An Alternative on the Usage of Marine Mollusc Heparin as the Halal Anticoagulant Source among Muslim Consumers

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Abstract
Halal pharmaceuticals are on the rise as far-sighted businesses compete in the sector and obtain halal certification, particularly in Malaysia, South Korea and Indonesia. One of the most necessary issues to take into consideration is the development of anticoagulants in halal pharmaceuticals. Heparin serves as an anticoagulant and potential as an anticancer agent. Organs and tissues such as lungs, liver, ileum, skin, lymph, and thymus in certain mammals and vertebrates contain most of heparin. However, heparin usually derived from pig derivatives and provided through the chemical extraction from pig intestine, which are clearly not syariah-compliant. The objective of this review paper is to describe the potential of marine molluscs as an alternative source of halal heparin for its anticoagulant effects in the pharmaceutical sector. The heparin extracted from marine molluscs have a different blood-coagulating system compared to mammals. The potential of heparin extract of marine molluscs as a halal alternative source were refined and discussed, also expected to meet the requirements of halal pharmaceuticals for Muslim consumerism.

Keywords: halal pharmaceuticals, heparin, marine molluscs, anticoagulant, muslim consumers

1.0 Introduction
Muslim consumers over the world spend US$ 2.2 trillion in 2018 around the food, pharmaceutical and wellness domains that are influenced by ethical consumption demands driven by Islamic religion. Based on Thomson Reuters’ State of the Global Islamic Economy Report 2019/20, Muslim pharmaceutical expenditure in 2018 was approximately US$92 billion from $87 billion the previous year. It is expected to rise to US$ 134 billion by 2024 (Reuters, 2019). Based on these statistics, halal pharmaceuticals are on the rise as far-sighted
businesses compete in the sector and obtain halal certification, particularly in Malaysia, South Korea and Indonesia. Besides, OIC governments are promoting for halal vaccinations and medicines to be developed (Reuters, 2019). One of the most necessary issues to take into consideration is the development of anticoagulants in halal pharmaceuticals.

Heparin is a natural anti-inflammatory substance in the body that can prevent blood clots (Mousavi et al., 2015). These substances are released by mast cells from intermediary tissues and stored as granules in the body cells (Mulloy et al., 2017). Heparin is secreted into the inter-cell material and inhibits fibrinogen from forming fibrin clots, which released from the blood capillary (Ma et al., 2017). Heparin also neutralizes the protons and inhibits the thrombin activity (Onishi et al., 2016). Thus, as Mucopolysaccharide acid, heparin functions as antitrombin, antitromboplastin and antiplatelet to prolong the blood clotting time in most tissues, especially in the liver (Caughey, 2016).

Heparin serves as anticoagulants (antigens) and potential anticancer agents (Lokwani et al. 2014). It is usually derived from pig derivatives (Geraldine et al., 2004) and is usually available through the removal of chemicals from pork and cow lungs (e.g., Bedford & O’Brien, 1977; Guan et al., 2016; St Ange et al., 2016). However, heparin extracts of molluscs have begun to be used on mammals (Maccari & Volpi, 2016; Odeleye et al., 2019). From the point of halal pharmaceutical view, the level of purity determination is emphasized. The purity analysis for medication is easily achieved if it is produced by synthetic substances (Zarif et al., 2013; Ogden, 2016). Existing issues on purity of current heparin source make Mollusc as an alternative source that meet the halal requirement. The objective of this review paper is to describe the potential of marine molluscs as an alternative source of halal heparin for its anticoagulant effects in the pharmaceutical sector for Muslim consumerism.

2.0 Literature Review

2.1 Halal pharmaceutical and Muslim Consumerism

Islam, the religion of Muslims, offers specific consumer safety rules and values, also highlights the ethical and moral consequences of upholding consumer rights. Religion becomes more critical for Muslim consumers and their fundamental rights should include the protection of their beliefs (Ayob, 2017).
Halal pharmaceutical is an important aspect, which becomes a resource that helps to enhance the economic growth and development. This sector is also critical for Muslim consumers in ensuring their right to practice the religion (Ramli et al., 2017). The Malaysian Standard of Halal Pharmaceutical is the most appropriate document to be adopted with a view to standardizing the performance and protection of halal pharmaceutical products (Halim et al., 2014).

2.2 Mollusc and The Halal Status of Marine Sources

According to the Malaysia Halal Certification Manual (Third Revision) 2014 (MPPHM 2014), animal-derived materials should meet the following requirements as a halal guarantee for raw material and ingredient requirements:

“5.1 Requirements of Raw Materials/ Ingredient/ Processing Aid:
   i. Ensure raw material/ ingredient sources are halal and safe;
   ii. Raw material/ ingredient which are sourced from animal shall have a valid halal certificate;
   iii. Sources of imported animal-based raw materials shall come from approved plants by JAKIM and Department of Veterinary Services (DVS);
   iv. Raw material without halal certification shall be accompanied with complete specification (indicating material composition, flow chart and its raw material sources);
   v. Raw materials, processing aid and product/ menu shall be listed in detail in the application form; and
   vi. Non-halal raw material/ ingredient is not allowed to be stored in the premise.”

Based on MPPHM 2014, non-halal animal sources and derivatives are considered as not reaching halal meaning. The fatwa of necessity on the use of cow derivatives is due to the emergency and critical situation of the medical aspect (Ab Halim et al., 2015), as the best option after the source of pig. However, its halal status is easily exposed to the question of which involves the animal handling, e.g., halal slaughtering (Fuseini et al., 2016). Therefore, the lawful alternative sources are preferred to use. The sources from pig and improper or unslaughtered cow, and its derivatives are obviously non-halal or dubiously halal.
Mollusc, as well as pig and cow, contain high extracts of heparin (Zhu et al., 2019). According to the preferences of Muslim consumers, mollusc, a marine animal life, is closer to halal compared to land animal. In this regard, Islam permits substances from marine life as a source of medicines and food. The Quran has stated this related issue in a few verses.

Lawful to you is game from the sea and its food as provision for you and the travelers, but forbidden to you is game from the land as long as you are in the state of ihram. And fear Allah to whom you will be gathered.

(Al-Ma’idah 5:96)

And it is He who subjected the sea for you to eat from it tender meat and to extract from it ornaments, which you wear. And you see the ships plowing through it, and [He subjected it] that you may seek of His bounty; and perhaps you will be grateful.

(Al-Nahl 16:14)

It is Allah who subjected to you the sea so that ships may sail upon it by His command and that you may seek of His bounty; and perhaps you will be grateful.

(Al-Jaathiyah 45:12)

2.3 Heparin Sources from Mammals and Other Vertebrates

Based on the preference of Muslim customers, mammals and other vertebrates, including non-predatory wild animals, domesticated and non-predatory birds, domestic animals ruminants and pseudo-ruminants, are halal (Benzertiha et al., 2018). The lungs, liver, ileum, skin, lymph, and thymus are the organs and tissues that contain most of the heparin of some selected mammals and vertebrates (Table 1 & Figure 1). The heparin content is highest in (µg/g dry tissue) (Volpi, 2005; Volpi & Maccari, 2017):

a. Lungs: cow (300), dog (217), and pig (211)
b. Liver: dog (141), cow (50), and cat (1)
c. Ileum: bow (1015), dog (400), and pig (113)
d. Skin: mice (175), cow (108), and cat (63)
e. Lymph: pig (242), cow (180), and dog (160)
f. Thymus: cow (286), guinea pig (112), rat (20), and dog (20).

The highest total heparin content in selected animals are:

a. Cow (2156)
b. Dog (1094)
c. Pig (585)

Depending on the preferences of Muslim consumers, the heparin source from a dog and a pig is completely haram. Whereas the heparin source from a cow is doubtful when it comes to halal slaughtering procedure.

Table 1: Distribution of heparin in mammals and other vertebrates (adapted from Volpi 2005; Volpi & Maccari 2017).

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Rabbit*</th>
<th>Guinea Pig*</th>
<th>Rat**</th>
<th>Dog**</th>
<th>Cat**</th>
<th>Pig**</th>
<th>Cow*</th>
<th>Human**</th>
<th>Chicken*</th>
<th>Snake**</th>
<th>Lizard**</th>
<th>Frog***</th>
<th>Fish*</th>
<th>Shark***</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µg/g dry tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>&lt;1</td>
<td>70</td>
<td>67</td>
<td>217</td>
<td>63</td>
<td>211</td>
<td>300</td>
<td>8</td>
<td>0.5</td>
<td>0.3</td>
<td>0.0</td>
<td>0.6</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td></td>
<td>141</td>
<td>1</td>
<td>&lt;1</td>
<td>50</td>
<td>&lt;1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.8</td>
<td>1.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Ileum</td>
<td>&lt;1</td>
<td>27</td>
<td>1</td>
<td>400</td>
<td>87</td>
<td>113</td>
<td>1015</td>
<td>32</td>
<td>0.5</td>
<td>0.9</td>
<td>0.2</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Kidney</td>
<td>&lt;1</td>
<td>4</td>
<td>&lt;1</td>
<td>2</td>
<td>6</td>
<td>&lt;1</td>
<td>26</td>
<td>&lt;1</td>
<td>0.1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.5</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Aorta</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>9</td>
<td>102</td>
<td>&lt;1</td>
<td>2</td>
<td>150</td>
<td>&lt;1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Muscle</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>36</td>
<td>9</td>
<td>&lt;1</td>
<td>5</td>
<td>2</td>
<td>&lt;1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Spleen</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>11</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.9</td>
</tr>
<tr>
<td>Skin</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>175</td>
<td>15</td>
<td>63</td>
<td>2</td>
<td>108</td>
<td>39</td>
<td>0.4</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Lymph</td>
<td>&lt;1</td>
<td>11</td>
<td>5</td>
<td>160</td>
<td>74</td>
<td>242</td>
<td>180</td>
<td>41</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymus</td>
<td>&lt;1</td>
<td>112</td>
<td>20</td>
<td>20</td>
<td>10</td>
<td>286</td>
<td>35</td>
<td>47</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendix</td>
<td>&lt;1</td>
<td>17</td>
<td>38</td>
<td>20</td>
<td>47</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Halal sources if ritually slaughtered, **Haram sources, ***Khilaf
2.4 Heparin Content in Mollusc

The discovery of heparin sources of marine molluscs opens new dimensions in meeting halal pharmaceutical needs of Muslim consumers. Mollusc has a different blood clotting system compared to mammals. Heparin in mollusc is able to accelerate the activation of mammalian blood clotting enzyme through inhibitor enzyme; antithrombin III (ATIII). Heparin is expected to potentially interact with endogenous antitrombin such as protease as an inhibitor enzyme (Volpi & Maccari, 2017).

Heparin in mammals is released from mast cells in response to specific inflammatory agents such as IgE (Immunoglobulin E) antibodies or anaphylatoxins. The discovery of mast cells by Paul Ehrlich in 1879, led to the scientific finding of heparin through basic staining techniques (Ehrlich, 1879). Different studies on concentration of heparin in cow’s fetal and adult tissue (Nader et al., 1982) have shown a positive correlation between the number of mast cells and heparin concentrations. It means that the high number of mast cells also exhibit high concentration of heparin.

Mast cell in mammals, which contains heparin, is accumulated in the lymphoid organs and in the tissues, which is exposed to the external environment (i.e., skin, lungs, intestines), and this
polysaccharide plays a proposed role against external parasites (Nader et al., 2004). *Anomalocardia brasiliana* (*A. brasiliana*), is an invertebrate type of mollusc living shallowly submerged in intertidal sediment (Santhanam et al., 2019). Heparin and GAG sulfate such as histamine are obtained from some mollusc organ of *A. brasiliana*. Heparin is found in granules inside the cytoplasm that resembles mast cells (Dietrich et al., 1985, Pejler et al., 1987). The positive correlation between heparin and histamine content is found in the labium palate, intestine, ctenidium, mantle and foot tissue of *A. brasiliana*. Distribution of heparin in invertebrates is shown in Table 2.

Table 2: Distribution of heparin in invertebrates (adapted from Volpi 2005; Volpi & Maccari 2017)

<table>
<thead>
<tr>
<th>Class and Species</th>
<th>Average MM (kDa)</th>
<th>Anticoagulant Activity (USP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molluscs</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Cyprina islandica</em></td>
<td>nd</td>
<td>95</td>
</tr>
<tr>
<td><em>Mactrus pussula</em></td>
<td>nd</td>
<td>100</td>
</tr>
<tr>
<td><em>Mercenaria mercenaria</em></td>
<td>18</td>
<td>348 (Anti-IIa)</td>
</tr>
<tr>
<td><em>Anomalocardia brasiliana</em></td>
<td>32</td>
<td>320</td>
</tr>
<tr>
<td><em>Donax striatus</em></td>
<td>20</td>
<td>220</td>
</tr>
<tr>
<td><em>Tivela mactroides</em></td>
<td>25</td>
<td>180</td>
</tr>
<tr>
<td><em>Tapes phylippinarum</em></td>
<td>14</td>
<td>350</td>
</tr>
<tr>
<td><em>Callista chione</em></td>
<td>11</td>
<td>97</td>
</tr>
<tr>
<td>Crustacea</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Ucides cordatus</em></td>
<td>nd</td>
<td>60</td>
</tr>
<tr>
<td><em>Dedrocephalus brasiliensis</em></td>
<td>10</td>
<td>52</td>
</tr>
<tr>
<td><em>Penaeus brasiliensis</em></td>
<td>9</td>
<td>60</td>
</tr>
<tr>
<td>Annelida</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Aphrodite longicornis</em></td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td><em>Hermodice carunculata</em></td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Echinodermata</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mellita quinquiesperforata</em></td>
<td>12</td>
<td>50</td>
</tr>
<tr>
<td>Cnidaria</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Physalia sp.</em></td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td><em>Mnemiopsis sp.</em></td>
<td>nd</td>
<td>nd</td>
</tr>
</tbody>
</table>

Note: nd—not detected, the molecular mass and the anticoagulant activity are reported.

Preparation of heparin from mammalian tissues raises concerns particularly after oversulfated chondroitin sulfate (CS) contamination of
cow spongiform encephalopathy in Europe (Volpi & Maccari, 2017). In this regard, tissues from cows are now rarely used in heparin production. Hence, alternative source from porcine is used, but with growing concern from the religious perspective, especially Muslim consumerism regarding its halal status. Considering this conflict, heparin preparation through biochemical pathway is expected to be the best alternative, e.g. recombinant cell culture of mammals or non-mammals via large-scale fermentation process (Datta et al., 2017).

An antimalarial substance which adapted to the heparin structure is potentially reactive with a particular anticoagulant protease group (Aláez-Versón et al., 2017). It is also expected to reduce the side effects of heparin by avoiding unwanted interactions with other proteins. Furthermore, it is also expected to treat infectious diseases (Mycroft-West et al., 2018), inflammation (Joshi et al., 2016), and also control cell growth in wound healing (Ishihara et al., 2018) and cancer (Mudit & El Sayed 2016).

3.0 Conclusion and Recommendations

The potential of heparin extracts from molluscs is expected to meet the requirements of halal pharmaceuticals compared to the sources of mammals and vertebrate animals that are clearly illegal or easily misleading halal status. This is of utmost important for the Muslim consumers as the heparin source from molluscs has no issue involving ethics and law, and has high future economic potential especially for halal consumerism. In the future, a study on bioavailability of heparin derived from mollusc compared to heparin derived from cows and pigs is suggested to further strengthen the confidence of Muslim consumers.

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References


