Journal of Applied Pharmaceutical Science Vol. 10(07), pp 116-126, July, 2020
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2020.10715
ISSN 2231-3354

Bioactive compounds of *Boesenbergia* sp. and their anti-inflammatory mechanism: A review

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ARTICLE INFO

Received on: 04/11/2019
Accepted on: 23/05/2020
Available online: 04/07/2020

Key words:
B. rotunda, flavonoid, kaempferol, panduratin A, quercetin, Zingiberaceae.

ABSTRACT

Boesenbergia sp. (*Zingiberaceae*) has been empirically used in Indonesia, to treat rheumatism. The rhizome of *Boesenbergia rotunda* contains essential oils (nerol, camphor, cineole, fenchene, hemanthidine, and limonene), flavonoids (alpinetin, boesenbergin, cardamonin, pinostrobin, pinocembrin, geraniol, panduratin, and silybin), and polyphenols (caffeic acid, coumaric acid, chlorogenic acid, hesperidin, kaempferol, naringin, and quercetin), which explain its many interesting pharmacological activities (antifungal, anti-inflammatory, antimicrobial, antibacterial, anticancer, antimutagenic, antiparasitic, antiulcer, antileukemia, hepatoprotective, and antiviral). This review focuses on the bioactive compounds in *Boesenbergia* sp. and their molecular mechanism in reducing inflammation. Of all bioactive compounds, panduratin A and 4-hydroxypanduratin A have proven their activity in inhibiting the production of nitric oxide and PGE_2 as well as on tumor necrosis factor-alpha. Moreover, this paper also provides other uses of this plant species as well as future study aspects.

INTRODUCTION

Inflammation is the body's response in combatting pathogens or destructing chemicals (cytokines and histamines). The cascade of inflammatory-related mediators frames the acute inflammatory response, which is activated by recruiting granular white blood cells and frequently resolves the outcome recovery. Understanding how the inflammatory process is triggered might be beneficial for developing the strategies to inhibit the inflammatory responses (Ward and Lentsch, 1999).

Various therapeutics are being used to stop or reduce the inflammation process, such as nonsteroidal anti-inflammatory drugs and corticosteroids. Unfortunately, these drugs have been reported, case by case, for their unfavorable effects, for example, the increase of blood pressure, peptic ulceration, acute kidney dysfunction, and other serious conditions (Attiq *et al*., 2017).

The plants of Zingiberaceae family, for example, *Boesenbergia rotunda* (L.) Mansf. (Eng-Chong *et al*., 2011; Jing *et al*., 2010; Yusuf *et al*., 2013), *Renealmia alpinia* (Nunez *et al*., 2004), and *Zingiber zerumbet* (Taha *et al*., 2010), have been extensively investigated for their potential phytoconstituents and molecular mechanism.

Boesenbergia rotunda contains various phytoconstituents, classified into two major groups – namely, flavonoids and chalcone derivatives (pinocembrin, pinostrombin, alpinetin, panduratin, cardamonin, quercetin, and kaempferol) (Eng-Chong *et al*., 2012; Rosdianto *et al*., 2020), which might indicate a great benefit for drug discovery (Jing *et al*., 2010; Yusuf *et al*., 2013). Since this plant serves as the wide range of traditional medicine applications, many thorough studies were carried out to assess its pharmacology activities, such as antiulceration (Abdelwahab *et al*., 2011), hepatoprotective (Mahmood *et al*., 2010; Salama *et al*., 2013), *Helicobacter pylori* inhibitor (Bhamarapravati *et al*., 2006), anti-inflammatory (Isa *et al*., 2012), anticancer (Cheah *et al*., 2011; Isa *et al*., 2013), antiallergic (Madaka & Tewtrakul, 2011), antibacterial (Udomthanadech *et al*., 2015; Zainin *et al*., 2013), antileptospiral (Chander *et al*., 2016), antioxidant (Chiang *et al*., 2017), anti-dengue viral (Chee *et al*., 2010; Kiat

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et al., 2006), antiherpes viral (Wu *et al*., 2011), wound-healing (Mahmood *et al*., 2010), antimutagenic, antibacterial, antifungal, analgesic, antipyretic, antispasmodic, insecticidal, larvicidal, and pupicidal (Ching *et al*., 2007; Jaiptech *et al*., 2010; Phukerd *et al*., 2013) activities.

This review focuses on the bioactive compounds in *Boesenbergia* sp. and their mechanism as anti-inflammatory agents. Moreover, this paper also provides other utilities of *Boesenbergia* sp. as well as its future study aspects (Table 1). The required pieces of information were obtained by searching keywords which include *Boesenbergia*, Zingiberaceae, flavonoids, kaempferol, panduratin, and quercetin, among published articles until March 2020 in authentic scientific databases.

Methods

The literature search was performed on PubMed database using the following keywords: "*Boesenbergia* sp." [Medical Subject Headings (MEeSH) terms] or "Zingiberaceae" [all fields] and "*B. rotunda*" [Subheading] or "Zingiberaceae" [all fields] or "bioactive compounds" [all fields] or "bioactive compounds" [all fields] or "pharmacological activity of *B. rotunda*" [MeSH terms] or "pharmacological activity of *B. rotunda*" [all fields] or "anti-inflammatory activity of *B. rotunda*" [MeSH terms] or "anti-inflammatory activity of *Boesenbergia* sp." [all fields]. A search on other scientific databases using the same keywords was done for additional data.

Ethnobotany Facts

Zingiberaceae, a family of lasting herbs, are aromatic, with fleshy tuberous or nontuberous rhizomes. Zingiberaceae plants are widely distributed throughout the tropics, especially in Indonesia, and comprise 150 species of ginger (Habsah *et al*., 2000; Ibrahim *et al*., 2010). Ginger plants are extensively utilized to enhance food taste, cure diseases, beverages, perfume, and so forth (Abdelwahab *et al*., 2010; Taha *et al*., 2010). Recent molecular studies such as chloroplast DNA, nuclear internal transcribed spacer, random amplified polymorphic DNA, plastid regions, pollen-based classifications, amplified fragment length polymorphism, and single-strand conformation polymorphism have been employed to taxonomically classify *Boesenbergia* species (Chen and Xia, 2011; Kress *et al*., 2002; Techaprasan *et al*., 2006; Techaprasan *et al*., 2008; Vanijajiva *et al*., 2005).

Phytoconstituents

The active phytoconstituents of *B. rotunda* are (1) flavonoids including alpinetin, boesenbergin, cardamonin, pinostrobin, pinocembrin, geraniol, panduratin, and silybin (Fig. 1) (Ching *et al*., 2007; Morikawa *et al*., 2008; Yusuf *et al*., 2013); (2) essential oils including camphor, cineole, fenchene, hemanthidine, and limonene (Fig. 2) (Baharudin *et al*., 2015); and (3) polyphenols including caffeic acid, coumaric acid, chlorogenic acid, hesperidin, kaempferol, naringin, and quercetin (Fig. 3) (Jing *et al*., 2010; Rosdianto *et al*., 2020).

Anti-Inflammatory Mechanism of Boesenbergia sp.

Table 1 shows all the pharmacological activities of *B. rotunda*; however, this review study will only focus on the anti-inflammatory mechanism of this plant.

In the Asia region, particularly in Indonesia, *B. rotunda* has been empirically utilized to treat various types of inflammation. Its flavonoids (panduratin A, 4-hydroxypanduratin A, cardamonin, 2′,4′,6′-trihydroxychalcone, uvangoletin, panduratin C, boesenbergin A, 2′,6′-dihydroxy-4′-methoxychalcone, hydroxypanduratin A, (−)-isopanduratin A, (+)-krachaizin B, (−)-krachaizin B, quercetin, and kaempferol) extracted from the tuberous root of *B. pandurata* had been studied for their anti-inflammatory activity (Chahyadi *et al*., 2014; Isa *et al*., 2012; Rho *et al*., 2011; Tewtrakul *et al*., 2009; Tuchinda *et al*., 2002; Yun *et al*., 2003).

Panduratin A and Hydroxypanduratin A inhibit TNF-α and the production of nitric oxide

Nitric oxide (NO) plays a key role in maintaining vascular function. The overproduction of NO could damage the tissue and is related to acute and chronic inflammation. An anti-inflammatory study in Thailand reported that phytoconstituents isolated from the extract of *B. rotunda* strongly inhibit NO production, for example, panduratin A, hydroxypanduratin A, and cardamonin. Moreover, a medium strength of inhibitory activity on tumor necrosis factor-alpha (TNF-α) was observed for both panduratin A and hydroxypanduratin A (Tewtrakul *et al*., 2009). The NO inhibitors are favorable because NO regulates cerebral blood flow and nociception in migraine-induced animal models (Wong and Lerner, 2015).

Panduratin A and Hydroxypanduratin A inhibit PGE_2 production

Prostaglandin synthase catalyzes two separate reactions: (1) the addition of O_2 to oxygenate the arachidonic acid molecule until an unstable prostaglandin G_2 (PGG_2) is produced and (2) PGG_2 then migrates to the peroxidase site where it reacts with the hemin group to generate prostaglandin H_2 (PGH_2) (Levita *et al*., 2009). PGH_2 is subsequently converted into the active PGE_2, PGI_2, PGD_2, $PGF_{2\alpha}$, and thromboxane A_2 (Nørregaard *et al*., 2015). Both panduratin A and hydroxypanduratin A strongly inhibit PGE_2 production (Tewtrakul *et al*., 2009). The inhibition of PGE_2 production could lessen inflammatory symptoms and pain (Sugita *et al*., 2016).

Boesenbergia rotunda inhibits the infiltration of inflammatory cells in the hepatic bile ducts

The extract of *B. rotunda* reduces the inflammation caused by *Opisthorchis viverrini* and induced by N-nitrosodimethylamine administration in rats. This study proved that there was a decrease in the number of inflammatory cells infiltrated into the hepatic bile ducts as well as the serum alanine transaminase and direct bilirubin level (Boonjaraspinyo *et al*., 2010).

Boesenbergia rotunda accelerates wound healing in rats

A wound recovery is a dynamic process of repairing cellular structures in damaged tissue. Wound abridgment occurs throughout the recovery process commencing in the fibroblastic stage followed by the proliferative stage (Midwood *et al*., 2004). Flavonoids have been proven to promote the wound-healing process due to their antimicrobial activities, which is responsible for wound contraction and increased the rate of epithelialization.

Table 1. Pharmacology activity of *B. rotunda.*

Pharmacology activity	Study	Extract dose	Result	References
Anti-inflammatory	*In vivo* and *in vitro*	20, 200, and 2,000 µg/ear	IC_{50} of hydroxypanduratin A and panduratin A were 84 and 12 µg/ear, respectively.	Tuchinda *et al*., 2002
			methanol (MeOH) extract, NO (IC_{50} = 0.175 µM), and PGE_2 (IC_{50} = 0.0195 µM)	
	In vitro	Not mentioned	5-Hydroxy-7-methoxyflavone (IC_{50} = 5.3 µM)	Yun *et al*., 2003
			5-Hydroxy-3,7,4′-trimethoxyflavone (IC_{50} = 30.6 µM	
			5-Hydroxy-7,4′-dimethoxyflavone (IC_{50} = 24.5 µM)	
			5-Hydroxy-3,7,3′,4′-tetramethoxyflavone (IC_{50} = 16.1 µM)	
	In vitro	5-Hydroxy-3,7-dimethoxyflavone; 370 mg	5-Hydroxy-3,5,7,4′-tetramethoxyflavone (IC_{50} = 24.7 µM)	Tewtrakul *et al*., 2009
		5-Hydroxy-7-methoxyflavone; 230 mg		
		5-Hydroxy-3,7,4′-trimethoxyflavone; 280 mg		
		5-Hydroxy-7,4′-dimethoxyflavone; 125 mg		
		5-Hydroxy-3,7,3′,4′-tetramethoxyflavone; 54 mg		
		3,5,7-Trimethoxyflavone;		
		not mentioned.		
			Reduction in the inflammatory cells surrounding the hepatic bile ducts.	
		Fingerroot diet.	NO IC_{50} of kaempferol, α-rhamnoisorobin, afzelin, and kaempferitin was 15.4, 37.7, >100, and >100	
		Not mentioned.	NF-kB: nuclear factor-kappaB-mediated luciferase assays, respectively.	
			IC_{50} kaempferol and α-rhamnoisorobin were 15.4 and 37.7 µg/ml, respectively.	Boonjaraspinyo *et al*., 2010
	In vivo and *in vitro*		IC_{50} of boesenbergin A was significant at 12.5–50 µg/ml	
		Not mentioned		Rho *et al*., 2011
	In vitro			Isa *et al*., 2012
	In vitro			

continued

Pharmacology activity	Study	Extract dose	Result	References
Aphrosidiac	*In vivo*	60, 120, and 240 mg/kg	Ethanol extract increased the diameter of seminiferous tubules and the weights of the testicular and seminal vesicle.	Sudwan *et al*., 2007
			Fresh juice rhizome increased the fertility by improving sperm's quality.	
			The aqueous extract increased sperm count and motility, increased testis and epididymis weight, and increased serum testosterone level.	
		60, 120, and 600 mg/kg	MeOH extract increased serum testosterone level and percentage of sperm viability and motility.	Yotarlai *et al*., 2011
	In vivo			
		500 and 100 mg/kg/day		Morakinyo *et al*., 2008
	In vivo			
		100 and 300 mg/kg/day		Mazaheri *et al*., 2014
	In vivo			
Antimicrobial				
Anti-*H. pylori*	*In vitro*	200 µg/ml	Pinostrombin minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) were 125 and 150 µg/ml, respectively.	Bhamarapravati *et al*., 2006
			MIC: 3.125	
	In vivo and	Not mentioned	Inhibition *H. pylori* infection	Mahady *et al*., 2006
	in vitro	Fed with *B. rotunda*		
Antiamoeboic activity for HIV patient	*In vitro*	1,000 µg/ml	$CHCl_3$ extract IC_{50} 45.8 µg/ml; MeOH extract IC_{50} 57.6 µg/ml	Sawangjaroen *et al*., 2006
Antimutagenic	*In vitro*	Not mentioned	The antimutagenic IC_{50} values of pinocembrin chalcone, cardamonin, pinocembrin, pinostrombin, hydroxypanduratin A, and panduratin A were 5.2 ± 0.4, 5.9 ± 0.7, 6.9 ± 0.8, 5.3 ± 1.0, 12.7 ± 0.7, and 12.1 ± 0.8 µM, respectively.	Trakoontivakorn *et al*., 2001
			5-Hydroxy-7-methoxyflavanone, 5,7-dihydroxyflavanone, and 7-hydroxy-5-methoxyflavanone have an antimutagenic activity percentage of 56.5%, 93.0%, and 96.5%, respectively.	
	In vivo	30 and 60 mg/kg		Atun *et al*., 2013

continued

Pharmacology activity	Study	Extract dose	Result	References
Antiparasitic	*In vitro*	31.25–1,000 µg/ml	$CHCl_3$ and MeOH extract MIC values of 250 and 250, respectively.	Sawangjaroen *et al*., 2005
			$CHCl_3$ and MeOH extract IC_{50} 44.48 and 78.30 µg/ml, respectively.	
Antibacterial	*In vitro*	10 µl of 1% extract	MeOH extract MIC and MBC values ranged 0.019–2.5 and 0.039–5.0 µg/ml, respectively.	Zainin *et al*., 2013
			$CHCl_3$ extract MIC methicillin-resistant Staphylococcus aureus (MRSA) and *Streptococcus mutans* values >512 and 512 µg/ml, respectively	
			MetOH extract MIC MRSA and *Streptococcus mutans* values >512 and 512 µg/ml, respectively.	
	In vitro	250 µg/disk	$CHCl_3$ extract MIC_{50} and MIC_{90} 7.81 µg/ml.	Voravuthikunchai *et al*., 2005
			Ethanol extract MIC value 16 µg/ml.	
	In vitro	Not mentioned		Limsuwan and Voravuthikunchai, 2013
				Teethaisong *et al*., 2018
	In vitro	20 µl extract		
Antifungal	*In vitro*	1,000 µg/ml	MIC 8–10 µg/ml and >=10% (v/v).	Sawangjaroen *et al*., 2006
Antiulcer	*In vivo* and *in vitro*	50, 100, 200, and 400 mg/kg	MeOH extract inhibition (%) reduction ulcer index for doses 50, 100, 200, and 400 mg/kg were 50.72%, 66.82%, 84.98%, and 95.22%, respectively.	Abdelwahab *et al*., 2011
Anticancer	*In vivo* and *in vitro*	10–100 µg/ml	Ethanol extract IC_{50} MCF-7, HT-29, and SF 3,169 cells values were 21.3 ± 0.3, 32.5 ± 1.5, and 49.5 ± 2.6 µg/ml, respectively.	Kirana *et al*., 2003
			IC_{50} against LS174T and MCF-7 cells were 12.0 ± 1.6 and 31.7 ± 5.4 µg/ml, respectively.	
			MeOH extract IC_{50} 13.5 µM (PC3 cell lines) and 14 µM (DU145 cell lines).	
	In vivo and *in vitro*	100 µg/ml	Inhibition of apoptotic-related procaspases 3, 6, 8, and 9	Zaeoung *et al*., 2005
	In vivo and *in vitro*		MeOH extract IC_{50} 71 ± 1.41 µg/ml (CaOV3 ovarian cancer); 66.5 ± 2.12 µg/ml (MB-231); 51 µg/ml (MCF-7); 65.5 ± 2.12 µg/ml (HeLa); 52 ± 4.24 µg/ml (HT-29)	Yu *et al*., 2003
		10–100 µg/ml	MeOH IC_{50} 4.4 µg/mL (A549 cell)	
	In vivo and *in vitro*			Jing *et al*., 2011
	In vivo and *in vitro*	10–100 µg/ml		Cheah *et al*., 2011
		10–100 µg/ml		
Antileukemia	*In vivo* and *in vitro*	30, 15, 7.5, 3.75, 1.875, 0.9375, and 0.46875 µg/ml	Hexane and $CHCl_3$ extract inhibit the growth of HL-60 cancer cell lines.	Sukari *et al*., 2007
Antiviral	*In vivo* and *in vitro*	100 µg/ml	$CHCl_3$ and MeOH extract inhibition (%) HIV-1 protease were 64.92% and 51.92%, respectively.	Tewtrakul *et al*., 2003
			IC_{50} panduratin A (18.7 ± 0.8 µM) and hydroxypanduratin A (5.6 ± 0.7 µM)	
	In vitro	100 µM		Cheenpracha *et al*., 2006

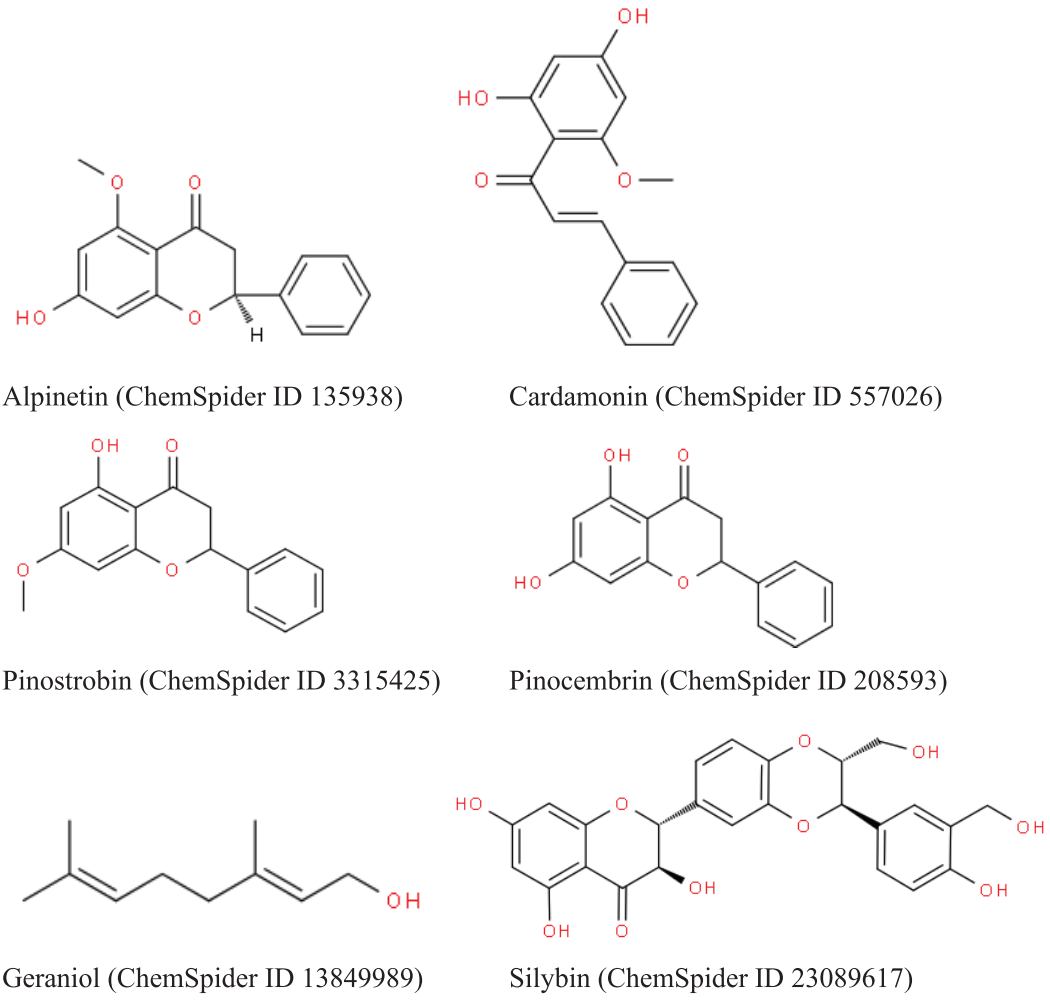


Figure 1. 2D structure of flavonoids in *B. rotunda* (downloaded from http://www.chemspider.com/).

Flavonoids could inhibit lipid peroxidation by preventing the onset of cell necrosis and improving vascularity. Therefore, any compound that reduces lipid peroxidation is predicted, which might be able to enhance the viability of collagen fibers, increase blood circulation, halt the cell damage, and stimulate the DNA synthesis (Getie *et al*., 2002).

The ethanolic extract of *B. rotunda* rhizome could accelerate wound healing in rats (Mahmood *et al*., 2010). This plant extract, which contains various types of free radical scavenging molecules – for example, flavonoids and polyphenols, has exhibited antioxidant activity (Shindo *et al*., 2006). Antioxidants significantly play an important role in the wound-healing process and block the oxidative damage (Martin, 1996).

Boesenbergia rotunda and pinostrobin reduce ulcer inflammation

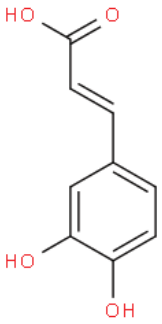
Boesenbergia rotunda has been utilized empirically to cure ulcers by the people in Thailand and Indonesia. The antiulcer activity of the methanol extract of *B. rotunda* and its phytoconstituent pinostrobin has been studied by Abdelwahab *et al.* It was reported that *B. rotunda* extract and pinostrobin revealed the cytoprotective effects on ulcer-induced rats. This plant extract also significantly decreased submucosal edema and leukocyte infiltration (Abdelwahab *et al*., 2011).

Boesenbergia rotunda and panduratin A as anticancer

Kirana *et al*. (2003) assayed through eleven species of *Zingiberaceae* and discovered that *B. rotunda* and *Zingiber aromaticum* indicated the highest inhibition toward the growth of MCF-7 breast cancer and human HT-29 colon cancer cells (Kirana *et al*., 2003). An additional study of panduratin A on the same cell lines has also proven similar potent inhibitory properties and a nontoxic result to the rats (Kirana *et al*., 2007).

B. rotunda volatile oils revealed cytotoxic activities against MCF-7 (IC_{50} 31.7 ± 5.4 µg/ml) and LS174T cell lines (Zaeoung *et al*., 2005). In a separate study, Jing *et al*. (2011) demonstrated that *B. rotunda* possessed a moderate inhibitory activity against $CaOV_3$ ovarian cancer, breast cancer malone dialdehyde-MB-231, MCF-7, HeLa cervical cancer, and HT-29 colon cancer cell growth as compared to three other *Boesenbergia* species: *B. pulchella* var. *attenuate* and *B. armeniaca* (Jing *et al*., 2011).

In 2006, Yun *et al.* demonstrated that panduratin A could prevent the growth of prostate cancer cell lines (PC3 and DU145) in a time- and dose-dependent manner. An immunofluorescence



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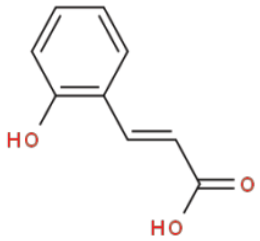

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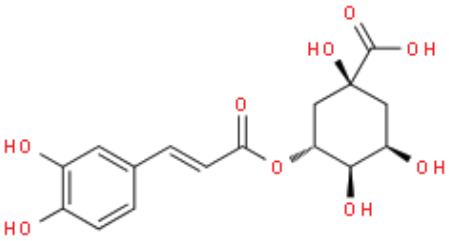

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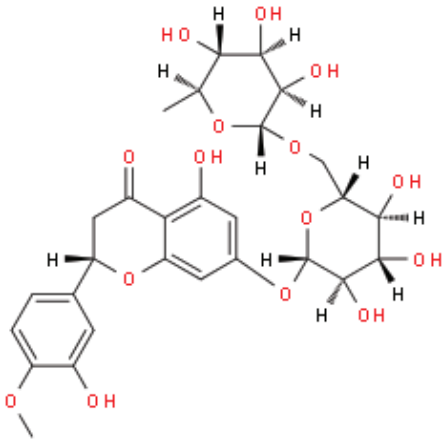

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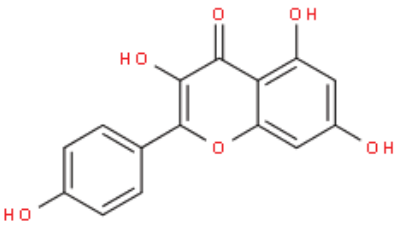

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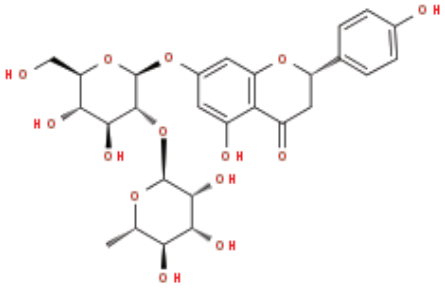
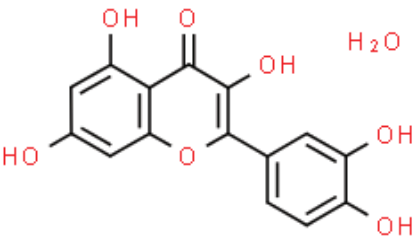


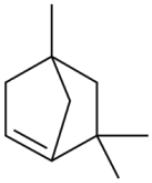
Naringin (ChemSpider ID 390868)



Quercetin (ChemSpider ID 12269344)

Figure 2. 2D structure of essential oils in *B. rotunda* (downloaded from http://www.chemspider.com/).

Camphor (ChemSpider ID 139902)



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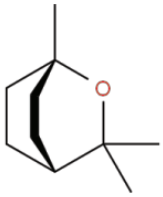
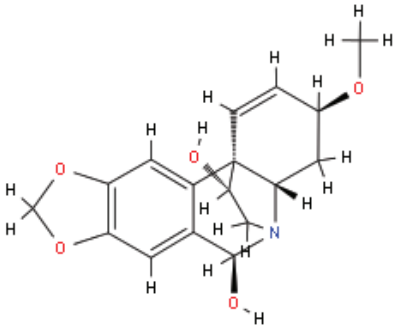


Cineole (ChemSpider ID 21111689)



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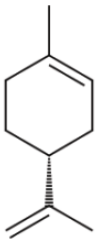

Limonene (ChemSpider ID 389747)

Figure 3. 2D 2D structure of polyphenols in *B. rotunda* (downloaded from http://www.chemspider.com/).

assay revealed that panduratin A activated the induction of apoptosis in both cell lines by inhibiting apoptotic-related procaspases 3, 6, 8, and 9 (Yun *et al*., 2006). Panduratin A also exhibited inhibitory activities against the growth of A549 human non-small cell lung cancer cells (Cheah *et al*., 2011).

The antileukemia activity of *B. rotunda* rhizome extracts has been investigated and revealed that the chloroform extract and boesenbergin A could inhibit the growth of HL-60 cell line (Sukari *et al*., 2007).

Panduratin A inhibits NF-kappaB translocation to the nucleus

Panduratin A could inhibit the translocation of NF-kappaB from the cytoplasm to nuclei (Cheah *et al*., 2011).

Toxicity Study

The toxicity of the *B. rotunda* extract was studied in normal healthy rats by exposing the animals to high doses of the rhizome extract (2 and 5 g/kg of BW) (Mahmood *et al*., 2010; Manosroi *et al*., 2017; Salama *et al*., 2012). An *in vivo* study indicated that the ethanol extract of *B. rotunda* was not toxic as there were no significant changes in the body weight of the rats. Moreover, all hematological and histopathological parameters did not show any adverse changes (Lim, 2016; Saraithong *et al*., 2010). Meanwhile, pinostrobin and pinocembrin revealed no mutagenic effect or toxicity toward Wistar rats, which confirmed the safety of these compounds (Charoensin *et al*., 2010).

CONCLUSION

The traditional utilities of *B. rotunda* rationalize that this plant could be upgraded to the next level of drug discovery study. Nonetheless, the molecular mechanism of panduratin A and 4-hydroxypanduratin A of *B. rotunda* has described their activity in inhibiting the production of nitric oxide and PGE_2 as well as on TNF-α. Panduratin A also inhibits the translocation of NF-kappaB to the nucleus, which might contribute to this plant's anti-inflammatory activity. Furthermore, the ethanolic extract of *B. rotunda* was considered not toxic as it did not alter the body weight and hematological parameters of rats.

ACKNOWLEDGMENT

The publication fee is funded by Doctoral Dissertation Grant 2019 of the Ministry of Research and Technology and Higher Education, the Republic of Indonesia (10/E1/KP.PTNBH/2019).

CONFLICTS OF INTEREST

There are no conflicts of interest related to the publication of this paper.

FUNDING

None.

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How to cite this article:
Rosdianto AM, Puspitasari IM, Lesmana R, Levita J. Bioactive compounds of *Boesenbergia* sp. and their anti-inflammatory mechanism: A review. J Appl Pharm Sci, 2020; 10(07):116–126.