Synergistic Antibacterial Effects of Chitosan-Caffeic Acid Conjugate against Antibiotic Resistant Acne-related Bacteria

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Abstract: The object of this study was to discover an alternative therapeutic agent with fewer side effects against acne vulgaris, which is one of the most common skin diseases. Acne vulgaris often associates with acne-related bacteria such as Propionibacterium acnes, Staphylococcus epidermidis, Staphylococcus aureus and Pseudomonas aeruginosa, some of which exhibit a resistant against commercial antibiotics used in the treatment of acne vulgaris (tetracycline, erythromycin, and lincomycin). In the current study, we evaluated in vitro antibacterial activity of chitosan-phytochemical conjugates against acne-related bacteria. Three of chitosan-phytochemical conjugates used in this study showed stronger antibacterial activity than that of chitosan (unmodified control). Chitosan-caffeic acid conjugate (CCA) exhibited the highest antibacterial activity against acne-related bacteria with minimum inhibitory concentration values of 8 μg/mL to 256 μg/mL. In addition, the MICs of antibiotics against antibiotic resistant P. acnes and P. aeruginosa strains were dramatically reduced in the combination with CCA, suggesting that CCA would restore the antibacterial activity of the antibiotics. The analysis of fractional inhibitory concentration indices clearly revealed a synergistic antibacterial effect between CCA and the antibiotics. Thus, the median $\sum$FIC values against the antibiotic resistant bacterial strains were ranged from 0.375 to 0.533 in the combination mode of CCA and antibiotics.

Keywords: Acne vulgaris; Antibiotic resistance; Chitosan-phytochemical conjugates; Synergistic antibacterial effect

1. Introduction

One of the most common skin diseases is acne vulgaris, affecting around 80% of young adults (11 to 30 years). It can cause permanent physical scar resulting in intense emotional scar, which might lead to clinical depression and social phobias [1,2]. Propionibacterium acnes, Staphylococcus epidermidis, S. aureus, and Pseudomonas aeruginosa are known as skin pathogenic bacteria associated with acne vulgaris. These bacteria are related to the development of inflammation and abnormal follicular keratinization [3]. P. acnes develops acne inflammatory by metabolizing sebaceous triglycerides into fatty acids which chemotactically attract neutrophil [4,5]. Normally, antibiotics are used as acne treatment to kill the bacteria. Among them, erythromycin, lincomycin, and tetracycline are usually chosen for the antibiotic therapy [6,7]. However, antibiotics have several side effects when these are used for a long period, such as emergence of resistant bacteria, immune hypersensitivity, and organ...
damage [5,8]. Therefore, the development of alternative therapeutic agents with strong antibacterial activity and less side effects are needed to be researched.

Marine organisms are an attractive resource to develop natural derived antimicrobial agents against pathogenic microbes including fungi, bacteria, and virus [9,10]. Chitosan is one of mucopolysaccharides of marine origin, being biodegradable, biocompatible, and low-toxicity. It has been applied to food and pharmaceutical industry due to its several bioactivities including anti-inflammatory, antioxidant, antitumor, and enzymatic inhibitory effect [11-13]. Therefore, there is a growing interest in developing novel chitosan derivatives with a novel functionality [14]. However, as described above, most studies related chitosan and its derivatives have been focused on the biological activities such as antioxidant, antitumor, and anti-inflammatory effect, not antimicrobial activity [15-17]. It has been previously reported that chitosan derivatives conjugated with phytochemicals (caffeic acid, ferulic acid, and sinapic acid), which exhibited strong antibacterial activity against pathogenic bacteria [12,18]. However, no further experiment was progressed against other pathogenic bacteria, especially acne-related bacteria. Therefore, in the present work, the antibacterial activity of chitosan-phytochemical conjugates against the acne-related bacteria was evaluated. The results obtained in this study will provide valuable information to develop an alternative therapeutic agent for treating acne vulgaris.

2. Results

2.1. Antibacterial effect of chitosan-phytochemical conjugates against acne-related bacteria

Hydroxycinnamic acids (HAs) including caffeic acid, ferulic acid, and sinapic acid are naturally occurring phytochemicals from plants and have been used in pharmaceutical, cosmetics, and food industry [18,19,20]. In this study, chitosan-phytochemical conjugates were synthesized by conjugating HAs into the chitosan backbone according to the previous method [12,18]. It was then assessed an antibacterial activity of chitosan-phytochemical conjugates against acne-related bacteria. In order to quantitatively evaluate its antibacterial activity, it was investigated an antibacterial activity of the chitosan-phytochemical conjugates against acne-related bacteria using MIC assay. The MIC values of the chitosan-phytochemical conjugates were determined by the two-fold serial dilution method, and the MIC values are summarized in Table 1. The MIC values of the unmodified chitosan were in the range of 16 µg/mL to 512 µg/mL against acne-related bacteria. Moreover, the chitosan-phytochemical conjugates possessed lower MIC values than those of the unmodified chitosan ranging from 8 µg/mL to 256 µg/mL. The highest antibacterial activity was observed in the treatment of CCA. The MICs of CCA were determined in a range of 8 µg/mL to 256 µg/mL against acne-related bacteria. CFA and CSA showed the MIC values of 16 µg/mL to 256 µg/mL against acne-related bacteria.

**Table 1.** Minimum inhibitory concentrations (MIC) of the chitosan-phytochemical conjugates against acne-related bacteria

<table>
<thead>
<tr>
<th>Strain</th>
<th>CCA 1</th>
<th>CFA 2</th>
<th>CSA 3</th>
<th>Unmodified chitosan</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> KCTC 1927</td>
<td>8</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td><em>S. epidermidis</em> KCTC 1370</td>
<td>64</td>
<td>64</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em> KCTC 1637</td>
<td>16</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td><em>Propionibacterium acnes</em> KCTC 3314</td>
<td>256</td>
<td>256</td>
<td>256</td>
<td>512</td>
</tr>
<tr>
<td><em>P. acnes</em> isolate 2874</td>
<td>256</td>
<td>256</td>
<td>256</td>
<td>512</td>
</tr>
<tr>
<td><em>P. acnes</em> isolate 2875</td>
<td>128</td>
<td>256</td>
<td>256</td>
<td>256</td>
</tr>
</tbody>
</table>

1 CCA, chitosan-caffeic acid; 2 CFA, chitosan-ferulic acid; 3 CSA, chitosan-sinapic acid
Interestingly, chitosan, and the chitosan-phytochemical conjugates showed very strong antibacterial activity against P. aeruginosa in the MICs range of 16 to 32 μg/mL, while Mazurova et al. [21] reported that MICs of natural substances (gallic acid, methyl gallate, ethyl gallate, propyl gallate, octyl gallate, carvacrol, thymol, and eugenol) have range of 300 to 2,400 μg/mL. Generally, P. aeruginosa has high-level resistance to antibiotics and substances derived from natural materials due to the low permeability and the action of multidrug efflux pumps [5,22]. In addition, our previous result revealed that the chitosan conjugates are non-toxic to human skin keratinocytes cells [23]. Considering these points, chitosan and its phytochemical derivatives will be very useful for a commercial application since these compounds are broad spectrum natural antibiotics acting both Gram-positive and Gram-negative bacteria related with acne vulgaris.

2.2. Antibiotic resistance of acne-related bacteria against commercial antibiotics

The generally available therapeutic option for the treatment of acne vulgaris is an antibiotic application to kill the acne-related bacteria. For the antibiotic therapy, tetracycline, erythromycin, and lincomycin are generally used in the treatment [6,7]. With the increasing of antibiotic application, the increased prevalence of the antibiotic resistant bacteria has been reported [24]. Also, it has been previously reported on the antibiotic resistance of acne-related bacteria. According to the report by Lee et al. [25], P. acnes strains have high-level resistance to erythromycin (MIC of 2,048 μg/mL). However, S. epidermidis and S. aureus were found to be sensitive for tetracycline, erythromycin, and lincomycin in the MIC ranges of 0.125 μg/mL to 8 μg/mL. In addition, Cristina et al. [26] reported that P. acnes strains highly resistant to erythromycin and clindamycin. In this study, it was investigated the antibiotic resistant of acne-related bacteria used in this study. The antibiotic resistant was measured qualitatively using MIC assay (Table 2). The antibiotic resistant profile of each bacteria was then determined based on the analysis of MIC breakpoint [27].

Table 2. Minimum inhibitory concentration (MIC) of tetracycline, erythromycin and lincomycin against acne-related bacteria

<table>
<thead>
<tr>
<th>Strain</th>
<th>Erythromycin</th>
<th>Lincomycin</th>
<th>Tetracycline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus KCTC 1927</td>
<td>2</td>
<td>4</td>
<td>0.5</td>
</tr>
<tr>
<td>Staphylococcus epidermidis KCTC 1370</td>
<td>0.125</td>
<td>0.25</td>
<td>2</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa KCTC 1637</td>
<td>16</td>
<td>64</td>
<td>0.125</td>
</tr>
<tr>
<td>Propionibacterium acnes KCTC 3314</td>
<td>1,024</td>
<td>1,024</td>
<td>32</td>
</tr>
<tr>
<td>P. acnes isolate 2874</td>
<td>1,024</td>
<td>1,024</td>
<td>16</td>
</tr>
<tr>
<td>P. acnes isolate 2875</td>
<td>0.125</td>
<td>1</td>
<td>0.125</td>
</tr>
<tr>
<td>Soussy's MIC breakpoints 1</td>
<td>1-4 1</td>
<td>2-8 1</td>
<td>4-8 1</td>
</tr>
</tbody>
</table>

1 Soussy et al. (1994)

2.3. Synergistic antibacterial effect between CCA and antibiotics against acne-related bacteria

With the emergence of multidrug resistant bacteria, the need for new antibiotics or therapeutic agents is increased [28,29]. It has been demonstrated that one of the more effective strategies in developing new drugs or alternative therapies is the restoration of antibiotic activity in combination with antibacterial materials derived from natural products and traditional medicines against drug-resistant bacteria [12,30-32]. Based on these reports, an interaction between chitosan-phytochemicals and commercial antibiotics were estimated by the checkerboard method as stated above and the results were presented in Table 3. Among of chitosan-phytochemicals, CCA was chosen for further study since CCA exhibited the highest antibacterial activity against acne-related bacteria.
Table 3. Minimum inhibitory concentrations (MIC) and fractional inhibitory concentration (FIC) indices of chitosan-caffeic acid (CCA) in combination with antibiotics against antibiotic resistant acne-related bacteria

<table>
<thead>
<tr>
<th>Strains</th>
<th>Test compound</th>
<th>MIC (μg/mL)</th>
<th>Median $\Sigma FIC^1$</th>
<th>$\Sigma FIC_{max}^2$</th>
<th>$\Sigma FIC_{min}^3$</th>
<th>Minimum concentration for observing synergy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. acnes</em> KCTC 3314</td>
<td>CCA</td>
<td>256</td>
<td>0.533</td>
<td>1.016</td>
<td>0.188</td>
<td>64.0</td>
</tr>
<tr>
<td></td>
<td>Tetracycline</td>
<td>32</td>
<td></td>
<td></td>
<td></td>
<td>4.0</td>
</tr>
<tr>
<td><em>P. acnes</em> isolate 2874</td>
<td>CCA</td>
<td>256</td>
<td>0.502</td>
<td>1.004</td>
<td>0.375</td>
<td>64.0</td>
</tr>
<tr>
<td></td>
<td>Tetracycline</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td>4.0</td>
</tr>
<tr>
<td><em>P. acnes</em> KCTC 3314</td>
<td>CCA</td>
<td>256</td>
<td>0.502</td>
<td>1.004</td>
<td>0.188</td>
<td>32.0</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>1,024</td>
<td></td>
<td></td>
<td></td>
<td>64.0</td>
</tr>
<tr>
<td><em>P. acnes</em> isolate 2874</td>
<td>CCA</td>
<td>256</td>
<td>0.502</td>
<td>1.016</td>
<td>0.313</td>
<td>64.0</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>1,024</td>
<td></td>
<td></td>
<td></td>
<td>128.0</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em> KCTC 1637</td>
<td>CCA</td>
<td>16</td>
<td>0.5</td>
<td>1.063</td>
<td>0.266</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td><em>P. acnes</em> KCTC 3314</td>
<td>CCA</td>
<td>256</td>
<td>0.504</td>
<td>1.016</td>
<td>0.375</td>
<td>64.0</td>
</tr>
<tr>
<td></td>
<td>Lincomycin</td>
<td>1,024</td>
<td></td>
<td></td>
<td></td>
<td>256.0</td>
</tr>
<tr>
<td><em>P. acnes</em> isolate 2874</td>
<td>CCA</td>
<td>256</td>
<td>0.502</td>
<td>1.016</td>
<td>0.313</td>
<td>64.0</td>
</tr>
<tr>
<td></td>
<td>Lincomycin</td>
<td>1,024</td>
<td></td>
<td></td>
<td></td>
<td>256.0</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> KCTC 1637</td>
<td>CCA</td>
<td>16</td>
<td>0.375</td>
<td>1.063</td>
<td>0.266</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>Lincomycin</td>
<td>64</td>
<td></td>
<td></td>
<td></td>
<td>16.0</td>
</tr>
</tbody>
</table>

$^1 \Sigma FIC$, the sum of FICs; $^2 \Sigma FIC_{min}$, minimum $\Sigma FIC$; $^3 \Sigma FIC_{max}$, and the maximum $\Sigma FIC$; The FIC index indicated synergistic effect: <0.5, marked synergy; 0.5 to <1.0, weak synergy; 1.0, additive; >1.0 to <2.0, subadditive; 2.0, indifferent; >2.0, antagonistic.
As shown in Table 2, the MICs of tetracycline, erythromycin, and lincomycin against antibiotic resistant *P. acnes* strains were ranged from 16 μg/mL to 1,024 μg/mL. However, the MICs against the *P. acnes* strains were dramatically reduced in combination with CCA (Table 3). The MICs of tetracycline against *P. acnes* KCTC 3314 and isolate 2874 strains were fairly reduced up to 4 μg/mL when administered combination with 256 μg/mL of CCA. Comparing the MICs of the tetracycline alone (16 μg/mL to 32 μg/mL), the MICs has decreased 2- to 3-fold in the combination of tetracycline-CCA. In addition, the MICs of erythromycin and lincomycin against the *P. acnes* strains were also dramatically decreased 2- to 4-folds in the combination with CCA, as resulting the median FIC indices were from 0.502 to 0.504. Thus, these results indicated that the combination of CCA with commercial antibiotics used in acne infection resulted in a synergistic effect against the antibiotic resistant *P. acnes* strains. In analogy to the antibacterial effect against the antibiotic resistant *P. acnes* strains, a synergistic antibacterial effect against an antibiotic resistant *P. aeruginosa* KCTC 1637 stain was also observed in CCA-erythromycin and CCA–lincomycin combination. The median ΣFIC indices were from 0.375 to 0.500, indicating a marked synergy effect between lincomycin and CCA and a weak synergy between erythromycin and CCA.

These results were also accordance with the report by Eom et al. [12] that chitosan-derived conjugates clearly reversed antibacterial activity of β-lactam antibiotics against methicillin-resistant *S. aureus* (MRSA) in the combination mode. The median ΣFIC indices were in the ranges of 0.375 to 0.563. Also, it has been previously reported that phlorotannins of an edible brown seaweed *Eisenia bicyclis* exhibited a synergistic antibacterial effect with the FIC indices ranging from 0.502 to 1.000 against antibiotic resistant *P. acnes* strains in combination with the antibiotics used in this study [5]. Kim et al. [33] reported that a synergy effect between an edible brown algae (*Sargassum serratifolium*) extract and the antibiotics with the median ΣFIC indices from 0.270 to 0.550 against *P. acnes* strains. Compared with these results, it was clear that CCA showed comparably strong synergistic antibacterial effect against antibiotic resistant acne-related bacteria in combination with the antibiotics.

3. Discussion

In this study, we evaluated the antibacterial activity of chitosan-phytochemical conjugates against acne-related bacteria such as *P. acnes*, *S. epidermidis*, *S. aureus*, and *P. aeruginosa*. The results of antibacterial effect of chitosan-phytochemical conjugates against acne-related bacteria were accordance with the previous reports that the chitosan-phytochemical conjugates exhibited higher antimicrobial activity than that of unmodified chitosan [12,18]. The MICs of chitosan-phytochemical conjugates were in the range of 32 μg/mL to 512 μg/mL against foodborne pathogens, while the MICs of the unmodified chitosan were in the range of 128 μg/mL to 1,024 μg/mL. Thus, the chitosan-phytochemical conjugates possessed lower MIC values than those of the unmodified chitosan, indicating that the conjugating increased antibacterial activity.

Bacterial cell surface is a unique structure and a major target for the development of antibacterial agents. Positively charged chitosan interacts with the negatively charged bacterial cell surface, leading to weakening of the cell wall either by cell wall damage alone or accompanied by cell lysis [25,34]. Furthermore, chitosan conjugated with HAs increase the affinity of chitosan for bacterial cell envelope composed with lipid layer because of lipophilicity of HAs possessing unsaturated chain [18,35]. In analogy to chitosan-polyphenol conjugates, the antibacterial activity of chitosan phytochemical conjugates were accelerated by affecting bacterial cell envelope integrity and altering cell permeability by means of interacting with the envelope [25,36]. Up to date, there are several reports on the control of acne-related bacteria. However, these studies focused on the antibacterial activity of natural compounds derived from terrestrial organisms. Furthermore, these compounds exhibited lower antibacterial activity against acne-related bacteria compared to the chitosan and chitosan-phytochemical conjugates [3,37]. Thus, to the best of our knowledge, it is first report on chitosan and its derivate exhibiting antibacterial activity against acne-related bacteria.

In comparison with the Soussy’s MIC breakpoints, it turned out that *P. acnes* KCTC 3314, *P. acnes* isolate 2874, and *P. aeruginosa* KCTC 1637 were considered to be highly resistant to the antibiotics.
In particular, both \textit{P. acnes} strains have high-level resistant to erythromycin and lincomycin with the MICs of 1,024 \(\mu\text{g/mL}\) (Table 2). However, \textit{P. acnes} isolate 2875 strain is an antibiotic susceptible bacterium to the three antibiotics. The obtained results in this study were almost similar with the previous result [5].

The results of synergistic antibacterial effect between CCA and antibiotics against acne-related bacteria showed that the CCA has synergistic antibacterial effects in combination with tetracycline, erythromycin, and lincomycin against acne-related bacteria. Furthermore, these results strongly suggested that CCA would restore the antibacterial activity of old commercial antibiotics, which were lost its antibacterial activity against some antibiotic resistant bacteria. Thus, the chitosan-phytochemical conjugate might have potential to use as an adjunct in the treatment of the antibiotic-resistant bacteria. However, some issues still remain to be examined in future studies. For example, an important issue is to elucidate on the restoring mechanism of antibacterial activity of old antibiotics losing the effectiveness of the treatment. It was previously reported that \(\beta\)-lactam antibiotics will restore the antibacterial activity against MRSA through the suppression of penicillin-binding protein 2a production, a key determinant for \(\beta\)-lactam antibiotic resistance, by chitosan-phytochemical conjugate [12]. No further information is currently available on other antibiotic resistant acne-related bacteria. It will be needed more study to address this issue.

4. Materials and Methods

4.1. Preparation of chitosan-phytochemical conjugates

Chitosan (average MW 310 kDa and 90% degree of deacetylation) was provided from Kitto Life Co. (Seoul, Korea). Phytochemicals including caffeic acid, ferulic acid, and sinapic acid were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA). All other chemicals and reagents used in this study were of analytical grade and commercially available. Chitosan-phytochemical conjugates were kindly provided by Prof. Jae-Young Je, Pukyong National University. The conjugates were prepared according to the previous method with a minor modification [11]. In brief, chitosan (0.25 g) was dissolved in 2% acetic acid (25 mL), and then 1.0 M hydrogen peroxide (0.5 mL) containing ascorbic acid (0.054 g) was added. After incubating at room temperature for 30 min, 0.14 mM of phytochemicals (caffeic acid, ferulic acid, and sinapic acid) were added in the mixture and then reacted for 24 h at room temperature. The resulting chitosan-phytochemical conjugates were chitosan-caffeic acid conjugate (CCA), chitosan-ferulic acid conjugate (CFA), and chitosan-sinapic acid conjugate (CSA), respectively. A control (unmodified chitosan) was also treated with the same procedures without the addition of phytochemicals.

4.3. Bacterial strains and culture conditions

The type bacterial strains were obtained from the Korean Collection for Type Cultures (KCTC; Daejeon, Korea); \textit{P. acnes} KCTC 3314, \textit{S. aureus} KCTC 1927, \textit{S. epidermidis} KCTC 1370, and \textit{P. aeruginosa} KCTC 1637. Two of \textit{P. acnes} clinical isolates were provided by the Gyeongsang National University Hospital (Jinju, Korea), a member of the National Biobank of Korea. \textit{P. acnes} strains were anaerobically cultivated in brain heart infusion broth (Difco, Detroit, MI, USA) supplemented with 1.0% glucose, and incubated at 37°C for 72 h in a CO\(_2\) incubator (NAPCO 5400; General Laboratory Supply, Pasadena, TX, USA) in a 10% CO\(_2\)-humidified atmosphere. Other bacteria were grown aerobically at 37°C in Mueller-Hinton broth (MHB; Difco).

4.4. Determination of minimum inhibitory concentration (MIC)

The interaction between chitosan-phytochemical conjugates and antibiotics including tetracycline, erythromycin, and lincomycin against acne related bacteria was tested by the checkerboard method [40]. The synergy effect between chitosan-phytochemical conjugates and the antibiotics was evaluated as a FIC index [40]. Each FIC index was calculated using this equation:

\[
\sum \text{FIC} = \text{FIC}_A + \text{FIC}_B = \frac{C_A}{MIC_A} + \frac{C_B}{MIC_B}
\]
where MIC\(\alpha\) and MIC\(\beta\) are the MICs of drugs A and B alone, respectively, and CA and CB are the concentrations of the drugs in combination respectively. The synergistic effect was evaluated as a FIC index. The interaction was defined as synergistic if the FIC index was <1.0, additive if the FIC index was 1.0, subadditive if the FIC index was between 1.0 to <2.0, indifferent if the FIC index was 2, and antagonistic if the FIC index >2. Synergy was further sub-classified as marked (FIC index, <0.50) and weak (FIC index, between 0.50 to <1.0).

5. Conclusions

In this study, we evaluated the antibacterial activity of chitosan-phytochemical conjugates against acne-related bacteria such as \(P.\) \(acnes\), \(S.\) \(epidermidis\), \(S.\) \(aureus\) and \(P.\) \(aeruginosa\). Among of chitosan-phytochemical conjugates tested in this study, CCA exhibited the highest antibacterial activity against all of acne-related bacteria. Furthermore, the combination of CCA with antibiotics used in the treatment of acne vulgaris resulted in restoring antibacterial activity of the old-fashioned antibiotics against the skin pathogenic bacteria. Thus, the results obtained in this study strongly suggested that chitosan-phytochemical conjugates such CCA will be a good candidate to develop an alternative therapeutic agent with lower side effect for the treatment of acne vulgaris.

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Author Contributions: Ji-Hoon Kim and Young-Mog Kim conceived of and designed the experiments. Daeung Yu, Sung-Hwan Eom, and Song-Hee Kim contributed reagents/materials/analysis tools and performed experiments. Junghwan Oh and Won-Kyo Jung analyzed the data. Daeung Yu, Sung-Hwan Eom and Young-Mog Kim wrote the paper.

Conflicts of Interest: The authors declare no conflicts of interest.

References


