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Review Article

Bioactivity of substances isolated from natural products on mollusks *Biomphalaria glabrata* (Say, 1818) (Planorbidae): a review

Bioatividade de substâncias isoladas de produtos naturais em moluscos *Biomphalaria glabrata* (Say, 1818) (Planorbidae): uma revisão

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Abstract

Schistosomiasis is a neglected tropical disease caused by parasitic worms of several species of the genus *Schistosoma*. Transmission occurs by parasitic larvae that stay in freshwater snails of the genus *Biomphalaria*. Thus, the search for new products that are biodegradable has increased the interest in products of plant origin. The aim of this article is to review the isolated substances from natural products that showed molluscicidal activity against the species *Biomphalaria glabrata* in order to reevaluate the most promising prototypes and update the progress of research to obtain a new molluscicide. We perform searches using scientific databases, such as Scientific Electronic Library Online (SciELO), Google schoolar, PUBMED, Web of Science and Latin American and Caribbean Literature on Health Sciences (LILACS). From 2000 to 2022, using the keywords “isolated substances”, “molluscicidal activity” and “*Biomphalaria glabrata*”. In the present study, it was possible to observe 19 promising molluscicidal molecules with a lethal concentration below 20 µg/mL. Of these promising isolates, only 5 isolates had the CL_{90} calculated and within the value recommended by WHO: Benzoic acid, 2’,4’,6’-Trihydroxydihydrochalcone, Divaricatic acid, Piplartine and 2-hydroxy-1,4-naphthoquinone (Lapachol). We conclude that beyond a few results in the area, the researches don’t follow the methodological pattern (exposure time and measure units, toxicity test), in this way, as they don’t follow a pattern on the result’s exposure (LC), not following, in sum, the recommended by WHO.

Keywords: schistosomiasis, bioactive substances, molluscicidal activity, aquatic molluscs.

Resumo

A esquistossomose é uma doença tropical negligenciada causada por vermes parasitas de várias espécies do gênero *Schistosoma*. A transmissão ocorre por larvas parasitas que ficam em caramujos de água doce do gênero *Biomphalaria*. Assim, a busca por novos produtos biodegradáveis tem aumentado o interesse por produtos de origem vegetal. O objetivo deste artigo é revisar as substâncias isoladas de produtos naturais que apresentaram atividade moluscicida contra a espécie *Biomphalaria glabrata* a fim de reavaliar os protótipos mais promissores e atualizar o progresso das pesquisas para a obtenção de um novo moluscicida. Realizamos buscas em bases de dados científicas, como Scientific Electronic Library Online (SciELO), Google acadêmico, PUBMED, Web of Science e Literatura Latina-Americana e do Caribe em Ciências da saúde (LILACS). De 2000 a 2022, utilizando as palavras-chave “substâncias isoladas”, “atividade moluscicida” e “*Biomphalaria glabrata*”. No presente estudo, foi possível observar 19 moléculas moluscicidas promissoras com concentração letal abaixo de 20 µg/mL. Destes isolados promissores, apenas 5 isolados tiveram o CL_{90} calculado e dentro do valor recomendado pela OMS: ácido benzóico, 2’,4’,6’-triidroxidihidrocalcona, ácido divaricático, piplartina e 2-hidroxi-1,4-naftoquinona (Lapachol). Concluímos que além de poucos resultados na área, as pesquisas não seguem o padrão metodológico (tempo de exposição e unidades de medida, teste de toxicidade), assim como não seguem um padrão na exposição do resultado (CL), não seguindo, em suma, o recomendado pela OMS.

Palavras-chave: esquistossomose, substâncias bioativas, atividade moluscicida, moluscos aquáticos.

1. Introduction

Schistosomiasis is a neglected tropical disease caused by parasitic worms of several species of the genus *Schistosoma*. These worms are usually found in areas without basic sanitation (Matos-Rocha et al., 2020; Rapado et al., 2013). WHO data estimate that about 239 million people in 78 countries worldwide are infected with the disease.

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Of these countries, 52 are endemic, with moderate to high transmission, resulting in approximately 200.000 deaths per year (WHO, 2022). Brazil is the most affected country in the Americas (Brasil, 2014), with 1.5 million infected, mainly in the states of the Northeast region (Brasil, 2017).

This endemic disease can be caused by three main species of *Schistosoma: Schistosoma haematobium* (occurs in Africa and the Middle East), *Schistosoma mansoni* (occurs mainly in Africa, South America and the Middle East) and *Schistosoma japonicum* (Asia). The main cause of urinary schistosomiasis is *S. japonicum* and the other parasites of intestinal schistosomiasis (Llanwarne and Helmby, 2021; Aguoru et al., 2022).

In Brazil, the intermediate hosts of *Schistosoma mansoni* with the greatest epidemiological importance are: *Biomphalaria tenagophila*, *Biomphalaria straminea* and *Biomphalaria glabrata*, with emphasis on the snail *B. glabrata*, this is due to its susceptibility to infection by the parasite and distribution in the Brazilian states (Brasil, 2014).

1.1. Biological cycle

Transmission occurs when permanent hosts affected by schistosomiasis contaminate freshwater sources with their feces containing parasite eggs, which hatch in the water – releasing the first larval form called miracidia. In turn, the miracidia infect molluscs, intermediate hosts (obligatorily), where after about 2 to 5 weeks, the second larval and infected form, called cercariae, in an aquatic environment with abundant light and heat begin to be released through the contaminated mollusk, and migrate to the definitive host and infect it by actively penetrating through the skin (Brasil, 2014).

1.2. Treatment

The medicine indicated for the treatment of schistosomiasis is Praziquantel, which is absorbed by the parasite and acts quickly. It causes spastic cerebral palsy and death of the parasite. It has good healing efficiency (80%) and mild and transient adverse effects. However, its repeated use in endemic areas, may favor the selection of *S. mansoni* strains resistant to the drug (Gryseels et al., 2001).

1.3. Combat and control

WHO (2022) recommends a comprehensive strategy for the control of Schistosomiasis that includes: preventive chemotherapy administering Praziquantel, provision of safe drinking water, sanitation, health education for behavior change and, finally, the control of mollusks, which aims to remove intermediate host snails to interrupt the transmission chain. This can be done by a variety of methods: environmental control, biological control, chemical control, among others (WHO, 2022).

According to the WHO, the only substance recommended to date to control molluscs that are vectors of this disease is the synthetic molluscicide Niclosamide. This substance is used on a large scale in schistosomiasis control programs. However, this synthetic substance raises concerns about toxicity to other species, due to the low selectivity, contamination of the environment and the resistance of the mollusks *B. glabrata* (Costa et al., 2015; Rangel et al., 2022).

According to this context, the search for new products that are biodegradable has increased the interest in products of plant origin. It is important that this product is selective for mollusks of the genus *Biomphalaria*, not being toxic to the environment, and mainly, for non-target species (Cantanhede et al., 2010).

1.4. Natural products to combat schistosomiasis

Research on natural products generally starts with their use by the population, through popular knowledge and use (ethnopharmacology), with no scientific basis on their mechanism of action (Viegas Junior et al., 2006).

In the 1930s, tests for molluscicides from natural products were reported for the first time. Among the species tested are aqueous extract from the stem of *Sejania spp*. (cipó-timbó) and fruits of the genus *Sapindus spp*., and all the plant species described were tested on the species *B. glabrata* (Brasil, 2008). Many plants have been tested as a source of potential molluscicides (Vasconcelos and Schall, 1986), among which *Euphorbia milii var hislopii* has been described as a very promising plant molluscicide, with latex showing molluscicidal activity with concentrations below 0.5 ppm under laboratory conditions and can be easily grown in endemic areas, in addition to being biodegradable, demonstrating to be even less harmful to non-target organisms, meeting WHO requirements (Vasconcelos and Schall, 1986; Augusto and Mello-Silva, 2018; Alberto-Silva et al., 2022).

1.5. Plant chemistry

Primary plant metabolism are the biosynthetic routes of basic substances, essential for the survival of plant species such as sugars, amino acids, fatty acids, nucleotides and derived polymers. However, secondary metabolism is the synthesis mechanism responsible for the defense of plants against predators, pathogenic microorganisms and other plants. It composition vary according to the plant species, and may have: alkaloids, glycosides (flavonoids, saponins, anthraquinones, cardiotonics), tannins, mucilages, terpenes and phytohormones (Verpoorte and Memelink, 2002; Koch, 2004).

The biological activity of a plant can be associated with a pure (isolated) molecule or with the set of molecules it contains in its natural state (phytocomplex). Thus, despite the fact that many plant species have high molluscicidal activity, none of them has, to date, the fundamental requirements for the use of this molluscicide of plant origin on a large industrial scale (Brasil, 2008). Most reports of natural products, in fact, molluscicide use crude extracts and fractions, with only a few isolated substances being tested. Thus needing more studies focused on isolated substances, giving the natural continuity that the research needs.

The objective of the study, at first, was to review the isolated substances from natural products that showed molluscicidal activity against the species *Biomphalaria glabrata* over a period of twenty years, between 2000 and 2020. Secondly, we evaluated the most promising prototypes and we seek to update the progress of research for these molecules to obtain a new molluscicide.

2. Materials and Methods

A search was carried out on scientific databases, such as Scientific Electronic Library Onlin (SciELO), Google Scholar, PUBMED, Web of Science and Latin American and Caribbean Literature on Health Sciences (LILACS). It was researched in the period between 2000 to 2022, using the keywords "isolated substances", "molluscicidal activity" and "*Biomphalaria glabrata*". The descriptor "AND" was used, as all key words are essential in the search. One hundred and fifty-one articles were found. Among these, only twelve were related to the purpose of this review, portraying the molluscicidal activity of isolated substances originating from natural products on *B. glabrata* over a period of twenty-two years. Most found in these databases were articles related to synthetic substances, crude extracts, fractions and biological activity of isolated substances on other mollusc species and in the treatment of the disease. Through the articles directly related to the proposal of this review, it was possible to analyze the main families, species and parts of the plant used to isolate the substance with molluscicidal potential (Figure 1).

3. Results

The results of this research showed that in the studied period, 12 articles were found related to isolated substances tested on *B. glabrata* (Table 1).

Santos et al. (2000), analyzed the compound Lapachol (2-hydroxy-1,4-naphthoquinone) derived from the species *Tabebuia impetiginosa*, known as ipe purple (Bignoniaceae). This isolated compound has several therapeutic activities, such as antiviral, antimicrobial, antimalarial, among others, however, its use must be restricted due to its toxicity in certain concentrations (Tavares et al., 2013). In the bioassay, ten snails with a shell diameter between 14-18 mm were used. Mollusks were exposed to Lapachol during the 24-hour period and analyzed for mortality over 96 hours. This compound was shown to be effective against mollusks showing lethal concentrations at 10%, 50% and 90% of this population, in the values, 1.06, 2.57 and 6.18 ppm (μg/mL), respectively.

Pasi et al. (2009), studied the species *Cephalaria ambrosioides*, a robust herb 150 cm high, widely used as an antitumor agent. The genus *Cephalaria* belongs to the family Dipsacaceae, in which it is considered the most advanced family of dicots. From the roots of *C. ambrosioides*, six compounds were isolated, namely, 6α-hydroxy-hydagenic acid, Hederagenic acid, Leontoside A (akebosideStb), Kalopanax saponin A (α-hederin), saponin PG (sapindoside B) and dipsacoside B The first two isolated compounds correspond to the class of triterpenes and the others to the class of saponin. In the molluscicidal activity, the species *B. glabrata* were used and the tests were carried out within 24 hours. Triterpenoids showed relatively high molluscicidal activity, that is, they were effective in controlling the intermediate host. The compounds Leontoside A (akebosideStb), Kalopanax saponin A (α-hederin) and saponin PG (sapindoside B), were toxic at concentrations of 5.4 μg/mL, 6.2 μg/mL and 12.8 μg/mL, respectively.

Baloch et al. (2010) isolated from *Euphorbia cauducifolia* latex, belonging to the Euphorbiaceae family, six substances of the diterpene class, namely: 13-acetoxy-20-O-angeloyl-12-deoxypholia (1), 13-O-[N- (2-aminobenzoyl)] anthraniloyl-20-acetoxy-12-deoxypholia (2), 13,20-O-dibezoyl-12- deoxypholia (3), 13,20-O-diangeloyl-12-deoxyph butterfly (4), 13-O-angeloyl-20-O- [N- (2-aminobenzoyl)] anthraniloyl-12-deoxypholia (5), 13- O-tigloyl-20-O- [N- (2-aminobenzoyl)] anthraniloyl-12-deoxypholia (6), 13-O-benzoyl-20-O-[N- (2-aminobenzoyl)] anthraniloyl-12-deoxypholia (7), 13-O-hexanoyl-20-O- [N- (2-aminobenzoyl)] anthraniloyl-12-deoxypholia (8). The eight compounds isolated from latex were used to test the activity against the species *B. glabrata*. In the bioassay, ten mollusks were used and they were exposed to the isolated compounds within 24 hours to analyze the lethality. According to the results it was possible to obtain the lethal concentrations of 50% of the population of each compound isolated on the intermediate host. In compound (1) the LC_{50} = 12.3 ng/mL; (2) = 13.8 ng/mL; (3) = 25.5 ng/mL; (4) = 24.5 ng/mL; (5) = 26.4 ng/mL; (6) = 25.8 ng/mL; (7) = 26.1 ng/mL and (8) = 26.7 ng/mL (Baloch et al., 2010).

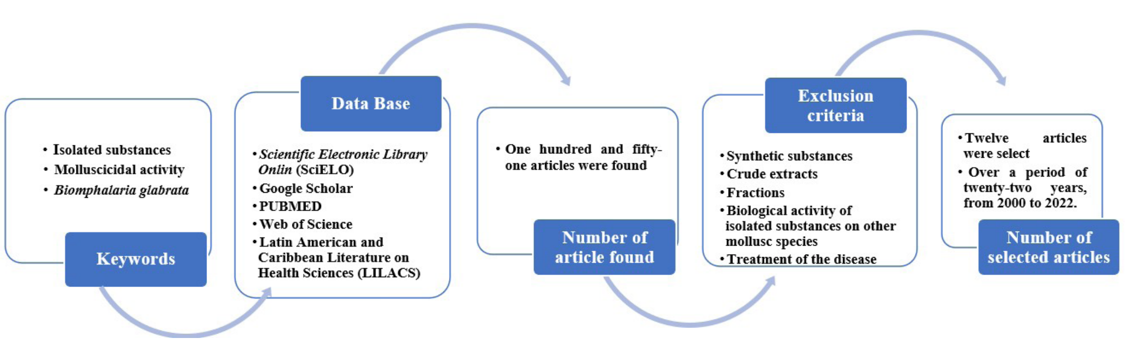

Figure 1. Flowchart of the methodology.

Table 1. Substances Isolated from Natural Products used in the control of *B. glabrata*.

Family	Species	Part used	Isolated substance	Class	Reference
Sapotaceae	*Manilkara subsericea*	Leaves	Myricetin	Flavonoid	Faria et al. (2018)
			Quercetin	Flavonoid	
			Ursolic acid (semi-purified)	Triterpenoid	
Piperaceae	*Piper diospyrifolium*	Leaves	Flavokawain A	Flavonoid / Chalcone	Rapado et al. (2014)
			4-hydroxy-3- (3,7,11-trimethyldodeca2,5,10-trienyl) / Benzoic acid		
	Piper cumanense	Leaves	2',4',6'-Trihydroxydihydrochalcone		
	Piper gaudichaudianum	Leaves	Dihydroflavokawain C		
Euphorbiaceae	*Jatropha elliptica*	Roots	Diethyl 4-phenyl-2,6-dimethyl-3,5-pyridinodicarboxylate	Alkaloid	Santos et al. (2014)
Cladoniaceae	*Cladia aggregata*	Lichens	Barbatic acid	Phenolic compound	Martins et al. (2017)
Dipsacaceae	*Cephalária ambrosioides*	Roots	6α-hydroxy-hydagenic acid	Triterpene	Pasi et al. (2009)
			Hederagenic acid		
			Akeboside Stb / Leontoside A	Saponin	
			Kalopanax saponin A or α-hederin		
			Saponin PG or Sapindoside B		
			Dipsacoside B		
Oscillatoriaceae	*Lyngbya bouillonii*	Cyanobacteria	Cyanolide A	-	Pereira et al, 2010
Ramalinaceae	*Ramalina aspera*	Lichens	Divaricatic acid	Depsids	Silva et al. (2018, 2019)
Euphorbiaceae	*Euphorbia cauducifolia*	Latex	13-acetoxy-20-O-angeloyl-12-deoxyphorbol	Diterpenes	Baloch et al. (2010)
			13-O-[N-(2-aminobenzoyl)] anthraniloyl-20-acetoxy-12-deoxyphorbol		
			13,20-O-dibezoyl-12-deoxyphorbol		
			13,20-O-diangeloyl-12-deoxyphorbol		
			13-O-angeloyl-20-O-[N-(2-aminobenzoyl)]-anthraniloyl-12-deoxyphorbol		
			13- O-tigloyl-20-O-[N-(2-aminobenzoyl)]anthraniloyl-12-deoxyphorbol		
			13-O-benzoyl-20-O-[N- (2-aminobenzoyl)]-anthraniloyl-12-deoxyphorbol		
			13-O-hexanoyl-20-O-[N-(2-aminobenzoyl)]-anthraniloyl-12-deoxyphorbol		
Piperaceae	*Piper tuberculatum*	Roots	Piplartine	Amide	Rapado et al. (2013)
Bignoniaceae	*Tabebuia impetiginosa*	-	2- hydroxy-1,4-naphthoquinone / Lapachol	Quinones	Santos et al. (2000)
Zingibiraceae	*Curcuma longa L.*	Commercial product	[1,7- bis (4-hydroxy-3-methoxyphenyl) -1,6-heptadiene-3,5-dione] / Curcumin	_	Matos et al. (2019)

Pereira et al. (2010), isolated the compound Cyanolide-A from cyanobacteria of the *Lyngbya bouillonii* species belonging to the Oscillatoriaceae family. This isolated compound was used to test molluscicidal activity against the species *B. glabrata*. Cyanolide-A was exposed to the mollusc in a 24-hour period and it can be analyzed that it proved to be very promising and effective, since the lethal concentration for 50% of the population was 1.2 µM (1.02 µg/mL). An advantage of this isolated compound is the ease of being solubilized in water, which contributes to the manipulation of this product in the control of population of these vectors.

Plants of the Piperaceae family have shown to be a promising source of secondary metabolites with different biological activities. A previous study was carried out, in which, it used the crude extract of the species *Piper tuberculatum*, in order to control the intermediate hosts responsible for completing the cycle of *schistosoma mansoni*. This crude extract showed molluscicidal activity against the species *B. glabrata*. Because of this, the compound Piplartine, belonging to the class of amides, was isolated through the roots of the species *P. tuberculatum*, in which, it is believed that this isolated compound is responsible for the antifungal, antiparasitic, antitumor activity found in the crude extract previously carried out. Ten adult mollusks with a shell diameter between 10-18 mm were used. These were exposed to Piplartin over a 24-hour period and assessed lethality for seven days. Compound alone caused 100% mortality after 24 hours and it was possible to obtain lethal concentrations 50 and 90, being 4.19 and 6.94 µg/mL, respectively (Rapado et al., 2013).

According to Rapado et al. (2014), some crude extracts from plants of the Piperaceae family proved to be effective in controlling the mollusk intermediate hosts of schistosomiasis, due to this, a deeper investigation was initiated using the genus, *Piper*. From the crude extract of the leaves of *Piper diospyrifolium*, two compounds were isolated, Flavokawain A and Benzoic acid (4-hydroxy-3-(3,7,11- trimethyldodeca -2,5,10-trienyl)). Compound 2',4',6'-Trihydroxydihydrochalcone was isolated from *Piper cumanense* leaves, in which it was carried out through several purification steps based on silica gel chromatography. The fourth compound, Dihydroflavokawain C, was isolated from *Piper gaudichaudianum* leaves. These compounds belong to the class of flavanols, except 4-hydroxy-3-(3,7,11- trimethyldodeca 2,5,10-trienyl) / Benzoic acid.

The biological tests carried out by Rapado et al. (2014) were carried out according to the methodology by WHO/1983. In the bioassay ten adult mollusks with a shell diameter between 10-18 mm were used, and were exposed to the isolated compounds within 24 hours, being checked for seven days. It was possible to evaluate the lethal concentrations at 50% and 90%, according to the mortality rate of the molluscs. Flavokawain A demonstrated moderate activity in the snails *B. glabrata*, obtaining 21.85 µg/mL and 27.97 µg/mL at 50% and 90% lethal concentrations, respectively. The compound Dihydroflavokawain C did not show molluscicidal activity, so it was not possible to calculate lethal concentrations. The substance 4-hydroxy-3-(3,7,11- trimethyldodeca 2,5,10-trienyl) / Benzoic acid obtained a moderate molluscicidal activity, finding a 50% lethal concentration equal to 7.28 µg/mL and the 90% lethal concentration equal to 10.04 µg/mL. Among these isolated compounds, the most effective and promising substance was 2',4',6'-Trihydroxydihydrochalcone, in which it was possible to obtain 5.35 µg/mL and 6.47 µg/mL in lethal concentrations at 50% and 90%, respectively.

Santos et al. (2014) conducted trials with the species *Jatropha ellipticada* family Euphorbiaceae, a shrub distributed throughout the north and west of Brazil, has a wide variety of therapeutic properties. The diethyl compound 4-phenyl-2,6-dimethyl-3,5-pyridinodicarboxylate was isolated from the roots of the ethanolic extract of the plant. This substance makes up the class of alkaloids. The bioassay was carried out according to the protocol of Santos et al. (2014). Adult mollusks of the species *B. glabrata* with shell diameter between 19-25 mm were used. In the results, the alkaloid proved to be effective, obtaining a 50% lethal concentration close to 16.60 µg/mL and a 90% lethal concentration equal to 36.43 µg/mL in a 24-hour test period.

According to some studies carried out previously, it was reported that the lichen stalk has secondary metabolites, with the ecological purpose of controlling slugs and land mollusks. Because of this, the possibility of using an isolated compound to test the activity of *B. glabrata* molluscs was foreseen. Barbatic acid (BAR) was extracted from the species *Cladia aggregata*, of the family Lichen. Adult mollusks with a shell diameter between 10-14 mm were used in the bioassay. These mollusks were exposed to acid in the 24-hour period, and the lethality in the 96-hour period was verified. According to the results, it was possible to obtain a lethal concentration on 50% of adult molluscs, being equal to 11.90 µg/mL (Martins et al., 2017).

The lichens are a symbiotic association, and are distributed in the whole world, occupying a variety of habitats. A lot of studies have mentioned some biological information and lichens's secondary metabolites, as well, their antimicrobial, antioxidant, cytotoxic, antitumoral and their molluscicidal effect. Another important effect, the lichens are considered bioindicators of environment pollution. These are organized in different classes, as, depsides, dibenzofurans, anthraquinones and others. The divaricatic acid was isolated from the species *Ramalina aspera*, belonging to the family Ramalinaceae with the finality of testing the molluscicide from the species *B. glabrata.* Adults mollusks were used with diameter from the shell between 10-14 mm, and these were exposed to acid during a 24 hour period, and evaluated lethality on an eight-day period. In the evaluation molluscicide was possible to obtain the lethal concentration on 10%, 50% e 90%, being them, 1.68; 3.58 and 5.49 µg/mL, respectively (Silva et al., 2018, 2019).

Faria et al. (2018) tested the species *Manilkara subsericea* corresponding to the family Sapotaceae and widely distributed in the National Park of Jurubatiba's Restinga, RJ, in which develops an important environment paper for the local population. Some studies previously demonstrated that crude extracts and fractions have antibacterial, insecticide and antivenom activity. Dry leafs were used for the preparation of the crude extracts, fractionations and isolation of some substances. From the fractionation were isolated the myricetin, quercetin, classified as flavonoids, and ursolic acid, classified as triterpenoid.

The authors used fifteen mollusks from the species *B. glabrata* with the pattern size between 10-12 mm diameter. The mollusks were exposed to isolated substances in a period of 24 hours, 48 hours, 72 hours and 96 hours. In the methodology, were used 24 wells's plates, with 2 mL per well from the isolated substances and the controls, being the water negative control and DMSO 1% (dimethylsulfoxide) and the positive control, the synthetic substance niclosamide (Santos et al., 2017). Was done an analysis of the experiments performed with the isolated substances, in which, can be obtained a lethal concentrations of 50% from the populations used in the experiment, being 1.16 μg/mL for myricetin, 26.68 μg/mL for quercetin and 40.8 μg/mL for the ursolic acid.

The *Curcuma longa* L. from the family Zingibiraceae, popularly known as saffron, is very used in the folcloric medicine and culinary to treat a lot of diseases. Was performed the curcumin's isolation ([1,7- bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione]), one abundand compound polyphenolic curcuminoid taken from the C. L. L. rhizome, in which, has different biological activities described. According to Matos et al. (2019), the biological test was performed from this isolated compound, but this substance was commercially bought by Sigma-Aldrich, St. Louis USA. The bioassay was accomplished according to the norms of WHO, in which were used ten mollusks *B. glabrata* youth and adults, with the shell diameter of 2 mm and 15-18 mm, respectively. The youth and adult mollusks were exposed to the curcumin on a 24 hours period and verified after a seven-day period. The lethal concentration values exposed to the curcumin from the youths were 42.29 μg/mL and 308 μg/mL to LC_{50} and LC_{90}, respectively. The values from LC_{50} and LC_{90} to the adults were 87.69 μg/mL and 409.60 μg/mL, in this proper order.

4. Discussion

Plant – based molluscicides establish an efficient low-cost alternative on the schistosomiasis's control, although, are commercialized only organic molluscicides, that is, synthetic. The studies involving natural products with activity against mollusks have been each time more frequent in the last decades, for being a more accessible possibility and less aggressive to the environment (Cantanhede et al., 2010).

The WHO (1983) determines that a molluscicide based on extracts with vegetable origin shows mortality of 90% on the snail's population in the concentration of 100 mg/L in 48 hours. Otherwise, the molluscicide activity related to the isolated vegetable compound is recognized when it is used concentrations equal or superior to 20 mg/L (or equally, 20 μg/mL) in 24 hours, causing 90% of lethality on this population. According to the research done by our group, it can be observed on Table 2 that the bigger part of the papers related to isolated substances are found in accord to the values preconized by WHO. The chemical structures can be viewed in Table 1S.

Another essential point is the preoccupation with the isolated compounds' selectivity, being preferable to found isolated substances that don't reach non target organisms. Even though the natural molluscicides are decomposed by the biological agents, even being in conformity with the WHO's measure, these substances can present harm to other organisms that belong to the same habitat. In this scenario, it is very important to the realization of toxicity tests, which ones were made by some authors (Rapado et al., 2013; Faria et al., 2018; Martins et al., 2017; Pasi et al., 2009; Silva et al., 2018, 2019).

Some studies related to the molluscicide of natural products evaluation, that reached positive results with extracts or isolated compounds, propose that the toxic activity is possibly related to the presence of secondary metabolites, as: tannins, steroids, saponins, terpenoids, flavonoids, among others (Cantanhede et al., 2010).

The saponins, which are present in the majority of the plants, according to some studies, are the responsible substances for the molluscicide activity. Although various species show molluscicide bioactivity, many of these species do not meet at essential requirements defined by the World Organization of Health so that a plant could be used on a large scale as a molluscicide (Brasil, 2008). Consequently, the deepening of the substances' studies already described as potent molluscicides and the discovery of new substances have extreme interest and relevance for the scientific community and for the population.

Pasi et al. (2009), isolated six compounds, four of them belonging to the saponins' class, and the rest to the triterpenes' class, being them the 6α-hydroxy-hydagenic acid, Hederagenic acid, Leontoside A (akebosideStb), Kalopanax saponin A (α-hederin), saponin PG (sapindoside B) and dipsacoside B, of the species *C. ambrosioides* (Dipsacaceae). These compounds were tested against the mollusk from the species *B. glabrata*. All these isolated substances demonstrated molluscicide activity on the value recommended by WHO, but weren't done toxicity tests on other organisms with these possible promising substances.

Camara et al. (2008) analyzed the Lapachol effect in mollusks from the species *B. glabrata*. Were used on the bioassay adult mollusks with the shell's diameter between 9-16 mm, the experiment was analysed on the period of 24 hours. It was possible to obtain the lethal concentration on 50 and 90, being them, 28.3 μg/mL and 41.9 μg/mL, respectively. The lethal concentration value 90 above 20 ppm can be due to the big variation in the age of the animals used, but the value two times above the recommended by WHO brings caveats. The authors performed a toxicity experiment on the species *Artemia salina* with the finality of analysing the toxic effect from Lapachol in non target organisms. It was possible to obtain the lethal concentration 50, being equal to 97.3 μg/mL. Analysing the experiments of molluscicide activity with the toxicity test, it was possible to observe that the value found on the test with *A. salina* was only around two times superior to the concentration used in the experiment with *B. glabrata*. Comparing this paper with the one from

Table 2. Molluscicide Activity of Isolated Substances in *Biomphalaria glabrata*.

Isolated Substance	Experiment (Time)	Shell Diameter	Concentration (CL_{50})	Concentration (CL_{90})
Myricetin	96 hours	10-12 mm	1.16 μg/mL	-
Quercetin	96 hours	10-12 mm	26.68 μg/mL	-
Ursolic acid (semi-purified)	96 hours	10-12 mm	40.8 μg/mL	-
Flavokawain A	24 hours	10-18 mm	21.85 μg/mL	27.97 μg/mL
4-hidroxi-3- (3,7,11- trimetildodeca2,5,10-trienil) / Benzoic acid	24 hours	10-18 mm	7.28 μg/mL	10.04 μg/mL
2',4',6'-Trihydroxydihydrochalcone	24 hours	10-18 mm	5.35 μg/mL	6.47 μg/mL
Dihydro flavokawain C	24 hours	10-18 mm	No activity	No activity
Dietil 4-fenil-2,6-dimetil-3,5-piridinodicarboxilato	24 hours	19-25 mm	16.60 μg/mL	36.43 μg/mL
Barbatic acid	24 hours	10-14 mm	11.90 μg/mL	-
6α-hidroxi-hidagenic acid	24 hours	-	>50 μg/mL	-
Hederagênic acid	24 hours	-	>50 μg/mL	-
AkebosideStb / Leontoside A	24 hours	-	5.4 μg/mL	-
Kalopanax saponin A ou α-hederine	24 hours	-	6.2 μg/mL	-
Saponin PG ou sapindoside B	24 hours	-	12.8 μg/mL	-
Dipsacosíde B	24 hours	-	>50 μg/mL	-
Cianolíde A	24 hours	-	1.2 μg/mL	-
Divaricatic acid	24 hours	10-14 mm	3.58 μg/mL	5.49 μg/mL
13-acetoxy-20-O-angeloyl-12-deoxyphorbol	24 hours	8-10 mm	12.3 ng/mL	-
13-O-[N-(2-aminobenzoyl)] anthraniloyl-20-acetoxy-12-deoxyphorbol	24 hours	8-10 mm	13.8 ng/mL	-
13,20-O-dibezoyl-12- deoxyphorbol	24 hours	8-10 mm	25.5 ng/mL	-
13,20-O-diangeloyl-12-deoxyphorbol	24 hours	8-10 mm	24.5 ng/mL	-
13-O-angeloyl-20-O-[N-(2-aminobenzoyl)] anthraniloyl-12-deoxyphorbol	24 hours	8-10 mm	26.4 ng/mL	-
13- O-tigloyl-20-O-[N-(2-aminobenzoyl)] anthraniloyl-12-deoxyphorbol	24 hours	8-10 mm	25.8 ng/mL	-
13-O-benzoyl-20-O-[N- (2-aminobenzoyl)] anthraniloyl-12-deoxyphorbol	24 hours	8-10 mm	26.1 ng/mL	-
13-O-hexanoyl-20-O-[N-(2-aminobenzoyl)] anthraniloyl-12-deoxyphorbol	24 hours	8-10 mm	26.7 ng/mL	-
Piplartine	24 hours	10-18 mm	4.19 μg/mL	6.94 μg/mL
2- hidroxi-1,4-naftoquinone / Lapachol	24 hours	14-18 mm	2.57 μg/mL	6.18 μg/mL
[1,7- bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] / Curcumin	24 hours	Young (2 mm)	42.29 μg/mL	308 μg/mL
		Adult (15-18 mm)	87.69 μg/mL	409.60 μg/mL

B. glabrata, can be perceived that the Lapachol had an action modestly promising, showing activity inside the WHO's recommendation, therefore still are necessary toxicity tests in other non target organisms from freshwater and field experiments.

Among the natural naphthoquinones, lapachol stands out, which can be considered one of the main representatives of the quinone group, and has been found as a constituent of plants of the Bignoniaceae, Verbenaceae and Proteaceae families. Its occurrence is higher in the Bignoniaceae family, particularly in the *Tabebuia* genus (Silva et al., 2003). Quinones have varied biodynamics, among them, many have properties: microbicides, trypanosomicidal, viral, antitumor and inhibitory of cell repair systems, studies in which they vary in different ways (Silva et al., 2003).

Rapado et al. (2013) isolated Piplartin from the roots of *P. tuberculatum* to evaluate the molluscicide activity on the species *B. glabrata.* It was possible to obtain 4.19 μg/mL on the lethal concentration 50 and 6.94 μg/mL on the lethal concentration 90. According to the Piplartin's efficiency in mollusks from the species *B. glabrata,* was performed in mollusks from the species *B. glabrata,* was performed acute toxicity test on microcrustaceans and on fishes, from the species *Daphnia similis* e *Danio rerio,* respectively. It was possible to obtain lethal concentrations 50 on the 24 hours period, being 7.84 µg/mL to *D. similis* and 2.0 µg/mL to *D. rerio*. It was also possible to analyse on the acute toxicity test some abnormalities during the experiment with *D. rerio,* as irregular natation, corporal hemorrhage, red pigmented spots, abnormal head shape, among other irregularities. In conformity with the obtained results, it can be concluded that the Piplartin was almost five times more toxic to *D. rerio* than to *D. similis*. In short, the Piplartin isn't indicated to the studies' continuity.

According to the World Health Organization (WHO, 2019), laboratory screening for molluscicides should be performed by testing adult molluscs and their eggs, but does not determine the shell size of this adult mollusc. However, many authors in their work use shells of very different sizes within the same test group, and we know that the variation in the body mass of these animals can influence the tests, since individuals with lower mass are potentially more susceptible, given that the lower capacity of these animals' defense mechanisms (such as mucus secretion and metabolism). This guideline also indicates that, in molluscicidal tests, mortality should be evaluated after 24 hours of exposure plus 24 to 72 hours of recovery of the animal. In this way, we signal again the importance of respecting the standardization indicated by the WHO.

Among the papers above mentioned, it can be observed that of the twenty-eight substances studied, nineteen are promising, being in agreement or close to the recommended by the World Health Organization (WHO, 1983). According to Table 3, it was possible to analyze that many papers use the lethal concentration 50, due to this, was used this concentration to compare the isolated substances with the recommended values by WHO, although the same express

Table 3. Promising Isolated Substances.

Isolated Substance	Experiment (Time)	Concentration (CL_{50})	Concentration (CL_{90})	Toxicity Test
Myricetin	96 hours	1.16 µg/mL	-	-
4-hidroxi-3- (3,7,11- trimetildodeca2,5,10-trienil) / Benzoic acid	24 hours	7.28 µg/mL	10.04 µg/mL	-
2',4',6'-Trihydroxydihydrochalcone	24 hours	5.35 µg/mL	6.47 µg/mL	-
Barbátic acid	24 hours	11.90 µg/mL	-	*Artemia salina* 100 µg/mL
AkebosideStb / Leontoside A	24 hours	5.4 µg/mL	-	-
Kalopanax saponin A ou α-hederin	24 hours	6.2 µg/mL	-	-
Saponin PG ou sapindoside B	24 hours	12.8 µg/mL	-	-
Cianolídeo A	24 hours	1.02 µg/mL	-	-
Divaricatic acid	24 hours	3.58 µg/mL	5.49 µg/mL	*Artemia salina* >400 µg/mL
13-acetoxy-20-O-angeloyl-12-deoxyphorbol	24 hours	12.3 ng/mL	-	-
13-O-[N-(2-aminobenzoyl)] anthraniloyl-20-acetoxy-12-deoxyphorbol	24 hours	13.8 ng/mL	-	-
13,20-O-dibezoyl-12- deoxyphorbol	24 hours	25.5 ng/mL	-	-
13,20-O-diangeloyl-12-deoxyphorbol	24 hours	24.5 ng/mL	-	-
13-O-angeloyl-20-O-[N-(2-aminobenzoyl)] anthraniloyl-12-deoxyphorbol	24 hours	26.4 ng/mL	-	-
13- O-tigloyl-20-O-[N-(2-aminobenzoyl)] anthraniloyl-12-deoxyphorbol	24 hours	25.8 ng/mL	-	-
13-O-benzoyl-20-O-[N- (2-aminobenzoyl)] anthraniloyl-12-deoxyphorbol	24 hours	26.1 ng/mL	-	-
13-O-hexanoyl-20-O-[N-(2-aminobenzoyl)] anthraniloyl-12-deoxyphorbol	24 hours	26.7 ng/mL	-	-
Piplartine	24 hours	4.19 µg/mL	6.94 µg/mL	*Daphnia similis* CL_{50} 7.32 µg/mL *Danio rerio* CL_{50} 1.69 µg/mL *Artemia salina* CL_{50} 32.3 µg/mL
2- hidroxi-1,4-naftoquinone / Lapachol	24 hours	2.57 µg/mL	6.18 µg/mL	*Artemia salina* CL_{50} 97.3 µg/mL

Table 4. Isolated Substances according to World Health Organizaion (WHO).

Isolated Substances	Experiment (time)	Concentration (CL_{50})	Concentration (CL_{90})	Toxicity test
4-hidroxi-3- (3,7,11- trimetildodeca2,5,10-trienil) / Benzoic acid	24 hours	7.28 µg/mL	10.04 µg/mL	-
2',4',6'-Trihydroxydihydrochalcone	24 hours	5.35 µg/mL	6.47 µg/mL	-
Divaricatic acid	24 hours	3.58 µg/mL	5.49 µg/mL	*Artemia salina* > 400 µg/mL
Piplartine	24 hours	4.19 µg/mL	6.94 µg/mL	*Daphnia similis* CL_{50} 7.32 µg/mL *Danio rerio* CL_{50} 1.69 µg/mL *Artemia salina* CL_{50} 32.3 µg/mL
2- hidroxi-1,4-naftoquinone / Lapachol	24 hours	2.57 µg/mL	6.18 µg/mL	*Artemia salina* CL_{50} 97.3 µg/mL

that the lethal concentration 90 of the isolated substances must be equal on inferior to 20 mg/L (or, equally, 20 µg/mL). From nineteen promising substances presents on Table 3, the toxicity test was performed only in four of the substances, in which were used *Artemia salina*, *Daphnia similis* or *Danio rerio.* In this way, it is suggested that be performed toxicity tests on the fifteen more isolated substances in toxicity models as the ones cited previously.

If we analyze only the isolated substances that answer the preconized by WHO as LC_{90} equal or smaller than 20 µg/mL and the exposure time until 48 hours, we can verify on Table 4, that from the nineteen promising isolated, only five would be according to WHO. We verified still that fourteen promising remaining are virtually out of the recommended by WHO, only for not having in their publications the values of LC_{90} demanded and/or in the suitable time. We also saw that many don't perform toxicity test and don't follow a pattern to the same; and when performed toxicity test, those are exposed only in $LC_{50,}$ making difficult a comparison with LC_{90} demanded by WHO.

5. Conclusion

In the present study, it was possible to observe that there are still few studies involving isolated substances until the moment: of the 12 selected articles, 28 isolated substances were described, being 27 with molluscicide activity and 19 promising molecules with lethal concentration below 20 µg/mL. From this promising isolated, only 5 isolated had LC_{90} calculated and inside the value recommended by WHO: Benzoic acid, 2',4',6'-Trihydroxydihydrochalcone, Divaricatic acid, Piplartine and 2-hydroxy-1,4-naphthoquinone (Lapachol). Inside the studied substances, a big part didn't realize the acute toxicity test on other organisms, and many showed results only in LC_{50}, not showing the LC_{90} required by WHO, even molecules with result on small concentrations. Like this, we conclude that beyond few results in the area, the researches don't follow the methodological pattern (exposure time and measure units, toxicity test), in this way, as they don't follow a pattern on the result's exposure (LC), not following, in sum, the recommended by WHO.

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Supplementary Material

Supplementary material accompanies this paper.
Table 1S: presentation of molecules of isolated substances
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