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REVIEW

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Therapeutic properties of *Punica granatum* L (pomegranate) and its applications in lung-based diseases: A detailed review

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Abstract

Respiratory diseases are the prime cause of death and disability worldwide. The majority of lung-based diseases are resistant to treatment. Hence, research on unique drugs/compounds with a more efficient and minimum side effect for treating lung diseases is urgent. *Punica granatum* L (pomegranate) fruit has been used in the prevention and treatment of various respiratory disorders in recent times. In vivo and in vitro studies have demonstrated that pomegranate fruit, as well as its juice, extract, peel powder, and oil, exert anti-proliferative, anti-oxidant, anti-microbial, anti-inflammatory, anti-cancer, and anti-tumorigenic properties by attenuating various respiratory conditions such as asthma, lung fibrosis, lung cancer, chronic obstructive pulmonary disease (COPD), and alveolar inflammation via modulating various signaling pathways. The current review summarizes the potential properties and medical benefits of pomegranate against different lung-based diseases, also highlighting its possible role in the lung fibrinolytic system. The available data suggest that pomegranate is effective in controlling the disease progressions and could be a potential therapeutic target benefiting human health status. Furthermore, this review also outlines the preclinical and clinical studies highlighting the role of pomegranate in lung diseases further evoking future studies to investigate the effect of intake of this antioxidant fruit in larger and well-defined human clinical trials.

Practical applications

- This review outlines the putative pharmacologic benefits of *P. granatum* L (pomegranate) in treating various chronic lung-based diseases such as lung cancer, COPD, ARDS, asthma, lung fibrosis, and cystic fibrosis.
- This review also highlights the possible inhibitory role of *P. granatum* L (pomegranate) in the lung fibrinolytic system triggering the fibrinolytic markers.
- This review summarizes the preclinical and clinical studies using in vitro, in vivo, and human models highlighting the potential role of *P. granatum* L (pomegranate) in lung diseases.
- This review evokes future research to investigate the effect of intake of pomegranate fruit in well-defined human clinical trials.

Abbreviations: AMPK, activated protein kinase; ARDS, acute respiratory distress syndrome; BLM, bleomycin; COPD, chronic obstructive pulmonary disease; CRD, chronic respiratory diseases; IFN-δ, interferon δ; IL-1β, interleukin 1 beta; IL-6, interleukin 6; IPF, idiopathic pulmonary fibrosis; MAPK, mitogen-activated protein kinase; MMP, matrix metallopeptidase; mTOR, the mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain enhancer of activated B cells; *P. granatum* L, *Punicagranatum* Lythraceae; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha.

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KEYWORDS
alveolar inflammation, anti-oxidant, pomegranate, respiratory diseases, therapeutic agent

1 | INTRODUCTION

Lungs are the primary organs associated with the respiratory system that helps us to breathe. Lungs are prone to continuous immune reactions as it experiences the entry of several foreign particles into the respiratory system (Kemter & Nagler, 2019; Milette et al., 2019). Lung-related diseases cause an immense health burden. Chronic respiratory diseases (CRD) are among the leading causes of mortality worldwide. Victims of lung disorders often experience long-lasting difficulties, where one of the major causes includes treatment side effects along with psychosocial struggles (Tereso et al., 2019). CRD is of unrestricted cell proliferation. CRD has no single defined cause but carries several risk factors such as smoking tobacco, infection, radiation exposure, pollution in the air, obesity, and alcohol consumption. Research over the past decades has established various epigenetic/environmental agents that play a prime role in the development and progression of CRD (Bartling & Hofmann, 2019; Kolb & Vašáková, 2019). Globally, millions of people die of CRD, and also new CRD incidences are reported in the United States alone; more than 80% of these deaths are prominent in middle-income/low-income countries (Abegunde et al., 2007; Obi et al., 2018). Despite several considerable advancements in treatment options, the cases and mortality levels of CRD continues to increase. Therefore, attention should be focused on the prevention of CRD as an ultimate strategy for the management of cancer. CRD-related deaths may well be prevented through lifestyle variation, mostly through dietary means. Naturally occurring agents from dietary fruits and vegetables have received considerable attention for the prevention and treatment of CRD. These natural agents are safe and cost-efficient in contrast to expensive chemotherapeutic treatments, which results in significant side effects (Patel et al., 2018; Younis et al., 2018). *Punica granatum* L. (pomegranate) is a natural polyphenol-rich in biologically active compounds such as ellagic acid, gallic acid, punicalagin, flavonoids, anthocyanins, hydrolyzable tannins, and ellagitannins (Table 1). There are studies also on the new purple queen pomegranate. A recent study by Balli et al. (2020) has reported the nutraceutical profile of purple queen pomegranate from cultivated trees on reclaimed dredged sediments. This study revealed the proteomic database of pomegranate juice and peel reporting increased concentrations of ellagitannins and anthocyanins. This study also reported a significantly higher concentration of glucose and galacturonic acid in the remediated sediment of purple queen pomegranate (Balli et al., 2020). Combination of these aggregates the superior anti-oxidant properties of pomegranate (Husari et al., 2017). Ellagic acid is considered one of the major components of the pomegranate fruit. Apart from its role as fruit or its juice or oil/extract, it also carries medicinal properties such as antibacterial, anti-inflammatory, anti-proliferative, and anti-tumorigenic properties (Ouachrif et al., 2012; Sharma et al., 2017, Mabrouk et al., 2019). Evidence also states that *P. granatum*, exhibits anti-parasitic properties by significantly attenuating parasitemia via reducing oxidative stress and inflammatory responses (Hafiz et al., 2016; Mubaraki et al., 2016). The medicinal properties of this fruit have fascinated the researcher's interest globally to work on it. The pomegranate fruit has been widely utilized for treating and preventing various diseases by regulating several signaling pathways, suggesting pomegranate fruit as a promising chemopreventive/chemotherapeutic agent (Shayganni et al., 2016). Throughout history, this fruit has great value. No studies have summarized the potential role of this nature's fruit on respiratory diseases. Hence, the current review summarizes the therapeutic role of *P. granatum* L in lung-related diseases which includes exploration of preclinical as well as clinical studies, emphasizing the potential importance of pomegranate in the prevention and treatment of lung diseases like asthma, idiopathic pulmonary fibrosis (IPF), lung cancer, chronic obstructive pulmonary disease (COPD), and cigarette smoke exposure. Also, the future aspects of using this safe chemoprotective drug in other lung diseases like cystic fibrosis, acute respiratory distress syndrome (ARDS), pneumonia, and pulmonary edema. The present review gives an overview of the insights into the role of pomegranate in the therapy of respiratory diseases.

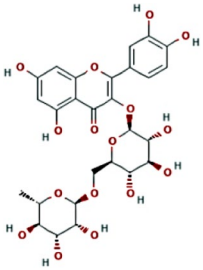
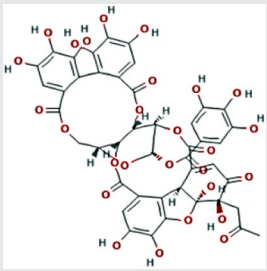
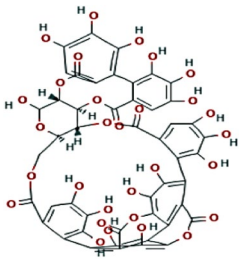
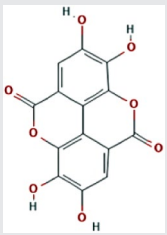
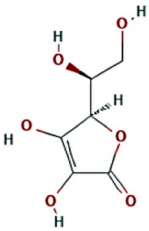
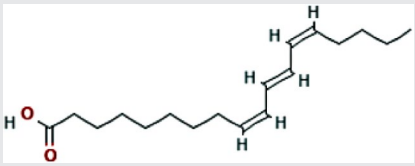
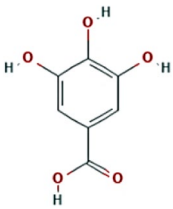
2 | METHODOLOGY (DATABASE SCREEN)

We screened PubMed and google scholar with the keywords pomegranate, *Punica granatum*, respiratory diseases, pomegranate in lungs, types of *Punica granatum* in lung diseases, pomegranate in COPD, pomegranate in lung fibrosis, pomegranate in asthma, pomegranate in lung cancer, structure, pomegranate in alveolar inflammation, pomegranate in health and diseases, and *Punica granatum* clinical trials till date. Full texts of these screened articles were screened for inclusion in this review. Articles that evaluated the therapeutic measure of pomegranate against possible chronic lung diseases evaluating possible signaling targets were included for this review.

3 | RESULTS AND DISCUSSION

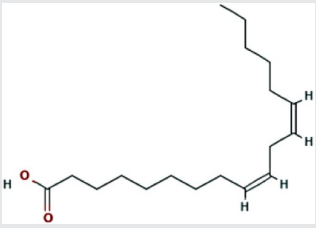
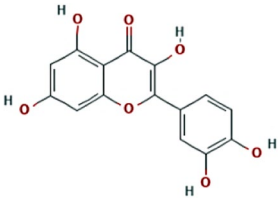
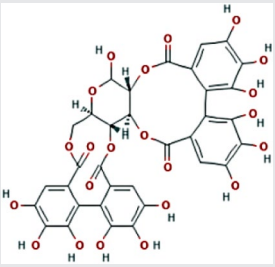
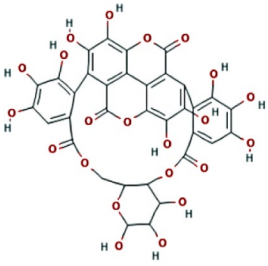
A total of 110 articles were found after a preliminary search of the articles. Title and abstracts were screened, and after that 24 articles were excluded from further review. Full-text screening of the remaining 86 articles was done. Among these, a total of 86 articles were included in the final review. Articles screened are cited

TABLE 1 Chemical structures of the active compounds in pomegranate

Active compound	Structure	PubChem CID
Flavonoids		53,787,266
Ellagitannin		10,033,935
Punicalagin		44,584,733
Ellagic acid		5,281,855
Ascorbic acid		54,670,067
Punicic acid		5,281,126
Gallic acid		370

(Continues)

TABLE 1 (Continued)

Active compound	Structure	PubChem CID
Linoleic acid		5,280,450
Quercetin		5,280,343
Pedunculagin		442,688
Punicalin		5,388,496

in particular subheadings below revealing the potent role of *Punica granatum* in chronic lung diseases.

4 | WHY IS *P. granatum* L USED AS AN EFFECTIVE THERAPY TO TREAT DISEASES?

P. granatum L, pomegranate fruit, is considered one of nature's richest sources of anti-oxidants. *P. granatum* L is known as nature's power fruit worldwide. For the past decades, pomegranate fruit tree is said to possess remarkable medicinal activities. The pomegranate tree belongs to the Middle East and a few Asian countries (Mubaraki et al., 2016). As mentioned above pomegranate fruit consist of potent anti-oxidants like anthocyanins, tannins, and flavonoids, which further are considered as anti-atherogenic. This unusual biochemical composition of pomegranate fruit has attracted many scientists to study the healing property of this fruit. Thereby, these characteristics of pomegranate fruit make it a healthy supplement and potential in preventing various diseases including lung-related diseases (Aviram & Rosenblat, 2012).

5 | *P. granatum* L IN RESPIRATORY DISORDERS

5.1 | *P. granatum* L in asthma

Asthma is CRD associated with various inflammatory cells and proteins. Asthma is a complex inflammatory respiratory disease that includes hypersecretion of mucus, inflammatory eosinophils, and airway hyperresponsiveness which ultimately makes breathing difficult by triggering wheezing, coughing, and shortness of breath (Oliveira et al., 2013; Rayees et al., 2014; Tattersfield et al., 2002). As a treatment measure, asthma is managed by rescue inhalers which contain corticosteroids that are found effective in treating symptoms of chronic asthma but are also responsible for adverse side effects that severely limit the long-term use of these inhalers (Barnes, 2004; Oliveira et al., 2013). A study by Oliveira et al. (2013) was the first approach that revealed that *P. granatum* L fruit can be an effective therapy in asthma treatment. The study demonstrated ethanolic extract from the leaves of *P. granatum* L represents a beneficial biological activity in an in vivo

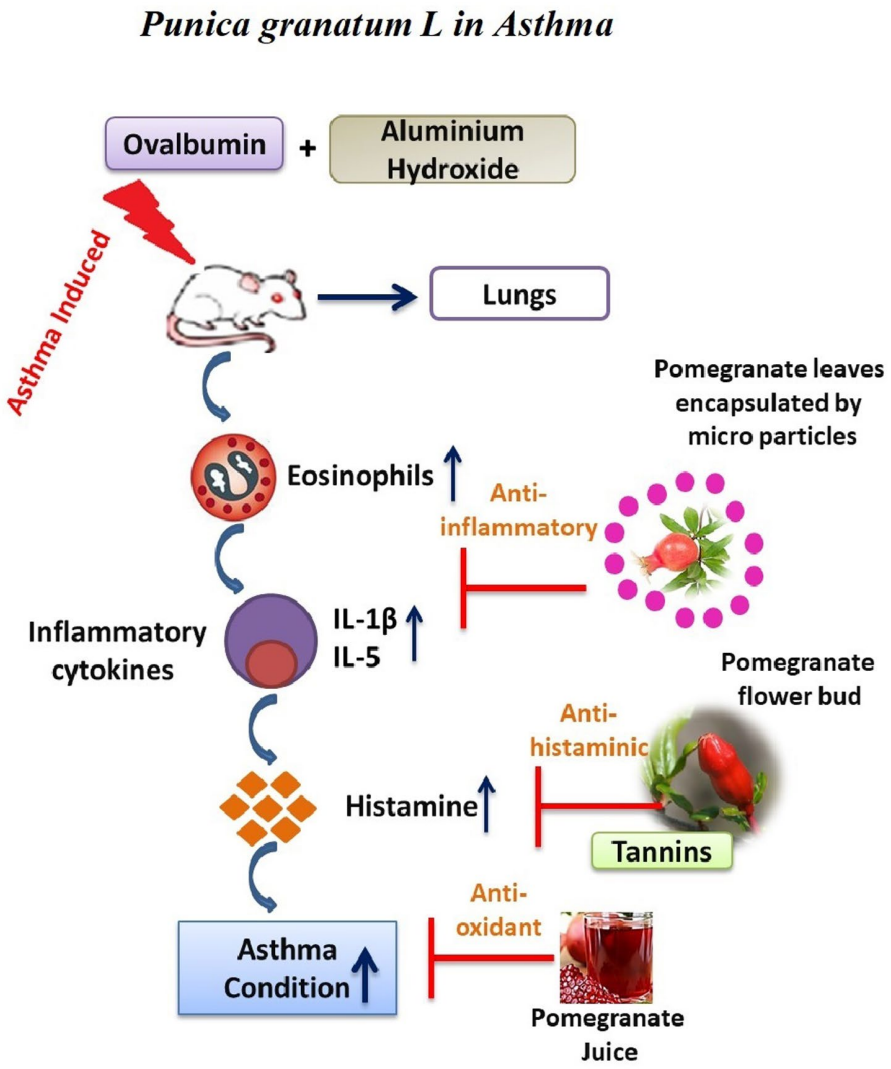


FIGURE 1 *Punicagranatum* L activity in asthma. As studies reveal, in vivo models of induced asthma (induced by ovalbumin and aluminum hydroxide) result in elevated levels of eosinophils via activating inflammatory cytokine IL-1β and IL-5 via increasing histamine levels ultimately increasing the asthma condition. Pomegranate encapsulated by microparticles inhibits asthma symptoms, whereas pomegranate flower buds act as anti-histaminic and pomegranate juice represents anti-oxidant properties essential in treating asthma

model of asthma. The highlight of this study was that the leaves extract was encapsulated in biodegradable microparticles which had a maximum therapeutic potential as compared to the extract in solution form. This suggested that its appropriate delivery of pomegranate leaves derivatives into the lungs may treat allergic diseases like asthma. These microparticles inhibited eosinophils, decreased cytokines like IL-1β and IL-5, and attenuated protein levels in the lungs (Oliveira et al., 2013; Rayees et al., 2014). Studies have also shown that the flower buds of *P. granatum* L can also react as a therapy for the traditional treatment of asthma. A study by Barwal et al. (2009) demonstrated an anti-histaminic property of pomegranate flower buds in a murine asthma model using Swiss albino mice via using clonidine-induced catalepsy and haloperidol-induced catalepsy using the dose of 50 and 100 mg/kg, p.o. This study concluded that tannins from pomegranate flower buds could exhibit anti-histaminic property which could contribute to its role in treating asthma (Pontonio et al., 2019). Recent studies revealed that pomegranate juice fermented with lactic acid is rich in antioxidants and could be a preventive measure for diseases including asthma (Alanbaki et al., 2019). Recent pieces of evidence stated that pomegranate along with licorice has been proved to be effective in cough management which could result as a potential therapy for asthma treatment (Zheng et al., 2010). These findings put forward the effective potentiality of *P. granatum* L endorsed as a therapeutic drug in treating asthma (Figure 1).

5.2 | P . granatum L in lung injury and IPF

IPF is a devastating, fatal respiratory age-related disorder that is characterized by damage, thickening, and scarring of alveolar tissue. The stiffness of the alveolar tissue results in improper

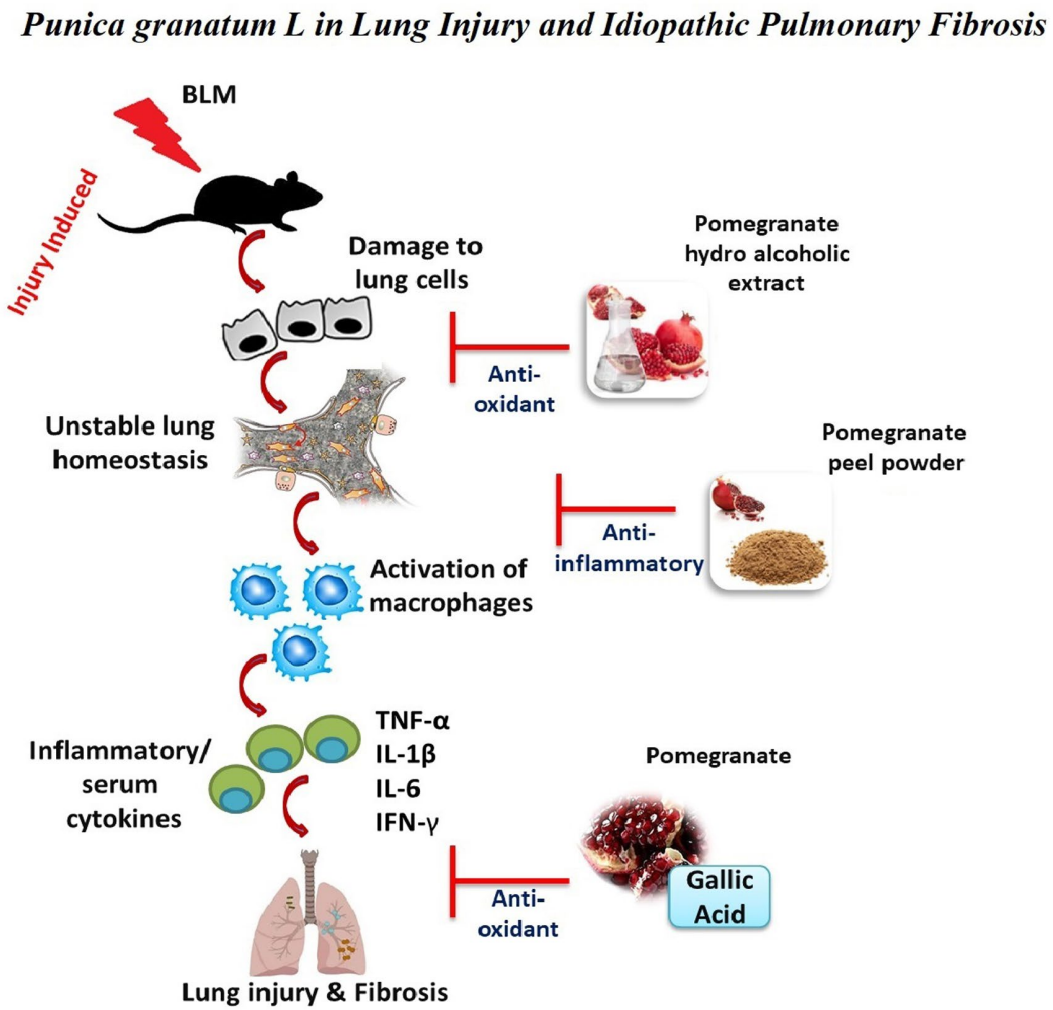


FIGURE 2 *Punicagranatum* L activity in lung injury and fibrosis. As mentioned by various studies, BLM-induced lung injuries in murine models damage the lung epithelium and disturb the lung homeostasis leading to activation of macrophages via elevating inflammatory/serum cytokines like IL-1β, IL-6, TNF-α, and IFN-δ by causing pulmonary injury leading to lung fibrosis. Pomegranate hydro alcoholic extract inhibits BLM-induced lung fibrosis, whereas pomegranate peel powder is an anti-inflammatory that decreases the levels of cytokines. Pomegranate is essential in the treatment of lung fibrosis. BLM, bleomycin

functioning of the lungs (Zheng et al., 2010). Due to its unknown cause, it is termed as "idiopathic," but recent studies have become a topic of debate (Shaikh et al., 2019). Currently, there is no effective treatment for IPF. The main focus of the treatment discovered so far is to control as much as possible the symptoms and reduce the progression of the disease. As the condition becomes more advanced, it results in respiratory dysfunction (Chen et al., 2017). *P. granatum* L was also found to be effective in terms of treating IPF. Studies have reported that hydroalcoholic extracts of the seeds of *P. granatum* L reflected a progressive effect against bleomycin-mediated pulmonary fibrosis by exhibiting its anti-oxidant activities with an appropriate dosage of 400 mg/kg in male Spraque–Dawley rat (Hemmati et al., 2013). A study by Şen et al. (2014) was the first approach that demonstrated that pomegranate extract along with carvacrol could be effective in treating methotrexate-mediated lung oxidative injury leading to lung fibrosis in the murine model. Pomegranate extract and carvacrol combination could result in enhancing the homeostasis of the lungs (Şen et al., 2014). Recent shreds of evidence reveal that the peel powder of *P. granatum* L also carries anti-fibrotic, anti-oxidant, anti-inflammatory, and anti-apoptotic activities. Pre-treating the murine models with pomegranate peel powder resulted in a protective effect in treating pulmonary injury (Salama & Faried, 2018). As mentioned, pomegranate fruit is rich in gallic acid which has anti-oxidant properties; emerging sources have also reported that gallic acid inhibits bleomycin-induced oxidative lung damage and fibrosis. The result showed that dietary supplements rich in gallic acid will be an effective adjuvant therapy in decreasing lung injury and fibrosis. This study highlighted the regulatory role of gallic acid on lung toxicity due to bleomycin treatment demonstrated by evaluating lung and serum cytokine expressions, oxidative stress biomarkers, and histopathological alterations of alveolar tissue (Nikbakht et al., 2018). All these studies depicted the beneficial role of *P. granatum* L as a therapy for lung injury and fibrosis (Figure 2).

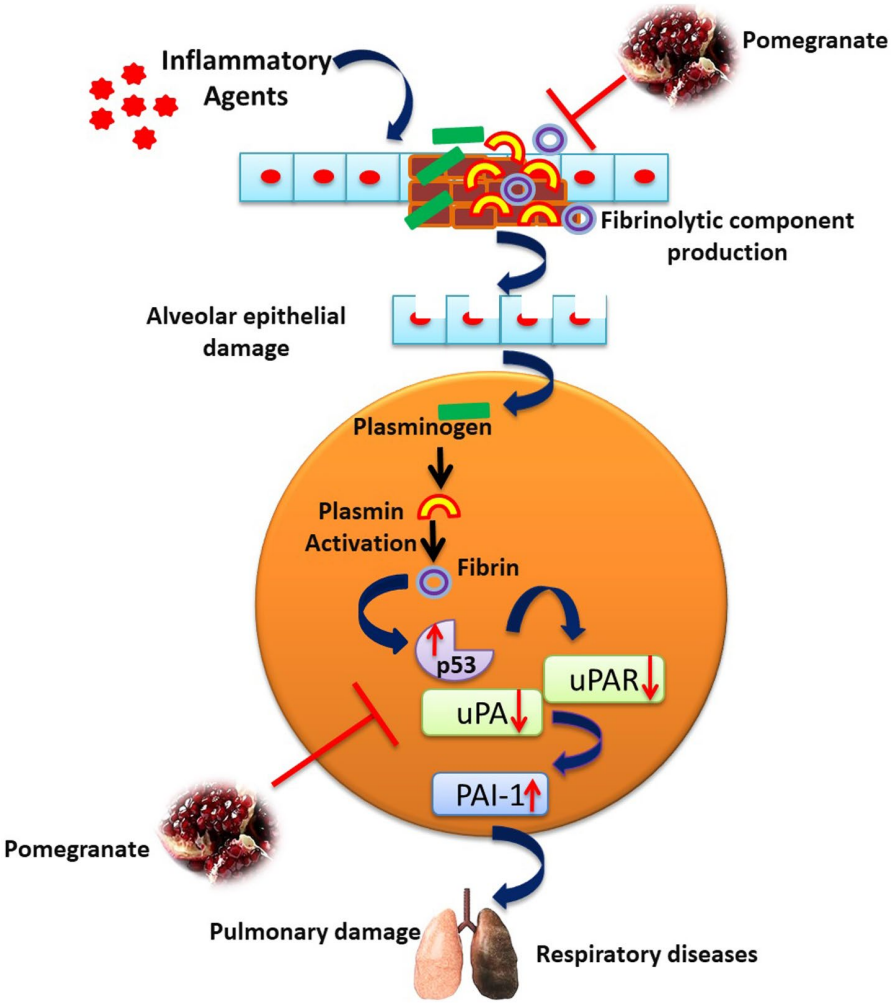


FIGURE 3 Possible role of *Punicagranatum* in targeting the fibrinolytic system in the lungs. Inflammatory agents damage the lung epithelial cells leading to activation of fibrinolytic enzymes such as plasminogen, which further produces plasmin. Plasmin denatures into fibrin as a consequence of alveolar injury leading to the production of tumor-suppressing gene p53 further increasing the expression of the fibrinolytic marker PAI-1 and decreasing levels of uPA and uPAR. All together contribute to the development of pulmonary disorders. *Punicagranatum* intervention would possibly reverse this effect

5.2.1 | The possible role of *P. granatum* L in lung fibrinolytic system

The fibrinolytic system is known to discard fibrin from the vascular system. It consists of the proenzyme called plasminogen which is operative to activate the enzyme plasmin which plays a major role in the degradation of fibrin. In humans, the fibrinolysis system is a proteolytic enzymatic process in the blood which prevents the growth of a blood clot (Collen et al., 1986; Talamo, 2018). Fibrinolysis is said to be regulated by particular molecular interactions between the plasminogen activators. Attenuation of fibrinolysis may occur at the plasmin level or its activators level (Gall et al., 2018). Alveolar epithelial cells are considered to be the major targets that activate the fibrinolytic components, namely, tumor suppressor gene p53, plasminogen activator inhibitor-1 (PAI-1), urokinase-type plasminogen activator (uPA), and its receptor (uPAR), The elevated levels of p53 leads to activation of apoptosis process in lungs and other members of the fibrinolytic system, contributing to the pathogenesis of pulmonary injury. The association of fibrinolytic components, such as PAI-1, uPA, and uPAR, with p53 is responsible for the regulation of the fibrinolytic properties and signaling molecules, which is important in maintaining the integrity of the cell (Kwaan et al., 2019). The fibrinolytic system could be a major target in respiratory diseases (Bhandary, 2016). Our previous and current studies produce strong evidence highlighting the role of the natural component curcumin in targeting the fibrinolytic component via inhibiting PAI-1 and its interactions with p53 (Gouda et al., 2018; Gouda, Shaikh, et al., 2018; Shaikh et al., 2020). Further, interesting approaches can be carried out using *P. granatum* L via studying its role in targeting the fibrinolytic system in the lungs (Figure 3).

5.3 | *P. granatum* L in lung cancer

The incidence of lung cancer has been increasing at alarming rates worldwide, specifically due to the fashion of smoking. Lung cancer today is the major cause of cancer-related deaths in the world,

representing 28% of overall cancer deaths (Barta et al., 2019; Khan et al., 2007; Miravitlles et al., 2021). Researchers have revealed that controlling this pulmonary cancer is tough by surgical and conventional therapeutic approaches (Miravitlles et al., 2021). The prognosis of lung cancer is poor with an overall 10%–14% survival rate in the United States; higher incidences are found in men as compared to women (Khan et al., 2007; Miravitlles et al., 2021). Scientists have found out that postponding the development of lung cancer activity might be a major strategy in controlling lung cancer (Gall et al., 2018; Talamo, 2018). Researchers state that the use of fruits and vegetables which supply cancer-fighting properties is appropriate in lung cancer studies (Siegel et al., 2019). Various in vitro and in vivo studies reveal that pomegranate carries an ability to fight against lung cancer (Garon et al., 2008). Past studies by Khan et al. showed that *P. granatum* L fruit extract significantly reduced the viability of adenocarcinoma human alveolar basal epithelial cells with a dosage of (50–150 μg/ml) of pomegranate extract for 72 hr; the minimal result was also reported in normal human bronchial epithelial cells (NHBE) with the same dosage (Khan et al., 2008). This study also observed that induction of WAF1/p21 and KIP1/p27 results in cell cycle arrest in the G0/G1 phase in a dose-dependent manner resulting in the inactivation of MAPK PI3K/Akt and NF-κB signaling molecules. Further, confirming the same in murine model via implantating the A549 cells in an in vivo model and proving pomegranate fluid as drinking liquid resulting in reduction of lung tumors via indicating *P. granatum* L as an effective beneficiary chemopreventive drug in treating human lung cancer (Adhami et al., 2009; Khan et al., 2008). Pomegranate fruit extracts oral infusion also results in restoring the phosphorylation of AMPKα which is considered as an upstream down regulator of mTOR in a murine model of lung cancer (Li et al., 2016). Recent studies revealed that pomegranate leaf extract blocks the invasion and migration of H1299 cells via attenuating the levels of matrix metalloproteinase (MMP) such as MMP-2 and MMP-9 in vitro indicating that pomegranate leaf extract can result as a protective chemotherapeutic compound in the treatment of non-small cell lung carcinoma via inhibiting apoptosis, cell cycle arrest, cell proliferation, migration, and invasion (Mannino & Buist, 2007). The above mentioned various studies indicate the effective role of pomegranate fruit as a beneficial therapy for lung cancer (Figure 4).

5.4 | *P. granatum* L in COPD and cigarette smoking

COPD is a respiratory disorder affecting the airways (Halbert et al., 2006). COPD continues to be a global health issue with a major cause of mortality, morbidity, and health care universally. Cigarette

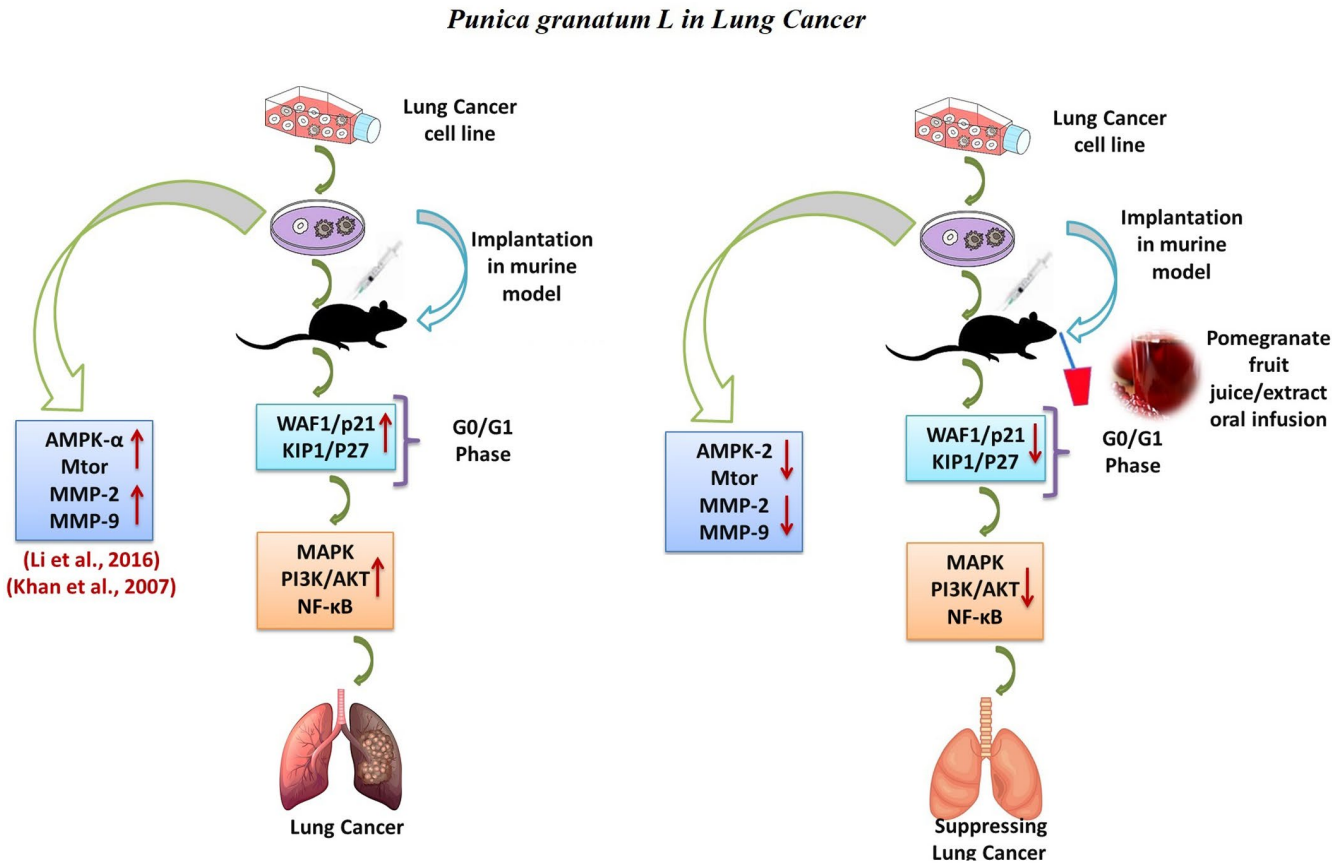


FIGURE 4 *Punicagranatum* L activity in lung cancer. Lung cancer cell lines and implanting lung cancer cell lines in a murine model expressed imbalance in the cell cycle by elevation of WAF1/p21 and KIP1/p27 in G0/G1 phase via activating MAPK, PI3K/AKT, and NF-kB signaling leading to the prognosis of lung cancer. Further activation of AMPK-α, mTOR, MMP-2, and MMP-9 is also encountered in vitro. The reverse scenario is reported with an oral infusion of pomegranate juice

smoking has been highlighted as a major risk factor for developing COPD universally; various other factors include exposure to infections, air pollution, occupational hazards, etc. also stand equally important (Halbert et al., 2006; Sullivan et al., 2000). COPD is a chronic lung disease that obstructs the airflow from the lungs ultimately causing difficult breath. Growing sources of evidence stated that the population worldwide resulted in an increased burden of COPD in the coming years (Mannino, & Buist, 2007; Ramírez-Venegas et al.; 2019; Sullivan et al., 2000). The future challenge is considered to be the implementation of preventive and management measures that are cost-effective and result in accurate COPD treatment (Mannino, & Buist, 2007; Magitta et al., 2018). Stating the role of pomegranate fruit as a therapeutic measure for COPD, past studies by Cerdá et al. (2006) stated that pomegranate juice adds no effect on COPD patients. This clinical study found no difference between the COPD victims and those patients taking pomegranate juice supplements (Ramírez-Venegas et al., 2019). On the other hand, growing sources of pieces of evidence revealed that pomegranate juice plays a vital role in inhibiting the effect of cigarette smoke on human alveolar cells in vitro. In this study levels of inflammatory molecules activated on cigarette smoke exposure were decreased on the addition of pomegranate juice (Miravitlles et al., 2021). Exposure to cigarette smoke leads to elevated oxidative injury to the lungs. Hushari and Shabban proved that the levels of inflammatory molecules elevated due to cigarette smoke exposure in an in vivo model was found to be decreased by supplementation of pomegranate juice. In this study, *P. granatum* L fruit (80 μmol kg^{-1} day^{-1}) could significantly reduce cigarette smoke-induced apoptosis and oxidative stress by inhibiting the levels of inflammatory cytokines. Mice were exposed to acute cigarette smoke extract for 3 days and on chronic cigarette smoke extract exposure for 1–3 months. *P. granatum* L fruit decreased the levels of TNF-α by restoring lung cell architectures. Moreover, pomegranate juice inhibited the damaging effect of cigarette smoke exposure on cultured human pulmonary cells. This supplementation was also found to decrease emphysematous alterations in the chronic in vivo model (Husari & Sabban, 2014). The incidence of COPD is increasing drastically. Preventive and treatment approaches should be implemented at the earliest. Even though past studies are contradictory, the recent studies put forward that pomegranate fruit attenuates the effect of cigarette smoke and acts as a safe pulmonary agent to treat COPD.

5.5 | *P. granatum* L in alveolar inflammation

Lungs are protected from the inhaled infectious mediators by the pulmonary epithelium which makes the healing ability of the lung epithelium critical for recovering from the infectious insults in reforming the epithelial barrier and restoring the respiratory functions (LaCanna et al., 2019). *P. granatum* L has proved to be effective in treating pulmonary inflammation. The study by Bachoual et al. (2011) revealed that the aqueous peel extract of *P. granatum L* fruit inhibited alveolar inflammation induced by lipopolysaccharide (LPS) in mice. This also attenuated the formation of myeloperoxidase and human neutrophil reactive oxygen species (ROS) (Bachoual et al., 2011; Baradaran et al., 2020). As already mentioned in this review, the synergistic anti-inflammatory contribution of pomegranate extract which was encapsulated with microparticle was used for the asthma in vivo model. These outcomes also contributed to the alternative use of pomegranate fruit in treating alveolar inflammation. The anti-oxidative ability of *P. granatum* L juice also resulted in vanishing the alveolar inflammatory alterations in lung tissue (Cukurova et al., 2012). Literature suggests that aqueous *P. granatum* L at 80 μmol kg^{-1} day^{-1} effectively suppressed the apoptosis process, levels of alveolar inflammatory components, and oxidative stress in the murine model by reducing lung inflammation (Bachoual et al., 2011; Baradaran et al., 2020). Another study revealed the involvement of pomegranate in attenuating the expression levels of inflammatory cytokine TNF-α and normalized the alveolar architectures during inflammation (Aviram & Rosenblat, 2012; Husari & Sabban, 2014). The anti-oxidant activity of the pomegranate juice is also reported to diminish inflammatory alterations in lung tissue (Husari & Sabban, 2014). Pomegranate juice supplementation was also reported to reduce the alveolar inflammation by suppressing the levels of inflammatory mediators in the cigarette smoke-exposed murine model by attenuating emphysematous alterations observed in the chronic in vivo model (Cukurova et al., 2012; Younis et al., 2019). All these findings highlight the pivotal role of pomegranate fruit in treating the alveolar injury.

6 | *P. granatum* L IN OTHER DISORDERS

P. granatum L, the pomegranate fruit as mentioned above, is one of the ancient fruits. In holy books, this fruit is mentioned as one of the paradise fruits in ancient times. In Ayurveda medicine, this fruit is utilized in treating diarrhea, parasitic infections, ulcers, etc. Pomegranate exerts several essential effects on normal health due to its antibacterial, anti-oxidant, antibacterial, anti-inflammatory, and antiviral activities (Ouachrif et al., 2012; Sharma et al., 2017; Viuda-Martos et al., 2010). Literature also reports immune-modulating and anti-cancer effects possed by this natural fruit (Wu and Tian, 2017); *P. granatum* L contributes to lowering blood pressure and cholesterol levels as well as cardiac risk factors. The fruit has also been reported to attenuate abnormal platelet aggregation and reduces the risk of cardiac arrest, strokes, and embolic disorders. *P. granatum* L possesses therapeutic potential against certain conditions like depression, obesity, osteoporosis, osteoporosis, dysentery, and Alzheimer's disease. *P. granatum* L has also been reported as a protection source for skin-related diseases (Thangavelu et al., 2017). A limited number of studies also depict the antiviral effects of pomegranate reported against the clinically relevant herpes virus, influenza virus, poxviruses, and human immunodeficiency (HIV-1) virus (Haidari et al., 2009). This natural fruit also holds promise in augmenting wound healing rates. A study reported that the peel of *P. granatum* L was applied as ointment regularly for up to 12 days to

TABLE 2 Summarizing role of pomegranate in other diseases

Reference cited	Source of pomegranate	Disease type	Preclinical study model	Preclinical studies effect	Clinical studies
Dianat et al. (2015); Razani et al. (2017); Kazemirad & Kazerani., 2020	Pomegranate fruit juice	Ischemia and reperfusion-induced arrhythmias	Adult Wistar rats	Pomegranate juice exhibited an anti-arrhythmic and cardioprotective effect. Also improved/controlled the oxidative stress markers such as SOD, GPX, CAT, and MDA Decreased the levels of CaCl2-induced arrhythmias in rats	Consumption of pomegranate juice for 5 days in patients hospitalized with symptoms of ischemic heart disease significantly attenuated the serum levels of troponin and MDA in these patients
Ramírez-Venegas et al. (2019); Husari and Sabban (2014)	Pomegranate flower ellagic acid (EA) Pomegranate flower hydroalcoholic extract	Intestinal/colon inflammation	Colon cell line Swiss albino mice	Attenuated TNF-α-treated NF-Kb and COX-2 activation Attenuated myeloperoxidase (MPO) activity and lipid peroxidation, histopathological alterations, MDA levels in the colon, and histamine levels in the colon	To date, only one clinical trial is registered which is ongoing at phase I. The study is on the role of pomegranate juice ellagitannins in the modulation of inflammation in inflammatory bowel diseases. (Registered in December 2016, http://www.clinicaltrials.gov)
Adams et al. (2006); Hayouni et al. (2011); Baradaran et al. (2020)	Pomegranate compound delphinidin	Rheumatoid arthritis/joint inflammation	Human rheumatoid arthritis synovial cell line DBA/1 Lac J mice	Decreased histone acetyltransferase and NF-κB activation Decreased the interleukin 6 (IL-6) level and suppressed inflammatory signal transduction pathways in mouse macrophages	Two Capsules of pomegranate extract 250 mg/day for 8 weeks) improved disease condition via reducing oxidative stress and few inflammatory blood biomarkers and oxidative stress in 30 rheumatoid arthritis patients
Albrecht et al. (2004); Shukla et al. (2008); Bachoual et al. (2011); Seong et al. (2011); Ghavipour et al. (2017); Ramírez-Venegas et al. (2019)	Pomegranate juice, peel, seed, and oil	Prostate cancer	LNCaP, PC-3, and DU 145 cell lines Sprague–Dawley rats	Attenuation of invasion, proliferation, and phospholipase A2 (PLA2) expression Reduced testosterone-induced prostatic hyperplasia, prostatic acid phosphatase activity, prostate weight, and total glutathione	A two-stage phase-II clinical trial including 46 prostate cancer victims with rising serum prostate-specific antigen (PSA) post-surgery was evaluated. As a result, 35% of subjects faced reducing levels of serum (PSA)
Albrecht et al. (2004); Ramírez-Venegas et al. (2019)	Pomegranate seed oil	Breast cancer	MDA-MB–231 breast cancer cell lines	Inhibition of vascular endothelial growth factor in inhibitory factor (MIF) and MCF–10A and MCF–7 elevating migration	Fermented pomegranate juice
Mehta and Lanskyy et al. (2004); Pantuck et al. (2006); Ammar et al. (2015)	Pomegranate emulsion	Hepatocellular cancer	Sprague–Dawley rats	Acted as a chemopreventive agent by decreasing multiplicity, size, incidence, number, multiplicity, and volume of hepatic nodules	–
Aviram et al. (2004); Bishayee et al. (2011); Bhatia et al. (2013); Vilahur et al., 2015); Asgary et al. (2013)	Pomegranate extract	Cardio-vascular disorders	The coronary cardiac disease model	Reduced atherosclerosis, serum MCP-1, MCP-1 in plaque, macrophage infiltration, lipid accumulation, ECG abnormalities, MCP-1 in heart, cardiac fibrosis, and cardiac enlargement	A study on 10 atherosclerotic subjects with 1-year consumption of pomegranate juice significantly decreased common carotid intima-media thickness (IMT), systolic blood pressure, and serum lipid peroxidation
Kazemirad & Kazerani., 2020	Pomegranate juice		Pigs	Suppressing hyperlipemia-induced coronary endothelial dysfunction by regulation of the Akt/endothelial nitric oxide synthase pathway	After 3 years, further 16% decrease in serum lipid peroxidation

(Continues)

TABLE 2 (Continued)

Reference cited	Source of pomegranate	Disease type	Preclinical study model	Preclinical studies effect	Clinical studies
César et al. (2003); Badria and Zidan (2004); Sastravaha et al. (2005)	Pomegranate phytotherapeutic gel	Dental disorders	Streptococci strains	Inhibition of microbial dental infection	The clinical trial was carried out on 20 subjects with oral abnormalities. Pomegranate gel helped in decreasing the colony-forming unit (CFU). Better miconazole clinical response in maximum patients with good oral hygiene score in the miconazole group and the longer duration of miconazole
	Pomegranate EA		*Candida albicans*		
	Pomegranate hydroalcoholic extract				
Afaq et al. (2005); Syed et al. (2006); Kasai et al. (2006)	Pomegranate fruit extract	Skin diseases	Human epidermal keratinocytes	Prevents the adverse ultraviolet effects Acted as a photo-chemo preventive compound by suppressing ultraviolet A and B radiation-induced damage	Clinical studies were carried out on 26 patients while giving them ellagic acid orally which was rich in pomegranate extract in ellagic acid in both high and low doses. Results revealed improved ultraviolet-induced skin pigmentation

TABLE 3 Status of clinical trials on respiratory conditions using pomegranate as an intervention

clinicaltrial.gov Identifier	Respiratory disease involved	Intervention used	Study title	Study status
NCT00655031	Respiratory rhinovirus infection	Pomegranate concentrate (POMx)	Trial to evaluate the use of pomegranate concentrate (POMx) for prevention of experimental rhinovirus infection	Completed
NCT00617318	Common cold Influenza Cough		Pomegranate products for prevention of common cold	Completed
NCT01564849	Chronic respiratory rhinosinusitis Nasal polyp Sinusitis Rhinitis	Pomegranate fruit extract	The clinical efficacy of topical nasal pomegranate fruit extract for patients with chronic rhinosinusitis	Unknown
NCT00987012	Respiratory influenza Swine flu	Pomegranate juice	The influence of fortified pomegranate juice (*Punica granatum*) on seasonal influenza and swine flu patients	Unknown

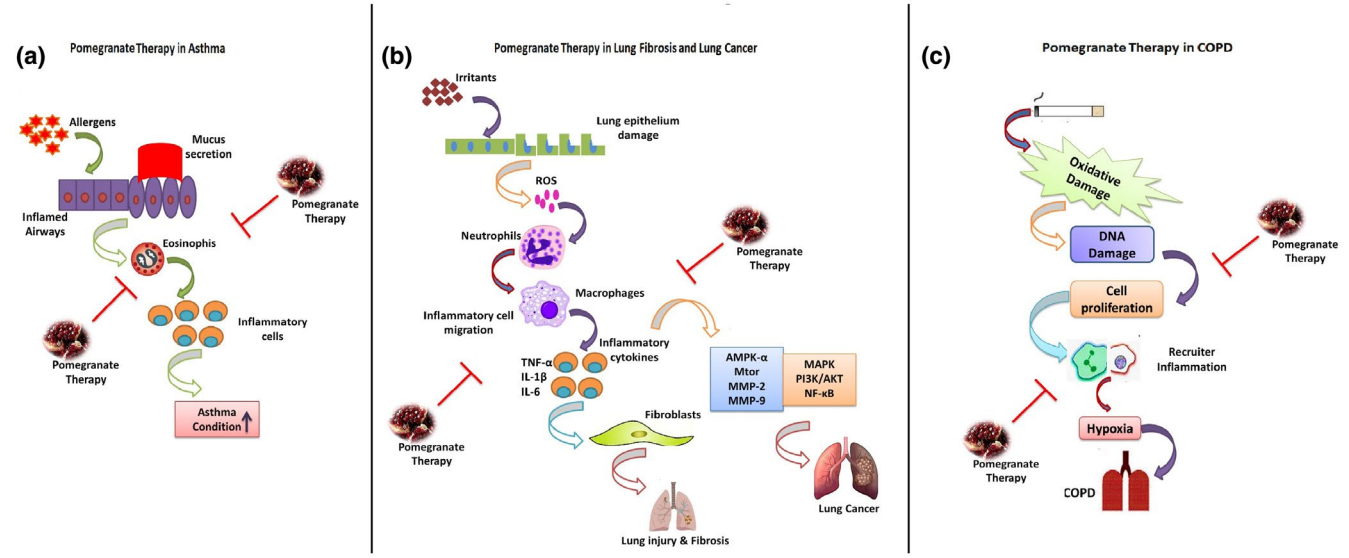


FIGURE 5 Combined representation depicting *Punicagranatum* L as an effective therapy in asthma, lung fibrosis, lung cancer, and COPD: (a) Pomegranate effect in asthma. (b) Pomegranate effect in lung fibrosis and cancer. (c) Pomegranate effect in COPD

guinea pig wounds. This leads to an increase in DNA/protein synthesis and collagen by elevating the rate of wound healing (Hayouni et al., 2011). Recent research studied the pharmacological role of pomegranate as anti-inflammatory, anti-cancer, and anti-oxidant in various diseases as in Table 2, which summarizes the contribution of pomegranate in several diseases apart from respiratory diseases (Adams et al., 2006).

7 | CLINICAL TRIALS USING *P. granatum* L IN RESPIRATORY DISEASES

Few clinical trials are reported using pomegranate as an intervention in different respiratory conditions as depicted in Table 3.

8 | CONCLUSION AND FUTURE PERSPECTIVES

In the current era, the prevention of respiratory diseases by natural dietary components is quite a promising sector of pulmonology that draws notable attention from researchers from both clinical and basic sciences due to the proven ability of natural dietary compounds to prevent or suppress chronic diseases. In the current review, the effective contribution of *P. granatum* L in treating lung-related diseases was explored. Despite the abundant literature on the potential effects of pomegranate on various diseases, its definitive impact of pomegranate in treating lung-based diseases remains unclear. The *P. granatum* L phytochemical reservoir, which is termed as "power fruit of nature" exerting anti-inflammatory, anti-oxidant, antibacterial, probiotic, wound healing, and antiviral activities, represents heuristic medicinal value for the treatment of chronic diseases (Thangavelu et al., 2017). To date, scientific research with promising health outcomes of pomegranate has been carried out in in vitro and in vivo models. The present review concludes that pomegranate is an effective therapy in lung diseases like asthma, lung fibrosis, lung cancer, and COPD (Figure 5). There are few clinical trials currently ongoing to evaluate the putative health benefits of pomegranate on respiratory conditions. So far, the effective role of pomegranate is widely studied on diseases like diabetes, cardiovascular diseases, and gastric diseases (Adams et al., 2006). But very few studies are on respiratory diseases. However, the current review relates to establishing the key component of pomegranate exerting its therapeutic effects via targeting the mechanisms through which it contributes to suppressing lung-based issues. Accumulating different research provided various extensive evidence related to the therapeutic properties of pomegranate. Studies have revealed that the whole pomegranate fruit, as well as its peel, flower, extract, juice, and oil, acts as a promising therapeutic agent, as they exert anti-proliferative, anti-inflammatory, anti-proliferative, anti-oxidant, etc. effects by regulating numerous signaling pathways (Adams et al., 2006; Hayouni et al., 2011; Ogawa et al., 2002). Convincing therapeutic outcomes with pomegranate supplementation depends upon the appropriate dose choice and timing of administration (Ogawa et al., 2002).

Furthermore, in vitro and in vivo studies are required to assess the therapeutic effect of *P. granatum* L alone as well as in combination with other compounds with a clear emphasis on the design of the study to explain the health benefits of this fruit on several other lung diseases like ARDS, cystic fibrosis, pneumonia, and emphysema. It is very important to precisely determine the appropriate dosage and timing of pomegranate administration to elucidate its protective effect on the lungs. Pomegranate is a normal fruit available easily in our day to day life; research has proved its benefits in respiratory as well as other possible conditions. Considerable

evidence represents both in vitro and in vivo efficacy of *P. granatum* L against growth and promotion of respiratory diseases. However, well-designed human clinical trials are important to validate the effectiveness of this natural fruit either alone or in combination with other therapies for the prevention and treatment of lung-related diseases (Seong et al., 2011; Shukla et al., 2008). The uncountable pharmacologic benefits of this natural fruit encourage more future studies.

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CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Formal analysis; Investigation; Project administration; Supervision; Writing-review & editing: Bhandary. *Investigation; Writing-original draft; Writing-review & editing*: Shaikh.

ETHICS

For this review, formal consent is not required.

SUBSTANTIAL WORK IS DONE BY CONTRIBUTORS

The contributors are actively involved in working on chronic respiratory diseases like lung fibrosis and COPD. The contributors have published various articles stating the potential effect of natural product curcumin in respiratory conditions. Since *P. granatum* L also is from a natural source having similar potential, an attempt has been taken to explore its role in chronic respiratory conditions.

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