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Resveratrol as a Chemopreventive Agent in Lung Cancer Therapy

Fransisca Dela Verna^{1*}

¹Master's Programme in Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

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*Corresponding author:

Fransisca Dela Verna

E-mail address:

fdelaverna@gmail.com

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ABSTRACT

For decades, lung cancer has been the most widespread cancer in the world and the leading cause of cancer death. Lung malignancy is the superior cause of death in Indonesia, accompanying the second topmost number of new cases. The low survival rate of lung cancer patients reflects the therapy's low success rate due to side effects and cancer cells' resistance to chemotherapy and radiotherapy. Combination therapy, which includes the use of chemopreventive agents, can reduce the risk of side effects and resistance. Natural product-based chemopreventive agents used together with accompanying chemical anti-cancer drugs and/or actinotherapy can overcome cancer cell resistance, improve therapy effectiveness, and reduce side effects. Resveratrol is a compound belonging to the non-flavonoid polyphenolic group contained, particularly in vine fruits, berries, and some nuts. Resveratrol exhibits anti-cancer activity, according to considerable in vitro and in vivo studies, and hence has what it takes to be reasonably applied as a chemopreventive compound. The discovery of resveratrol's chemopreventive mechanism against lung cancer is expected to enable the development of a chemopreventive compound that can be used together with accompanying chemical anti-cancer drugs and/or actinotherapy.

1. Introduction

For decades, lung cancer has been the most widespread cancer in the world among varieties of cancer detected in 185 countries. Due to its dismal prognosis, lung malignancy is the superior cause of death worldwide, making up 1.8 million deaths, which is 18.4% of cancer deaths. According to Globocan (Global Cancer Observatory) data from 2018, Indonesia has the third-highest incidence of lung cancer, with 30,023 new cases per year.¹

Because chemotherapy drugs and radiotherapy are harmful to normal tissues, they frequently cause side effects that are severe enough to impact the quality of life in patients with lung cancer. The presence of

resistance to chemotherapeutic drugs and radiotherapy, on the other hand, influences the low success rate of therapy. Lung cancer patients have a low 5-year survival rate that is 16% as a consequence of resistance to radiation therapy and chemotherapy.² Therefore, in order to improve treatment effectiveness while lowering side effects, comprehensive cancer therapy must be developed.

Chemopreventive agents are a type of cancer treatment that can be used in combination with radiotherapy or chemotherapy. Sporn developed the definition of chemoprevention in 1976, which is reversing, suppressing, or preventing carcinogenesis from progressing to invasive cancer by using natural,

synthetic, or biological substances.³ Several chemopreventive agents came to be demonstrated to sensitize malignant cells to chemotherapy as well as radiation treatments, indicating that they could be used as chemotherapy and radiotherapy potentiators. Exploring natural products is one way to uncover active compounds with chemopreventive potential.^{3,4}

Resveratrol is one of the active compounds with the potential to be developed as a chemopreventive agent. Resveratrol was discovered as the main active compound in *Polygonum cuspidatum* dried roots, which is often used to treat fungal infections and cardiovascular disease in China and Japan. Resveratrol possesses antioxidant, anti-inflammatory, chemopreventive, chemotherapeutic, cardioprotective, neuroprotective, and hepatoprotective effects, according to prior research.² Resveratrol's activity as a chemopreventive and chemotherapeutic agent can be seen at each stage of carcinogenesis.

Carcinogenesis involves four stages: "initiation, promotion, conversion, and progression." Resveratrol also has the ability to modulate signaling transduction networks that control cells in the dividing, proliferating, apoptosis, angiogenesis, spreading, and migrating, as well as inflammation processes, making it a chemopreventive agent.⁵

The number of literature reviews that discuss the potential of resveratrol as a chemoprevention agent that can also be applied as a supplementary therapy in lung cancer treatment has been limited until now. Thus, a literature study on resveratrol's modulation of signaling pathways in lung cancer, as well as its effects when combined with chemotherapeutic drugs and radiation, is required.

Lung cancer

Epidemiology of lung cancer

The epithelial cells that make up the bronchi and other areas of the lungs, such as the bronchioles and alveoli, are where lung cancer develops. Over 2.1 million new occurrences of lung cancer are reported to be found each year, according to the International Agency for Research on Cancer, with 58% of cases

occurring in developing countries. In Indonesia, lung cancer is the primary cancer-related mortality, with a 26 per 100,000 population death rate. Lung cancer has the highest prevalence in the male population, with 19.4 incidences per 100,000 population, or 22,440 new cases every year.

Lung cancer classification

Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), each of which has three subtypes (squamous cell cancer, adenocarcinoma, and large cell cancer), are the two categories by which lung cancer is categorized based on its histological type. The NSCLC subtypes are grouped according to their similarity in treatment and prognosis. NSCLC types make up 75–80% of all occurrences of lung cancer, which is the most common type. The most prevalent subtype of lung cancer seen among smokers, smokers in the past, and non-smokers is adenocarcinoma. Women and young people are more likely to have the adenocarcinoma subtype. SCLC lung cancer grows more rapidly than NSCLC lung cancer. However, SCLC responds effectively to chemotherapy and radiotherapy, making its growth more controllable. Unlike SCLC lung cancer, NSCLC is generally less sensitive to radiation and chemotherapy.⁶

Etiology of lung cancer

Somatic mutations brought on by occupational or environmental exposures, as well as lifestyle factors, are the primary cause of lung cancer in the majority of cases, with inherited germ cell alterations accounting for only 1% of cases. Somatic mutations can affect a wide range of genes, including oncogenes, tumor suppressors, cell cycle and apoptosis regulators, as well as genes that regulate the DNA repair process. Pulmonary carcinogenesis is a multi-step process in which lung epithelial cells undergo molecular and cellular changes. The microenvironment of lung cells is altered by frequent exposure to carcinogens. Carcinogens cause oxidative stress, especially reactive oxygen and nitrogen species, as well as inflammation and reactive electrophilic metabolites. These

substances have the ability to interfere with DNA. Damage to double-stranded DNA can result from ionizing radiation that produces reactive oxygen intermediates (ROI). Polycyclic aromatic hydrocarbons found in vehicle exhaust gases, tobacco smoke, soot, and smoked meat can enter the body through a number of routes, including inhalation, ingestion with food, and skin absorption, where they generate DNA-adducts and oxidative DNA damage, resulting in somatic mutations.⁷

Lung cancer carcinogenesis

DNA damage that is sustained over time can result in replication process mistakes, a disruption of normal cell function, and unregulated cell growth and proliferation. Genomic instability is a characteristic of cancer, resulting in uncontrolled cell growth signals and resistance to cell death processes. In the early phases of tumorigenesis, genomic stability must be maintained to prevent lung cancer carcinogenesis, which can be accomplished by balancing the availability of free radicals and antioxidants. That is, through the mechanism of free radical scavenging, detoxification, and removal of carcinogenic metabolites from the body by increasing the activity of phase 2 enzymes, detoxification enzymes. Hence the number of free radicals in the body is reduced.⁸

Treatment of lung cancer

Resection surgical procedures, chemical anti-cancer drugs, actinotherapy, anti-cancer targeted agents, and combination therapy are among the therapeutic options for lung cancer, according to the National Cancer Management Committee's 2015 guidelines. According to the type of lung cancer that's been diagnosed, NSCLC and SCLC, there are two different categories of treatments for lung cancer. In early-stage patients (stage I or II) with adequate lung parenchymal conditions, for lung cancer of the NSCLC type, surgical procedure is the main option of therapy. Radiotherapy can be used as definitive curative therapy for lung cancer type NSCLC at stage I with comorbidities complicating surgery, as combination

therapy with concurrent chemotherapy at stages II and III, as pre-operative adjuvant therapy to reduce tumor size, and post-operatively in stage IIIA, and as palliative therapy in stage IV and to prevent and reduce pain, bleeding, and obstruction of blood vessels or bronchi.

Chemotherapeutic agents are used as neoadjuvant in the early stages, as postoperative adjuvants in stages IIA, IIB, and IIIA, and as palliative therapy in the later stages. Target therapy using Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor (EGFR-TKI) class, which includes Gefitinib, Erlotinib, and Afatinib, can be beneficial for NSCLC-type patients who have positive mutated EGFR expression and are responsive to these drugs. SCLC treatment is divided into two groups: limited-stage disease, which is treated with a combination of platinum-based chemotherapy and thoracic radiation for curative purposes, and advanced stage (extensive-stage disease), which is treated with a combination of chemotherapy or palliative radiotherapy for primary and metastatic lesions.⁹

Combination therapy using chemotherapeutic agents and radiation is given in certain cases, such as patients not eligible for surgery and elderly patients who have severe comorbidities or contraindications to surgery. Chemotherapeutic agents used in chemotherapy regimens for lung cancer therapy are platinum-based chemotherapy (cisplatin, carboplatin) and new generation drugs that do not contain platinum as first-line chemotherapy, whereas docetaxel and pemetrexed are used as second-line chemotherapy. Chemotherapy and radiation treatments can be given at the same time (concurrent therapy), at different times (alternating therapy), or in a different order (sequential therapy).⁹ Chemotherapy for lung cancer frequently causes undesirable gastrointestinal effects commonly, including nausea, throwing up, constipation, loose bowels, and anorexia. Other common side effects include discomfort, fever, and side effects on specific organs, such as cardiotoxicity, hepatotoxicity, and kidney toxicity.¹⁰

Chemopreventive agent

The clinical approach to using chemopreventive agents can be categorized into primary, secondary, and tertiary chemoprevention. Primary chemoprevention is aimed at the "healthy" population or populations who do not have cancer but have risk factors for lung cancer, such as smokers, COPD sufferers with a smoking history, and people with a cancer family history. Secondary chemoprevention aims to prevent a recurrence, cancer progression, and metastasis in patients with precursor lesions that can lead to lung cancer, such as severe dysplasia, whereas tertiary chemoprevention aims to prevent a recurrence, cancer advancement, and metastasis.^{11,12} Furthermore, this chemopreventive agent has recently been discovered to be capable of overcoming chemotherapy and radiotherapy resistance.⁴

Resveratrol

Sources of resveratrol

Red wine, pistachios, peanuts, as well as grape and berries skins, generally contain resveratrol. Resveratrol concentrations in different red wines range from 0.1 to 14.3 mg/L, whereas they are lower in white wine, which is 0.1–2.1 mg/L, due to the lower level of polyphenolic components. Resveratrol concentrations in grapes range from 0.16 to 3.54 g/g, with dried grape skins having the highest concentration at up to 24 g/g.¹³

Resveratrol chemical structure

A polyphenolic compound with a stilbene structure, resveratrol (3,4,5-trihydroxy stilbene) is non-flavonoid. Plants respond to environmental stresses like pathogenic attacks, particularly fungal infection, in addition to UV radiation by producing the secondary metabolite that is stilbene.¹⁴ Resveratrol is present in plants in two forms of chemical structure: trans-isomeric and cis-resveratrol, which are formed from two aromatic rings of phenol joined by a double styrene chain. The more investigated form of resveratrol, trans-resveratrol, which is highly absorbable and has biological effects such as cell cycle

retardation, differentiation, apoptosis, and anti-proliferation.^{15,16}

Resveratrol absorption, bioavailability, and metabolism

Because resveratrol has limited water solubility, it must bind to plasma proteins such as albumin and lipoproteins in order to be distributed throughout the body. The resveratrol complex's interaction with plasma proteins will facilitate resveratrol absorption into cells. In the gut, resveratrol is absorbed either through passive diffusion or by forming interactions with membrane transporters like integrins. The transepithelial diffusion pathway accounts for roughly 75% of resveratrol absorption in humans after oral administration. Free-form trans-resveratrol rapidly binds to albumin and human plasma lipoproteins. When resveratrol and albumin or lipoproteins complex reaches albumin and lipoprotein receptors on cellular membranes, it dissociates, releasing resveratrol and allowing it to enter cells.¹⁷

The majority of the glucuronide and sulfate conjugates formed during the rapid metabolism of resveratrol are excreted in the urine. The cis form of resveratrol has a lower bioavailability because glucuronidation occurs 5–10 times faster in the cis form than in the transform. Resveratrol undergoes phase II metabolism in the liver, and by increasing phase II liver detoxification enzyme activity, it can accelerate its own metabolism. The maximum possible plasma resveratrol level (C_{max}) was 50 M with an 8-hour half-life in healthy subjects who received a 5 g daily dosage of resveratrol for 29 days.¹⁸ Large dosages of resveratrol up to 5 g/day appear to be well-tolerated and safe, according to Phase I clinical trials.¹⁹

Through glucuronidation, process resveratrol is quickly catabolized, and efflux proteins allow glucuronidated resveratrol to move out of the cell. This efflux mechanism severely limits the bioavailability of resveratrol, which, when given through the oral route, is thought to be barely 1%.²⁰ To increase the bioavailability and penetration of resveratrol into cells, nanoparticles were developed to carry and deliver

resveratrol to target organs.²¹ Intranasal injection of resveratrol, in addition to oral administration, is the preferred route of administration since it is simple and has been found to be effective in lung cancer chemoprevention research in mice. When administered intranasally, resveratrol is more efficiently delivered to the lungs, whereas transdermal delivery can be used for continuous resveratrol administration, providing long-term systemic resveratrol exposure. To allow for a longer exposure to unmetabolized resveratrol and hence optimize in vivo action, this pharmacokinetic profile could be improved by pharmaceutical chemistry approaches.²²

Resveratrol's role in oxidative stress prevention

An increase in free radicals without a corresponding rise in antioxidant levels is what leads to oxidative stress in the body. DNA structural alterations, including base-pair mutations, tumor suppressor gene inactivation, and abnormalities in controlling the activity of proteins and genes that regulate cell division, differentiation, and death, are all affected in the stages of carcinogenesis. Cancer initiation, genomic instability, and overall malignant transformation can all result from the accumulation of DNA damage and mutations in the body. A substance known as a blocking agent can prevent tumor initiation during the carcinogenesis stage in a variety of ways. By attaching to superoxide radicals (O₂⁻) and hydroxyl radicals, resveratrol can block DNA interactions with endogenous free radicals (OH⁻). Resveratrol can reduce the development of procarcinogens into carcinogens by inhibiting the activity of specific cytochrome P450 (CYP) enzymes and preventing interactions between DNA and chemical carcinogens. Resveratrol, on the other hand, increases the activity of phase II detoxification enzymes, allowing more potentially carcinogenic chemicals to be excreted.²³

The administration of resveratrol was able to reduce DNA fragmentation induced by cigarette smoke condensate and activate the apoptotic pathway as a protective mechanism in bronchial epithelium,

thereby preventing the formation of pre-cancerous lesions.²¹

Under typical pathophysiological conditions, the inducible COX cyclooxygenase-2 (COX-2) cannot be found in the majority of tissues. Inflammatory stimuli, specific cytokines, and tumor promoters will all increase COX-2 expression. VEGF secretion, which stimulates the growth of new blood vessels in tumors, is regulated by COX-2. In vitro study using the A549 cell line, the use of resveratrol and paclitaxel in combination has been demonstrated to suppress COX-2 expression. Resveratrol's inhibitory effect on COX-2 expression can also inhibit the synthesis of PGE-2, preventing lung cancer tumor cells from proliferating. The NF- κ B pathway is hypothesized to be involved in resveratrol's reduction of COX-2 production.²⁴

Role of resveratrol in NF- κ B pathway activation inhibition

A pro-inflammatory transcription factor known as NF-B is implicated in the control of cell new blood vessel formation, proliferation, and migration. The classical/canonical pathway and the alternative/non-canonical pathway are two ways to activate NF- κ B. Pro-inflammatory cytokines produced in response to viral or microbial infection activate the classical pathway, whereas members of the tumor necrosis factor (TNF) family activate the alternative pathway. Pro-inflammatory genes and cell proliferation regulators are targeted by the activated NF- κ B pathway. I κ B kinase (IKK) is a protein that regulates inflammation and cell proliferation as well as suppresses the NF- κ B pathway. NF- κ B is found in the cytosol in an inactive state, where it forms a complex with the inhibitory protein I κ B α .

In rats, NF- κ B is essential for the development of lung adenocarcinoma, and inhibiting it causes the tumor to shrink. Resveratrol inhibited nuclear translocation of p65/p50 and NF- κ B activation in a dose-dependent manner. The addition of resveratrol doses had a substantial impact on p65/p50 translocation into the nucleus inhibition and NF- κ B activation. The suppression of TNF- α expression

is another mechanism by which resveratrol inhibits the alternative pathway of NF- κ B activation.^{24,25}

Role of resveratrol in cell cycle inhibition

Malignancy progresses as a result of a loss of control over cell growth, resulting in the uncontrolled proliferation of cancer cells. Resveratrol was able to induce cell cycle arrest in the G0/G1 phase by decreasing the expression of cyclin D1, cyclin-dependent kinase (CDK) 4, and CDK6, and increasing the expression of CDK inhibitors, particularly p21 and p27, according to the results of cell cycle analysis.²⁶

Role of resveratrol in apoptotic process induction

If the stage of cancer initiation has occurred, chemopreventive agents as suppressing agents work by influencing the stage of promotion and progression of carcinogenesis. One of the anti-tumor effects of resveratrol is through the mechanism of the apoptotic pathway by activating caspase-3, which is the executor of apoptotic signal transduction. Through the process of apoptosis, pre-cancerous cells and cancer cells can be eliminated, thereby preventing the promotion process in the carcinogenesis stage.^{2,24}

Resveratrol can induce apoptosis via modulating the expression of Bcl-2, a member of the pro-apoptotic protein family that acts as a sensor for cellular damage and initiates the activation of other proteins involved in cell death. The Bax and Bak genes, which are members of the Bcl-2 gene family and are major regulators of the intrinsic pathway of apoptosis, are upregulated by resveratrol. According to research published in 2015 by Ma et al., resveratrol doses of 50, 60, and 70 g/ml were able to induce apoptosis in H520 cancer cells, which was accompanied by an increase in Bax protein expression as the resveratrol dose was increased, while Bcl-2 protein expression significantly decreased as the resveratrol dose was increased. The amount of cytochrome c released from the mitochondria into the cytoplasm was used to prove that apoptosis occurs via an intrinsic process involving the release of signaling molecules from the mitochondria. There was an increase in the amount of

cytochrome c in the cytosol in H520 cancer cells when the dose of resveratrol (50, 60, and 70 g/ml) was increased.²⁷

Resveratrol has previously been shown to inhibit the proliferation of the human lung cancer cell line A549 by activating Caspase-3. As the concentration of resveratrol was increased, the proliferation of A549 cancer cells was inhibited with stronger anti-proliferative properties, according to the results of the MTT assay.^{2,24} The cytotoxic potential of resveratrol against A549 cancer cells was expressed in IC50 values of $8.9 \pm 1.3 \mu\text{M}$. In vivo study on a xenograft mouse model implanted with A549 cancer cell suspension also showed an association between increasing resveratrol dose and increased anti-tumor efficacy. In comparison to control and administration of doses of 15 and 30 mg/kg, resveratrol at a dose of 60 mg/kg had the greatest effect in suppressing tumor volume enlargement. Observation of the body weight of mice for 15 days of resveratrol administration in all groups of resveratrol doses did not show any side effects. Even the group of mice that received the largest dose of resveratrol still had good locomotion or locomotion behavior.²

Resveratrol can increase the efficacy of cisplatin against H520 cancer cells by promoting cell death through apoptotic mechanisms and mitochondrial dysfunction. The use of the combination of cisplatin and resveratrol showed greater anti-cancer activity than the use of resveratrol or cisplatin alone. The use of the combination of cisplatin and resveratrol showed greater anti-cancer activity than the use of resveratrol or cisplatin alone. This anti-cancer activity can be seen from the viability of cancer cells on the MTT assay, the expression of the Bcl-2 protein family, Bax protein, and the amount of cytochrome c released. The results of the analysis of Bcl-2 protein family expression in H520 cancer cells stimulated by cisplatin showed that cisplatin (5 g/ml) and resveratrol (55 g/ml) decreased Bcl-2 expression and increased Bax expression, while the combination of cisplatin and resveratrol caused a more marked decrease in Bcl-2 expression and resulted in more Bax expression when compared to

cells treated with a single agent, either resveratrol or cisplatin alone.²⁷

Role of resveratrol in the suppression of anti-apoptotic protein expression

NSCLC, the most common type of lung cancer, is known to express high levels of survivin, which prevents cancer cells from undergoing apoptosis. Survivin levels beyond a certain threshold are associated with a poor prognosis. By lowering the expression of the anti-apoptotic protein survivin, the combination of resveratrol and erlotinib can trigger apoptosis in erlotinib/EGFR mutant PC-9 erlotinib-resistant NSCLC lung cancer cell lines. The inhibition of the AKT pathway is assumed to be responsible for the suppression of survivin expression in NSCLC lung cancer cell lines by the combination of resveratrol and erlotinib.²⁸

Role of resveratrol in angiogenesis and metastasis inhibition

Cancer cells can form new blood arteries (neovascularization) to meet their own nutritional and oxygen needs. Vascular Endothelial Growth Factor (VEGF) is one of the initiation signals in the angiogenesis process. Through COX-2 inhibition, the combination of resveratrol and paclitaxel was able to diminish VEGF expression in the lung cancer cell line A549.²⁹ Tumor growth involves a number of processes that culminate in tumor metastasis. E-cadherin is the principal molecule of intercellular adhesion in epithelial cells, and it is responsible for the majority of human malignancies (80-90%). The loss of E-cadherin function promotes the activity of invasive cancer cells.³⁰ Epithelial-mesenchymal transition (EMT), which causes changes in the shape and motility of epithelial cells, is characterized by repression of E-cadherin expression in cancer cells. ZEB, Twist, zinc finger protein (Snail, Slug), and TGF- β -induced EMT are among the transcription factors that have been shown to suppress the expression of E-cadherin.³¹ Resveratrol suppresses TGF- β induced EMT in A549 lung cancer cells by upregulating E-cadherin

expression while downregulating vimentin, fibronectin, and EMT-inducing transcription factors that are Slug and Snail at a concentration of 20 M.³²

Role of resveratrol in chemotherapy and radiation sensitization of lung cancer cells

Resistance to chemotherapeutic agents can occur due to the presence of an ATP-binding cassette (ABC) transporter. Several previous studies have discovered that overexpression of the ABC transporter is involved in the resistance of lung cancer to chemotherapeutic drugs such as doxorubicin, paclitaxel, etoposide, and vincristine, particularly in NSCLC. The expression of ABC transporters such as P-gp, lung resistance protein (LRP), and multidrug resistance-associated proteins (ABCC1, 2, and 3) promotes the efflux mechanism of anti-cancer drugs from cancer cells. Inhibition of ABC transporter action to reverse chemotherapy resistance may increase chemotherapy efficacy.³³

Resveratrol is able to sensitize lung cancer cells to radiation by inducing cellular senescence, thereby limiting the lifespan and proliferative capacity of cancer cells. The combination of resveratrol and radiation increased the aging of cancer cells in NSCLC cancer cell lines more than either resveratrol or radiation alone. Resveratrol causes cancer cells to age by activating the P53 signaling pathway, which is a cell response to DNA damage induced by ionizing radiation. The occurrence of apoptosis and cell aging is a sign for assessing the therapeutic response to cancer radiation.³⁴

The combination of paclitaxel and resveratrol was able to reduce the viability of NCI-H460 cells to a lower level than the use of resveratrol or paclitaxel alone. The use of resveratrol increased the anti-proliferative and cell cycle inhibitory effects of paclitaxel in the G2/M phase against the multidrug-resistant cell line type NSCLC NCI-H460. When paclitaxel was given in combination with resveratrol, the expression of the ABC transporter transport function in NCI-H460 cells was lower than when they were given separately. Decreased expression of ABC transporters may be

involved in the chemosensitizing effect of resveratrol in NSCLC. The effect of resveratrol on the sensitization of NCI-H460 cells to paclitaxel is mediated by inhibiting the expression and function of P-gp, LRP, and ABCC2.³³

2. Conclusion

The development of resveratrol as a chemopreventive agent from natural and synthetic materials could be a promising strategy for improving the efficacy and safety of anti-cancer therapy and thereby increasing lung cancer patient's life expectancy and quality of life. In vivo, animal studies and clinical trials are needed to investigate the effect of the combination of chemopreventive agents with conventional anti-cancer therapy, and further research is needed to optimize resveratrol bioavailability, determine the pharmacokinetic, pharmacodynamic, and safety profile of resveratrol in lung cancer patients.

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