

## Fingerroot (*Boesenbergia pandurata*) : A Prospective Anticancer Therapy

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### Abstract

Beside as a spice in Indonesian cooking, Fingerroot (*Boesenbergia pandurata*) regularly is used as a mixture of herbal medicine. Scientifically, the phytochemical content of the fingerroot rhizome showed some therapeutical effects such as antibacterial, anti-inflammatory, anti or pro-oxidant, and also anticancer. In this article, we summarize some studies especially about anticancer activity of fingerroot and its constituent compound. We found that fingerroot is capable of inhibiting various pathways of cell physiology processes. One potential pathway to be inhibited by fingerroot is Poly (ADP-ribose) polymerase (PARP) which has role in apoptotic induction. In the future, it is necessary to purify the extract to obtain maximum efficacy and also formulation studies of fingerroot will be interesting to do to.

**Keywords :** *fingerroot, anti-cancer, chemopreventive, herbal medicine*

### FINGERROOT AND THE UTILIZATION BY THE SOCIETY

Fingerroot (*Boesenbergia pandurata*) (Figure 1) are members of the Zingiberaceae tribe that grows widely in Southeast Asia (Chahyadi, et al., 2014). Fingerroot are perennial plants with short stems replaced by pseudostems and formed by leaf sheaths and can grow up to 50 cm. The leaves of this plant in general 3-4 strands with a width of 7-11 cm and a length of 25-50 cm. The leaves are undivided and oval or elongated. Fingerroot rhizome surfaces are light brown and the inner rhizome is yellow, oval-shaped and has a very aromatic odor. The rhizome resembles the radius growing from the center (Delin & Larsen, 2000). In Indonesian Herb Pharmacopeia, it described that that the length of rhizome is approximately 25 mm, width to 15 mm and thickness 2 - 5 mm.

Regularly, fingerroot is used as a mixture of herbal medicine or as a spice in cooking in Indonesia (Tewtrakul, et al., 2003). In addition, the fingerroot is also utilized as natural dyes and traditional remedies (Ongwisespaiboon & Jiraungkoorskul, 2017). According to the traditional heritage, mentioned in a book published by AgroMedia (2007), fingerroot are often used to sprue, dry cough, skin diseases or diarrhea. The phytochemical content of the fingerroot rhizome has been used as antibacterial, anticancer, anti-inflammatory, and antioxidant (Zainin, et al., 2013; Udomthanadech, et al., 2015; Cheah, et al., 2011; Isa, et al., 2012; Chiang, et al., 2017).

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Figure 1. *Boesenbergia pandurata*.

## CONSTITUENT COMPOUND OF FINGERROOT

Fingerroot have been identified to contain a wide variety of flavonoid compounds and essential oils that have a wide range of biological activities. Flavonoids are the most common secondary metabolites found in fingerroot. More than 51 pieces of flavonoid constituent compounds in fingerroot have been isolated and determined by their structure and the three main flavonoids of which are chalcone, flavanon and flavones (Chahyadi, *et al.*, 2014) (Figure 2).

Chalcone compounds contained in fingerroot is like cardomin, cardamonin, boesenbergin A, boesenbergin B, dihidromethoxychalcone and panduratin A, (Jantan, *et al.*, 2001) and its isomers, such as isopanduratin A, isopanduratin A1, hydroxypancluesin (Nguyen, *et al.*, 2017). While the flavanon founded in fingerroot including

pinostrobin, pinocembrin, alpinetin and 5-hydroxy-7-methoxyflavonone (Jantan, *et al.*, 2001). Flavones themselves do not have the prenylated derivatives found in fingerroot. Some examples of non-prenylated flavonoids contained in the fingerroot rhizome derived from chalcone and hydrochalcone classes (Chahyadi, *et al.*, 2014). Furthermore, Morikawa, *et al.* (2008) also reported four new compounds, two diastereomers of rotundaflavones Ia and Ib, and IIa and IIb together with two previously discovered compounds, 5,7-dihydroxy-8-geranylflavanone and 7-methoxy-5-hydroxy 8-geranylflavanone.

Fingerroot is reported to contain a variety of essential oils that have identified their structure and activity. Essential oils in the fingerroot consist of oxygenated and non-oxygenated monoterpenes. The main compounds of essential oils most commonly found in the fingerroot constituents are  $\gamma$ -terpinene, geraniol, camphor,  $\beta$ -ocimene, 1,8-cineole, myrcene, borneol, camphene, methyl cinnamate, terpineol, geranial, and neral (Pandji, *et al.*, 1993; Jantan, *et al.*, 2001; Norajit, *et al.*, 2007; Miksusanti, *et al.*, 2008). In addition, there are also small volatile oils such as nerolidol, citral, limonene, and 11-dodecen-1-ol (Norajit, *et al.*, 2007).

## ANTICANCER ACTIVITY OF FINGERROOT

Various effects of fingerroot rhizomes have been found in both the extract and the isolates of the compounds contained. Fingerroot extracts known

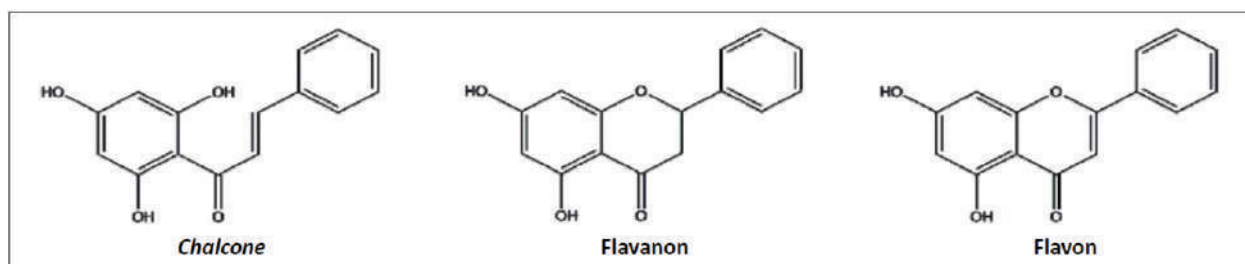


Figure 2. Chalcone, flavanone, and flavone structures. They are the main flavonoid compounds present in the fingerroot (Chahyadi *et al.*, 2014).

to have anticancer effects include, methanolic extracts, ethanolic extracts, and chloroform extracts. Furthermore, the synthesis and isolate compounds of the fingerroot also have anticancer effects, including panduratin A, boesenbergin A, cardamonin, and pinostrobin. Chemoprevention effect are possessed by extracts and/ or fingerroot rhizome isolates include antioxidant activity, apoptotic induction, cell cycle modulation, and anti-angiogenesis.

Fingerroot methanolic extracts are known to act as tumor promoters inhibitors in EBV-induced human B-lymphoblastoid (Raji) cell cells (Murakami, *et al.*, 1993). In addition, according to research Kirana, *et al.* (2007), the fingerroot ethanolic extract was able to reduce the formation of aberrant crypt foci in azoxymethane-induced mouse modeling. Meanwhile, chloroform extract from the fingerroot was known to have cytotoxic activity against HL-60

blood cell cancer and pancreatic cancer cells PANC-1 (Sukari, *et al.*, 2007; Win, *et al.*, 2007) (Table 1.)

Panduratin A, is a typical isolated constituent compound. This compound is able to induce apoptosis and modulate the cell cycle. Panduratin A is able to induce apoptosis in HT-29 colon cancer cells via PARP cleavage and decreased procaspase-3 levels. In prostate cancer cells such as PC3 and DU145, panduratin A induces apoptosis through PARP cleavage and acinus degradation (Yun, *et al.*, 2006). Meanwhile in A549 lung cancer cells, panduratin A inhibits the translocation of NF-κB from the cytoplasm to the nucleus causing apoptosis (Cheah, *et al.*, 2011).

Moreover, Panduratin A is able to modulate the cell cycle in G0/G1 phase in colon cancer cells of HT-29 (Kirana, *et al.*, 2007) and cell cycle arrest in G2/M phase in A549 lung cancer cells (Cheah, *et*

**Table 1. Chemoprevention Effects of Fingerrot Extracts.**

Extracts	Chemoprevention effect	Biological effects	References
Methanol extracts	Tumor promoters inhibitor	Inhibition of EBV-induced promoter tumor in human B-lymphoblastoid cells (Raji).  Antiproliferative effect against five cancer cell lines: ovarian (CaOV3), breast (MDA-MB-231 and MCF-7), cervical (HeLa) and colon (HT-29) cancer cell lines.	Murakami, <i>et al.</i> , 1993  Jing, <i>et al.</i> , 2010
Ethanol extracts	-	Reduced formation of aberrant crypt foci in azoxymethane-induced mouse modeling.  Antiproliferative effect against T47D breast cancer cells.  Anti-proliferative activity and apoptosis induction against HeLa and vero cell lines.	Kirana, <i>et al.</i> , 2007  Ujjantari, <i>et al.</i> , 2009  Listyawati, 2015
Chloroform extracts	-	Cytotoxic activity against human promyelocytic cancer cells (HL-60) and human pancreatic cancer cells (PANC-1).  Antiproliferative effect against T47D breast cancer cells.	Sukari, <i>et al.</i> , 2007 Win, <i>et al.</i> , 2007  Atun and Arianingrum, 2015

*al.*, 2011). In the context of antimetastasis studies, panduratin A significantly showed inhibition of MMP-2 secretion in A549 lung cancer cells through inhibition of NF- $\kappa$ B (Cheah, *et al.*, 2013). *In vivo* study also mentioned that panduratin isolates proved to inhibit MMP-9 (Hwang, 2013) (Table 2).

The second most studied compound in the fingerroot is boesenbergin A which is the first prenylated flavonoid isolated from the fingerroot. Boesenbergin A is able to induce apoptosis through stimulation of caspase-9 expression, caspases-3, -6, -7; the increase of Bax: Bcl-2 ratio; and an increase in the number of ROS in A549 lung cancer cells. In the same cancer cell, boesenbergin A is capable of causing cell cycle arrest in the sub-G1 phase (Isa, *et al.*, 2013) (Table 3).

Cardamonin which is a chalcone compound contained in the fingerroot has anti-cancer stem cells activity. *In vitro*, cardamonin is able to inhibit stem cell-related gene expressions, such as ALDH1, SOX2, c-MYC, OCT4, NANOG and stem cell-associated histone modifier genes, ie EZH2, SETDB1, and SMYD3. In addition, in xenograft

mice modeling, cardamonin with doxorubicin was able to inhibit tumor growth and reduce CSCs pools *in vivo* by eliminating doxorubicin-upregulated "stemness" genes (Jia, *et al.*, 2016) (Table 4).

Pinostrobin has anti-angiogenesis activity and is able to induce apoptosis. According to Parwata, *et al.* (2014), oral administration of pinostrobin may inhibit fibrosarcoma growth in benzopiren-induced mice. In addition, pinostrobin is able to inhibit the path of bFGF and VEGF on the chorio allantois membrane of chicken embryos induced by basic fibroblast growth factor (Pratomo, *et al.*, 2014). Furthermore, pinostrobin was also able to increase ROS levels by up to two-fold compared to cell control without treatment in PC12 renal cell modeling (Xian, *et al.*, 2012) (Table 5).

## THE PROSPECT OF FINGERROOT AS ANTICANCER THERAPY

Fingerroot have been explored as a potential anti-cancer, both extracts, and isolates. Related studies of fingerroot encompass *in vitro*

**Table 2. Chemoprevention Effects of Panduratin A.**

Extracts	Chemoprevention effect	Biological effects	References
Apoptosis induction	PARP, procaspase-3	Causes PARP cleavage and procaspase-3 decrease in HT-29 colon cancer cells.	Yun, <i>et al.</i> , 2006
	PARP	Causes PARP cleavage and acinus degradation in PC3 and DU145 prostate cancer cells.	Yun, <i>et al.</i> , 2006
Cell cycle modulation	-	Cell cycle arrest at G0/G1 phase in HT-29 colon cancer.	Kirana, <i>et al.</i> , 2007
Apoptosis induction and cell cycle modulation	NF- $\kappa$ B	Induces apoptosis by inhibiting NF- $\kappa$ B translocation from cytoplasm to nucleus and cell cycle arrest at G2/M phase in A549 cell.	Cheah, <i>et al.</i> , 2011
Antimetastasis	MMP-2	Inhibit MMP-2 secretion in 549 lung cancer cells through NF- $\kappa$ B inhibition by <i>in vitro</i> study.	Cheah, <i>et al.</i> , 2013
	MMP-9	Inhibit MMP-9 secretion in 549 by <i>in vivo</i> study.	Hwang, 2013

**Table 3. Chemoprevention Effects of Boesenbergin A.**

Extracts	Chemoprevention effect	Biological effects	References
Apoptosis induction	Caspase-9, caspases-3, -6, -7, Bax, Bcl-2	Stimulates caspase-9 expression and caspases -3, -6, and -7, and increases Bax: Bcl-2 ratio in A549 cell.	Isa, et al., 2013
	ROS	Stimulates ROS in A549 lung cancer cells.	Isa, et al., 2013
Cell cycle modulation	-	Cell cycle arrest at sub-G1 phase on A549 cell.	Isa, et al., 2013

and *in vivo* studies. *In vitro* studies of fingerroot activities include breast cancer cells, lung cancer, colon cancer, blood cancer, pancreatic cancer, prostate cancer. Meanwhile, previous *in vivo* studies have used azoxymethane-induced mouse modeling, benzopyrene-induced mice, and xenograft mice modeling. As well as the reported studies, fingerroot show their potential as a potent chemopreventive agent. Fingerroot is capable of inhibiting various pathways of cell physiology processes such as cell cycle modulation, apoptotic induction, tumor promoters inhibitor, anti-angiogenesis, anti-cancer stem cells, and pro-oxidant activity.

Anticancer activity of fingerroot is closely related to the constituent which is contained in the fingerroot rhizomes. There are four compounds in fingerroot that are potential to be developed

as anticancer, ie panduratin A, boesenbergin A, cardamonin, and pinostrobin. Therefore, future study is focused on the development of these four compounds either in the form of extract or compound isolate. So it is necessary to purify the extract to obtain maximum efficacy.

From the above explanation, it can be seen that the fingerroot is very potential to prevent breast cancer. One potential pathway to be inhibited by fingerroot is Poly (ADP-ribose) polymerase (PARP) which is one of the pathways in apoptotic induction. In the future, the study about fingerroot constituents that are responsible for its anticancer activity is needed to be conducted. By doing the exploration, we are able to know the target molecular action of fingerroot because it is necessary to standardize the fingerroot anti-cancer activity. Molecular

**Table 4. Chemoprevention Effects of Cardamonin.**

Extracts	Chemoprevention effect	Biological effects	References
Apoptosis induction and anti-angiogenesis	-	Oral treatment is able to inhibit fibrosarcoma growth in benzopyren-induced mice.	Parwata, et al., 2014
Anti-angiogenesis	bFGF and VEGF	Inhibition of bFGF and VEGF pathways in corio alantois embryo chicken membrane induced basic fibroblast growth factor (bFGF).	Pratomo, et al., 2014
ROS induction	ROS	Increased ROS levels up to twice that cell control in PC12 kidney cells.	Xian, et al., 2012

**Table 5. Chemoprevention Effects of Pinostrobin.**

Extracts	Chemoprevention effect	Biological effects	References
Apoptosis induction and anti-angiogenesis	-	Oral treatment is able to inhibit fibrosarcoma growth in benzopiren-induced mice.	Parwata, <i>et al.</i> , 2014
Anti-angiogenesis	bFGF and VEGF	Inhibition of bFGF and VEGF pathways in corio alantois embryo chicken membrane induced basic fibroblast growth factor (BFGF).	Pratomo, <i>et al.</i> , 2014
ROS induction	ROS	Increased ROS levels up to twice that cell control in PC12 kidney cells.	Xian, <i>et al.</i> , 2012

study can be done with the latest methods such as DNA-pull down assay, DNA-micro array, and Next Generation Sequencing (NGS).

Pull down assay is a selective and sensitive method to look at the interaction between compounds and proteins in cells. Furthermore, to know the expression of genes in large numbers can be done with DNA microarray assay. In addition, to know the DNA sequence can be done by DNA sequencing with Next Generation Sequencing (NGS). From the results of DNA sequencing can be known sequence of DNA bases and compared with wild type. With these three methods, it can be known the molecular anticancer activity of fingerroot.

*In vivo* study on anticancer activity of fingerroot has not hitherto been able to give a clearer picture of the fingerroot molecular pathway. To support the use of clinical findings, it is necessary to do *in vivo* research by animals modelling that implanted with certain types of cancer. With the *in vivo* model, it can be known that the effect can resemble the body system and can also be determined the therapeutic dose. Furthermore, *in vivo* experiments are required for the development of fingerroot constituents as both nutraceutical and pharmaceutical. In addition, exploration of anticancer activity can be done by *in silico* method using molecular

docking. With docking, predictable interactions between compounds in fingerroot with proteins in the body are targeted for fingerroot molecular action actions. Docking can be done in a short time and can be obtained many results at once.

Furthermore, to facilitate the use of fingerroot, exploration is necessary to formulate fingerroot. The formulation of the fingerroot extract should be performed to standardize the required dosage, increase the solubility of the ingredients and to improve patient compliance. The formulation type that recommended for the use of fingerroot is tablets, pills, or capsules. The formulation studies of fingerroot will be interesting to do to materialize that fingerroot can be used as a dosage form to be clinically tested later. In-depth exploration of fingerroot is necessary for full-use intuitive encryption in the direction of molecular and more comprehensive clinical use.

## CONCLUSION

In brief, fingerroot and its constituent exhibit potency to be used as the anti-cancer. Although there has been a lot of study about the anticancer activity of fingerroot, yet the further study still needed to be expanded, includes molecular, *in vivo*, *in silico*, and formulation studies.

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