 1988). Similarly, copper, cadmium, chromium, mercury, nickel, and vanadium have all been reported

to generate reactive radicals in the presence of H_2O_2 (Matsumoto 2020; Valko et al. 2005).

Wool is used to make sweaters, suits, etc., and approximately 1 million tons of wool are produced per year (International Wool Textile Organisation 2016). Natural fibers have many hydrophilic (–OH and –COOH) groups, which have a high affinity for metals. In particular, in wool keratin, amino acids with nitrogen-containing side chains (lysine, arginine, and particularly histidine) exhibit a strong affinity toward metal ions (Craig et al. 1954; Cuadrado et al. 2000). However, the outer layer of wool cuticle cells (scales) is protected by a high degree of cystine cross-linking, and the surface is hydrophobic. In a previous study, we used chlorine treatment to remove these cuticular cells, which drastically improved metal cation adsorption (Akioka et al. 2021).

This study investigates the antibacterial property of natural fibers (particularly wool) adsorbed with light rare-earth ions using simple immersion in solutions of light rare-earth salts (nitrates; primarily, cerium nitrate). Furthermore, the underlying mechanism of antibacterial action in the rare-earth-adsorbed fabric is elucidated. We also compared the antibacterial activities following treatment using other rare-earth elements. Finally, we tested the proposed treatment on silk and cotton fabrics.

Experimental

Materials

Woven fabric of merino wool was supplied by The Japan Wool Textile. Co., Ltd., Osaka, Japan. The average diameter of a single wool fiber was 20.5 μm. Chlorination was carried out by passing the fabric through a solution comprising sodium hypochlorite and potassium permanganate. This is a standard industrial anti-shrinkage treatment method followed by suppliers (Kawahara 1981).

A mixed solution was prepared with 10 mg L^{-1} each of 16 kinds of rare-earth ions. The solution contained inductively coupled plasma (ICP) standard solution F, cerium (III) nitrate ($Ce(NO_3)_3$), cerium (IV) diammonium nitrate (($NH_4)_2[Ce(NO_3)_6]$), lanthanum (III) nitrate ($La(NO_3)_3$), gadolinium (III) nitrate ($Gd(NO_3)_3$), and cerium (III) acetate hydrate ($Ce(CH_3COO)_3 \cdot H_2O$). These chemicals were purchased from Kanto Chemical Co., Inc., Tokyo, Japan. Other chemicals were purchased from Solvay Special Chem, Tokushima, Japan. In some experiments, powdered CeO_2 (Solvay Special Chem) was used in place of $Ce(NO_3)_3$ to produce a high pH immersion liquid. Electron spin resonance (ESR) measurements were performed using H_2O_2 (Kanto Chemical Co. Inc.), and 5-(2,2-dimethyl-1,3-propoxycyclophosphoryl)-5-methyl-1-pyrroline *N*-oxide (CYPMPO) (Cayman Chemical Co., Ltd.) was used as a

spin-trapping agent. The $Ce(NO_3)_3$ used in the safety test was provided by Santoku Corporation, Hyogo, Japan.

The wool surfaces were examined by scanning electron microscopy (SEM) (JSM-6610LA, JEOL Corporation, Tokyo, Japan) at an accelerating voltage of 20 kV and magnifications of $\times 1000, \times 2500$, and $\times 5000$.

ICP mass spectrometry

The concentrations of various ions in the aqueous solution were quantified using inductively coupled plasma–atomic emission spectrometry (ICP-AES) (ICPE-9800, Shimadzu, Kyoto, Japan). The woven fabric was immersed in the mixed standard solution containing 10 mg L^{-1} each of 16 kinds of rare-earth ions at an input of 10 g of fabric per liter of solution (referred to as g L^{-1} fabric to solution hereafter) and stirred at room temperature (20–25 °C) for 24 h. The recovery of the rare-earth ions was defined as the change ratio of metal concentration after immersion:

$$\text{Recovery (\%)} = \left[(C_b - C_a)/C_b \right] \times 100, \tag{1}$$

where C_a and C_b are the metal ion concentrations after and before immersion, respectively.

Antibacterial treatment of woven wool fabric

Wool with an input of 10 g L^{-1} fabric to solution was immersed in an aqueous solution of $Ce(NO_3)_3$ with a cerium concentration of 5% o.w.f (the weight of antibacterial agents against the weight of fiber). In some tests, 12% o.w.f cerium (III) acetate $(Ce(CH_3COO)_3)$ was used instead of $Ce(NO_3)_3$ at the same concentrations to increase the pH

of the immersion liquid. The immersion time ranged from 40 min to 48 h. Following immersion, the fabric was thoroughly washed with water, dried at room temperature, and then subjected to antibacterial tests. Furthermore, the woven fabric was washed 10 or 50 times for 4 min following Japanese Industrial Standard (JIS) L-2017-103, and the antibacterial activity was then evaluated after each wash cycle and the final wash cycle to determine the suitability for practical application.

Three immersion liquids were prepared using $(NH_4)_2[Ce(NO_3)_6]$, $La(NO_3)_3$, or $Gd(NO_3)_3$ at the concentrations mentioned above. Another suspension contained 10% o.w.f CeO_2 powder in distilled water. We evaluated the antibacterial properties of fabrics following immersion in these four liquids, as well as that of pure CeO_2 powder.

Antibacterial analysis

The antibacterial properties were analyzed following the protocol outlined in JIS L 1902:2015 and ISO 20743. Before analysis, all fabric samples were sterilized in an autoclave. Subsequently, 0.2 mL of solution containing *Escherichia coli* (gram negative) or *Staphylococcus aureus* (gram positive, $1-3 \times 10^5$ colony forming units mL^{-1}) and 0.05% of a nonionic surface-active agent (Tween 80, Bio Medical Science, Tokyo, Japan) were inoculated onto the woven fabric samples (Fig. 1). A fabric without rare-earth element treatment was used as the control.

After culturing the inoculated samples for 18 h in a dark room at 37 ± 2 °C, the bacteria were washed from the fabrics using a standard saline solution. The number of viable bacteria in the post-wash solution was determined following a pour plate method. The antibacterial activity was defined

Fig. 1 Procedures for chlorine pretreatment, rare-earth adsorption, and antibacterial activity test
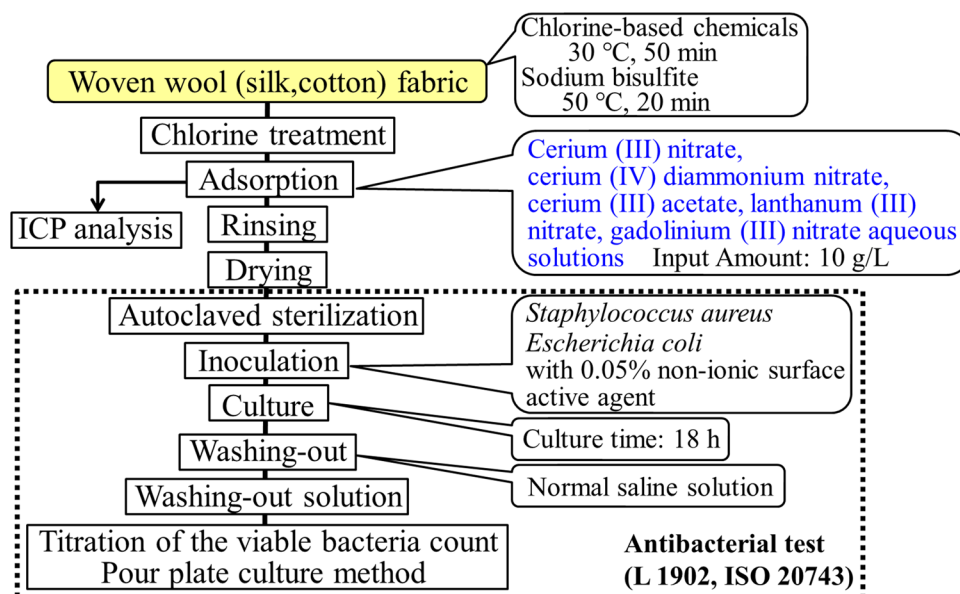
in terms of viable bacteria count compared to the reference. The mathematical equation is given as follows:

$$\text{Antibacterial activity} = \log\left(C_{\text{ref\_culture}}/C_{\text{ref\_inoc}}\right) - \log\left(C_{\text{s\_culture}}/C_{\text{s\_inoc}}\right), \tag{2}$$

where $C_{\text{ref\_culture}}$ and $C_{\text{ref\_inoc}}$ are the viable bacteria counts on the reference (untreated) fabric after culturing and immediately after inoculation, respectively, and $C_{\text{s\_culture}}$ and $C_{\text{s\_inoc}}$ are the corresponding counts on the treated fabric sample. An activity value of 2 or higher indicates antibacterial effect.

The antibacterial properties of cerium-ion-adsorbed fabric samples were tested after 50 detergent wash cycles in an electric washing machine at 40 °C. Each cycle consisted of the following steps: 5 min washing, purging, 2 min rinsing, air drying, 2 min rinsing, spinning, and line drying.

ESR spectroscopy

The formation of active oxygen free radicals in the reaction between H_2O_2 and Ce^{3+} adsorbed on the woven fabric surface was monitored using ESR spectroscopy (X-Band CW Electron Spin Resonance, Bruker EMX Plus). H_2O_2 is produced in bacterial mitochondria during energy metabolism. To observe unstable and short-lived free radicals through ESR spectroscopy, it is necessary to stabilize them; thus, the spin trap method was used. First, woven fabrics with adsorbed Ce^{3+}, La^{3+}, or Gd^{3+} (the sample shape did not affect the results) were immersed in an H_2O_2 aqueous solution (1.6 μM; 6.7 g L^{-1} fabric to solution). The sample was stabilized at 25 °C for 30 min. Subsequently, 200 μL of the immersion liquid was taken and added to CYPMPO (a spin trap agent) and stirred, followed by ESR analysis. All rare-earth metal ions were modified using each nitrate solution described above.

Safety of cerium nitrate

The safety of $Ce(NO_3)_3$ in the immersion liquid for antibacterial treatment was evaluated through an in vitro skin irritation test (OECD Guidelines for the Testing of Chemicals (GTC) No. 439) using a human 3D cultured epidermis model (LabCyte EPI-MODEL24 SIT, Japan Tissue Engineering Co., Ltd., Aichi, Japan). In addition, a microbial mutagenicity test (Occupational Safety and Health Law in Japan) was conducted with *Salmonella typhimurium* (TA100, TA1535, TA98, and TA1537) and *E. coli* (WP2uvrA) using the pre-incubation method. Finally, a skin sensitization test (OECD GTC, No. 442B) was performed on a CBA/J mouse using the local lymph node assay (LLNA): BrdU-ELISA. Next, an acute oral toxicity test (OECD GTC, No. 420) was conducted on female Crl:CD(SD) rats. The detailed experimental procedure is shown in Electronic Supplementary Material. These tests were conducted at the Japan Chemical Innovation and Inspection Institute in accordance with the following laws, guidelines, and standards: (a) Act on the Welfare and Management of Animals, Law No. 105, 1973; (b) Standards for the Care and Custody of Animal Experiments and for the Alleviation of Pain and Suffering, Japan's Ministry of the Environment, 2006; (c) Basic Guidelines for the Implementation of Animal Experiments, etc., in Institutions Complementary to the Ministry, Japan's Ministry of Health, Labour and Welfare, 2006; (d) Basic Guidelines for the Implementation of Animal Experiments, etc., in Research Institutions under the Jurisdiction of the Ministry, Japan's Ministry of Agriculture, Forestry and Fisheries, 2006; (e) Basic Guidelines for the Implementation of Animal Experiments, etc., in Research Institutions, etc., Japan's Ministry of Education, Culture, Sports, Science and Technology, 2006; and (f) Guidelines for the Appropriate Implementation of Animal Experiments, Science Council of Japan, 2006.

Results

Influence of chlorination on rare-earth adsorption

Figure 2 shows SEM images of the chlorinated woven wool fabric before and after immersion in a $Ce(NO_3)_3$ aqueous solution. No particles were observed on the surface of wool fibers descaled by chlorination, especially after the antibacterial treatment. This indicates that Ce^{3+} was adsorbed on the fabric and that it left no residue.

To investigate the influence of chlorination on the adsorption of rare-earth ions on woven wool fabrics, chlorinated and non-chlorinated fabrics were immersed in a standard solution containing 10 mg L^{-1} of 16 rare-earth ions for a period of 24 h at room temperature. Then, the recovery of each type of rare-earth ion was determined. As shown in supplementary Fig. S-1, chlorination enhanced the recovery for each rare-earth element by two- or threefold. Scandium, europium, and thulium could be recovered in high amounts. However, selective recovery was not achieved.

Antibacterial activity

Table 1 compares the antibacterial activities of the chlorinated woven wool fabrics toward *S. aureus*. When the immersion liquid contained 5% o.w.f $Ce(NO_3)_3$, the chlorinated fabric treated at 65 °C for 40 min demonstrated

Fig. 2 SEM images of chlorinated wool surface before (**a**, **c**, **e**) and after (**b**, **d**, **f**) Ce adsorption. The fabric was immersed in a 5% o.w.f Ce(NO$_3$)$_3$ aqueous solution at 98 °C for 40 min at an input of 10 g L^{-1} fabric to solution, washed with running water, and then air-dried
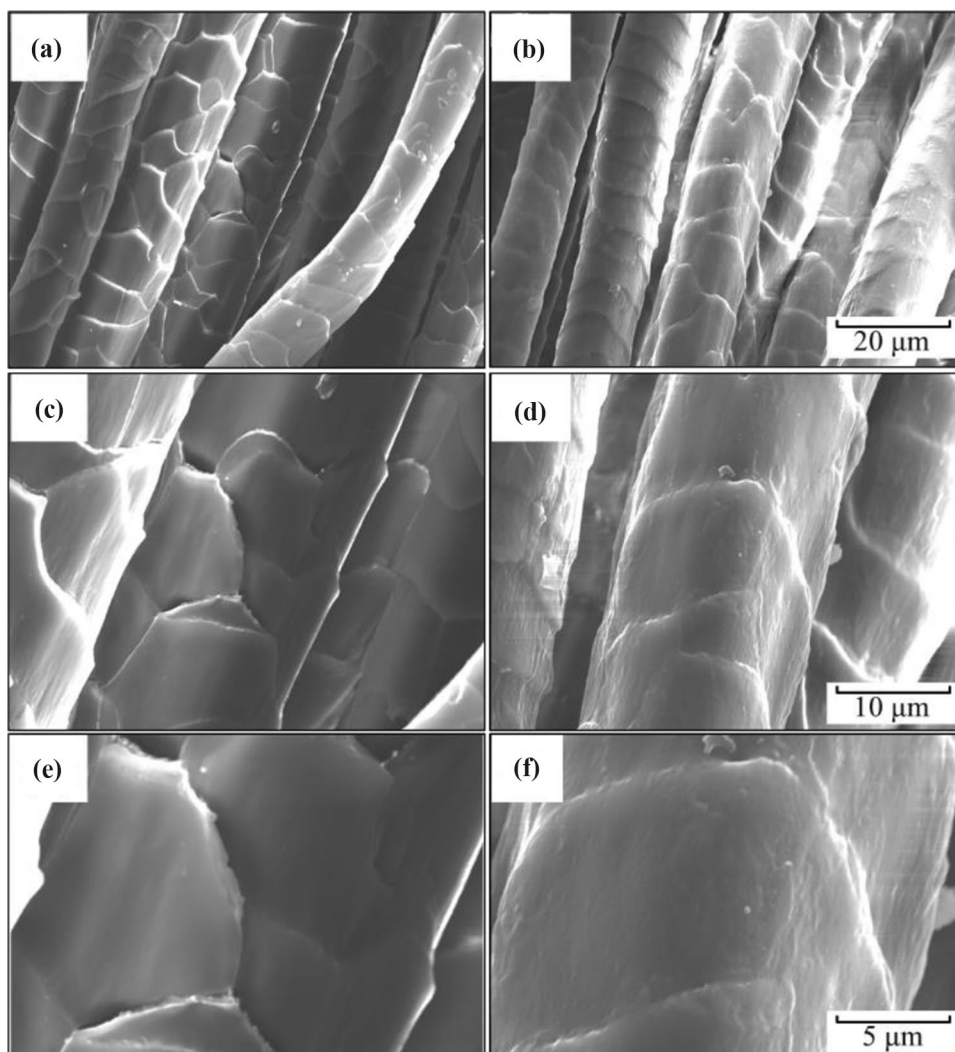

Table 1 Antibacterial activity of chlorinated woven wool fabrics toward *S. aureus* after different antibacterial treatments

Agent	Treatment conditions	Logarithm of viable bacteria count		Antibacterial activity
		Just after inoculation	After culture	
Ce(NO$_3$)$_3$	5% o.w.f, 65 °C, 40 min	4.48	5.32	1.7
Ce(NO$_3$)$_3$	5% o.w.f, 98 °C, 40 min	4.35	2.32	4.7
Ce(CH$_3$COO)$_3$	5% o.w.f, 65 °C, 40 min	4.51	2.19	4.9
Ce(CH$_3$COO)$_3$	5% o.w.f, 85 °C, 40 min	4.53	2.08	5.0

poor antibacterial activity toward *S. aureus* (1.7), which can be attributed to the low Ce^{3+} adsorption. When the Ce(CH$_3$COO)$_3$ aqueous solution was used for 40 min instead, high antibacterial activity was observed (approximately 4.9 and 5.0 at 65 and 85 °C, respectively). In particular, as shown in Table 1, a higher immersion temperature led to enhanced antibacterial activity. After Ce^{3+} adsorption, no signs of fabric discoloration were observed.

Table 2 compares the antibacterial activities against *S. aureus* from chlorinated wool without rare-earth treatment (control fabric) and after treatment with Ce(NO$_3$)$_3$, (NH$_4$)$_2$[Ce(NO$_3$)$_6$], or Ce(CH$_3$COO)$_3$ aqueous solution. Data were recorded before and after predetermined washing cycles. On the control fabric, the bacteria count increased after culturing regardless of the number of washing cycles, and the negative activity (−0.6) indicated that the fabric

Table 2 Antibacterial activity of rare-earth-treated chlorinated woven wool fabrics toward *S. aureus* before and after specific washing cycles (treatment conditions: 5% o.w.f, 98 °C, 40 min)

Agent	Washing condition	Logarithm of viable bacteria count		Antibacterial activity
		Just after inoculation	After culture	
No antibacterial treatment	Before washing	4.49	7.58	− 0.6
Ce(NO$_3$)$_3$	Before washing	4.35	2.32	4.7
	After 10 washes	4.35	2.31	4.7
	After 50 washes	4.36	3.20	3.9
(NH$_4$)$_2$[Ce(NO$_3$)$_6$]	Before washing	4.42	1.94	5.1
	After 10 washes	4.47	1.98	5.1
	After 50 washes	4.32	4.06	3.0
Ce(CH$_3$COOH)$_3$	Before washing	4.53	2.08	5.0
	After 50 washes	4.53	4.08	3.0

Table 3 Antibacterial activity of the CeO$_2$ powder and chlorinated woven wool fabric immersed in CeO$_2$ sol

Bacteria	Sample	Logarithm of viable bacteria count		Antibacterial activity
		Just after inoculation	After culture	
S. aureus	CeO$_2$ powder	< 1.3	< 1.3	≥ 2.6
E. coli	CeO$_2$ powder	< 1.3	< 1.3	≥ 3.1
S. aureus	Wool treated with CeO$_2$ sol (10% o.w.f, 98 °C, 40 min)	4.42	7.50	− 0.5

did not inhibit bacterial growth. The fabrics treated with Ce(NO$_3$)$_3$ and (NH$_4$)$_2$[Ce(NO$_3$)$_6$] aqueous solutions demonstrated considerable antibacterial activity (approximately 4.7 and 5.0, respectively), both immediately after treatment and after 10 wash cycles. The activity decreased after 50 washes but still remained substantial. This implies that the antibacterial activity is unaffected by the valence of cerium.

The 5% o.w.f Ce(NO$_3$)$_3$ aqueous solution was strongly acidic (pH < 1), whereas the pH was 3.8 in the Ce(CH$_3$COO)$_3$ aqueous solution. Fabric samples treated with these solutions at 98 °C for periods exceeding 40 min demonstrated high antibacterial activities (4.7 and 5.0, respectively) before washing, and after 50 cycles, the activities remained at 3.9 and 3.0, respectively.

Table 3 compares the antibacterial activities of CeO$_2$ powder and chlorinated wool fabric immersed in CeO$_2$ suspension (10% o.w.f). Although the pure CeO$_2$ powder had some antibacterial activity (≥ 2.6 toward *S. aureus* and ≥ 3.1 toward *E. coli*), fabrics treated with a CeO$_2$ sol (10% o.w.f) at 98 °C for 40 min failed to inhibit *S. aureus* (antibacterial activity: − 0.5). This means that the CeO$_2$ particles did not adhere to the wool surface.

Table 4 lists the antibacterial activities toward *S. aureus* when chlorinated woven wool fabric was immersed in Ce(NO$_3$)$_3$, La(NO$_3$)$_3$, and Gd(NO$_3$)$_3$ aqueous solutions under similar conditions. The antibacterial activities were 4.7, 5.8, and 5.9, respectively.

Table 4 Antibacterial activity of chlorinated woven wool treated with Ce(NO$_3$)$_3$, La(NO$_3$)$_3$, and Gd(NO$_3$)$_3$ aqueous solutions toward *S. aureus* (treatment conditions: 5% o.w.f, 98 °C, 40 min)

Agent	Logarithm of viable bacteria count		Antibacterial activity
	Just after inoculation	After culturing	
Ce(NO$_3$)$_3$	4.35	2.32	4.7
La(NO$_3$)$_3$	4.30	< 1.3	> 5.8
Gd(NO$_3$)$_3$	4.40	< 1.3	> 5.9

When the unchlorinated wool fabric was treated with a more concentrated Ce(NO$_3$)$_3$ solution (12% o.w.f), either at room temperature (20–25 °C) for 48 h or at 98 °C for 2 h, the fabric adsorbed enough Ce^{3+} to display excellent antibacterial activity toward *S. aureus* (approximately 5.6, Table 5). A similar trend was observed toward *E. coli* (antibacterial activity: approximately 6.2).

To explore the application potential for other natural fabrics, we also used the Ce(NO$_3$)$_3$ aqueous solution to treat woven silk and cotton fabrics. The corresponding results are shown in Table 6. The as-treated silk and cotton exhibited antibacterial activities of 5.8 and 5.2, respectively, which were reduced after 50 washes to 2.9 and 4.8, respectively.

Table 5 Antibacterial activity of the *unchlorinated* woven wool fabric toward *S. aureus* and *E. coli* following treatments with Ce(NO$_3$)$_3$ aqueous solution at 12% o.w.f

Bacteria	Sample	Treatment conditions	Logarithm of viable bacteria count		Antibacterial activity
			Just after inoculation	After culturing	
S. aureus	Wool	12% o.w.f, RT, 48 h	4.4	< 1.3	≥ 5.6
		12% o.w.f, 98 °C, 2 h	4.4	< 1.3	≥ 5.6
E. coli	Wool	12% o.w.f, RT, 48 h	4.4	< 1.3	≥ 6.2
		12% o.w.f, 100 °C, 2 h	4.4	< 1.3	≥ 6.2

Table 6 Antibacterial activity of woven wool, silk, and cotton treated with Ce(NO$_3$)$_3$ aqueous solution toward *S. aureus* (treatment conditions: 5% o.w.f; 40 min; wool: 98 °C, silk and cotton: 65 °C)

Sample	Washing condition	Logarithm of viable bacteria count		Antibacterial activity
		Just after inoculation	After culturing	
Wool[a]	Before washing	4.35	2.32	4.7
	After 10 washes	4.35	2.31	4.7
	After 50 washes	4.36	3.20	3.9
Silk	Before washing	4.30	1.22	5.8
	After 10 washes	4.21	3.42	3.6
	After 50 washes	4.39	4.09	2.9
Cotton	Before washing	4.40	1.91	5.2
	After 10 washes	4.36	2.05	4.9
	After 50 washes	4.34	2.22	4.8

[a]Chlorinated wool

Generation of active oxygen free radicals

To examine the generation of free active oxygen radicals, we recorded the ESR spectra of H$_2$O$_2$ aqueous solutions following the immersion of wool and silk fabrics with and without adsorbed rare-earth ions (Ce^{3+}, La^{3+}, or Gd^{3+} on wool; Ce^{3+} on silk). The spectra (Fig. 3a, b) showed no peaks in the 3480–3550 G range when the sample did not contain rare-earth ions. In contrast, all fabrics treated with rare-earth ions demonstrated peaks corresponding to significant amounts of ·OH radicals (Frejaville et al. 1995).

Safety and potential of cerium nitrate in the antibacterial treatment for wool

We examined the safety of the Ce(NO$_3$)$_3$ immersion liquid used for the antibacterial treatment through several tests. First, we employed a human 3D cultured epidermis model to evaluate whether Ce(NO$_3$)$_3$ was a skin irritant. The cell viability with Ce(NO$_3$)$_3$ was 72.5% (100% under distilled water), which exceeded the judgment criterion of 50%.
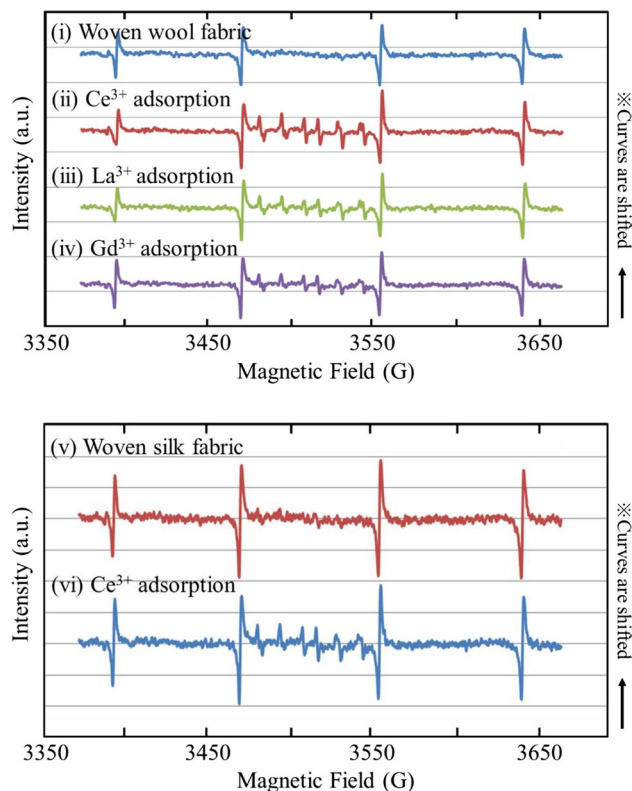

Fig. 3 a ESR spectra of woven wool fabric (i) in the as-provided state and after the adsorption of (ii) Ce^{3+}, (iii) La^{3+}, and (iv) Gd^{3+}. **b** ESR spectra of woven silk fabric (v) in the as-provided state and (vi) after adsorption of Ce^{3+}. In all cases, the aqueous solution contained 1.6 μM H$_2$O$_2$, and the immersion time was 30 min

Therefore, under the conditions of this test, it was judged to be a "non-irritant" (GHS classification). In the next test, the presence or absence of microbial mutagenesis by Ce(NO$_3$)$_3$ in *S. typhimurium* and *E. coli* was investigated, and the number of revertant mutant colonies in all test strains was less than twice the reference value; therefore, Ce(NO$_3$)$_3$ was judged to have a "non-mutagenic ability." For the third test, LLNA: BrdU-ELISA was performed on female CBA/J mice to determine whether or not Ce(NO$_3$)$_3$ was a skin sensitizer using a stimulation index (SI) as an indicator. The

SI was < 1.6, which indicated "non-sensitization." Finally, during the acute oral toxicity study, no severe adverse reactions, including death, were seen in all the five rats, and no abnormalities were observed in the general condition or body weight of the rats. However, because borderline protuberance projection of the forestomach was observed in one rat at autopsy, the hazard classification for acute toxicity to rats due to oral administration of $Ce(NO_3)_3$ under the conditions of this study was "Category 5" (GHS). These results demonstrate the safety of $Ce(NO_3)_3$.

Discussion

Influence of chlorination on rare-earth adsorption

The SEM images (Fig. 2) show no noticeable disintegration of the wool, indicating that the fabric quality was retained. In addition, the absence of cerium particles on the surface suggests that cerium may be attached to the fiber surface in the form of an ionic complex.

Chlorination increased the recovery for each type of rare-earth ion in supplementary Fig. S-2. Such enhancement is attributed to sulfonic acid groups ($-SO_3H$) generated by oxidation of disulfide bonds in the wool scale, and partial cleavage of the polypeptide chain to produce hydrophilic groups ($-OH$, $-COOH$, and $-NH_2$). Thus, Ce^{3+} and other metal cations in the solution are attracted strongly to the surface groups (e.g., imidazole in histidine and carboxyl and sulfonic acid groups) and bind to the wool fibers (Kawahara 1981).

Antibacterial activity

The 5% o.w.f $Ce(NO_3)_3$ aqueous solution contains nitric acid and is strongly acidic (pH ˂1) (Table 1). For example, wool decomposes in hot concentrated sulfuric acid. Because $Ce(CH_3COO)_3$ aqueous solution at the same concentration has a significantly higher pH (3.8), we assume that it causes less damage to the wool while still imparting antibacterial properties. Treatment at high temperature increases the number of collisions between Ce^{3+} ions and adsorption sites on the wool surface due to enhanced molecular movement. Because of its low quantity, we could not directly observe cerium on the fiber using SEM in association with the energy-dispersive X-ray technique. However, the high antibacterial activity before and after washing can be attributed to the strong adsorption of cerium ions. A previous study found that adsorbing Ag onto natural fibers such as wool and silk imparts antibacterial properties (Tsukada 2004); however, the fibers were stained black during this process. In contrast, the wool was not significantly discolored after the cerium-based antibacterial treatment used in the present

study. Therefore, the proposed treatment does not affect the natural color of the fabric or its subsequent dyeing.

In Table 2, cerium demonstrates antibacterial activity regardless of its valence. Ce^{4+} is relatively stable in oxidizing acidic solutions (such as sulfuric acid and nitric acid), but it can be gradually converted to Ce^{3+} by redox reaction with the exchanger and possibly oxidized to Ce^{4+} again (Sanpei et al. 2002). The ability of cerium to cycle between Ce^{3+} and Ce^{4+} states at oxygen vacancy sites is well known (Heckert et al. 2008). This may explain their similar antibacterial effects.

Previously, Kuang et al. (2011) demonstrated the high antibacterial activity toward *E. coli* from CeO_2 powder, especially CeO_2 nanoparticles. Our experiment confirmed this result (Table 3). However, the chlorinated wool fabric itself had no antibacterial effect (−0.6 toward *S. aureus*), and there was no improvement after treating it with 10% o.w.f CeO_2 suspension at 98 °C for 40 min (−0.5). In comparison, immersing the chlorinated woven wool fabric in 5% o.w.f $Ce(NO_3)_3$ aqueous solution was effective (antibacterial activity of 4.7 before washing cycles, as described in Tables 1 and 2). Therefore, compared to the CeO_2 particles, cerium ions in the solution adhere much better on the fabric surface without requiring additional immobilization steps, such coating them with polymers for attachment to fibers.
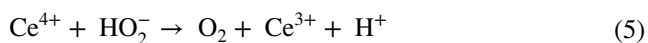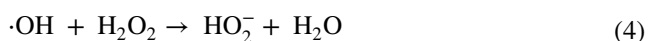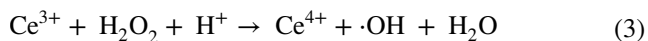
The antibacterial activities of $La(NO_3)_3$ and $Gd(NO_3)_3$ were better than that of $Ce(NO_3)_3$ (Table 4). Therefore, nitrate aqueous solutions of multiple rare-earth ions can function as antibacterial agents. Moreover, as in the case of cerium, no discoloration was observed in the woven wool fabric treated with $La(NO_3)_3$ and $Gd(NO_3)_3$ aqueous solutions. We also found that a more concentrated $Ce(NO_3)_3$ solution could produce excellent antibacterial properties even in wool fabrics without chlorine pretreatment (Table 5). Therefore, the proposed antibacterial treatment has considerable versatility.

Finally, we extended the antibacterial treatment to woven silk and cotton fabrics, and cerium adsorption appeared to be stronger on cotton than silk. According to the hard and soft acids and bases theory, the carboxyl group ($-COOH$) in wool is a hard base, whereas in silk and cotton, the hard base is the hydroxyl group ($-OH$, from the amino acid and cellulose, respectively). Ce^{3+} as a hard acid is therefore expected to be easily adsorbed on silk and cotton. Importantly, silk and cotton can adsorb enough Ce^{3+} without any pretreatment, such as chlorination, because the functional groups involved in adsorption are already exposed.

Generation of active oxygen free radicals

The ESR spectra obtained for the samples and H_2O_2 aqueous solutions (Fig. 3a, b) reveal that all fabrics treated with rare-earth solutions generated characteristic peaks, indicating the

presence of ·OH radicals. In contrast, no peaks were observed for the fabrics without adsorbed rare-earth ions. The ·OH radicals are generated from the following series of reactions (Fenton-like reaction) (Heckert et al. 2008) that are similar to the Fenton/Haber–Weiss reaction.

$$Ce^{3+} + H_2O_2 + H^+ \rightarrow Ce^{4+} + \cdot OH + H_2O \tag{3}$$

$$\cdot OH + H_2O_2 \rightarrow HO_2^- + H_2O \tag{4}$$

$$Ce^{4+} + HO_2^- \rightarrow O_2 + Ce^{3+} + H^+ \tag{5}$$

The metabolic activity in bacteria generates H_2O_2, which diffuses through the cell membrane and can be detected in the extracellular space (Patella et al. 2021) and can become co-adsorbed with the rare-earth ions on the fabric to produce hydroxyl radicals (·OH) in accordance with Eq. (3). The strongly oxidizing ·OH (Liszkay et al. 2003) breaks down the cell walls to react with H_2O_2. This may explain the antibacterial properties of our treated fabrics. The generation of the Ce^{3+} ion from Ce^{4+} and HO^{2-} (obtained from Eq. (4)) can be attributed to the instability associated with the Ce^{4+} state in Eq. (5). Therefore, the antibacterial activity of cerium ions is expected to be retained for a long period. Besides the generation of ·OH from H_2O_2 (confirmed by ESR in this study), other factors may also contribute to the antibacterial properties of cerium, such as ion valence fluctuation and inactivation of enzymes (Matsumoto et al. 2020).

Owing to the mismatch between the natural abundance of different rare-earth elements and their changing market demands, there is currently an excess of light rare-earth elements, of which, cerium is dominant. The solution of this "balance problem" requires finding new ways to utilize the light rare-earth elements. This study confirmed that light rare-earth ions, especially cerium, display antibacterial effects when adsorbed on wool, cotton, and silk. Thus, these ions may be used as a safe material for treating various fabrics, with potential applications in medical facilities and disaster relief operations.

Matsumoto et al. (2020) reported that CeO_2 in suspension exhibits little activity toward Φ6. In contrast, heteropoly acids containing cerium strongly inhibit the influenza virus (Liu et al. 2004). Moreover, when polyacids are adsorbed by electrostatic interaction at cationic lysine residues in the active site of human immunodeficiency virus, viral inactivation can occur due to transport of inorganic metal to the virus (Judd et al. 2001). In the present study, the adsorption of rare-earth ions (e.g., cerium) on wool can be attributed to interaction with the nitrogen in amino acids (such as histidine) to form a complex. However, such interaction does not occur with CeO_2 particles. Therefore, samples containing cerium adsorbed on wool may have potential antiviral

activity against SARS-CoV-2 (Ito et al. 2021). Although experiments with actual virus have not been performed, it is known that lysine exists at the active site of SARS-CoV-2 (Yoshimoto 2020), and that chemical modification of lysine residue can affect protein function (such as inactivating alkaline phosphatase (Chen et al. 2005)). Cerium in complex oxides has also exhibited a high alkaline phosphatase enzyme inactivation rate (Matsumoto et al. 2020), which implies that inactivation of enzyme proteins such as alkaline phosphatase is a potential mechanism of antibacterial activity, in addition to the pseudo-Fenton reaction caused by reactive oxygen species, as supported by the results in present study. Cerium ions adsorbed on basic amino acids (arginine, lysine, and histidine) (Craig et al. 1954) in wool can potentially move to the lysine side chains of viruses attached to the wool surface and cause viral inactivation. Manufacturing fabrics with antimicrobial properties would make it easier to disinfect clothes and other items. In particular, if fabrics containing cerium ions are effective against enveloped viruses, then they may be used in face masks, medical uniforms and scrubs, patient gowns, bedclothes, and so on, to help combat COVID-19 and other infectious diseases in the future. The related research should be carried out in collaboration with medical researchers and clinicians.

Conclusions

We introduced cerium, a light rare-earth element with declining demand in recent years, into woven wool fabric as a potential antibacterial agent. The wool fabric was first chlorinated to remove the cuticle layer on the fiber surface, enhancing the adsorption of different rare-earth ions. The antibacterial treatment involves immersing the fabric in a $Ce(NO_3)_3$ aqueous solution at a fixed temperature for a predetermined time. The result is significant (antibacterial activity against *S. aureus*: 4.7 after treatment and 3.9 after 50 wash cycles) for chlorinated wool fabric treated with 5% o.w.f cerium at 98 °C for 40 min. The treated fabrics also showed effective values against *E. coli*. Similar results were observed for silk and cotton fabrics (5% o.w.f, 65 °C, 40 min) with values of 5.8 and 5.2 after treatment and 2.9 and 4.8 after 50 wash cycles, respectively. La^{3+} and Gd^{3+} also demonstrated excellent antibacterial properties when adsorbed on wool fabric (activities: approximately 5.8 and 5.9, respectively). For a milder reaction condition, $Ce(CH_3COOH)_3$ aqueous solution could be used in place of the highly acidic $Ce(NO_3)_3$ solution, with comparable antibacterial activity after 40 min immersion (4.9 at 65 °C and 5 at 85 °C). The observed antibacterial effects can be attributed to ·OH radicals formed during the Fenton reaction involving the

H_2O_2 produced in microbial metabolism under the catalytic action of Ce^{3+}, La^{3+}, or Gd^{3+}. This was supported by the observation of ·OH radical peaks in the ESR spectral profiles, when H_2O_2 aqueous solution was added with fabrics containing rare-earth ions (Ce^{3+}, La^{3+}, and Gd^{3+} for wool; and Ce^{3+} for silk). In the future, this method of imparting antibacterial properties could be applied to personal clothing as well as medical and first-aid supplies (such as masks, patient gowns, and bandages).

Data availability All data generated or analyzed during this study are included in this published article.

Declarations

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

Human or animal rights The above-mentioned tests were conducted at the Japan Chemical Innovation and Inspection Institute in accordance with the following laws, guidelines, and standards: (a) Act on the Welfare and Management of Animals, Law No. 105, 1973; (b) Standards for the Care and Custody of Animal Experiments and for the Alleviation of Pain and Suffering, Japan's Ministry of the Environment, 2006; (c) Basic Guidelines for the Implementation of Animal Experiments, etc., in Institutions Complementary to the Ministry, Japan's Ministry of Health, Labour and Welfare, 2006; (d) Basic Guidelines for the Implementation of Animal Experiments, etc., in Research Institutions under the Jurisdiction of the Ministry, Japan's Ministry of Agriculture, Forestry and Fisheries, 2006; (e) Basic Guidelines for the Implementation of Animal Experiments, etc., in Research Institutions, etc., Japan's Ministry of Education, Culture, Sports, Science and Technology, 2006; and (f) Guidelines for the Appropriate Implementation of Animal Experiments, Science Council of Japan, 2006.

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