**Abstract:** Lung cancer remains to be the leading cause of cancer-related deaths worldwide. Despite significant advances in cancer therapy over the last decade, momentum has been gaining for an alternative approach of utilizing medicinal plants for cancer prevention and management. Pomegranate research has revealed great promise for both cancer prevention and treatment. Pomegranate peel is a rich source of polyphenols. Ultrasound-assisted extraction (UAE) is an evolving technique for the extraction of such bioactive compounds. This study aimed to optimize UAE conditions for pomegranate peel extract and to improve the antioxidant activity and antitumor effects of the extracts on human non-small cell lung carcinoma A549 cells. The effects of extraction temperature (30-50-70°C) and sonication time (20-30-40 mins) were studied and the total phenolic content (TPC) and total flavonoid content (TFC) were calculated for each extract. The antioxidant and anticancer activities of the extracts were determined using DPPH and MTT assays, respectively. It was found that the optimized conditions for UAE were an extraction temperature of 50°C and a sonication time of 40 min. At the optimum conditions, the highest TPC and TFC were recorded with 45.58%, 150.718 mg GAE/g of extract, and 95.58 mg RE/g of extract, respectively, and the antioxidant activity was enhanced with an IC50 value of 0.037 µg/ml. The optimized extract showed more distinct anticancer activity against A549 lung cancer cells. These results indicated that the pharmaceutical quality of pomegranate peels could be improved by optimizing the ultrasonic extraction conditions.

**Keywords:** Lung cancer; Pomegranate; Ultrasound-assisted extraction; Optimization; Polyphenols; Flavonoids; Antioxidant; Antitumor