



Molluscicides against the snail-intermediate host of *Schistosoma*: a review

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Abstract

Schistosomiasis, a neglected tropical disease (NTD), is one of the most prevalent parasitoses in the World. Certain freshwater snail species are the intermediate host in the life cycle of schistosome species. Controlling snails employing molluscicides is an effective, quick, and convenient intervention strategy to prevent the spread of *Schistosoma* species in endemic regions. Advances have been made in developing both synthetic molluscicides and molluscicides derived from plants. However, at present, the development of molluscicides is not adapted to the actual demand for snails and schistosoma controlling. We undertake a systematic review of exploitation and application of synthetic molluscicides and molluscicides derived from plants to combat intermediate host snails. The detailed molluscicidal activity, structure–activity relationship, structural feature, and possible mechanism of some molluscicides are also highlighted, which may afford an important reference for the design of new, more effective molluscicides with low environmental impact and realize the aim of controlling schistosome at transmission stages.

Keywords Molluscicides · *Schistosoma* · Snails · Molluscicidal activity · Mechanism

Introduction

Schistosomiasis, a neglected tropical disease (NTD), is one of the most important infectious parasitoses of humans and animals in the tropical and subtropical regions (Njoroge et al. 2014; Thétiot-Laurent et al. 2013). It is estimated that schistosomiasis could affect more than 200 million people in approximately 70 countries (WHO (World Health Organization) 2021, 2020). About 700 million people live in endemic area (Colley et al. 2014). Six species of the genus *Schistosoma* including *S. japonicum*, *S. mansoni*, *S. haematobium*, *S. mekongi*, *S. malayensis*, and *S. intercalatum* can cause disease in people (Gryseels et al. 2006). The life cycle of the

parasite is complex with an intermediate host (*Oncomelania* snails), definitive host (humans and mammals), and seven lifecycle stages involving the adult worm, egg, miracidium, mother sporocyst, daughter sporocyst, cercariae, and schistosomulum (Colley et al. 2014; Guo et al. 2008, 2015). It is a great challenge to control schistosomiasis in undeveloped regions because of financial burden and environmental pressures. The current strategies for schistosomiasis control mainly rely on snail control, drug treatment (such as Praziquantel), advanced sanitation, and health education (Limpanont et al. 2020). Although the present method for the control of schistosomiasis is largely based on drug treatment, snail control using molluscicides still plays a crucial role (de Souza 1995; Yuan et al. 2005; Wang et al. 2009).

There are three major species of snails acting as the intermediate hosts: *Oncomelania hupensis* (*O. hupensis*) for *S. japonicum*, *Biomphalaria* species for *S. mansoni*, and *Bulinus* species for *S. haematobium* (Sturrock 1995). At present, three main strategies including biological control, ecological control, and molluscicidal control have been carried out for the control of schistosome snails (Lardans and Dissous 1998; McCullough et al. 1980). For biological control, some natural predators of snails such as aquatic birds, turtles, fish, crayfish, and insects have been considered as well as

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competitor snails (Madsen 1990; Ohmae et al. 2003; Pointier and Jourdan 2000; Li et al. 2016). Furthermore, some small creatures such as trematodes, leeches, nematodes, rotifers, and ostracods can attack or devour the snails (Younes et al. 2017). However, the above biological control experiments were often investigated in the laboratory; further field studies are essential in evaluating the control of the snails. The ecological control is also a useful approach including advanced sanitation, agricultural and hydrological exploitation and management (Dong et al. 2018; Liang et al. 2018). However, the potential risk factors are negligible including the limited natural resources, extreme climate changes, and severe financial burden (Lo et al. 2018).

Up to now, the application of molluscicides is the most effective intervention strategy for the control of snails in endemic regions (King et al. 2015). For example, chemical treatment using molluscicides was performed in an area of 78,308.26 hectare in China, and environmental improvements were only carried out in an area of 4738.37 hectare in 2018 (Zhang et al. 2019). Great efforts have been made to explore all kinds of molluscicidal substances including chemical and plant molluscicides (Perrett and Whitfield 1996; de Paula-Andrade et al. 2019). Herein, we undertake a systematic review of molluscicides, and their detailed molluscicidal activity, structure–activity relationship, and possible mechanism of some molluscicides are also highlighted.

Development of chemical molluscicides

Inorganic salts

Copper sulfate (CuSO_4)

Copper sulfate (compound 1, Table 1, Tab. S1, see [Supplementary materials](#)) was evaluated as molluscicides to combat *B. alexandrina* snails in Egypt (Hoffman and Zakhary 1953). The mortality of snails could reach 100% within 2 weeks at 0.25 ppm. Copper sulfate is an inexpensive inorganic salt. However, the toxicity of the molluscicides on non-target organisms and secondary environmental pollution issues are not ignorable.

Calcium cyanamide

Calcium cyanamide (2, Table 1) was previously reported as an efficient molluscicide for *O. hupensis* and has low toxicity for fish and other aquatic animals (Wei et al. 2008). The mortality of snails was up to 100% after 2 days at 80 ppm in immersion experiments, which is not good for a molluscicide. In pesticide spraying experiments in the laboratory, the mortality of snails was also 100% after 1 day with the concentration of 30 g/m². While in natural field conditions, the

mortality of snails was 97.18% at 50 ppm. In the field spraying experiments, the mortalities of snails were 81.11% and 96.03% in the concentrations of 30 and 50 g/m² in 15 days, respectively (Wei et al. 2008). Calcium cyanamides exhibited low toxicity to other aquatic animals at the effective concentration. Further molluscicidal mechanism investigation showed that calcium cyanamide could damage epithelial cells, hepatocytes, and muscle cells of snails (Xia et al. 2010). However, for calcium cyanamide, the toxicological explorations are worth of further investigation for practical applications.

Organic molluscicides




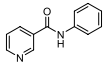

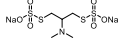
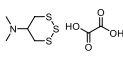
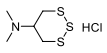

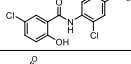
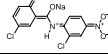
Sodium 2,3,4,5,6-pentachlorophenolate (NaPCP) and its derivatives

Sodium 2,3,4,5,6-pentachlorophenolate (3, Table 1) was found to have molluscicidal activity (LC_{50} = 0.54 ppm, LC_{100} = 2.0 ppm, 48 h) in immersion experiments (Moon et al. 1958; Zhang et al. 2006). In field experiments, NaPCP was effective at dosages of 10–20 ppm (immersion method) and 5–10 g/m² (spraying method). Furthermore, NaPCP could kill snail eggs, young snails, and adult snails (Zhang et al. 2006). However, NaPCP has toxicity against fish, aquatic animals, and mammals, along with the risk of teratogenicity, carcinogenesis, and mutagenicity (Xi et al. 2016). In addition, the technical products of NaPCP often contain highly toxic tetrachloro dibenzodioxines and dibenzofuranes, and that these agents can also arise from light exposure or heat (fire) of pentachlorophenol-contaminated objects. Subsequently, the molluscicidal activity of sodium 2,5-dichloro-4-bromophenol (4, Table 1) was explored for the control of *O. nasophora* in immersion experiments (Kajihara et al. 1979). The LC_{50} and LC_{90} values of sodium 2,5-dichloro-4-bromophenol were 0.54 ppm and 1.59 ppm. Additionally, this compound showed lower toxicity than NaPCP for carp, rainbow trout, and killifish.

N-Bromoacetamide and its derivatives

N-Bromoacetamide (5, Table 1) exhibited molluscicidal activity against adult snails, young snails, and snail eggs, and low toxicity to fish (Zhu et al. 1984). The LC_{50} and LC_{90} values were 0.64 ppm and 1.0 ppm in immersion experiments in 24 h, respectively. The mortality of snails exceeded 80% after 7 days at a surface concentration of 1 g/m² in spraying tests (Zhu et al. 1984). In particular, N-bromoacetamide has the advantages of low-dosage, good solubility in water, low toxicity and non-mutagenicity, which may be an ideal molluscicidal candidate. Nicotinilide (6, Table 1) was also found to have the same molluscicidal activity as N-bromoacetamide (Sukumaran

Table 1 The chemical structure and molluscicidal activity of molluscicides

No	Chemical structure	Derivatives	Molluscicidal activity (ppm)				Species, stage (exp. Time)	Reference
			LC ₅₀	LC ₉₀	LC ₁₀₀	morality		
1	<chem>CuSO4</chem>				0.2 5		<i>B. alexandrina</i> snails (14 d)	Hoffman and Zakhary, 1953
2	<chem>CaNCN</chem>				80		<i>O. hupensis</i> (48 h)	Wei et al., 2008
3			0.54		2.0		<i>O. hupensis</i> (48 h)	Moon et al., 1958; Zhang et al., 2006
4			0.54	1.59			<i>O. nasophora</i> (48 h)	Kajihara et al., 1979
5			0.64	1.0			<i>O. hupensis</i> (24 h)	Zhu et al., 1984
6			0.23				<i>Lymnaea luteola</i> , immature snails (24 h)	Sukumaran et al., 2004
			0.77				<i>Lymnaea luteola</i> , young mature snails (24 h)	
			0.59				<i>Lymnaea luteola</i> , adult snails (24 h)	
7				10			<i>O. hupensis</i> (3 d)	Xu et al., 2003
8			48				<i>O. hupensis</i> (24 h)	Xi et al., 2000
9						82% at 25 ppm	<i>O. hupensis</i> (24 h)	Wu et al., 1998
10						80% at 1-2 g/m ²	<i>O. hupensis</i> (24 h)	Dai et al., 2001
11			44.4				<i>O. hupensis</i> (24 h)	Zhu et al., 2006
12			0.2	0.6	1			Gonnert, 1961
13					0.4		<i>O. hupensis</i> (24 h)	Yuan et al., 2011

et al. 2004). The LC₅₀ values of nicotinanilide against different stages of snails were 0.23 ppm (immature snails), 0.77 ppm (young mature snails), and 0.59 ppm (adult snails) in 24 h, respectively. In field immersion experiments, nicotinanilide could kill 95% of the snails at the concentration of 1–2 ppm in 3 days. Nicotinanilide was

also harmless to humans, animals, fish, and plant (Sukumaran et al. 2004). Disadvantages include strong irritation to human skin, low toxicity to snail eggs, and high cost, which seriously restrict the large-scale application of the molluscicide.

Table 1 (continued)

14			0.261	0.370			<i>B. glabrata</i> (24 h)	Wang et al., 2016;
			0.172	0.325			<i>B. straminea</i> (24 h)	He et al., 2017
			0.241	0.334			<i>B. pfeifferi</i> (24 h)	
15		15a: R ¹ = H, R ² = Cl;			1		<i>B. alexandrina</i> (24 h)	Nabih and Metri, 1973 Nabih and Metri, 1973
		15b: R ¹ = NO ₂ , R ² = Cl;			1			
16					1			
17					1			
18						80% at 2 ppm		
19		19a: R = Cl				80% at 5 ppm	<i>B. alexandrina</i> (24 h)	Nawwar et al., 1994
		19b: R = CH=CHNO ₂						
20		20a: R = Cl			1		<i>B. alexandrina</i> (24 h)	Nawwar, 1994a
		20b: R = CH=CHNO ₂				20% at 1 ppm		
21			0.05	0.21			<i>B. straminea</i> snail eggs (24 h)	Wang et al., 2018
			0.50	0.98			<i>B. straminea</i> adult snails (24 h)	
22			0.09	0.39			<i>B. straminea</i> snail eggs (24 h)	
			0.51	0.78			<i>B. straminea</i> adult snails (24 h)	
23			1.8				<i>B. glabrata</i> (24 h)	de Abreu et al., 2001
24		24a: R = OH	8.2					
		24b: R = NHHNH ₂	0.7					

Dipterex

Dipterex (7, Table 1) is an important organic phosphorous pesticide. Dipterex displayed promising molluscicidal

activity, and the mortality of snails was 96% at 10 ppm in 3 days (Xu et al. 2003). After treatment, the head and foot of snails were paralyzed, and snails began to die out slowly.

Table 1 (continued)

25			7.6					
26			6.4					
27		27a: R = H	8.5				<i>B. glabrata</i> (24 h)	Bond et al., 1969
		27b: R = 2,4-Cl ₂	12					
		27c: R = <i>p</i> -NHCOCH ₃	8.5					
		27d: R = <i>p</i> -OCH ₃	22					
28			1.3					
29			8.89	16.82			<i>Bulinus truncatus</i> (24 h)	Lahlou et al., 2004
30			3.60	4.47				
31			7.71	14.14				
32		32a: R ¹ = H, R ² = OH, R ³ = H, R ⁴ = H, R ⁵ = OCH ₃ , R ⁶ = H,				12.5% at 10 ppm	<i>B. glabrata</i> (24 h)	Adewunmi et al., 1987
		32b: R ¹ = OCH ₃ , R ² = OCH ₃ , R ³ = OCH ₃ , R ⁴ = H, R ⁵ = H, R ⁶ = H,				81.3% at 10 ppm		
		32c: R ¹ = OH, R ² = OH, R ³ = H, R ⁴ = OCH ₃ , R ⁵ = OCH ₃ , R ⁶ = H,			10			
		32d: R ¹ = ONa, R ² = ONa, R ³ = H, R ⁴ = OCH ₃ , R ⁵ = OCH ₃ , R ⁶ = H			10			
		32e: R ¹ = OH, R ² = OCH ₃ , R ³ = H, R ⁴ = OCH ₃ , R ⁵ = OCH ₃ , R ⁶ = H			10			
		32f: R ¹ = OCH ₃ , R ² = OCH ₃ , R ³ = H, R ⁴ = OCH ₃ , R ⁵ = OCH ₃ , R ⁶ = H				37.5% at 10 ppm		
		32g: R ¹ = H, R ² = OH, R ³ = H, R ⁴ = OCH ₃ , R ⁵ = OCH ₃ , R ⁶ = OCH ₃				20% at 10 ppm		
		32h: R ¹ = OH, R ² = OH, R ³ = H, R ⁴ = OCH ₃ , R ⁵ = OCH ₃ , R ⁶ = OCH ₃			10			

Nereistoxin pesticides

Nereistoxin pesticides are important bionic pesticides derived from nereistoxin. These compounds have attracted more attention because of their low toxicity and residue to fish and aquatic animals. The representative nereistoxin

pesticides are bisultap (**8**, Table 1), thiocyclam hydrogen oxalate (**9**, Table 1), and trithialan (**10**, Table 1) (Wu 2007). The LC₅₀ of bisultap **8** was 48 ppm in 24 h. Mortality among snails reached 100% at 20 ppm in 72 h in immersion tests (Xi et al. 2000). For bisultap **8**, the mortality of snails was up to 100% in spraying experiments

Table 1 (continued)

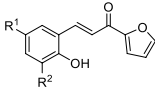
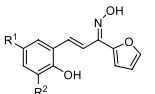
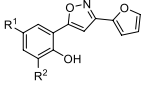
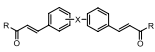
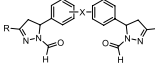
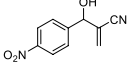
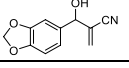
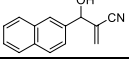
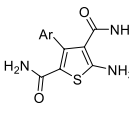
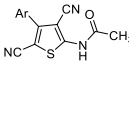
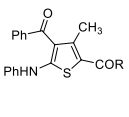
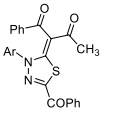
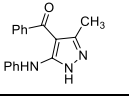
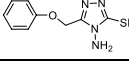
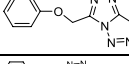
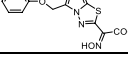
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		32j: $R^1 = \text{OCH}_3$, $R^2 = \text{OCH}_3$, $R^3 = \text{H}$, $R^4 = \text{H}$, $R^5 = \text{N}^+(\text{CH}_3)_2\text{Cl}$, $R^6 = \text{H}$,			10		
33		33a: $R^1 = R^2 = \text{H}$				20% at 2 ppm	Nawwar et al., 1993
		33b: $R^1 = R^2 = \text{Cl}$				30% at 2 ppm	
		33c: $R^1 = \text{Br}$, $R^2 = \text{H}$				20% at 2 ppm	
34		34a: $R^1 = R^2 = \text{H}$				30% at 2 ppm	
		34b: $R^1 = R^2 = \text{Cl}$			2		
		34c: $R^1 = \text{Br}$, $R^2 = \text{H}$				70% at 2 ppm	
35		35a: $R^1 = R^2 = \text{H}$				230% at 2 ppm	
		35b: $R^1 = R^2 = \text{Cl}$				60% at 2 ppm	
		35c: $R^1 = \text{Br}$, $R^2 = \text{H}$				70% at 2 ppm	
36		36a: $X = 2\text{-O}(\text{CH}_2)_2\text{O-2}'$, $R = \text{Ph}$				20% at 20 ppm	Barsoum et al., 2006
		36b: $X = 2\text{-O}(\text{CH}_2)_2\text{O-2}'$, $R = 4\text{-ClC}_6\text{H}_4$;				30% at 20 ppm	
		36c: $X = 2\text{-O}(\text{CH}_2)_2\text{O-2}'$, $R = 4\text{-FC}_6\text{H}_4$				10% at 20 ppm	
		36d: $X = 2\text{-O}(\text{CH}_2)_2\text{O-2}'$, $R = 4\text{-CH}_3\text{C}_6\text{H}_4$				0% at 20 ppm	
		36e: $X = 2\text{-O}(\text{CH}_2)_2\text{O-2}'$, $R = 2\text{-thienyl}$				10% at 20 ppm	
		36f: $X = 4\text{-O}(\text{CH}_2)_2\text{O-4}'$, $R = \text{Ph}$				20% at 20 ppm	
		36g: $X = 4\text{-O}(\text{CH}_2)_2\text{O-4}'$, $R = 4\text{-ClC}_6\text{H}_4$				0% at 20 ppm	
		36h: $X = 4\text{-O}(\text{CH}_2)_2\text{O-4}'$, $R = 4\text{-CH}_3\text{C}_6\text{H}_4$				0% at 20 ppm	
37		37a: $X = 2\text{-O}(\text{CH}_2)_2\text{O-2}'$, $R = \text{Ph}$				30% at 20 ppm	
		37b: $X = 2\text{-O}(\text{CH}_2)_2\text{O-2}'$, $R = 4\text{-ClC}_6\text{H}_4$;				20% at 20 ppm	
		37c: $X = 2\text{-O}(\text{CH}_2)_2\text{O-2}'$,				50% at 20 ppm	

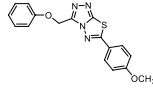
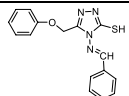
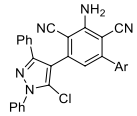
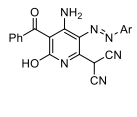
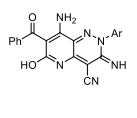
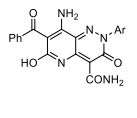
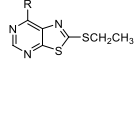
Table 1 (continued)

		R = 4-FC ₆ H ₄				ppm		
		37d : X = 2-O(CH ₂) ₂ O-2', R = 4-CH ₃ C ₆ H ₄				10% at 20 ppm		
		37e : X = 2-O(CH ₂) ₂ O-2', R = 2-thienyl				20% at 20 ppm		
		37f : X = 4-O(CH ₂) ₂ O-4', R = Ph				40% at 20 ppm		
		37g : X = 4-O(CH ₂) ₂ O-4', R = 4-ClC ₆ H ₄				30% at 20 ppm		
		37h : X = 4-O(CH ₂) ₂ O-4', R = 4-CH ₃ C ₆ H ₄				0% at 20 ppm		
38			6.64	9.23			<i>B. glabrata</i> (24 h)	Vasconcellos et al., 2006
39			7.30	10.64				
40			17.1	22.7				
41		41a : Ar = 4-ClC ₆ H ₄	0.6043				<i>Indoplanorbis exustus</i> (24 h)	Kanawade et al., 2011
		41b : Ar = 3,5-(CF ₃) ₂ C ₆ H ₃	0.7506					
		41c : Ar = 2,4-F ₂ C ₆ H ₃	0.6067					
42		42a : Ar = 4-ClC ₆ H ₄	0.6511					
		42b : Ar = 3,5-(CF ₃) ₂ C ₆ H ₃	0.7403					
		42c : Ar = 2,4-F ₂ C ₆ H ₃	0.7628					
43		43a : R = Ph	15.6	20			<i>B. alexandrina</i> (24 h)	Fadda et al., 2009
		43b : R = OH	19	23				
		43c : R = OEt	18	20				
		43d : R = CH ₃	16	22				
44		44a : Ar = Ph	8	10				
		44b : Ar = <i>p</i> -CH ₃ -C ₆ H ₄	5.5	9				
		44c : Ar = <i>p</i> -CH ₃ O-C ₆ H ₄ Ph	6	11				
45			13	18				
46					10		<i>B. alexandrina</i> (24 h)	El Shehry et al., 2010
47					10			
48						80% at 10 ppm		

at a surface concentration of 10 g/m² in 24 h (Xi et al. 2000). Thiocyclam hydrogen oxalate **9** also displayed the high molluscicidal activity, and the mortality of snails exceeded 82% in immersion experiments (25 ppm) and spraying experiments (2.5–5 g/m²) in 24 h (Wu et al. 1998). Trithialan (**10**) had molluscicidal activity at the

surface concentration of 1–2 g/m² in 3 days, and the mortality of snails exceeded 80% in field experiments (Dai et al. 2001). The structural relationships of nereistoxin pesticides showed that the cyclic compounds **9** and **10** have stronger molluscicidal activities than compound **8**, and compound **10** has excellent activities in the condition

Table 1 (continued)

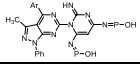
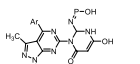
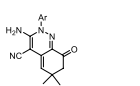
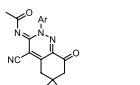
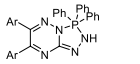
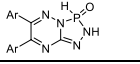
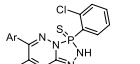
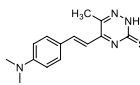
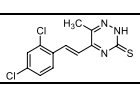
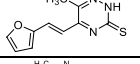
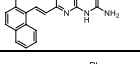
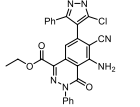
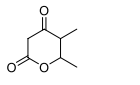
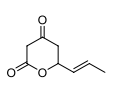
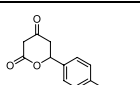
49						70% at 10 ppm		
50						30% at 10 ppm		
51		51a: Ar = 2-thienyl	13	>15			B. alexandrina (24 h)	Abdelraze k et al., 2006
		51b: Ar = 4-CH ₃ C ₆ H ₄	13	14				
		51c: Ar = 4-ClC ₆ H ₄	12	>15				
		51d: Ar = C ₆ H ₅	11	>15				
52		52a: Ar = C ₆ H ₅				12	B. alexandrina (24 h)	Abdelraze k and Fathy, 2005
		52b: Ar = 4-ClC ₆ H ₄				8		
		52c: Ar = 4-CH ₃ C ₆ H ₄				>1 2		
		52d: Ar = 4-OCH ₃ C ₆ H ₄				>1 5		
		52e: Ar = 2-CNC ₆ H ₄				6		
53		53a: Ar = C ₆ H ₅				12		
		53b: Ar = 4-ClC ₆ H ₄				10		
		53c: Ar = 4-CH ₃ C ₆ H ₄				>1 5		
		53d: Ar = 4-OCH ₃ C ₆ H ₄				>1 5		
54		54a: Ar = C ₆ H ₅				15		
		54b: Ar = 4-ClC ₆ H ₄				10		
		54c: Ar = 4-CH ₃ C ₆ H ₄				>1 5		
		54d: Ar = 4-OCH ₃ C ₆ H ₄				>1 5		
55		55a: R = Cl				25	B. alexandrina (24 h)	El-Bayouk i and Basyouni, 1988
		55b: R = CH(CN) ₂	25					
		55c: R = CH(CN)CO ₂ Et				40% at 25 ppm		
		55d: R = NHCH ₃				25% at 25 ppm		
		55e: R = NHCH(CH ₃) ₂				0% at 25 ppm		
		55f: R = NHC ₅ H ₆				70% at 25 ppm		
		55g: R = NHC ₆ H ₄ OCH ₃ -p				60% at 25 ppm		

of high humidity and high temperature (Wu 2007). As a green molluscicide, trithialan **10** has the features of less pollution, good solubility in water, and convenient operation, which can also inhibit snails moving. However, the real molluscicidal activity of the above molluscicides was easily influenced by the surroundings.

Metaldehyde

Metaldehyde (**11**, Table 1) (the formulation of 40% water emulsion) exhibited good molluscicidal and climbing-inhibition activity against snails in laboratory and field experiments (Zhu et al. 2006). The LC₅₀ values of metaldehyde

Table 1 (continued)

		55h: R = NH-thiazolyl				25% at 25 ppm		
		55i: R = NHCH ₂ furyl			25			
56						30% at 50 ppm	<i>B. alexandrina</i>	Bakhotma et al., 2019
57						30% at 50 ppm		
58		58a: Ar = Ph	8	11			<i>B. alexandrina</i>	Abdelrazeek et al., 2006a
		58b: Ar = 4-Me-C ₆ H ₄	7	15				
		58c: Ar = 4-Cl-C ₆ H ₄	7	9				
59		59a: Ar = Ph	8	13			<i>B. alexandrina</i>	Ali et al., 2008
		59b: Ar = 4-Me-C ₆ H ₄	9	>15				
		59c: Ar = 4-Cl-C ₆ H ₄	7	9				
60						30% at 50 ppm	<i>B. alexandrina</i>	
61						20% at 50 ppm		
62						30% at 50 ppm		
63					50		<i>B. alexandrina</i>	Abdel-Rahman et al., 2003
64						20% at 50 ppm		
65						0% at 50 ppm		
66						30% at 50 ppm		
67			9	13			<i>B. alexandrina</i>	Abdelrazeek et al., 2006
68			62.599	96.954			<i>B. glabrata</i>	de Souza et al., 2004
69			23.031	40.262			egg masses	(96 h)
70		70a: R = H	24.700	39.399				

were 0.78 g/m² (in 24 h), 0.44 g/m² (in 48 h), and 0.46 g/m² (in 72 h) in spraying experiments, respectively. When

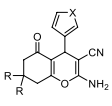
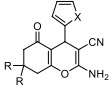
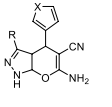
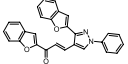
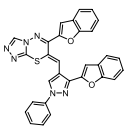
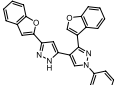
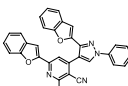
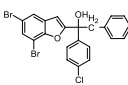
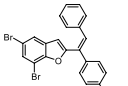
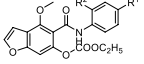
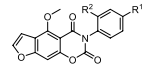
Table 1 (continued)

		70b: R = OCH ₃	45.030	54.924				
71			5.47	9.00			<i>Bulinus truncatus</i> (24 h)	Lahlou et al., 2004
72		X = -O-Glc-Rha	8.91	17.00				
73			>10	>10			<i>B. alexandrina</i> (24 h)	Abdelrazeek et al., 2007
74			8	>10				
75			4	6				
76		76a: R = H	7	>10				
		76b: R = CH ₃	4	7				
77			6	10				
78		78a: R = CH ₃	11	>15			<i>B. alexandrina</i> (24 h)	Abdelrazeek et al., 2006
		78b: R = Ph	13	>> 15				
79		79a: R = CH ₃	6	8				
		79b: R = Ph	13	>> 15				
80		80a: R = CH ₃	8	10				
		80b: R = Ph	14	>> 15				
81		81a: R = CN	13	>> 15				
		81b: R = COOC ₂ H ₅	15	>> 15				
		81c: R = CONH ₂	14	>> 15				
82		82a: R ¹ = R ² = CN	7	10				

snails were immersed in the solution of metaldehydes, the molluscicides also showed high activity (LC₅₀ = 44.4 ppm, 24 h; 27.4 ppm, 48 h; 24.8 ppm, 72 h, respectively). The

mortality of snails exceeded 90% after 7 days at 2 g/m² in spraying experiments.

Table 1 (continued)

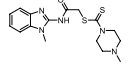
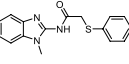
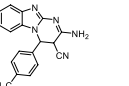
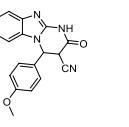
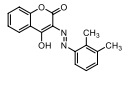
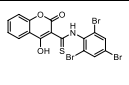
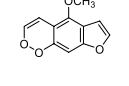
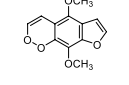
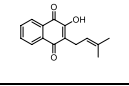
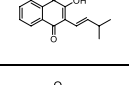
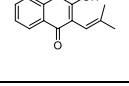
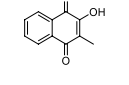
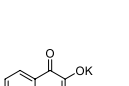
		82b : R ¹ = R ² = COOC ₂ H ₅	9	15				
83		83a : R = CH ₃ , X = O	5				<i>B. alexandrina</i> (24 h)	Abdelraze k et al., 2004
		83b : R = CH ₃ , X = S	10					
		83c : R = H, X = O	11					
		83d : R = H, X = S	>17					
84		84a : R = CH ₃ , X = O	8				<i>B. alexandrina</i> (24 h)	Abdelraze k et al., 2006a
		84b : R = CH ₃ , X = S	11					
		84c : R = H, X = O	12					
		84d : R = H, X = S	>17					
85		85a : R = Me, X = O	6	<7			<i>B. alexandrina</i> (24 h)	Abdelraze k et al., 2006a
		85b : R = Ph, X = O	8	14				
		85c : R = Me, X = S	10	10				
		85d : R = Ph, X = S	>15	>15				
86					10		<i>B. alexandrina</i> (24 h)	El Shehry et al., 2010
87				10				
88					70% at 10 ppm			
89					80% at 10 ppm			
90						56.67% at 5 ppm	<i>Lymnea acuminata</i> (24 h)	Giri and Mishra, 1984
91						41.67% at 5 ppm		
92		92a : R ¹ = Cl, R ² = H		2			<i>B. alexandrina</i> (24 h)	Hassan et al., 2006
		92b : R ¹ = Cl, R ² = Cl			2			
		92c : R ¹ = NO ₂ , R ² = Cl				60% at 2 ppm		
		92d : R ¹ = NO ₂ , R ² = H			2			
93							<i>B. alexandrina</i> (24 h)	Hassan et al., 2006

Nicosamide and its derivatives

Nicosamide (**12**, Table 1) (named Bayer-73) was reported for its molluscicidal activity (LC₅₀ = 0.2 ppm; LC₉₀ = 0.6 ppm; LC₁₀₀ = 1 ppm) by Gonnert and Schranfstatler at the sixth International Congress for Tropical

Medicine and Malaria 1959 (Gonnert 1961). Nicosamide displayed strong molluscicidal activity against different kinds of snails, and its LC₅₀ values for *B. glabrata*, *B. straminea*, and *B. pfeifferi* were 0.070 ppm, 0.049 ppm, and 0.076 ppm, respectively (He et al. 2017). Importantly, adult snails, young snails, and snail eggs are sensitive to

Table 1 (continued)

94			20	40			<i>B. alexandrina</i> (24 h)	Nofal et al., 2002
95			35	80				
96			45	70				
97			50	80				
98						58.33% at 5 ppm	<i>Lymnea acuminata</i> (24 h)	Giri and Mishra, 1984
99						68.33% at 5 ppm		
100						100% at 5 ppm; 69% at 2 ppm	<i>B. boissi</i> (24 h)	Schönberg and Latif, 1954
101						69% at 5 ppm; 9% at 2 ppm		
102			2.57	6.18			<i>B. alexandrina</i> (24 h)	dos Santos et al., 2000
103			1.53	4.30				
104			4.02	7.15				
105			5.19	18.46				
106			2.70	6.72			<i>B. alexandrina</i> (24 h)	dos Santos et al., 2001
			1.43	2.52			<i>B. alexandrina</i> snail eggs	

niclosamide (He et al. 2017). Now, niclosamide is the only molluscicide recommended by the World Health Organization (WHO) because of its high efficiency, low toxicity to mammals, and low concerns of pesticide residue (WHO (World Health Organization) 1993). However, niclosamide has the disadvantages of poor solubility in water,

high toxicity to fish and other non-target biota, which can induce upward climbing movement for snails.

To solve the solubility problem of niclosamide, 50% wetttable powder of niclosamide ethanolamine salt (WPN) has been prepared from niclosamide ethanolamine salts, fillers, dispersants, and wetting agents. Yang et al. tested

Table 1 (continued)

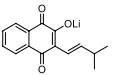
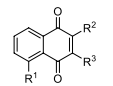
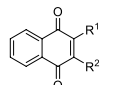
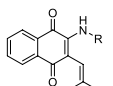
							(24 h)	
10 7		107a: R = CH ₂ CH(OCH ₃) ₂	66.9 μM	101.5 μM				
		107b: R = CH ₂ Ph	89.0 μM	/				
		107c: R = Ph	/	/				
10 8		108a: R = H	49.3 μM	72.1 μM			<i>B. glabrata</i> (24 h)	Silva et al., 2005
		108b: R = CH ₂ COOH	206.6 μM	330.1 μM				
		108c: R = CH ₂ CH ₂ OH	72.6 μM	102.8 μM				
		108d: R = CH ₂ CH(OCH ₃) ₂	54.9 μM	75.9 μM				
		108e: R = CH ₂ CH=CH ₂	23.8 μM	44.8 μM				
		108f: R = CH ₂ Ph	/	/				
		108g: R = CH ₂ CH ₂ CH ₂ CH ₃	13.8 μM	23.5 μM				
108h: R = CH ₂ CH ₂ Ph	45.2 μM	57.6 μM						
10 9			7.6 μM	12.5 μM				
11 0			3.05	4.71			<i>B. glabrata</i> (24 h)	Lima et al., 2002
			0.33	0.48			<i>B. glabrata</i> snail eggs (24 h)	
11 1		111a: R ¹ = H, R ² = CH ₂ CH ₂ CH(CH ₃) ₂	0.98	1.98			<i>B. glabrata</i> (24 h)	Lima et al., 2002a
		111b: R ¹ = Ac, R ² = CH ₂ CH=C(CH ₃) ₂	6.91	11.55				
		111c: R ¹ = Ac, R ² = CH=CHCH(CH ₃) ₂	1.66	3.08				
		111d: R ¹ = CH ₃ , R ² = CH ₂ CH=C(CH ₃) ₂	7.72	15.17				
		111e: R ¹ = H, R ² = CH ₂ N(CH ₃) ₂	3.82	16.67				
11 2			4.62	23.92			Lima et al., 2002a	

the field molluscicidal activity of WPN in the marshland of an island along the Yangtze River (Jiangsu province, P. R. China) (Yang et al. 2012). WPN was sprayed once, twice, thrice, and four times in three different types of regions including low-density, medium-density, and high-density snail groups. The mortality of snails increased with the

increasing times of molluscicide applications (Yang et al. 2010).

Although some surfactants were added into the WPN to form small suspended particles, however, the WPN formulation could be easily destroyed during transportation and storage, and formed large scales of niclosamide particles,

Table 1 (continued)

11 3			3.049	4.710			<i>B. glabrata</i> (24 h)	Ribeiro et al., 2009
11 4		114a: R ¹ = OH, R ² = H, R ³ = H	1.475	9.352				
		114b: R ¹ = OAc, R ² = H, R ³ = H	1.213	3.774				
		114c: R ¹ = OMe, R ² = H, R ³ = H	2.459	6.252				
		114d: R ¹ = OH, R ² = Br, R ³ = H	1.181	4.404				
		114e: R ¹ = OAc, R ² = Br, R ³ = H	0.948	2.205				
		114f: R ¹ = OMe, R ² = Br, R ³ = H	0.746	1.563				
		114g: R ¹ = OH, R ² = H, R ³ = Br	2.494	5.654				
		114h: R ¹ = OAc, R ² = H, R ³ = Br	0.893	1.659				
		114i: R ¹ = OMe, R ² = H, R ³ = Br	0.475	1.492				
		114j: R ¹ = H, R ² = CH ₃ , R ³ = H	2.998	4.481				
11 5		115a: R ¹ = OH; R ² = H	28.3	41.9			<i>B. glabrata</i> (24 h)	Camara et al., 2008
		115b: R ¹ = OCH ₃ ; R ² = H	10.2	17.0				
		115c: R ¹ = OCH ₃ ; R ² = Br	2.1	4.2				
		115d: R ¹ = R ² = Br	16.7	28.4				
		115e: R ¹ = N ₃ ; R ² = H	7.4	13.1				
		115f: R ¹ = NH ₂ ; R ² = H	20.0	29.9				
		115g: R ¹ = NHCH ₂ Ph; R ² = H	23.8	44.1				
		115h: R ¹ = NHCH ₂ CH ₂ NHCH ₂ Ph; R ² = H	64.3	92.7				
115i: R ¹ = NHCH ₂ CH=CH ₂ ; R ² = H	32.9	50.8						
11 6		116a: R = H	157.26 μM	208.50 μM			<i>B. glabrata</i> (24 h)	Barbosa et al., 2005
		116b: R = CH ₂ COOH	224.77 μM	305.75 μM				
		116c: R = CH ₂ CH ₂ OH	132.91 μM	176.71 μM				
		116d: R =	111.11	143.23				

resulting in poor dispersion performance in water. Therefore, 4% nicosamide ethanolamine salt dust powder (4% NESDP) was prepared from nicosamide ethanolamine salt, fillers, and auxiliaries. He et al. tested the molluscicidal activity of 4% NESDP and WPN in hilly areas (He et al. 2007). The molluscicidal activity of 4% NESDP was significantly

higher than that of WPN in the ditches without clearing away grasses after 3, 7, and 15 days. When the experiments were carried out in the slope lands, the activity of 4% NESDP was also significantly higher than that of WPN after 3, 7, and 15 days. Therefore, 4% NESDP should be more suitable for application in arid and semi-arid areas (He et al. 2007).

Table 1 (continued)

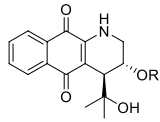
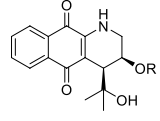
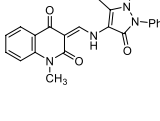
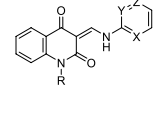
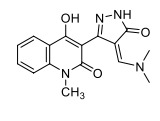
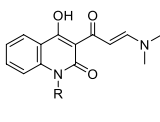
		$\text{CH}_2\text{CH}(\text{OCH}_3)_2$	μM	μM			
		116e: R = $\text{CH}_2\text{CH}=\text{CH}_2$	13.65 μM	28.85 μM			
		116f: R = CH_2Ph	113.05 μM	148.95 μM			
		116g: R = $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	23.07 μM	36.53 μM			
		116h: R = $\text{CH}_2\text{CH}_2\text{Ph}$	89.03 μM	135.95 μM			
11 7		117a: R = H	/	/			
		117b: R = CH_3	64.55 μM	89.63 μM			
11 8		118a: R = H	/	/			
		118b: R = CH_3	99.00 μM	164.18 μM			
11 9			28.14	46.83			<i>B. alexandrina</i> (24 h)
			19.31	29.96			<i>L. natalensis</i> (24 h)
12 0		120a: R = CH_3 , X = N, Y = CH, Z = CH	20.13	32.36			<i>B. alexandrina</i> (24 h)
			14.90	27.96			<i>L. natalensis</i> (24 h)
		120b: R = CH_3 , X = CH, Y = CH, Z = N					
12 1			66.21	121.20			<i>B. alexandrina</i> (24 h)
12 2		122a: R = CH_3	47.15	89.18			<i>B. alexandrina</i> (24 h)
			40.41	59.88			<i>L. natalensis</i> (24 h)
		122b: R = CH_2CH_3	20.20	29.00			<i>B. alexandrina</i> (24 h)
			19.01	53.03			<i>L. natalensis</i> (24 h)

Table 1 (continued)

		12c: R = CH ₂ CH ₂ CH ₂ CH ₃	15.88	34.40			<i>B. alexandrina</i> (24 h)	
			15.80	61.10			<i>L. natalensis</i> (24 h)	
12 3			5				<i>B. glabrata</i> (24 h)	Kujime et al., 1992
12 4			20					
12 5			3.9	4.8			<i>B. alexandrina</i> (24 h)	El Bardicy et al., 2012
12 6			1.3	2.2				
12 7			1.47	2.12				
12 8			1.74	2.64				
12 9			2.95	4.1				

Subsequently, a suspension concentrate of niclosamide (SCN) derived from a mixture of niclosamide, alkyl polyglycosides (APG-0810), glycerol, sodium carboxymethyl cellulose, sodium benzoate, and distilled water was explored by Dai et al. (Dai et al. 2008). The size of SCN ranged from 0.28 to 19.95 μm , and above 90% of which were less

than 10 μm . The content of niclosamide in SCN was about 25.44% (w/w). The immersion experimental results showed that for adult snails, the LC₅₀ values of SCN were 0.047 ppm (24 h), 0.041 ppm (48 h), and 0.041 ppm (72 h), respectively; and for young snails, the LC₅₀ values were 0.063 ppm (24 h), 0.047 ppm (48 h), and 0.044 ppm (72 h), respectively.

Table 1 (continued)

130			2.6	3.5				
131			0.63	0.91				
132		132a: R ¹ = Cl, R ² = H, R ³ = H	4.68	6.16			<i>O. hupensis</i> (24 h)	Guo et al., 2016
		132b: R ¹ = Cl, R ² = H, R ³ = CH ₃	4.07	5.37				
		132c: R ¹ = Cl, R ² = H, R ³ = OCH ₃	3.80	5.01				
		132d: R ¹ = NO ₂ , R ² = H, R ³ = H	7.07	9.33				
		132e: R ¹ = NO ₂ , R ² = H, R ³ = CH ₃	5.75	7.58				
		132f: R ¹ = R ² = Cl, R ³ = H	6.61	8.71				
		132g: R ¹ = R ² = Cl, R ³ = CH ₃	4.71	6.21				
		132h: R ¹ = R ² = Cl, R ³ = OCH ₃	10	13.18				
133		132i: R ¹ = R ² = Cl, R ³ = N(CH ₃) ₂	6.17	8.13				
		132j: R ¹ = R ² = Cl, R ³ = NO ₂	4.65	6.11				
		132k: R ¹ = Cl, R ² = H, R ³ = R ⁴ = CH ₃	4.36	5.75				
		132l: R ¹ = Cl, R ² = H, R ³ = R ⁴ = OCH ₃	3.78	4.97				
		132m: R ¹ = R ² = Cl, R ³ = R ⁴ = CH ₃	5.37	7.08				
133		132n: R ¹ = R ² = Cl, R ³ = R ⁴ = OCH ₃	6.55	8.62				
		132o: R ¹ = R ² = Cl, R ³ = NO ₂ , R ⁴ = OCH ₃	5.34	7.03				
133		132p: R ¹ = Cl, R ² = H, R ³ = OCH ₃	2.69	3.55				
		132q: R ¹ = NO ₂ , R ² = H, R ³ = OCH ₃	5.01	6.61				

The LC₅₀ values for adult and young snails in 24 h were both half that of WPN (Dai et al. 2008).

Additionally, for snail eggs, the LC₅₀ values of SCN were 0.051 ppm (24 h), 0.050 ppm (48 h), and 0.047 ppm (72 h), respectively; and the LC₅₀ values of WPN were 0.103 ppm (24 h), 0.096 ppm (48 h), and 0.087 ppm (72 h), respectively

(Dai et al. 2008). For SCN, in the laboratory spraying experiments, the mortalities of all tested groups were 100% at the surface concentration of 0.5 g/m². However, for WPN, the mortalities of snails (*O. hupensis*) were 60–100%, lower than that of SCN groups at the surface concentration of 1.0 g/m². In field immersion and spraying experiments, the

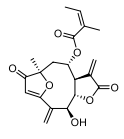
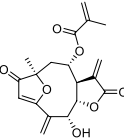
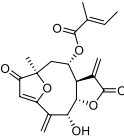
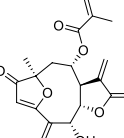
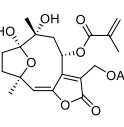
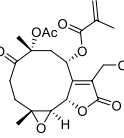
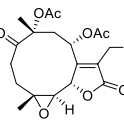

Table 1 (continued)

		132r: R ¹ = R ² = Cl, R ³ = OCH ₃	9.95	12.95				
13 2		132s: R ¹ = Cl, R ² = H	> 100	> 100				
13 2		132t: R ¹ = Cl, R ² = H	> 100	> 100				
13 3						10% at 25 ppm	<i>B. alexandrina</i> (24 h)	El-Sakka et al., 1994
13 4						50% at 25 ppm		
13 5						100% at 25 ppm		
13 6						70% at 25 ppm		
13 7						80% at 25 ppm		
13 8			56.48				<i>B. peregrina</i> (24 h)	
13 9			48.68					
14 0			88.25					

mortalities of snails for SCN were higher than that of WPN. When the snails were exposed in 0.5 ppm of SCN for 1, 2, and 3 days, the mortalities were 72%, 92%, and 100%, respectively, higher than that of WPN with a lethal concentration of 1.0 ppm. In field spraying test, for SCN with the concentration of 0.5 g/m², the mortalities of snails were

77~93% (3 days), 83~99% (7 days), and 74~99% (15 days), respectively. However, for WPN with the concentration of 1.0 g/m², the mortalities of snails were 58~70% (3 days), 64~91% (7 days), and 68~92% (15 days). The toxicity test showed that the acute toxicity of SCN was less than WPN. The novel formulation of SCN suspension is physically

Table 1 (continued)

14 1			27.99					
14 2			35.35					
14 3			50.13					
14 4			28.53					
14 5			68.48					
14 6			38.18					
14 7			78.70					
14 8		148a: R = H	13.92				B. <i>alexandrina</i> (24 h)	Radwan et al., 2008
		148b: R = CONHCH ₃	32.81					
14		149a: R = H	101.59					

more stable, more effective, and less toxic. Therefore, it can be more useful for controlling snails in endemic areas of schistosomiasis.

In order to reduce the amount of niclosamide, decrease the toxicity and environmental issues, and provide a convenient way for practical applications, developing novel

formulations of niclosamide is still a highly effective strategy for the control of snails (You et al. 2016). Huang's group explored the molluscicidal activity of 4% niclosamide ethanolamine salt powder-granula (PG) derived from niclosamide ethanolamine salt and additives (You et al. 2016). Compared with 4% NESDP, PG showed lower

Table 1 (continued)

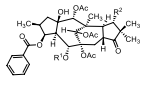
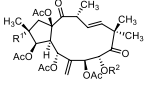
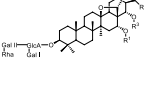
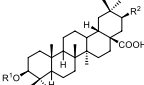
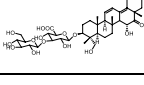
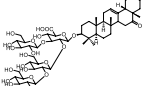
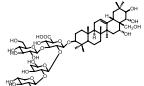
9		149b: R = CONHCH ₃	10.88						
150		150a: R = H	21.85						
		150b: R = CONHCH ₃	35.80						
151		151a: R = H	40.55						
		151b: R = CONHCH ₃	31.34						
152		152a: R = H	76.91						
		152b: R = CONHCH ₃	108.21						
153		153a: R = H	50.46						
		153b: R = CONHCH ₃	34.63						
154		154a: R = H	24.28						
		154b: R = CONHCH ₃	9.71						
155		155a: R = H	20.74						
		155b: R = CONHCH ₃	5.43						
156			1.16	8.91			<i>B. glabrata</i> (24 h)	Dos Santos and Sant'Ana, 1999	
			1.14	2.06			<i>B. glabrata</i> snail eggs (24 h)		
157			58.04	206.16			<i>B. glabrata</i> (24 h)		
158		158a: R = CH ₃ CO ₂					90% at 50 ppm	<i>B. alexandrina</i> (24 h)	Abdelgaleil et al., 2002
		158b: R = H					100% at 50 ppm		
159							40% at 50 ppm		

mortalities of the snails (*O. hupensis*) in laboratory test. However, in field experiments, for PG, the mortalities of snails were 91.71% (1 day) and 92.91% (3 days), which were higher than that of 4% NESDP with the mortalities of snails of 71.09% (1 day) and 90.11% (3 days). 4% PG

has the advantages of good adsorption and penetrability, which may be more suitable for field applications.

To solve the solubility of niclosamide, emulsifiable concentrate of 25% niclosamide (ECN) was further prepared from niclosamide, organic solvents, and emulsifiers (Dai et al. 2007). In immersion experiments, the LC₅₀ values

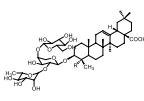
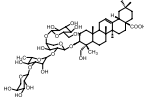
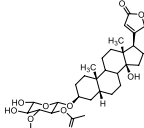
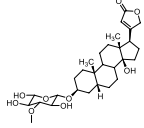
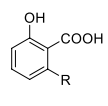
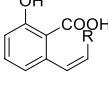
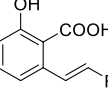
Table 1 (continued)

160		160a: R ¹ = CH ₃ CO, R ² = CH ₃ CO ₂				60% at 50 ppm		
		160b: R ¹ = CH ₃ CO ₂ CH ₂ CO, R ² = CH ₃ CO ₂				100% at 50 ppm		
		160c: R ¹ = HOCH ₂ CO, R ² = H				0% at 50 ppm		
161		161a: R ¹ = CH ₃ CO ₂ , R ² = (CH ₃) ₂ CHCO				100% at 50 ppm		
		161b: R ¹ = CH ₃ CO ₂ , R ² = CH ₃ CH=CCH ₂ CO				100% at 50 ppm		
		161c: R ¹ = H, R ² = (CH ₃) ₂ CHCO				60% at 50 ppm		
162		162a: R ¹ = H, R ² = angeloyl, R ³ = propanoyl				25% at 1.5 ppm	<i>B. glabrata</i> (24 h)	Apers et al., 2001
		162b: R ¹ = acetyl, R ² = angeloyl, R ³ = propanoyl				15% at 1.5 ppm		
		162c: R ¹ = H, R ² = angeloyl, R ³ = angeloyl	0.5			100% at 1.5 ppm		
163		163a: R ¹ = S ¹ , R ² = OOCCH=CHPh	2				<i>B. glabrata</i> (24 h)	Nihei et al., 2005
		163b: R ¹ = S ¹ , R ² = H	2					
		163c: R ¹ = S ² , R ² = OOCCH=CHPh	2					
		163d: R ¹ = S ³ , R ² = OOCCH=CHPh	8					
164						15% at 30 ppm	<i>P. canaliculata</i> (24 h)	Chen et al., 2020
165						21.25% at 30 ppm		
166			0.701				<i>O. hupensis</i> (24 h)	Jia et al., 2019
			1.975				<i>B. alexandrina</i> (24 h)	
			1.396				<i>B. truncates</i> (24 h)	

of ECN were 0.041 ppm (24 h), 0.032 ppm (48 h), and 0.029 ppm (72 h), respectively, significantly lower than the control groups of SCN and WPN. ECN has more chance to contact snails, resulting in better molluscicidal activities. However, the addition of solvents and emulsifiers causes higher cost of molluscicide and environmental pollution.

Three new polymeric controlled release formulations of niclosamide (B1, B2, and B3) against *B. alexandrina* were developed by Kenawy et al. (Kenawy and Rizk 2004). These polymeric formulations were prepared either by the chemical modifications of poly(glycidyl methacrylate) or by physical entrapment of the niclosamide in calcium

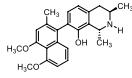
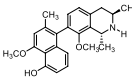
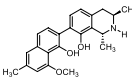
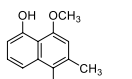

Table 1 (continued)

16 7		167a: R = CH ₂ OH				90% at 10 ppm	<i>B. alexandrina</i> (24 h)	Ekabo and Farnsworth, 1996
		167b: R = CH ₃				100% at 10 ppm		
		167c: R = CHO				0% at 10 ppm		
16 8						70% at 10 ppm		
16 9			5.39				<i>Monacha obstructa</i> (24 h)	Alzabib et al., 2019
17 0			4.30					
17 1		171a: R = C ₁₃ H ₂₇	3.95	5.86			<i>O. hupensis</i> (24 h)	Yang et al., 2008
		171b: R = C ₁₅ H ₂₉	1.49	4.74				
		171c: R = C ₁₇ H ₃₃	11.37	17.75				
17 2		172a: R = CH ₂ CH ₂ CH ₃	107.2 μM	786.6 μM			<i>O. hupensis</i> (48 h)	Zhang et al., 2011
		172b: R = CH ₂ (CH ₂) ₃ CH ₃	73.1 μM	243.6 μM				
		172c: R = CH ₂ (CH ₂) ₂ CH ₃	50.9 μM	98.2 μM				
		172d: R = CH ₂ (CH ₂) ₇ CH ₃	43.7 μM	135.7 μM				
		172e: R = CH ₂ (CH ₂) ₆ CH ₃	56.9 μM	362.9 μM				
		172f: R = CH ₂ (CH ₂) ₉ CH ₃	47.2 μM	338.7 μM				
		172g: R = Phenyl	0.0644 μM	283.9 μM				
17 3		173a: R = CH ₂ CH ₂ CH ₃	56.1 μM	115.9 μM				
		173b: R = CH ₂ (CH ₂) ₃ CH ₃	54.2 μM	214.5 μM				
		173c: R = CH ₂ (CH ₂) ₂ CH ₃	27.5 μM	74.3 μM				

alginate beads. In the immersion experiments, LC₅₀ values were 0.098 ppm (B1), 1.09 ppm (B2), and 0.073 ppm (B3), respectively. For B3, the mortality of snails was still up to 100% after 10 days. The polymeric molluscicide (B3) showed the highest molluscicidal activity than B1 and B2.

Recently, Harras et al. reported a new polymeric molluscicide-attractant from niclosamide and L-glutamate by a controlled-release technology to control *B. alexandrina* (Kenawy et al. 2020). The alginate niclosamide-L-glutamate formulation had good affinity ability to snails. The polymeric formulations B_{3-4b}-L-glutamate (0.3 ppm

Table 1 (continued)

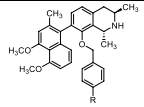
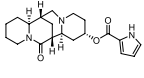
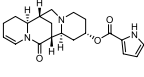
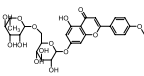
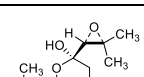
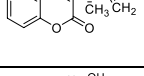
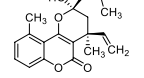
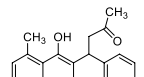
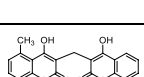
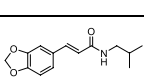
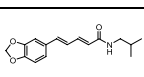
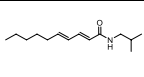
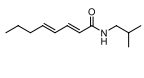
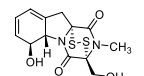
				μM				
			173d: R = CH ₂ (CH ₂) ₇ CH ₃	23.6 μM	68.3 μM			
			173e: R = CH ₂ (CH ₂) ₈ CH ₃	31.4 μM	88.7 μM			
			173f: R = CH ₂ (CH ₂) ₉ CH ₃	22.4 μM	50.9 μM			
			173g: R = Phenyl	37.2 μM	122.0 μM			
17 4						20		<i>B. glabrata</i> (24 h)
17 5						40		<i>B. glabrata</i> (24 h)
17 6						>4 0		<i>B. glabrata</i> (24 h)
17 7						>4 0		<i>B. glabrata</i> (24 h)
17 8			178a: R ¹ = H, R ² = CH ₃			40		
			178b: R ¹ = H, R ² = Et			20		
			178c: R ¹ = H, R ² = <i>i</i> -Pr			10		
			178d: R ¹ = H, R ² = Bzl			10		
			178e: R ¹ = CHO, R ² = CH ₃			10		
			178f: R ¹ = CHO, R ² = <i>i</i> -Pr			20		
			178g: R ¹ = CHO, R ² = Ac			>4 0		
			178h: R ¹ = CHO, R ² = Bz			40		
			178i: R ¹ = CHO, R ² = H			>1 00		
			178j: R ¹ = Ac, R ² = H			>4 0		
			178k: R ¹ = Me, R ² = H			>4 0		
17			179a: R = Br			3.1 3		

niclosamide and 75% L-glutamate) caused the aggregation of snails and showed 100% mortality after 5 days. The novel polymer-niclosamide-L-glutamate not only prolonged the validity and efficiency of the niclosamide, but also still was effective at low concentrations with

increasing concentrations of the applied attractants, which could reduce the toxicity to the ecosystem.

Though excellent advances on novel niclosamide formulations have been accomplished, there is still a huge challenge to reduce the toxicity through the structure modification strategy.

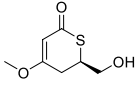
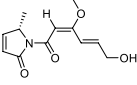
Table 1 (continued)

9		179b: R = Cl			6.2			
		179c: R = NO ₂			12.5			
		179d: R = CF ₃			6.2			
180					130		<i>B. glabrata</i> (48 h)	Kubo et al., 1984
181					inactive			
182			36.12				<i>O. hupensis</i> (24 h)	Han and Chen, 2014
183					25		<i>B. glabrata</i> (24 h)	Kady et al., 1992
184					25			
185						25% at 25 ppm		
186					25			
187								
188			200				<i>B. glabrata</i> (24 h)	Kubo et al., 1984a
189			>200					
190			>200					
191			200					
191			0.101	0.355			<i>O. hupensis</i> (24 h)	Guo et al., 2011
			0.062	0.121			<i>O. hupensis</i> (48 h)	

Yuan et al. reported the sodium of niclosamide sodium quinoid-2', 5-dichloro-4'-nitrosalicylanilide (**13**, Table 1) (LDS) obtained through the reaction of NaOH with niclosamide (Yuan et al. 2011). LDS showed better solubility in water and ethanol, and lower toxicity than that of niclosamide. The molluscicidal activities of 10% LDS and 50%

WPN were further investigated (Yuan et al. 2011). In immersion experiments, the mortalities of snails for LDS and WPN were 100% and 96.7% at 0.4 ppm in 72 h, respectively. In spraying experiments, the mortalities of snails for LDS and WPN were up to 100% and 97.3%, respectively. In field immersion and spraying experiments, LDS and WPN

Table 1 (continued)

			0.022	0.066			<i>O. hupensis</i> (72 h)	
19 2			8.3 μM				<i>B. glabrata</i> (24 h)	Pereira et al., 2011
19 3			6.0 μM					

showed the similar molluscicidal activities (Xu et al. 2007; Zhang et al. 2013). In addition, LDS exhibited climbing-inhibition effect against snails (*O. hupensis*), and the cost of LDS was also less than that of WPN (Xia et al. 2014).

In 2016, a series of salicylanilide ester derivatives was explored by Wang et al. (Wang et al. 2016). Preliminary structure–activity relationships (SARs) of the synthesized compounds showed that essential ester moieties could improve or maintain the bioactivity. The molecular structure bearing 4-methoxy phenyl ester (**14**, Table 1) exhibited potent molluscicidal activity among the synthetic products. In spraying experiments, the LC_{10} , LC_{50} , and LC_{90} values of **14** against *O. hupensis* were 0.055, 0.206, and 0.773 g/m³, respectively. In addition, the MLC_{50} value of **14** was 0.45 mmol/m², which was superior to that of niclosamide (0.51 mmol/m²). The toxicity experiments revealed that **14** exhibited lower cytotoxicity against HEK293 cells compared with niclosamide. Furthermore, compound **14** was selected to test fish toxicity assessment using *Danio rerio* as model organism in ecotoxicological testes. The LC_{10} , LC_{50} , and LC_{90} values of **14** were 19.53, 30.57, and 47.85 ppm. It is notable that **14** exhibited no toxicity to *Danio rerio* at 0.25 ppm (the LC_{50} of niclosamide is 0.25 ppm). He et al. also reported the molluscicidal activity of compound **14** against *Biomphalaria* species (He et al. 2017). The LC_{50} values of **14** against *B. glabrata*, *B. straminea*, and *B. Pfeifferi* were 0.261, 0.172, and 0.241 ppm, respectively. However, the LC_{50} values of niclosamide were 0.070, 0.049, and 0.076 ppm under the same conditions, demonstrating an approximately four fold-increased molluscicidal activity compared with that of **14**. The acute lethal toxicity test to *Danio rerio* displayed that the LC_{50} (96 h) value of **14** was 17.15 ppm, which is much less toxic than niclosamide (1 ppm). The above results mean that compound **14** shows negligible toxicity to fish and may be an environmentally friendly molluscicide candidate that surpassed the present niclosamide.

Recently, the molluscicidal activity of 4-methoxy phenyl ester (niclosamidate, **14**) wettable powder (WP) in field was

further investigated by Wang et al. (2017). The compound also exhibited high molluscicidal activity in the spraying experiments, and the mortality of snails was up to 81.8% at the surface concentration of 8.0 g/m². When the molluscicide was used in the immersion trials, the mortality of snails was 72.7% at 4.0 g/m². Satisfactorily, 4-methoxy phenyl ester wettable powder (WP) showed no toxicity on aquatic organisms including tadpoles, frogs, shell fish, and shrimps. But niclosamide could cause the death of fish and shellfish within 2 h under the same conditions. Furthermore, local fish toxic tests were carried out using crucian, cyprinoid, and chub as model fish. For 4-methoxy phenyl ester wettable powder (WP), the mortality of the tested fish was 50% at the concentration of 12.8 g/m³ after 72 h. However, for niclosamide, the mortality of snails was up to 100% at the concentration of 0.5 g/m³ within 4 h. In field experiment, niclosamide exhibited the effective molluscicidal activity at 1 g/m³. Undoubtedly, 4-methoxy phenyl ester wettable powder (WP) exhibited very low toxicity to local fishes and other aquatic organisms compared with niclosamide, which can be used in aquaculture ponds.

In 1973, some substituted tetralins (**15–18**, Table 1) were explored as molluscicides against *B. alexandrina* snails (Nabih and Metri 1973). For compounds **15–17**, the mortality rates of snails were up to 100% at 1 ppm, which were similar with the activity of niclosamide. However, the cost of these compounds was much higher than niclosamide. Nawwar et al. evaluated the molluscicidal activity of salicylamides containing piperidine moieties against *B. alexandria* snails (Nawwar et al. 1994). Compounds **19a–b** (Table 1) showed the moderate molluscicidal activity. Subsequently, Nawwar et al. further evaluated the activity of salicylamides containing amino acid moieties (Nawwar et al. 1994). For compounds **20a** (Table 1), the mortality of snails was up to 100% at 1 ppm.

For niclosamide and its derivatives, developing of novel formulations and rational structural modification may be an important research area.

Pyridylphenylureas

Wang et al. developed a series of pyridylphenylurea derivatives against *B. straminea* snails through the introduction of a urea functional group into the structure of nicotinilide (Wang et al. 2018). For compounds **21** and **22** (Table 1), the mortalities against adult snails were all up to 100% at 1.0 ppm, and the LC₅₀ values were 0.50 ppm and 0.51 ppm in immersion experiments, respectively (LC₉₀ = 0.98 and 0.78 ppm). And the LC₅₀ values against snail eggs were 0.05 ppm and 0.09 ppm, respectively (LC₉₀ = 0.21 and 0.39 ppm). The acute lethal fish toxicity experimental results revealed that the safe dose of compound **22** was up to 5 ppm, which was higher than that of the effective molluscicidal dose (LC₉₀, 0.78 ppm).

Furthermore, compound **21** (named PPU07) was made into the form of 25% PPU07 sulfate WP. The field molluscicidal activity and toxicity of 25% PPU07 sulfate WP were investigated against *O. hupensis* and local fish (Chen et al. 2019). In the spraying experiments, the mortality of snails was up to 95% at the concentration of 2.0 g/m². When snails were exposed in the 2.0 g/m³ of the 25% PPU07 sulfate WP, the mortality reached 96%. In the spraying and immersion trials, the WHO-recommended molluscicidal concentrations of niclosamide were 1 g/m² and 1 g/m³, respectively. Additionally, 25% PPU07 sulfate WP showed little toxicity to local fish and other aquatic organisms at the effective molluscicidal concentrations. PPU07 could be explored as promising molluscicide candidate for the control of snails.

Nitro-compounds

Abreu et al. explored the molluscicidal activity of nitroaromatic compounds against *B. glabrata* snails (de Abreu et al. 2001). Compounds **23–26** (Table 1) presented a significant bioactivity and the LC₅₀ values of them (**23**, LC₅₀ = 1.8 ppm; **24a**, LC₅₀ = 8.2 ppm; **24b**, LC₅₀ = 0.7 ppm; **25**, LC₅₀ = 7.6 ppm; **26**, LC₅₀ = 6.4 ppm) were lower than 10 ppm in 24 h. Further electrochemical tests revealed that the presence of the electro-active NO₂ group in the molecular structures was crucial for the retention of molluscicidal activity. Bond et al. also discovered the molluscicidal activity of 4-(substituted phenoxy)-3,β-dinitrostyrenes against *B. glabrata* (Bond et al. 1969). The LC₅₀ values of compounds **27a–d** (Table 1) were 8.5, 12, 8.5, and 22 ppm, respectively. It is notable that β-nitrostyrene **28** (Table 1) displayed the best activity among the tested compounds (LC₅₀ = 1.3 ppm).

Phenolic compounds

Lahlou et al. prepared some phenolic compounds for the control of *Bulinus truncates* snails (Lahlou 2004). Compounds **29–31** (Table 1) demonstrated good molluscicidal activity (**29**, LC₅₀ = 8.89 ppm, LC₉₀ = 16.82 ppm; **30**, LC₅₀ = 3.60 ppm, LC₉₀ = 4.47 ppm; **31**, LC₅₀ = 7.71 ppm, LC₉₀ = 14.14 ppm). The compound **30** was the most effective among the phenolic products.

Chalcones and its derivatives

Adewunmi et al. tested the molluscicidal activity of a serial of chalcones and chalcone epoxides (**32**, Table 1) against *B. glabrata* snails (Adewunmi et al. 1987). An appropriate hydrophile-lipophile balance in the structure of chalcones should facilitate the improvement of activity. For example, the mortality of compound **32c** against snails was up to 100% at 10 ppm in 24 h; however, the activity of compound **32f** declined dramatically (37.5% mortality) when the two OH groups were methylated. Furthermore, the epoxidation of the chalcones also resulted in the loss of molluscicidal activity. Nawwar et al. investigated the molluscicidal activity of several 1-(hydroxy/substituted phenyl) propenones (**33–35**, Table 1) against *B. alexandria* snails (Nawwar et al. 1993). The activity of the prepared compounds was related to the conjugated system. Compounds **34a–c** showed the best results among the synthetic products. Especially compound **34b** afforded 100% mortality of the snails at 2 ppm in 24 h. When the furan moiety was removed, the molluscicidal activity exhibited negative results. Barsoum et al. evaluated the molluscicidal activity of bis[1-aryl-2-propen-1-ones] (chalcones) (**36a–h**, Table 1) and bis[3-aryl-4,5-dihydro-1H-pyrazol-1-carboxaldehydes] (**37a–h**, Table 1) against *B. alexandrina* snails (Barsoum et al. 2006). Most of the synthesized products showed moderate bioactivity at 20 ppm in 24 h. Compounds **37** exhibited superior molluscicidal activity than those of **36a–h**. The substitution of F and Cl groups on pyrazol rings of substrates should enhance the molluscicidal activity.

3-Hydroxy-arylpropanenitriles

Vasconcellos et al. evaluated the molluscicidal activity of 3-hydroxy-arylpropanenitriles (**38–40**, Table 1) against *B. glabrata* snails (Vasconcellos et al. 2006). Compound **38** showed the highest activity among the tested compounds in 24 h (**38**, LC₅₀ = 6.64 ppm, LC₉₀ = 9.23 ppm; **39**, LC₅₀ = 7.30 ppm, LC₉₀ = 10.64 ppm; **40**, LC₅₀ = 17.71 ppm, LC₉₀ = 22.7 ppm). Compound **40** displayed the lowest toxicity to snails, which could be attributed to the different hydrophilic-lipophilic ability of the naphthalene nucleus. The detailed structural-activity relationships of the

3-hydroxy-arylpropanenitriles should be further explored in future experiments.

Five-membered heterocycles

Kanawade et al. explored novel thiophenedicarboxamide and dicyanothiopheneacetamide derivatives for the control of *Indoplanorbis exustus* snails (Kanawade et al. 2011). The LC₅₀ values of compounds **41a** and **42a** (Table 1) were 0.6043 and 0.6511 ppm in immersion experiments, respectively. Fadda et al. evaluated the molluscicidal activity of thiophene, thiadiazole, and pyrazole derivatives (**43–45**, Table 1) against *B. alexandrina* snails (Fadda et al. 2009). Thiadiazole derivatives (**44a–c**) possessed higher activity than that of thiophene derivatives (**43a–d**) apparently because of the strong electron-donating effect of the thiadiazole ring. For example, compounds **44b** and **44c** demonstrated the best activity with the LC₅₀ value of 5.5 ppm and 6 ppm, respectively. The surface of snails demonstrated the effusion of the gelatinous materials, which could cause the toxic effect on the cell membranes and resulted in hemolysis and subsequent death (Fadda et al. 2009).

El Shehry et al. carried out the molluscicidal activity of 3-((2,4-dichlorophenoxy)methyl)-1,2,4-triazolo(thiadiazoles and thiadiazines) (**46–50**, Table 1) against *B. alexandrina* snails (El Shehry et al. 2010a, b). Compounds **46** and **47** displayed 100% mortality of snails at 10 ppm in 24 h. However, the other compounds (**48–50**) showed moderate to low activity against snails. Abdelrazek et al. developed a series of pyrazole derivatives for the control of *B. alexandrina* snails. Products **51a–d** (Table 1) exhibited good molluscicidal activity in immersion experiments (LC₅₀ = 11–13 ppm; LC₉₀ ≥ 14 ppm) (Abdelrazek et al. 2006a, b).

Six-membered N-heterocycles

Some novel functionally substituted pyridines and pyridazines (**52–54**, Table 1) were prepared and evaluated against *B. alexandrina* snails in 24 h (LC₁₀₀ = 6–15 ppm) (Abdelrazek and Fathy 2005). The electron-withdrawing groups on the aromatic ring (Ar group) of the tested compounds (**52b**, **53b**, **54b**) showed higher molluscicidal activity in 24 h.

El-Bayouki et al. discovered the molluscicidal activity of some thiazolo[5,4-d]pyrimidines (**55**, Table 1) against *B. alexandrina* snails (El-Bayouki and Basyouni 1988). Compounds **55a** and **55i** showed more effective activity, and the mortalities of snails were up to 100% at 25 ppm in 24 h. Bakhotmah et al. evaluated the molluscicidal activity of the phosphorus compounds bearing an amino pyrimidine-substituted pyrazolo[3,4-d]pyrimidine moiety against *B. alexandrina* snails (Bakhotmah 2019). For compounds **56** and

57 (Table 1), the mortalities of snails were all only 30% at 50 ppm in immersion experiments in 24 h.

Abdelrazek et al. developed new cinnoline derivatives and evaluated the molluscicidal activity to *B. alexandrina* snails (Abdelrazek et al. 2006a). Compounds **58–59** (Table 1) possessed good effects on the snails (**58a**, LC₅₀ = 8 ppm, LC₉₀ = 11 ppm; **58b**, LC₅₀ = 7 ppm, LC₉₀ = 15 ppm; **58c**, LC₅₀ = 7 ppm, LC₉₀ = 9 ppm; **59a**, LC₅₀ = 8 ppm, LC₉₀ = 13 ppm; **59b**, LC₅₀ = 9 ppm, LC₉₀ > 15 ppm; **59c**, LC₅₀ = 7 ppm, LC₉₀ = 9 ppm). Compounds **58c** and **59c** showed superior activities mainly attributed to the 4-chlorophenyl group. Ali et al. explored the molluscicidal activity of phosphorus-containing 3-hydrazino-1,2,4-triazines against *B. alexandrina* snails (Ali et al. 2008). However, the tested products (**60–62**, Table 1) showed low activity at 50 ppm in 24 h. Abdel-Rahman et al. investigated a series of 6-methyl-5-styryl-1,2,4-triazin-3-thiol derivatives for the control of *B. alexandrina* snails (Abdel-Rahman et al. 2003). Compounds **63**, **64**, and **66** (Table 1) had the moderate molluscicidal activity at 50 ppm in immersion experiments in 24 h. The *p*-dimethylamino, 1, 2, 4-dichloro phenyl, and β-naphthol moieties should play an essential role against snails. The molluscicidal activity of phthalazin-one **67** (Table 1) was also investigated for the control of *B. alexandrina* snails, and the LC₅₀ value was 9 ppm in 24 h (**67**, LC₉₀ = 13 ppm) (Abdelrazek et al. 2006a, b).

Pyrane derivatives

Souza et al. evaluated the molluscicidal activity of the 5,6-dimethyl-dihydro-pyran-2,4-dione and 6-substituted analogous (de Souza et al. 2004). Compounds **68–70** (Table 1) showed moderate activity against *B. glabrata* egg masses. The substitution of the propenyl or phenyl group in C-6 position of dihydro-pyran-2,4-diones could improve the molluscicidal activity. Flavones **71** and **72** (Table 1) were developed for the control of *Bulinus truncatus* snails, and the LC₅₀ values of them were 5.47 ppm and 8.91 ppm in 24 h, respectively (**71**, LC₉₀ = 9 ppm; **72**, LC₉₀ = 17 ppm) (Lahlou 2004).

Abdelrazek et al. synthesized and evaluated the molluscicidal activity of new chromene and pyrano[2,3-c]pyrazole derivatives (**73–77**, Table 1) against *B. alexandrina* snails (Abdelrazek et al. 2007). Compounds **75** and **76b** afforded the most effective activity. The decoration of dimethyl substituents in the cyclohexanone ring and the fused pyran ring might improve molluscicidal bioactivity. For **76b**, the NH of the indolyl moiety afforded the chelation effect, resulted in the enhancement of molluscicidal activity. The pyrane derivatives **78–82** (Table 1) were prepared for the control of *B. alexandrina* snails. All synthesized products exhibited generally moderate molluscicidal activity in immersion experiments. The most effective of them are **79a**, **80a**, **82a**,

and **82b** ($LC_{50} < 10$ ppm). It seemed that pyranopyrazole derivative **79a** should be a promising leading compound after appropriate modifications in future (Abdelrazek et al. 2006a, b).

Abdelrazek et al. discovered the molluscicidal activity of 5-oxo-5,6,7,8-tetrahydro-4H-chromene derivatives against *B. alexandrina* snails (Abdelrazek et al. 2004). The LC_{50} values of compounds **83a** and **84a** (Table 1) were 5 ppm (17.61 nM) and 8 ppm (28.17 nM) in 24 h, respectively, which are still far inferior to niclosamide ($LC_{100} = 1$ ppm). New pyrano derivative **85a** (Table 1) exhibited the highest activity against *B. alexandrina* snails within the pyrano[2,3-c]pyrazole series (Abdelrazek et al. 2006a), which should be modified and considered in future research.

Benzofuran derivatives

El Shehry et al. screened the molluscicidal activity of some pyrazole, isoxazole, pyridine, pyrimidine, 1,4-thiazine, and 1,3,4-thiadiazine derivatives incorporating benzofuran moiety (**86–89**, Table 1) against *B. alexandrina* snails (El Shehry et al. 2010a, b). Compound **86** showed the highest molluscicidal activity and the mortality of snails was up to 100% at 10 ppm in immersion experiments in 24 h. Compounds **87–89** displayed good to moderate activity among the tested products. Giri et al. found that 1-aryl-1-(substituted benzofur-2-yl)-2-benzylcarbinols (**90**, Table 1) and 1-aryl-1-(substituted benzofur-2-yl)-2-phenylethylenes (**91**, Table 1) exhibited moderate activity against *Lymnaea acuminata* snails (Giri and Mishra 1984a, b). Hassan et al. developed furo-salicylanilides for the control of *B. alexandrina* snails (Hassan et al. 2006). Compounds **92b** and **92d** showed lower molar concentration than that of Bayluscicide. However, cyclization of compound **92b** to afford compound **93b** (Table 1) resulted in the decrease of molluscicidal activity.

Benzimidazole derivatives

Nofal et al. developed the molluscicidal activity of benzimidazole derivatives for the control of *B. alexandrina* snails (Nofal et al. 2002). Compounds **94** and **95** (Table 1) exhibited moderate molluscicidal activity at 24 h in immersion experiments. However, the polycyclic benzimidazole derivatives **96–97** showed worse molluscicidal activity.

Coumarin derivatives

Giri et al. developed the molluscicidal activity of 3-substituted 4-hydroxycoumarin derivatives for the control of *Lymnaea acuminata* snails (Giri and Mishra 1984a, b). The compounds **98** and **99** (Table 1) showed the good molluscicidal activity at 5 ppm, and the mortalities of snails

were 58.33% and 68.33% in 24 h, respectively. Schönberg et al. explored the molluscicidal activity of furocoumarins against *Biomphalaria alexandrina* snails (Schönberg and Latif 1954). Compounds **100** and **101** (Table 1) killed 100% and 69% of the snails at 5 ppm in immersion experiments in 24 h, respectively.

Lapachol and its derivatives

Lapachol (**102**, Table 1) is a notable natural product from *Tecoma heptaphylla* (Vell Mart.) (*Bignoniaceae*). Lapachol showed poor molluscicidal activity against snails in earlier reports (Marston et al. 1984). Santos et al. re-investigated the activity of lapachol and its derivatives against the *B. glabrata* snails (dos Santos et al. 2000). In immersion experiments, the tested compounds **102–105** (Table 1) showed a significant molluscicidal activity against adult snails in 24 h (compound **102**, $LC_{50} = 2.57$ ppm, $LC_{90} = 6.18$ ppm; compound **103**, $LC_{50} = 1.53$ ppm, $LC_{90} = 4.30$ ppm; compound **104**, $LC_{50} = 4.02$ ppm, $LC_{90} = 7.15$ ppm; and compound **105**, $LC_{50} = 5.19$ ppm, $LC_{90} = 18.46$ ppm). Additionally, compound **104** exhibited the highest molluscicidal activity against snail eggs ($LC_{50} = 0.014$ ppm, $LC_{90} = 0.070$ ppm) in immersion experiments in 24 h. Furthermore, the activity of 2-hydroxy-3-substituted-aminomethyl derivatives was also investigated against snail eggs. However, the activity of them was lower than compounds **102–105**. Santos et al. developed a soluble potassium salt of lapachol **106** (Table 1) from the reaction of lapachol with KOH (dos Santos et al. 2001). The LC_{50} values of **106** against *B. glabrata* adult snails and eggs reached 2.70 and 1.43 ppm after 24 h in the immersion experiments, respectively. Silva et al. developed a series of amino and hydrogenated lapachol derivatives (**107–108**, Table 1) for the control of *B. glabrata* snails (Silva et al. 2005). Compounds **107a**, **107b**, **108a**, **108c**, **108d**, **108e**, and **108h** showed medium toxicity against snails ($23.8 < LC_{50} < 89.0$ mmol/L) in immersion experiments. However, **107c**, **108b**, and **108f** were less active ($LC_{50} > 200$ mmol/L). It is notable that compounds **108g** and **109** (Table 1) exhibited significant molluscicidal activity and the LC_{50} values were 13.8 and 7.6 mmol/L in 24 h, respectively.

The molluscicidal activity of the potassium salt of isolapachol (**110**, Table 1) was explored for the control of *B. glabrata* (Lima et al. 2002a, b). Compound **110** exhibited good activity against adult snails (24 h LC_{50} 3.05 ppm, LC_{90} 4.71 ppm) and snail eggs (24 h LC_{50} 0.33 ppm, LC_{90} 0.48 ppm) in immersion experiments. However, **110** showed high toxicity against fishes (*T. nilotica*) (24 h LC_{50} 2.05 ppm, LC_{90} 2.43 ppm) and planktonic crustaceae (*A. salina*) (24 h LC_{50} 2.05 ppm, LC_{90} 2.43 ppm). Lima et al. evaluated the molluscicidal activity of lapachol and its derivatives and analogues for the control of *B. glabrata* snails (Lima et al.

2002a). The LC_{50} values of compounds **111a** and **111c** (Table 1) against adult snails were 0.98 and 1.66 ppm in 24 h, respectively. Compounds **111b**, **111d**, **111e**, and **112** (Table 1) also displayed the moderate molluscicidal activity, with LC_{50} values in the range of 3.82–7.72 ppm in 24 h.

Ribeiro et al. prepared some naphthoquinones and evaluated the molluscicidal activity of compounds **113–114** (Table 1) for the control of *B. glabrata* snails (Ribeiro et al. 2009). The LC_{50} values of the tested products ranged from 0.475 to 3.049 ppm in 24 h. Camara et al. evaluated the molluscicidal activity of naphthoquinone derivatives for the control of *B. glabrata* snails (Camara et al. 2008). The presence of a bromine group in compound **115c** (Table 1) resulted in almost 15-fold molluscicidal activity compared to compound **115a**. However, these synthesized products exhibited obvious toxicity to the brine shrimp *A. salina* (Camara et al. 2008). Barbosa et al. developed new 2-aminoalkyl substituted anthraquinones from norlapachol for the control of *B. glabrata* snails (Barbosa et al. 2005). Compounds **116a–h** (Table 1) displayed moderate activity. The increase of polarity of molecules can lead to the decrease of bioactivity (for **116b** and **116c**), which exhibits a similar trend to that of amino lapachol derivatives reported by Silva's group (Silva et al. 2005). Therefore, compound **116g** displays the best molluscicidal activity among the tested products. However, the molluscicidal activity was sharply diminished when the aminoalkyl substituted compounds were converted into the cyclic molecules **117** and **118** (Table 1).

The above findings confirm the importance of lapachol and its derivatives as promising molluscicides.

Quinoline derivatives

Serials of novel enaminones derived from 4-hydroxyquinolinones (**119–122**, Table 1) were prepared by Abass' group (Abass and Mostafa 2005). Part of these products exhibited good molluscicidal activity of against *B. alexandrina* and *Lymnaea natalensis* snails ($LC_{50} < 20$ ppm). For compounds **122a–c**, the structure–activity relationship showed that the molluscicidal activity increased with the improvement of the lipophilicity of the molecules. In addition, the acute toxicity of the tested molluscicides against *D. magna* was also explored, and the experimental results revealed that the candidate compounds showed 0% mortality at LC_{50} concentrations after 48 h. Kujime et al. evaluated the molluscicidal activity of acridone alkaloids against *B. glabrata* snails (Kujime et al. 1992). Compounds **123** and **124** (Table 1) showed moderate bioactivity in 24 h. El Bardicy et al. evaluated the molluscicidal activity of aminoalkylamino substituted neo- and norneocryptolepine derivatives (**125–131**, Table 1) against *B. alexandrina* snails (El Bardicy et al. 2012). The LC_{50} values of the tested products were 0.63–3.9 ppm in 24 h.

Our group discovered the molluscicidal activity of 3-substituted quinazolinone derivatives **132** (Table 1) through a scaffold hopping approach using a pseudo-ring based on the intramolecular hydrogen bond formation (Guo et al. 2016). Most of the tested compounds showed good molluscicidal activity against *O. hupensis* with the LC_{50} values ranged from 2.69 to 10 ppm. The preliminary structure–activity relationship exhibited that the aromatic rings are essential for C section and the electron-donating groups on the C ring can promote the molluscicidal activity.

Thioxanthene derivatives

El-Sakka et al. evaluated thioxanthene derivatives (**133–137**, Table 1) against *B. alexandrina* snails (El-Sakka et al. 1994). Compounds **136–137** showed considerable activity, and **135** possessed the highest mortality in 24 h at 25 ppm.

Development of plant molluscicides

Chemical molluscicides are still the most convenient option for the control of snails and have been used successfully in practical applications (Perrett and Whitfield 1996). However, the registered chemical molluscicides (such as niclosamide, copper sulfate, and sodium pentachlorophenate) are still rare due to high cost, toxicity to non-target organisms, high residual risk, and relatively complicated synthesis process (Brackenbury and Appleton 1998). Some plant molluscicides are considered inexpensive and environmental friendly to the health of aquatic organisms and mammals, and some pure compounds have also been isolated from plant and proven to have molluscicidal activity against snails. Development of natural plant molluscicides may be a suitable alternative for snail control (Zhu et al. 2010).

Sesquiterpene lactones

Borkosky et al. evaluated the molluscicidal activity of sesquiterpene lactones from the tribe *Vernonieae*, family Asteraceae (Borkosky et al. 2009). The tested products **138–147** (Table 1) demonstrated moderate molluscicidal activity against *B. peregrina* snails. The LC_{50} values ranged from 27.99 to 88.25 ppm in 24 h.

Monoterpenoids

Radwan et al. evaluated the molluscicidal activity of monoterpenoid derivatives (**148–155**, Table 1) for the control of *B. alexandrina* snails (Radwan et al. 2008). Most of the compounds showed molluscicidal activity; especially compound **155b** was the most effective among the tested compounds ($LC_{50} = 5.43$ ppm). Furthermore, mixing

compounds **154a** and **155a** with piperonyl butoxide (PBO) afforded the LC_{50} values of 2.69 and 2.72 ppm in 24 h, respectively.

Diterpenoids

Dos Santos et al. discovered the molluscicidal activity of diterpenoids (**156–157**, Table 1) isolated from *Jatropha elliptica* (Pohl) Muell. Arg (dos Santos and Sant'Ana 1999). Compared with product **157**, products **156** showed molluscicidal with the LC_{50} values of 1.16 ppm (adult snails) and 1.14 ppm (snail eggs) in 24 h. However, product **157** was not active against *B. glabrata* snails at a concentration of 100 ppm. Abdelgaleil et al. extracted some diterpenes (**158–161**, Table 1) from *Euphorbia paralias* L and evaluated the molluscicidal activity against *B. alexandrina* snails (Abdelgaleil et al. 2002). Most of the obtained products showed moderate molluscicidal activity except product **160c**. Notably, among the isolated products, product **158b** showed the best activity with the 100% mortality at 15 ppm in 24 h. The preliminary structure–activity relationship of the tested products exhibited that paraliane diterpenes (**158a–b**) showed higher activity than segetane diterpenes (**159**, **160a–c**) to snails. For paraliane diterpenes, the acetoxy group at C1 in compound **158a** was unfavorable for the improvement of activity. In the case of **160a–c**, the presence of acetoxy group (R^2) facilitated the molluscicidal activities, which were similar to **161a–c**.

Triterpenoid saponins

Molluscicidal activity of triterpenoid saponins from *Maesa lanceolata* was assessed by Apers et al. (2001). Among the tested products, compound **162c** (Table 1) showed the best activity against *B. glabrata* snails and the LC_{50} value was 0.5 ppm in 24 h. Novel triterpene saponins (**163a–d**, Table 1) were isolated from African medicinal plant, *Pachyelasma tessmannii* for the control of *B. glabrata* snails (Nihei et al. 2005). The LC_{50} values of **163a–d** were 2, 2, 2, and 8 ppm within 24 h, respectively. Triterpenoid saponins **164** and **165** (Table 1) were extracted from the roots of *Pueraria peduncularis* (Chen et al. 2020). The two products **164** and **165** displayed moderate molluscicidal activity with the mortalities of 15% and 21.25% at 30 ppm in 24 h, respectively. A pentacyclic triterpenoid saponin **166** (Table 1) was extracted from the seed pomace of *Camellia oleifera*, which was widely cultivated in South China (Jia et al. 2019). Product **166** has been named as tea-seed distilled saponin (TDS) and been registered as Luo-Wei by the Ministry of Agriculture (MoA) of China. Compound **166** showed significant molluscicidal activity against *O. hupensis*, *B. alexandrina*, and *Bulinus truncatus*, and the LC_{50} values were 0.701 ppm,

1.975 ppm, and 1.396 ppm in 24 h, respectively. In addition, TDS showed moderate toxicity to Japanese quail and shrimp, and high toxicity to zebrafish (96 h LC_{50} = 0.15 ppm). For all that, TDS may be a promising candidate molluscicide of plant origin to eliminate snails in high-risk areas. Ekabo et al. tested the novel saponins (**167–168**, Table 1) extracted from *Serjania salzmanniana* for the control of *B. alexandrina* snails (Ekabo and Farnsworth 1996). For products (**167a–b**, **168**), the mortalities of snails were 70–100% at 10 ppm in 24 h. However, product **167c** exhibited no activity at 10 ppm.

Cardiac glycosides

The two molluscicidal active cardiac glycosides, cerberin **169** and neriifolin **170** (Table 1), were isolated from the stems of *Adenium obesum* (Alzabib et al. 2019). Products **169** and **170** had significant molluscicidal activity against *Monacha obstructa* snails with LC_{50} values of 5.39 and 4.30 ppm in 24 h, respectively.

Ginkgolic acids

Yang et al. evaluated the molluscicidal activity of ginkgolic acids (**171a–c**, Table 1), isolated from *Ginkgo sarcotesta* against *O. hupensis* (Yang et al. 2008). Product **171b** showed the best molluscicidal activity among the isolated components. The LC_{50} value of **171b** was 1.49 ppm against *O. hupensis*. Zhang et al. tested the molluscicidal activity of ginkgolic acid derivatives against *O. hupensis* (Zhang et al. 2011). Compounds **172** and **173** (Table 1) displayed moderate bioactivity in immersion experiments. The preliminary structure activity relationship showed that the *E*-isomers (**173**) were superior to *Z*-isomers (**172**). Prolonging the chain lengths of alkenyl on aromatic cycle structures could enhance molluscicidal activity.

Alkaloids

Bringmann et al. evaluated the molluscicidal activity of naphthylisoquinoline alkaloids (**174–179**, Table 1) from *Triphyophyllum* and *Ancistrocladus* species (Bringmann et al. 1996, 1998). Most of the tested products demonstrated moderate activity against *B. glabrata* snails. Compounds **178c–e** showed the best activity and the LC_{100} values of them were 10 ppm in 24 h. However, compounds **176**, **177**, and **178 g–k** exhibited no significant activities. It is notable that the LC_{100} values of products **179a–d** were 3.13–12.5 ppm. Kubo et al. tested the molluscicidal activity of quinolizidine alkaloids from the African medicinal plant *Calpurnia aurea* (Papilionaceae) against *B. glabratus* snails (Kubo et al. 1984a, b). For compound **180** (Table 1), the snail mortality was up to 100% mortality at 130 ppm in 48 h.

However, the similar compound **181** (Table 1) did not kill snails even at 1000 ppm.

Acacetin derivatives

Buddleja lindleyana is an important traditional medicinal plant in China. Acacetin-7-rutinoside **182** (Table 1) was isolated from the *n*-butanol fraction of fresh *B. lindleyana* leaves by Han et al. The structure of **182** was characterized through NMR (Han and Chen 2014). Product **182** had moderate molluscicidal activity against *O. hupensis* with the LC₅₀ value of 36.12 ppm in 24 h.

Coumarins

Kady et al. evaluated the molluscicidal activity of coumarins from *Ethulia conyzoides* (**183–185**, Table 1) and of dicumarol (**186**, Table 1) (Kady et al. 1992). Compounds **183**, **184**, and **186** possessed good molluscicidal activity against *B. glabrata* snails. Especially, the LC₉₀ values of compound **183** were 19–23.5 ppm for all age-group snails in 24 h. In addition, compound **183** could kill cercariae of schistosome at 25 ppm. However, compound **185** exhibited poor molluscicidal activity.

Isobutylamides

Kubo et al. evaluated the molluscicidal activity of isobutylamides isolated from the East African medicinal tree *Fagara macrophylla* (Rutaceae) (Kubo et al. 1984a). Compounds **187** and **190** (Table 1) showed considerable activity against *B. glabratus* snails. However, compounds **188** and **189** (Table 1) were ineffective in killing snails.

Gliotoxin and others

Guo et al. found the gliotoxin (**191**, Table 1) by extracting the rhizospheric strain from *Phytolacca acinosa* Roxb (Guo et al. 2011). The structure of **191** was confirmed by NMR and LC–MS. The LC₅₀ values of **191** against *O. hupensis* were 0.101 ppm (24 h), 0.062 ppm (48 h), and 0.022 ppm (72 h), respectively. Pereira et al. isolated compounds **192** and **193** (Table 1) from the assemblage of *Palmyra Atoll Cyanobacteria* to kill *B. glabrata* (Pereira et al. 2011). The LC₅₀ values of **192** and **193** were 8.3 μM and 6.0 μM in 24 h, respectively. In addition, the equimolar mixture of **192** and **193** afforded the higher activity with the LC₅₀ value of 5.0 μM in 24 h.

In addition, several plants, such as *Phytolacca dodecandra* (Endod) (Karunamoorthi et al. 2008), *Solanum xanthocarpum* (Changbunjong et al. 2010), *Annona squamosa*

(Tiwari 2012), *Thuja orientalis* (Singh and Singh 2009), *Stryphnodendron polyphyllum* (Vinaud et al. 2008), *Calotropis procera* and *Adenium arabicum* (Al-Sarar et al. 2012), *Eomecon chionantha* (Peng et al. 2011), *Balanites aegyptiaca* (Brimer et al. 2007), *Meryta denhamii* (Hassan et al. 2010), *Anagallis arvensis* (Abdel-Gawad et al. 2000), *Dioscorea zingiberensis* (Liu et al. 2001), *Balanites aegyptiaca* (Molla et al. 2013), *Eupatorium adenophorum* (Zou et al. 2009) and so on, have already been identified as useful to control the intermediate hosts of trematodes. However, the chemical structure of these molluscicidal active ingredients from the plant should be elucidated in future work.

Mechanism research

Recently, some achievements on the discovery of novel chemical and natural molluscicides have been accomplished to control snails (Chen et al. 2019; de Paula-Andrade et al. 2019). For the development of new molluscicides, exploration of the mechanism is important for the enhancement of molluscicidal activity and the reduction in non-target toxicity (Huang 2019a, b). Most of the molluscicides can induce the injury of snail soft tissues and influence the activity of key enzymes, leading to the changes of a serial of physiological and biochemical characteristics, and finally resulting in the death of snails (Nie et al. 2009).

Effect of molluscicides on snail soft tissues

He et al. (2017) investigated the ultrastructural features and changes of the soft tissues of *B. glabrata* snails including tentacle, mantle, plantaris, and hepatopancreas after treatment with salicylanilidate and niclosamide through the scanning electron microscopy (SEM) and transmission electron microscope (TEM) (He et al. 2017). The SEM photographs showed that salicylanilidate and niclosamide caused swelling of the tentacle and deformation of cilia in the mantle. Salicylanilidate mainly damaged the rough endoplasmic reticulum, and resulted in the aggregation of heterochromatin and vacuolization of the mitochondria, as well as polymorphic changes of the nucleus. In contrast, niclosamide primarily caused polymorphic alterations of the nucleus, substantial heterochromatin aggregation, and partially destructed the rough endoplasmic reticulum. Li et al. also observed the ultra-structural changes of cerebral the ganglion of *O. hupensis* after treatment with niclosamide (Li et al. 1997). The mitochondrion of neural fibers, neuroglial cells, neurons, and neuropil displayed denaturation and necrosis, and the content of glycogen in neurons was also reduced obviously. Tan et al. found

that the muscular fold of snail became smoother and the muscular structure was destroyed by the combination of arecoline with sodium pentachlorophenate or niclosamide (Tan et al. 2001).

LDS or WPN could reduce the number of mitochondria of *O. hupensis* and damage the mitochondrial cristae (Xiong et al. 2016). The gathered heterochromatin was also polarized. These molluscicides might further decrease the number of ribosomes in the rough endoplasmic reticulum (rERs), and loose the myofilaments in muscle cells. At the same time, cytoplasm in some liver cells was gathered together. The above phenomena indicated that molluscicides could damage cell structures and organelles, and inhibit the movement ability of snails, which might cause harmful effects on the liver and energy metabolism. SEM photographs showed that the 1-(4-chlorophenyl)-3-(pyridin-3-yl)urea and 1-(4-bromophenyl)-3-(pyridin-3-yl)urea could also destroy the tentacles and sub-tegumental tissue (Wang et al. 2018). The tegumental surface of the mantle and the columellar muscle of foot plantaris exhibited turgidity, blebbing, exfoliation, erosion, and chap, and the cilia became tangled, adherent, and peeled off from the issue.

The influence of the seed of *Camellia sinensis* (L.) *O. Kuntze* on the tegument of soft tissues of *O. hupensis* was explored by SEM (Wang et al. 1997). The tegument of head of snails exhibited serious damage and deformity after treatment with the drug. The snail foot was also thickened and wrinkled, and infiltrated with numerous cells. The drug destroyed the tissue of the mantle and visceral sac at liver of snails.

The fluid extracted from *Nerium indicum* leaves caused swelling on the surface of head, foot, and mantle soft tissues of *O. hupensis* (Chen et al. 2001). The rupture and exfoliation of parts of the tissue surface were also observed. The numbers, size, depth, and distribution of the holes on the tissue surface changed obviously (Chen et al. 2001). Additionally, the surface of the visceral sac of liver swelled, and became rough, accompanied with the increasing clearance and irregular holes.

Ke et al. (1999) discovered the damage in exterior tissues of the head, foot, and liver of *O. hupensis* after treatment with water extract from *Pterocarya stenoptera* leaves by SEM. The head, foot muscle, and mantle of the snail swelled, which were destroyed seriously and the lip exhibited serious deformity after treatment with the 1.0% water extract. The drugs could also cause numerous holes in visceral sac liver.

The observation of *Eomecon chionantha* alkaloids (ECA) on the genital system of *O. hupensis* was carried out by Sun et al. (2005). ECA could destroy the genital system of snails. The oocyte of *O. hupensis* was obviously atrophied, and the spermatogonium exhibited pyknosis.

Based on the above observation, some molluscicides could damage the head, foot, mantle, liver, visceral sac, gonad, and neural fiber of snails, which influenced the activity, energy metabolism, detoxification, genital, and nervous systems leading to the death of snails.

Effect of molluscicides on key enzyme activity of snails

Enzymes are essential to snails and are often being explored to evaluate the interactions between drugs and target organisms. The change of enzyme activity often means the changes of the physiology or pathology in the snail body (Pu et al. 2008). Generally, nitric oxide synthase (NOS) and cholinesterase (CHE) are involved in neural signal transduction; malondialdehyde (MDA) reflects the level of lipid peroxidation; superoxide dismutase (SOD) and peroxidase (POD) are involved in anti-oxidative stress; alanine aminotransferase (ALT), aspartate aminotransferase (AST), glutamic-pyruvic transaminase (GPT), and glutamic-oxaloacetic transaminase (GOT) reflect liver function. They are all related to stress responses of snails. Other enzymes such as glycogen, succinate dehydrogenase (SDH), malic dehydrogenase (MDH), acid phosphatase (ACP), alkaline phosphatase (AKP), cytochrome c oxidase (CCO), glucose-6-phosphatase (G-6-Pase), and lactate dehydrogenase (LDH) are involved in the process of carbohydrate metabolism.

Mello-Silva et al. (2010) evaluated the carbohydrate metabolism alterations in *B. glabrata* snails exposed to *Euphorbia splendens* var. *hislopii* latex. Latex could cause the decrease of the glycogen levels in the carbohydrate deposits. The latex of *Euphorbia splendens* should be used as a promising natural molluscicide.

A suspension concentrate of niclosamide could reduce the enzyme activity of NOS, CCO, CHE, SDH, and LDH in *O. hupensis* (Li et al. 2006). The neurotransmitter and energy systems were interrupted by niclosamide, which resulted in the disorder of the physiological functions and caused the death of snails. Salicylanilidate was further selected to investigate the effects on some important enzymes of snails (He et al. 2017). The activities of AKP, ACP, LDH, NOS, and AChE showed that salicylanilidate could inhibit the LDH, NOS, and AChE activities and increase the AKP activity. Salicylanilidate could also reduce the transcriptional levels of ACP, NOS, and SOD in the hepatopancreas. However, the 1-(4-bromophenyl)-3-(pyridin-3-yl)urea improved ACP and NOS activities and exhibited no obvious alterations in the activities of AChE and SOD (Wang et al. 2018).

Exposure to LDS and WPN molluscicide inhibited carbohydrate metabolism (CCO, SDH, G-6-Pase), while the activity of LDH increased in muscle tissue (Xiong et al. 2016). These changes of carbohydrate metabolism patterns could decrease energy supply and lead to lactic acid accumulation.

The activity of CHE in the pellicle of snails was inhibited after treatment by LDS or WPN in 24 h, which was significantly lower than in the control group. In addition, the levels of NOS, ALT, and SOD were found to be increased at early stages, which might lead to a stress response of snails to the molluscicides and finally cause fatal damage in liver and nervous system. According to the experimental results, LDS and WPN showed similar effects although LDS-treated snails exhibited more serious damages in the liver and a stronger inhibition activity of enzymes related with aerobic respiration and stress response. However, the molecular and enzymatic level mechanism researches are worth of further considerable explorations to develop novel molluscicides in future.

Activities of CCO and AChE enzymes were reduced significantly after treatment by META-Li (Zhu et al. 2007), while the activities of LDH and NOS increased significantly. However, the activity change of SDH was not obvious. The energy metabolism and nerve transmission should be destroyed by META-Li.

Han et al. (2012) explored the enzyme histochemical profiles of CCO, LDH, SDH, NOS, and CHE in the soft tissues of *O. hupensis* using the active ingredient of *Buddleia lindleyana* (AIBL) as a potent and safe plant molluscicide. The results displayed that AIBL could impair the activities of CCO, LDH, SDH, NOS, and CHE, which disturbed the transfer of neurotransmitter and energy supply in snails and ultimately destroyed their various physiological functions, resulting in the death of snails.

It was found that the enzymatic activities of LDH, SDH, AChE, CCO, and NOS in the muscle fibers, ganglia, mouth, liver, pharyngeal cavity, and tegumentary membrane decreased after being treated with HL (Zhang et al. 2007). The mechanism of HL is similar to that of niclosamide.

The glycogen content of snail livers decreased obviously being treated by SAN, which indicated that the energy metabolism was suppressed (Sun et al. 2011). However, the level of MDA did not change significantly. Therefore, SAN has no significant effect on the lipid peroxidation of snails. Furthermore, the activities of ALT, AST, ACP, AKP, and SOD were increased significantly, which demonstrated that the liver cells, cytomembranes, and organelles of snails were damaged after treatment with SAN. The changes of above enzymes meant that SAN could destroy the metabolism of liver, hepatotoxicity, and hepatic disorder.

Chen et al. (2007) explored the molluscicidal mechanism of the extract of *Ginkgo biloba* sarcotesta by benzoinum (EGSB) against *O. hupensis*. EGSB could significantly inhibit ChE, ALT, ALP, and MDH activities both in the cephalopodium and liver. However, EGSB could not affect LDH activity in the cephalopodium and the liver. The molluscicidal action of EGSB was also different to that of niclosamide in some extent.

Mahmoud et al. (2011) investigated the mechanism of *Datura stramonium* and *Sesbania sesban* against *B. alexandrina* snails. The glucose and total protein concentrations in hemolymph of snails were decreased after being treated with these plants. However, the activities of the enzymes AST, ALT, ACP, and AKP were increased significantly in hemolymph, which indicated that the liver of snails was damaged by molluscicides. The crude extracts of the *Calendula micrantha officinalis* and *Ammimajus* could also inhibit the activities of ALT and AST, reduce the total protein content, and promote the lipid contents in the hemolymph of *B. alexandrina* or *Bulinus truncatus* snails (Rawi et al. 1996).

The water extracts of *Pterocarya stenoptera* and *Rumex japonicus* could increase the activity of GPT and GOT, which damaged the liver functions of *O. hupensis* (Ke et al. 2000). Molluscicide B002 could reduce the activity of NOS in the center ganglions, heart wall, testes, ovary, and pharyngeal cavity of snails. However, niclosamide had no effect on the NOS of snails (Hang et al. 2001).

Esterase isozyme (EST) plays an important role in the body's antidotal pathways. Chen et al. (2008) investigated the influences of stemona alkaloids on esterase isozyme (EST) activity and glycogen content of *O. hupensis*. The activity of esterase isozymes firstly increased, and then decreased until the activation was almost lost. The content of glycogen also decreased in the experimental group. The changes of EST activity revealed that the snails have certain detoxification effect at low concentration of the molluscicide. However, the detoxification systems were destroyed completely with the time extended or at higher concentration of stemona alkaloids. The extracts of *Alternanthera philoxeroides*, *Nerium Indicum Mill*, *Pterocarya stenoptera DC*, and *Rumex japonicum Houtt* all exhibited similar effect on the activity of EST in *O. hupensis* snails (Feng et al. 2008; Wang et al. 2006).

The MDA content of the liver in snails increased significantly after being treated with the water extract of *Arisaema erubescens* schott (Ke et al. 2006). However, the activities of POD and SOD in the treated liver were decreased significantly. The water extract of *Arisaema erubescens* schott could cause an oxidative damage and an obvious decrease of antioxidant ability of *O. hupensis* liver, which might play an key role in reducing the detoxification ability of liver and, finally, resulting in the death of snails.

Conclusion and future outlook

There is no doubt that molluscicides may play an important role in controlling of schistosomiasis transmission in endemic countries (Zhang et al. 2019). Novel ideal molluscicides should fulfill the following requirements (Fenwick 1987; Cao and Wang 2008; Huang 2019a, b): (1) high

toxicity to snails at low concentration; (2) very low acute and chronic toxicity to non-target organisms; (3) without adverse effect in the food chain; (4) good stability for 18 months or more; (5) acceptable cost and safe for users. For chemical molluscicides, on the one hand, developing new chemical entities (NCE) is a promising strategy for snail controlling through rational drug design on molecular levels. Therefore, hunting appropriate drug targets of snail is crucial for pharmacologists. Exploring the effect of the present molluscicides on key enzyme activity of snails should provide important references for the development of novel enzyme inhibitors to kill snails (Xiong et al. 2018). On the other hand, developing new formulations based on the available molluscicides (such as niclosamide, LDS, PPU07) is an alternative method in practical applications. Novel formulations such as WPN, NESDP, SCN, and ECN have also been successfully utilized in endemic areas (Xu et al. 2005). However, the stability of these new formulations should be screened, and simultaneously require more field experiments in future works.

Plant molluscicides attract more and more attention. However, some unfavorable factors should not be overlooked (Li et al. 2002): (1) low content of the active ingredients resulted in low molluscicidal activity; (2) regional limitations for some specific molluscicidal plants; (3) relative complicated extraction process resulting in high cost; (4) environmental pollution because of the application of fresh molluscicidal plants. In addition, for plant molluscicides, the characterization of the structures of active ingredients is also very important, which could provide the reference for the development of novel chemical molluscicides and later modifications (Whitfield 1996). However, developing novel, low-toxicity, and highly effective plant molluscicides and elucidating the possible mechanism in detail are still great challenges.

For laboratory and field testing of molluscicides for schistosomiasis (WHO (World Health Organization) 2019), we have: (1) for the new candidate molluscicide compound and for new end-use formulations of existing molluscicide compounds, an optimum effective dose should be determined based on the dose–response curve. The manufacturer's label claim may also be considered to decide the optimum dose to be tested; (2) the efficacy of exposure in immersion bioassay and residual activity at this effective dose is then determined according to the immersion bioassay. The efficacy cut-off is the 80% mortality and the effective residual action is the duration until when the mortality in treatments remains $\geq 80\%$; (3) a dose–response curve is needed to determine LC_{50} and LC_{95} values. The results are recorded in a standard data recording form. The relationship between dose and mortality is analyzed using log-probit (Finney 1971) or logit regression; (4) from the dosages tested against a target species in the small-scale or simulated field trials, the

minimum efficacious dosage (mortality and residual effect) should be selected as the optimum field application dosage for each type of habitat; (5) the WHO cut-off for the efficacy of a molluscicide formulation against adult snails is $\geq 80\%$ mortality in 24 h post-exposure. The residual efficacy of the molluscicide is calculated as the duration (days) when mortality in snails remains $\geq 80\%$.

The present mechanism investigations for chemical and natural molluscicides focus on the simple interactions between molluscicides and some enzymes, and lack visual evidence in structural biology. Therefore, investigating the structure biology of target enzymes/proteins and studying the corresponding the action sites could help in designing novel molluscicides to combat snails (Wu et al. 2006). We believe that the original and innovative molluscicides will soon emerge after the above issues are resolved by more scientists, followed by a prompt growth in advancements.

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Declarations

Conflict of interest The authors declare no competing interests.

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