Sources of Cysteine-Based Pharmaceutical Drugs and Their Halal Aspects in Pharmaceutical Product Development

Dzikri Anfasa Firdaus*, Fikri Hidayatul Jihad, Siti Inayah Majreha Mursaha

1)Faculty of Mathematics and Natural Science, IPB University, Jl. Agatis. Dramaga Campus IPB, Bogor, West Java, 16880, INDONESIA
2)Department of Exegesis and Quranic Sciences, Faculty of Islamic Theology, Al-Azhar University, Cairo

ABSTRACT

Indonesia has the largest Muslim population in the world; therefore, supplements and medicines consumed must be halal (permissible under Islamic law). Cysteine is an essential amino acid crucial for biological functions in humans. Cysteine can be used as a mucolytic agent to help thin mucus in respiratory diseases, such as bronchitis or chronic obstructive pulmonary disease (COPD). It also serves as an antidote to acetylcysteine synthesis. Cysteine is a precursor of acetylcysteine and acetaminophen for detoxification purposes or to counteract paracetamol (acetaminophen) overdose, a commonly used drug to relieve pain and reduce fever. Additionally, it functions as a supplement. This research aims to comprehensively review the sources of cysteine, its production, and its use in pharmaceuticals, as well as the opinions of scholars regarding the halal aspects that need to be considered when developing pharmaceutical products containing cysteine. The methods employed included searching through references from research articles obtained from Google Scholar, ScienceDirect, NCBI, Elsevier, and the Qur'an, Hadiths, and other Islamic literature sources. The compound structures were visualised using the ChemSketch tool from ACD/Labs. Mucolytic and acetaminophen drugs, such as acetylcysteine, can be derived from both animal and plant sources through chemical and nonchemical separation processes. Cysteine is a precursor of acetylcysteine synthesis. Cysteine sourced from specific organs, such as pig hair, has differing opinions among scholars regarding its permissibility. However, the prevailing view and fatwa tend to lean towards its prohibition, depending on the source, process, and urgency of its use.

1. Introduction

Indonesia has a large Muslim population. According to data from the Directorate General of Population and Civil Registration (Dukcapil) of the Ministry of Home Affairs, as of June 2021, out of a total population of 272.23 million, 236.53 million people (86.88%) are Muslims. Therefore, the consumption of food, beverages, and medicines must adhere to halal principles. Article 135 of Government Regulation No. 39 of 2021 stipulates that food, beverages, medicines, cosmetics, chemical products, biological products, genetically engineered products, and consumables must be halal. This includes the processes of slaughter, processing, storage, packaging, distribution, sale, and presentation.

Cysteine is commonly used in the production of food and pharmaceuticals due to its numerous applications. As a food additive, it is used as a dough softener, high-protein beverage, and meat flavor enhancer (Taufik et al. 2020; Noer & Irma 2021). Moreover, cysteine is utilized in the development of medications for thinning mucus in conditions such as asthma, cystic fibrosis, chronic obstructive pulmonary disease, COVID-19, and paracetamol (acetaminophen) poisoning, which is prevalent in COVID-19 patients with prolonged fever (Khuroo 2020). Additionally, cysteine can be taken as an antioxidant supplement (Packer & Colman 1999). Cysteine can be extracted from both plant and animal sources. For example, it can be obtained from the hydrolysis of pig bristles, human hair, bird feathers, and plants (Eason et al. 2002; Riemenschneider et al. 2005; Zharif et al. 2021). However, the use of cysteine in pharmaceuticals derived from these sources raises concerns among consumers about their permissibility and halal status.

The research project seeks to conduct a thorough examination of cysteine’s sources, production, and application in pharmaceuticals, as well as the perspectives of scholars on the halal aspects that need to be considered when creating pharmaceutical products containing cysteine. The methodology involves searching through references from research articles obtained from Google Scholar, ScienceDirect, NCBI, Elsevier, and other Islamic literature sources such as the Qur'an, Hadiths, and other sources. To illustrate the chemical structures and reaction mechanisms, the ChemSketch tool from ACD/Labs was utilized. This literature review pertains to the sources of cysteine, its application as a medicinal product, and the halal aspects that need to be taken into account when developing pharmaceutical products containing cysteine.

2. Methodology

The process of preparing this article review involves sourcing references from a variety of research articles that were obtained through searches conducted on Google Scholar, ScienceDirect, NCBI, Elsevier, and other Islamic literature sources. This literature review focuses on the origins of cysteine, its utilization, the synthesis of acetylcysteine, and its halal status from an Islamic perspective. Compound structures were created using the ChemSketch tool from ACD/Labs. No changes were made to the citation.
Table 1. Sources, Isolation Methods, and Characterization of Cysteine

<table>
<thead>
<tr>
<th>Source of Cysteine</th>
<th>Isolation and Characterization Methods</th>
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<tr>
<td>Mollusk Blood (Mytilus edulis) (Charlet et al. 1996)</td>
<td>Amino acid analysis using reversed-phase HPLC.</td>
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<tr>
<td>Chicken Eggs (Mori et al. 2020)</td>
<td>Amino acid analysis using high-performance liquid chromatography (HPLC).</td>
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The synthesis of acetylcysteine can be carried out by initially dissolving L-cysteine (0.50 g, 4.1 mmol) and sodium acetate trihydrate (1.11 g, 8.2 mmol) in a THF-water solution (90:10 v/v, 10 mL) in the absence of gas, and stirred at room temperature for 20 minutes under nitrogen. The reaction mixture is then cooled to 0 °C, and acetic anhydride (0.44 g, 4.3 mmol) is added dropwise. The reaction is stirred for 16 hours at room temperature under nitrogen. The clear solution is then cooled and acidified to pH 1 with concentrated HCl (Yamamoto et al. 2021) (Figure 3). Additionally, the synthesis of acetylcysteine can be achieved through an alternative method. N-acetyl-1H-benzo[1,2]thiazole is prepared by reacting acetic acid with an equimolar mixture of 1H-benzo[1,2]thiazole and SOCl2 at room temperature, 21 °C, for 2 hours (Katrizky et al. 2003). SOCl2 is a highly reactive compound that can vigorously react with water and other chemicals. It is advisable to adhere to safety regulations when using this reagent. The resulting product is recrystallized using a mixture of acetone and diethyl ether (v:v 50%) (Ziaeae & Ziaeae 2021) (Figure 4).
The critical aspect in assessing the two synthesis methods for acetylcysteine (illustrated in figures 3 and 4) is the role of cysteine, which could potentially be sourced from prohibited materials such as pig hair. According to the MUI fatwa, acetylcysteine derived from cysteine obtained from pig hair is deemed unacceptable for use as a mucolytic and acetaminophen.

4. Discussion

Cysteine is a type of amino acid that is frequently found in a variety of proteins and enzymes. Its distinctiveness lies in the presence of a reactive thiol group within its chain, which is a characteristic that sets itself apart from other amino acids (Hunt 1985; Gmünder et al. 1990; Demirkol et al. 2004) (as depicted in Figure 1). Cysteine has significant importance due to the various roles it plays, such as serving as a control for thiol functionalization, participating in heavy metal detoxification in living organisms, contributing to the antioxidant capabilities of tissues and mitochondria, playing a role in blood clotting in mammals, facilitating transport across cell membranes, and being involved in electrochemical sensing (Sirkö et al. 2004; Wirtz et al. 2004; Wirtz & Droux 2005; Borase et al. 2015).

Cysteine is accessible from both plant and animal sources. Traditionally, animal products like meat, eggs, and dairy have been the primary sources of cysteine, known for their comprehensive nutritional profile (Chung et al. 1994; Magboul et al. 2001; Rosyidi 2007; Mori et al. 2020). However, the inclusion of plant-based sources like grains, legumes, and specific plants expands the range of amino acids available to consumers.

Expectorants are drugs that are used to alleviate a productive cough. These drugs work by breaking the bonds between mucopolysaccharides and mucoproteins in the mucus, which reduces its viscosity and alters its properties (Rohman 2018). Acetaminophen, a commonly used analgesic in the United States, is also known to be the leading cause of acute liver failure in the country (Clark et al. 2012). N-acetylcysteine (NAC) is one of the most commonly prescribed expectorants, and it contains the amino acid L-cysteine with thiol groups and acetyl groups attached to its nitrogen atom (Radomska-Lesniewska et al. 2018) (see Figure 2). NAC is the acetylated form of L-cysteine and has been used clinically for over four decades. NAC functions as an antioxidant and free radical scavenger, stimulates glutathione synthesis, and has vasodilatory properties due to its effects on nitrate (Moore 2012). NAC is effective in preventing hepatocyte necrosis caused by NABQI (a metabolite of paracetamol poisoning) and may also be effective for CCl4 and chloroform poisoning. However, oral administration of NAC may cause side effects such as nausea and vomiting. Intravenous administration should be slow and done gradually, as rapid administration can cause flushing and hypotension, and should not be given to patients allergic to this medication (Sadewa et al. 2021).

The views of classical and contemporary scholars toward pigs are explained based on the Qur’an, Hadith, and statements from scholars. The wording that Allah has stated in that verse uses the term “Lahm Khinizar,” which translates to pig meat. Therefore, the critical question arises: Does

![Figure 4. Synthesis of Aestilcysteine (Ziaee & Ziaee 2021)](image1)

![Figure 5. Synthesis of Aestilcysteine (Ziaee & Ziaee 2021)](image2)
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does this mean that other parts of the pig are considered permissible by Allah? Why does Allah only mention specific parts of the pig? Is the relationship between meat and halal animal tissue important? In particular, those in the field of exegesis, have provided various interpretations. Imam Alusi (1943), in his exegesis "Ruuhul Maani," argues that the pig, along with all its parts, is deemed Haram. The specificity of mentioning or not mentioning parts is significant as it is an essential part of the animal for consumption. Other parts follow the rulings of the meat, with those parts being considered subordinate and integral to the meat. Imam Baidowi (2004) in his exegesis "Anwar Al Tansil wa Arba'at Al Takwil" supports a similar perspective within the context of this discussion.

The secret behind using the term ‘meat’ in that verse is to unequivocally reject the notion that pig meat is superior and better than the meat of other animals. This rejection is also directed toward those who deny the prohibition of the pig. Imam Alusi (1943), Imam Al Qurtubhi (2006) and others emphasize "Tafsir Al Qurtubi," argue that the specificity of mentioning "Laam Khiniriz" without reference to other parts indicates the overall prohibition of the pig, whether slaughtered or not, encompassing other parts such as fat, grease, bones, and other components. Furthermore, in his exegesis, Imam Al Qurtubhi (2006) states that there is no difference of opinion that the entire pig is prohibited, except for its hair.

Imam Ibn Kathir (2015) in his work "Tafsir Ibn Kathir" states that Allah prohibits pig meat, whether slaughtered or not, including its fat/grease. The prohibition of pig fat/grease is because this part falls under the term ‘Laam Khiniriz.’ In his commentary, Imam Zamakhshari (2010) in his work "Kasyaf an Haqaiqi Tanzil" shares the same view within the context of this discussion. Imam Ar-Razi (1981), through his phenomenal work "Matahil Al Ghab," contends that scholars unanimously agree that pigs and all their parts are prohibited. According to pigs are outwardly prohibited, it does not fall under the term "pig meat," although scholars unanimously agree on the prohibition and impurity of pigs. However, there are differing opinions among scholars regarding the permissibility of utilizing pig hair.

Some scholars permit the use of pig hair for sewing purposes. According to the renowned contemporary exegete, Imam Thahir Ibn Ashur (1984) in his book "Tahir Wa Tanwir," he analyzes that the mention of the term ‘meat’ is directed towards consumption. Therefore, it does not imply permission to consume other parts.

Imam Nawawi (2005) in his book "Majmu’ Syarh Muhadabas," particularly in the chapter on Athimah, expresses the opinion of followers of the Shia school that using impure substances for medical treatment is allowed if a pure substitute is not available. However, once a pure alternative is found, using the impure substance becomes prohibited. A hadith is cited, stating, “Indeed, Allah has not made your well-being dependent on what is prohibited for you.” From this, Imam Nawawi (2005) concludes that using impure substances for treatment becomes prohibited when a pure and non-prohibited alternative is available. Followers of the Shia school also argue that it is permissible to use impure substances for medical treatment if health experts, particularly pharmacologists, state that there is no alternative except the impure substance, or if a trustworthy medical practitioner advises it. On the other hand, Imam Ahmad Abidin (2010), in his book "Abdul Aziz bin Abdussalam," (1944), in his book "Qawaid Ahkam," contends that it is permissible to use impure substances for treatment if a pure alternative is not available, prioritizing health and safety over avoiding impure substances.

According to Dr. Asma Fathi Ali (2016) in her research titled "Shinmah dawlah wa Mi'am Fighy," the scholars unanimously agree on the prohibition of consuming anything derived from pigs in normal conditions. Therefore, mucolytic and acetaminophen drugs containing acetylcysteine, is often the source of these drugs. However, acetylcysteine, can be derived from both plant and animal sources through various separation processes. Cysteine, which is a precursor for the synthesis of acetylcysteine, is often the source of these drugs. However, there are differing opinions among scholars regarding the permissibility of cysteine sourced from specific organs, such as pig hair. The prevailing view and fatwa tend to lean towards its prohibition, taking into consideration the source, process, and urgency of its use.

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