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Millipede Secretions as a Potential Source of Antibiotics: A Mini Review

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A wide range of compounds are produced by a group of arthropods known as millipedes, some of which have been demonstrated to have antibacterial and antifungal qualities. These substances may contain novel antibiotics, which are desperately needed to combat the epidemic of antibiotic resistance. Millipede secretions are natural and have less adverse effects than certain manufactured antibiotics. Millipedes may also be a more sustainable source of antibiotics because they are a renewable and reasonably abundant resource. In this direction, this mini review discusses the antibacterial potentials of some common millepedes including *Ophistreptus guineensis, Pachybolus ligulatus, Pelmatojulus ligulatus, Apfelbeckia insculpta, Nedyopus dawydoffiae, and Anurostreptus sculptus.* Preliminary investigations point to the high potential of applying these organisms in the fight against bacteria resistance to antibiotics. More investigations are however required to ascertain the safety and effectiveness of the secretions,

Keywords: Millipedes, Arthropods, Antibiotics, Bacteria, Millipede Secretion.

1. Introduction

Millipedes are members of the Diplopoda class of arthropods. These creatures get their name because two pairs of jointed legs are present in most of their body segments. The lengths of millipedes range from 2 mm (1/16 in) to over 35 cm (14 in), and their number of segments can vary from eleven to over 300 (Marek *et al*., 2021, Raghu *et al*., 2018). Millipedes are a diverse spectrum of sizes and shapes. The majority of them have a colour that is either black or brown, although some have vivid colours or aposematic colouring, which denotes danger. Although they resemble prawns, crayfish, and lobster, millipedes are not insects. They pass through dirt and organic things slowly, and they are cylindrical or slightly flattened. clearing off rotting vegetation and reviving the soil. (Wagner *et al*., 2020, Blower, 1985, Marek, 2015, Srisonchai *et al.,* 2016). As decomposers of epigeic litter, millipedes generate large volumes of excrement that are dispersed across the soil profile at various depths. Excrements add substances to the soil that are easier and faster to absorb (Kime 2000 and David, 2014).

The centipede and millipede were among of the earliest animals to live on Earth. Their fossil record goes back around 430 million years, to the late Silurian period. Their common names, 1000 and 100 feet, respectively, are taken from Latin and their various heights. No millipede had 1000 legs prior to the discovery of a new species in 2021 with 1306 legs (Marek *et al*., 2021)

Millipedes are the third most diversified class of terrestrial arthropods, with 12,000 officially recognised species. One of the most obvious traits that all members of the class Diplopoda have in common is the presence of two exocrine defence glands in the body somites, which secrete a variety of volatile compounds that are tentatively classified as phenols, quinones, alkaloids, and cyanogenic substances (Vujisić *et al*., 2011, Klem, 2017)

The majority of pleurotegites in chemically defense-equipped species have two ozadenes that open dorsally or laterally through ozopores. The content of these glands is known to be released by millipedes primarily during defensive behaviour, though other possible uses have been proposed, such as serving as an alarm signal, a pheromone-containing material, a parasite repellent, or a carrier of antibacterial and antifungal activity (Shear, 2015). However, only 170 species of these organisms have had their chemical defence capabilities studied (Banks *et al*., 2024, Stanković *et al*., 2016).
In this this mini review therefore, the antibacterial potentials of some common millepedes are explored. This is with the hope of triggering widespread interest in the area with the potential of sustainably applying secretions from these

organisms in the fight against bacteria resistance to antibiotics.

2. Methodology

The mini review was conducted by systematically searching relevant articles on Google, Google Scholar, Science Direct, and Pubchem as the source of the articles used with the following keywords and phrases: millepedes, millipede secretion, isolation and characterization of millepedes, microbial activity of millepedes, and characterization of millepede secretion.

3. Antibiotic Resistance

Medication known as antibiotics is used to both treat and prevent bacterial infections (Krell & Matilla, 2022). On the other hand, when bacteria adapt as a result of antibiotic use, antibiotic resistance develops. a situation when germs change through time and become resistant to medications, making infections harder to treat and increasing the chance of disease spread, severe illness, and even death (Chinemerem *et al*., 2022). The ability of a bacterium to resist or tolerate the effects of antibiotics is known as bacterial resistance (Dadgostar, 2019).

The capacity of a microbe to resist the growth-inhibiting or death effects of an antibiotic at concentrations that are clinically feasible. Antibiotic resistance is an increasingly prevalent worldwide issue wherein antibiotics lose their effectiveness in treating infectious diseases for which they were originally intended

The World Health Organisation (WHO) has now warned that antibiotics are "running out of time," which is increasing concerns that antibiotic resistance may spread to previously unheard-of levels. Nosocomial infections have been rising steadily as a result of the advent of drug-resistant bacteria, which has presented a significant obstacle to the treatment of clinical infectious disorders.3. Since bacterial infections are one of the main causes of disease and death worldwide, antibiotic resistance is increasing. Regularly emerging new resistance mechanisms proliferate globally, endangering the ability to treat common infectious diseases (Chinemerem *et al*., 2022).

Antibiotic resistance is a serious issue in healthcare due to its propensity to spread globally and the ensuing limited treatment options. Treatment for infections like gonorrhoea, pneumonia, TB, blood poisoning, and food-borne illnesses becomes more challenging, if not impossible, when drugs lose their effectiveness. Bacterial infections are a concern again, decades after the first patients were treated with antibiotics. The post-antibiotic era is quickly drawing near, and unless prompt and decisive action is done, ordinary diseases and mild injuries might become deadly once more.

4. Antibiotic Resistance: A Global Menace

The rise in antimicrobial resistance (AMR) is one of the biggest problems of our day. According to the Centres for Disease Control and Prevention (2019), AMR microorganisms are currently responsible for 2.8 million infections, over 35,000 annual fatalities in the United States, and 700,000 annual deaths globally (Krell & Matilla, 2022).

Remarkably, current projections suggest that 10 million deaths per year due to AMR infections will occur in 2050 if immediate action is not taken (Dadgostar , 2019). overtaking cancer as the world's leading cause of death. Longer hospital stays, a rise in second-line treatments, and treatment failure are all consequences of AMR. According to estimates, treating AMR infections can cost up to $50,000 per patient and episode, and the United States needs to spend $20 billion annually to alleviate AMR (Dadgostar, 2019). AMR has an effect on agricultural productivity in addition to the health of humans and animals.

To effectively eliminate AMR infections in humans, animals, and plants, immediate action is required.

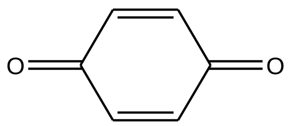
5. Millipedes Secretions

Millipedes (Diplopoda) protect themselves from microorganisms and predators by secreting defence secretions that can be toxic or unattractive. Chemicals such as phenols, alkaloids, cyanogenic chemicals, and quinones are among the defence mechanisms employed by millipedes (Shear, 2015, David, 2015, Arab, *et al.,* 2003, Wu, *et al.,* 2007, Kuwahara *et al.,*2007, Wood *et al.,*2000, Bodner and Raspotning, 2007, Sekulic *et al.,*.2014, Bodner *et al.,* 2016, Shimizu *et al.,* 2015, Ishida *et al.,* 2016, Rodriguz *et al.,* 2018, Illic *et al.,* 2018). The chemical composition of some millipedes are summarized in Table 1 while the structure of some compounds found in millipede secretions are given in Figure 1.

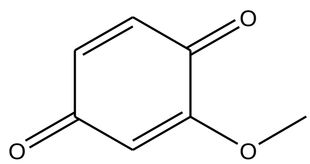
Table 1: Chemical compositions of some millipedes

Entry	Millipede	Chemical compositions	References
1	*Pachyiulus hungaricus*	1,4-Benzoquinone , 1,4-Benzoquinone, 2-Methyl-1,4-benzoquinone, 2-Hydroxy-3-methyl-1,4-benzoquinone, 2-Methoxy-3-methyl-1,4-benzoquinone, 2-Methoxy-1,4-benzoquinone, 1,4-Dihydroxy-benzene (hydroquinone), 2,3-Dimethoxy-1,4-benzoquinone, 2-Methyl-hydroquinone, 2,3-Dimethoxy-hydroquinone, 2-Methyl-3,4-methylene-dioxypheno, Pentyl tetradecanoate , Hexyl tetradecanoatea , Pentyl pentadecanoateb, Pentyl pentadecanoate, Hexyl pentadecenoate , Hexyl tetradecanoate, Pentyl pentadecanoateHexyl pentadecanoate	Stanković *et al*. (2016)
2	*Telodeinopus aoutii*	Benzoquinones p-Benzoquinone, Toluquinone, 2-Methoxy-3-methylbenzoquinone, 2-Ethylbenzoquinone , 2-Methoxybenzoquinone , 2,3-Dimethoxybenzoquinone, 2,3-Dimethoxy-5-methylbenzoquinone , Naphthoquinone	Deml and Huth (2019)
3	*Brachydesmus troglobius Daday*	Benzaldehyde, Benzyl alcohol, Benzoylnitrile, Benzoic acid, Mandelonitrile benzoate	Makarov *et al*. (2012)
4	*Typhloiulus bureschi*	1,4-benzoquinone, 2-methyl-1,4-benzoquinone, 4-methylphenol, 2-ethyl-1,4-benzoquinone, 2-hydroxy-3-methyl-1,4-benzoquinone, 4-ethylphenol, 2-methoxy-3-methyl-1,4-benzoquinone, 2-ethyl-3-methoxy-1,4-benzoquinone, 2,3-dimethoxy-1,4-benzoquinone, 2,3-dimethoxyhydroquinone, 2-methyl-3,4-methylenedioxyphenole, 2,3-dimethoxy-5-methyl-1,4-benzoquinone,	Makarov *et al*. (2017)
5	*Nopoiulus kochii Cibiniulus phlepsii,*	2-Methyl-1,4-benzoquinone , 2-Hydroxy-3-methyl-1,4-benzoquinone, 2-Methoxy-3-methyl-1,4-benzoquinone, 2,3-Dimethoxy-1,4-benzoquinone,2-Methylhydroquinone, 2-Methoxy-3-methylhydroquinone , 2,3-Dimethoxyhydroquinone , 2-Methyl-3,4-(methylenedioxy)phenol, 2,3-Dimethoxy-5-methyl-1,4-benzoquinone , 2,3-Dimethoxy-5-methylhydroquinone , 2,5-Dimethoxy-3-methyl-1,4-benzoquinone , Hexyl oleate, Octyl oleate	Ljubodrag *et al*. (2014)
6.	*Anurostreptus sculptus*	1,4-Benzoquinone, 2-Methyl-1,4-benzoquinone, 2-Methoxy-3-methyl-1,4-benzoquinone, 2-Methoxy-1,4-benzoquinone, 3,4-Dimethoxyphenol, Hexyl pentadecanoate	Anuwat *et al*. (2023)
7.	*Brachycybe lecontii*	Buzonamine 6,6a-epoxy-8,8-dimethyldodecahydropyrrolo[2,1-a]isoquinoline	Jones *et al*. (2022)
8	*Cylindroiulus boleti, Leptoiulus trilineatus Megaphyllum bosniense,*	2-methoxy-3-methyl-1,4- benzoquinone , 2-methyl-1,4-benzoquinone. 2- Methoxy-5-methylhydroquinone	Ljubodrag *et al*. (2011)
9	*Acladocricus setigerus*	1,4-benzoquinone , toluquinone (2-methyl-1,4-benzoquinone), 2-ethyl-1,4-benzoquinone , 2-hydroxy-3-methyl-1,4-benzoquinone , 2-methoxy-3-methyl-1,4-benzoquinone , hydroquinone, 2-methoxy-3,6-dimethyl-1,4-benzoquinone , 2,3-dimethoxy-1,4-	Xiaogang *et al*.(2007)

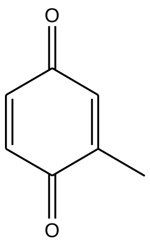
		benzoquinone , 2-methylhydroquinone , 2,3-dimethoxyhydroquinone, 2-methyl-3,4-methylenedioxypheno, 2,3-dimethoxy-5-methyl-1,4-benzoquinone , 2-methoxy-3-methylhydroquinone, 2,3-dimethoxy-5-methylhydroquinone	
10.	*Gosodesmus claremontus*	Gosodesmine	Madeline *et al*. (2020)
11.	*Spirobolida*	Chitin	Raghu *et al*. (2018)
12	*Cylindroiulus boleti Megaphyllum bosniense M. unilineatum*	1,4-benzoquinone , 2-methylbenzoquinone , 2-hydrox y-3-methyl-1,4-benzoquinone , 2-methoxy-3-methyl-1,4- benzoquinone 2,3-dimethoxy-1,4-benzoquinone , 2-methoxy-5-methylhydroquinone , 2-methylhydroquinone , 2,3-dimethoxyhydroquinone , 2-methyl-3,4-methyle nedioxyphenol, 2,3-dimethoxy-5-methyl-1,4-benzoquinone , 2-methoxy-3-methylhydroquinone and 2,3- dimethoxy-5-methylhydroquinone	Bojan *et al*. (2018)
13	*Unciger Transsilvanicus*	Phenol, p-cresol, toloquinone and 2-methoxy-3-methyl-1,4-benzoquinone. Hydroquinone, isopentyl hexacosatetraenoate and isopentyl esters	Tatjana *et al*. (2014)



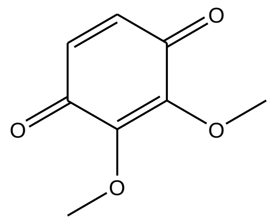
1,4-Benzoquinone (p-benzoquinone) (Ilić *et al.*, 2018)



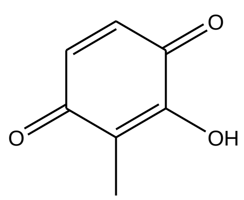
2-Methoxy-1,4-benzoquinone (Stanković *et al.*,2016)



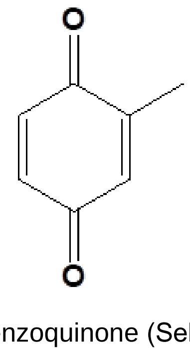
2-Methyl-1,4-benzoquinone (Ilić *et al.*, 2018)



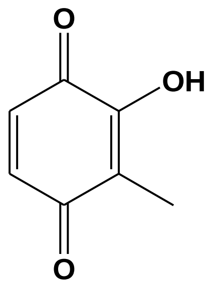
2,3-Dimethoxy-1,4-benzoquinone (Tummanam *et al*, 2023)



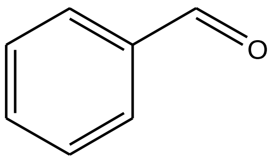
2-Hydroxy-3-methyl-1,4-benzoquinone (Stanković *et al.*,2016)



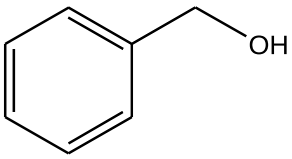
2-methyl-1,4-benzoquinone (Sekulić *et al.*, 2014)



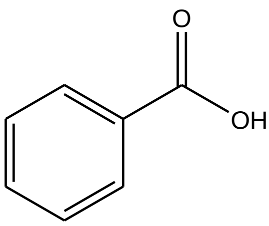
hydroxy-3-methyl-1,4-benzoquinone (Sekulić *et al.*, 2014)



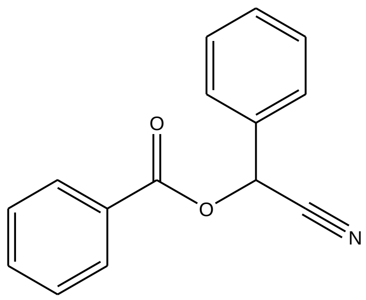
Benzaldehyde (Makarov *et al*., 2012)



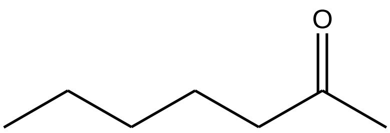
Benzyl alcohol (Makarov *et al*., 2012)



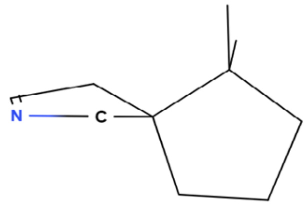
Benzoic acid (Makarov *et al*., 2012)



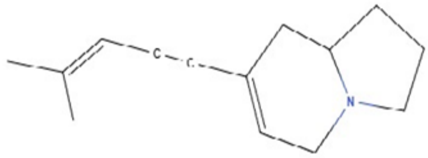
Mandelonitrile benzoate (Makarov *et al*., 2012)



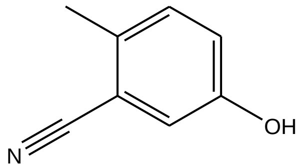
heptan-2-one (Makarov *et al*., 2012)



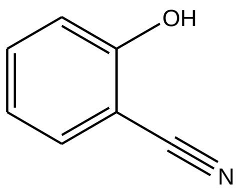
Polyzonimine (Kunert *et al*., 2023)



Gosodesmine(Hassler *et al*., 2020)



5-Hydroxy-2-methylbenzonitrile (Glukhova *et al*., 2018)



2-Hydroxybenzonitrile (Glukhova *et al*., 2018)

Figure 1: Structures of some compounds present in millipede.

6. Millipedes Secretion as Antibiotics

The literature has extensively established the poisonous and repulsive effects of millipede chemical secretions (Shears 2015, Weldon, *et al.,* 2003 and *Alagesan, 2016)*. Glomerin and homoglomerin poisoned arachnids and vertebrates that ate millipedes Glomeris marginata (Villers, 1789) . Ants are repelled by the protective allomone para-cresol (Shears *et al., 2007* and Sekulic *et al.,* 2014). During laboratory testing for blood samples containing benzoquinones from Orthoporus dorsovittatus (Verhoeff, 1938), mosquitoes Aedes aegypti fed less frequently (Weldon *et al.,* 2003).

Carroll *et al*. 2005 conducted laboratory testing to determine the long-term effectiveness of benzoquinones as a prophylactic measure against the lone star tick, Amblyomma americanum (Alagesan, 2016).

Millipedes are eaten by the Bobo tribe of Burkina Faso to increase the meal's calorie content and perhaps have antimalarial properties (Enghoff *et al.,* 2014). The Red-fronted lemurs, Eulemur rufifrons, consume millipedes as part of their defence against intestinal parasites. They do this by first chewing and squeezing arthropods, which releases protective fluids (Peckre *et al., 2018)*. Coati Nasua spp. have been observed to roll their prey (Weldone *et al., 2006)*. Millipedes are chosen by representatives of the tropical batrachofauna to augment their diet.

Alkaloids from swallowed millipedes and ants were discovered in the derma glands of toxic frogs (Daly *et al., 2000, Clark et al*., 2005). Spiropyrrolizidine oximes, which are present in the skin of Panamanian Dendrobates pumilio, are produced by chemical secretions from beetles and millipedes Rhinotus purpureus (Pocock, 1894, *Clark et al*., 2005, Saporito *et al., 2003)*. Both traditional and conventional medicine use the pharmacologically-based chemicals found in arthropods for medicinal purposes (Illit *et al., 2018, Dandawate et al* 2010, Meyer-Rochow, 2017).

Millipede defensive secretions are intriguing prospects for drug development and biological research due to their complex chemical makeup, which has a variety of pharmacological implications. A number of millipede defence compounds are proven to have strong antibacterial properties against a range of diseases, including bacteria, fungus, and even some parasites. Quinones, alkaloids, and phenolic derivatives are some substances that have demonstrated notable antibacterial and antifungal properties. The wide range of bioactive characteristics demonstrated by these substances has sparked increased interest in the pharmacological potentials of millipede defence chemicals in recent times (Jung et, al. 2023).

7. Antibacterial Activities of Some Millipedes

Table 2 summarizes the antibacterial activities of some millipedes against certain bacterial pathogen whereas Table 3 highlights the antimicrobial activities of some millipede against both gram-positive and gram-negative pathogens. The mechanism of antimicrobial action of these millipedes is described in Figure 2 showing several stages from secretions to denaturation of protein, inhibition of metabolism, pathogenic repulsion, etc.

Table 2: Antibacterial activities of some millipedes against some bacterial pathogen.

Entry	Millipedes Species	Bacterial pathogen	References
1	*Sophistreptus guineensis s. Pachybolus ligulatus v. Secreations*	*methicillin-sensitive and -resistant Staphylococcus aureus.*	Pesewu *et al*. (2015)
2	*O. Guineensis + p. Ligulatus aganst*	*S. aureus and E. coli*	Billah *et al*, (2015)
3	*Apfelbeckia insculpta*	*Escherichia coli*	Billah *et al*. (2015)
4	*Nedyopus dawydoffiae*	*S. fimicarius, S. griseoplanus, S. pratensis, S. setonii and S. spororaveus*	Glukhova *et al*. (2018)
5	*Anurostreptus sculptus*	*Bacillus cereus, Staphylococcus aureus, Staphylococcus aureus, (Escherichia coli, Escherichia coli, Pseudomonas aeruginosa, and Salmonella ser. Typhi*	Tummanam *et al*. (2023)
6	*Cylindroiulus Boleti*	*S. aureus, Escherichia coli, Erwinia*	Ilić *et al*. (2018)
7	*Ophistreptus guinecensis and Phachybolus ligulatus v.*	*s. aureus, E. coli*	Pesewu *et al*.(2015)
8	*Megaphyllum Unilineatum*	*Aeromonas hydrophila*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Xanthomonas arboricola*, *Listeria monocytogenes*, *Staphyllococcus aureus* and *Bacillus subtilis*	Ilić *et al*. (2019)

Table 3: Antimicrobial activities of some millipede on both Gram-Positive and Gram-Negative pathogens

Entry	Millipedes Species	Activity	References
1	*Sophistreptus guineensis s. Pachybolus ligulatus v. Secreations*	Antibacterial	Pesewu *et al*. (2015)
2	*O. Guineensis + p. Ligulatus aganst*	Antibacterial	Billah *et al*. (2015)
3	*Apfelbeckia insculpta*	Antibacterial and Antifungal	Billah *et al*. (2015)
4	*Nedyopus dawydoffiae*	Antibacterial	Glukhova *et al*. (2018)
5	*Anurostreptus sculptus*	Antibacterial and Antifungal	Tummanam *et al*. (2023)
6	*Cylindroiulus Boleti*	Antibacterial	lić *et al*. (2018)
7	*Ophistreptus guinecensis and Phachybolus ligulatus v.*	Antibacterial	Pesewu *et al*. (2015)
8	*polydesmida*	Antibateriak and Antifunga	Omura *et al*. (2002)
9	*megaphyllum bosniense m. unilineatum*	Antibateriak and Antifunga	Ilić *et al*. (2018)
10	*pachyiulus hungaricus*	Antioxidant, antineurodegenerative, and anti-Fusarium effects	Ilić *et al*. (2019)
11	*Megaphyllum Unilineatum*	Antibacterial, antifungal Antioxidant, antineurodegenerative, and anti-Fusarium effects	Ilić *et al*. (2019)
12	*spirobolida, and spirostreptida*	Antibacterial and antifungal	Voigtländer and Balkenhol (2006)

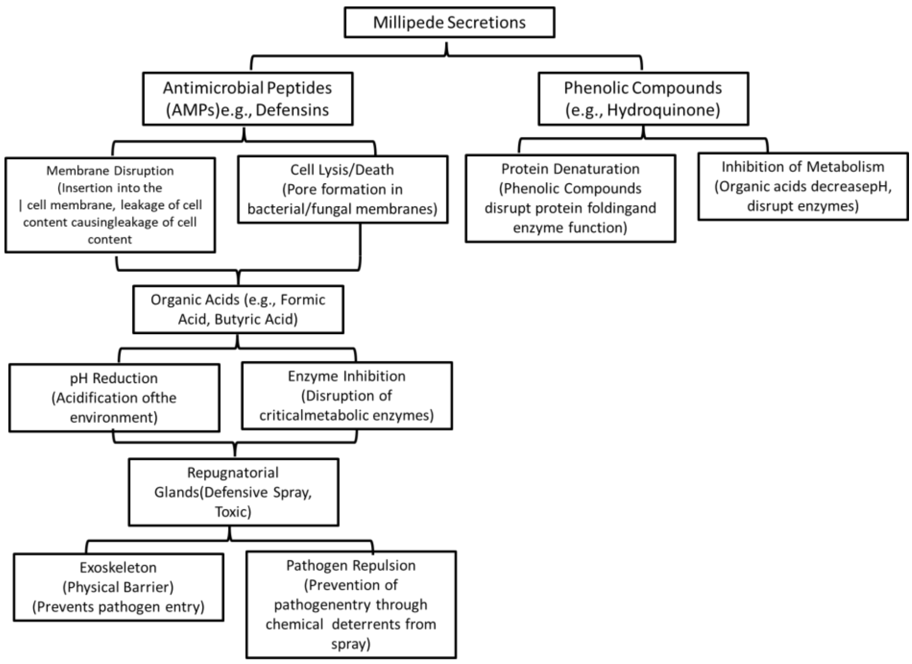


Figure 2: Mechanisms of antimicrobial action of millipedes.

8. Conclusion

One intriguing approach to combating the growing worldwide danger of antibiotic resistance is the investigation of millipede secretions as a possible source of new antibiotics. The exocrine defense glands of millipedes, which are members of the class Diplopoda, enable them to create a wide range of chemical substances. Quinones, phenols, alkaloids, and cyanogenic chemicals are among the compounds that have demonstrated noteworthy antibacterial and antifungal characteristics. Research has indicated that these secretions are effective against a range of pathogens, such as Bacillus cereus, Escherichia coli, and methicillin-resistant Staphylococcus aureus (MRSA).

The potential of millipede secretions is significant given the pressing need for novel antibiotics in light of the emergence of antibiotic-resistant bacteria. In addition to having antibacterial qualities, these natural substances also seem to have less side effects than certain synthetic antibiotics. Furthermore, the secretions of millipedes are a potentially sustainable source of novel antibiotics due to their renewable and relatively plentiful nature.

Even though the initial results are promising, more investigation is necessary to completely comprehend the mechanisms, safety, and effectiveness of these secretions. Extensive research and clinical trials will be necessary to ascertain their feasibility as an innovative tool in the battle against bacteria resistant to antibiotics. If effective, medications made from millipedes could greatly improve our capacity to fight infectious diseases and deal with the threat that antibiotic resistance poses to world health.

Conflict of interest

The authors declare no conflict of interest.

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