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Review Article

# Anticancer potential of Panduratin A against non-small cell lung cancer

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## Abstract

Lung cancer is one of the leading causes of cancer death worldwide and ranks first in the number of cancer cases that occur in men and fourth in women in Jakarta. Small cell lung cancer (SCLC) accounts for 15% of lung cancer cases, whereas non-small cell lung cancer (NSCLC) accounts for 85% of instances. Exposure to carcinogens, heavy metals, and polycyclic aromatic hydrocarbons (PAHs) increases lung cancer risk. Repeated exposure to carcinogens can cause genetic mutations by forming DNA adducts. Genetic mutations commonly occur in EGFR, the p53 tumor suppressor gene, and failure in apoptosis. Conventional therapy has limitations such as severe side effects, drug resistance, and treatment costs. Therefore, a new strategy is needed to use natural plant compounds as chemopreventive agents or to slow cancer growth. Panduratin A is a natural chalcone-derived compound isolated from fingerroot or Temu Kunci (*Boesenbergia pandurata*). This compound exerted various antibacterial, anti-inflammatory, antioxidant, and anticancer activities. Panduratin A's anticancer mechanisms included cell cycle arrest, induction of apoptosis, and anti-angiogenesis in several cancer cell lines. Panduratin A was also selectively cytotoxic and inhibited the PI3K/Akt signaling pathway.

***Keywords:*** *Angiogenesis, apoptosis, Boesenbergia pandurata, temu kunci, panduratin A*

## Abstrak

Kanker paru merupakan salah satu penyebab utama kematian akibat kanker di seluruh dunia dan menempati urutan pertama dalam jumlah kasus kanker yang terjadi pada pria dan keempat pada wanita di Jakarta. Kanker paru sel kecil menyumbang 15% kasus kanker paru, sedangkan tipe non-sel kecil menyumbang 85% kasus. Paparan karsinogen, logam berat, dan hidrokarbon aromatik polisiklik meningkatkan risiko kanker paru. Paparan berulang terhadap karsinogen dapat menyebabkan mutasi genetik dengan membentuk hasil tambahan DNA. Mutasi genetik umumnya terjadi pada *epithelial growth factor receptor* (EGFR), gen tumor supresor p53, dan kegagalan apoptosis. Terapi konvensional memiliki keterbatasan seperti efek samping yang parah, resistensi obat, dan biaya pengobatan. Oleh karena itu, diperlukan strategi baru untuk memanfaatkan senyawa tumbuhan alami sebagai agen kemopreventif atau memperlambat pertumbuhan kanker. Panduratin A merupakan senyawa alami turunan kalkon yang diisolasi dari akar temu kunci (*Boesenbergia pandurata*). Senyawa ini memiliki berbagai aktivitas antibakteri, antiinflamasi, antioksidan, dan antikanker. Mekanisme antikanker Panduratin A meliputi penghentian siklus sel, induksi apoptosis, dan anti-angiogenesis pada beberapa lini sel kanker. Panduratin A juga bersifat sitotoksik selektif dan menghambat jalur pensinyalan PI3K/Akt.

**Kata Kunci**: Angiogenesis, apoptosis, *Boesenbergia pandurata*, temu kunci, panduratin A

## Background

Lung cancer kills more people than any other type of cancer in the world, with only 15% of people being able to survive it.[1] The Population-Based Cancer Registry in Jakarta stated that lung cancer is the most common type of cancer in men and the fourth most common type in women.[2] Resistance during treatment, especially at an advanced stage, causes high mortality.[3] The leading cause of lung cancer was smoking, accounting for 80–90% of cases. Then, followed by other factors such as occupational exposure, family history, genetic susceptibility, and chronic obstructive pulmonary disease (COPD).[4]

According to the WHO, lung cancer is classified as non-small cell lung cancer (NSCLC) with 85% of cases and the remaining 15% of small cell lung cancer (SCLC). NSCLC is divided into squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. Adenocarcinoma is the most common subtype, accounting for more than 40% of cases.[5] Exposure to carcinogens, heavy metals, and polycyclic aromatic hydrocarbons (PAHs) increases the risk of lung cancer.

Repeated exposure to carcinogens can cause genetic mutations by forming DNA adducts. Genetic mutations commonly occur in EGFR, the p53 tumor suppressor gene, and failure in apoptosis.[6-8] In several cases of NSCLC, it was found that Bcl-2 was overexpressed and up-regulated by Bax, causing the Bax per Bcl-2 ratio to be higher than 1. The heterodimerization of this complex, which controls the level of apoptosis, made it more resistant to apoptosis.[9]

Treatment of NSCLC is mostly stage specific. Patients with stage I-II could be treated with surgery, radiotherapy for non-surgical patients, and systemic therapy. Systemic therapy includes chemotherapy, immunotherapy, and targeted therapy.[10] The limitations of conventional therapy, such as drug side effects and treatment costs, lead to the urgency of developing a new therapeutic strategy. There were promising opportunities for utilizing natural plants as chemo-preventive agents in preventing or slowing disease progression. So, natural compounds from medicinal plants can be used to make new anticancer drugs that are safe and work well.[11,12]

Panduratin A is a hexenyl chalcone derivative isolated from Temu Kunci (*Boesenbergia pandurata*). Temu Kunci has been used for a long time as an ingredient in food and as a traditional treatment for aches and pains, coughs, rheumatism, fungal infections, and colic.[13] Panduratin A is reported to have antibacterial, anti-inflammatory, and antioxidant activities.[14,15] Recent studies have demonstrated the potential of panduratin A for anticancer activity in inhibiting cell proliferation in breast cancer cells, induction of apoptosis in colon cancer cells, cell cycle arrest in prostate cancer cells, and cytotoxic activity in melanoma cells.[16] This review aims to give a detailed understanding of the proposed anticancer mechanism of panduratin A for developing therapy against non-small cell lung cancer (NSCLC).

### Panduratin A

Panduratin A is a chalcone-derived compound isolated from the rhizome of Temu Kunci (B. Pandurata).[17] A researcher has succeeded in isolating 12% of Panduratin A from Temu Kunci rhizome ethanol extract. This compound has the molecular formula of $C_{26}H_{30}O_4$ with a molecular weight of 406.5.[18] Panduratin A has been reported to have various activities, such as anti-inflammatory in periodontitis, hepatoprotection in a mouse model of liver cirrhosis, inhibitory activity against muscle atrophy, and its potential in treating atopic dermatitis.[19-21] Panduratin A also has anticancer effects on breast cancer, prostate cancer, colon cancer, skin cancer, and lung cancer cell lines. It does this by stopping the cell cycle and causing apoptosis.[12,16,22-24]

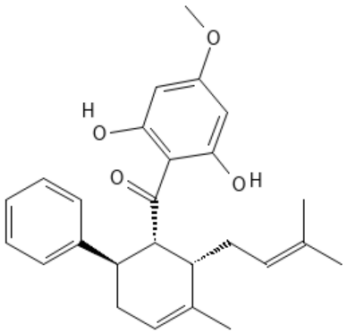


**Figure 1.** Chemical structure of Panduratin A[24]

### Anticancer mechanism of Panduratin A

#### *Cycle cell arrest*

Two regulatory proteins regulate phase transitions in the cell cycle, namely positive and negative cell regulators. Positive cell regulators include cyclin and CDK (cyclin-dependent kinase), while negative cell regulators include p21 and

p27. Decreased cyclin levels (CDK becomes inactive) followed by increased expression of negative regulators (p21 and p27) can lead to cell cycle arrest. During the cell cycle, five CDKs are active. They are active in the G1 phase (cdk2, cdk4, and cdk6), the S phase (cdk2), the G2 and M phases (cdk1), and the S phase (cdk2).[25]

Cyclin B1 and cdc2 protein levels in prostate cancer cells were reduced by panduratin A, as shown by the study in PC3 and DUI145 cell lines. This suggested its involvement in cell cycle arrest in the G2/M phase. Meanwhile, in breast cancer cell lines, panduratin A decreased cyclin D1, which played a role in the G1 phase. Thus, it can be proposed that panduratin A can cause cell cycle arrest at G0/G1. The expression of cyclin D1, cyclin E1, cdk2, cdk4, and cdk6 in prostate cancer cells is reduced in a dose-dependent pattern following administration of panduratin A.[12,16,24]

Negative regulators such as p21 and p27 are bound to CDK or the CDK-cyclin complex to regulate and inhibit cell cycle activity. A study using breast cancer cells showed that panduratin A could induce the expression of p21 and p27. In another study using adenocarcinoma lung cancer (A549 cells), there was an increase in the expression of p53 and p21. The p53 tumor suppressor gene controls the expression of p21. Expression and activation of p27 and p21 mediated via CDK inhibition may contribute to growth arrest or cell cycle arrest. These results show that panduratin A can change the function of important regulatory proteins in the cell cycle.[12,16,24,26]

### *Apoptosis Induction*

Panduratin A incubation in HT-29 cells caused an increase in DNA fragmentation, and morphological changes such as chromatin condensation and nuclear changes as a sign of apoptosis occurred. Caspases are the main mechanism of apoptosis and consist of initiators (caspases 2,8,9,10), which play a role in the initiation of the apoptotic pathway, and effectors (caspases 3,6,7), which play a role in the cleavage of cellular components. Panduratin A causes time-dependent proteolytic cleavage of PARP via procaspase-3 activation. During apoptosis, this activation leads to a buildup of 116 kDa fragments of PARP that are cut into 85 kDa pieces. 13 PC3 and DU145 also have their initiator caspase 9, 8, and procaspase 3,6 turned on by Panduratin A.[12,20,27]

Meanwhile, the extrinsic pathway might be triggered when a cell receives a death signal from another cell in the form of a ligand that binds to the death receptor to activate apoptosis through caspase 8. Panduratin A causes the expression of FADD (Fas-associated death domain) to increase and up-regulate the Fas receptor protein, as well as increased expression of TRAIL (TNF-related apoptosis-inducing ligand). There was a significant increase in Bax and a decrease in time-dose-dependent Bcl-2 expression, thereby changing the Bax: Bcl-2 ratio. In breast cancer cell lines (MCF-7), studies also found an increase in activity and expression of mitochondrial cytochrome C, caspase 7,8,9, and an elevation in the ratio of Bax: Bcl-2. Studies in the lung cancer adenocarcinoma (A549) cell line showed that Panduratin A-induced cell death due to apoptosis is mediated by caspase-3 activation and results in PARP cleavage. Therefore, panduratin A caused apoptosis through the extrinsic pathway and the mitochondria-dependent apoptosis pathway.[12,16,28]

### *Angiogenesis inhibition*

Angiogenesis is the process of forming new blood vessels from existing ones to deliver oxygen and nutrients for the metabolism of tissues or cells in the wound-healing phase. Extracellular matrix reshuffle accelerates the basal membrane degradation followed by endothelial cell migration, proliferation, and the formation of new matrix components to form new blood vessels during angiogenesis. Vascular endothelial growth factor (VEGF) controls the growth and movement of endothelial cells, which are the building blocks of every blood vessel.[29] Panduratin A suppressed VEGF, cell proliferation, cell migration, invasion, and tube formation morphogenesis.[30]

Matrix metalloproteinase-2 (MMP-2) is an enzyme that degrades extracellular matrix components and plays a role in cell migration under physiological and pathological conditions. MMP-2 is considered an angiomodulator because it can control the formation of new blood vessels for the growth and spread of cancer. Tumor cells cause MMP activity to rise out of control and interfere with the immune system by stopping tumor cells from being killed.[31] MMP-2 secretion and the formation of F-actin stress fibers can be suppressed by panduratin A to prevent migration in endothelial cells in HUVEC cell lines. The anti-angiogenic properties of panduratin A also inhibit neo-vessel formation in murine cells and angiogenesis in zebrafish embryos.[30]

### *The potential effect of Panduratin A on NSCLC in the PI3K/Akt pathway*

Anticancer agents might achieve therapeutic goals and effectiveness if they are specifically toxic to tumor cells and less toxic to normal cells. Studies of Panduratin A on various cancer cell lines have been carried out to assess the antitumor effect through various mechanisms. The cytotoxic effect of panduratin A on healthy cells in the form of hepatic epithelial cells and human fibroblasts showed that healthy cells were more resistant.[30] Studies on healthy breast cell lines also showed no effect compared to breast cancer cell lines. Thus, it can be proposed that panduratin A is selectively cytotoxic.[16] As previously mentioned, Panduratin A caused apoptosis by turning on caspase-3 and stopping the cell cycle by making an adenocarcinoma lung cancer cell line express p21 and p53.[28]

PI3K, a protein heterodimer that consists of p85 and p110. Phosphorylated PI3K activated Akt and continued until downstream signaling occurred. The PI3K/Akt/mTOR pathway is one of the main pathways regulating cancer cell survival, metastasis, and autophagy. Utilization of inhibitors of PI3K, Akt, and mTOR has been developed and used to treat cancer. The following are examples of drugs that have been clinically approved, such as copanlisib (PI3K inhibitor) for follicular lymphoma, perifosine (Akt-inhibitor) for neuroblastoma, and temsirolimus (mTOR inhibitor) for some solid tumors. A study using a nutrient-poor model using the PANC-1 cell line showed that panduratin A inhibited the PI3K/Akt/mTOR signaling pathway.[23]

Based on all the above references, we proposed the anticancer mechanism of Panduratin A as depicted in Figure 2.

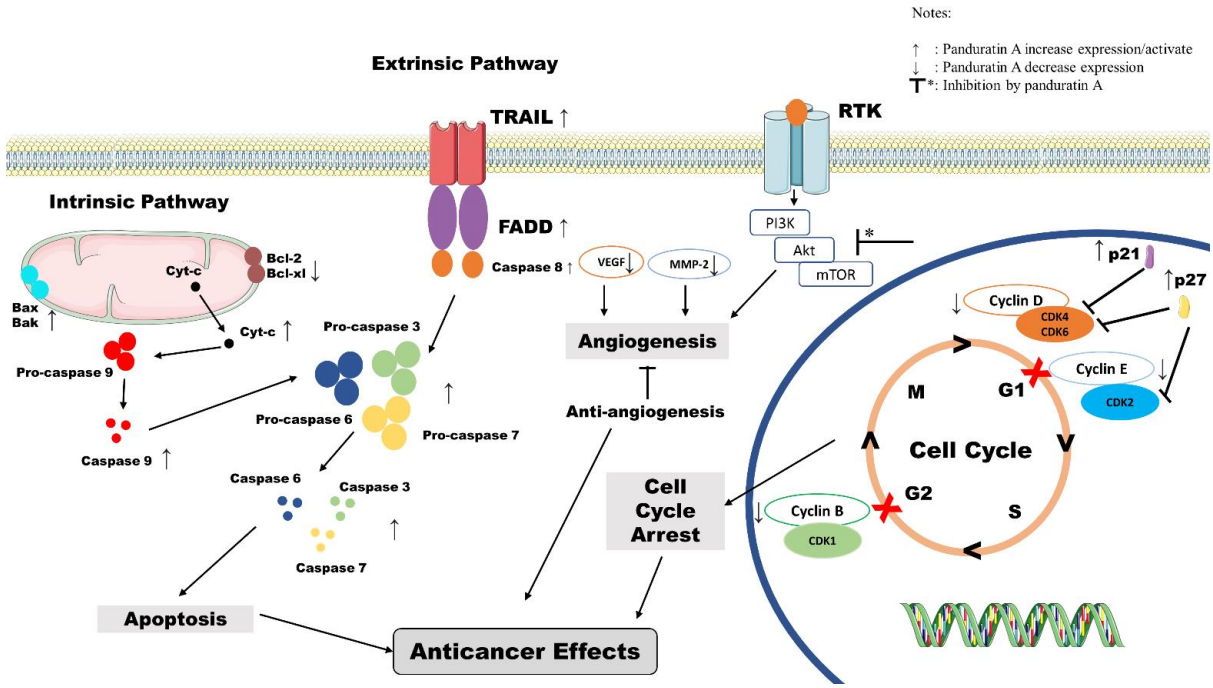


**Figure 2.** Proposed anticancer mechanism of Panduratin A
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### *Safety and dose study of panduratin A and temu kunci extract*

In the *in vitro* cytotoxicity test against MCF-7 and T47D cell lines, administration of panduratin A gave IC50 values of 15 µM and 17.5 µM for 24 hours. In addition, non-tumorigenic MCF-10A cells were also examined, which showed that PA administration had no adverse effect and did not affect the proliferation of these cells.[16] In an acute toxicity study using female rats, panduratin A at a dose of 250 mg/kg did not show any toxicity. Biochemical parameters also showed that oral administration of panduratin A did not affect kidney and liver function.[27] Another study also conducted an acute toxicity test of the ethanol

extract of Temu Kunci rhizome using Wistar albino rats. The study's results showed that the LD50 value was greater than 4000 mg/kg BW, and there were no changes in behaviour, symptoms of toxicity, or lethal effects.[32]

A human dose study was carried out based on allometric scale data on mice, rats, and dogs. This study used panduratin A as a marker to assess systemic levels and estimate clearance based on allometric scaling. The estimated daily dose of the extract is 1500 mg for gingivitis, and clinical trials have been planned to determine efficacy. The factor of species differences had to be considered in predicting human doses. Several factors must be considered, such as differences in pharmacodynamic parameters (sensitivity and capacity of the receptor) and pharmacokinetics (protein binding, distribution, metabolism, and excretion). On the other hand, allometric scaling might be the best way to figure out doses based on what scientists know.[18]

The summary of experimental studies of panduratin A in cancer is given in Table 1.

**Table 1.** Summary of available studies with Panduratin A in cancer

| Study (Author, year) | Design | Main outcome of Panduratin A |
|---|---|---|
| Yun MJ et al., 2006[12] | *In vitro* study of panduratin A in postate cancer cell (PC3 and DU145) | • IC50 of 13.5-14 μM in PC3 and DU145 cells<br>• No effect in normal human prostate cells.<br>• Inhibit procaspases 9, 8, 6 and 3<br>• Increase Bax/BCl2<br>• Upregulating TRAIL |
| Trakoontivakorn et al., 2001[13] | *Salmonella typhimurium* mutagenicity-based assay | • Antimutagenic effect of panduratin A at 12 μM |
| Yun MJ et al., 2003[15] | *In vitro* in RAW 264.7 | • Inhibits NO and PGE at 0.175 μM<br>• Inhibit LPS-induced NF-kB transcription |
| Liu Q et al, 2018[16] | *In vitro* study in MCF-7 and MCF-10A | • IC50 of 15 μM in MCF-7 cells<br>• No effect on MCF-10A (normal breast cells)<br>• G0/G1 arrest<br>• Downregulation of CDK4<br>• Decreased in cyclin D1 |
| Lai et al. 2015[22] | *In vitro* study in melanoma cells (A375) | • Panduratin A caused apoptosis by prolonged ER stress |
| Sun S et al., 2021[23] | *In vitro* study in PANC-1 human pancreatic cancer cells | • Cytotoxic to pancreatic cells at 1.6 μM<br>• Inhibits PI3K/Akt/mTOR autophagy |
| Cheah SC et al., 2011[24] | *In vitro* study in A549 human non-small cell lung cancer | • IC50 at 10.8 μM<br>• Inhibits NF-kB translocation from cytoplasm to nucleus |
| Lai SL et al. 2012[30] | *In vitro* study in HUVEC cells and *in vivo* study in zebrafish embryo | • IC50 of 6.9 μM on HUVEC cells<br>• Angiogenesis effect in zebrafish embryo at 15 μM |

Note:
CDK: cyclin dependent kinase; ER: endoplasmic reticulum; HUVEC: human umbilical vein endothelial cells; HSC: hepatic stellate cells; LPS: lipopolysaccharides; PDGF: platelet-derived growth factor; TGF-β1: Transforming growth factor beta 1; TRAIL: TNF-related apoptosis inducing ligand.

Multiple studies have examined the effects and molecular mechanisms of panduratin A on cancer cells, indicating that the substance has selective cytotoxic effects on cancer cells but not on healthy cells. However, no research has demonstrated panduratin A's efficacy in an animal model of non-small cell lung cancer. To validate the potential utility of panduratin A in the treatment of non-small cell lung cancer, further rigorous research in animal models that mirror human pathophysiology should be conducted. Prior to the start of clinical trials on humans, an extensive range of safety studies in animal models should be performed

## Conclusion

According to the available literature, Panduratin A has several anticancer mechanisms, including cell cycle arrest, apoptosis induction, and angiogenesis inhibition. However, using Panduratin A to treat NSCLC requires further extensive study. On the other hand, the anticancer mechanism and selective cytotoxicity of Panduratin A are promising. There still a lot of research to be done on the dynamics, kinetics, and safety of NSCLC therapies

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