

TRACKING THE SOURCE OF ANTIMICROBIAL PRODUCTION FROM HOUSE FLY (*Musca domestica*): RIGHT-WING OF FLY OR GUT SYSTEM ? - A MINI-REVIEW

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Abstract: The house fly (*Musca domestica*) is a vector of disease-causing bacteria because of its habit of perching and feeding on various substrates of pathogenic bacteria. His role as a disease carrier contradicts the hadith narrated by Bukhari, which is "If a fly falls into your vessel, drown it and then remove it because one of its wings carries disease and the other is the cure". This hadith indicates the presence of antimicrobial compounds produced from the body of flies. Various research reports show that the truth of this hadith is that there are antimicrobial-producing bacterial symbionts on the wings of flies (left and right) that can kill pathogenic bacteria on one of the wings or both. Antimicrobial compounds are also produced naturally in the digestive tract of flies from the larval stage to adulthood as a response to the body's defense against the presence of pathogenic bacteria in their bodies. The antimicrobial compounds are lysozyme, defensin, cecropin, dipterin, and several antimicrobial peptide compounds. This compound can also be removed mechanically through pressure (the process of immersing the fly's body in water). This shows that the process of drowning aims to extract or release antimicrobial compounds from the digestive tract of flies to neutralize pathogenic bacteria that have mixed in the liquid in specific containers. This review aims to examine various reports related to antimicrobial substances produced in flies and their evidence in this hadith.

Keywords: antimicrobial; bacterial symbionts; digestive tract; house flies; left-wing; right-wing

Abstrak: Lalat rumah (*Musca domestica*) merupakan vektor pembawa bakteri penyebab penyakit karena kebiasaan hinggap dan makan pada berbagai substrat bakteri patogen. Perannya sebagai pembawa penyakit memiliki kontradiksi dengan hadist yang diriwayatkan oleh Bukhari yaitu "Jika seekor lalat jatuh ke bejana kamu, tenggelamkanlah kemudian singkirkan, karena salah satu sayapnya membawa penyakit dan sayap lainnya adalah obatnya". Hadist ini mengindikasikan adanya senyawa antimikroba yang dihasilkan dari tubuh lalat. Berbagai laporan penelitian menunjukkan bahwa kebenaran hadist ini yaitu pada sayap lalat (kiri dan kanan) terdapat bakteri simbiosis penghasil antimikrob yang mampu membunuh bakteri patogen pada salah satu sayap atau keduanya. Senyawa antimikrob juga dihasilkan secara alami dalam pencernaan lalat sejak tahap larva hingga dewasa sebagai respons pertahanan tubuh terhadap keberadaan bakteri patogen ditubuhnya. Senyawa antimikrob tersebut berupa lisozim, defensin, cecrofin, dipterin dan beberapa senyawa peptida antimikrob. Senyawa ini juga dapat dikeluarkan secara mekanik melalui tekanan (proses

penenggelaman tubuh lalat dalam air). Hal ini menunjukkan bahwa proses penenggelaman lalat kedalam air bertujuan untuk mengekstrak atau mengeluarkan senyawa antimikrob dari pencernaan lalat untuk menetralkan bakteri patogen yang telah bercampur dalam cairan di wadah tertentu. Review ini bertujuan untuk mengkaji berbagai laporan terkait senyawa antimikrob yang dihasilkan pada tubuh lalat dan pembuktiannya pada hadist tersebut.

Kata kunci: antimikrob; bakteri simbiosis; lalat rumah; sayap kanan; sayap kiri; saluran pencernaan

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Introduction

The housefly, *Musca domestica*, is a potential agent of disease transmission (Nazni et al., 2005). Transmission of the disease is caused by microbial transmission by house flies which are biological and mechanical. The mechanical transmission of microbes can be carried by outside vectors which have been exposed to sites of microbial sources (Yap et al., 2008). House flies in their life will land on various solid materials and even liquids such as human feces, animal feces, carcasses, garbages. Moreover, others make them a vector for disease transmissions, such as cholera, shigellosis, and salmonellosis in food (Nazni et al., 2005). Flies also play an important role in the spread of antibiotic-resistant bacteria in hospitals (Nazari et al., 2017). This is a key factor in the spread of microbes by house flies. However, the role of house flies as only agents for the spread of this disease is contrary to the hadith narrated by Al-Bukhari, namely the Prophet Muhammad SAW (peace be upon him) said: "If a fly falls to your vessel, let him dip all of it (into the vessel), and then remove it, for in one of its wings has the ailment and the other has the cure (antidote for it) (Al-Bukhory, 2007). This hadith is a matter of debate because it is generally known that flies are vectors of disease that originate from dirty places and are transmitted to food or drink. Through this hadith, it is clear that it has bacteria on one wing and have a bacterial/antibacterial defense on the other wing.

Based on this, various studies have been carried out to prove that there is an antidote or antibacterial from one of them. In line with the meaning of the hadiths that are increasingly developing in society, it is said that the wing that is meant as an antidote or antibacterial in flies is right-wing, and the one that carries pathogenic bacteria is left-wing. This claim was proven microbiologically by isolating bacteria from the right and left wings of the house fly. The results showed that there were no bacteria found on the right wing and found the presence of bacteria on the left wing (Atta, 2014). In addition, the right-wing of fly *M. domestica* is neutralization in drinks that *Escherichia coli* has contaminated.

This evidence is shown by the absence of *E. coli* on the right-wing of flies (Claresta et al., 2020). These results have not been able to prove with certainty the presence of antidotes or antimicrobials from the fly's right-wing. It is necessary to develop and detect the types of antibiotics/antibacterial on the right-wing so that the meaning of the hadith is clear. In addition, it is also necessary to calculate how long the flies were exposed to drinks and immersion of these flies in drinks to find out how much influence their ability to neutralize pathogenic microbes in drinks.

Mechanically the wing of the house fly does not play an essential role in the process of mechanical transmission of bacteria from the substrate or perch due to the low transfer rate of bacteria to the wings and poor retention of bacteria on the wing during house fly activities such as strong wing movements when flying. Tended to eliminate bacteria from the wings of house flies (Yap et al., 2008). The fast-wing movement of *M. domestica* was able to eliminate and reduce as much as 86% of the population of *E. coli* and *Pseudomonas aeruginosa* for 10 minutes (Jacques et al., 2017). This transmission process needs to be linked to the suspicion of an antimicrobial compound from one of the wings of a housefly. Based on the hadith and these facts, there are two indications, namely that one of the outer surfaces (wings) of flies contains antibiotics that can kill bacteria, and antibiotics are produced from the digestive tract of house flies and the best way to release (free) these antibiotics is by immersing the flies in the liquid. The evidence study can be traced through the microbes present on the wings (left and right) that make it possible to produce antimicrobial compounds, or the production of antimicrobial compounds takes place in the body of the house fly *M. domestica*.

Bacteria on Housefly's Body

The activity of house flies, which can land on various dirty substrates, causes the fly's body to carry various types of bacteria. Several types of bacteria have been isolated from flies, including feces, vomit, external surface, and internal organs. The types of bacteria found, namely *Bacillus* sp., *Coccobacillus* sp., *Staphylococcus* sp., *Micrococcus* sp., *Streptococcus* sp., *Acinetobacter* sp., *Enterobacter* sp., *Proteus* sp., *E.coli*, *Klebsiella* sp., *Pseudomonas* spp., *Bacillus* spp., *Enterobacter* spp., *Salmonella* spp., *Proteus* spp. (Nazni et al., 2005; Yalli et al., 2017) and *Clostridium difficile* (Davies et al., 2016). Of the total types of bacterial populations found, three species of bacteria dominate *Bacillus* sp. (31.1%), *Staphylococcus* spp. (22.9%), *E. coli* (11.6%) (Nazari et al., 2017).

The dominance of the types of microbes in flies will be different if the overall immersion of the fly's body into the water is carried out as narrated by Al Bukhary, namely "let him dip all of it (into the vessel), and then remove it." The microbes isolated from house flies by immersing them for 1 hour were then transferred, namely *E. coli*, *P. aeruginosa* (Proteobacteriaceae), and *Bacillus subtilis* (Firmicutes). In addition, fungi such as *Aspergillus niger*, *Rhizopus stolonifer*, and *Candida albicans* were found. However, when tested against each

other, these three bacteria and fungi will show antagonistic activity. *B. subtilis* was able to inhibit the growth of *E. coli* and *P. aeruginosa*, and the three fungi (Galal et al., 2019).

The antagonistic activity of these bacteria is thought to be due to their ability to secrete enzymes or compounds that have antagonistic and/or antimicrobial properties as it is known that *B. subtilis* is known to be able to produce biosurfactants that can inhibit the growth of *Salmonella*, *Shigella*, and *Staphylococcus* (Moore et al., 2013). In addition to biosurfactants, *B. subtilis* is also capable of producing metabolite compounds based on its biosynthetic pathways, namely polyketides (PKs), non-ribosomal peptides (NRPs) (Caulier et al., 2019), antimicrobial cyclic lipopeptides (CLPs) (DeFilippi et al., 2018). These results indicate that there are bacteria in the body of the flies with antagonistic/antimicrobial abilities and can inhibit pathogenic bacteria originating from the substrate previously exposed to. However, it has not been confirmed that the bacteria originated from the fly's right or left wing, which confirms this statement "one of its wings has the ailment, and the other has the cure (antidote for it)."

Bacteria Originated from The Fly's Right and Left-Wing

The number of bacteria found on flies' right and left wings has a large population. Bacteria from each wing can be isolated by preserving the fly in a sterile tube, then transferred to a sterile petri dish with a filter paper base to remove residue on the fly's body surface. Each wing was isolated on a nutrient agar medium. The growing bacteria were identified morphologically, gram staining, biochemically, and molecularly (Kanan et al., 2020). The number of bacteria on the right-wing is slightly more, namely 5.78×10^3 CFU/ml, while on the left-wing, as much 5.6×10^3 CFU/ml. As for the body of flies, found as many 5.98×10^3 CFU/ml (M. Al-Tae & Gh. Alsammak, 2011). Several species of bacteria were found from the total number of bacteria found on the left and right wings of the fly. Several species of bacteria are found on both wings, like the genus *Bacillus*, *Pseudomonas*, *Proteus* and *Micrococcus* (Table 1.).

The presence of bacteria on each wing, such as *Brucella melitensis*, *Sphingobacterium* sp., *A. faecalis*, *Bacillus* sp., *G. proteobacterium*, and *E. asburiae*, is reported to have antibacterial activity against pathogenic bacteria *E. coli* and *S. aureus* (Kanan et al., 2020). Apart from affecting pathogenic bacteria from outside the body, the presence of bacteria on each wing turned out to have antagonistic activity between bacteria on the wing itself. Bacteria isolated from the right and left wings showed different antibacterial activity against the same and opposite wing bacterial isolates. Species that have antagonistic properties are *Streptomyces* spp. (right-wing) and *B. mycoides* (left-wing). The *Streptomyces* group of bacteria has been recognized as the best producer of antibiotics, one of which is the new antibiotic picolinamycin which can inhibit the growth of *S.*

aureus, as Multi-Drug Resistant (MDR) bacteria (Maiti et al., 2020). Meanwhile, the second type of bacteria, namely *B. mycoides*, is a bacterium that can produce biosurfactants (Najafi et al., 2010) and anti-tumor polysaccharides produced (Farag et al., 2020). Both types of bacteria can inhibit growth *B. cereus*, *Acinetobacter* spp., *P. vulgaris*, *Aeromonas* spp., *M. luteus*, *E. coli*, *S. aureus*, *P. aeruginosa*, *Lactobacillus* spp., *M. roseus*, *Alcaligenes* spp., and *Neisseria* spp. (M. Al-Tae & Gh. Alsammak, 2011). Some of these bacteria are reported to be pathogenic bacteria found in food or drink carried by flies.

Table 1. The type of bacteria found on the wings of flies *M. domestica*

Right-wing	Left-wing	References
<i>Bacillus cereus</i>	<i>Lactobacillus</i> spp.	
<i>Acinetobacter</i> spp.	<i>Bacillus mycoides</i>	
<i>Proteus vulgaris</i>	<i>Proteus vulgaris</i>	(M. Al-Tae & Gh. Alsammak, 2011)
<i>Streptomyces</i> spp.	<i>Alcaligenes</i> spp.	
<i>Aeromonas</i> spp.	<i>Neisseria</i> spp.	
<i>Micrococcus luteus</i>	<i>Micrococcus roseus</i>	
<i>Pseudomonas aeruginosa</i>	<i>Pseudomonas aeruginosa</i>	
<i>Staphylococcus aureus</i>	<i>Alcaligenes faecalis</i>	(Kanan et al., 2020; M. Al-Tae & Gh. Alsammak, 2011)
<i>Escherichia coli</i>	<i>Bacillus</i> sp.	
<i>Brucella melitensis</i>	<i>Enterobacter asburiae</i>	(Kanan et al., 2020)
<i>Sphingobacterium</i> sp.	<i>Gamma proteobacterium</i>	

The presence of bacteria on the wings and showing antagonism to pathogenic bacteria on the other wings indicates that the statement "one of its wings has the ailment and the other has the cure (antidote for it)" is that the bacteria on each wing have a role in the inhibition of pathogenic bacteria. This means that if pathogenic bacteria are on the left-wing, the antagonistic bacteria from the right wing will inhibit the growth of pathogenic bacteria on the left-wing and vice versa. This indicates that both wings have microbial communities or species of bacteria that function as producers of antimicrobials for protection from the fly's body. Antagonistic properties were also found from bacteria derived from the digestion of house flies, namely *Bifidobacterium minimum*. These bacteria have antibiotic activity against bacteria *E. coli* and *Staphylococcus* sp. (Kanan et al., 2020). The presence of bacteria in the digestion of flies indicates antimicrobial compounds produced from the digestion of house flies. The presence of bacteria on the wings and stomach of flies as a producer of antimicrobials cannot be separated from the behavior of flies in foraging for food on a microbe-contaminated substrate, causing a defense response.

Immune Response and Production of House Fly Antimicrobial Compounds

Insects are organisms suitable for searching for new antimicrobials, one of which represents the house fly. It is because insects are in constant contact with

pathogenic microorganisms. Dense population habitat, but very few infected. Their resistance to disease and their low rate of extinction/death have resulted in them being consistently successful in the evolutionary process. Until now, the antibiotics used to come from bacteria. Insects are known to be able to produce antibiotics and have a different structure, and are underived from bacteria (Clarke et al., 2002). Naturally, food ingredients that contain bacteria that flies ingest enter the digestive tract by passing through the proventriculus to the middle intestine. A type-II peritrophic matrix (PM) protects the middle intestinal epithelium, which functions as an exclusive physical barrier to microbes (Hegedus et al., 2009; Lehane, 1997; Wang et al., 2020). Although bacteria cannot penetrate PM, large molecules, including digestive enzymes and antimicrobial effectors produced by the intestinal epithelium, easily cross and act on targets in the lumen (Richards & Richards, 1977).

The transmission of bacteria in fly feces necessitates survival in these harsh mid-intestinal conditions, including trapping in PM, digestive processes, and antimicrobial defenses, as they move peristalsis towards the rectum for excretion (Joyner et al., 2013). Lysozymes play a role in destroying/lysing these microbes. This enzyme is one of the immune effectors of flies (Gill et al., 2017). Lysozyme can be found in the flies' digestive tract. Lysozyme is an antibacterial enzyme and plays a role in cutting β -1.4 glycosidic linkage connecting N-acetylmuramic acid and N-acetylglucosamine, representing a constituent of bacterial cell wall peptidoglycan (Phillips, 1967).

Lysozyme enzymes are found in the larval and adult stages because this stage requires stimulation of an increase in the body's immune system against bacteria (Nayduch & Joyner, 2013). At this stage, the flies are mobile to forage on substrates that contain many pathogenic bacteria. Meanwhile, the pupal phase does not produce antimicrobials because the pupa is permanent and has a protective barrier, thereby reducing the possibility of exposure to pathogens (Clarke et al., 2002). At each stage of their development, the types of bacteria can exhibit this activity, such as *Bacteroides coprosius*, *Koukoulia aurantiaca*, and *Schineria* sp. found at the larval *Neisseria* sp. in pupae, *Macrococcus* sp., *Lactococcus garvieae*, *Kurthia gibsonii* in the adult stage. *Proteobacteria* and *Bacteroidetes* exist in three stages of development. *Firmicutes* are only present in pupae and adult flies (Wei et al., 2013). The high relative abundance of adult fly microbiota results in high amino acid metabolism compared to larvae and (pre-) pupal stages and increased signal transduction, biodegradation, and xenobiotic metabolism (de Jonge et al., 2020). It indicates a compound that can be produced for self-protection and to kill the microbes it carries.

Lysozyme activity is influenced by enzyme activity, changes in pH, and effectors such as AMP to degrade the microbial cell envelope when the number of bacteria found is above an undetermined threshold level (Nayduch & Joyner, 2013). The synergy of antimicrobial peptides (AMP) and digestive enzymes can

more significantly broaden the activity spectrum and facilitate lysozyme access to the cell wall (Chalk et al., 1994; Mumcuoglu et al., 2001). Similarly, processing of lysozyme from peptidoglycan has been shown to facilitate binding to peptidoglycan-recognition proteins (PGRPs) and induction of consequent immune response pathways (Park et al., 2007) thereby providing a complex response from insects in antibacterial defense strategies. Fly immune regulatory gene expression consists of factor 4E-binding protein (thor), a putative c-Jun N-terminal kinase (JNK), and a putative serine protease of the Toll pathway (spheroid) and effectors in the form of cecropin, dipterin, attacin, defensin, and lysozyme (Gill et al., 2017).

Antimicrobial production and induction of the fly's immune response against pathogenic bacteria are indicated by the high antibacterial activity of flies when infected with pathogenic bacteria. *M. domestica* fly larvae extract inoculated by *E. coli* and *S. aureus* bacteria has higher antibacterial activity than native larvae extract (without bacterial inoculation) (Hou et al., 2007). These results indicate a similar principle of action for the utilization of *Hepialis* larvae infected with *Cordyceps* in traditional Chinese medicine. That infected larvae possess higher antimicrobial activity. When infected with microorganisms, insects will activate three interconnection reactions: proteolytic fluid, a cellular defense reaction consisting of phagocytosis, and encapsulation of microorganisms that carry out an attack and rapid synthesis of antimicrobial peptides from the body fat (Hoffmann et al., 1996). This mechanism causes the infected insects to contain more bioactive chemical compounds whose active molecules and clinical efficacy are still unknown.

The notable production of compounds in infected insects is proven in the extracts of *M. domestica* larvae to be able to inhibit gram-positive bacteria such as *Staphylococcus aureus*, *Bacillus subtilis*, and gram-negative bacteria such as *E. coli* ATCC25922, *Shigella dysenteriae*, *Salmonella typhimurium*, *Bacterium pyocyaneum* (Hou et al., 2007). The different compositions of these bacterial cells caused antibacterial sensitivity between gram-positive and gram-negative. Gram-negative bacteria have a phospholipid outer membrane composed of lipopolysaccharide components. In contrast, gram-positive bacteria only have peptidoglycan in the outer layer of their cell walls, whose permeability is ineffective as a barrier to entry of these compounds (Nostro et al., 2000).

As previously known, house flies or other insects have a peritrophic matrix/membrane (PM), which prevents the insect's middle gut from external microbial invasion. This membrane is composed of the PM protein, but the role of the PM protein in immune regulation is unclear. The new PM protein (MdPM-17) was isolated from *M. domestica* have 635 bp of MdPM-17 cDNA encoding 158 amino acid residues. This amino acid residue consists of two chitin-binding type-2 domains and 19 amino acids as a signal peptide. MdPM-17 is expressed the most in the midgut (digestive tract) and moderate levels in body fat, foregut, and

Malpighian tubules. MdPM-17 recombinant protein silencing through RNA interference resulted in the expression of antimicrobial peptide genes (defensins, cecropins, and dipterin). It has occurred after the inoculation of exogenous microbes *E. coli*, *S. aureus*, and *C. albicans*. The infected larva by exogenous microbes showed higher Antimicrobial Peptides (AMP) gene expression. It suggests that the MdPM-17 protein is associated with the antibacterial response of house flies (Wang et al., 2020). The presence of antimicrobials as an immune response in larvae raises various antimicrobial findings in the larval stage that can inhibit various pathogenic bacteria (Table 2).

Table 2. The type of antimicrobial compounds on the larvae of flies *M. domestica*

Antimicrobial compound	Target bacteria	References
Antibacterial peptide MD7095	<i>B. thuringiensis</i> , <i>B. subtilis</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>E. coli</i>	(Lu et al., 2006)
Antimicrobial peptide Cecropin (Mdc)	Gram-positive and gram-negative bacteria as well as multiple drug resistance (MDR) bacteria	(Lu et al., 2012)
Antimicrobial peptide (MDAP-2)	<i>Pasteurella multocida</i> , <i>Salmonella pullorum</i> , pathogenic <i>E. coli</i>	(Pei et al., 2014)
Antifungal peptide (MAF-1)	<i>Candida albicans</i>	(Fu et al., 2009)
1-lysophosphatidylethanolamine (C16:1)	<i>Bacillus thuringiensis</i> and the yeast <i>Saccharomyces cerevisiae</i>	(Meylaers et al., 2004)
Phenylacetaldehyde	Methicilin-Resistant <i>Staphylococcus aureus</i>	(Ali et al., 2018; Arora et al., 2011)

The type of antimicrobial compound produced in the larval stage is thought to be the main antimicrobial compound in defense of the house fly (*M. domestica*) from pathogenic microbes to become adult flies (Akhtar et al., 2009; Nayduch & Joyner, 2013; Petridis et al., 2006). The presence of these antimicrobial compounds accumulating and being found in the digestive system of house flies indicates that these compounds will be excreted naturally or with pressure assistance. Insect antimicrobial peptides are expressed in the fat body and secreted into the hemolymph in response to the presence of bacteria and fungi that cause infection (Chen et al., 1988; Gillespie et al., 1997). With the presence of bacteria in the fly's body, it can release antimicrobial compounds. The action of immersing the fly's body into water puts pressure on the fly's body, causing antimicrobial peptides to come out of the body and mix with food/drink to kill

pathogenic microbes. The immersion of the fly's body into water causes the fly to lack oxygen (anoxia), which causes an increase in stress and affects metabolism (Harrison et al., 2006). The main adverse effect is decreased ATP production, affecting the ion gradient (Storey & Storey, 1990). Naturally, the fly's body will carry out the anoxia recovery process and cause the reestablishment of energy and ion homeostasis (Woods & Lane, 2016), minimizing oxidative damage to the tracheal system resulting in reactive oxygen species (ROS) (Doelling et al. 2014). ROS can damage body components such as proteins, DNA, lipids, damage cell function, kill external cells, reduce performance, or kill insects ((Woods & Lane, 2016). We assumed the compound could leave the body through the external pressure, for example, caused by drowning a fly so that it can lyse all the bacteria it carries. By drowning the fly, there is pressure inside the cell so that the enzyme or antimicrobial compound will come out and kill all bacteria caused by flies, as mentioned in the hadith in the form of "If a fly falls to your vessel, let him dip all of it (into the vessel), and then remove it."

Conclusion

The studies related to the antimicrobials produced by the house fly *M. domestica* showed that the antimicrobials of the *M. domestica* house fly originated from the antagonistic bacteria found on the right and left wings of *M. domestica*. These bacteria can inhibit any pathogenic bacteria that attach to each part of the wing. Apart from being found on the wings, bacteria are found in the digestive tract, producing antimicrobials to kill pathogenic bacteria. Furthermore, flies also released antibiotic compounds as a form of self-defense response from pathogenic bacteria during their life. They are present in the digestive tract, formed from the larval stage to adulthood. The larvae can produce several compounds such as lysozyme, defensin, cecropin, dipterin, and antimicrobial peptides outside the body in response to the body's defenses. If triggered by the very high number of pathogenic microbes in the fly's body, it can be released. In addition, the target substrate can be secreted mechanically through pressure (by drowning) in the fly's body. Furthermore, there needs to be a study of the amount of concentration of antimicrobial compounds released by bacteria on the wings (left and right) or the digestive tract by explaining the origin of the antimicrobial compounds that have the most role as "antidotes" of disease to prove the hadith.

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