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## Review Article

# Mechanistic Insights into Punicalagin's Cytotoxic Effects on Lung Cancer Cells: A Review

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## ABSTRACT

Lung cancer continues to be one of the primary causes of cancer-related deaths globally, emphasizing the importance of developing novel therapeutic interventions. Despite advancements in conventional treatments such as chemotherapy, radiotherapy, and immunotherapy face challenges like drug resistance and toxicity, prompting interest in natural compounds. Punicalagin, a polyphenolic compound derived from *Punica granatum* (Pomegranate) has demonstrated a significant anticancer property. This review provides a comprehensive analysis of the effects of punicalagin on lung cancer cells. It explores multiple mechanisms through which punicalagin exerts its cytotoxic activity, including apoptosis induction, cell cycle arrest, and oxidative stress modulation while selectively targeting cancer cells. Also includes the combination of punicalagin with the standard therapies which may enhance efficacy and reduce side effects. Despite its potential, punicalagin faces challenges such as low bioavailability, and variability in response limiting its clinical application. However, this review should focus on elucidating its molecular mechanisms, evaluating its in-vivo efficacy and safety, improving its pharmacokinetic properties, conducting preclinical and clinical studies, and exploring synergistic effects with conventional lung cancer treatments. Also, this review presents extensive data on punicalagin's potential in lung cancer treatment, encouraging the way for further research into its clinical use.

## INTRODUCTION

### Lung cancer

Cancer is a condition associated with the overproduction of reactive oxygen species (ROS). It remains a significant global health challenge due

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to its high rates of morbidity and mortality. This life-threatening condition can spread to other organs, particularly if not detected in its early stages.<sup>1</sup> Among various types of cancer, lung cancer is the primary cause of death worldwide.<sup>2,3</sup> Lung cancer has a high mortality rate and is the leading cause of cancer-related deaths worldwide, resulting in approximately 1.6 million fatalities annually.<sup>4</sup> Its high fatality rate has made it the most common cause of cancer-related mortality.<sup>5</sup> Lung adenocarcinoma is the most common type of lung cancer, occurring in both smokers and non-smokers, as well as individuals under 45 years old. In male smokers, it constitutes approximately 30% of primary lung tumors, while in female smokers the percentage rises to 40%.<sup>6</sup> Despite being in stage I, where the cancer has not metastasized, the survival rate remains lower than 70%.<sup>7</sup> Although it can develop in any part of the lung, 90%–95% of lung cancers originate from epithelial cells, bronchi, and bronchioles. In some cases, it may also arise from other supporting tissues within the lungs, such as blood vessels.<sup>8</sup> In most lung cancer patients, the lymph nodes are the first site of metastasis. A pre-operative evaluation of lymph node involvement is crucial in determining further treatment options. During surgery, lymph nodes are removed and examined under a light microscope for analysis. If tumor cells are detected in the lymph nodes, the patient is recommended for additional chemotherapy.<sup>9</sup> Lung cancer is among the most frequently diagnosed malignancies in the United States. However, a significant number of cases are detected at advanced stages, which are often incurable.<sup>10</sup> In 2018, an estimated 2.1 million new cases of lung cancer were reported globally, along with 1.8 million deaths, accounting for 18.4% of all cancer-related fatalities.<sup>11</sup> Through a series of genetic and epigenetic alterations, lung cancer evolves in multiple steps, leading to damage in crucial genes controlling the cell cycle.<sup>12</sup> Several newly

developed antineoplastic agents have shown greater promise in managing advanced lung cancer compared to previous treatments.<sup>10</sup> Currently, carboplatin and paclitaxel are the commonly used chemotherapeutic drugs.<sup>13</sup> Treatment options for lung cancer include radiotherapy, chemotherapy, surgery, immunotherapy, and targeted therapy. Surgery and radiotherapy are primarily used for early-stage lung cancer; however, these approaches carry a high risk of cancer recurrence.<sup>14</sup>

## Overview Of Lung Cancer

### a) Etiology & Risk Factors

In a 20-year study, Doll and Peto observed a decline in mortality among British male physicians who quit smoking compared to those who continued. Fifteen years after quitting, the overall mortality rate of ex-smokers was similar to that of non-smokers. Although lung cancer mortality declined after quitting smoking, it remained twice as high as in non-smokers even after 15 years.<sup>15</sup> Smoking is the primary risk factor for lung cancer, accounting for approximately 75–80% of lung cancer-related deaths.<sup>16</sup> The rising incidence of lung cancer is linked to various risk factors, including lifestyle choices, environmental exposures, and genetic predisposition. Among these, tobacco smoke, radon, asbestos, and arsenic exposure have been identified as significant contributors to the increasing rates of lung cancer.<sup>17</sup> Smoking rates are greater in men at 27%, while 23% of women report smoking. The risk of developing lung cancer increases with both the number of cigarettes smoked per day and the duration of smoking.<sup>16</sup> Individuals who live or work near smokers are exposed to cigarette smoke through passive inhalation, which increases their risk of developing lung cancer. Around one-third of lung cancer cases in non-smokers who live with smokers are linked to passive smoking.<sup>18</sup>



Additional risk factors for lung cancer include exposure to chromium, nickel, polycyclic aromatic hydrocarbons, inorganic arsenic compounds, and bis-(chloromethyl) ether. There is also evidence suggesting that individuals carrying an  $\alpha$ 1-antitrypsin deficiency allele may have an increased risk of developing lung cancer.<sup>19</sup> Radon is a gas formed from the decay of radium-226 and generates substances that release  $\alpha$ -particles, potentially harming cells and raising the risk of cancerous changes. Inadequate ventilation in homes and buildings, especially in basements, can cause radon to build up, raising exposure levels and the risk of lung cancer.<sup>20</sup> Asbestos is a well-known carcinogen that elevates the risk of lung cancer in individuals exposed to airborne fibers. The risk increases with the level of exposure and is significantly higher in those who also smoke.<sup>21</sup>

## b) Classification of Lung Cancer

Lung cancer is traditionally categorized into two main histological types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), based on differences in disease progression and treatment strategies. NSCLC accounts for approximately 85% of all lung cancer cases, with the most common subtypes being adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.<sup>22</sup>

**Lung cancers are classified into two types:**

### 1) Small Cell Lung Cancer

Small cell lung cancer (SCLC) is closely linked to cigarette smoking and features small, distinct cells microscopically, setting it apart from non-small cell lung cancer (NSCLC).<sup>23</sup> SCLC typically originates centrally in the lung, growing along the walls of large bronchi.<sup>24</sup> The cancer cells multiply rapidly, forming large tumors that quickly spread throughout the body.<sup>25</sup> SCLC is the most

aggressive and fast-growing type of lung cancer, accounting for approximately 20–25% of all lung cancer cases. It has a rapid growth time of about 29 days, and due to its aggressive progression, most patients are diagnosed with metastatic disease.<sup>26,27</sup>

### 2) Non-Small Lung Cancer

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for approximately 80% of all cases. It is further classified into three main subtypes:

- **Adenocarcinoma**

Adenocarcinoma is the most common type of lung cancer found in nonsmokers and women, accounting for approximately 30–40% of all lung cancer cases and up to 50% of NSCLC cases.<sup>28,29</sup> Typically, it originates in the lung's outer (peripheral) regions, arising from glandular cells that produce mucus.<sup>30</sup> In some cases, adenocarcinomas develop around scar tissue and have been linked to asbestos exposure.<sup>31</sup> With a tendency to grow toward the edges of the lung, they exhibit a doubling time of approximately 161 days. Compared to squamous cell carcinoma, adenocarcinomas have a higher tendency to metastasize.<sup>27</sup>

- **Squamous Cell Carcinoma**

Squamous cell carcinoma, also known as epidermoid carcinoma, accounts for about 30-40% of primary lung tumors.<sup>32</sup> This type is commonly found in the central thoracic area and shows steady growth, with a growth time of 88 days. It is the most likely type of lung cancer to remain centrally located.<sup>27</sup> Squamous cell carcinoma commonly develops around major bronchi in a stratified or pseudoductal arrangement. Histologically, it is

characterized by epithelial pearl formation and individual cell keratinization.<sup>33</sup>

### • Large Cell Carcinoma

Large cell carcinoma is characterized by tumor cells that are large and lack specific morphological traits. This subtype, often termed undifferentiated carcinoma, is the least frequent type of NSCLC, comprising approximately 10–15% of lung cancer diagnoses.<sup>34</sup> These tumors typically develop in the peripheral regions of the lung and grow at a rate similar to squamous cell carcinoma, with a doubling time of approximately 86 days.<sup>27</sup> Prognosis and treatment options depend on the extent of disease progression at diagnosis, which is classified based on tumor size (T), lymph node involvement (N), and distant metastasis (M).<sup>35</sup>

### c) Signs & Symptoms

Lung cancer does not present with specific diagnostic signs or symptoms. Many symptoms observed in lung cancer patients are also common in smokers or individuals with other conditions, such as upper respiratory tract infections. The symptoms largely depend on the size and location of the primary tumor as well as the presence of metastatic disease. Additional signs associated with local tumor spread include superior vena cava syndrome, which causes facial, neck, and shoulder edema due to compression of the superior vena cava by an enlarging tumor. Another condition, Pancoast's syndrome, manifests as shoulder or arm pain, resulting from the tumor compressing the brachial plexus.<sup>10</sup>

### Symptoms associated with the primary tumor in lung cancer:<sup>10,36</sup>

The growth and spread of cancer within lung tissues and surrounding areas can disrupt normal breathing, leading to various symptoms, including:

- Cough
- Shortness of breath
- Wheezing
- Chest pain
- Coughing up blood (hemoptysis)
- If the cancer invades nerves, it may cause shoulder pain that radiates down the arm (Pancoast's syndrome) and paralysis of the vocal cords, resulting in hoarseness.
- If the esophagus is affected, it may lead to difficulty in swallowing (dysphagia).

### Symptoms associated with metastasis:<sup>10,37</sup>

If lung cancer spreads to the bones:

- It may cause severe bone pain.
- Bone involvement can lead to neurological symptoms, including blurred vision, headaches, seizures, or stroke-like symptoms such as weakness or loss of sensation in certain body parts.
- Patients with brain metastases may experience headaches, cognitive decline, seizures, and signs of encephalopathy.

### Paraneoplastic symptoms:<sup>38</sup>

Lung cancers are often associated with symptoms caused by the production of hormone-like substances by tumor cells.

- Paraneoplastic syndromes are commonly observed in SCLC but can also occur with other tumor types.
- The most frequent paraneoplastic syndrome seen in NSCLC is the release of a parathyroid hormone-like substance, leading to elevated calcium levels in the bloodstream.

### d) Treatment



Lung cancer can be treated using various approaches, depending on its type and stage of progression. Common treatment options include:

### 1) Surgery<sup>36</sup>

Cancerous tissues are surgically removed through resection, a procedure that involves excising the tumor along with a margin of healthy tissue to ensure complete removal. The extent of resection depends on the tumor size, location, and spread.

### 2) Chemotherapy<sup>39,40</sup>

#### Chemotherapy for SCLC

Chemotherapy is the primary treatment for small-cell lung cancer (SCLC) because it is highly responsive to these drugs. Since SCLC tends to metastasize early, chemotherapy helps target both the primary tumor and microscopic cancer cells that may have spread throughout the body. Even at an early stage, SCLC may have invisible cancer cells spread outside the lungs, highlighting the importance of systemic therapy. Small-cell lung cancer (SCLC) is typically treated with a combination of chemotherapy drugs, often including either cisplatin or carboplatin (Paraplatin). Common chemotherapy combinations for initial treatment include:

- EP – cisplatin and etoposide
- Carboplatin and etoposide
- GemCarbo (gemcitabine and carboplatin)

SCLC generally responds well to these treatments. However, if the cancer returns after initial therapy, alternative chemotherapy regimens may be used, such as:

- CAV (cyclophosphamide, doxorubicin, and vincristine)
- CAVE (CAV plus etoposide)

- ACE (doxorubicin, cyclophosphamide, and etoposide)

#### Chemotherapy for NSCLC

Chemotherapy is used to treat non-small cell lung cancer (NSCLC) in several situations, including:

- After surgery – To eliminate any remaining cancer cells and reduce the risk of recurrence in early-stage lung cancer.
- Before, after, or alongside radiotherapy – To shrink tumors in locally advanced lung cancer or enhance the effectiveness of radiation therapy.
- For metastatic cancer – When the cancer has spread to other parts of the body, chemotherapy helps control its growth and manage symptoms.

#### Chemotherapy after surgery

For early-stage non-small cell lung cancer (NSCLC), chemotherapy after surgery (adjuvant chemotherapy) is used to lower the risk of recurrence. It is more effective when using a combination of drugs rather than a single agent.

Common chemotherapy combinations include:

Cisplatin or Carboplatin (Paraplatin) combined with at least one of the following:

- Vinorelbine
- Gemcitabine
- Paclitaxel (Taxol)
- Docetaxel (Taxotere)
- Doxorubicin
- Etoposide
- Pemetrexed

The choice of drugs depends on factors like tumor stage, patient health, and specific cancer characteristics. Chemotherapy uses medications to destroy or reduce cancer cells and can be given

orally as pills or through an intravenous (IV) route. Chemotherapy drugs may be classified as follows:

- Alkylating agents (or) DNA-damaging agents

Alkylating agents function by modifying cellular DNA through chemical interactions. They add alkyl groups to electronegative groups, leading to DNA damage and preventing cancer cell replication. Some examples include: Cisplatin, Oxaliplatin, Carboplatin, Chlorambucil, Cyclophosphamide, Mechlorethamine, and Melphalan.

- Antimetabolites

Antimetabolite drugs mimic purines or pyrimidines, the essential components of DNA, thereby disrupting cell division. They are commonly used due to their effectiveness, with key examples including Methotrexate, Fludarabine, and Cytarabine.

- Plant alkaloids and terpenoids

These plant-derived compounds prevent cell division by disrupting microtubule activity, which is essential for spindle fiber formation and chromatid separation. Examples include vinca alkaloids (derived from *Catharanthus roseus*) and taxanes. The vinca alkaloids include: Vincristine, Vinorelbine, Vinblastine, and Vindesine.

- Podophyllotoxins

These naturally occurring compounds are chiefly extracted from the American mayapple (*Podophyllum peltatum*). They prevent the cells from entering the G1 phase and also affect DNA synthesis. Two cytostatic drugs derived from podophyllotoxin are: Etoposide and Teniposide.

- Taxanes

Taxanes are plant-based compounds that increase the stability of microtubules, thereby preventing the separation of chromatids during mitotic anaphase. Examples of taxanes include: Paclitaxel and Docetaxel.

- Topoisomerase inhibitor

Topoisomerases are enzymes essential for maintaining the topology of DNA. Interfering with these enzymes prevents the normal functions of DNA, such as transcription, replication, and repair.

**Type I inhibitors** include irinotecan and topotecan.

**Type II inhibitors** include amsacrine, etoposide phosphate, and etoposide.

- Antitumor antibiotics

Essential drugs included in this category are dactinomycin, daunorubicin, idarubicin, and mitoxantrone.

- Hormones

Prednisone and dexamethasone are hormonal drugs that, when used in high doses, can trigger cell death and reduce inflammation in lymphoma or lymphocytic leukemia cells.

- Monoclonal antibodies

Monoclonal antibodies attach themselves to tumor-specific antigens, enhancing the immune response against tumor cells. Examples include rituximab, cetuximab, and trastuzumab. Some monoclonal antibodies, such as imatinib mesylate, act as tyrosine kinase inhibitors, targeting specific abnormalities in cancer cells. Imatinib specifically targets the Philadelphia chromosome, which is common in Chronic Myeloid Leukemia (CML),

and is also used to treat gastrointestinal stromal tumors.

### 3) Chemotherapy and radiotherapy

Giving chemotherapy before or after radiotherapy can sometimes help eliminate early-stage non-small cell lung cancer (NSCLC) in patients who are not candidates for surgery. The chemotherapy drugs used in these cases are typically the same as those mentioned previously. For advanced NSCLC, chemotherapy can help prolong life, even if a complete cure is not possible. If the patient is in relatively good health, doctors may recommend a combination of chemotherapy and radiotherapy, known as chemoradiation, to improve treatment outcomes.

### 4) Chemotherapy for locally advanced NSCLC or cancer that can spread<sup>41</sup>

Locally advanced lung cancer describes cancer that has spread from the lung to surrounding tissues or lymph nodes, while metastatic lung cancer indicates that the disease has spread to distant organs or lymph nodes. These chemotherapy combinations are used to slow disease progression and improve survival outcomes.

Treatment involves a combination of either cisplatin or carboplatin with one of the following drugs:

- Gemcitabine (Gemzar)
- Paclitaxel (Taxol)
- Vinorelbine (Navelbine)
- Docetaxel (Taxotere)
- Pemetrexed (Alimta)

### 5) Radiation<sup>36</sup>

The treatment of cancer with X-rays is called radiotherapy. It works by killing cancer cells and

is often used alone or in combination with surgery and/or chemotherapy to treat lung cancer. Radiotherapy is commonly administered externally with linear accelerators that aim X-rays at the targeted cancer site. However, in some cases, brachytherapy is used, where a small amount of radiation is placed directly inside the lung to target the tumor more precisely.

## e) Natural Compounds used in the treatment of lung cancer

### 1) Ginsenosides

Ginsenosides, the main bioactive components extracted from ginseng, are widely used in East Asia and North America for their antitumor, immunomodulatory, antioxidant, and anti-inflammatory properties. Among their metabolites, Protopanaxadiol (PPD) and Protopanaxatriol (PPT) exhibit significant anticancer effects, with PPT being particularly effective in inhibiting the viability and invasiveness of lung cancer cells, especially lung squamous cells.<sup>42</sup> Ginsenosides primarily exert their anticancer effects on lung, breast, liver, and colorectal cancers. The key bioactive compounds responsible for these effects include Ginsenoside Rg3, Rh2, and compound K.<sup>43</sup>

### 2) Curcumin

Turmeric, a spice native to India, is widely used in curries and as a natural colorant. It contains three bioactive polyphenols: curcumin (CUR), demethoxycurcumin (DMC), and bisdemethoxycurcumin (BMC).<sup>44</sup> Curcumin is particularly well known for its antioxidant and anticancer properties<sup>45</sup> and its anticancer activity was first confirmed in 1980 by Kuttan and colleagues using in vitro and in vivo models.<sup>46</sup> Zhang *et al.* later demonstrated that curcumin



exerts anticancer effects in human lung adenocarcinoma cells resistant to A549/DDP.<sup>47</sup>

### 3) Camptothecin

Camptothecin (CPT) is a quinoline alkaloid originally derived from *Camptotheca acuminata* and was first synthesized by Wall and Wani in 1966.<sup>48</sup> Topotecan, a derivative of camptothecin, has been widely used as both a first-line and second-line chemotherapeutic drug for SCLC. Irinotecan, in combination with cisplatin, has also been employed in the treatment of SCLC.<sup>49</sup> Recent in vitro and in vivo research has demonstrated that camptothecin (CPT) and its derivatives—like irinotecan (CPT-11), belotecan (CKD-602), and 10-hydroxy camptothecin (HCPT)—possess strong anti-tumor effects against multiple cancers, including ovarian, non-small cell lung cancer (NSCLC), and treatment-resistant colorectal cancer. Several other camptothecin analogs are currently in different stages of clinical development.<sup>50</sup> However, their use is associated with side effects, including diarrhea, fatigue, myelosuppression, stomatitis, nausea, vomiting, abdominal pain, hair loss, and peripheral neuropathy.<sup>51</sup>

### 4) Artemisinin

Artemisinin-based drugs, including dihydroartemisinin, artemether, artemisinin, and artesunate, have been reported to exhibit significant anticancer activities against both hematological and solid tumors. These compounds demonstrate selective cytotoxicity toward malignant cells.<sup>52</sup> Studies have shown that artemisinin possesses a wide range of pharmacological effects, including anti-inflammatory, antiviral, and anti-tumor properties.

□ Artemisinin is known for its low toxicity and has demonstrated the ability to reduce

inflammation, tumor spread, and cancer cell growth while enhancing apoptosis.<sup>53</sup>

### 5) Cinnamon

Cinnamon is a widely used spice and traditional herbal medicine that has been valued for its antioxidant and free radical scavenging properties for centuries.<sup>54</sup> Whole cinnamon and its active components have demonstrated significant anti-tumor activity across various types of cancer.<sup>55</sup> Cinnamon can function as an insulin mimic, enhancing insulin activity, stimulating glucose metabolism in cells, and influencing apoptosis.<sup>56</sup>

### 6) $\beta$ -elemene ( $\beta$ -ELE)

$\beta$ -elemene is a natural sesquiterpene extracted from turmeric, a traditional Chinese herbal medicine, and is classified as a noncytotoxic class II antineoplastic drug.<sup>57</sup> It has been approved for the treatment of various cancers, including brain, breast, prostate, ovarian, and lung cancer, without severe side effects. Studies have shown that  $\beta$ -elemene can inhibit the migration, invasion, and proliferation of lung cancer cells while also enhancing their radiosensitivity.<sup>58</sup>

### 7) Gambogic (GA)

GA is a natural product extracted from Han's Geng Huang resin. With a molecular formula of  $C_{38}H_{44}O_9$  (628.34 g/mol), GA is considered a promising anti-tumor compound due to its low toxicity, resistance to many cell lines, and multiple mechanisms of action.<sup>59</sup> The National Medical Products Administration has approved GA for treating advanced lung, liver, stomach, breast, and colon cancers following successful clinical trials.<sup>60</sup>

### 8) Triptolide (TPL)

TPL was first isolated from the Chinese herbal medicine *Tripterygium wilfordii* in 1972. It is a



diterpene lactone compound containing three epoxy groups and serves as the main active component of *Tripterygium wilfordii*.<sup>61</sup> TPL has demonstrated the ability to inhibit cancer cell growth and exhibits preclinical anti-tumor activity against various types of cancers, including neuroblastoma, lung cancer, breast cancer, acute myeloid leukemia (AML), osteosarcoma, ovarian cancer, prostate cancer, and multiple gastrointestinal cancers such as stomach, liver, colon, and pancreatic cancers.<sup>62</sup>

## 9) Emodin (ED)

Emodin is a natural anthraquinone compound extracted from the rhubarb rhizome.<sup>63</sup> Previous studies have shown that emodin exhibits antiproliferative effects on various cancer cells, including lung cancer, pancreatic cancer, breast cancer, colorectal cancer, leukemia, and hepatocellular carcinoma.<sup>64</sup> It can inhibit the growth of A549 lung cancer cells by inducing apoptosis through the external apoptosis pathway and causing cell cycle arrest.<sup>65</sup>

## 10) Resveratrol (RSV)

Resveratrol has been found to exhibit numerous biological properties, including antioxidant, antifungal, neuroprotective, anti-inflammatory, antiviral, and anticancer effects.<sup>66</sup> In vitro and in vivo studies suggest that resveratrol can be used for the treatment of various human cancers, including lung, skin, breast, blood, cervical, and bone cancers, as well as gastrointestinal tumors.<sup>67</sup>

## Need For Novel Therapeutic Approaches

Despite advancements in cancer therapy, several challenges persist that necessitate the search for innovative treatment strategies:

### 1) Drug Resistance

A major obstacle in cancer therapy is the emergence of resistance to chemotherapy. Cancer cells develop this resistance through mechanisms like enhanced drug efflux, activation of DNA repair pathways, and avoidance of apoptosis, ultimately resulting in treatment failure.<sup>68</sup>

### 2) Severe Side Effects

Conventional cancer therapies frequently cause toxic side effects such as immunosuppression, organ damage, and secondary malignancies. Chemotherapeutic drugs, in particular, lack specificity for cancer cells, resulting in harm to healthy tissues.<sup>69</sup>

### 3) Cancer Heterogeneity

Genetic and epigenetic variations within tumors lead to cancer heterogeneity, causing differences in treatment responses among patients. This complexity highlights the necessity for personalized and targeted therapies.<sup>70</sup>

### 4) Metastasis and Recurrence

Many existing cancer treatments have difficulty eradicating stem cells, which are central to the recurrence and metastasis of tumors. Developing new strategies to target these resistant cell populations is crucial.<sup>71</sup>

## Punicalagin

Pomegranate (*Punica granatum L.*) has been recognized as a medicinal plant since ancient times and is often associated with longevity and health.<sup>72,73</sup> All parts of the tree, including peel, were pharmaceutically used worldwide as, the Chinese use the pericarp for the treatment of diarrhea, metrorrhagia, metro taxis, and bellyache; the flower is used as a food supplement to treat diabetes mellitus in Unani medicine; the bark and root are believed to have anthelmintic and

vermifugic properties in Ayurvedic medicine; South Africa people employ the fruit for the treatment of diarrhea. Across various cultures, different parts of the tree have been used for medicinal purposes such as treating digestive issues in Chinese medicine, diabetes in Unani medicine, and parasitic infections in Ayurveda.<sup>74,75,76,77,78</sup> Modern applications of pomegranate include its use in managing cardiovascular diseases,<sup>79</sup> cancer,<sup>80</sup> oral hygiene,<sup>81</sup> and cosmetics.<sup>82</sup> The peel, in particular, is a rich source of bioactive compounds like ellagitannins, proanthocyanidins, flavonoids, ellagic acid, gallic acid, punicalagin, and punicalin.<sup>83,84,85</sup> Punicalagin (PUN) is the most abundant compound found in pomegranate peel and serves as its primary active ingredient.<sup>86,87</sup> It is a hydrolyzable tannin and a key component of pomegranate leaves and husks.<sup>88</sup> Research by Gil et al.<sup>89</sup> indicates that hydrolyzable tannins, including PUN, contribute to 87% of the antioxidant activity in pomegranate juice, where its concentration can exceed 2 g/L. PUN.<sup>90</sup> Along with ellagic acid (EA) and its derivatives, has demonstrated antimutagenic and antioxidant properties, as well as the ability to protect DNA.<sup>91</sup> It exhibits antioxidant<sup>92</sup>, antibacterial<sup>93</sup>, antiviral<sup>94</sup>, and anti-inflammatory effects.<sup>95</sup> PUN is also utilized in managing various health conditions, including cardiovascular diseases, diabetes, diarrhea, bronchitis, asthma, bleeding disorders, fever, cough, inflammation, atherosclerosis, AIDS, oral and skin ulcers, malaria, prostate cancer, hypertension, periodontal disease, hyperlipidemia, male infertility, vaginitis, erectile dysfunction, obesity, pediatric cerebral ischemia, and Alzheimer's disease.<sup>96</sup> Punicalagin has been shown to exhibit anticancer effects against various cancer cell lines, including those of colon<sup>97</sup>, ovarian<sup>98</sup>, prostate<sup>99</sup>, and lung cancer<sup>100</sup>, by inhibiting cell proliferation and inducing cell cycle arrest and apoptosis. Substantial evidence

highlights its diverse biological activities, including its role in combating cancer, cardiovascular diseases, liver disorders, and inflammation.<sup>101</sup> In vivo studies have demonstrated punicalagin's anti-angiogenic properties by suppressing blood vessel growth in the chorioallantoic membrane of chickens.<sup>99</sup> Recent pharmacological research suggests that punicalagin and its polyphenols possess significant neuroprotective potential against Alzheimer's disease, Parkinson's disease, stroke, and stress.<sup>102,103</sup> However, concerns remain regarding its bioavailability and concentration, prompting in vivo bioavailability studies.

### Overview Of Punicalagin

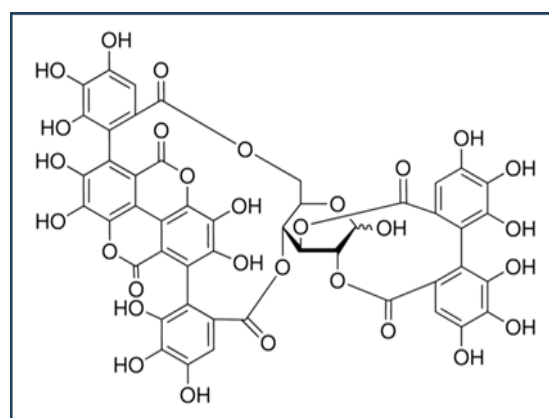


**Fig. No. 1: Chemical Structure of Punicalagin**

Punicalagin (PUN), with the molecular formula  $C_{48}H_{28}O_{30}$  and a molecular weight of 1084.72 Da, is the largest known phenolic compound. It appears as a brown-yellow amorphous powder with strong polarity and is soluble in water, methanol, ethanol, acetonitrile, and other organic solvents.<sup>105</sup> Structurally, PUN consists of a Galloyl Hexahydroxydiphenoyl (HHDP) unit, a galloyl unit, and a glucose unit, with the HHDP unit linked to glucose at C2 and C3, and the galloyl unit attached at C4 and C6.<sup>106</sup> Each molecule contains 16 phenolic hydroxyl groups, significantly more than the 3–4 found in other phenolic substances, making it one of the most potent antioxidants.

PUN exists in  $\alpha$ - and  $\beta$ -isomeric forms, with their ratio varying based on pH, peaking at pH 3.5 before declining as pH increases from 3.5 to 8.<sup>107</sup> Factors such as light, heat, acids, bases, and strong oxidants can influence its stability, and it can form complexes with  $\text{Fe}^{3+}$  and  $\text{Cu}^{2+}$ .<sup>108</sup> Pomegranate peel contains the highest known PUN levels among common fruits, reaching 10–50 mg/g. Moreover, the concentration process does not alter PUN's composition, properties, or content, suggesting that concentrated pomegranate juice retains its health benefits.<sup>109</sup>

### a) Solubility, Stability, and Pharmacokinetics

#### Solubility<sup>110</sup>

Punicalagin exhibits high water solubility, exceeding 20 mg/mL, but has limited solubility in non-polar solvents such as n-octanol. To improve its solubility in these solvents, complexation with phospholipids has been utilized, significantly increasing its n-octanol solubility from 0.005 mg/mL to 0.26 mg/mL.

#### Stability<sup>111</sup>

Punicalagin remains stable under specific conditions:

- **Storage:** It retains stability for at least one year when kept at  $-20^{\circ}\text{C}$ .
- **Solution Stability:** Aqueous solutions can be preserved at  $-20^{\circ}\text{C}$  for up to two months.

However, certain factors can compromise its stability:

- **Environmental Factors:** Heat, solar radiation, extreme pH levels, and strong oxidizers can lead to degradation.

- **Metal Ions:** Interaction with metal ions like  $\text{Fe}^{3+}$  and  $\text{Cu}^{2+}$  can result in complex formation, potentially affecting its stability.

### Pharmacokinetics<sup>112</sup>

After consumption, punicalagin is hydrolyzed to produce ellagic acid, which is then further metabolized by the gut microbiota into urolithins bioactive compounds that are more efficiently absorbed into the bloodstream.

### b) Pharmacological Activities

Punicalagin has been found to induce apoptosis in promyelocytic leukemia cells, colon cancer cell lines, and glioma cells while also inhibiting cancer cell proliferation and regulating inflammatory subcellular signaling pathways.<sup>113,114</sup> It shows potential as a broad-spectrum antiviral agent capable of reducing recurrent disease-causing viruses.

#### • Antibacterial Activity

Research has demonstrated punicalagin's antibacterial properties against Gram-positive and Gram-negative bacteria. Punicalagin and ellagic acid exhibit antimicrobial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and certain *Clostridia* species.<sup>115</sup> At higher concentrations, punicalagin not only suppresses the growth of cariogenic bacteria but also inhibits the development of biofilms. It reduces acid and extracellular polysaccharide production by *Streptococcus mutans* at sub-bactericidal levels, indicating its potential role in preventing tooth decay.<sup>116</sup>

#### • Antiviral Activity

Punicalagin has demonstrated antiviral activity against viruses that utilize cell surface glycosaminoglycans (GAGs) for host cell entry.



Studies have shown its effectiveness in inhibiting human cytomegalovirus (HCMV), herpes simplex virus (HSV-1), hepatitis C virus (HCV), respiratory syncytial virus (RSV), measles virus (MV), and dengue virus (DENV) at various concentrations without significant cytotoxicity.<sup>117</sup> Research by Tito *et al.* reported that punicalagin and ellagic acid could inhibit the interaction between the Spike protein and ACE2 receptor while reducing viral 3CL protease activity in vitro, suggesting the potential of pomegranate extract for preventing and treating SARS-CoV-2 infections.<sup>118</sup>

#### • Antioxidant Activity-Oxidative Stress

Various antioxidants, including punicalagin (PUN), its metabolite ellagic acid (EA), and urolithins, have been recognized for their protective effects against oxidative stress.<sup>119</sup> Some studies suggest that PUN and punicalagin derivatives may have superior free radical scavenging abilities compared to EA due to their higher degree of hydroxylation.<sup>120</sup> Research by Sun *et al.* indicated that PL exhibited the lowest lipid peroxidation (LPO) inhibitory capacity among the three. While all compounds demonstrated strong antioxidant properties, their effectiveness varied depending on the type of free radicals, with EA being more effective than PUN or PL in preventing oxidative damage in vivo, particularly in intestinal tissue.<sup>121</sup>

#### • Genotoxicity

Studies in cattle have shown that consuming large amounts of ellagitannins, particularly punicalagin (PUN), may lead to hepatotoxicity and nephrotoxicity.<sup>122,123</sup> However, research on pomegranate extracts has identified tannins as antioxidants, though some genotoxic activity has been observed.<sup>124</sup> In contrast, repeated oral administration of high doses of PUN to rats over

37 days was found to be non-toxic, suggesting its potential safety for human use.<sup>123</sup> A study by Zahin *et al.* indicated that PUN and ellagic acid (EA) did not exhibit mutagenic effects on *Salmonella typhimurium* but instead provided protection against DNA damage and demonstrated strong antiproliferative activity. Both compounds have shown comparable antimutagenic properties against various mutagens, making them promising candidates for future anticancer treatments.<sup>125</sup>

#### • Hepatoprotective Activity

Fouad *et al.* demonstrated that punicalagin (PUN) could protect against cyclophosphamide (CYP)-induced hepatotoxicity in rats. CYP, an alkylating agent used for cancer treatment and immunosuppression, is associated with significant toxic effects that limit its therapeutic efficacy.<sup>126</sup> The liver metabolizes CYP into phosphoramidate and acrolein, which enhance the production of reactive oxygen species (ROS), leading to oxidative stress. This process activates the NF- $\kappa$ B signaling pathway, triggering an inflammatory response and promoting the release of proinflammatory cytokines such as TNF- $\alpha$  and IL-1 $\beta$ .<sup>127</sup> Acrylamide (ACR) exposure induces oxidative stress and apoptosis in brain and liver tissues. In rats administered ACR (50 mg/kg for 11 days), severe motor impairments were observed. Pretreatment with PUN, especially at a 20 mg/kg dosage, showed a protective effect against ACR-induced damage in the examined tissues. The antioxidant and antiapoptotic properties of PUN are considered key mechanisms underlying its protective effects.<sup>128</sup>

#### • Antidiabetic-Ant obesity Activity

A recent study on metabolic disorders, including diabetes and obesity, revealed that punicalagin (PUN), ellagic acid (EA), and urolithin A can inhibit key enzymes involved in carbohydrate and



triglyceride metabolism, such as DPP-4,  $\alpha$ -glucosidase ( $\alpha$ -GLU), and lipase.<sup>129</sup> Research by Wu *et al.* further demonstrated that PUN and EA significantly suppressed lipid accumulation in 3T3-L1 adipocytes in a dose-dependent manner. The 3T3-L1 cell line, derived from Swiss mouse embryos, is a widely recognized model for adipocyte studies. Their findings indicated that 5.24  $\mu\text{g/mL}$  (5  $\mu\text{M}$ ) of PUN and 4.5  $\mu\text{g/mL}$  (15  $\mu\text{M}$ ) of EA exhibited inhibitory effects comparable to those of C75 and EGCG but at considerably lower concentrations. This suggests that PUN and EA have a stronger inhibitory impact on fatty acid synthase (FAS) than traditional FAS inhibitors such as C75, cerulenin, and EGCG.<sup>130</sup>

### **Cytotoxic Effects of Punicalagin On Lung Cancer Cells**

Multiple studies have highlighted the cytotoxic and antiproliferative effects of punicalagin on lung cancer cell lines, notably A549 and H1299. The MTT assay has demonstrated that punicalagin reduces cell viability in a dose-dependent manner.<sup>131</sup> These results indicate its potential as a natural anticancer agent for lung cancer treatment.

#### **Mechanisms of Action:**

##### **1) Apoptosis Induction**

Apoptosis serves as a key mechanism by which punicalagin exerts its cytotoxic effects on lung cancer cells.<sup>132</sup> It induces apoptosis in A549 cells by activating caspases and promoting PARP cleavage.<sup>133</sup> Punicalagin enhances the expression of pro-apoptotic markers like caspase-3 and Bax while suppressing anti-apoptotic proteins such as Bcl-2. This apoptotic pathway has been validated in both leukemia and lung cancer cells.<sup>132</sup>

##### **2) Reactive Oxygen Species (ROS) Generation**

Punicalagin protects organs and cells from oxidative stress-induced damage by scavenging free radicals and inducing Nrf-2 expression, which regulates numerous antioxidant response element-dependent genes to mitigate the effects of oxidant exposure.<sup>133</sup> It increases intracellular ROS levels, leading to oxidative stress-induced cell death. Excessive ROS production disrupts mitochondrial function, triggering apoptosis in lung cancer cells.<sup>134</sup>

##### **3) Cell Cycle Arrest**

Research suggests that punicalagin disrupts cell cycle progression, particularly by inhibiting DNA synthesis in the S-phase, contributing to its anticancer effects. It induces G1-phase cell cycle arrest by modulating cyclin-dependent kinases (CDKs). The downregulation of CDK4 and cyclin D1 reduces lung cancer cell proliferation.<sup>135</sup>

##### **4) Selectivity Towards Cancer Cells**

A key characteristic of punicalagin is its selective cytotoxicity. Research shows that it inhibits the growth of lung cancer cells with little effect on normal lung epithelial cells (MRC-5), highlighting its potential for targeted cancer treatment.<sup>136</sup> Punicalagin exerts strong cytotoxic effects on lung cancer cells through apoptosis induction, ROS generation, and cell cycle arrest. Its selective toxicity underscores its potential as an anticancer agent, though further *in vivo* studies and clinical trials are necessary to confirm its safety and effectiveness.

### **Potential Of Combining Punicalagin with Conventional Lung Cancer Therapies**

Punicalagin, a polyphenolic compound from pomegranates (*Punica granatum*), exhibits anticancer properties, including cytotoxic effects on lung cancer cells.<sup>137</sup> Its mechanisms of action



suggest that combining punicalagin with conventional lung cancer treatments, such as chemotherapy, radiotherapy, and immunotherapy, may improve therapeutic outcomes while minimizing adverse effects.

### 1) Synergistic Cytotoxicity and Chemotherapy

Chemotherapy remains a primary treatment for lung cancer, but its effectiveness is often hindered by drug resistance and toxicity. Research indicates that punicalagin can enhance the efficacy of chemotherapeutic agents. In leukemia cell lines, punicalagin increased the cytotoxicity of daunorubicin while reducing toxicity to normal cells.<sup>138</sup> Despite the limited number of lung cancer-specific studies, current findings imply that punicalagin may help make lung cancer cells more responsive to chemotherapy, potentially improving treatment results.

### 2) Enhancement of Radiotherapy Outcomes

Radiotherapy works by generating reactive oxygen species (ROS) to induce DNA damage in cancer cells. Punicalagin has been shown to elevate intracellular ROS levels, leading to apoptosis in lung cancer cells.<sup>134</sup> This suggests that combining punicalagin with radiotherapy could enhance tumor cell death while potentially allowing for lower radiation doses and minimizing side effects.

### 3) Potential Integration with Immunotherapy

Immunotherapy, particularly immune checkpoint inhibitors, has transformed lung cancer treatment. Research indicates that polyphenols like punicalagin exhibit immunomodulatory effects, which may strengthen immune responses against tumors.<sup>139</sup> Further investigation is needed, integrating punicalagin with immunotherapy

could enhance antitumor immunity and improve therapeutic outcomes.

### 4) Selective Cytotoxicity Towards Cancer Cells

A significant drawback of conventional cancer therapies is their toxicity to healthy cells. Studies show that punicalagin specifically triggers cell death in lung cancer cells such as A549, while leaving normal lung epithelial cells unharmed.<sup>136</sup> This selectivity highlights its potential as an adjunct therapy, potentially mitigating the adverse effects of chemotherapy and radiotherapy. Integrating punicalagin with conventional lung cancer therapies offers a promising approach to enhancing treatment efficacy. Its capacity to improve chemotherapy and radiotherapy outcomes, coupled with its immunomodulatory effects and selective cytotoxicity, underscores its potential as a complementary therapeutic agent. However, additional preclinical and clinical investigations are necessary to confirm its effectiveness in lung cancer treatment.

## Challenges And Limitations

### a) Low Bioavailability of Punicalagin

The clinical application of punicalagin is limited by its low bioavailability, primarily due to poor absorption, extensive metabolism, and rapid elimination.<sup>140</sup> To enhance its therapeutic potential, several strategies have been explored to improve its bioavailability and cellular uptake.

### Factors contributing to Low Bioavailability:

#### 1) Hydrophilicity and molecular size

Punicalagin's strong hydrophilicity and large molecular weight restrict its passive diffusion across the intestinal epithelium, resulting in



limited absorption within the gastrointestinal tract.<sup>141</sup>

## 2) Metabolic transformation

After being consumed, punicalagin is broken down into ellagic acid, which is then further converted by gut microbes into biologically active urolithins.<sup>142</sup> These metabolites possess greater bioavailability than punicalagin but may exhibit distinct biological activities.

## 3) Rapid elimination

Punicalagin and its metabolites undergo extensive hepatic metabolism and are rapidly eliminated, restricting their systemic availability.<sup>143</sup>

### b) Selective cytotoxicity towards lung cancer cells

1) **A549 Lung Cancer Cells:** Research indicates that punicalagin triggers apoptosis in A549 lung cancer cells by inhibiting STAT3 translocation and promoting reactive oxygen species (ROS) generation.<sup>144</sup>

2) **Non-Toxic to Normal Cells:** Punicalagin has demonstrated cytotoxic effects in various cancer cell lines, including A549, while sparing normal human kidney epithelial cells (293T). This selective cytotoxicity highlights its potential as a cancer treatment option with reduced toxicity to normal tissues.<sup>145</sup>

### c) Variability across lung cancer cell lines

1) **A549 and H1299 Cells:** Punicalagin exerts a dose-dependent cytotoxic and antiproliferative effect on A549 and H1299 lung cancer cells by upregulating pro-apoptotic factors like Bax, caspases 3 and 9, and cytochrome C while downregulating the anti-apoptotic protein Bcl-2.<sup>146</sup>

2) **A549 Cells:** Punicalagin triggers apoptosis in A549 cells by generating reactive oxygen species (ROS) and inhibiting STAT3 translocation, resulting in mitochondrial dysfunction and cell death.<sup>144</sup>

3) **A549 and 22RV1 Cells:** Punicalagin exhibits dose-dependent cytotoxicity in A549 lung cancer cells and 22RV1 prostate cancer cells while sparing normal human kidney epithelial cells (293T), indicating its selective toxicity toward cancer cells.<sup>145</sup>

## Future Directions<sup>131,147</sup>

1) **Elucidation of Molecular Mechanisms:** Although studies demonstrate that punicalagin induces apoptosis in lung cancer cells by inhibiting STAT3 activation and generating reactive oxygen species (ROS), its precise molecular interactions remain unclear. Further research should aim to identify specific molecular targets and signaling pathways modulated by punicalagin to enhance its potential in cancer therapy.

2) **In Vivo Efficacy and Safety Studies:** Most existing evidence on punicalagin's anticancer properties is based on in vitro studies. In vivo research is essential to assess its therapeutic efficacy, optimal dosage, pharmacokinetics, and potential toxicity in animal models. Such studies will offer critical insights into its behavior in complex biological systems and guide the development of clinical trials.

3) **Enhancement of Bioavailability:** Punicalagin's clinical potential is constrained by its low bioavailability. Investigating advanced delivery systems, including nanoparticles, liposomes, and molecular conjugation, could improve their absorption and therapeutic efficacy.



- 4) **Synergistic Effects of Conventional Therapies:** Investigating the combination of punicalagin with chemotherapy or radiation could reveal synergistic effects that enhance cancer-fighting potential while reducing side effects. These combination approaches could contribute to more effective lung cancer treatment strategies.
- 5) **Clinical Trials:** Advancing from preclinical research to human clinical trials is crucial for confirming punicalagin's safety and therapeutic potential in lung cancer treatment. Phase I trials should determine safety and optimal dosing, while Phase II and III trials will assess efficacy and monitor adverse effects in broader patient populations.
- 6) **Exploration of Autophagic Pathways:** Punicalagin has been linked to autophagy induction in certain cancer cell lines. Investigating its role in autophagic cell death in lung cancer cells could reveal additional therapeutic mechanisms and expand its potential applications in cancer treatment.

## CONCLUSION

Lung cancer continues to pose a major global health concern, marked by high death rates and poor long-term survival, even with progress in conventional therapies. Punicalagin, a polyphenolic compound derived from pomegranate, has demonstrated promising anticancer properties against lung cancer cells by inducing apoptosis, generating oxidative stress, and arresting the cell cycle. Its selective toxicity towards cancer cells suggests it could serve as a safer alternative or complementary therapy to conventional treatments. Furthermore, combining punicalagin with chemotherapy, radiotherapy, or immunotherapy may enhance therapeutic effectiveness while reducing side effects.

However, obstacles such as poor bioavailability, metabolic variability, and the need for comprehensive in vivo and clinical investigations remain. Future studies should prioritize optimizing its pharmacokinetic profile, uncovering its precise molecular targets, and assessing its role in autophagy regulation. Ongoing research may establish punicalagin as a promising component of future lung cancer treatment approaches.

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