Egyptian Journal of Aquatic Biology & Fisheries
Zoology Department, Faculty of Science,
Ain Shams University, Cairo, Egypt.
ISSN 1110 – 6131
Vol. 25(3): 23 – 38 (2021)
www.ejabf.journals.ekb.eg

Marine, freshwater, and terrestrial snails as models in the biomedical applications

Amina M. Ibrahim [1], Ahmed A. Hamed [2] , Mosad A. Ghareeb [3*]

[1]Environmental Research and Medical Malacology Department, Theodor Bilharz Research Institute, Giza, 12411, Egypt
[2]Microbial Chemistry Department, National Research Centre, Dokki, Egypt
[3]Medicinal Chemistry Department, Theodor Bilharz Research Institute, Giza, 12411, Egypt
[*]**Corresponding Author: m.ghareeb@tbri.gov.eg**

ARTICLE INFO

Article History:
Received: March 15, 2021
Accepted: April 27, 2021
Online: May 25, 2021

Keywords:
Snails,
Molluscan gastropods,
Marine snails,
Freshwater snails,
Terrestrial snails,
Secondary metabolites

ABSTRACT

A snail is a member of the molluscan gastropods that has a cosmopolitan distribution, inhabiting marine, freshwater and terrestrial habitats. The present review highlights the importance of the snails as they have medical and veterinary applications, besides being considered as excellent indicators of ecosystem health like *Biomphalaria* sp., and *Lymnaea stagnalis* freshwater snails. Also, snails have been proved to be excellent models in neurophysiology, especially on learning and memory formation like *Aplysia californica* marine snail and *Lymnaea stagnalis* freshwater snails. Marine snails produce antimicrobial secondary metabolites that exhibit anticancer, antibiotic, antiviral, neurotoxic, or anti-inflammatory properties. These materials can be obtained from the extracts of *Babylonia spirata*, *Buccinulum corneum*, *Buccinum undatum*, *Littorina littorea* "called littorerin", *Haliotis laevigata* or *H. rubra*, *Murex pectin*, *Tegula gallina*, conotoxins released from *Conus magus*, and hemocyanins of *Rapana venosa* snails. Freshwater snails have many bioactive compounds that have antimicrobial activity. These materials like, the extracted proteins from *Bellamya dissimilis*, *Bithynia pulchella*, *Melanoides tuberculata*, and *Pila* sp, mucus extracted from *Pomacea canaliculata* and *Faunus ater*; or the hemolymph of *Pomacea insularium* snail. Terrestrial snails can be used in the traditional medicine as they have pharmacologically active compounds, like mucus from *Helix* sp., *Achatina achatina*, *Achatina fulica*, and *Eremina desertorum* snails, or proteins extracted from *Cryptozona bistrialis* snails. Conclusively, snails have a lot of biomedical, nutritional and economic importance.

INTRODUCTION

A snail is a word used for most of the members of the molluscan gastropods that has a calcareous shell that is large enough to contain the animal body **(Jörger *et al.*, 2010)**. It can be found in every continent on Earth, inhabiting marine, freshwater and terrestrial habitats **(Burnie and Kindersley, 2011; Sao Mai, 2014)**. These snails were characterized by their biomedical and nutritional efficacies, and then the present review will make a spot on some of these important usages and properties. These snails varied in

their sizes from small to medium. The smallest known snail in the whole world is an adult *Acmella nana* that measuring only 0.79 millimeter in size **(Vermeulen *et al.*, 2015)**. The largest known land gastropod is the African giant snail *Achatina achatina*, the largest recorded specimen was 39.3 centimeters from snout to tail when fully extended with a shell length of 27.3 cm **(Páll-Gergely *et al.*, 2015)**. They characterized by their slow movemen. They served an important role in the ecosystem as some are herbivores, omnivores, and carnivores. Although they are hermaphrodites, they have to mate with another snail in order to fertilize their eggs **(Pavlova, 2001)**. They have considerable human relevance, including as food resources, pests, and vectors of disease. Their shells are used as decorative objects and are incorporated into jewelry **(Sahley *et al.*, 1981)**. Malacology is a Greek word means the study of the soft body invertebrates especially the mollusks **(Prié, 2019)**. Molluscs possess a wide range of species living in marine, terrestrial, and freshwater habitats **(Hayes *et al.*, 2009)** like slugs, snails, squid and octopus **(Sturm *et al.*, 2006)**. Medical malacology is concerning with mollusks with medical, veterinary, and agricultural applications. Some mollusk can serve as an intermediate host of parasitic diseases, as schistosomiasis and fascioliasis (**Fig. 1**) **(Vinarski, 2014)**.

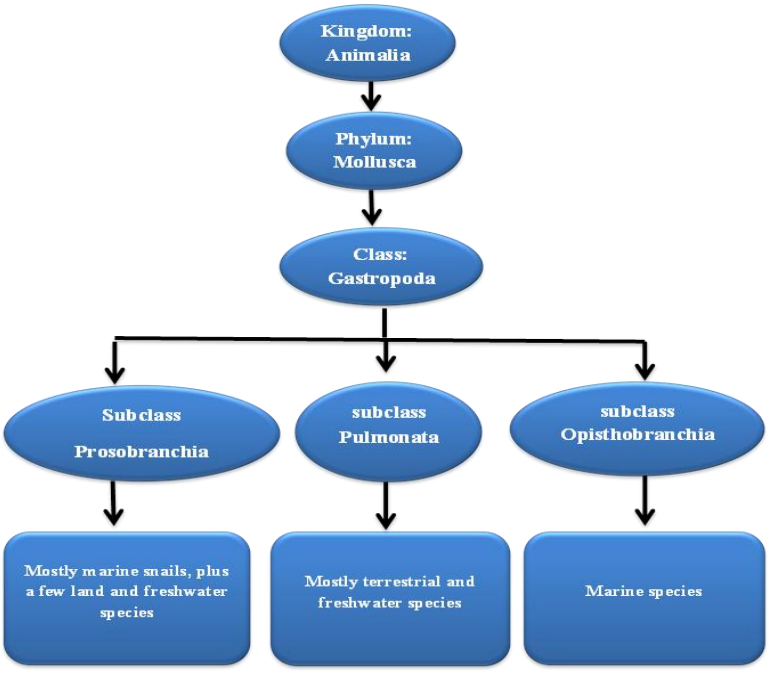


Fig. (1): Classification of snails.

Phylum Mollusca

The name came from the Latin word molluscus meaning soft bodies. It is the second largest invertebrate phylum after the Arthropoda, comprising more than 400,000 species **(Sao Mai, 2014; Vinarski et al., 2020)**. Marine mollusks represented about 23% of all marine species. Geographically, molluscs are widespread in all continents, except of Antarctic. They inhabited all types of the environments; terrestrial, marine and freshwater

habitat, but patterns of their diversity and distribution are different in various regions **(Neubauer *et al.*, 2015)**. They have many commercially and nutritionally important. Because of their advanced nervous system, molluscs were used in the field of neurobiology in the 20th century **(Rivi *et al.*, 2020)**. Not all the interactions between man and molluscs are to man's benefit however, slugs and snails are in some places serious pests of crops, and are often a nuisance in people's gardens. Some can help in spreading of diseases by acting as the intermediate host like *Biomphalaria alexandrina* snails in schistosomiasis *mansoni*. Phylum Mollusca is a very diverse (85,000 species) group of mostly marine species **(Vinarski *et al.*, 2020)**, with a variety of morphological variations. This phylum can be segregated into eight classes **(Dang *et al.*, 2015)** including Gastropoda, Bivalvia, Scaphopoda, Cephalopoda, Polyplacophora, Monoplacophora, Caudofoveata, and Solenogastres.

Class Gastropoda ("stomach foot")

It is the largest class of molluscs, comprising over 80% of all molluscs. It includes snails and slugs **(Strong *et al.*, 2008)**. Within the gastropods, there are three subclasses (Fig. 1). Although 60-70% of molluscs are marine **(Bieler, 1992)**, they are also well represented in freshwater and terrestrial habitats **(Hayes *et al.*, 2009)** and have a biomedical and veterinary importance, since they act as the intermediate hosts for some parasitological diseases **(Pirger *et al.*, 2018)**. Gastropods are considered excellent indicators of ecosystem health in general, and they can act as early warning sentinels of habitat deterioration because they are sensitive to changes in their environment **(Tallarico, 2015)**. Also, they have been confirmed to be brilliant model animals because they are sensitive to anthropogenic inputs, globally distributed, have biochemical pathways that are similar to the vertebrate systems **(Pirger *et al.*, 2018)**. Also, terrestrial, marine and freshwater snails have proved to be excellent models in neurophysiology and behavioral ecology, due to their “simple” nervous system **(Benjamin, 2012)**. Gastropod model organisms can mirror the alteration in the neurobiology, especially on learning and memory formation **(Coustau *et al.*, 2015)**. *Lymnaea stagnalis* (pond snail) have been used in the pollution biomonitoring programs, and in wide ranges of ecotoxicological experiments **(Pirger *et al.*, 2018)**.

Marine snails as models for Biomedical Research

Sea snails or marine gastropods are used as a food source and as a treatment for a wide range of medicinal conditions **(Ulagesan and Kim, 2018)**. Also, they have been used as models in biomedical research **(Pati *et al.*, 2015)**. These organisms have attracted special attention in the last three decades for their ability to produce interesting pharmacological active compounds. All marine organisms have the potential to produce antimicrobial secondary metabolites **(Kaviarasan *et al.*, 2012)**, like sterols, polyproprionates, alkaloids, terpenes, fatty acid derivatives, and macrolides **(Dang *et al.*, 2015)**. Marine natural products as well as fungal extacts exhibit a wide range of pharmaceutically relevant bioactivities, including anticancer, antibiotic, antiviral, antimicrobial,

antioxidant, antibiofilm, larvicidal, snailicidal, antiaflatoxigenic, neurotoxic, or anti-inflammatory properties **(El-Neekety *et al.*, 2016; Hathout *et al.*, 2016; Abdel-Aziz *et al.*, 2018; Abdel-Wareth and Ghareeb, 2018; Abdel-Wareth *et al.*, 2019a,b; Ghareeb *et al.*, 2019; Shawky *et al.*, 2019; Ghareeb *et al.*, 2020a; Hamed *et al.*, 2020; Elkhouly *et al.*, 2021)**. Overall, the secondary metabolites that have been investigated were only from a tiny proportion (<1%) of molluscan species **(Benkendorff, 2010; Benkendorff, 2014)**. Some biomedical applications of marine snails are summarized in Table 1 **(Li, 1960; Orlando *et al.*, 1996; Health, 1999; Defer *et al.*, 2009a, 2009b; Velkova *et al.*, 2009; Benkendorff, 2010; Nesterova *et al.*, 2010; Nesterova *et al.*, 2011; Periyasamy *et al.*, 2012; Akhmedov *et al.*, 2014; Benkendorff *et al.*, 2015; Dang *et al.*, 2015; Turner *et al.*, 2018; Ghareeb *et al.*, 2020b)**. *Aplysia californica* marine snail can be used as an excellent model in neurobiological and behavioral studies. It has a simple brain and large nerve cells that have confined locations. The presence of a single synaptic connection can lead directly to better understanding of learning processes and memory storage **(Health, 1999; Akhmedov *et al.*, 2014)**. Marine natural products have a wide range of pharmaceutically bioactivities **(Petersen *et al.*, 2020)**. The Crude tissue extracts of *Babylonia spirata* marine snails have antimicrobial activity against nine bacterial and three fungal pathogens **(Periyasamy *et al.*, 2012)**. Most marine snail extracts that showed antiviral activities were glycopeptides or peptides **(Dang *et al.*, 2015)**. *Buccinulum corneum* Kelletinin A, has antiviral activities through inhibition of viral transcription and DNA/RNA synthesis **(Orlando *et al.*, 1996)**.

The extracts from the whole Whelk have acidic properties which are responsible for its antibacterial and antiviral activities against human viruses **(Defer *et al.*, 2009a)**. The lyophilized fractions of *L. littorea* called littorerin showed antibacterial and antiviral activities against human viruses **(Defer *et al.*, 2009b)**. Aqueous extract of the abalone *Haliotis laevigata* or *H. rubra* showed antiviral activities against polyomavirus, influenza A virus, and poliovirus **(Li, 1960; Benkendorff, 2010)**. The extracts of *Tegula gallina* showed antibacterial and antiviral activities **(Dang *et al.*, 2015)**. The Muricidae family of marine Mollusca produced the ancient dye tyrian purple (Fig. 2), and they were used in the traditional medicines. Extracts from a number of Muricidae species showed antimicrobial, anti-inflammatory, anti-cancer, muscle-relaxing, and pain relieving activities **(Benkendorff *et al.*, 2015)**.

Table (1): Examples of marine snails used in biomedical applications

Snail name and species	Medical importance	Reference(s)
Aplysia californica	A valuable model in studies of neurobiology and behavior	**(Health, 1999; Akhmedov *et al.*, 2014)**
Babylonia spirata	Its tissue extracts showed antimicrobial activity against nine bacterial and three fungal pathogens.	**(Periyasamy *et al.*, 2012)**
Buccinulum corneum	Kelletinin A [ribityl-pentakis (p-hydroxybenzoate)] inhibited viral transcription and DNA/RNA synthesis	**(Orlando *et al.*, 1996; Benkendorff, 2010)**
Buccinum undatum	80% SPE fraction from the acidic extract of whole organism showed antiviral activity	**(Defer *et al.*, 2009a)**
Conus magus	The toxin released, known as conotoxin conopeptides are currently being developed as analgesics for the treatment of neuropathic pain	**(Turner *et al.*, 2018; Ghareeb *et al.*, 2020b)**
Haliotis laevigata and *Haliotis rubra*	Aqueous extract has antiviral activity against Polyomavirus, influenza A virus, and poliovirus	**(Li, 1960; Benkendorff, 2010)**
Periwinkle *Littorina littorea*	Peptide extract from whole organism (littorein) showed antiviral activity	**(Defer *et al.*, 2009b)**
Murex pectin	Muricidae extracts showed antimicrobial, antiviral, and anti-cancer activities	**(Benkendorff *et al.*, 2015)**
Rapana venosa	Their hemocyanin showed antiviral activity by preventing virus of the attachment to cells and inhibited the replication of Epstein-Barr virus and Herpes simplex virus type 1	**(Velkova *et al.*, 2009; Nesterova *et al.*, 2010; Nesterova *et al.*, 2011; Benkendorff *et al.*, 2015)**
Tegula gallina	Their extracts showed antiviral activity	**(Dang *et al.*, 2015)**

Conus magus snails are predators that attack prey with a venomous sting. The toxin released, known as conotoxin (Fig. 3), is a peptide with internal disulfide linkages. Conotoxins can bring about paralysis in humans, indicating that this toxin attacks neurological targets **(Becker and Terlau, 2008)**. A number of these conopeptides are currently being developed as analgesics for the treatment of neuropathic pain **(Hamdi, 2011; Ghareeb *et al.*, 2020b)**.

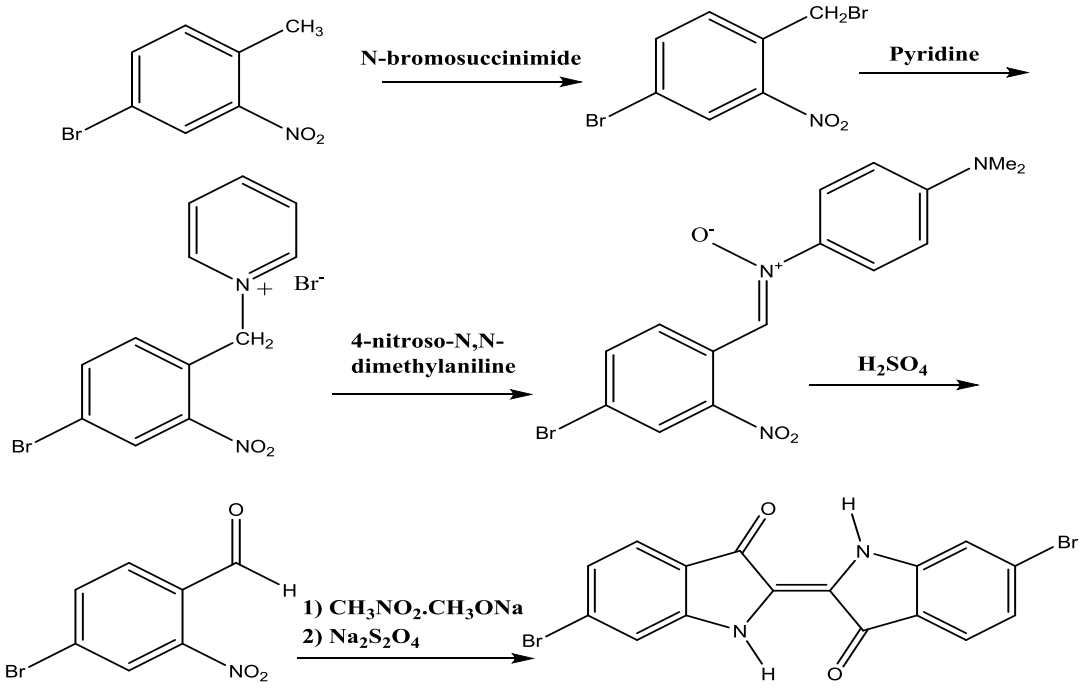


Fig. (2): Tyrian purple: 6, 6'-Dibromoindigo (**Benkendorff *et al.*, 2015**).

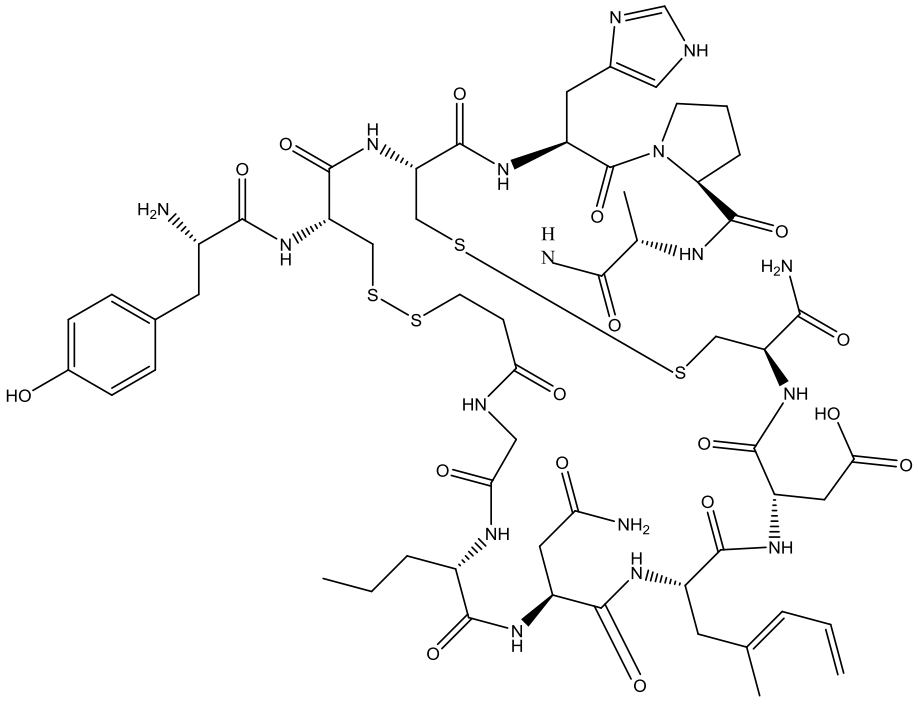
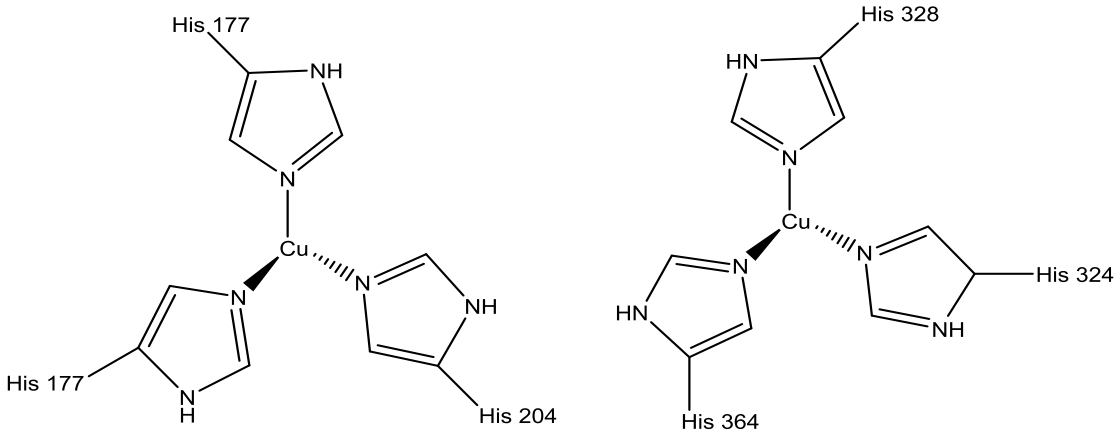
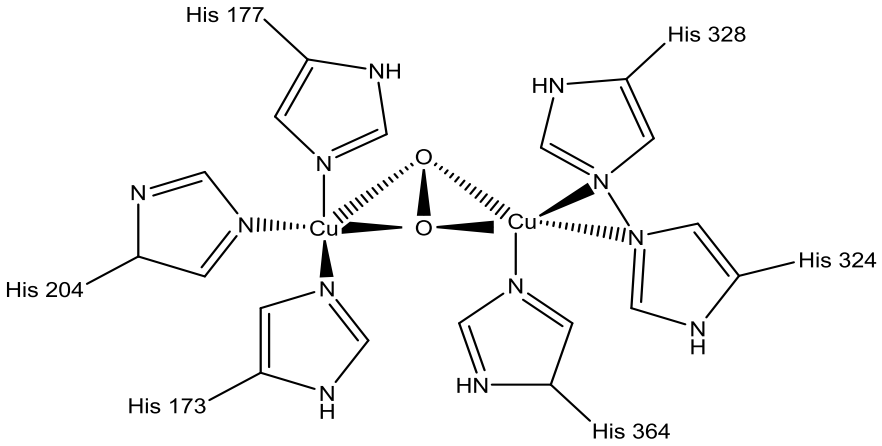


Fig. (3): Chemical structure of alpha-conotoxin SIA (**Becker and Terlau, 2008**).

Molluscan hemocyanins (Fig. 4) consist of highly specific monosaccharide compositions that have significant immunostimulatory properties. *Rapana venosa* hemocyanin contains at least 28 different compositions of heterogeneous mixture of different glycans. This hemocyanin showed antiviral effects mostly against human viruses **(Velkova *et al.*, 2009; Dang *et al.*, 2015)** by preventing the viral attachment or inhibition of viral transcription.



Deoxyhemocyanin



Oxyhemocyanin

Fig. (4): Hemocyanin structures (**Velkova *et al.*, 2009**).

Freshwater snails as models for biomedical research

The freshwater Mollusca (snails and bivalves) are almost cosmopolitan in their distribution **(Strong *et al.*, 2008)**. This group of aquatic invertebrates demonstrates high

adaptive ability; its representatives may be found in almost all types of inland water bodies and are represented in the symbiotic fauna **(Vinarski *et al.*, 2020)**. These Freshwater gastropods could be used as a model for ecotoxicology assessments and as pollution indicators for different substances, as they have a rapid growth index and short life cycles **(Tallarico, 2015)**.

Medically and economically important snail-transmitted diseases

Snail-borne parasitic diseases are major parasitic diseases that pose risks to human health and cause major socioeconomic problems in many tropical and sub-tropical countries. The freshwater snails are considered to be intermediate hosts of these diseases because humans harbor the sexual stages of the parasites and the snails harbor the asexual stages. These diseases target many organs, such as the lungs, liver, biliary tract, intestines, brain, and kidneys, leading to overactive immune responses or even death (Table 2) **(Lu *et al.*, 2018)**.

Table (2): Some freshwater snails that transmit diseases

Disease	Snail
Schistosomiasis	*Biomphalaria*, *Bulinus*, *Oncomelania*
Fascioliasis	*Lymnaea* sp.,
Paragonimiasis	*Melanoides* and *Thiara* genera
Angiostrongyliasis	Terrestrial and freshwater snails

Freshwater snails have many bioactive compounds that can be used in the biomedical medicine (Table 3). The foot tissue extracts from freshwater snails *Bellamya* spp. and *Pila* sp, are rich in proteins, minerals and vitamins (A, B, D). Besides being used as main nutritional supplement, it can be used for inflammatory disorders **(Prabhakar and Roy, 2009)**. The extracted proteins using Bradford's method from different snails like *Bellamya dissimilis*, *Bithynia pulchella*, and *Melanoides tuberculata* showed antimicrobial activity against various pathogenic bacterial and fungal cultures **(Ulagesan and Kim, 2018)**.

Snail mucus is known by its potential antimicrobial activity. This mucus serves in preventing moisture evaporation and providing resistant to infection by any microorganisms. *Pomacea canaliculata* and *Faunus ater* crude mucus extracts showed antimicrobial activity **(Ferrer and Pajarillaga, 2013; Nantarat *et al.*, 2019)**. Also, the hemolymph of *Pomacea insularium* snail and the whole animal extracts can be used as an antimicrobial agent for many different pathogens **(Packia Lekshmi *et al.*, 2015)**.

Table (3): Examples of freshwater snails used in biomedical research

Snail name and species	Medical importance	References
Bellamya dissimilis	Its extracted protein showed antibacterial and antifungal activities. Also, the tissue extracts can be used to treat inflammatory problems	**(Prabhakar and Roy, 2009; Ulagesan and Kim, 2018)**
Biomphalaria sp.,	Serves as sensitive bioindicators for aquatic ecosystem health	**(Ibrahim *et al.*, 2018; Amorim *et al.*, 2019)**
Bithynia pulchella	Its extracted protein showed antibacterial and antifungal activities.	**(Ulagesan and Kim, 2018)**
Faunus ater	Its crude mucus extract showed antimicrobial activity.	**(Ferrer and Pajarillaga, 2013)**
Lymnaea stagnalis	- Can be used as a bioindicator of ecosystem health - A valuable model in studies of neurobiology and behavior	**(Ibrahim *et al.*, 2018; Fodor *et al.*, 2020)**
Melanoides tuberculata	Its extracted protein showed antibacterial and antifungal activities.	**(Ulagesan and Kim, 2018)**
Pila globosa, *Pila virens*	Its extracted protein showed antibacterial and antifungal activities. Also, the tissue extracts can be used to treat inflammatory problems	**(Prabhakar and Roy, 2009; Ulagesan and Kim, 2018)**
Pomacea insularium	The hemolymph and the whole animal extracts can be used as an antimicrobial agent for many different pathogens.	**(Packia Lekshmi *et al.* 2015)**
Pomacea canaliculata	Its crude mucus extract showed antimicrobial activity. - Antibacterial activity against pathogenic bacteria that causing skin diseases.	**(Ferrer and Pajarillaga, 2013; Nantarat *et al.*, 2019)**

Both *Biomphalaria* sp., and *Lymnaea stagnalis* freshwater snails serve as sensitive bioindicators for aquatic ecosystem health **(Amorim *et al.*, 2019)**. *Biomphalaria alexandrina* snails could be used as biomonitor to screen the deleterious effects of insecticide **(Ibrahim *et al.*, 2018)**, herbicide **(Ibrahim and Sayed, 2019)**, and heavy metal **(Habib *et al.*, 2016)** as causes of the environmental pollution. Also, *Lymnaea stagnalis* snails can be used as a model to study the function of the nervous system from molecular signaling to behavior. This is because it has well-characterized central, peripheral nervous and neuroendocrine systems and its large neurons **(Fodor et al., 2020)**. *L. stagnalis* snail has been recognized as a useful organism to examine the effects of pharmacologically active compounds and micro- and nanoplastics on aquatic organisms **(Amorim *et al.*, 2019)**.

Terrestrial snails as models for biomedical research

Some terrestrial snails can be used in the traditional medicine (Table 4). The terrestrial land snail *Helix* spp. mucus has a wide range of enzymes, glycosaminoglycans, and prostaglandins, which may contribute to its biological effects **(Nantarat *et al.*, 2019)**. This mucus serves in protection of the animal from desiccation and infection by microorganisms, as it has the antimicrobial activity. *Achatina achatina* and *Achatina fulica* crude mucus extracts showed antimicrobial activity **(Ferrer and Pajarillaga, 2013; Nantarat *et al.*, 2019)**. Also, mucus form *Helix aspersa muller* showed

antimicrobial activity and several therapeutic proprieties, such as skin protection and wound repair. These properties due to that the mucous is composed of mucopolysaccharides called helixcomplex **(Gentili *et al.*, 2020)**.

Eremina desertorum snails have rich mucus that consists of mucopolysaccharides and glycoproteins **(Skingsley *et al.*, 2000)**. This mucus is used in wounds, superficial healing, and muco-adhesive formulations for ocular, nasal, gastro-intestinal, buccal, and vaginal drug administration as it had wonderful therapeutic activities **(Adikwu and Okafor, 2012; Hatuikulipi *et al.*, 2016; Ali *et al.*, 2018)**.

Land snails have been used as food resources because of their high content of protein. This protein contents can be used as biomedical sources to treatment many medicinal conditions, as it has antimicrobial activities. The extracted proteins from *Cryptozona bistrialis* snails showed antimicrobial activity against various pathogenic bacterial and fungal cultures **(Ulagesan and Kim, 2018)**.

Table (4): Examples of some terrestrial snails used in biomedical applications

Snail name and species	Medical importance	References
Achatina fulica	Its extracted protein showed antibacterial and antifungal activities. Its crude mucus extract showed antimicrobial activity.	**(Ferrer and Pajarillaga, 2013; Ulagesan and Kim, 2018; Nantarat *et al.*, 2019)**
Achatina achatina	Its extracted protein showed antibacterial and antifungal activities.	**(Ferrer and Pajarillaga, 2013)**
Cryptozona bistrialis	Its extracted protein showed antibacterial and antifungal activities.	**(Ulagesan and Kim, 2018)**
Eremina desertorum	Its mucus consists of mucopolysaccharides and glycoproteins. It is used in wounds, superficial healing and muco adhesive formulations.	**(Skingsley *et al.*, 2000; Ali *et al.*, 2018)**
Helix aspersa muller	*H. aspersa* mucus (Helixcomplex) has a bio-adhesive efficacy and defensive properties. Due to its antimicrobial activity, it can be used as skin protection and wound repair agent.	**(Gentili *et al.*, 2020)**
Helix lucorum and *Helix vulgaris*	Their hemocyanin showed antiviral activity by inhibiting the viral DNA replication	**(Velkova *et al.*, 2009; Nesterova *et al.*, 2010; Nesterova *et al.*, 2011; Benkendorff *et al.*, 2015)**

CONCLUSION

Gastropods snails (marine, freshwater and terrestrial) proved to be effective model animals and bioindicators of the ecosystem health. They could be excellent examples of the application of biological science to modern medicine through producing therapeutically useful natural compounds and secondary metabolites that have antimicrobial activities like proteins, hemocyanin, conotoxins, and mucus. This review is helpful for the pharmaceutical industries that need to develop drugs of natural origin and suplements.

Author contributions:

A.M.I. designed and elaborated the manuscript. A.A.H and M. A.G., critically revised and improved the manuscript. All the authors approved the final version of the manuscript.

REFERENCES

Abdel-Aziz, M.S.; Ghareeb, M.A.; Saad, A.M.; Refahy, L.A. and Hamed, A.A. (2018). Chromatographic isolation and structural elucidation of secondary metabolites from the soil-inhabiting fungus *Aspergillus fumigatus* 3T-EGY. Acta Chromatogr., 30(4): 243-249.

Abdel-Wareth, M.T.A. and Ghareeb, M.A. (2018). Bioprospecting certain freshwater-derived fungi for phenolic compounds with special emphasis on antimicrobial and larvicidal activity of methyl gallate and p-coumaric acid. Egypt. J. Chem., 61(5): 500-510.

Abdel-Wareth, M.T.A.; Ghareeb, M.A.; Abdel-Aziz, M.S. and El-Hagrassi, A.M. (2019a). Snailicidal, antimicrobial, antioxidant and anticancer activities of *Beauveria bassiana*, *Metarhizium anisopliae* and *Paecilomyces lilacinus* fungal extracts. Egypt. J. Aquat. Biol. Fish., 23(2): 195-212.

Abdel-Wareth, M.T.A.; El-Hagrassi, A.M.; Abdel-Aziz, M.S.; Nasr, S.M. and Ghareeb, M.A. (2019b). Biological activities of endozoic fungi isolated from *Biomphalaria alexandrina* snails maintained in different environmental conditions. Int. J. Environ. Stud., 76(5): 780-799.

Adikwu, M.U. and Okafor, J.O. (2012). Application of the Animal Products Mucin and Honey in Wound Healing : A Pathophysiology, Therapeutics and Pharmaceutical Review. Afr. J. Pharm. Pharmacol., 3: 1-17.

Ali, M.T.; Ashari, M.F.; Wijaya, S.P.R.; Lestari, E. and Wijayanti, R. (2018). Evaluation of wound healing effect of eel mucus ointment (Belutidine) in mice by incision model. J. Nat. Remedies, 18: 1-9.

Akhmedov, K.; Kadakkuzha, B.M. and Puthanveettil, S.V. (2014). *Aplysia ganglia* preparation for electrophysiological and molecular analyses of single neurons. J. Vis. Exp., 83: 51075.

Amorim, J.; Abreu, I.; Rodrigues, P.; Peixoto, D.; Pinheiro, C.; Saraiva, A.;

Carvalho, A.P.; Guimarães, L. and Oliva-Teles, L. (2019). *Lymnaea stagnalis* as a freshwater model invertebrate for ecotoxicological studies. Sci. Total Environ., 669: 11-28.

Becker, S. and Terlau, H. (2008). Toxins from cone snails: Properties, applications and biotechnological production. Appl. Microbiol. Biotechnol.,79: 1-9.

Benjamin, P.R. (2012). Distributed network organization underlying feeding behavior in the mollusk *Lymnaea*. Neural Syst. Circuits, 2(4): 1-16.

Benkendorff, K. (2010). Molluscan biological and chemical diversity: secondary metabolites and medicinal resources produced by marine molluscs. Biol. Rev., 85: 757-775.

Benkendorff, K. (2014). Chemical diversity in molluscan communities: From natural products to chemical ecology. Chap, pp. 13-4.

Benkendorff, K.; Rudd, D.; Nongmaithem, B.D.; Liu, L.; Young, F.; Edwards, V.; Avila, C. and Abbott, C.A. (2015). Are the traditional medical uses of Muricidae molluscs substantiated by their pharmacological properties and bioactive compounds?. Mar. Drugs,13: 5237-5275.

Bieler, R. (1992). Gastropod Phylogeny and Systematics. Annu. Rev. Ecol. Evol. Syst., 23: 311-338.

Burnie, D. and Kindersley, D. (2011). Animal; The Definitive Visual Guide To The World's Wildlife. Dorling Kindersley Ltd, Sep 1, 2011 - Nature - 632 pages; ISBN-13: 978-0756686772.

Coustau, C.; Gourbal, B.; Duval, D.; Yoshino, T.P.; Adema, C.M. and Mitta, G. (2015). Advances in gastropod immunity from the study of the interaction between the snail *Biomphalaria glabrata* and its parasites: A review of research progress over the last decade. Fish and Shellfish Immunol., 46: 5-16.

Dang, V.T.; Benkendorff, K.; Green, T. and Speck P. (2015). Marine Snails and Slugs: a Great Place To Look for Antiviral Drugs: TABLE 1. J.Virol., 89:8114-8118.

Defer, D.; Bourgougnon, N. and Fleury, Y. (2009a). Screening for antibacterial and antiviral activities in three bivalve and two gastropod marine molluscs. Aquaculture, 293: 1-7.

Defer, D.; Bourgougnon, N. and Fleury, Y. (2009b). Detection and partial characterisation of an antimicrobial peptide (littorein) from the marine gastropod *Littorina littorea*. Int. J. Antimicrob. Agents, 34: 188-190.

Elkhouly, H.I.; Hamed, A.A.; El Hosainy, A.M.; Ghareeb, M.A. and Sidkey, N.M. (2021). Bioactive secondary metabolite from Endophytic *Aspergillus Tubenginses* ASH4 isolated from *Hyoscyamus muticus*: Antimicrobial, antibiofilm, antioxidant and anticancer activity. Pharmacog. J., 13(2): 434-442.

El-Neekety, A.A.; Abdel-Aziz, M.S.; Hathout, A.S.; Hamed, A.A.; Sabry, B.A.; Ghareeb, M.A.; Aly, S.E. and Abdel-Wahhab, M.A. (2016). Molecular identification of newly isolated non-toxigenic fungal strains having antiaflatoxigenic, antimicrobial and antioxidant activities. Der Pharm. Chem., 8: 121-134.

Ferrer, E.M.P. and Pajarillaga, S.M.N. (2013). Comparison of antimicrobial activity of

mucus from terrestrial and freshwater snail species. B.S. Biology Thesis.

Fodor, I.; Hussein, A.A.A.; Benjamin, P.R.; Koene, J.M. and Pirger, Z. (2020). The natural history of model organisms: The unlimited potential of the great pond snail, lymnaea stagnalis. Elife, 9: 1-18.

Gentili, V.; Bortolotti, D.; Benedusi, M.; Alogna, A.; Fantinati, A.; Guiotto, A.; Turrin, G.; Cervellati, C.; Trapella, C.; Rizzo, R. and Valacchi, G. (2020). HelixComplex snail mucus as a potential technology against O3 induced skin damage. PLoS One, 15: e0229613.

Ghareeb, M.A.; Hamed M.M.; Saad, A.M.; Abdel-Aziz, M.S.; Hamed, A.A. and Refahy, L.A. (2019). Bioactive secondary metabolites from the locally isolated terrestrial fungus. *Penicillium* sp. SAM16-EGY. Pharmacogn. Res., 11: 162-170.

Ghareeb, MA.; Khalaf, O.M.; Abdel-Aziz, M.S.; Saad, A.M.; Madkour, H.M.F.; El-Ziaty, A.K. and Refahy, L.A. (2020a). Chemical profiles and bio-activities of different extracts of *Terfezia* species and their other associated fungi. Curr. Bioact. Compd., 16(3): 308-319.

Ghareeb, M.A.; Tammam, M.A.; El-Demerdash, A. and Atanasov, A.G. (2020b). Insights about clinically approved and Preclinically investigated marine natural products. Curr. Res. Biotechnol., 2: 88-102.

Habib, M.R.; Mohamed, A.H.; Osman, G.Y.; Mossalem, H.S.; Sharaf El-Din, A.T. and Croll, R.P. (2016). *Biomphalaria alexandrina* as a bioindicator of metal toxicity. Chemosphere, 157: 97-106.

Hamdi, S. (2011). Red sea crustacia and gastropod shells of ras sudr region (northeast of the Gulf of Suez), Egypt. Egypt. J. Aquat. Biol. Fish., 15: 29-42.

Hamed, A.A.; Soldatou, S.; Qader, M.M.; Arjunan, S.; Miranda, K.J.; Casolari, F.; Pavesi, C.; Diyaolu, O.A.; Thissera, B.; Eshelli, M.; Belbahri, L.; Luptakova, L.; Ibrahim, N.A.; Abdel-Aziz, M.S.; Eid, B.M.; Ghareeb, M.A.; Rateb, M.E. and Ebel, R. (2020). Screening fungal endophytes derived from under-explored Egyptian marine habitats for antimicrobial and antioxidant properties in factionalised textiles. Microorganisms, **8**: 1617.

Hatuikulipi, T.N.; Kouachi, M.; Bouchetob, L.E.; Naimi, D.; Bp, E. and Naimi, D. (2016). Preventive effect of *Helix aspersa* slime against experimentally chemo-induced colitis in rat. Der Pharm. Lett., 8: 200-206.

Hathout, A.S.; EL-Neekety, A.A.; Abdel Aziz, M.S.; Sabry, B.A.; Hamed, A.A.; Ghareeb, M.A. and Aly, S.E. (2016). Novel Egyptian bacterial exhibiting antimicrobial and antiaflatoxigenic activity. J. Appl. Pharm. Sci., 6: 001-010.

Hayes, K. A.; Cowie, R.H.; Jorgensen, A.; Schulthei, R.; Albrecht, C. and Thiengo, S.C. (2009). Molluscan models in evolutionary biology: Apple snails (Gastropoda: Ampullariidae) as a system for addressing fundamental questions. Am. Malacol. Bull., 27: 47-58.

Health, N.R.C. (US) C. (1999). on the O. R. in H., NRC, Marine Organisms as Models for Biomedical Research, in: From Monsoons to Microbes: Understanding the Ocean's

Role in Human Health. National Academies Press (US), pp. 0-309.

Ibrahim, A.M. and Sayed, D.A. (2019). Toxicological impact of oxyfluorfen 24% herbicide on the reproductive system, antioxidant enzymes, and endocrine disruption of *Biomphalaria alexandrina* (Ehrenberg, 1831) snails. Environ. Sci. Pollut. Res., 26: 7960-7968.

Ibrahim, A.M.; Ahmed, A.K.; Bakry, F.A. and Abdel-Ghaffar, F. (2018). Hematological, physiological and genotoxicological effects of Match 5% EC insecticide on *Biomphalaria alexandrina* snails. Ecotoxicol. Environ. Saf., 147: 1017-1022.

Jörger, K.M.; Stöger, I.; Kano, Y.; Fukuda, H.; Knebelsberger, T. and Schrödl, M. (2010). On the origin of Acochlidia and other enigmatic euthyneuran gastropods, with implications for the systematics of Heterobranchia. BMC Evol. Biol., 10: 323.

Kaviarasan, T.; Siva, S.R. and Yogamoorthi, A. (2012). Antimicrobial secondary metabolites from marine gastropod egg capsules and egg masses. Asian Pac. J. Trop. Biomed., **2**: 916-922.

Li, C.P. (1960). Antimicrobial Effect of Abalone Juice. Exp. Biol. Med., 103: 522-524.

Lu, X.T.; Gu, Q.Y.; Limpanont, Y.; Song, L.G.; Wu, Z.D.; Okanurak, K. and Lv, Z.Y. (2018). Snail-borne parasitic diseases: An update on global epidemiological distribution, transmission interruption and control methods. Infect. Dis. Poverty, **7**: 1-16.

Nantarat, N.; Tragoolpua, Y. and Gunama, P. (2019). Antibacterial activity of the Mucus Extract from the Giant African Snail (*Lissachatina fulica*) and Golden Apple Snail (*Pomacea canaliculata*) against pathogenic bacteria causing skin diseases. Trop. Nat. Hist., 19: 103-112.

Nesterova, N.V.; Zagorodnya, S.D.; Moshtanska, V.; Dolashka, P.; Baranova, G.V.; Golovan, A.V. and Kurova, A.O. (2011). Antiviral activity of hemocyanin isolated from marine snail *Rapana venosa*. Antivir. Res., 90: A38.

Nesterova, N.; Dolashka-Angelova, P.; Zagorodnya, S.; Moshtanska, V.; Baranova, G.; Golovan, A. and Kurova A. (2010). *In vitro* investigation of cytotoxic action of hemocyanins on cell cultures. Antivir. Res., 86: A63.

Neubauer, T.A.; Harzhauser, M.; Georgopoulou, E.; Kroh, A. and Mandic, O. (2015). Tectonics, climate, and the rise and demise of continental aquatic species richness hotspots. Nat. Acad. Sci., 112: 11478-11483.

Orlando, P.; Strazzullo, G.; Carretta, F.; De Falco, M. and Grippo, P. (1996). Inhibition mechanisms of HIV-1, Mo-MuLV and AMV reverse transcriptases by Kelletinin A from Buccinulum corneum. Experientia, 52, 812-817.

Packia Lekshmi, N.C.J.; Viveka, S.; Anusha, S.; Jeeva, S.; Raja Brindha, J. and Selva Bharath, M. (2015). Antibacterial activity of fresh water crab and snail and isolation of antibacterial peptides from haemolymph by sds-page. Int. J. Pharm. Pharm. Sci., 7: 109-114.

Páll-Gergely, B.; Hunyadi, A.; Jochum, A. and Asami, T. (2015). Seven new hypselostomatid species from China, including some of the world's smallest land snails

(Gastropoda, Pulmonata, Orthurethra). *Zookeys*. 523: 31-62.

Pati, P.; Sahu, B.K. and Panigraphy, R.C. (2015). Marine molluscs a s potential drug cabinet: an overview. Indian J. Geo-Mar. Sci., 44(7): 961-970.

Pavlova, G.A. (2001). The process of crawling by means of musucular contractions, jeb.biologists.org.

Periyasamy, N.; Srinivasan, M. and Balakrishnan, S. (2012). Antimicrobial activities of the tissue extracts of *Babylonia spirata Linnaeus*, 1758 (Mollusca: Gastropoda) from Thazhanguda, southeast coast of India. Asian Pac. J. Trop. Biomed., 2: 36-40.

Petersen, L.-E.; Kellermann, M.Y. and Schupp, P.J. (2020). Secondary Metabolites of Marine Microbes: From Natural Products Chemistry to Chemical Ecology, in: YOUMARES 9-The Oceans: Our Research, Our Future. Springer International Publishing, pp. 159-180.

Pirger, Z.; Zrinyi, Z.; Maász, G.; Molnár, É. and Kiss, T. (2018). Pond Snail Reproduction as Model in the Environmental Risk Assessment: Reality and Doubts, In book: Biological Resources of Water, pp. 33-53.

Prabhakar, A.K. and Roy, S.P. (2009). Ethno-medicinal uses of some shell fishes by people of kosi river Basin of north-Bihar, India. Stud. on Ethno-Med., 3: 1-4.

Prié, V. (2019). Molluscs,Encyclopedia of Caves (Third Edition). Elsevier.

Rivi, V.; Benatti, C.; Colliva, C.; Radighieri, G.; Brunello, N.; Tascedda, F. and Blom, J.M.C. (2020). *Lymnaea stagnalis* as model for translational neuroscience research: From pond to bench. Neurosci. Biobehav. Rev., 108: 602-616.

Sahley, C.; Gelperin, A. and Rudyt, J.W. (1981). One-trial associative learning modifies food odor preferences of a terrestrial mollusc (conditioning/slug/Limax). Proc. Natl. Acad. Sci. U. S. A., 78: 640-642.

Sao Mai, D. (2014). Shellfish (Molluscs and Crustacea): Characteristics of the Groups, in: Encyclopedia of Food Microbiology: Second Edition. Elsevier Inc., pp. 376-388.

Shawky, B.T.; Nagah, M.; Ghareeb, M.A.; El-Sherbiny, G.M.; Moghannem, S.A.M. and Abdel-Aziz, M.S. (2019). Evaluation of antioxidants, total phenolics and antimicrobial activities of ethyl acetate extracts from Fungi grown on rice straw. **J**. Renew. Mater., 7(7): 667-682.

Skingsley, D.R.; White, A.J. and Weston, A. (2000). Analysis of Pulmonate Mucus By Infrared Spectroscopy. J. Molluscan Stud., 66: 363-372.

Strong, E.E.; Gargominy, O.; Ponder, W.F. and Bouchet, P. (2008). Global diversity of gastropods (Gastropoda; Mollusca) in freshwater. Hydrobiologia, 595: 149-166.

Sturm, C.F.; Pearce, T.A. and Valdés, Á. (2006). The Mollusks: Introductory comments. In book: The Mollusks: A Guide to their Study, Collection, and Preservation, 1st Edition: Chapter 1, Universal Publishers, pp.1-7.

Tallarico, L.D. (2015). Freshwater Gastropods as a Tool for Ecotoxicology Assessments in Latin America. Am. Malacol. Bull., 33: 1-7.

Turner, A.H.; Craik, D.J.; Kaas, Q. and Schroeder, C.I. (2018). Bioactive compounds isolated from neglected predatory marine gastropods. Mar. Drugs, 16: 118.

Ulagesan, S. and Kim, H.J. (2018). Antibacterial and antifungal activities of proteins extracted from seven different snails. Appl. Sci., 8: 1362.

Velkova, L.; Todorov, D.; Dimitrov, I.; Shishkov, S.; Beeumen, J.V. and Dolashka-Angelova, P. (2009). *Rapana venosa* hemocyanin with antiviral activity. Biotechnol. Biotechnol. Equip., 23: 606-610.

Vermeulen, J.J.; Liew, T.S. and Schilthuizen, M. (2015). Additions to the knowledge of the land snails of sabah (Malaysia, Borneo), including 48 new species. *Zookeys*. 531: 1-139.

Vinarski, M.V. (2014). The birth of malacology. When and how?. Zoosyst. Evol., 90: 1-5

Vinarski, M.V.; Bolotov, I.N.; Aksenova, O.V.; Babushkin, E.S.; Bespalaya, Y.V.; Makhrov, A.A.; Nekhaev, I.O. and Vikhrev, I.V. (2020). Freshwater Mollusca of the Circumpolar Arctic: a review on their taxonomy, diversity and biogeography. Hydrobiologia, pp.1-28.