AN OVERVIEW OF QUANTITATIVE AND QUALITATIVE APPROACHES ON THE SYNTHESIS OF HETEROCYCLIC KOJIC ACID SCAFFOLDS THROUGH THE MULTI-COMPONENT REACTIONS

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Abstract – Multi-component reactions as powerful synthetic methods were developed to provide efficient complex scaffolds, including kojic acid, through the one-pot one-step fashion. This review highlights the progress of multicomponent reactions covering kojic acid under different conditions through, short reaction time, higher yields, and environmental friendliness via producing various molecules. The aim of this paper is to review the literature from 2015 to 2020 via quantitative and qualitative approaches.

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1. INTRODUCTION
In 1912, Yabuta described the steamed rice were inoculated with Aspergillus oryzae and some acid was extracted through petroleum ether named koji acid. In 1916, Yabuta used the name kojic acid, and
corrected the molecular formula to $\text{C}_6\text{H}_6\text{O}_4$.\textsuperscript{1} Saito\textsuperscript{2} discovered kojic acid, as the demanding inhibitor of tyrosinase, which was used in food such as crab, shrimp, and vegetables in the food industry due to antioxidant activity and natural antibiotic.\textsuperscript{3,4} Kojic acid is a fungal metabolite which was produced by various species such as Aspergillus, Acetobacter, and Penicillium. Another source of kojic acid is through fermentation of glucose, sucrose, acetate, ethanol, arabinose, and xylose because of carbon sources by Aspergillus falavus.\textsuperscript{5,6} Another source of kojic acid or 5-hydroxy-2-hydroxymethyl-(4H)-pyran-4-one is from leaves of common bearberry, to protect skin via lightening properties.\textsuperscript{7} Among all compounds of kojic acid scaffold, pyranopyranes as a fused oxygenated structures\textsuperscript{8} are one of the essential classes which have biological activities, like antibacterial,\textsuperscript{9} anti-cancer,\textsuperscript{10} antianaphylactic.\textsuperscript{11} The kojic acid derivatives have many applications in cosmetic,\textsuperscript{12} medicine,\textsuperscript{13} food,\textsuperscript{14} agriculture,\textsuperscript{15} and chemical productions.\textsuperscript{16} Kojic acid \textbf{1} is a well-known tyrosinase inhibitor,\textsuperscript{17} due to its structural similarity to phenolic substrates.\textsuperscript{18} This compound could chelate copper through the active site of the enzyme; therefore, the reasonable inhibitory effect has been expected.\textsuperscript{19} There are most commercially available tyrosinase inhibitors such as arbutin \textbf{2} and hydroquinone \textbf{3}, which were shown in Figure 1. In terms of natural resources limitation, it is necessary to be synthesized.\textsuperscript{4}

![Figure 1. The structure of some tyrosinase inhibitors](image)

The three-component reaction of kojic acid, aldehyde or 1,3-dicarbonyl motifs, and malononitrile is one of the most important process to provide heterocyclic motifs using different catalysts such as InCl\textsubscript{3},\textsuperscript{20} CAN,\textsuperscript{21} Al\textsubscript{2}O\textsubscript{3},\textsuperscript{22} Bi(OTf)\textsubscript{3},\textsuperscript{23} CeCl\textsubscript{3}·7H\textsubscript{2}O/SiO\textsubscript{2},\textsuperscript{24} FeCl\textsubscript{3}·SiO\textsubscript{2},\textsuperscript{25} Fe\textsubscript{3}O\textsubscript{4}@SiO\textsubscript{2},\textsuperscript{26} imidazole,\textsuperscript{27} piperidine,\textsuperscript{28} Et\textsubscript{3}N,\textsuperscript{29} and NH\textsubscript{4}VO\textsubscript{3}.\textsuperscript{30} This reaction can be accomplished under ultrasonic irradiation.\textsuperscript{32} In continuous our previous work\textsuperscript{32-35} in multicomponent reaction in organic compounds, kojic acid was reviewed through quantitative and qualitative approaches.

Based on Scopus database, there are about 288 research papers related to kojic acid from 2015-2020, which demonstrates the publication rate of kojic acid. The chart of documents related to kojic acid by subject area was shown in Figure 2.
The data based on source title about kojic acid shows that 21 published papers in Bioorganic Chemistry and take the first rank among others which shows the biological activities of kojic acid derivatives (Figure 3).
Three-Fields Plot on the “kojic acid” research area was shown in Figure 4, which demonstrated the relationship title (right column), top keywords plus (middle column), and abstract (left column). The words accounted as Keywords Plus are words or phrases that frequently appear in the titles of an article’s references, and appear in the title of the article itself. The keywords plus in Figure illustrates “kojic acid,” “tyrosinase inhibitor”, “synthesis” or “molecular docking” which papers in middle column. The attractive keyword plus for the title of the selected papers are “kojic acid”, “synthesis”, “derivatives”, “tyrosinase”, “activity”, “inhibitors”, “molecular”. In the abstract column, kojic acid as a keyword was selected in all papers with the title of kojic, tyrosinase, inhibitors, synthesis with tyrosinase and kojic, and acid due to the strong relation between tyrosinase and kojic acid as an inhibitor.

Figure 4. Three-Fields Plot of Top abstracts, Top Keywords Plus, and Top titles on “Kojic Acid.”

The evolution of the title words in “kojic acid” from 2015 to 2020 as shown in Figure 5 indicates a clear increasing trend of the title words in the bioorganic chemistry by the time.
2. THE SYNTHESIS OF KOJIC ACID DERIVATIVES THROUGH DIFFERENT REACTIONS

2.1 2-Substituted aryl(amino)kojic acid derivatives

Magnetic nanoparticle-supported molybdate sulfuric acid (MNPs-MSA) was synthesized to be used as a catalyst in the one-pot synthesis of the 2-substituted aryl(amino)kojic acid scaffolds 6 from various aldehydes 5, aniline 4, and kojic acid 1 at room temperature without using solvent as shown in Scheme 1.\(^{36}\)

\[
\text{ArCHO} \quad \text{ArNH}_2 \quad \text{O} \quad \text{OH} \quad \text{O} \quad \text{MNPs-MSA, solvent free} \quad \text{55-70 min, rt} \quad 94-97% \\
\text{Ar = C}_6\text{H}_5, 4-\text{MeOC}_6\text{H}_5, 4-\text{ClC}_6\text{H}_5, 4-\text{BrC}_6\text{H}_5, 2-\text{naphthyl, 4-HOC}_6\text{H}_5, 2-\text{ClC}_6\text{H}_5, 2-\text{BrC}_6\text{H}_5, 2-\text{OMeC}_6\text{H}_5, 4-\text{MeC}_6\text{H}_5}
\]

Scheme 1. The synthesis of 2-substituted aryl(amino)kojic acid scaffolds 6

2.2. Dihydropyranopyran derivatives

The dihydropyranopyran derivatives 8 as the corresponding compounds were programmed through three-
component reactions by kojic acid 1, different aromatic aldehydes 5, and malononitrile 7 in the presence of the nano-ZnO as catalyst (Scheme 2). Furthermore, this process was accomplished in different conditions via various catalysts as shown in Table 1.

![Scheme 2. The synthesis of the dihydropyranopyran structures 8](image)

Table 1. The synthesis of the dihydro pyranopyran structures 8 through different catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>nano-ZnO</td>
<td>reflux</td>
<td>1-2 h</td>
<td>81-94</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>H₂O</td>
<td>β-cyclodextrin</td>
<td>70</td>
<td>1 h</td>
<td>83-96</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>Zn(L-proline)₂</td>
<td>reflux</td>
<td>0.5-6 h</td>
<td>88-92</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>H₂O</td>
<td>Co NPs</td>
<td>rt</td>
<td>60-100</td>
<td>70-95</td>
<td>40</td>
</tr>
<tr>
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<td>solvent-free</td>
<td>(SB-DBU)Cl</td>
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<td>41</td>
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<tr>
<td>7</td>
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<td>Fe₃O₄@SiO₂-IL-FC</td>
<td>rt</td>
<td>10-15</td>
<td>81-96</td>
<td>42</td>
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<tr>
<td>9</td>
<td>H₂O</td>
<td>MCM-41-SO₃H</td>
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<td>35-50</td>
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<td>H₂O</td>
<td>Cu₂O-CP</td>
<td>rt</td>
<td>1 h</td>
<td>85-92</td>
<td>44</td>
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<tr>
<td>11</td>
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<td>Fe₃O₄@SiO₂-s-triazinium</td>
<td>100</td>
<td>20-45</td>
<td>85-98</td>
<td>45</td>
</tr>
</tbody>
</table>

1,8-Diazabicyclo[5.4.0]undec-7-ene immobilized on silica

2.3. Bis-2-aminodihydropyrano[3,2-b]pyran-3-carbonitrile derivatives

In this process, terephthalaldehyde 9 was applied to treat with malononitrile 7 and kojic acid 1 in the presence of the cobalt nanoparticles to yield the corresponding bis-2-aminodihydropyrano[3,2-b]pyran-3-carbonitrile 10 as the target compounds (Scheme 3).
Scheme 3. The synthesis of the bis-2-aminodihydropyrano[3,2-b]pyran-3-carbonitrile derivatives 10

2.4. Pyranochromene derivatives

The synthesis of pyranochromene structures 12 was developed through the three-component reactions of kojic acid 1, different aromatic aldehydes 5, and dimerone 11 by the nano-Bi$_2$O$_3$-ZnO as the catalyst as shown in Scheme 4. The catalyst Bi$_2$O$_3$-ZnO was synthesized by a sol-gel method by Bi$^{3+}$ which was supported on ZnO nanoparticles to yield Bi$_2$O$_3$ as heterogeneous catalysis with metal oxides. There are other reports related to this method under different conditions, as illustrated in Table 2.

Scheme 4. The synthesis of pyranochromene structures 12

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Ref.</th>
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</thead>
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<td>1-2 h</td>
<td>75-84</td>
<td>37</td>
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<td>2</td>
<td>solvent-free</td>
<td>PMAA-Fe$_3$O$_4$</td>
<td>110</td>
<td>10-25</td>
<td>64-96</td>
<td>46</td>
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<tr>
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<td>H$_2$O</td>
<td>$\beta$-cyclodextrin</td>
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<td>2 h</td>
<td>73-85</td>
<td>38</td>
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<tr>
<td>4</td>
<td>solvent-free</td>
<td>[SiPrPy]AlCl$_4$@MNP</td>
<td>110</td>
<td>20-40</td>
<td>85-95</td>
<td>47</td>
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</table>

2.5. 2-Substituted aryl(indolyl)kojic acid derivatives

Magnetic nanoparticle-supported molybdate sulfuric acid (MNPs-MSA) was synthesized to be used as catalyst in the one-pot synthesis of the 2-substituted aryl(indolyl)kojic acid scaffolds 14 as the target compounds from various aldehydes 5, indole 13 and kojic acid 1 at room temperature under the solvent-
free condition as shown in Scheme 5. This method was also accomplished in the presence of the different catalysts such as nano SiO$_2$-OSO$_3$H, FAU-Zeolite, and InCl$_3$ through various conditions which were illustrated in Table 3.

Scheme 5. The synthesis of 2-substituted aryl(indolyl)kojic acid scaffolds 14

Table 3. The synthesis of the 2-substituted aryl(indolyl)kojic acid derivatives 14 under different conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Ref.</th>
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</thead>
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<tr>
<td>1</td>
<td>solvent-free</td>
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<td>37-57</td>
<td>88-96</td>
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<td>EtOH</td>
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<td>reflux</td>
<td>40-75</td>
<td>80-98</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
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<td>FAU-Zeolite</td>
<td>110</td>
<td>45-85</td>
<td>82-97</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>solvent-free</td>
<td>InCl$_3$</td>
<td>120</td>
<td>55-85</td>
<td>75-90</td>
<td>50</td>
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</table>

2.6. 2-Aminodihydropyrano[3,2-b]pyran-3-cyano derivatives

In this study, azido-KA 1 was treated with malononitrile 7 and different aldehydes 5 to yield 2-aminodihydropyrano[3,2-b]pyran-3-cyano cores 15 by using Fe$_3$O$_4$@MCM-41@DABCO as a catalyst at a suitable temperature. It is important to know that the synthesis of 2-aminodihydropyrano[3,2-b]pyran-3-cyano derivatives 15, was accomplished using the magnetic nano-mesoporous Fe$_3$O$_4$@MCM-41@DABCO as catalyst in EG as a solvent. Also, this process was examined through different catalysts such as NH$_4$Cl, Fe$_3$O$_4$, and Fe$_3$O$_4$@MCM-41@DABCO which the last one gained high yield (Scheme 6).
In this method, DABCO (1,4-diazabicyclo[2.2.2]octane)-modified magnetite was treated with the silica-MCM-41 shell to provide Fe$_3$O$_4$@silica-MCM-41@DABCO, which is used for the synthesis of 2-aminodihydropyrano[3,2-b]-pyran-3-cyano derivatives as the corresponding compounds. To obtain 2-aminodihydropyrano[3,2-b]pyran-3-cyano derivatives, different conditions were used as shown in Table 4.

Table 4. The synthesis of the 2-aminodihydropyrano[3,2-b]pyran-3-cyano derivatives under different conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Ref</th>
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<tr>
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<td>EG</td>
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<td>trace</td>
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<tr>
<td>2</td>
<td>EG</td>
<td>Fe$_3$O$_4$</td>
<td>100</td>
<td>12 h</td>
<td>15</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>EG</td>
<td>Fe$_3$O$_4$@silica-MCM-41@DABCO</td>
<td>100</td>
<td>3-15</td>
<td>99</td>
<td>51</td>
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<tr>
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<td>NH$_4$Cl</td>
<td>78</td>
<td>12-24 h</td>
<td>90-99</td>
<td>52</td>
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</table>

2.7. MISCELLANEOUS DERIVATIVES

In another work, Asghari and co-workers designed the novel catalyst by pyridine-4-carboxylic acid (PYCA) functionalized Fe$_3$O$_4$ nanoparticles as a magnetic hybrid heterogeneous catalyst to provide pyrano[3,2-b]pyranones through the one-pot three-component reactions by various aromatic aldehydes, kojic acid, and ethyl cyanoacetate under solvent-free conditions. The pros of this method were to be benign, simple by high yields and the catalyst was readily separated by the external magnet (Scheme 7).
In 2015, Teimuri-Mofrad and co-workers designed the process to obtain aminokojic acids 19, 20, respectively, through one-pot multicomponent reaction, by the reaction of kojic acid 1, various aromatic aldehydes 5 or bis-aldehyde 8 and different heteroaromatic amines 18 in the presence of the cerium(III) sulfate as catalyst under the ball-milling condition at room temperature via solvent-free conditions (Schemes 8, 9).

Scheme 8. The synthesis of aminokojic acids 19

Scheme 9. The synthesis of aminokojic acids 20

Novel kojic acid derivatives 22 were synthesized through a three-component condensation reaction as shown in Scheme 10. In this process, different aromatic aldehydes 5 reacted with Meldrum’s acid 21, and kojic acid 1, in EtOH using DABCO-functionalized mesoporous SBA-15 as a catalyst. To obtain the
heterogeneous nonporous, solid-base catalyst, 1,4-diazabicyclo[2.2.2]octane was immobilized on mesoporous SBA-15 to give SBA-15-DABCO. The products were evaluated for their antioxidant activity via 1,1-diphenyl-2-picrylhydrazyl radical-scavenging compound.\(^{55}\)

Scheme 10. The synthesis of novel kojic acid derivatives 22

Multi-component assembling of various salicylaldehydes 23, kojic acid 1, and different substituted malononitriles 16 was disclosed by Elinson and co-workers in the presence of the sodium acetate, as a catalyst in EtOH to provide the substituted 2-amino-4-[3-hydroxy-6-(hydroxymethyl)-4-oxo-(4\(H\))-pyran-2-yl]-(4\(H\))-chromene-3-carbonitriles or -3-carboxylates 24 as products in 75–96% yields (Scheme 11).\(^{56}\)

Scheme 11. The synthesis of 2-amino-4-[3-hydroxy-6-(hydroxymethyl)-4-oxo-(4\(H\))-pyran-2-yl]-(4\(H\))-chromene-3-carbonitriles or -3-carboxylates 24

In this process, a novel class of kojic acid derivatives 1 was treated with the \(\alpha\)-amino acid 25, and different aldehydes 5 through a three-component decarboxylative coupling reaction to provide 2-pyrrolidinyl and 2-piperidinyl substituted kojic acids 26 under thermal conditions as shown in Scheme 12.\(^{57}\)
Pahlavan and co-workers reported the three-component reaction by \(N\)-methylimidazole 27, variously activated acetylenes 28 and kojic acid 1 to afford 2,3-dihydroimidazoles 29 as shown in Scheme 13.\(^{58}\)

Rahman and co-workers developed the new approach through a one-pot three-component reaction of 3-methyl-1\(H\)-pyrazol-5-amine 30, various aldehydes 5 and kojic acid 1 to provide fused pyridines 31 (Scheme 14). In this process, the triazine diphosphonium hydrogen sulfate ionic liquid used was supported on nano-silica to produce the catalyst APTDPHS-\(n\)SiO\(_2\) to yield fused pyridine structures.\(^{59}\)
In another attempt, the synthesis of the fused pyridines 33 was accomplished through the three-component reaction of various aldehydes 5, kojic acid 1, and 6-amino-1,3-dimethyluracil 32 using the ionic liquid aminopropyl-1,3,5-triazine-2,4-diphosphonium hydrogen sulfate supported on nano-silica, as catalyst without using solvent as shown in Scheme 15.

![Scheme 15. The synthesis of fused pyridine derivatives 33](image)

The APTADPHS-\(n\)SiO\(_2\) catalyst was examined for the synthesis of \textit{bis}-annulated pyridine derivatives 34, 35 respectively from terephthalaldialdehyde or isophthalaldialdehyde as \textit{bis}-aldehydes 11, kojic acid 1 and 6-amino-1,3-dimethyluracil 32 to produce the \textit{bis}-pyridines 34 and 35 in acceptable yields under solvent-free conditions (Schemes 16, 17).

![Scheme 16. The synthesis of \textit{bis}-pyridine derivative 34](image)
A novel magnetic metal-organic structured NiFe$_2$O$_4$@MOF-5 was applied by Zhang and co-workers to yield 2-substituted aryl(indolyl)methylkojic acid derivatives 36, 37. In this process, 2-substituted aryl(indolyl)methylkojic acid cores 36 and 37 were provided through one-pot, the three-component reaction from dialdehydes 8, indole 13 and kojic acid 1 (1 mmol) (Scheme 19) or (2 mmol) (Scheme 20) under solvent-free conditions respectively.

A series of 2-methoxy-3-(2-amino-3-cyano-6-(hydroxymethyl)-8-oxo-4,8-dihydropyrano[3,2-b]pyran-4-yl)quinolone 39 as corresponding compounds were synthesized by Kumarasamy and co-workers in 2019.
In this study, various 2-methoxy-3-formylquinolones 38 were treated with malononitrile 7, and kojic acid 1 to furnish the product 39 in the presence of the metal triflates Yb(OTf)$_3$ through one-pot, multi-component reaction under microwave conditions (Scheme 20).$^{61}$

Scheme 20. The synthesis of the 2-methoxy-3-(2-amino-3-cyano-6-(hydroxymethyl)-8-oxo-4,8-dihydropyran[3,2-b]pyran-4-yl)quinolone derivatives 39

The target compounds 6-amino-2-(hydroxymethyl)-8-aryl-7-(phenylsulfonyl)pyrano[3,2-b]pyran-4(8H)-ones 41 as pyran-annulated heterocyclic derivatives were synthesized through multi-component reaction. In this process, different aromatic aldehydes 5 reacted with kojic acid 1 and phenylsulfonylacetonitrile 40 using nano-cellulose-$\text{OSO}_3\text{H}$ as catalyst to yield the target compounds 41 (Scheme 21).$^{62}$

Scheme 21. The synthesis of the 6-amino-2-(hydroxymethyl)-8-aryl-7-(phenylsulfonyl)-pyrano[3,2-b]pyran-4(8H)-one derivatives 41

3. CONCLUSIONS

In conclusion, using kojic acid conclusively established a wide-ranging of compounds with high biological activities. The presence of this compound in pharmaceutical applications shows the importance...
of the different releasing scaffolds through different conditions. Also, in this review the importance of the kojic acid was studied through biobliometric approaches.

ABBREVIATION

<table>
<thead>
<tr>
<th>Abbreviate</th>
<th>Full name</th>
<th>Abbreviate</th>
<th>Full name</th>
</tr>
</thead>
<tbody>
<tr>
<td>KA</td>
<td>kojic acid</td>
<td>EG</td>
<td>ethylene glycol</td>
</tr>
<tr>
<td>FAU-Zeolite</td>
<td>faujasite</td>
<td>Yb(OTf)$_3$</td>
<td>ytterbium(III) triflates</td>
</tr>
<tr>
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<td>chlorosulfonic acid</td>
<td>PYCA</td>
<td>pyridine-4-carboxylic acid</td>
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<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2.]octane</td>
<td>APTDPHS-nSiO$_2$</td>
<td>triazine diphosphonium hydrogen sulfate ionic liquid- nano-silica</td>
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<td>MNPs-MSA</td>
<td>nanoparticle-supported</td>
<td>molybdate sulfuric acid</td>
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REFERENCES AND NOTES


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