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Mini Review

Secondary metabolites and biological activity of *Pentas* species: A minireview





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ABSTRACT

Article history: Received 25 October 2017 Revised 20 December 2017 Accepted 21 December 2017 Available online 27 December 2017 The genus *Pentas* belongs to the Rubiaceae family, which contains approximately 40 species. Several *Pentas* species were reported to be used as a folk treatment by African indigenous people in treating some diseases such as malaria, tapeworms, dysentery, gonorrhea, syphilis and snake poisoning. This article covers the period from 1962 to 2017 and presents an overview of the biological activity of different

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2090-1232/© 2018 Production and hosting by Elsevier B.V. on behalf of Cairo University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). Keywords: Pentas Lanceolata Rubiaceae Anthraquinone Iridoid Antiplasmodial Healing

Introduction

The genus *Pentas* belongs to the botanical plant family Rubiaceae. It consists of about 40 species, many of them used widely by indigenous people in Africa as medicinal plants. It is a flowering plant found mainly as an herb or shrub (*P. bussi* and *P. nobilis*), herb or subshrub (*P. lanceolata* and *P. zanzibarica*) or subshrub only (*P. paviflora*). The stem length varies between 60 and 2 m in the case of subshrubs and between 2 and 4 m if a shrub. The shape of the leaves is ovate, oblong, lanceolate or elliptic, while the flower shape is dismorphus, subsessile or unimorphous [1].

This genus is commonly used in the treatment of tropical and other diseases such as malaria (*P. micrantha* and *P. longiflora*) [2,3], tapeworms (*P. longiflora*), itchy rashes and pimples [4] (*P. longiflora* and *P. decora*), gonorrhea, syphilis and dysentery (*P. brussei*), cough (*P. micrantha*) [4], dysmenorrhea, headache and pyrexia (*P. purpurea*) [5], hepatitis B [6], mental illness and epilepsy (*P. schimperiana*) [7], lymphadenitis, abdominal cramps, ascariasis, snake poisoning, retained placenta and some veterinary diseases (*P. lanceolata*) [8,9].

Iridoids and highly oxygenated compounds have been shown to be the most common secondary metabolites of this genus. These plants have not been intensively studied to determine their biological characteristics. Several reports have found that some of their biological activity is antimalarial and antimicrobial [10–13]. However, *P. lanceolata* is the only species that has been tested for analgesic and wound-healing properties, whereas very few examples were studied as having antitumor characteristics [11,14–16]. The secondary metabolites that were identified in this genus are a common feature of the Rubiaceae family; however, there are some examples that have only been expressed in this genus [17]. This review endeavors to provide a comprehensive and up-to-date compilation of documented biological activities and the phytochemistry of the *Pentas* genus.

Phytochemical screening of Pentas species

The chemistry of *Pentas* species does not exhibit great diversity. The common active constituents of *Pentas* species can be considered chemotaxonomic markers. The main groups of secondary metabolites that were isolated are simple phenolic compounds, naphthoquinones, napthohydroquinones, anthraquinones, and iridoids. Furthermore, few examples of alkaloids, triterpenes, sterols, and chromenes were identified. The isolated compounds, structures, species, solvents of extraction and extracted organs are compiled in the Tables 1–8) which are displayed below.

Simple phenolic compounds

Two examples of simple phenolics (**1** and **2**) were identified in the colleters of *P. lanceolata* by GC–Ms chromatography in a greater amount than in the stipules without colleters (Table 1) [18].

Pentas species and describes their phytochemical traits. As a conclusion, the main secondary metabolites from Pentas species are quinones, highly oxygenated chromene-based structures, and iridoids. Pentas species are widely used in folk medicine but they have to be more investigated for their medicinal properties. © 2018 Production and hosting by Elsevier B.V. on behalf of Cairo University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Naphthoquinones

P. longiflora was the only source among the genus *Pentas* from which naphthoquinones (**3**–**7**) were separated. Pantagolin **3** [19] and isagarin **5** were identified for the first time in the roots of *P. longiflora*, whereas psychorubrin **4** is a common constituent of other Rubiaceae species: *Psychotria camponutans* [20] and *Mitracarpus frigidus* (Table 2) [17].

Naphthohydroquinones

Busseihydroquinone A **8** [23] and the very recently discovered parvinaphthols A **10** and B **11** [24] were named after *P. bussei* and *P. parvifolia*, respectively. They are as well as the naphthohydroquinones (**9** and **11**) have been identified only in *Pentas* species (Table 3).

Chromene-based structures

This class of compounds is widespread in different species of *Pentas* as well as the other members of Rubiaceae. Compounds **14–17**, **25** and **28** were discovered as novel compounds in 2003 in *P. longiflora*, *P. bussei*, and *P. parvifolia*. Additionally, an isolation of known compounds **21–24** from the root of *P. longiflora* [22,25] was reported; these were similarly identified in another plant of Rubiaceae (*Rubia cordifolia*) [26]. Scopoletin **13** is a very common coumarin found broadly in many genera of Rubiaceae [17] (Table 4).

Anthraquinones

The anthraquinones are the major class of secondary metabolites in *Pentas*. They are also commonly found as mixtures of closely related pigments in the Rubiaceae family. Some members of this family have been used for centuries as a source of natural dye for textiles [17]. Many *Pentas* species produced anthraquinones in the form of aglycone (**30–42**) (Table 5) [10,11,22,25,21] or as glycosides (**43–46**) (Table 6) [24,25,29]. Two dimeric structures of anthraquinone named schimperiquinones, A **47** and schimperiquinones B **48** (Table 6), were isolated from *P. schimperi* as novel structures in 2014 [30]. Anthraquinones seem to be very important to the antiplasmodial activity expressed by *Pentas* [10].

Iridoids

Iridoids are monoterpenoid cyclopentanopyran type glycosides [31], which are common constituents of *P. lanceolata*. The first study to identify iridoids in *P. lanceolata* was performed by Schripsema and his coworkers in 2007 [32]. In this study, seven iridoid glycosides were identified from the aerial parts of *P. lanceolata*. Furthermore, asperuloside **49** and asperulosidic acid **50**, which are characteristic iridoids of Rubiaceae, and five iridoids **51–55** were isolated (Table 7) [32]. The ethanolic extract of *P. lanceolata*

Simple phenolics identified in P. lanceolata.

Isolated compound	Structure	Species	Extract/Organ	Ref.
4-Hydroxycinnamic acid 1	он	P. lanceolata	MeOH/Colleters	[18]
Thymol 2	HO			

Table 2

Naphthoquinones (3–7) isolated from P. longiflora.

Isolated compound	Structure	Species	Extract/Organ	Refs.
Pentalongin 3		P. longiflora	Hexane, (DCM/MeOH)/Root	[19]
Psychorubrin 4	О			[10]
Isagarin 5			Hexane/Root	[21]
Methyl 2,3-epoxy-3-prenyl-1,4-naphthoquinone-2-carboxylate ${f 6}$				[22]
Methyl 3-prenyl-1,4-naphthoquinone-2-carboxylate 7				

Table 3

Naphthohydroquinones (8-12) isolated from Pentas species.

Isolated compound	Structure	Species	Extract/Organ	Refs.
Busseihydroquinone A 8 $R_1 = H, R_2 = OH, R_3 = OCH_3, R_4 = CH_3, R_5 = H$		P. bussei	Crystallized out as needles from (DCM/MeOH)/Root	[23]
Methyl 8-hydroxy-1,4,6,7-tetramethoxy-2-naphthoate 9 R1 = CH ₃ , R ₂ = OH, R ₃ = OCH ₃ , R ₄ = CH ₃ , R ₅ = H	R40		Hexane/Root	[25]
Parvinaphthols A 10	Ŕ₅ Ó	P. parvifolia	(DCM/MeOH)/Root	[24]
$R_1 = H, R_2 = OH, R_3 = OH, R_4 = CH_3, R_5 = H$				
Parvinaphthols B 11				
$R_1 = H, R_2 = H, R_3 = H, R_4 = H, R_5 = OH$				
1,4,5-Trihydroxy-3-methoxy-6-(3,7,11,15,19-pentamethyleicosa-2,	ОН		EtOAc/Root	[25]
6,10,14,18-pentaenyl)naphthalene 12				

(Forssk.) Deflers was analyzed. A total of 12 compounds were identified, and ten of them were iridoid glucosides. Among these, compounds **57–60** were identified for the first time in *P. lanceolata* in addition to a new iridoid **61** (Table 7) [28]. Recently, two new iridoids, namely, 13*R*-methoxy-*epi*-gaertneroside **56** and 13*S*-methoxy-*epi*-gaertneroside **57**, were identified by way of bio-guided sub-fractionation. They were identified in the immunomodulatory active sub-fractions of *P. lanceolata* (Table 7) [35].

Terpenes, sterols, saponins, and alkaloids

These classes of secondary metabolites are not common in *Pentas* species. They have only been isolated from *P. lanceolata*. These are triterpenes (oleanolic **58** and ursolic acids **59**), sterols (campesterol **60**, β -stigmasterol **61**) and sesquiterpene (caryophyllene **62**) was found in the colleters of *P. lanceolata* (Table 8) [17,18]. The identified alkaloids **71** and **72** were an oxindole skeleton (Table 8) [36].

Chromene-based structures (**13–29**) separated from *Pentas* species.

solated compound	Structure	Species	Extract/Organ	Refs.
copoletin 13		P. longiflora	EtOAc/Root	[22]
/lethyl 5,10-dihydroxy-7-methoxy-3-methyl-3-(4-methyl-3-pentenyl)-3H-benzo[f] chromene-9-carboxylate 14	HOLOO	P. bussei P. parvifolia	Hexane/Root	[27] [25]
	ОН			[]
Methyl 5,10-dihydroxy-7-methoxy-1,1,3a-trimethyl-1a,2,3,3a,10c,10d-hexahydro-1 <i>H</i> -4- oxacyclobuta[3,4]indeno[5,6- <i>a</i>]naphthalene-9-carboxylate 15		P. bussei		
	O H H H			
-Methoxy-2-methyl-2-(4-methyl-3-pentenyl)-2H-benzo[h]-chromene-7,10-diol 16	HO	P. bussei,P. parvifolia		
-Methoxy-2,2-dimethyl-2 <i>H</i> -benzo[<i>h</i>]chromene-7,10-diol 17	но стон			
Busseihydroquinone B 18	OH	P. bussei	(DCM/MeOH)/	[23]
	0 HO	P. parvifolia	Root DCM/Root	[25]
Busseihydroquinone C 19		P. bussei	(DCM/MeOH)/ Root	[23]
Busseihydroquinone D 20		Ť		
Aollugin 21		P. longiflora	Hexane, (DCM/	[22,28
	HO	P. lanceolata	MeOH) /Root MeOH/Colleter	[18]
-Hydroxymollugin 22	о о	P. longiflora	Hexane/Root	[22]
-Methoxymollugin 23			DCM/Root	
	HO			
rans-3,4-Dihydroxy-3,4-dihydromollugin 24 is-3,4-Dihydroxy-3,4-dihydromollugin 25	он он		Hexane/Root	
Parvinaphthols C 26 R = Me Busseihydroquinone E 27		1 P. parvifolia P. bussei	2 (DCM/MeOH)/ Root	3 [24]

Table 4	(continu	ed)
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Isolated compound	Structure	Species	Extract/Organ	Refs.
[(3α,3'α,4β,4'β)-3,3']-Dimethoxy- <i>cis</i> - [4,4' <i>-bis</i> (3,4,5,10-tetrahydro-1 <i>H</i> -naphtho[2,3-c] pyran)]-5,5',10,10'-tetraone 28		P. longiflora	Hexane/Root	[22]
Busseihydroquinone E 29		3.1 P. parvifolia	3.2 (DCM/ MeOH)/Root	3.2 [24]

0 R₁

Anthraquinones (30-42) that are abundant in different species of Pentas.

Isolated compound	Derivati	/es				Species	Extract/Organ	Refs
	R ₁	R ₂	R ₃	R ₄	R ₅			
Tectoquinone 30	Н	CH ₃	Н	Н	Н	P. micrantha	MeOH, (DCM/MeOH)/Root	[11]
						P. lanceolata	(DCM/MeOH)/Root	[10]
Rubiadin 31	OH	CH ₃	OH	Н	Н	P. micrantha	MeOH,(DCM/MeOH)/Root	[11]
						P. zanzibarica	MeOH/Stem	[22
						P. lanceolata	(DCM/MeOH)/Root	[10]
Rubiadin-1-methyl ether 32	OCH ₃	CH ₃	OH	Н	Н	P. micrantha	MeOH, (DCM/MeOH)/Root	[11]
						P. zanzibarica	Methanol/Stem	[22
						P. lanceolata	(DCM/MeOH)/Root	[10]
Nordamnacanthal 33	OH	СНО	OH	Н	Н			[11]
Damnacanthal 34	OCH ₃	CHO	OH	Н	Н	P. micrantha	MeOH, (DCM/MeOH)/Root	[11]
						P. zanzibarica	MeOH/Stem	[22
						P. lanceolata	(DCM/MeOH)/Root	[10
Lucidin-ω-methyl ether 35	OH	CH ₂ OCH ₃	OH	Н	Н	P. micrantha	MeOH, (DCM/MeOH) /Root	[11
						P. lanceolata	(DCM/MeOH)/Root	[10
Damnacanthol 36	OCH ₃	CH ₂ OH	OH	Н	Н	P. micrantha	MeOH, (DCM/MeOH)/Root	[11
						P. lanceolata	(DCM/MeOH)/Root	[10
5,6-Dihydroxylucidin-11-O-methyl ether 37	OH	CH ₂ OCH ₃	OH	OH	OH	P. micrantha	MeOH, (DCM/MeOH)/Root	[11
5–6-Dihydroxydamnacanthol 38	OCH ₃	CH ₂ OH	OH	OH	OH			[11
						P. lanceolata	(DCM/MeOH)/Root	10
Munjistin ethyl ester 39	OH	COOCH ₃	OH	Н	Н	P. micrantha	MeOH, (DCM/MeOH) /Root	[11
40	Н	OCH ₃	CH ₃	Н	Н	P. longiflora	DCM/Root	[25
41	CH ₃	Н	OH	Н	Н	0,1	,	
42	Н	CH ₂ OH	Н	Н	Н	P. schimperi	EtOAc/Stem bark	[30

Biological activities of Pentas species

Antiplasmodial activity

Endale and his coworker discussed the antiplasmodial activities of *P. longiflora* and *P. lanceolata*. They mentioned that the dichloromethane/methanol (1:1) extract of the roots indicated *in vitro* antiplasmodial activity against chloroquine-resistant (W2) (IC₅₀: $0.93 \pm 0.16 \mu$ g/mL) and chloroquine-sensitive (D6) strains (IC₅₀: 0. $99 \pm 0.09 \mu$ g/mL) of *Plasmodium falciparum* [10]. Pentalongin **3** and psychorubrin **4** (Table 2) were tested against the same strains, W2 and D6, in the same study. The IC₅₀ values of the first were 0. 27 ± 0.09 and $0.23 \pm 0.08 \mu$ g/mL, respectively, and for compound **4** (Table 2) were 0.91 ± 0.15 and $0.82 \pm 0.24 \mu$ g/mL, respectively [10]. However, all of the previous results were lower than the reference compounds, which were chloroquine and mefloquine [10]. In 2013, those researchers found that the crude methanol root extract of *P. micrantha*, which is used as an antimalarial in East Africa, exhibited moderate antiplasmodial activity against W2 (IC₅₀: $3.37 \pm 0.74 \mu g/mL$) and D6 (IC₅₀: $4.00 \pm 1.86 \mu g/mL$) strains. Anthraquinones

30–36 and **38–39** (Table 5) were examined for the same strains, but they were not active [11].

Antimicrobial properties

P. decora was used traditionally in Western Uganda as an antifungal [12]. This common medicinal usage encouraged Ahumuza et al. to analyze the plant to determine whether this traditional use has a scientific basis or not. The ethanolic extract

Anthraquinones glycosides (43-46) and anthraquinone dimers (47, 48) that are distributed in different Pentas species.



Isolated compound	Derivatives		Species	Extract/Organ	Refs.
	R ₁	R ₂			
Rubiadin-1-methylether-3- O - β -primeveroside 43	OCH ₃	CH ₃	P. bussei	EtOAc/Root	[25]
			P. lanceolata	MeOH/Root,	
				50% EtOH/Leaves	
			P. zanzibarica	MeOH/Stem	[29]
Rubiadin-3-O-β-primeveroside 44	OH	CH ₃	P. parvifolia	MeOH/Root	[25]
			P. zanzibarica	MeOH/Stem	[29]
Damnacanthol-3-O-β-primeveroside 45	OCH ₃	CH ₂ OH	P. parvifolia	MeOH/Root	[25]
			P. bussei		
			P. zanzibarica	MeOH/Stem	[29]
Lucidin-3- O - β -primeveroside 46	OH	CH ₂ OH	P. parvifolia	MeOH/Root	[25]
			P. bussei		
			P. zanzibarica	MeOH/Stem	[29]
Schimperiquinones A 47	0	0	P. schimperi	EtOAc/Stem bark	[30]
$R_1 = OH, R_2 = CH_3$, İ ,	İ .			
Schimperiquinones B 48	r y y	$\uparrow \uparrow \uparrow \uparrow \uparrow \uparrow \uparrow$			
$R_1 = H, R_2 = OH$					
		$\dot{R}_2 \dot{R}_2 \parallel$			

of *P. decora* leaves was studied for four fungal strains: *Epidermophyton floccosum, Microsporum canis, Trichophyton rubrum* and *Candida albicans.* The inhibitory zone of 2000 mg/mL of the plant extract was 4.8 ± 0.4 and 3.7 ± 0.2 mm against *C. albicans* and *M. canis,* respectively, while the other two fungal strains were not sensitive. Both results were greater than that of clotrimazole. They attributed the results to the presence of alkaloids and terpenoids, which are well-known to be biologically active in the treatment of fungal infections [12]. The ethanolic extract of *P. longiflora* (100, 500 and 100 µg/mL in 95% ethanol) was tested among another 19 extracts of some medicinal Rwandese plants against *Mycobacteria.* It inhibited the growth of *M. simiue* and *M. avium* at a concentration of 1000 µg/mL, whereas *M. tuberculosis* was less sensitive to it [13].

Wound healing

The ethanol flower extract of *P. lanceolata* was evaluated for its effect on wound healing. This was assessed using an excision wound model. Significant increments in granulation tissue weight, tensile strength, glycosaminoglycan, and hydroxyproline content were found. A group of rats treated with the extract at 150 mg/kg/day for 10 days *via* the oral route showed incremental improvement in the wound contraction relative to the untreated one, which may be due to increased collagen deposition, alignment, and maturation [14].

Analgesic effect

Suman et al. reported that *n*-hexane of leaves of *P. lanceolata* exhibited significant activity in relieving the pain from the acetic acid-induced writhing method [15]. The percentage of inhibitory activity was 61.91% at a dose of 200 mg/kg of the extract, whereas it was 75% at 150 mg/kg of aspirin.

Immunomodulatory activity

Ethyl acetate and *n*-butanol extracts of *P. lanceolata* and 13*R*epi-gaertneroside **52** (Table 7) were discovered to be immunostimulants at both the humoral and cellular levels. This evaluation was performed on specific-pathogen-free chickens vaccinated against Newcastle disease (ND) virus. Increases in lymphocytes and macrophages were observed in the blood of poultry. These fractions (Ethyl acetate and *n*-butanol extracts of *P. lanceolata*), in addition to compound **52** (Table 7), appeared to decrease the mortality from ND in chickens [35].

Antitumor activity

Minimal literature has found a cytotoxic effect in the Pentas species. The methanolic root extract of P. micrantha and anthraquinones 30-36 and 38-39 (Table 5) revealed low cytotoxicity on the breast cancer cell line MCF-7 [11]. The compounds busseihydroquinone E 29 (Table 4), busseihydroquinone C 19 (Table 4), and rubiadin-1-methyl ether 32 (Table 5) exhibited the most potent cytotoxic activity within a survey done for some quinones separated from the roots of P. parvifolia and P. bussei. They had IC_{50} values of 62.3, 48.4 and 54.4 μM against the MDA-MB-231 ER-negative human breast cancer cell line, respectively [24]. Damnacanthal 34 (Table 5) proved to have a moderate influence on CCRF-CEM leukemia cells (IC₅₀: $3.12 \pm 0.27 \mu$ M) and against the drug-resistant cell line MDA-MB-231-BCRP (IC₅₀: $7.02 \pm 0.51 \mu$ M) by apoptosis in comparison with doxorubicin. This antiproliferative activity was attributed to reactive oxygen species (ROS) production and mitochondrial membrane potential (MMP) disruption [16].

Conclusions and future perspective

The main active constituents that were purified from *Pentas* are quinones, highly oxygenated chromene-based structures, and

Iridoids from P. lanceolata.

Isolated compound	Structure	Species	Extract/Organ	Refs.
Asperuloside 49	H. H	P. lanceolata	MeOH/Aerial parts MeOH/Colleter EtOH/Entire plant	[32] [18] [33,34]
Asperulosidic acid 50			MeOH/Stem and leaves EtOH/Entire plant	[32] [33,34
Tudoside 51	GGIC COOCH3		MeOH/Colleter EtOH/Entire plant	[18] [28]
13 <i>R-epi</i> -Gaertneroside 52		P. lanceolate	MeOH/Aerial parts	[32]
13 <i>R-epi</i> -Epoxygaertneroside 53	HO HO H H O H O H O G G COOCH ₃ O H O G G COOCH ₃		EtOH/Entire plant	[28]
E-Uenfoside 54 Z-Uenfoside 55	HO H H H COOCH ₃ H OGIC OH		MeOH/Aerial parts EtOH/Entire plant	[32] [28]
.oganin 56	он но-(MeOH/Colleter	[18]
Deacetyl-asperulosidic acid 57	HO COOH		EtOH/Entire plant	[28]
xoside 58	он боіс соон			
Griselinoside 59	OCH OGIC OCOCH3			
5β,7β-Epoxysplendoside 60	H ₃ CO- COOCH ₃			
61	HO OH OGIC COOCH3 H OGIC OH OGIC		EtOH/Entire plant	[28]
	но			

(continued on next page)

Table 7 (continued)

Isolated compound	Structure	Species	Extract/Organ	Refs.
13 <i>R</i> -Methoxy- <i>epi</i> -gaertneroside 62 13 <i>S</i> -Methoxy- <i>epi</i> -gaertneroside 63	COOCH ₃ COOCH ₃ OGIC H ₃ CO-, HO	P. lanceolate	80% Aqueous MeOH/Aerial parts	[35]

Table 8

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Terpenes, sterols, Saponin and Oxindole alkaloids identified in P. lanceolata.

Isolated compound	Structure	Species	Extract/Organ	Refs.
Oleanolic acid 64 R ₁ , R ₂ = CH ₃ Ursolic acid 65 R ₁ = H, R ₂ , R ₃ = CH ₃		P. lanceolata	MeOH/Colleter	[17,18]
Campesterol 66		P. lanceolata	MeOH/Colleter	[17,18]
β-Stigmasterol 67	HO			
Caryophyllene 68	H			
3-0-β-fucosyl-quinovic acid 69	Гисове-0		50% EtOH/Leaves	[36]
Quermiside 70	Соон			
Speciophylline 71			100% EtOH/Leaves	
72				

iridoids. *P. lanceolata* has represented the sole source of iridoids, whereas the naphthoquinones have been attributed exclusively to *P. longiflora* until now. *Pentas* species are widely used in folk medicine in many tropical regions. However, more attention should be paid to this plant in terms of its medicinal properties.

The most interesting medicinal use of *Pentas* is antimalarial (which is attributed to the anthraquinones) and wound-healing activity; however, it did not show very promising antitumor activity. Further investigation should be conducted to evaluate this plant group with biological assays to address this research gap.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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