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

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**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, anticanncer, antitumoragenic, antiparasitic, antiucler, 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 PGE2, 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 combating 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 alpina* (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, pinostrobin, 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 (Bhmarapravati 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), anti leptospiral (Chander et al., 2016), antioxidant (Chiang et al., 2017), anti-dengue viral (Chee et al., 2010; Kiat...
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) (Bahrurudin 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 (cardamomin, 2′,4′,6′-trihydroxychalcone, uva-colin, 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 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 PGE2 Production

Prostaglandin synthase catalyzes two separate reactions: (1) the addition of O2 to oxygenate the arachidonic acid molecule until an unstable prostaglandin G2 (PGG2) is produced and (2) PGG2 then migrates to the peroxidase site where it reacts with the heme group to generate prostaglandin H2 (PGH2) (Levita et al., 2009). PGH2 is subsequently converted into the active PGE2, PGI2, PGD2, PGF2α, and thromboxane A2 (Norregaard et al., 2015). Both panduratin A and hydroxy-panduratin A strongly inhibit PGE2 production (Tewtrakul et al., 2009). The inhibition of PGE2 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.

<table>
<thead>
<tr>
<th>Pharmacology activity</th>
<th>Study</th>
<th>Extract dose</th>
<th>Result</th>
<th>References</th>
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<tbody>
<tr>
<td>Anti-inflammatory</td>
<td>In vivo and in vitro</td>
<td>20, 200, and 2,000 µg/ear</td>
<td>IC₅₀ of hydroxypanduratin A and panduratin A were 84 and 12 µg/ear, respectively. Methanol (MeOH) extract, NO IC₅₀ = 0.175 µM, and PGE₂ IC₅₀ = 0.0195 µM</td>
<td>Tuchinda et al., 2002</td>
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<td></td>
<td>In vitro</td>
<td>Not mentioned</td>
<td>5-Hydroxy-7-methoxyflavone IC₅₀ = 5.3 µM, 5-Hydroxy-3,7,4′-trimethoxyflavone IC₅₀ = 30.6 µM, 5-Hydroxy-7,4′-dimethoxyflavone IC₅₀ = 24.5 µM, 5-Hydroxy-3,7,3′,4′-tetramethoxyflavone IC₅₀ = 16.1 µM</td>
<td>Yun et al., 2003</td>
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<td></td>
<td>In vitro</td>
<td>5-Hydroxy-3,7-dimethoxyflavone; 370 mg</td>
<td>Reduction in the inflammatory cells surrounding the hepatic bile ducts.</td>
<td>Tewtrakul et al., 2009</td>
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<td>5-Hydroxy-7-methoxyflavone; 230 mg</td>
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<td>5-Hydroxy-3,7,4′-trimethoxyflavone; 280 mg</td>
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<td></td>
<td>5-Hydroxy-7,4′-dimethoxyflavone; 125 mg</td>
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<td>5-Hydroxy-3,7,3′,4′-tetramethoxyflavone; 54 mg</td>
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<td></td>
<td></td>
<td>3,5,7-Trimethoxyflavone; not mentioned</td>
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<td></td>
<td>In vivo and in vitro</td>
<td>Not mentioned</td>
<td>NO IC₅₀ of kaempferol, α-rhamnoisorobin, afzelin, and kaempferitin was 15.4, 37.7, &gt;100, and &gt;100</td>
<td>Boonjaraspinyo et al., 2010</td>
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<td></td>
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<td>5-Hydroxy-3,5,7,4′-tetramethoxyflavone IC₅₀ = 24.7 µM</td>
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<td>In vitro</td>
<td>Not mentioned</td>
<td>NF-κB: nuclear factor-kappaB-mediated luciferase assays, respectively. IC₅₀ of kaempferol and α-rhamnoisorobin were 15.4 and 37.7 µg/ml, respectively.</td>
<td>Rho et al., 2011</td>
</tr>
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<td></td>
<td>In vitro</td>
<td></td>
<td>IC₅₀ of boesenthergin A was significant at 12.5–50 µg/ml</td>
<td>Isa et al., 2012</td>
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<th>Pharmacology activity</th>
<th>Study</th>
<th>Extract dose</th>
<th>Result</th>
<th>References</th>
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<tr>
<td>Aphrodisiac</td>
<td><em>In vivo</em></td>
<td>60, 120, and 240 mg/kg</td>
<td>Ethanol extract increased the diameter of seminiferous tubules and the weights of the testicular and seminal vesicle. 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. MeOH extract increased serum testosterone level and percentage of sperm viability and motility.</td>
<td>Sudwan <em>et al.</em>, 2007</td>
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<td></td>
<td><em>In vivo</em></td>
<td>60, 120, and 600 mg/kg</td>
<td></td>
<td>Yotarlai <em>et al.</em>, 2011</td>
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<td></td>
<td><em>In vivo</em></td>
<td>500 and 100 mg/kg/day</td>
<td></td>
<td>Morakinyo <em>et al.</em>, 2008</td>
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<td></td>
<td><em>In vivo</em></td>
<td>100 and 300 mg/kg/day</td>
<td></td>
<td>Mazaheri <em>et al.</em>, 2014</td>
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<tr>
<td><strong>Antimicrobial</strong></td>
<td><em>In vitro</em></td>
<td>200 µg/ml</td>
<td>Pinostrombin minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) were 125 and 150 µg/ml, respectively. MIC: 3.125 Inhibition <em>H. pylori</em> infection</td>
<td>Bhamarapravati <em>et al.</em>, 2006</td>
</tr>
<tr>
<td>Anti-<em>H. pylori</em></td>
<td><em>In vitro</em></td>
<td>1,000 µg/ml</td>
<td>CHCl₃ extract IC₅₀ 45.8 µg/ml; MeOH extract IC₅₀ 57.6 µg/ml</td>
<td>Sawangjaroen <em>et al.</em>, 2006</td>
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<td>Antiamoebic activity for HIV patient</td>
<td><em>In vitro</em></td>
<td>1,000 µg/ml</td>
<td>The antimutagenic IC₅₀ values of pinocembrin chalcone, cardamonin, pinocembrin, pinostrombin, hydroxy panduratin 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. 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.</td>
<td>Trakootivakorn <em>et al.</em>, 2001</td>
</tr>
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<td>Antimutagenic</td>
<td><em>In vitro</em></td>
<td>Not mentioned</td>
<td></td>
<td>Atun <em>et al.</em>, 2013</td>
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<td></td>
<td><em>In vivo</em></td>
<td>30 and 60 mg/kg</td>
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<tr>
<th>Pharmacology activity</th>
<th>Study</th>
<th>Extract dose</th>
<th>Result</th>
<th>References</th>
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<tbody>
<tr>
<td>Antiparasitic</td>
<td><em>In vitro</em></td>
<td>31.25–1,000 µg/ml</td>
<td>CHCl₃ and MeOH extract MIC values of 250 and 250, respectively. CHCl₃ and MeOH extract IC₅₀ 44.48 and 78.30 µg/ml, respectively.</td>
<td>Sawangjaroen et al., 2005</td>
</tr>
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<td>Antibacterial</td>
<td><em>In vitro</em></td>
<td>10 µl of 1% extract</td>
<td>MeOH extract MIC and MBC values ranged 0.019–2.5 and 0.039–5.0 µg/ml, respectively. CHCl₃ extract MIC methicillin-resistant Staphylococcus aureus (MRSA) and Streptococcus mutans values &gt;512 and 512 µg/ml, respectively. MeOH extract MIC MRSA and Streptococcus mutans values &gt;512 and 512 µg/ml, respectively.</td>
<td>Zainin et al., 2013</td>
</tr>
<tr>
<td>Antifungal</td>
<td><em>In vitro</em></td>
<td>1,000 µg/ml</td>
<td>MIC 8–10 µg/ml and &gt;10% (v/v).</td>
<td>Sawangjaroen et al., 2006</td>
</tr>
<tr>
<td>Antil ulcer</td>
<td><em>In vivo and in vitro</em></td>
<td>50, 100, 200, and 400 mg/kg</td>
<td>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.</td>
<td>Abdelwahab et al., 2011</td>
</tr>
<tr>
<td>Anticancer</td>
<td><em>In vivo and in vitro</em></td>
<td>10–100 µg/ml</td>
<td>Ethanol extract IC₅₀ 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. IC₅₀ against LS174T and MCF-7 cells were 12.0 ± 1.6 and 31.7 ± 5.4 µg/ml, respectively. MeOH extract IC₅₀ 13.5 µM (PC3 cell lines) and 14 µM (DU145 cell lines).</td>
<td>Kirana et al., 2003</td>
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<td></td>
<td><em>In vivo and in vitro</em></td>
<td>100 µg/ml</td>
<td>Inhibition of apoptotic-related procaspases 3, 6, 8, and 9</td>
<td>Zaeoung et al., 2005</td>
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<td></td>
<td><em>In vivo and in vitro</em></td>
<td>10–100 µg/ml</td>
<td>MeOH extract IC₅₀ 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)</td>
<td>Yu et al., 2003</td>
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<td><em>In vivo and in vitro</em></td>
<td>10–100 µg/ml</td>
<td>MeOH IC₅₀ 4.4 µg/mL (A549 cell)</td>
<td>Jing et al., 2011</td>
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<td></td>
<td><em>In vivo and in vitro</em></td>
<td>10–100 µg/ml</td>
<td>Hexane and CHCl₃ extract inhibit the growth of HL-60 cancer cell lines.</td>
<td>Cheah et al., 2011</td>
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<td>Antileukemia</td>
<td><em>In vivo and in vitro</em></td>
<td>30, 15, 7.5, 3.75, 1.875, 0.9375, and 0.46875 µg/ml</td>
<td>Hexane and CHCl₃ extract inhibit the growth of HL-60 cancer cell lines.</td>
<td>Sakari et al., 2007</td>
</tr>
<tr>
<td>Antiviral</td>
<td><em>In vivo and in vitro</em></td>
<td>100 µg/ml</td>
<td>CHCl₃ and MeOH extract inhibition (%) HIV-1 protease were 64.92% and 51.92%, respectively. IC₅₀ panduratin A (18.7 ± 0.8 µM) and hydroxypanduratin A (5.6 ± 0.7 µM)</td>
<td>Tewtrakul et al., 2003</td>
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<td></td>
<td><em>In vitro</em></td>
<td></td>
<td>100 µM</td>
<td>Cheenpracha et al., 2006</td>
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</table>
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 (IC₅₀ 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 CaOV₃ ovarian cancer, breast cancer male dehydro-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
Figure 2. 2D structure of essential oils in *B. rotunda* (downloaded from http://www.chemspider.com/).

Caffeic acid (ChemSpider ID 600426)  Coumaric acid (ChemSpider ID 553146)

Chlorogenic acid (ChemSpider ID 405788)  Hesperidin (ChemSpider ID 10176)

Kaempferol (ChemSpider ID 4444395)  Naringin (ChemSpider ID 390868)

Quercetin (ChemSpider ID 12269344)
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-a. 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.

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CONFLICTS OF INTEREST

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

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