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Global scenario of silica-associated diseases: A review on emerging pathophysiology of silicosis and potential therapeutic regimes

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ABSTRACT

Silicosis is an occupational fibrotic lung disease caused by exposure to respirable crystalline silica dust particles produced during industrial activities. Other crystalline silica-induced pulmonary disorders include a predisposition to mycobacterial infections, obstructive airway diseases, idiopathic pulmonary fibrosis, and lung cancer. This review paper discusses the burden of silicosis and associated co-morbidities in developed as well as developing countries globally using the published data of various government agencies, related organizations, and epidemiological findings. Moreover, it sheds light on diverse mechanisms of silicosis, outlining molecular events and peculiar alterations in lung parenchyma leading to this occupational lung disease. Evaluation of pathophysiological mechanisms could aid in the identification of novel target molecules and treatments; to date, there is no curative treatment for silicosis. In recent periods, a lot of attention has been focused on the development and fabrication of suitable nanocarriers for improved and sustained drug delivery in the pulmonary system. Nanoparticle-based therapeutic modality has been evaluated in *in-vitro* and *ex-vivo* silicosis models for prolongation of drug activity and improved therapeutic outcomes. The preclinical findings open the doors to clinical trials for operational and regenerative nanoformulations, which eventually create a positive change in medical practice. The following review summarizes various therapeutic approaches available and in the pipe line for silicosis and also stresses the preventive practices for effectively combating this occupational hazard.

Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; AECII, type 2 alveolar epithelial cells; ALI, acute lung injury; AMs, alveolar macrophages; APIs, active pharmaceutical ingredients; ARD, autoimmune rheumatic diseases; ARDS, acute respiratory distress syndrome; AS, artificial stone; ASIR, age-standardized incidence rate; ASW, artificial stone workers; BALF, bronchoalveolar lavage fluid; BFGF, fibroblast growth factor; BOCW, Building and other construction workers welfare board; Cav-1, Caveolin-1; CNT, carbon nanotube; COPD, chronic obstructive pulmonary diseases; CRH, chronic resting hypoxia; DALYs, disability-adjusted life-years; DECOS, The Health Council of the Netherlands; DHA, docosahexaenoic acid; DIF, diffuse interstitial fibrosis; ES, engineered stone; FN, fibronectin; FSD, fracking sand dust; GBD, Global Burden of Disease; HO-1, heme oxygenase-1; IARC, International Agency for Research on Cancer; ILO, International Labour Organization; IPF, idiopathic pulmonary fibrosis; LC, lung cancer; MARCO, Macrophage receptors with collagenous structure; MIP, muco-inert particles; MoA, modes of action; MRD, mixed respiratory diseases; MSHA, US Mine Safety and Health Administration; MSSU, IND Mobile Silicosis Surveillance Units; NIOSH, US National Institute of Occupational Safety and Health; NLRP3, NLR family pyrin domain 3; NPs, nanoparticles; OEL, occupational exposure limit; PAI-1, plasminogen activator inhibitor-1; PEF, peak expiratory flow; PEL, US permissible exposure limit; PFOB, perfluorooctylbromide; PMF, progressive massive fibrosis; PRPs, pattern recognition receptors; RCS, respirable crystalline silica; RD, renal diseases; REL, US recommended exposure limit; ROS, reactive oxygen species; SiO_2, silicon dioxide; SKP2, S-phase kinase-associated protein 2; STB, silico-tuberculosis; TJ, tight junction; TLV, threshold limit value; TUDCA, taurine-conjugated form of ursodeoxycholic acid; US, United States; VSMC, vascular smooth muscle cells; WHO, World Health Organization; ω-3 PUFA, ω-3 polyunsaturated fatty acid.

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1. Introduction

Silica is an oxide of silicon that exists in both non-crystalline and crystalline forms [1]. Respirable crystalline silica (RCS) is the toxic subtype implicated in silicosis and chronic obstructive lung disease (COPD) and is also carcinogenic [2–4]. Every year, about 2 million labourers in the United States (U.S.) and more than 230 million workers globally are exposed to crystalline silica [5]. Occupations associated with high RCS dust exposure include mining and quarrying, denim and sandblasting, stone manufacturing, glass and pottery making, construction, and silica flour mill operations [6–8]. However, in recent years, dry cutting of artificial stone has been associated with the generation of high RCS dust concentrations at the workplace [9].

Quartz, cristobalite, and tridymite are the three most common polymorphs of crystalline silica produced during active operations in working environments [10]. The RCS dust density in the respiratory zone and the active period of exposure are the major factors associated with the development of different forms of disease. Silicosis has three major forms of disease patterns, such as acute, chronic, and accelerated silicosis [10]. Continuous exposure to RCS dust leads to the deposition of dust particles in the lung parenchyma, where resident alveolar macrophages (AMs) act as first responders. Phagocytosis of RCS results in augmented oxidative stress [5] and apoptosis, or activation of AMs, which further leads to the recruitment of inflammatory cells and an initial alveolitis leading to acute silicosis. Moreover, the release of profibrotic cytokines leads to dense collagen deposition by fibroblasts in concentric bundles that constitute the silicotic nodule characteristic of chronic and accelerated silicosis [11].

Silicosis is preventable through operative workplace exposure controls, but once developed, no proven curative treatment is available [12]. Existing clinical management includes symptomatic management with cough suppressants, bronchodilators, and antibiotics [13]. Medications such as tetrandrine, pirfenidone, and nintedanib, which target inflammatory and fibrotic pathways, are under clinical trials [14]. However, lung transplantation remains the final frontier once all options are exhausted and the patient satisfies transplant criteria. In view of the above factors, there is a need for further research to find novel treatments.

Considering the chronic inflammation characteristics of silicosis, a better therapeutic benefit can be obtained by targeting multiple specific targets using combination therapies [15]. Gene profiling of patients with silicosis has revealed novel targets. Blocking of CS-induced gene expression, deletion of the genes encoding NLRP3 inflammasome components, inhibiting SKP2-mediated Beclin1 ubiquitination, LOC103691771 gene silencing [16–19], and up-regulating the production of hemeoxygenase (HO)-1 or glucocorticoid therapy [8] have demonstrated a potential therapeutic methodology for silicosis. In recent times, worldwide research has focused on the development of targeted therapies for lung pathologies. Nanotechnology has emerged as a promising newer therapy in recent times. Due to the number of biological barriers in the respiratory system (pulmonary tract, epithelia, mucus, blood-brain barrier, and bacterial biofilm), the use of nanotechnologies seems to be an extremely promising way to improve and enhance drug delivery and implement gene therapies [20].

In this review, sources and occupations associated with RCS dust exposure and the global prevalence of lung diseases, particularly silicosis, will be discussed. Existing therapeutic options and their outcomes have been systematically elaborated. The diverse mechanism of silicosis progression, enlisting pathways and molecular targets with emerging possible innovative therapeutic modalities, has been focused upon. The definite roles of nanomedicine in mitigating silica-induced fibrotic lung disease have been explored. Moreover, the role of preventive measures in the management of silicosis has been underlined.

2. Literature search process

An intensive search of published literature in journals, books, and other available online sources was pursued to explore the global scenario of fibrotic lung diseases with updated mechanisms of silicosis progression and its management through traditional and nanotechnology-based treatments. The online search of all literature was performed from March 2023 to August 2023. The relevant research and review, as well as case reports, were utilized to complete this systematic review. After due consideration, a total of 101 articles were selected from Science Direct (34), Google Scholar (30), PubMed (25), Springer (7), Research Gate (6), and Research Square (1). The search included keywords like “crystalline silica exposure," “fibrotic lung diseases," "silicosis," “silicosis management,” and “nanomedicine” in pulmonary diseases. To refer to all relevant literature, two or more keywords were searched together using the “AND” and “OR” terms. The process of records’ identification and screening and the eligibility and inclusion actions are given in Fig. 1. The maximum number of papers (> 90 %) considered for this study were from the last 5 years. However, the title, abstract, and paper content were measured for filtering the paper after being checked manually. The bibliography and citation management were performed using Mendeley software.

3. Accountable causes for silica dust-induced toxicity

Activities such as building, road construction, and metal mining are fairly demanding in both developed and developing countries due to constant urbanization. Industries supporting these activities include concrete slab, cement, stone quarrying, and tile production, accompanied by RCS dust production [21]. Moreover, working operations like pulverization, crushing, blasting, grinding and polishing of rocks, stones, and coal cause silica (SiO_2) dust generation [22]. Table 1 lists the general activities and occupational workstations where workers experience RCS exposure. RCS inhalation is linked with lung toxicity, which is proportional to the cumulative dose, whereas chronic silicosis develops over decades of exposure to a lower intensity of silica exposure [23]. Higher intensity of exposure over shorter periods (< 10 years) of time is associated with accelerated silicosis. These two forms of silicosis were recently found to be associated with certain occupations like engineered or artificial stone (AS) processing, construction, and sandblasting [11].

The AS is a popular and novel construction material and has direct relevance to the emergence of ‘accelerated silicosis’ among workers [17, 24,25]. The AS is made up of > 90 % silica, while natural stones like granite and marble have only 30 % and 3 % silica content, respectively [11]. The incorporation of resin- and silica-based AS in large-scale production began in 1986 and was associated with the occurrence of silicosis among AS workers (ASW). Further, the high severity and extremely short (~10 years) latency of the silicosis were found to be allied with ASW [26]. The possible reason for the short latency of lung disease among stonemasons was elaborated on in an earlier study. The report shows that the respirable dust emission from machined engineered stones had 80 % of very fine RCS particles (< 1 μm) containing quartz and cristobalite with a larger surface area as well as a higher surface charge. While natural stone dust had a lower surface area and charge with only 4–30 % of RCS and a higher (29–37 %) metal content [27]. Another study reported that the cutting of AS using a hand-operated circular saw generated a high concentration of RCS dust (44 mg/m^3 over a 30-min sampling period) with a very large proportion (94 %) of respirable particles [9]. This physical and chemical variability within engineered and natural stones with a large RCS density at the AS workplace justifies the short disease latency and the unique hazards posed by AS fabrication works.

The cement processing plant is the backbone of the construction industry and also poses hazards related to lung functions. A cross-sectional study on groups of respirable dust-exposed and non-exposed

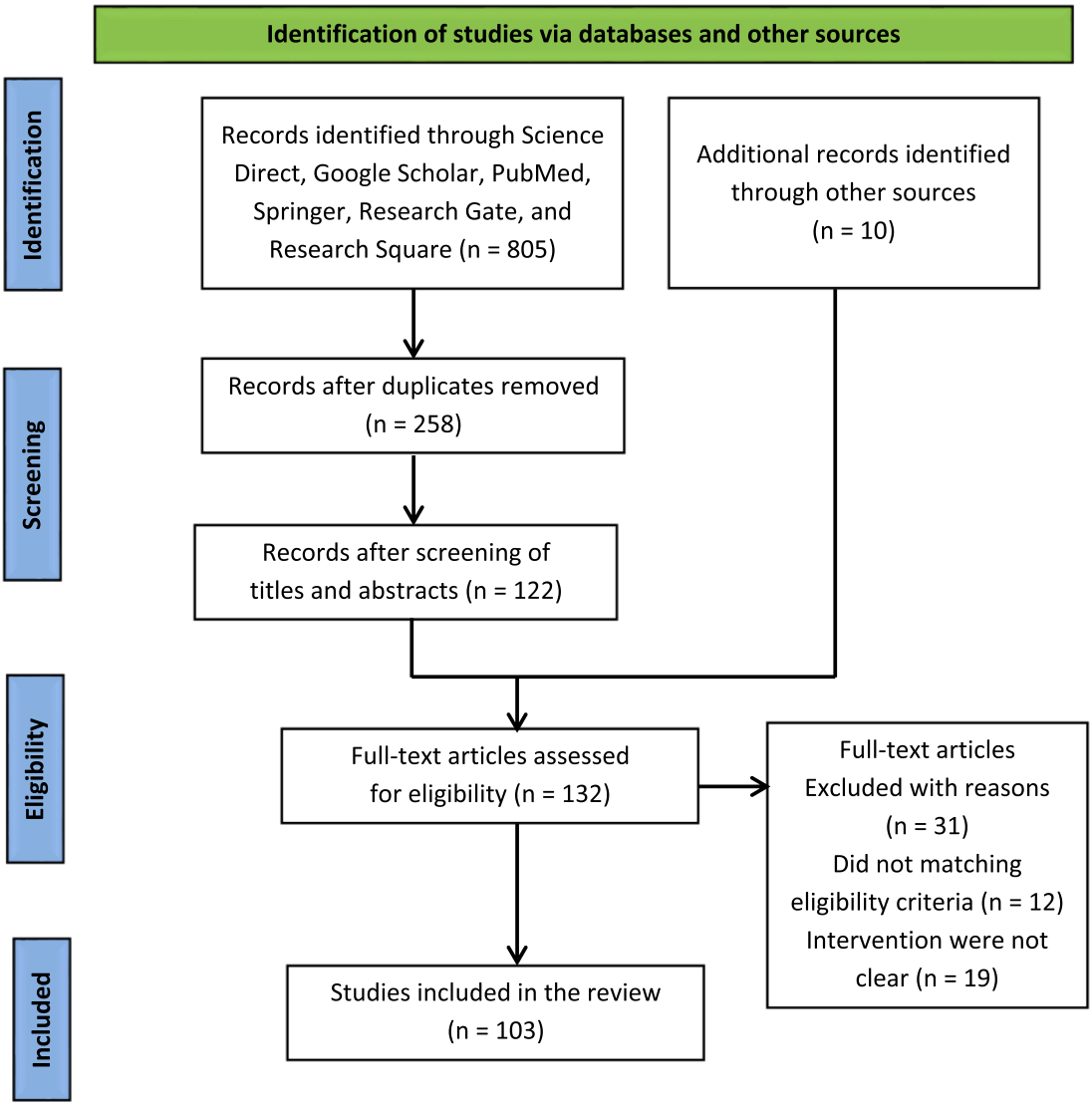

Fig. 1. PRISMA flow diagram.

workers in a cement factory reveals a significant difference in the peak expiratory flow (PEF) among both groups of workers, indicating hampered pulmonary functions. Expectedly, all affected workers were exposed to higher respirable dust concentrations of 1.77–6.12 mg/m3, with 0.026–0.044 mg/m^3 concentrations of RCS higher than the threshold limit value (TLV) of 1 mg/m^3 and 0.025 mg/m3, respectively, given by the American Conference of Governmental Industrial Hygienists (ACGIH) [28].

Sandblasting is another occupation where high crystalline silica containing sand has been used for abrasive blasting, resulting in the production of fine airborne RCS particles. Inhalation of such freshly fractured silica particles seems to produce a more severe lung reaction than aged silica and probably results in the progression of acute and accelerated forms of silicosis among sandblasters [29]. Along with sandblasters, workers engaged in unconventional oil and gas drilling works are also prone to developing silicosis. Fracking sand dust (FSD) is derived from sand ''Proppant'' which is generated during hydraulic fracturing of rocks to increase the flow and retrieval of natural gas. Such FSD contains RCS in good amounts and poses hazards of silicosis in workers [30].

Coal, metal, and non-metal mining professions are also associated with a risk of silicosis [8]. Every mining project has begun with the excavation of surrounding rock strata using blasting or drilling operations, which fairly produced a significant amount of respirable dust comprising huge RCS concentrations. The fracturing of silica resulted in the generation of the smallest-sized particles with the formation of "nearly free" surface silanols and highly reactive silicon-free radicals. These surface characteristics belong to freshly fractured silica are act as rate-determining factors for silicosis development [31]. In addition to surface characteristics, other factors such as intensity, duration, and the degree of peak RCS exposure are strongly correlated with the progression of all three forms of silicosis [32,33]. Besides, risky procedures, poorly hygienic working conditions, a lack of engineered control with poor exhaust ventilation, and the absence of personal protective equipment are underestimated culprits that ultimately contribute to the incidence of silicosis [34]. Silica exposure levels can vary depending on the type of work being done, resulting in different toxicity levels in the cement, sand mining, stone queries, AS industries, coal and other metal mining industries.

4. Epidemiology of silicosis and associated silica dust-induce disorders

Globally more than 230 million workers annually [5], while 23 million workers in China and 10 million workers in India are exposed to RCS [37]. Global Burden of Disease (GBD) study has identified

Table 1
Common operations and occupations that comprises exposure to free RCS [21,35,36].

Activities or tasks	Occupations and workers
Cutting	Crafts and sculpture, construction carpenters, bricklayers, plasterers, and tile setters, stone quarrymen and miners, metallurgical, jewellery and foundry, grindstone, glass and ceramics decorators
Drilling	Construction, tunnelling, quarrying and mining occupations, reinforced concrete layers and stonemasons, well drillers
Breaking and crushing	Construction, tunnelling, quarrying and mining occupations, glass, ceramic, and fine earthenware workers
Abrasive sand blasting	Production of dental and metal products, shipbuilding and repair, production of denim jeans and tombstone, boiler scaling
Grinding	Construction, quarrying and related milling
Sanding	Automobile repair (removal of paint and rust), Concrete stutterers and finishers
Excavation and digging	Agriculture, construction, quarrying and mining, tunnelling, potters
Furnace installation and repair	Iron and steel melting mills and foundries
Cleaning (dry sweeping, brushing, pressurised air blowing)	Glass and ceramics kilnmen, Concrete-mixer operations and cast concrete production, sculpture and jewellery workers

worldwide a total of 14,973 (in the year 1990) and 23,695 (in the year 2017) incident cases of silicosis (age-standardized incidence rate [ASIR] = 0.30 per 100,000), which represents 39 % of the 60,055 pneumoconiosis cases [38]. Notably, in 2017 same study described the epidemiology of silicosis in Asia and reported the highest number of incident cases in China (9066) and India (1464). This emergence of disease in both countries is firmly associated with the overproduction of RCS and lack of exposure safety measures in key industries such as coal, stone, and metal mining, construction and ordinances [37]. The worst scenario of silicosis in China was also highlighted in previous studies. Between 1991 and 1995 there were > 500,000 and 6000 new cases with 24 000 deaths reported annually [35]. The year-wise incidence of new cases in China was augmented in 2016 as 10,072 patients were diagnosed with silicosis and among which 43.78 % were concentrated in Sichuan, Hunan and Chongqing provinces and Beijing [9].

In the U.S., silicosis remains an important occupational lung disease, because millions of workers annually experience extreme RCS exposure, largely due to mining, construction and artificial as well as natural stone processing activities [5,37]. Similarly, Canada also has 350,000 workers potentially exposed to RCS each year at various working places [10]. There were 3600–7300 annual silicosis cases reported per year between the period of 1987–1996 from various RCS (0·05 mg/m^3 or more) associated occupational sites [35]. Nevertheless, several studies signify the role of RCS exposure in provoking another chronic disease in the US. The NIOSH funded silicosis surveillance program has identified 1048 silicosis cases from year 1988 to 2016 in Michigan. Additional chest radiographs and tuberculosis (TB) skin tests confirmed that 222 and 88 subjects were classified as progressive massive fibrosis (PMF) and had active TB respectively [21]. Further, a review investigation conducted to identify PMF cases from the National Coal Workers' Autopsy Study data set of 7762 historical and 1129 contemporary US coal miners. The author founds a significantly higher proportion of silica-type PMF (57 % vs. 18 %; $P < 0.001$) among contemporary miners ($n = 23$; PMF) compared with their historical counterparts ($n = 62$; PMF); suggesting the surprizing surge of severe disease in contemporary miners due to RCS exposure [31] (Table 2). Moreover, 8.3 %, 6.2 % and 1.9 % mortality respectively reported for LC, mixed respiratory diseases (MRD) and renal diseases (RD); attributed due to cumulative RCS exposure in the cohort of 2650 mine and mill workers at NJ, CA, AR, and WI states of US over seven decades (1945—2015) [39]. Recently, a case series of 52 Latino immigrant male silicosis patients dealing in engineered stone (ES) countertop fabrication identified by California Department of Public Health, USA demonstrated that PMF was diagnosed in 38 % patients, 19 % died and 12 % were alive with chronic resting hypoxia (CRH) [40]. The Canadian epidemiological study data of RCS-exposed occupational disease were summarized between the years 1938—1992 indicates the occurrence of 328–1190 silicosis as well as 31–83 cases for LC belonging to mixed type of occupational settings [41]. The coal and metal mining occupations are also at a higher risk of silicosis dominance. There were approximately 1300 silicosis incidences were reported from gold mines belongs to African countries in the year 2017 [37]. These outcomes justified silicosis as the most prevalent occupational lung impairment in both regions. The RCS-associated diseases and mortality records of various worldwide epidemiological studies are summarized in Table 2.

In the past few decades, industries related to the processing, manufacturing, and setting up of AS bathroom and kitchen countertop products have been booming. Countries like Australia, USA, Israel, and the European Union are experiencing a great emergence of silicosis cases due to the exposure of AS-generated high RCS particles [34]. Different studies have shown that the potential exposure of AS workers to RCS exceeds that of 3 million in European countries and 500,000 in Australia annually [10,33]. According to a systemic review by Leso et al. [34], 65 cases from Spain (2008–2016), 7 cases from Australia (2011–2016), and 147 cases from Israel (1997–2015) with 9 cases of ARD were associated with AS fabrication industries. In 2019, there were 350 projected AS-related silicosis cases in Australia, accounting for a vast socioeconomic impact [33]. As well, 99 confirmed cases of accelerated silicosis and 15 PMF associated with AS were identified by a government-funded case-finding program in Queensland, Australia, in the year 2019 [47]. Moreover, concerning the Cancer Council 2021 report [48] in 2011, nearly 587,000 workers in Australia experienced RCS exposure while working, of which 5758 will subsequently develop LC through the course of their lives (Table 2).

Besides silicosis, RCS-induced diseases are COPD, autoimmune or immunologic disorders (systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis), and chronic renal disease [2–4,49–52]. Whereas, silico-tuberculosis, LC, COPD, and MRD are important co-morbidities associated with RCS-induced silicosis [43,44,53]. As per the recent GBD study, COPD and LC appeared in the top ten leading causes of disability-adjusted life years (DALYs) in 2019. Additionally, the global burden of both diseases is 62.6 % in low- to middle-income countries, which will likely increase over the coming years due to unsuccessful dust control at work [54]. Using the data from the 28 cohort and six case-control epidemiological studies from various countries [41], the author reported LC cases in silicosis subjects (Table 2). The Danish cohort of 3.1 million workers showed an exposure-dependent association between RCS and combined autoimmune rheumatic diseases, with more than 30,000 reported incidents from 1979 to 2015 [3]. Another cohort of 34,204 former underground miners (1960–2013) from East Germany demonstrated that mortality of 533 (COPD), 2222 (MRD), and 2960 (LC) occurred due to constant RCS exposure [45].

The silicosis and other associated diseases as co-morbidities in India augmented in sandstone mines. Recently, a chest X-ray review of 529 former stone mine workers in Rajasthan alarmingly noted 275 radiological signs of silicosis and 40 suggestive of PMF. Expectedly 12.4 % of subjects with silicosis also had associated silico-tuberculosis (STB) co-morbidity [43]. Another cross-sectional study performed in 15 sandstone mines and over 174 workers in Jodhpur, India, reported 37.3 %, 7.4 %, 10.0 %, and 4.3 % prevalence for silicosis, STB, TB, and MRD, respectively [44]. In Rajasthan, a relief scheme for silicosis-affected beneficiaries has been implemented by the building and other construction workers (BOCW) welfare board since August 2015. Out of 4978 BOCW beneficiaries, 741 subjects died, which shows that the incidence of silicosis and associated deaths is much higher in the stone carving industry than in the mining industry [55].

Table 2
The global burden of RCS-induced occupational diseases.

Country	Study Period	Occupational settings	RCS exposed subjects	Silicosis incident or deaths	Other diseases	Ref.
China	2017	Mixed	23 million	9066		[37]
	2018	Stone work	-	81	-	[9]
	1991–1995	Mixed	-	500,000	-	[35]
	1970–1989	Mixed	-	932–4372	LC: 9–330	[41]
	1960–1974	Metal mining and pottery	34,018	5297	LC: 546	[42]
Hong Kong	1980–2005	Mixed	-	1419–3202	LC: 28–157	[41]
Japan	1979–1993	Mixed	-	2442	LC: 228	[41]
India	2017	Mixed	10 million	1739	PMF: 40	[43]
	2017–2019	Sand stone mining	174	65	TB: 17 STB: 13 MRD: 8	[44]
Israel	1997–2015	AS industry	-	147	ARD: 9	[34]
Argentina	2015–2017	Mixed		34		[37]
Brazil	1978–1998	Gold mining	-	4500	-	[35]
USA	1988–2016	Mining & construction	-	1048	TB: 88 PMF: 222	[21]
	1945–2015	Stone quarry and construction	2650	-	LC: 221 MRD: 165 RD: 51	[39]
	2019–2022	ES fabrication	-	52	PMF: 20 CRH: 10	[40]
	1999–2014	Mixed	99,700	335	-	[23]
	1971–2013	Mining	8891	-	PMF: 85	[31]
	1987–1996	Mixed	1.3 million	3600–7300	-	[35]
	1940–1983	Mixed	-	590–760	LC: 0–39	[41]
Canada	1938–1992	Mixed	-	328–1190	LC: 31–83	[41]
Australia	2019	Mixed		107	-	[37]
	2019	Stone industry	500,000	350	-	[33]
	2011–2016	AS fabrication	-	7	-	[34]
	1955–1994	Mixed	-	1467–2212	LC: 94–182	[41]
Italy	1943–2006	Pottery & bricks work	-	231–14929	LC: 10–798	[41]
Denmark	1979–2015	Mixed	3.1 M	-	ARD: 16941 SS: 998 RA: 12680 SLE: 2076 SVV: 1618	[3]
	1967–1974	Foundry	-	6144	LC: 161	[41]
Germany	1960–2013	Uranium ore mining	34,204	941	COPD: 533 MRD: 2222 LC: 2960	[45]
	1953–1985	Quarry	-	2475	LC: 27	[41]
Finland	2005–2014	Mixed	50,000	850	LC: 5	[36]
	1953–1991	Mixed	-	811	LC: 190	[41]
Sweden	1990–2014	Mixed	963	-	COPD: 64	[4]
	1931–1983	Ceramic, mine and quarry	-	280–3610	LC: 07–49 TB: 29	[41]
Spain	2006–2019	Mixed		283		[46]
	2008–2016	AS fabrication	-	65	-	[34]
UK	1990–1993	Mixed	600,000	400	-	[35]
Austria	1950–1960	Mixed	-	2212	LC: 182	[41]
Switzerland	1960–1978	Mixed	-	2399	LC: 180	[41]
Africa continent	2017	Gold mining	-	~1300	-	[37]

LC, lung cancer; PMF, progressive massive fibrosis; COPD, chronic obstructive pulmonary diseases; MRD, mixed respiratory diseases; CRH, chronic resting hypoxia; TB, tuberculosis; STB, silico-tuberculosis; RD, renal diseases; ARD, autoimmune rheumatic diseases; SS, systemic sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SVV, small vessel vasculitis.

5. Pathophysiology of silicosis

The human respiratory system is divided into two zones: the conducting zone and the respiratory zone, where gaseous exchange takes place. Inhaled air containing RCS particles between 5 and 10 μm are trapped in the conducting zone (nose, pharynx, larynx, trachea, bronchi, and bronchioles) and expelled out with the mucus secretion [53]. Whereas, very fine (< 5 μm) particles pass to the respiratory zone, including respiratory bronchioles and alveolar ducts, and ultrafine (< 2 μm) particles can easily be deposited in the pulmonary alveolar space of the lower respiratory tract [46]. Once RCS particles reach the lower respiratory zone, alveolar macrophages recognize and uptake silica particles via scavenger receptors, particularly macrophage receptors with collagenous structure (MARCO) [35,56]. This interaction ultimately leads to the toxicity of AM through the silica-induced production of reactive oxygen species (ROS) [9,37]. Silica toxicity results in the apoptosis or activation of AMs and initiates the recruitment of inflammatory cells at the pathological sites. Unfortunately, engulfed RCS particles remain undigested and are released from apoptotic AMs to re-induce toxicity in other phagocytic as well as epithelial cells [6,57]. Such continuous augmentation of ROS-mediated oxidative damage leads to activation of inflammasome assembly (NALP3/NLRP3) [5]. On the other hand, lysosomal leakage also promotes the inflammasome assembly following RCS exposure in AMs [19,58]. The NALP3/NLRP3 activation triggers the process of inflammation throughout the lung via the secretion of various cytokines such as IL-1β, IL-6, IL-10, and TNF-α

[59,60] and fibrotic molecules including TGF-β and fibroblast growth factor (bFGF) [61,62]. These molecular events lead to the formation of scar tissue in the lungs, i.e., lung fibrosis or silicosis [36], as shown in Fig. 1. Moreover, upon long-term exposure, RCS can be permanently retained in the lung parenchyma, and the progression of silicosis can therefore take place even after the termination of exposure or more than 20 years after exposure [3]. However, AS-associated silicosis demonstrates quick radiological progression, shorter latency, and accelerated loss of lung function [9]. Nevertheless, despite the enormous effort being expended toward explaining the mechanism of silicosis for a long time, recent studies have focused on precise molecular events associated with CS-induced silicosis.

The International Agency for Research on Cancer (IARC) classified silica as a group 1 human lung carcinogen in 1997. Long-term exposure to silica dust may induce carcinogenicity through RCS-mediated genotoxic damage with three probable modes of action (MoA), including direct, indirect, and secondary mechanisms. In a direct mechanism, RCS particles directly interact with DNA present in the nucleus, while RCS-induced oxidative stress-mediated DNA damage is an indirect effect. Whereas secondary MoA is common, genotoxicity is mediated by inflammation, e.g., phagocyte-derived oxidants (Fig. 2). DNA damages attributed to RCS-derived oxidative destruction are mainly associated with lung cancer [32,36,63].

Multiple precise molecular mechanisms of RCS-induced silicosis suggested in different studies are demonstrated in Table 3. Two recent investigations on single-cell sequencing in bronchoalveolar lavage fluid (BALF) from silicotic patients have indicated impaired interferon (IFN-γ) signaling in myeloid cells [19] and RAB20 (a member of the RabGTPase family) deficiency in AMs [58]. Both events were found to be linked with RCS-induced activation of the NLR family pyrin domain 3 (NLRP3) inflammasome and silicosis development. The activation of NLRP3 inflammasome and pattern recognition receptors (PRPs), leading to the discharge of IL-1β, TNF-α, and IFN-γ and increased NADPH oxidase activity, is resulting in continuous inflammation and lung fibrosis [5].

In response to RCS-induced AM activation, the expression of miR-205–5p and miR-503 was found to be down-regulated. Lower miR-205–5p expression is associated with high expression of S-phase kinase-associated protein 2 (SKP2)-mediated induction of E2F transcription factor 1 (E2F1) and Beclin1 ubiquitination with decreased autophagy [18]. Similarly, miR-503 downregulation was linked with improved EGFA and FGFR1 expression and activation of ERK/MAPK signaling [9]. These microRNA-derived molecular alterations were ultimately responsible for TGF-β1-mediated myofibroblast differentiation and ECM deposition in the alveolar space, leading to silicosis. Moreover, RCS-induced variations in lncRNAs [17] as well as mRNA expression [65] were also associated with the development of silicosis through fibroblast differentiation and collagen deposition in rats' lungs. The RCS-derived oxidative stress (iNOS and NOx production) triggers the secretion of histamine and serotonin from AMs and EMT of type II epithelial cells [13]. Both events over and over again promote fibroblast proliferation and ECM deposition, causing silicosis [63,67]. The ECM deposition is a crucial event in the establishment of silicosis. RCS-mediated RhoA activation through CD44 and up-regulation of YAP forms the CD44-RhoA-YAP signaling, which proved their role and

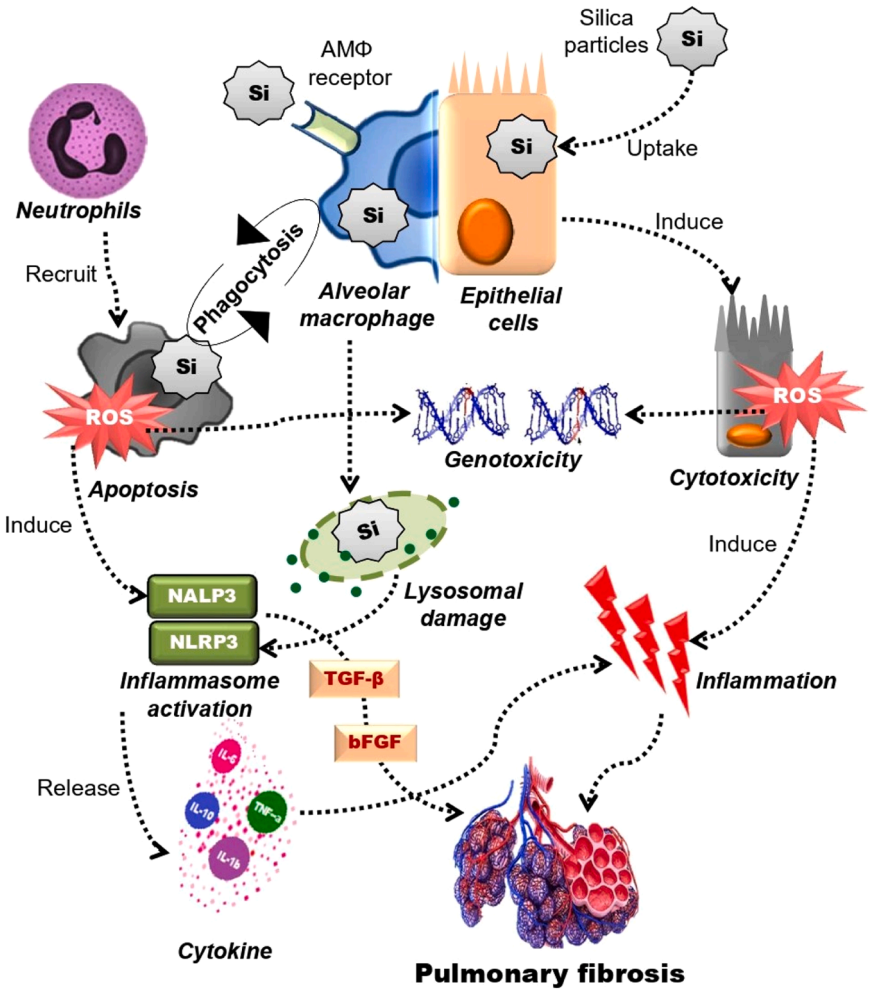

Fig. 2. Molecular mechanism of RCS-induce pulmonary fibrosis.

Table 3
Outline of studies representing pathophysiological mechanisms for RCS-induced silicosis.

Mechanism	Ref.
RCS phagocytosis – AMs apoptosis or activation – recruitment of inflammatory cells – initial alveolitis - release of pro-fibrotic cytokines – dense collagen deposition by fibroblasts – formation of silicotic nodule – AS	[8,11]
RCS triggers inflammation – alveolar wall distortion – collagen deposition – silicotic nodule formation – pulmonary fibrosis (silicosis)	[64]
RCS phagocytosis – ROS in AMs – cytokine secretion – mt Apoptosis – silicosis progression (induce autophagy related BECN1, Atg5, Atg7, Ulk1, and P62 gene expression)	[57]
RCS-stimulated AM – lysosomal damage – activate (PRRs) and NLRP3 inflammasome – lower RAB20 expression – increased SiO_2/phagosomal area – release IL−1β, TNF-α, and IFN- γ – increased NADPH oxidase and mitochondrial ROS – AMs death – inflammation continues – silicosis	[5,19, 58]
RCS exposure – increased m-RNA expression (*Spp1, Mmp12, Ccl7, Defb5, Fabp4 and Slc26a4*) – decrease *Lpo, Itln1, Lcn2* and *Dlk1* expression – fibroblast differentiation – up regulate Collagen type 1 expression – fibrosis (silicosis)	[65]
RCS engulfed by AM – increased m^6A RNA methylation – Up regulation of METTL3 – Down regulation of ALKBH5, FTO, YTHDF1, and YTHDF3 – progression of silicosis.	[66]
RCS-induced increased 149lncRNA & decrease 136 lncRNA expression – complement and coagulation cascades activation – VSMC apoptosis – TGF-β secretion – disturb TJ – collagen deposition – silicotic nodule formation – AS	[17]
RCS down regulates miR−205–5p – induced E2F1 — high expression of SKP2 – induced Beclin1 ubiquitination – lowers the autophagy – pulmonary fibrosis	[18]
RCS activates AMs – down regulates miR−503 – up regulate EGFA and FGFR1 expression – ERK/MAPK signalling activation – release TGF-β1, CTGF and PDGF – myofibroblast differentiation – ECM secretion – silicosis	[9]
RCS produce OS – induced cytotoxicity and inflammation – histamine and serotonin secretion by AMs – fibroblast proliferation – deposition of ECM – silicosis	[63]
RCS produce OS, inflammation and cytokine – fibroblast proliferation – EMT of hyperplastic of type II epithelial cell – spindle & elongated cells appearance – deposition of ECM – fibrosis (silicosis)	[67]
RCS-mediated 4–1BB expression on AMs & MH-S cells – cytokines, chemokine & MMPs secretion – activation of epithelial $CD4^+$ T cells & fibroblast – ECM & collagen deposition – tissue damage (silicosis)	[16]
RCS induce inflammation – RhoA activation through CD44 – up regulation of YAP – activation of CD44-RhoA-YAP signaling - formation of ECM – ECM-induce fibroblast activation/proliferation – pulmonary fibrosis (silicosis)	[15]
RCS-induced TGF-β1, TNF-α & IL−1β secretion – induction of EMT – down regulation of E-Cad – up regulation of Vimentin – induce abnormal deposition of ECM – fibrosis	[60]
RCS exposure – Inflammasome activation in BEC and AM – up regulate TLR4, MyD88 and TIRAP protein expressions – activate NFκB p65 cascade – release of IL−1β, IL−6, IL−10 and TNF-α – release of bFGF – silicosis	[58,62]
RCS exposure – up regulate FcεRI expression – FcεRI protein binds IgE – secretion of IL−1β, IL−6, and TNF-α – chronic lung inflammation – fibrosis (silicosis)	[68]
RCS – ROS secretion by AM – recruitment of leukocytes – KC/CXCL 1 production – up regulation of MIP−1α/CCL−3, MIP−2/CXCL−2, TNF-α and TGF-β – formation of granuloma – collagen deposition – fibrosis (silicosis)	[67,70]
RCS-induced iNOS activation in AMs – NO &NOx enzymes production – tissue damage – excessive repair and fibrosis	[13]
RCS phagocytosis – lysosome injury in AMs – increased autophagosomes – inflammation and fibrosis (silicosis)	[71]
RCS induced IL−17A – $FoxP3^+$ $CD103^+$ T_{RM}-like cell – increased IFN-γ production in $CD103^-$ T_{EM}-like cells – pathogenicity of silicosis	[72]
RCS-induced recruitment of bone marrow derived senescent cells – expression of Fgr tyrosine kinase and p16 –accumulation of α-SMA – fibroblast proliferation – silicosis	[73]
RCS-triggers CXCR4/CXCL12 up regulation – neutrophil extracellular trap formation – recruitment of B-lymphocytes & circulating fibrocytes ($CD45^+$ collagen I^+ $CXCR4^+$) – deposition of collagen I and α-SMA – pulmonary fibrosis	[74]
RCS trapped in alveoli – attenuate SOD3 expression – elevated expression of Timp1, Fsp1, and Mcp1 – RVSP elevation – fibrotic nodule – collagen deposition– fibrosis	[75]
RCS capture by AM via MARCO receptor – activation of inflammasome – higher expression of Npnt and other cytokines – collagen production – nodular lesson – silicosis	[56]

AMs, alveolar macrophages; ERK, extracellular signal-regulated kinase; HO-1, hemeoxygenase 1; Cav-1, caveolin-1; ROS, reactive oxygen species; PRPs, pattern recognition receptors; NLRP3, NLR family pyrin domain 3; IL-1β, interleukin-1beta; TNF-α, tumour necrosis factor α; NADPH, nicotinamide adenine dinucleotide phosphate; RAB20, member of RabGTPase family; Spp1, secreted phosphoprotein 1; Ccl7, C–C motif ligand 7; Defb5, beta-defensin 5; Fabp4, Fatty acid binding protein 4; Lpo, lipid peroxidation; Itln1, intelectin 1; Lcn2, lipocalin 2; Dlk1, delta-like homolog 1; m^6A, N^6–methyladenosin; METTL3, methyltransferases; ALKBH5 & FTO, demethylases; YTHDF1, and YTHDF3, RNA-binding proteins;lncRNA, long non-coding RNA; VSMCs, vascular smooth muscle cells; TJ, tight junction; AS, accelerated silicosis; miR-205–5p, microRNA-205–5p; E2F1, E2F transcription factor 1; SKP2, S-phase kinase-associated protein 2; miR-503, small non-coding RNA-503; VEGFA, vascular endothelial growth factor A; FGFR1, fibroblast growth factor receptor 1;CTGF, connective tissue growth factor; PDGF, platelet-derived growth factor; MAPK, mitogen-activated protein kinases; OS, oxidative stress; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; NAC, N-acetylcysteine; 4–1BB, surface glycoprotein that belongs to the tumour necrosis factor receptor family (TNFRSF9); MH-S, macrophage like cells; MMPs, matrix metalloproteinases; RhoA, Ras homolog family member A protein; CD44, cluster of differentiation 44; YAP, yes-associated protein; IM7, anti-CD44-antibody; DHI, dihydrotanshinone I; VP, verteporfin; TGF-β1, tumour growth factor-beta1; E-Cad, E-cadherin; AMPK, adenosine 5′-monophosphate (AMP)-activated protein kinase; mTOR, mammalian target of rapamycin; BEC, bronchial epithelial cells; TLR4, toll-like receptor 4; MyD88, myeloid differentiation factor 88; TIRAP, toll-interleukin 1 receptor domain containing adaptor protein; NFκB, nuclear factor-kappaB; IL-6, interlukin-6; IL-10, interlukin-10; bFGF, fibroblast growth factor; TAK-242, resatorvid; Ac-SDKP, N-acetyl-seryl-aspartyl-lysyl-proline; FcεRI, IgE high-affinity receptor; IgE, immunoglobulin E; MIP-1α, macrophage inflammatory protein-1 alpha; MCP-1, monocyte chemoattractant protein-1; MSCs, mesenchymal stromal cells;iNOS, inducible nitric oxide synthase; NO, nitric oxide; NOx, nitrogen oxide; TFEB, transcription factor EB; Tre, trehalose; T_{EM}, effector memory T cell; Treg, regulatory T cell; T_{RM}, resident memory T cell; TUDCA, tauroursodeoxycholic acid; INF-γ, interferon-gamma; Fgr, member of Srckinase family;α-SMA, alpha smooth muscle actin; CXCR4, C-X-C chemokine receptor type 4; AMD3100, plerixafor; SOD3, extracellular superoxide dismutase; Timp1, tissue inhibitor of metalloproteinase 1; Fsp1, fibroblast-specific protein 1; Mcp1, monocyte chemoattractant protein 1; RVSP, right ventricular systolic pressure; MARCO, macrophage receptor with collagenous structure; Npnt, nephronectin; α-TAT 1, alpha-tubulin N-acetyltransferase.

constructive effects for ECM and collagen deposition [15]. Moreover, the 4–1BB expression on AMs and MH-S cells is linked with RCS-mediated inflammation through cytokines and MMP secretion. Further activated epithelial CD4 + T cells induce ECM-mediated fibroblast activation and fibrosis in the lung tissue of rats exposed to silica [16]. Several studies verified the role of several new molecules and associated alterations in the experimental murine model of RCS-induced silicosis (Table 3). In detail, RCS particles in alveolar space trigger the expression of FcεRI, MIP-1α/CCL-3 and MIP-2/CXCL-2, IL-17A, Fgr tyrosine kinase, p16, CXCR4/CXCL12, and Npnt in AMs or epithelial cells. Which further induced the process of inflammation by secretion of IL-1β, IL-6, TNF-α, and TGF-β in the lung parenchyma of mice [56,68, 73]. The chronic inflammation promoted the accumulation of α-SMA and collagen fibers, eventually accelerating the non-reversible lung impairment known as silicosis.

Though numerous mechanisms elucidate the essentials of silicosis progression, lung pathology dominates the clinical picture of silicosis. Pathologically, silicosis comprises simple or nodular silicosis, complicated or accelerated silicosis with PMF, silicoproteinosis, and diffuse interstitial fibrosis (DIF). Simple silicosis can be defined as the presence

of inflamed hilar and peribronchial lymph nodes and silicotic nodules, predominantly in the upper lobe of the lung. In PMF, nodules become confluent, resulting in a large opacity of 1.5 cm or more in diameter with severe alveolitis and collagen deposition [9,17]. The minimal collagen deposition with the presence of fibrosis and alveolar space filling by lipoproteinaceous material are the characteristic features of silicoproteinosis [35].

6. Management and potential therapeutic targets

Despite being associated with significant morbidity and mortality, there is a paucity of therapeutic options for silicosis. Anti-inflammatory, anti-fibrotic drugs, lung lavage, and lung transplant are modalities described in the literature for the management of silicosis. In terms of steroid-based treatments, there is no evidence confirming the long-lasting benefit for patients with silicosis. Corticosteroids like prednisolone showed circumstantial improvement in total cell count and pulmonary function parameters in patients with chronic silicosis [35]. As a mainstay of treatment for silicosis, prednisolone and nintedanib inhibit plasminogen activator inhibitor-1 (PAI-1) (a marker associated with both inflammatory and pro-fibrotic pathways) expression [76]. Moreover, in a preclinical cohort, a 15 mg/kg diet dose of prednisone reduced RCS-induced autoimmunity in lupus-prone mice but did not extend survival time [77]. Although the efficacy of prednisolone is under debate due to lower therapeutic outcomes and annoying side effects, it has been the conventional strategy for the management of fibrotic lung diseases. Interestingly, flunisolide effectively inhibits the mediators responsible for chemokines (MIP-1α/CCL-3 and MIP-2/CXCL-2) and cytokines (TNF-α and TGF-β) secretion and contributes to the reduction of fibrosis in a CS-induced murine model of silicosis [69]. Table 4 summarizes recent treatment approaches for silicosis using *in vitro* and *in vivo* models. Naturally occurring terpenoids, oridonin [13], sapogenins, dioscin [57], and non-reducing disaccharide, trehalose [71], demonstrated protective effects and attenuated lung fibrosis in C57BL/6 mice and MH-S murine AM cell line models. Another investigation conducted in animal models showed that NAC [63] and fullerene [78] treatments successively reformed the RCS-induced fibrotic damages through improved E-cad and type 2 alveolar epithelial cells (AECII) count in lung parenchyma. Metformin (an anti-diabetic drug for type 2 diabetes) [60] and TUDCA (a taurine-conjugated form of ursodeoxycholic acid) [72] were also found to have potential benefits in animal models of pulmonary fibrosis, but no human studies exist to support their clinical use. The surface coating of quartz with two different commercial organosilanes; hydrophobic Dynasylan® PTMO and hydrophilic Dynasylan® SIVO 160, was found to reduce the quartz-specific toxicity in experimental *in vitro* and *in vivo* investigations [79]. Subsequently spraying with an organosilane materials including tetramethyl-silane (Prosil 28) (as opposed to or in combination with water), during industrial operations has been a possible mitigation strategy to protect workers directly exposed to RCS particles at workplaces [80]. Yet, the toxicity of organosilane coating of silica in human is unknown.

At present, *in vivo* and *in vitro* experiments have concentrated on identifying the potential target inflammatory and fibrotic pathways. Likewise, more efforts have been taken to understand the interaction

Table 4
Treatment strategies demonstrating targeted silicosis management in murine and cell line model.

Experimental PF Model(s)	Treatment(s)	Dose(s)	Target(s)	Study period(s)	Results	Ref.
Primary murine BLM-induced C57BL/6 J	Water-soluble fullerene ($C_{60}(OH)_{22}$)	10 mg/kg/ day i.p. up to 28 days	ROS, TGF-β1, TNF-α, AECII, α-SMA	0–21 days (preventive) 14–28 days (therapeutic)	Minimise ROS, TNF-α, TGF-β1, α-SMA, fibronectin, collagen, fibrosis and improved AECII count	[78]
Primary murine RCS-induced C57BL/6 & $Atg5^{flox/flox}Dppa3^{Cre/+}$ & MH-S cells (murine AMΦs)	Dioscin	80 mg/kg/day p.o. up to 56 days and 200 – 800 nM	AMΦs autophagy and mt-dependent apoptosis	0–7 days (inflammation stage) 50–56 days (fibrosis stage)	Induce BECN1, Atg5, Atg7, Ulk1, P62 genes, minimise mt-apoptosis, cytokines and fibrosis	[57]
Primary murine RCS-induce silicosis	Flunisolide	10 μg/mouse/ day i. n. from 21 to 27 day	MCP−1/CCL−2 chemokines, TNF-α and TGF-β	28 days	Inhibit granuloma and fibrosis, MIP−1α/CCL−3, MIP−2/CXCL−2, TNF-α, TGF-β, collagen deposition	[69]
Primary murine RCS-induced C57BL/6 & MH-S cells (murine AMΦs) PF	Oridonin	10 mg/kg s.c. and 1 μM	iNOS, NF-κB, Bcl−2, NLRP3	42 days	Suppressed iNOS by binding to Thr109 residue of iNOS target and attenuates PF progression	[13]
Primary murine RCS-induced C57BL/6 & MH-S cells (murine AMΦs) PF	Trehalose	2 gm/kg i.p. and 50 mmol/L	TFEB, apoptosis	7 & 56 days	TFEB overexpression, restoration of autophagy-lysosomal function and abate silicosis	[71]
Wild C57BL/6 J mice RCS-induce silicosis	NAC	1.73, 3.46 and 5.19 mg/20 gm/day p.o. for 24 hr to 5 months	ROS, antioxidants, oxidizing enzymes, E-cad	24 hr, 1, 2, 3, 4, 5 months	Release GSH-P_X, SOD, and T-AOC, down-regulate NOX_2, iNOS, SOD_2, and XO, induce E-cad & decrease vimentin and Cyt-C with silicosis	[63]
Wistar rats/ (THP−1) and (HBEC) RCS-induced cell lines	Metformin	100, 200, 400 mg/ kg/day for 28 days and 0.1–10 mM for 1–3 days	AMPK-mTOR Pathway & EMT process	28 days (in vivo) 72 hrs.	Reduce TGF-β,TNF-α,IL−1β, Vimentin, α-SMA. Increase E-cad, p-AMPK, MAP, LC3B & Beclin1. Reduce p-mTOR, p62 and inhibit PF *in vivo & in vitro*	[60]
Primary murine RCS-induced C57BL/6 PF	TUDCA	250 mg/kg/day i.p. upto 7 or 56 days	IFN-γ, IL−17A and Th cells	7 & 56 days	Decrease IFN-γ producing ($CD103^-$ T_{EM}) and IL−17A ($CD103^+$ T_{RM}) like T cells. Restrict T_{RM}-like Treg cells and fibrosis in lungs	[72]
Primary murine RCS-induced C57BL/6 and MH-S cells (murine AMΦs) PF	miR−205–5p agomir (overexpressed miR−205–5p)	Injected via tail vain in mice and transfected in cell line	E2F1/ SKP2/ Beclin1 axis.	7, 14, 28 and 56 days *in vivo* and 36 hr*in vitro*	Inhibit SKP2-mediated Beclin1 ubiquitination and promote autophagy with inhibition of PF in silicosis	[18]
Primary murine RCS-induced C57BL/6 and MRC−5 cells PF	miR−503 agomir	120 nmol/kg/ week for 4 weeks	TGF-β1-induced VEGFA, FGFR1 & MAPK/ERK signalling	28 days *in vivo* and 48 hour *in vitro*	Up-regulated miR−503 reduced TGF-β1 induced ERK1/2 phosphorylation and mitigated PF	[61]

BLM, bleomycin; i.p., intra-peritoneal; AECII, type 2 alveolar epithelial cells; p.o., per oral; i.n., intra-nasal; s.c., sub-cutaneous; T-AOC, total antioxidative; GSH-Px, glutathione peroxidase; XO, xanthine oxidase; MAP, microtubule-associated protein; LC3B, light chain 3B; MRC-5, human lung fibroblast cells

between AMs with inhaled RCS particles and silica-originated toxicity on pulmonary cells [12,62]. In that context, the various identified molecular targets and silicosis management approaches are depicted in Fig. 3. The multi-omics investigation in the silicosis mouse model discovered the N6-methyladenosine (m6A) methylation associated with "phagosome," "antigen processing and presentation," and "apoptosis." Hence, dysregulation of m6A methylation can be a viable strategy for silicosis treatment [66]. As stated somewhere, miR-503 [61] and miR-205–5p [18] are promising targets; for instance, improved expression certainly promotes macrophage autophagy and mitigates pulmonary fibrosis. Alongside, miR-542–5p also acts as a potential therapeutic target since it inhibits silica-induced lung fibrosis through the inhibition of Integrin α6 [56]. Crystalline silica-injured AMs expressed 4–1BB on their surface, and such signaling upheld cytokines, chemokines, and MMPs secretion *in vivo*. Sticking with this, the blockade of 4–1BB signaling may be targeted in the management of pulmonary fibrosis [16]. On the contrary, other two molecules, such as caveolin-1 (Cav-1) [64], which is the caveolae major functional protein, and antioxidant enzyme superoxide dismutase (SOD3) [75], both highly expressed in the lungs vasculature and possess anti-fibrotic properties and are potential markers for silicosis treatment. Other than elucidated management approaches, numerous additional molecular targets (Fig. 3) could potentially assist therapeutic efforts in animal and cell line models, but no data has been available on human studies.

Compensation is one of the crucial aspects of silicosis management, which deals with the financial backing and medical care of the victims. There is often variation in compensation arrangements according to different jurisdictions and government rules [35]. Several countries have evolved the disease diagnostic criteria for the eligibility determination of affected workers, which further facilitates the grant of suitable compensation schemes and benefits. Such diagnostic criteria include the autopsy specimen, chest x-ray interpretation according to an international convention, and computed tomography scanning designed and developed by the ILO [22]. Once silicosis is diagnosed according to ILO guidelines, a benefit has been provided to the disabled worker in the form of a change in job title, and in the event of death, the benefit (financial support) transfers to the dependents. In India, a compensation policy for silicosis has been established under the Mines Act, 1952, and the Employee Compensation Act, 2009. Moreover, in Rajasthan, India, the Pneumoconiosis Boards have been set up by making amendments to the Employees' Compensation (Occupational Diseases) Rules 1965. The board has been composed of radiologists, chest and general physicians, and Mobile Silicosis Surveillance Units (MSSU) were appointed for the detection of silicosis [55]. Based on these circumstances, it is necessary to adopt the systematic relief and rehabilitation programs of other developing countries for the management of the silicosis burden.

Silicosis is a highly prevalent and foremost cause of mortality in low- and middle-income countries, as well as in high-income countries. Therefore, additional planning and control are needed to identify and reverse silica hazards globally. There are three suggestive measures of silicosis prevention that include primary, secondary, and tertiary preventions with different criteria. The primary prevention includes the control of silica dust emission or transmission and exposure at the source and workers' levels. The surveillance of the working environment and workers' health is interrelated with secondary prevention. Whereas, tertiary preventive measures comprise work process modification, workers removed from dusty environments and their rehabilitation [35]. Regarding silicosis management and prevention, the handling of risk assessments by different committees from various countries discussed as follows. In 1974, a recommended exposure limit (REL) of 0.05 mg/m^3 for up to a 10-hours workday and 40-hours workweek for occupational exposure to RCS (including quartz, cristobalite, and tridymite) was fixed by NIOSH [23]. In the same year, silica sand was prohibited as an abrasive blasting material due to the controlling difficulties of RCS exposure and the silicosis hazards associated with sandblasters. Previously, in Great Britain in 1950 and in other European countries in 1966, the use of crystalline silica for blast cleaning operations was restricted [29]. A joint Global Program for the Elimination of Silicosis was established in 1995 by the ILO and the World Health Organization (WHO) committee. However, in the past decade, outbreaks of AS-associated silicosis have been reported from some small-scale companies and AS stone mines in both developing and developed countries.

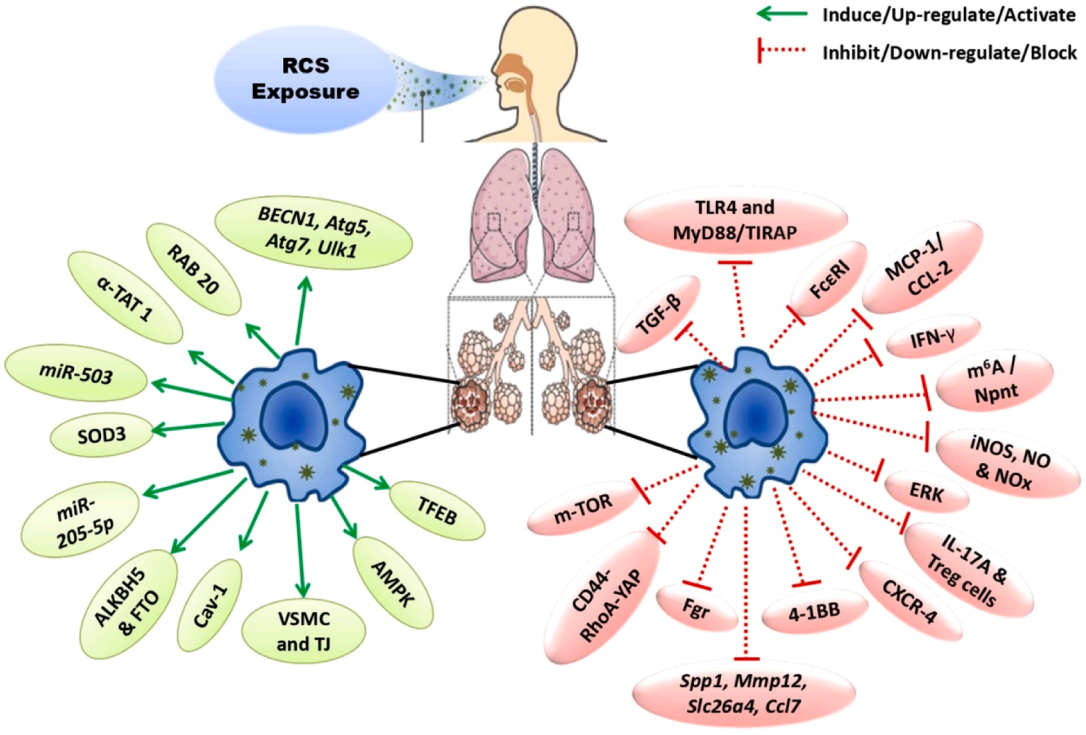

Fig. 3. Various molecular targets and allied methodologies for silicosis management.

Currently, the workplace RCS exposure standard in China is 0.2 mg/m^3 [9], while in Australia and USA it is reduced to 0.05 mg/m^3 as an 8-hours' time-weighted average per day for a 5-day working week [81]. Nevertheless, several epidemiological studies have instructed us to revise such occupational standards to protect against chronic silicosis. The Health Council of the Netherlands (DECOS) concluded that the non-stochastic genotoxic mode of action mediates the carcinogenicity of quartz, and hence the occupational exposure limit (OEL) for RCS was set at 0.075 mg/m^3. Moreover, in Canada, the workplace exposure limit for RCS was set at 0.1 mg/m^3 and further revised to 25 μg/m^3. Such lowering of the workplace exposure limit was influenced by animal and epidemiological data on carcinogenicity and inflammatory responses for inhalation exposure to RCS, which is equivalent to the Canada Labour Code to minimize silica hazards [82].

Silicosis is preventable through effective workplace exposure controls, including both wet cutting and local exhaust ventilation, the use of water feeds, furnished tools, and proper respiratory protection [24]. It is most important to make workers aware of the risk associated with silica dust inhalation. Occupational health surveillance, including chest X-rays and pulmonary function testing, should be conducted regularly to detect silicosis in a timely manner [9,23]. Moreover, it is necessary to recognize exposure histories and gain a better understanding of the cumulative lung burden essential to initiating disease [47]. Moreover, there is also a requirement for additional resources for workers' health education, the provision of respiratory protective equipment, and a growing awareness of occupational health issues [37]. Besides health education and risk awareness, the assessment of free silica content in the dust at the beginning of the job is requisite at the workplace with previous reports of silicosis. In addition, periodic RCS monitoring should be done at workplaces with high dust levels, and there should be provision for shortening of working hours or job rotation through administrative control [35]. However, early detection of silicosis is crucial to recognize the diseases at the pre-clinical stage and permit interventions that advance outcomes for workers.

7. Nanoapproches for treatment of fibrotic lung diseases

In recent years, the role of nanotechnology, especially in the field of biomedical sciences, including vaccine and gene delivery, anti-cancer treatments, and the delivery of active pharmaceutical ingredients (API) in fibrotic lung diseases, has gained significant consideration [83]. Nanoparticles (NPs) as a carrier system can provide several benefits, including protecting loaded APIs from inactivation, increased solubility and bioavailability, controlled or sustained release, and ultimately enhanced APIs' therapeutic efficiency while reducing undesirable side effects [84]. However, the thickened mucus gel layer covering the lung airways is one of the critical barriers that obstruct the long-lasting retention of inhaled therapeutics within the lungs. Further, the over-mucus secretion leading to a thickened mucus gel layer is commonly associated with obstructive lung diseases such as idiopathic pulmonary fibrosis (IPF), COPD, asthma, and silicosis. Together with mucus, several other biological barriers, including the pulmonary tract, epithelia, bacterial biofilm, and blood-brain barrier, have also been associated with such fibrotic lung pathologies. Nowadays, various engineered NPs have bypassed all these speculated barriers and proven to deliver APIs, drugs, or genes through different roots to damaged lung sites precisely. Interestingly, inhalation via the pulmonary route is the most straightforward method of drug as well as gene administration to the lung, owing to numerous advantages like fast absorption and onset of action, high permeability of the lungs, non-invasive nature, and better patient compliance [20,85].

Nanomedicine signifies a surprising opportunity for the enhancement of current therapies and also for the advancement of inventive treatment modalities for fibrotic lung diseases formerly considered untreatable. There are a variety of nanocarriers developed for drug delivery and improved treatment, like dendrimers, polymeric micelles, solid lipid nanocapsules, liposomes, magnetic nanoparticles, carbon nanotubes (CNT), and inhalable nanocomposites [86,87]. Moreover, several result-oriented studies have proven the potential of listed nanocarriers as a promising drug delivery modality in the management of pulmonary diseases.

A recent investigation demonstrating the intratracheal delivery of cerium oxide nanoparticles conjugated to microRNA-146a (CNP-miR146a) effectively increased the pulmonary levels of miR146a. Accumulation of miR146a results in the alteration of leukocyte recruitment, decreasing inflammation and oxidative stress, reducing collagen deposition, and preventing bleomycin-induced acute lung injury (ALI) in a murine model [88]. In the following year, a similar study showed comparable effects with the addition of lower pro-fibrotic gene expression for delayed treatment (3 days after inducing ALI) of CNP-miR146, which ultimately improved pulmonary biomechanics [89]. Chronic asthma is a highly prevalent and debilitating lung disease that can only be managed by symptomatic treatments. The newly developed thymulin-expressing plasmid loaded in engineered PEG-conjugated PBAE (PEG-PLGA) copolymer NPs was a thymulin-based gene therapy demonstrating good penetration through the airway mucus barrier in a murine allergic asthma model. The present nanotherapy effectively normalized the chronic inflammation, mechanical dysregulation, and pulmonary fibrosis that are associated clinical features of asthmatic lungs [85]. There are some novel NPs like curcumin-loaded PLGA nanoparticles coated with a muco-penetrating stabilizer (Pluronic) as a hydrogel-like microfluidic system [83], powdered poly(ethylene glycol) coated polystyrene nanoparticles (PS-PEG NPs) as a model muco-inert particles (MIP) [90], and aerosolized SCD-19-loaded nanoparticles (PLGA-MNP-SCD-19), a MIF's tautomerase enzymatic activity inhibitor [91], which showed suitable penetration through dense mucus barrier and aggressively removing bacterial infection residing in biofilms in cystic fibrosis.

The growing body of work advising nanotherapeutics is a new way applied to the lung, which will "open new doors" with the positive change in medical practice shortly. This statement of Sir William Olser is now proven as nanomedicine is extensively employed to diagnose, treat, and prevent pulmonary diseases and is also being applied to tackle the new emerging infectious diseases, including influenza A virus subtype H1N1, Middle East Respiratory Syndrome Coronavirus, and more recently, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [92]. The PF is a clinical outcome of a recent outbreak of SARS-CoV-2 infection-mediated acute respiratory distress syndrome (ARDS). PEGylated bilirubin nanoparticles (BRNPs) treatment effectively demonstrates their potent antioxidant and anti-inflammatory effects, long blood circulation half-life, and better accumulation at the irritated site of the bleomycin-induced murine PF model [93]. Moreover, the pathological appearances of PF and tumorigenic diseases are demonstrating the active contribution of cellular senescence, which is abundant in both humans and mice. Such senescence-associated disorder has been tackled with the gal-encapsulated cytotoxic drugs preferentially released within senescent cells. It reduces collagen deposition by restoring pulmonary function in PF and improves tumour xenograft regression during chemotherapy by minimizing the toxic side effects of cytotoxic drugs [94]. In continuation of present nanotheraputic approaches, highly expressed Zinc finger E-box binding homeobox 1 and 2 (ZEB1/2) genes in the early stages of PF silencing through small interfering ZEB1/2 (siZEB1/2) RNA delivered via a nanoscale Zr(IV)-based porphyrin metal-organic (ZPM) framework showed increased E-cadherin and decreased α-SMA levels, leading to alleviate early pulmonary fibrosis [95]. Another gene-silencing approach resulted in the efficient silencing of STAT3 expression and inhibiting chemokine receptor CXCR4 in pulmonary fibrosis, followed by the administration of perfluorooctylbromide (PFOB)-derived polycation/siRNA/PFOB nanoemulsions [96]. Similar gene-silencing practices to target CF, LC, and COPD were achieved with the development of siRNA-lipid nanoparticles (LNP-siRNA) dry powder pulmonary delivery systems using the

successful spray drying procedure. The system successfully penetrated the lung mucus layer, achieved up to 50 % gene silencing, and maintained strong integrity on mRNA and protein levels both *in vitro* and *ex vivo* [97].

Notwithstanding that several fibrotic as well as tumorigenic lung pathologies have been improved through numerous nanotherapeutic arsenals, no study has undertaken RCS-induced lung fibrosis silicosis management via a nanotechnological approach. Though synthetic drugs like prednisolone, nintedanib, and corticosteroids are effective in treating chronic silicosis, no evidence of long-term benefits to silicotic patients is attributed to these treatments [98]. Moreover, the extensive use of such synthetic medications usually develops adverse side effects [99]. As phytoconstituents have immense anti-oxidative potential, anti-fibrotic potential and negligible toxicity, it is worthy to employ herbal drug therapy for fibrotic lung injuries. Several phytochemicals like anthraquinone and steroidal sapogenins have proven their effective role in a silicosis mouse model, but due to their low solubility, poor bioavailability, and fast biotransformation in physiological conditions, their clinical application is severely hampered [100–102]. Concerning the positive effects of phytoconstituents against silicosis and considering their low bioavailability, we fabricated dioscin (steroidal sapogenins) and emodin (anthraquinone)-loaded PLGA (PLGA-DG-EDn) nanoparticles with appropriate surface characterization and validated their improved pharmacokinetics in rats [103]. Furthermore, these combined NPs have been tested against the RCS-induced lung fibrosis rat model, aiming to ameliorate progressive fibrotic damage.

8. Conclusion

Silicosis is a devastating, non-curable, and occasionally fatal disease, yet control of this disorder lies totally in its prevention. It constantly poses a foremost occupational health hazard amongst workers involved predominantly in building construction, mining, and stone fabrication works. Moreover, silicosis is a significant reason for respiratory morbidity and pulmonic function deficiency. Silico-tuberculosis, lung cancer, and COPD are common co-morbidities complicating the condition of silicosis. The overall data collection of studies summarized in this systematic review confirms the role of RCS doses and duration of exposure associated with different stages of silicosis. The review further extends the focus on the global prevalence of silicosis (and other silica-induced lung diseases) and the number of confirmed deaths. To tackle such a huge burden necessitates the advanced exploration of methods for diagnosis at the early stage of the disease and novel therapeutic strategies. Knowing the appropriate pathophysiological mechanism of silicosis progression and associated molecular targets should be a prime area of investigation, which helps to develop a suitable treatment modality at earliest. However, nanomedicine signifies a potential opportunity and a future for the advancement of inventive treatment modalities for fibrotic lung diseases. It can be applied in silicosis management by encapsulating the specific active drug molecules in a variety of suitable nanocarriers and delivering them to the targeted site of action. Besides silicosis treatment, the reduction of RCS exposure at the workplace, systematic screenings for early detection of disease, and providing truthful compensation to victims are crucial steps for reducing the global burden of silicosis. Moreover, health records and occupational hygiene should also be accurately retained to facilitate the calculation of disease proportions and latency periods according to different exposure consequences.

CRediT authorship contribution statement

Dhale Shrikrishna A: Writing – review & editing, Project administration, Conceptualization. **Malegaonkar Srikant:** Writing – review & editing, Conceptualization. **Dhok Archana:** Writing – review & editing, Supervision. **Suke Sanvidhan G:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Sherekar Prasad:** Writing – original draft, Methodology, Funding acquisition, Conceptualization.

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.

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Data availability

Data will be made available on request.

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