



Sources of cysteine-based pharmaceutical drugs and their halal aspects in product development

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ABSTRACT

Indonesia is characterized by the largest Muslim population globally, showing the need for supplements and medicines consumed to be halal (permissible under Islamic law). In this context, cysteine is an essential amino acid crucial for biological functions in humans. It is used as a mucolytic agent to help thin mucus in respiratory diseases, such as bronchitis or chronic obstructive pulmonary disease (COPD). Cysteine also serves as a supplement or an antidote to acetaminophen for detoxification or to counteract paracetamol (acetaminophen) overdose, a commonly used drug to relieve pain and reduce fever. Therefore, this research aims to comprehensively review sources of cysteine, production, and use in pharmaceuticals. This research also explores the opinions of scholars regarding halal aspects that need to be considered when developing pharmaceutical product containing cysteine. The methods used included searching through references of research obtained from Google Scholar, ScienceDirect, NCBI, Elsevier, the Qur'an, Hadiths, and other Islamic literature sources. The compound structures were visualized using the ChemSketch tool from ACD/Labs. The results showed that mucolytic and acetaminophen drugs, such as acetylcysteine, could be derived from both animal and plant sources through chemical and nonchemical separation processes. As a precursor of acetylcysteine synthesis, the permissibility of cysteine sourced from specific organs, such as pig hair, had different opinions among scholars. However, the prevailing opinions and fatwa tended to depend on prohibition, based on sources, process, and urgency of use.

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1 Introduction

Indonesia is characterized by the largest Muslim population globally. According to data from the Directorate General of Population and Civil Registration (Dukcapil) of the Ministry of Home Affairs, as of June 2021, a total population of 236.53 million (86.88%) among 272.23 million are Muslims. This shows that 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, as well as chemical, biological, genetically engineered product, and consumables must be halal. This includes the processes of slaughter, processing, storage, packaging, distribution, sale, and presentation of food ingredients such as cysteine.

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 often applied in the development of medications for thinning mucus in various conditions such as asthma, cystic fibrosis, chronic obstructive pulmonary disease, COVID-19, and paracetamol (acetaminophen) poisoning, which is prevalent in patients with prolonged fever (Khuroo 2020). It can also be taken as an antioxidant supplement (Packer & Colman 1999) extracted from various sources such as 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 regarding permissibility and halal status.

Based on the description, this research aimed to explore sources of cysteine, production, and application in pharmaceuticals, as well as the perspectives of scholars on halal aspects that require consideration when developing pharmaceutical product containing cysteine. The method used was searching through references of research obtained from Google Scholar, ScienceDirect, NCBI, Elsevier, and other Islamic literature sources such as the Qur'an, and Hadiths. To show the chemical structures and

reaction mechanisms, the ChemSketch tool from ACD/Labs was used. The research focuses on sources of cysteine, application as a medicinal product, and halal aspects that require consideration when developing pharmaceutical product containing cysteine.

2 Methodology

The method included sourcing references of research that were obtained through searches conducted on Google Scholar, ScienceDirect, NCBI, Elsevier, and other Islamic literature sources. The research focused on the origins of cysteine, use, the synthesis of acetylcysteine, and halal status from an Islamic perspective. Compound structures were developed using the ChemSketch tool from ACD/Labs. However, no changes were made to the citation, reference, or in-line citations, and the numbers within the text were not altered.

3 Result

3.1 Source of Amino Acid Cysteine

Cysteine is a type of amino acid commonly found in various proteins and enzymes. The uniqueness of cysteine is in the presence of a reactive thiol group in its chain, as shown in Figure 1 (Hunt 1985; Gmünder *et al.* 1990; Demirkol *et al.* 2004).

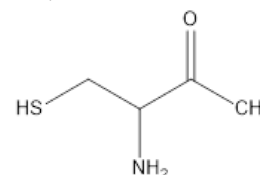


Figure 1: Cysteine amino acid structure (Cebi *et al.* 2017)

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Cysteine has been reported to be detected in samples of human hair, pig bristle, duck feathers, chicken feathers, and cow horns. This indicated the success of ATR-FTIR (Attenuated Total Reflectance-Fourier Transform Infrared) in showing the spectral bands of all sources of L-cysteine. The results emphasized the interpretation of transmittance values in ATR-FTIR, which successfully identified sources of L-cysteine. Specifically, various sources including human hair, pig bristles, duck feathers, chicken feathers, and cow horns were found to contain cysteine. This showed the need to interpret transmittance values in ATR-FTIR, which successfully determined the presence of amide I and amide II bands in all samples. By combining ATR-FTIR transmittance and PCA, all samples were differentiated into specific groups. According to Zharif *et al.* (2021), this method isolated cysteine-rich peptides from mussel blood (*Mytilus edulis*), as shown in Table 1. Cysteine proteases were found in milkweed latex (*Araujia hortorum*) and characterized with mass spectrometry by Priolo *et al.* (2000) after being separated using SDS-Polyacrylamide Gel Electrophoresis.

3.2 Cysteine as a Mucolytic and Acetaminophen

Expectorants are drugs that can alleviate a productive cough. N-acetylcysteine (NAC) is a widely used expectorant containing the amino acid L-cysteine, which has thiol and acetyl groups attached to its amino (-NH₂) group (Radomska-Lesniewska *et al.* 2016). As shown in Figure 2, NAC is the acetylated form of L-cysteine.

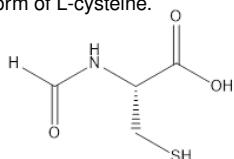


Figure 2: Acetylcysteine structure (Yamamoto *et al.* 2021)

Table 1: Sources, isolation methods, and characterization of cysteine

Source of Cysteine	Isolation and characterization methods
Human Hair (Zharif <i>et al.</i> 2021)	Characterization using ATR-FTIR and Raman spectroscopy
Mollusk Blood (<i>Mytilus edulis</i>) (Charlet <i>et al.</i> 1996)	Amino acid analysis using reversed-phase HPLC
Fruit Latex (<i>Araujia hortorum</i>) (Priolo <i>et al.</i> 2000)	The separation method uses SDS–Polyacrylamide Gel Electrophoresis and characterization using Mass Spectrometry
Chicken Feathers (Zharif <i>et al.</i> 2021)	Characterization using ATR-FTIR and Raman spectroscopy
Duck Feathers (Zharif <i>et al.</i> 2021)	Characterization using ATR-FTIR and Raman spectroscopy
Cow Horn (Zharif <i>et al.</i> 2021)	Characterization using ATR-FTIR and Raman spectroscopy
Sea Urchins (Zharif <i>et al.</i> 2021)	Characterization using ATR-FTIR and Raman spectroscopy
Rabbit Meat (Rosyidi 2007)	Amino acid analysis using high-performance liquid chromatography (HPLC)
Chicken Eggs (Mori <i>et al.</i> 2020)	Amino acid analysis using high-performance liquid chromatography (HPLC)

ATR-FTIR (Attenuated Total Reflectance-Fourier Transform Infrared), SDS (sodium dodecyl-sulfate)

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. The process is followed by stirring at room temperature for 20 minutes under nitrogen. Subsequently, the reaction mixture is 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 cooled and acidified to pH 1 with concentrated HCl (Yamamoto *et al.* 2021), as shown in Figure 3. Additionally, the synthesis of acetylcysteine can be achieved through an alternative method. N-acetyl-1H-benzotriazole is prepared by reacting acetic acid with an equimolar mixture of 1H-benzotriazole and SOCl₂ at room temperature, 21 °C, for 2 hours (Katritzky *et al.* 2003). SOCl₂ is a highly reactive compound that can vigorously react with water and other chemicals, showing the need to adhere to safety regulations. After the reaction, the resulting product is recrystallized using a mixture of acetone and diethyl ether (v:v 50%) (Ziaee & Ziaee 2021), as shown in Figure 4.

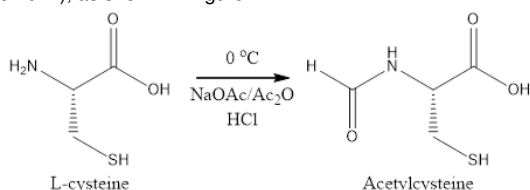


Figure 3: Synthesis of acetylcysteine (Yamamoto *et al.* 2021)

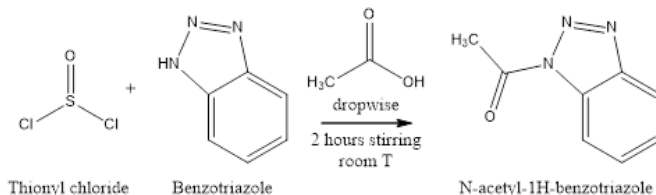


Figure 4: Synthesis of aestilcysteine (Ziaee & Ziaee 2021)

Approximately 3.22 g of N-acetyl-1H-benzotriazole were dissolved in 30 mm of methanol at room temperature, which was 21 °C. Subsequently, 2.42 g of L-cysteine was added to the solution, and the mixture was stirred for 3 hours, at a pH of 5. Due to the solubility of NAC in methanol, the solvent was allowed to evaporate overnight. To purify the synthesized product, three separation steps were carried out. The first step included stirring the dried residual solid in 50 mm of Milli-Q water for approximately 5 minutes to isolate unprocessed N-acetyl-1H-benzotriazole, as it was insoluble in Milli-Q water. After filtering the mixture, the residue solution was dried for the second step, where unreacted L-cysteine was separated using 25 mm of dry ethanol. This was followed by stirring for 5 minutes and filtering of L-cysteine as a precipitate. The residue solution contained NAC as product and benzotriazole as a byproduct. In the third purification step, 25 mm of diethyl ether was used as a solvent because benzotriazole was soluble in this solvent, while NAC remained insoluble. Therefore, the precipitated solid was filtered and dried under vacuum conditions and sent for characterization analysis, as shown in Figure 5 (Ziaee & Ziaee 2021).

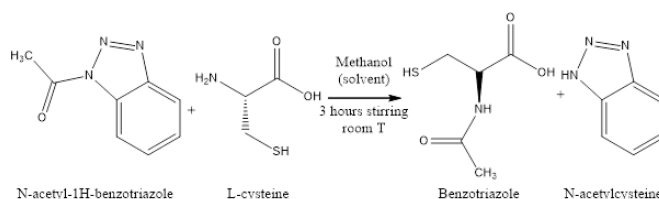


Figure 5: Synthesis of aestilcysteine (Ziaee & Ziaee 2021)

3.3 Views of Classical and Contemporary Scholars Towards Pigs

Allah SWT made Islam a perfect and universal religion due to various principles and rules such as prioritization of benefit. This benefit is the most important factor to consider in all aspects of human life, both in worldly and spiritual matters. In the development of human life, there are various kinds of problems. Allah made Islam a guide to answer each of these problems by providing many guidelines, pleasures, and conveniences. This guide permits and limits humans from whatever is prohibited in various provisions in the form of wealth and food as stated in the QS. Al Baqarah 172. Allah also details what things are forbidden, particularly regarding animals such as pig. Specifically, Allah says in several verses of the Koran QS Al Maidah: 4, QS. An Nahl: 115, and Al Baqarah: 173. Rasulullah SAW said

"From Abu Darda', he said: Rasulullah SAW said: Indeed, Allah has sent down disease and a cure for every disease, so seek treatment and do not seek treatment with what is haram." (HR. Abu Dawud). Ibn Mas'ud said "Indeed Allah has not created health for you in things that are forbidden to you" (this hadith was mentioned by Imam Bukhari).

Allah says clearly in QS. Al Baqarah: 173 which reads:

إِنَّمَا حَرَّمَ عَلَيْكُمُ الْمَيْتَةَ وَالدَّمَ وَنَحْمَ الْجَنْزِيرِ وَمَا أَهْلَ بِهِ لغيرِ اللَّهِ تَمَنِ اضْطَرَّ غَيْرَ بَاغٍ وَلَا غَادٍ فَلَا إِثْمَ عَلَيْهِ إِنَّ اللَّهَ غَفُورٌ رَحِيمٌ

"Indeed, Allah has only forbidden you carrion, blood, pork, and animals that (when slaughtered) are called (names) other than Allah. However, whoever is forced to (eat it) and does not want it and does not (also) exceed the limit, then there is no sin for him. Indeed, Allah is Forgiving, Most Merciful." QS. Al-Baqarah [2] : 173.

3.4 The Halal Status of Pharmaceutical Drugs Derived from Pig Parts

The critical aspect in assessing the two synthesis methods for acetylcysteine is the role of cysteine, as shown in Figures 3 and 4. This can potentially be sourced from prohibited materials such as pig hair. According to the MUI fatwa (2013), 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. The unique characteristics are attributed to the presence of a reactive thiol group within its chain (Hunt 1985; Gmünder *et al.* 1990; Demirkol *et al.* 2004) (as depicted in Figure 1). Cysteine has significant importance due to its various functions including serving as a control for thiol functionalization and participating in heavy metal detoxification in living organisms. Other functions include contributing to the antioxidant capabilities of tissues and mitochondria, playing a role in blood clotting in mammals, facilitating transport across cell membranes, and electrochemical sensing (Sirko *et al.* 2004; Wirtz *et al.* 2004; Wirtz & Droux 2005; Borase *et al.* 2015).

Traditionally, animal product such as 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 such as 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 mucoproteins and mucopolysaccharides in the mucus, which reduces viscosity (Rohman 2018). Acetaminophen is a commonly used analgesic in the United States, which is also known to be the leading cause of acute liver failure in the country (Clark *et al.* 2012). NAC is one of the most commonly prescribed expectorants, containing the amino acid L-cysteine with thiol and acetyl groups attached to its nitrogen atom (Radomska-Lesniewska *et al.* 2016), as shown in Figure 2. Moreover, NAC is the acetylated form of L-cysteine and has been used clinically for over four decades. It 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 can be effective for CCl₄ and chloroform poisoning. Despite these numerous benefits, oral administration of NAC may cause side effects such as nausea and vomiting. Therefore, intravenous administration should be slow and conducted gradually to avoid patients with allergies. This is because rapid administration can cause flushing and hypotension (Sadewa *et al.* 2021).

The opinions of classical and contemporary scholars toward pigs are explained based on the Qur'an, Hadith, and statements. The wording stated by Allah in the verse uses the term "Lahm Khinzir," which translates to pig meat. Therefore, the critical question arises: Does this mean that other parts of the pig are considered permissible by Allah? And why does Allah only mention specific parts of the pig? The interpretation within the context of this verse is extensive. Scholars, particularly those in the field of exegesis, have provided various interpretations. Imam Alusi (Alusi & Syihabuddin 1994), in his exegesis "Ruhul Maani," stated that the pig, along with all its parts, is deemed Haram. The specificity of mentioning "Lahm Khinzir" without reference to other parts is because meat is an essential part of the animal for consumption. Other parts follow the rulings of the meat, including those considered subordinate and integral. Imam Baidhowi (Baidhowi & Nashiruddin 2004) in his exegesis "Anwar At Tanzil wa Asrar At Takwil" supports a similar perspective within the context of this discussion.

The secret behind using the term 'meat' is to unequivocally reject the suggestion 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 pig meat (Alusi & Syihabuddin 1994). Imam Qurthubi in "Tafsir Al Qurthubi," stated that the specificity of mentioning "Lahm Khinzir" without reference to other parts showed the overall prohibition of the pig, whether slaughtered or not, including other parts such as fat/grease, bones, and other components. Furthermore, Imam Al-Qurthubi stated that there was no difference of opinion regarding the prohibition of the pig, except for the hair.

Imam Ibn Kathir in "Tafsir Ibn Kathir" stated that Allah prohibited pig meat, whether slaughtered or not, including its fat/grease. The prohibition of pig fat/grease is because this part falls under the term 'Lahm Khinzir' (pig meat). Similarly, Imam Zamakhshari (Al Zamakhshari & Mahmud 2010) in "Al Kasyaf an Haqaiqi Tanzil" shared the same opinion within the context of this discussion. Imam Ar-Rozi (1981), through the phenomenal work "Mafatihul Ghaib," contended that scholars unanimously agreed to the prohibition of pig and other parts. Regarding pig hair, 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 regarding the permissibility of using pig hair. Some scholars permit the use of pig hair for sewing purposes. According to the renowned contemporary exegete, Imam Thahir Ibn Ashur (Asyhur 1984) in "Tahir Wa Tanwir," stated that the term 'meat' was directed towards consumption. Therefore, it does not imply permission to consume other parts.

Imam Nawawi (Nawawi & Zakaria 2005) in his book "Majmu' Syarh Muhadzab," particularly in the chapter on Athimah, expresses the opinion of followers of the Shafi'i school that using impure substances for medical treatment is allowed when 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 (Nawawi & Zakaria 2005) concludes that using impure substances for treatment becomes prohibited when a pure and non-prohibited alternative is available. Followers of the Shafi'i school also argue that it is permissible to use impure substances for medical treatment. This is allowed when health experts, particularly pharmacologists, state that there is no alternative except the impure substance or based on a recommendation from a trustworthy Muslim doctor. However, Imam Izzudin Ibn Abdussalam (Bin Abdussalam & Al Anam 1994), in his book "Qawaid Ahkam," contends that it is permissible to use impure substances for treatment when a pure alternative is not available, prioritizing health and safety over avoiding impure substances.

According to Asma (2016) in "Shinaah dawaiyah fi Mizan Fiqh," the scholars unanimously agree on the prohibition of consuming substances derived from pig in normal conditions. Therefore, mucolytic and acetaminophen drugs containing acetylcysteine compounds sourced from pig hair are included in this research. The legal status of adding pharmaceutical elements derived from pig parts is divided into several conditions. First, when the element has no istihalah (change in chemical properties) and is added in significant amounts, it is prohibited for consumption unless in emergencies. However, when the added element is minimal, scholars have different opinions, with some permitting and others prohibiting. In this case, Asma adopts the permissive opinion. Second, when there is a dispute regarding the occurrence of istihalah, such as gelatin derived from pigs, scholars have different opinions. In this second scenario, Asma (2016) adopts the prohibitive opinion, there is no explicit mention of the legal status. Examining the two synthesis methods of acetylcysteine in Figures 3 and 4, cysteine is the critical point for the prohibition of acetylcysteine. This is because cysteine can potentially be obtained from forbidden sources such as pig hair. According to the opinion of Dr. Asma, the legal status falls into the first condition.

The MUI fatwa emphasizes the significance of consuming medicines that are free from impurities. It is essential to use permissible medical methods to ensure health protection and care, which is vital for safeguarding the five necessities of life. In search of treatment, medicines used for treatment must apply pure and halal ingredients. However, the use of medicines containing impure or forbidden substances is permissible in specific conditions. These include cases of necessity, where not using the medicine could threaten human life in the future. When there is no pure and halal alternative available based on a recommendation from competent and trustworthy medical professionals, the use of medicines containing impure or forbidden substances is permissible. It is also allowed for external treatment, provided that purification is performed. Acetylcysteine is a critical point for the prohibition of acetylcysteine, as it can potentially be obtained from forbidden sources such as pig hair. Based on the MUI fatwa, acetylcysteine derived from cysteine sourced from pig hair is considered prohibited for use as a mucolytic and acetaminophen.

Based on the Fatwa Darul Ifta Egypt No. 5668, there is a divergence of opinions among scholars regarding the acceptability of therapies or medications derived from prohibited sources such as pig components. The Maliki and Hanbali schools prohibit the use of treatments or medications originating from forbidden sources. However, the Hanafi and Shafi'i schools allow the use of treatments derived from forbidden sources under two conditions: First, the treatments or medications must be prescribed by a knowledgeable and trustworthy Muslim specialist physician. Second, there is no alternative medicine available from halal sources, making it necessary to use medicine derived from haram sources. This is allowed in emergency situations, as preserving human life takes precedence. Life is considered one of the five fundamental objectives of Sharia, and Islam is recognized as a comprehensive and universal religion that prioritizes well-being. In this context, acetylcysteine derived from pig hair has varying legal statuses depending on emergency conditions, physician recommendations, and the absence of alternative medicines.

5 Conclusion

In conclusion, this research showed that the use of mucolytic and acetaminophen drugs, including acetylcysteine, could be derived from both plant and animal sources through various separation processes. Cysteine served as a precursor for the synthesis of acetylcysteine, was found to be a significant sources of these drugs. However, there were different opinions among scholars regarding the permissibility of cysteine sourced from specific organs, such as pig hair. The prevailing opinion and fatwa tended to lean towards prohibition, considering sources, process, and urgency of use.

Conflict of Interest

The authors declare no conflict of interest.

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