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# Selenium nanoparticles enhance the chemotherapeutic efficacy of pemetrexed against non-small cell lung cancer

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ABSTRACT

Selenium (Se) plays an important role in the development and treatment of lung cancer, yet its specific mechanisms remain elusive. Lower Se level in serum was noted in lung cancer patients compared to normal controls. Therefore, developing effective therapeutic adjuvants containing Se might benefit the treatment of lung cancer patients. This study aimed to investigate the association between Se and the chemotherapeutic efficacy of lung cancer. Lentinan-modified selenium nanoparticles (LET-SeNPs) were created to develop and verify the effectiveness of Se containing adjuvant applied with pemetrexed on lung cancer cells. A synergistic effect was observed between LET-SeNPs and pemetrexed *in vitro*. The combination of LET-SeNPs and pemetrexed could induce reactive oxygen species overproduction, mitochondrial dysfunction and DNA damage, ultimately leading to cancer cell apoptosis. It is implied that LET-SeNPs might be a promising sensitizer to pemetrexed chemotherapy and could potentially enhance chemotherapy efficiency in non-small cell lung cancer.

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As one of the most common cancer types worldwide, lung cancer is the leading cause of cancer-related mortality [1]. Majority (75% or more) of lung cancer patient was diagnosed at stage III or IV at initial diagnosis [2], indicating a poor prognosis. Although the development of therapy has been greatly progressed in the past years, the survival rate is still at relative low level (less than 19%) [3]. According to the International Association of Cancer Registries report, there were approximately 2.5 million new cases of lung cancer each year, with approximately 1.8 million deaths attributed to this disease annually [4], which highlighted its significant threat to global public health.

The histological type of lung cancer is mainly comprised two categories: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), accounting for approximately 15% and 85% of all primary lung cancers, respectively [5]. To date, chemotherapy remains one of the most commonly used treatment methods for NSCLC [6]. Pemetrexed, as a folate analog metabolic inhibitor in mammalian cells, is commonly used alone or in combination with platinum-based drugs for NSCLC chemotherapy [7,8]. Although the clinical efficacy of pemetrexed has been confirmed, its side effects could not be ignored, such as fatigue, stomatitis, rash, renal toxicity, and neutropenia [9-11]. These adverse reactions not only increase the risk of hospitalization and mortality but also result in higher medical expenses for lung cancer patients [12]. Approximately 23% of patients undergoing pemetrexed-based therapy discontinued treatment due to therapy-related adverse events [13]. Consequently, it is imperative to develop an effective sensitizer to enhance the chemotherapeutic efficacy of pemetrexed and alleviate its side effects.

Selenium (Se) is an essential trace element for human health [14,15]. Se deficiency has been linked to diseases such as Keshan disease, Kashin-Beck disease, cardiovascular disease, diabetes, and cancer [16-21]. In a preliminary small-scale study, we found that lung cancer patients had significantly lower serum Se levels than healthy controls, suggesting that NSCLC patients were in a state of Se deficiency [22]. Therefore, reversing Se deficiencies may represent an innovative step forward in treating lung cancer patients. However, how the chemical form and structure of Se influence its

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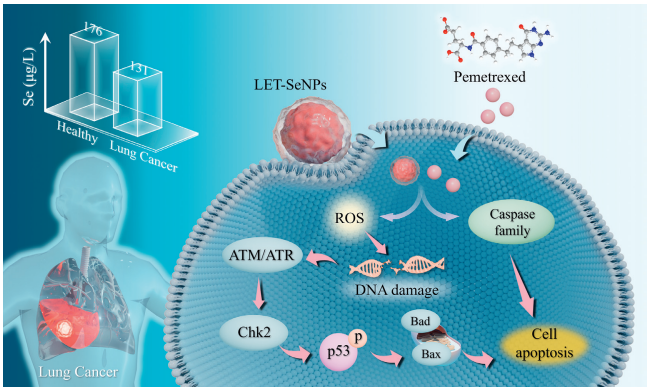
role in lung cancer therapy remains elusive. Our previous studies have revealed that Se possesses various functions, including antiviral [23], anti-allergic [24], anti-angiogenic [25], and immunomodulatory properties [26]. Meanwhile, elemental Se combined with radiotherapy could enhance radiotherapy efficacy while reducing side effects [27]. However, its effects on chemotherapy for NSCLC have not yet been explored.

Recently, nanomaterial-based cancer therapies were found to potentially overcome traditional therapy limitations [28,29]. When nanomaterials were combined with traditional drugs, the targeting of tumor cells and the toxicity of the drugs were enhanced, while side effects were decreased [30,31]. In light of the factors mentioned above, combining Se with nanotechnology for NSCLC treatment may be a viable option. Low toxicity, high absorption rate, and excellent biocompatibility made Se nanoparticles (SeNPs) promising for medicine [32]. The instability of SeNPs, however, resulted in them be transformed into inactive forms easily and as the consequence, having poor bioavailability. Fortunately, our recent studies have shown that SeNPs modified in specific ways could have greater potential for applications such as carriers for anticancer drugs or sensitizers for tumor treatment [33-37].

Hence, we examined whether the combination of modified SeNPs with pemetrexed could be an effective treatment option for NSCLC to enhance efficacy and mitigate chemotherapy-related adverse reactions. Furthermore, we investigated the potential mechanisms underlying the chemosensitizing effect of Se, aiming to elucidate the correlation between its chemical structural forms and its biological activities (Scheme 1).




**Scheme 1.** Se nanoparticles enhance the chemotherapeutic efficacy of pemetrexed against non-small cell lung cancer by inducing reactive oxygen species production and apoptosis.

A total of 200 healthy subjects (control group) and 200 lung cancer patients (case group) were recruited for this study. All study

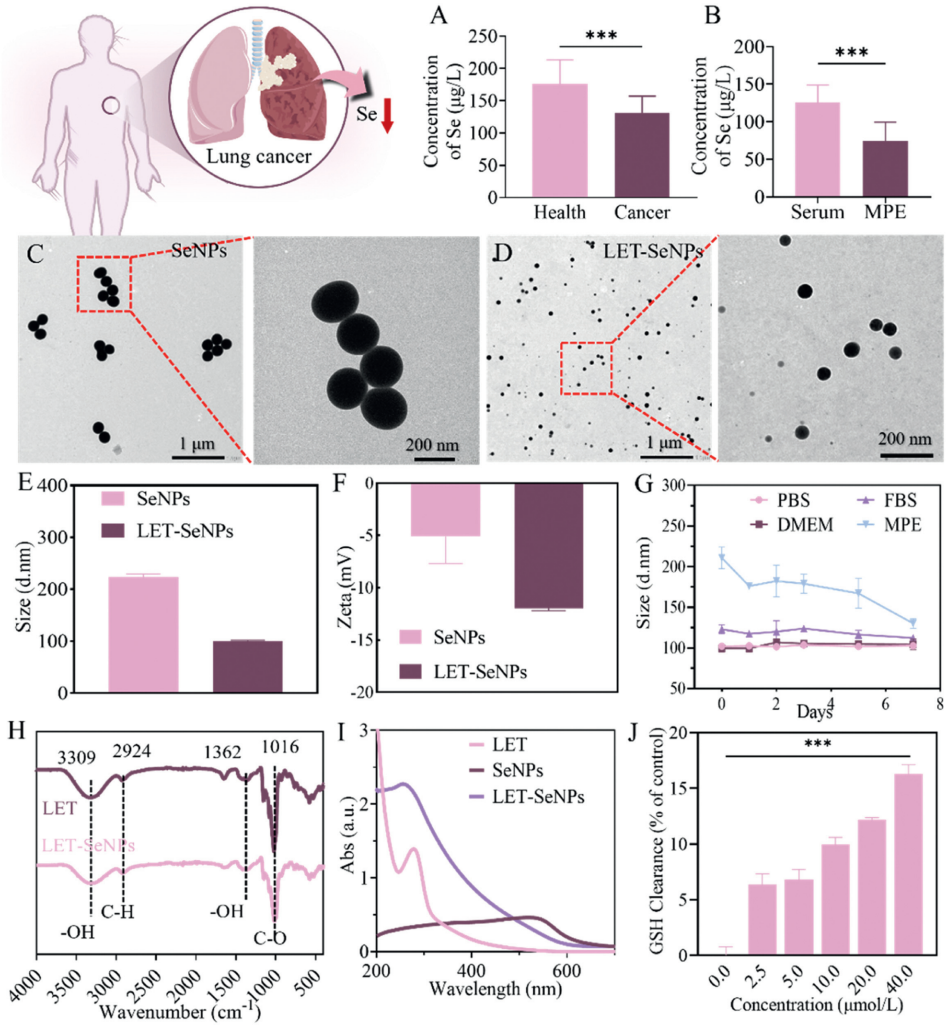



**Fig. 1.** Se concentrations and characterizations of SeNPs. (A) Serum Se concentrations in healthy controls and lung cancer patients. (B) Se concentrations in serum and MPE of the lung cancer patients. (C, D) TEM images of SeNPs and LET-SeNPs. (E) Particle sizes of SeNPs and LET-SeNPs. (F) Zeta potentials of SeNPs and LET-SeNPs. (G) Particle size variation trend of LET-SeNPs over 7 days. (H) FT-IR analysis of LET and LET-SeNPs. (I) UV–vis analysis of LET, SeNPs and LET-SeNPs. (J) GSH clearance of different LET-SeNPs concentrations. *** $P < 0.001$. The same below.

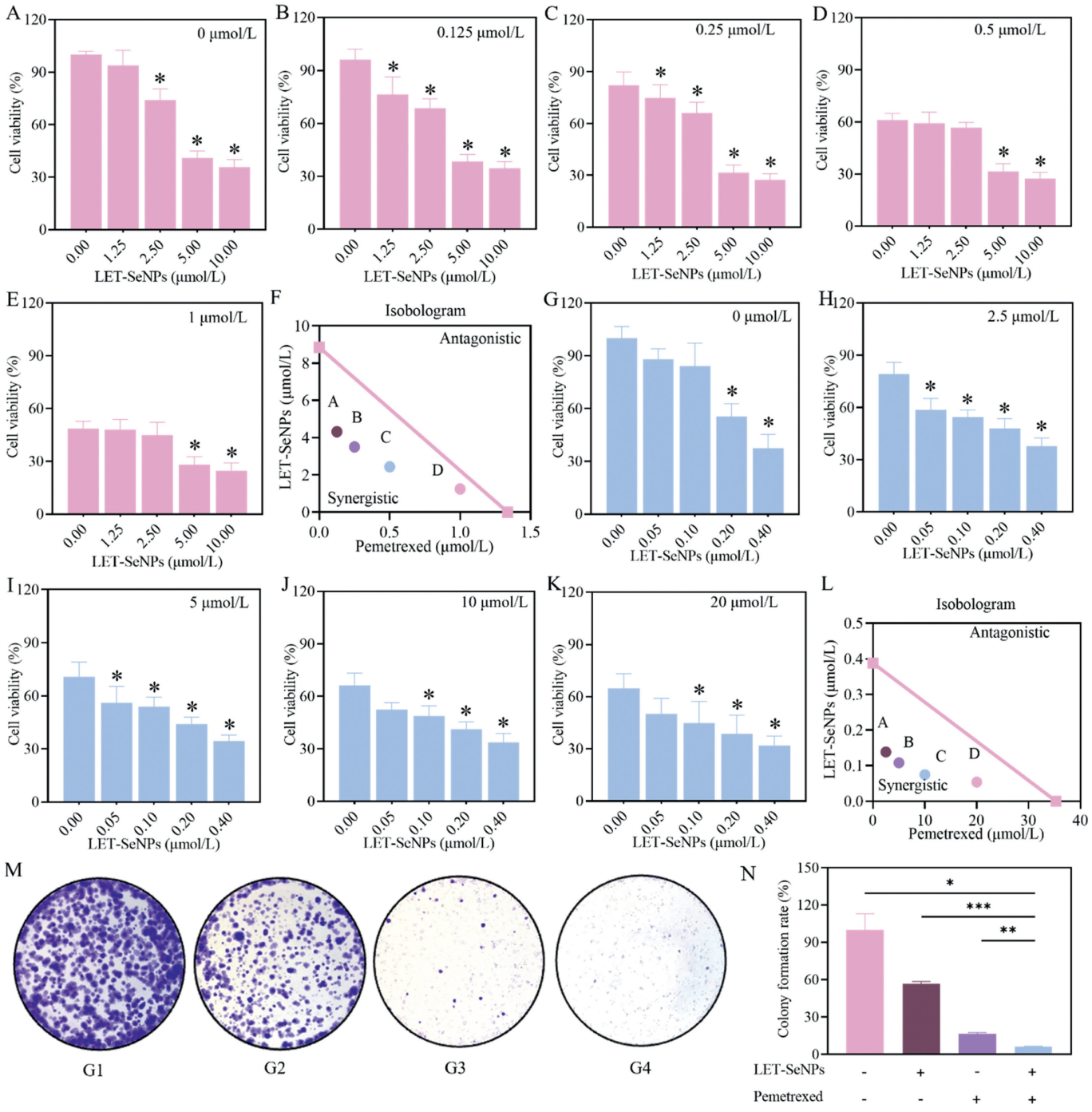



**Fig. 2.** Effects of LET-SeNPs combined with pemetrexed on lung cancer cell viability. (A-E) The effects of LET-SeNPs (0, 1.25, 2.5, 5, and 10 μmol/L) combined with different pemetrexed concentrations (0, 0.125, 0.25, 0.5, and 1 μmol/L) on A549 cells' viability. *: compared to 0 μmol/L of LET-SeNPs, $P < 0.05$. The same below. (F) Isobologram analysis of the combined effects on A549 cells. The points A-D in the isobologram correspond to the 50% growth inhibition rate in combined treatment. The same below. (G-K) The effects of LET-SeNPs (0, 0.05, 0.1, 0.2, and 0.4 μmol/L) combined with different pemetrexed concentrations (0, 2.5, 5, 10, and 20 μmol/L) on H1299 cells' viability. (L) Isobologram analysis of combined effects on H1299 cells. (M, N) Clonogenic assay of combined effects on A549 cells. G1: Control; G2: LET-SeNPs (5 μmol/L); G3: pemetrexed (0.25 μmol/L); G4: LET-SeNPs (5 μmol/L) combined with pemetrexed (0.25 μmol/L). * $P < 0.05$; ** $P < 0.01$. The same below.

subjects signed informed consent forms, and the study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (No. 2022.93) and Jinan University (No. JNUKY-2023–0112). There was a significant difference in serum Se concentration between control ($176.20 \pm 37.18$ μg/L) and case ($130.86 \pm 26.35$ μg/L) groups ($P < 0.001$) (Fig. 1A and Fig. S1A in Supporting information). Further investigation compared the Se concentration in serum and malignant pleural effusion (MPE) in 34 patients. It was found that the Se concentration in MPE was significantly lower than that in serum ($P < 0.001$) (Fig. 1B and Fig. S1B in Supporting information). These findings suggested a potential association between serum Se concentration and lung cancer. For addressing Se deficiencies and improving chemotherapy efficiency, SeNPs may provide a promising way to improve Se-based interventions.

Due to the natural instability of naked SeNPs, this study added lentinan (LET) as a stabilizer. The morphologies of SeNPs before and after LET modification were observed by transmission electron

microscope (TEM) and the particles were spherical in shape and varied in size. According to the TEM images, SeNPs had a particle size >100 nm (Fig. 1C), whereas LET-modified SeNPs (LET-SeNPs) had a particle size of <100 nm (Fig. 1D). The element mapping indicated the distribution of Se in LET-SeNPs in Figs. S2A–C (Supporting information). Analysis from the Malvern Zetasizer analyzer revealed that after LET modification, SeNPs particle sizes decreased from ~224.27 d.nm to ~99.90 d.nm (Fig. 1E), and the zeta potential changed from ~−5.10 mV to ~−11.97 mV (Fig. 1F). The particle sizes change of LET-SeNPs in phosphate buffer solution (PBS), fetal bovine serum (FBS), Dulbecco's modified Eagle medium (DMEM), and MPE over a 7-day period was also evaluated. There was almost no change in LET-SeNPs size in the first three media, while in MPE, size decreased from large to small (Fig. 1G). This result was also confirmed by the polymer dispersion index (PDI) (Fig. S3 in Supporting information). Comparison of LET and LET-SeNPs by Fourier transform infrared (FT-IR) spectroscopy demonstrated consistent peak patterns (Fig. 1H). The nanoparticles were further confirmed to have been modified through ultraviolet-visible absorption spectra (UV–vis) (Fig. 1I) and X-ray photoelectron spectroscopy (XPS) (Fig. S2D in Supporting information) analysis. A gradual increase in glutathione (GSH) consumption was observed as LET-SeNPs concentration increased, demonstrating LET-SeNPs' ability to clear GSH (Fig. 1J).

Next, the cytotoxicity of LET-SeNPs and pemetrexed in NSCLC cell lines (A549 and NCI-H1299) was detected using methyl thiazole tetrazolium (MTT) assays. As LET-SeNPs and pemetrexed concentrations increased, the viability of A549 and H1299 cells was decreased in a dose dependent pattern (Fig. S4 in Supporting information). A combined concentration of LET-SeNPs and pemetrexed was then selected according to the $IC_{50}$ value of each component alone, and the effects of the combination on A549 and H1299 viability were analyzed. The results showed that with a fixed concentration of pemetrexed, the viability of A549 cells was decreases along with the concentration increase of LET-SeNPs (1.25, 2.5, 5, and 10 μmol/L) (Figs. 2A–E and Table S1 in Supporting information). An isobologram analysis was further used to detect the sensitization property of LET-SeNPs and showed the data point of LET-SeNPs combined with pemetrexed (0.125, 0.25, 0.5, and 1.0 μmol/L) in A549 cells was below the additive line, indicating a synergistic antitumor effect between LET-SeNPs and pemetrexed (Fig. 2F). Similarly, when pemetrexed was fixed at a certain concentration, the viability of H1299 cells was decreased along with the concentration of LET-SeNPs increase (0.05, 0.1, 0.2, and 0.4 μmol/L) (Figs. 2G–K and Table S2 in Supporting information). The isobologram also indicated a synergistic effect between the two components (Fig. 2L).

In addition, the combination index (CI) was calculated to compare the effects of different drug concentrations: the smaller the CI value, the stronger the synergistic effect. In both A549 and H1299 cells, LET-SeNPs and pemetrexed showed synergistic effects based on their CI values. Specifically, in A549 cells, the minimum CI (0.34) was observed when the concentration of LET-SeNPs was 10 μmol/L and pemetrexed was 0.5 μmol/L, indicating the strongest synergistic effect between the two components. As well, in H1299 cells, the minimum CI (0.35) was observed when LET-SeNPs was 0.5 μmol/L and pemetrexed was 2.5 μmol/L. (see Tables S3 and S4 in Supporting information for details). LET-SeNPs in combination with pemetrexed had greater synergistic effects on A549 cells, so for the purpose of further validating the inhibitory effect of the drugs on the proliferation and migration capacities of lung cancer cells, A549 cells were selected. The results of the clonogenic assays showed that both LET-SeNPs and pemetrexed alone could inhibit colony formation effectively, whereas their combination could be more significant (Figs. 2M and N). A similar effect was observed in the cell scratch test results (Fig. S5 in Supporting information). In

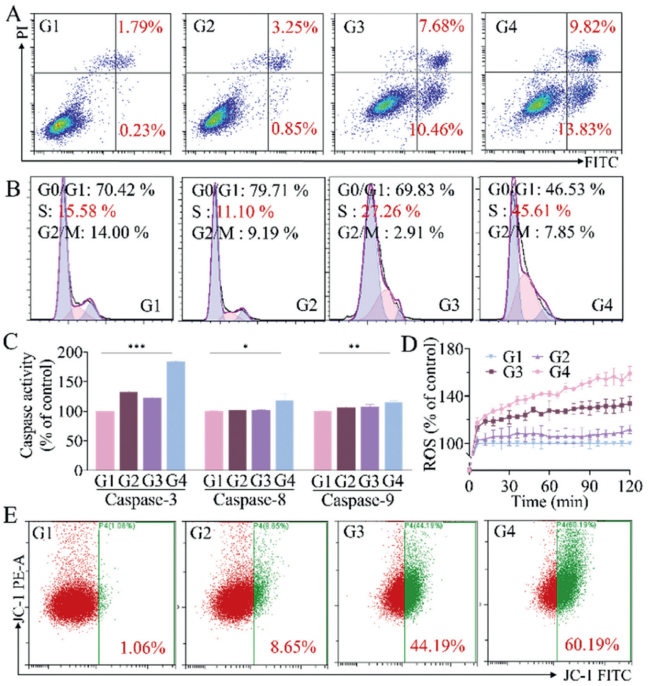



**Fig. 3.** Effects of LET-SeNPs combined with pemetrexed on cell apoptosis, cell cycle, Caspases activity, ROS level and mitochondrial function in A549 cells. (A) The apoptosis rate of A549 cells in different groups. G1: Control; G2: LET-SeNPs (10 μmol/L); G3: pemetrexed (0.5 μmol/L); G4: LET-SeNPs (10 μmol/L) combined with pemetrexed (0.5 μmol/L). The same below. (B) Cell cycle distribution analysis of A549 cells in different groups. (C) Effects of co-treatment on Caspases-3, Caspases-8, and Caspases-9 activity. (D) The variation trends of ROS in different groups for 2 h. (E) Percentages of monomeric JC-1 in different groups.

consequence, LET-SeNPs enabled pemetrexed-based chemotherapy to achieve advanced antitumor effects at lower doses.

During chemotherapy, cell apoptosis and cycle arrest are recognized as the two primary modes of cell death. In this regard, the synergistic mechanism between LET-SeNPs and pemetrexed was evaluated by flow cytometry. As depicted in Fig. 3A and Fig. S6A (Supporting information), drug combinations induced a greater amount of apoptosis than single drugs. Specifically, when LET-SeNPs (10 μmol/L) and pemetrexed (0.5 μmol/L) were applied individually, A549 cells' apoptotic rates were 4.10% and 18.14%, respectively. When the two components were used together, the apoptotic rate further increased to 23.65%. Therefore, the combined treatment of LET-SeNPs and pemetrexed effectively induced apoptosis in A549 cells. The caspases-3, -8, and -9 are cytoplasmic proteases with similar structures that play a crucial role in cell apoptosis [38]. Since LET-SeNPs caused significant chemotherapy-induced cell apoptosis on A549 cells, further studies were conducted to detect the effects of co-treatment on caspase activity and to identify the underlying mechanism. Based on fluorometric measurements, LET-SeNPs in combination with pemetrexed effectively enhanced caspases-3, -8, and -9 activity (Fig. 3C). These results indicated that LET-SeNPs could activate cell apoptosis mediated by the caspase signaling pathway. Additionally, pemetrexed alone treatment arrested A549 cells in the S phase, as indicated by the increase in the proportion of cells in the S phase from 15.58% to 27.26%. Upon co-treatment with LET-SeNPs, a significant enhancement in S-phase arrest was observed, which suggested that LET-SeNPs promoted pemetrexed-triggered S phase arrest (Fig. 3B and Fig. S6B in Supporting information). Mitochondria, serving as the primary site for cellular energy production, possess functionalities involved in signal transmission, cell cycle regulation, and apoptosis [39]. During energy production, mitochondria generate

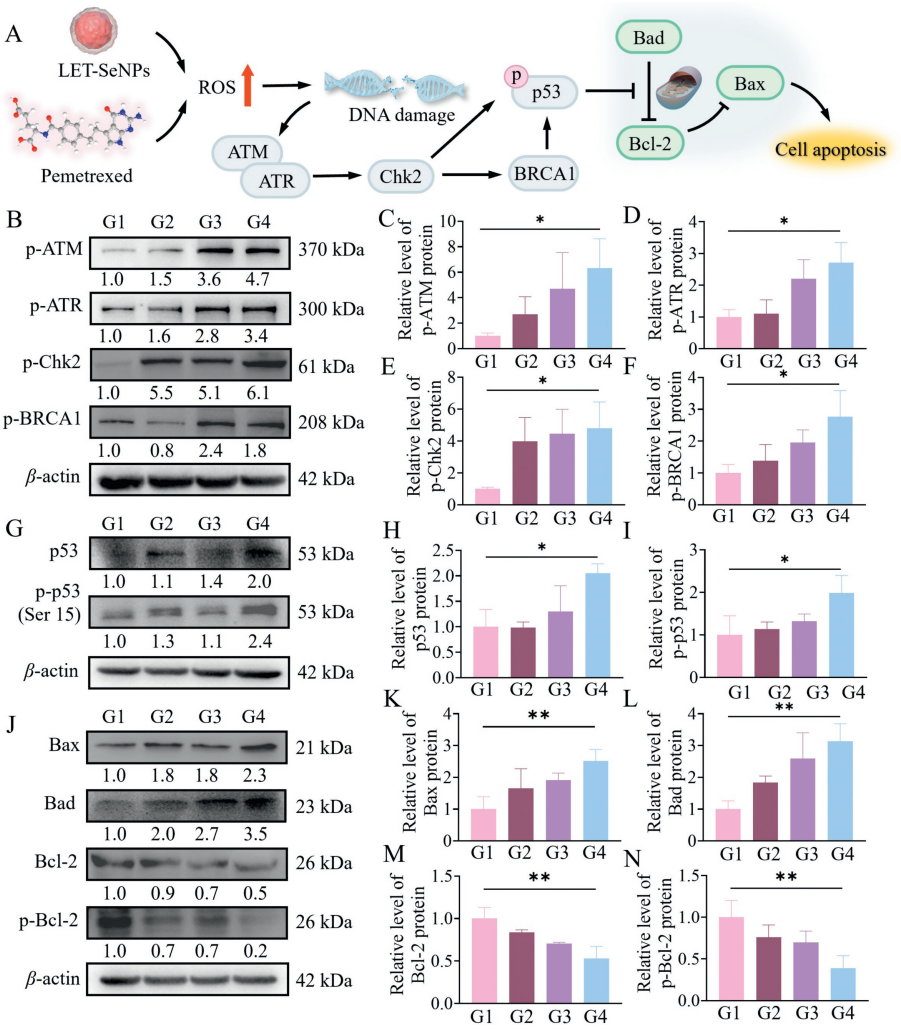



**Fig. 4.** Effects of LET-SeNPs combined with pemetrexed on protein expression in A549 cells. (A) The schema of LET-SeNPs combined with pemetrexed influencing protein expression. (B-F) Representative images and quantification of Western blot analysis of p-ATM, p-ATR, p-Chk2 and p-BRCA1 protein expression. G1: Control; G2: LET-SeNPs (10 μmol/L); G3: pemetrexed (0.5 μmol/L); G4: LET-SeNPs (10 μmol/L) combined with pemetrexed (0.5 μmol/L). (G-I) Representative images and quantification of Western blot analysis of p53 and p-p53 protein expression. (J-N) Representative images and quantification of Western blot analysis of Bax, Bad, Bcl-2 and p-Bcl-2 protein expression.

a mitochondrial membrane potential (MMP), which can change as cells undergo dysfunction or apoptosis. Hence, the impact of drug combinations on MMP in A549 cells was investigated using the JC-1 probe. The results analyzed by flow cytometry revealed that, compared to the drug alone groups, LET-SeNPs combined with pemetrexed exhibited the highest percentage of monomeric JC-1 (60.19%) (Fig. 3E and Fig. S6D in Supporting information). This result was also validated by fluorescence microscopy images (Fig. S6C in Supporting information).

Besides being the powerhouse of the cell, mitochondria also serve as primary sites for the generation of reactive oxygen species (ROS). Additionally, mitochondria serve as the main targets of the pro-apoptotic pathway induced by ROS: moderate levels of ROS can promote cell repair and growth, but excessive ROS production can affect MMP and lead to mitochondrial damage [40]. Based on this, the impact of LET-SeNPs combined with pemetrexed on ROS levels was examined using the 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA) probe. As shown in Fig. 3D, after the treatment of LET-SeNPs and pemetrexed, ROS levels in A549 cells exhibited varying degrees of elevation. At 120 min, the ROS level in A549 cells treated with pemetrexed increased to 133.51% compared to the control group. Furthermore, upon combined treatment with LET-SeNPs, the ROS level was significantly increased to 159.08% of control (Fig. S6E in Supporting information). These results suggested that the induction of excessive ROS could be a potential mechanism underlying the sensitization effect of LET-SeNPs in chemotherapy.

The underlying molecular mechanisms for how LET-SeNPs enhance the antitumor effect of pemetrexed in A549 cells were further investigated by Western blot analysis (Fig. 4A). As illustrated in Figs. 4B–F, the upregulation of proteins phospho-ataxia-telangiectasia modified (p-ATM) and phospho-ataxia-telangiectasia related (p-ATR) in response to DNA double-strand breaks (DSBs) was significantly enhanced (4.7 and 3.4-fold of control, respectively) following co-treatment with LET-SeNPs and pemetrexed. This finding further supported that the combination of two components induced ROS in lung cancer cells, leading to DNA damage. Simultaneously, there was a significant increase in the expression of phospho-checkpoint kinase 2 (p-Chk2) (6.1-fold compared to control), leading to the activation of downstream protein phospho-breast cancer susceptibility gene1 (p-BRCA1) (1.8-fold compared to control). Meanwhile, as depicted in Figs. 4G–I, the tumor-suppressive function of p53 was enhanced by the combination of LET-SeNPs and pemetrexed, as evidenced by the upregulation of both p53 expression and phosphorylation levels (2.0 and 2.4-fold compared to control, respectively). Additionally, the

ratio of phosphorylated p53 to total p53 was elevated (1.2-fold compared to control). Since the decreased mitochondrial membrane potential resulting in apoptosis, the expression of apoptosis-related proteins was detected (Figs. 4J–N). Specifically, the combination therapy group exhibited a significant increase in the expression of pro-apoptotic proteins Bax and Bad in lung cancer cells (2.3 and 3.5-fold compared to control, respectively), while the expression and phosphorylation of the anti-apoptotic protein Bcl-2 were downregulated (0.5 and 0.2 ratios of control, respectively). These evidences further supported the induction of apoptosis by the combination of LET-SeNPs and pemetrexed in lung cancer. In summary, co-treatment of LET-SeNPs and pemetrexed might trigger apoptosis of cancer cells through activation of the ATM/Chk2/p53 signaling pathway.

In summary, based on the investigation results of Se deficiency in lung cancer patients, LET-SeNPs might be used as a potential Se supplement. In this study, LET-SeNPs showed adequate dispersion and stability and were innovatively employed as chemosensitizers for pemetrexed. MTT and colony formation experiments demonstrated that LET-SeNPs could enhance the cytotoxicity of pemetrexed and decrease lung cancer cell proliferation. Further, LET-SeNPs combined with pemetrexed generated a large amount of ROS in lung cancer cells, which in turn, might reduce mitochondrial membrane potential and induce apoptosis of the cancer cell. Additionally, LET-SeNPs promoted the cell cycle arrest induced by pemetrexed. This study demonstrated the synergistic therapeutic effects of LET-SeNPs on pemetrexed in cancer treatment and provided new insights and strategies for NSCLC chemotherapy.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## CRediT authorship contribution statement

**Zhi Li:** Writing – original draft, Methodology, Formal analysis, Data curation. **Shuya Pan:** Visualization, Software, Formal analysis. **Yuan Tian:** Software, Formal analysis. **Shaowei Liu:** Methodology, Investigation. **Weifeng Wei:** Supervision, Resources, Methodology. **Jinlin Wang:** Supervision, Resources, Methodology. **Tianfeng Chen:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Ling Wang:** Writing – review & editing, Validation, Supervision, Funding acquisition.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.110018.

## References

[1] A. Leiter, R.R. Veluswamy, J.P. Wisnivesky, Nat. Rev. Clin. Oncol. 20 (2023) 624–639.
[2] H. Hall, A. Tocock, S. Burdett, et al., Thorax 77 (2022) 762–768.
[3] M. Guirado, E. Fernández Martín, A. Fernández Villar, A. Navarro Martín, A. Sánchez-Hernández, Clin. Transl. Oncol. 24 (2022) 1549–1568.
[4] F. Bray, M. Laversanne, H. Sung, et al., CA Cancer J. Clin. 74 (2024) 229–263.
[5] Y. Zhang, S. Vaccarella, E. Morgan, et al., Lancet Oncol. 24 (2023) 1206–1218.
[6] Y. Li, B. Yan, S. He, Biomed. Pharmacother. 169 (2023) 115891.
[7] G.V. Scagliotti, P. Parikh, J. Pawel, et al., J. Clin. Oncol. 41 (2023) 2458–2466.
[8] T. Gonzalez, M. Muminovic, O. Nano, M. Vulfovich, Int. J. Mol. Sci. 25 (2024) 1046.
[9] N. Rouw, R.J. Boosman, H. Bruinhorst, et al., Lung Cancer 146 (2020) 30–35.
[10] F. Li, H. Wang, Y. Xiang, et al., Transl. Lung Cancer Res. 12 (2023) 2381–2391.
[11] S. Visser, S.L.W. Koolen, P. Bruijn, et al., Eur. J. Cancer 121 (2019) 64–73.
[12] N. Rouw, M. Boer, R.J. Boosman, et al., Clin. Pharmacol. Ther. 111 (2022) 1103–1110.
[13] C. Gridelli, F. Marinis, M. Thomas, et al., J. Thorac. Oncol. 9 (2014) 991–997.
[14] M. Roman, P. Jitaru, C. Barbante, Metallomics 6 (2014) 25–54.
[15] A. Mojadadi, A. Au, W. Salah, P. Witting, G. Ahmad, Nutrients 13 (2021) 3256–3277.
[16] S.J. Fairweather-Tait, Y. Bao, M.R. Broadley, et al., Antioxid. Redox. Signal. 14 (2011) 1337–1383.
[17] M.P. Rayman, Lancet 379 (2012) 1256–1268.
[18] X.L. Liao, Z.H. Wang, X.N. Liang, et al., Diabet. Metab. Syndr. Obes. 13 (2020) 4755–4761.
[19] A.A. Al-Mubarak, N. Grote Beverborg, N. Suthahar, et al., Eur. J. Heart Fail. 24 (2022) 299–307.
[20] J.C. Avery, P.R. Hoffmann, Nutrients 10 (2018) 1203–1223.
[21] H. Chen, H. Zhang, L. Cao, et al., Cancer 14 (2022) 345–362.
[22] S. Liu, N. Li, H. Lai, et al., Adv. Funct. Mater. 34 (2024) 2401264.
[23] B. Deng, X. He, D. Wang, et al., Small Methods 7 (2023) e2300293.
[24] B. Xie, D. Zeng, M. Yang, et al., ACS Nano 17 (2023) 14053–14068.
[25] B. Feng, Y. Zhang, T. Liu, et al., Chin. Chem. Lett. 34 (2023) 108264.
[26] J. Ouyang, B. Deng, B. Zou, et al., J. Am. Chem. Soc. 145 (2023) 12193–12205.
[27] Y. Xu, H. Lai, S. Pan, et al., Biomaterials 305 (2024) 122452.
[28] Y. Feng, J. Wang, J. Cao, F. Cao, X. Chen, Exploration 4 (2024) 20230019.
[29] J. Wang, Q. Zhang, Y. Li, et al., Chin. Chem. Lett. 35 (2024) 108746.
[30] P. Zheng, J. Ding, Asian J. Pharm. Sci. 17 (2022) 1–3.
[31] Y. Wu, W. Chen, C. Wang, D. Xing, Chin. Chem. Lett. 35 (2024) 109096.
[32] Z. Zhang, Y. Du, T. Liu, K.H. Wong, T. Chen, Biomater. Sci. 7 (2019) 5112–5123.
[33] J. Huang, W. Huang, Z. Zhang, et al., ACS Appl. Mater. Interface. 11 (2019) 11177–11193.
[34] Y. Chang, J. Huang, S. Shi, et al., Adv. Mater. 35 (2023) 2212178.
[35] J. Ling, Y. Chang, Z. Yuan, et al., ACS Appl. Mater. Interfaces 14 (2022) 27651–27665.
[36] Y. Yang, Z. Zhang, Q. Chen, et al., Front. Bioeng. Biotechnol. 9 (2021) 758482.
[37] Z. Song, W. Luo, H. Zheng, et al., Adv. Healthc. Mater. 10 (2021) e2100149.
[38] Y. Yang, Y. Wang, L. Xu, T. Chen, Chin. Chem. Lett. 31 (2020) 1801–1806.
[39] E. Vringer, S.W.G. Tait, Cell Death Differ. 30 (2023) 304–312.
[40] F. Cai, K. Ye, M. Chen, et al., Chin. Chem. Lett. 34 (2023) 107945–107949.