Addissouky *et al.*
Bulletin of the National Research Centre (2024) 48:16
https://doi.org/10.1186/s42269-024-01174-6

Bulletin of the National Research Centre

REVIEW

Open Access

Oxidative stress and inflammation: elucidating mechanisms of smoking-attributable pathology for therapeutic targeting

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Abstract

Background Tobacco smoking remains a major preventable cause of disease and death worldwide. Combustible cigarettes release thousands of chemicals that can initiate inflammatory pathways leading to smoking-related illness. This review aims to synthesize current scientific knowledge on mechanisms of smoking-induced disease, epidemiological trends, and clinical strategies from recent literature.

Main body of the abstract At the cellular level, cigarette smoke triggers oxidative stress through reactive oxygen species (ROS), causing DNA damage. This provokes inflammatory signaling cascades mediated by damage-associated molecular patterns (DAMPs), receptors like RAGE and TLRs, and downstream cytokines. Smoking also disrupts apoptosis and autophagy. In the lungs, oxidative stress and inflammation from smoking play central roles in COPD pathogenesis. Smoking-induced oxidative DNA damage, chronic inflammation, and impaired immunity combine to promote lung carcinogenesis. For cardiovascular disease, smoking triggers endothelial dysfunction, platelet activation, and atherogenesis through oxidized LDL and effects on nitric oxide and adhesion molecules.

Short conclusion Given the unequivocal evidence of health risks, smoking cessation is critical to reducing preventable death and disability. Both counseling and pharmacotherapy have proven efficacy for quitting, but efficacy remains limited long-term. Emerging nicotine products like e-cigarettes have unknown impacts on cessation and population health. Comprehensive efforts encompassing prevention, screening, treatment innovation, harm reduction, and policy reform focused on curbing smoking-attributable morbidity and mortality are warranted.

Keywords Oxidative stress, Smoking cessation, Health disparities, E-cigarettes, Nicotine addiction

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Background

Tobacco smoking remains a major preventable cause of disease and death worldwide, with over 8 million deaths per year attributed to smoking (Kim et al. 2023). According to the World Health Organization (WHO), over 3.5 million people die annually due to cigarette smoking, and this number is projected to increase to 10 million per year by 2030 (Mustafa et al. 2023). Combustible cigarettes release a complex mixture of over 7000 chemical constituents upon inhalation, including carcinogens, oxidants, and toxins that can initiate inflammatory pathways leading to smoking-related illness (Putrik et al. 2022). Chronic obstructive pulmonary disease (COPD), lung cancers, atherosclerosis, stroke, and reproductive effects represent major causes of morbidity and mortality from smoking (Wolfe et al. 2023). At the cellular level, cigarette smoke triggers oxidative stress through reactive oxygen species (ROS), causing damage to DNA, lipids, and proteins (Liu et al. 2021). This provokes inflammatory signaling cascades mediated by damage-associated molecular patterns (DAMPs), receptors like RAGE and TLRs, and downstream cytokines and kinases (Pérez Ríos et al. 2023). Smoking also disrupts apoptosis and autophagy, contributing to premature cellular senescence (Kelsh et al. 2023a). In the lungs, oxidative stress and inflammation from smoking play central roles in COPD pathogenesis (Sun et al. 2023). Smoking-induced oxidative DNA damage, chronic inflammation, and impaired immunity combine to promote lung carcinogenesis (Stefaniak et al. 2022). For cardiovascular disease, smoking triggers endothelial dysfunction, platelet activation, and atherogenesis through oxidized LDL and effects on nitric oxide and adhesion molecules (Hameed and Malik 2024). While conventional cigarette smoking has declined, alternative nicotine delivery systems like e-cigarettes have rapidly gained popularity, creating questions around comparative health impacts vs traditional smoking (Arshad et al. 2023). Continued research across clinical, epidemiological, behavioral, and basic science domains remains vital to further curb smoking-induced disease through prevention, screening, treatment innovation, and evidence-based regulation (Luu et al. 2023). This review aims to synthesize current scientific knowledge on mechanisms of smoking-induced disease, epidemiological trends, and clinical strategies from recent literature. It provides an updated perspective encompassing conventional smoking, emerging nicotine products, disparities, screening tools, and innovations in treatment and policy. This analysis can inform stakeholders across public health, research, clinical practice, and regulation to further evidence-based efforts tackling smoking-attributable morbidity and mortality worldwide. It offers a comprehensive overview of an evolving landscape to support translation of findings into pragmatic initiatives improving prevention, equity, diagnostics, and smoking cessation locally and globally.

Main text

Disparities in smoking

While the health risks attributable to cigarette smoking are extensive and well-established, certain populations carry a disproportionate tobacco-related disease burden. Smoking prevalence differs substantially across socioeconomic, racial/ethnic, geographic, and vulnerable subpopulations. Understanding factors that influence tobacco use patterns and addiction vulnerability can inform public health initiatives aimed at reducing disparities and promoting health equity (Choi et al. 2022). Data from over 140 countries indicate individuals with low SES are consistently more likely to smoke. In the USA, smoking rates are the highest among adults living below the poverty line. The reasons for socioeconomic disparities are complex and multifactorial. Those of lower SES exhibit higher rates of psychosocial stress, less social support, targeted marketing by the tobacco industry, and reduced access to cessation resources—all factors associated with increased smoking. The financial stress of cigarette purchases can also represent a larger barrier to quitting (Wetzel et al. 2023).

Racial and ethnic differences in smoking prevalence also reflect disparities stemming from broad social determinants of health. In the USA, smoking rates are typically highest among American Indian/Alaskan Native populations, followed by whites. Rates tend to be lower among Hispanic/Latino and Asian Americans. However, patterns vary considerably across intersectional identities. Gender, cultural values, targeted marketing, and stress related to discrimination all likely contribute to tobacco use disparities between racial/ethnic groups. Geographic disparities in smoking prevalence also exist between countries as well as subnationally within countries (Adinkrah et al. 2023). The Eastern Mediterranean, Southeast Asian, and Western Pacific regions have some of the largest male smoking prevalence globally. Rates also tend to be higher in rural compared to urban areas. In the USA, states like West Virginia, Kentucky, and Louisiana have adult smoking rates above 25%, while states like California, Utah, and Connecticut are below 15%. State policies, norms, education funding, and tobacco industry presence all may shape these geographical differences (Dai et al. 2021). Certain vulnerable populations also exhibit dramatically elevated smoking rates, including individuals experiencing homelessness, those with mental illness or substance abuse disorders, and members of the LGBTQ + community. Chronic stress, targeted

industry marketing, peer influences, and frequent exclusion from prevention messages all likely contribute to increased tobacco use susceptibility. Incarcerated populations similarly have skyrocketing smoking rates (up to 80–90% in some facilities) attributable to stress, secondhand smoke exposure, and unrestricted access to tobacco products in many correctional settings (Tam et al. 2023).

Statistical analysis of recent research on e-cigarettes

A cross-sectional study of over 75,000 youth across 75 countries found the prevalence of current e-cigarette use rose significantly from 3.6 to 4.6% between 2014–2016 and 2017–2019 (Sreeramareddy et al. 2022). Dual use of e-cigarettes and conventional cigarettes also increased from 1.6 to 2.4% over this period. These trends raise public health concerns about e-cigarette adoption and dual use among adolescents (Alaamri and Naser 2023). However, a U.S.-based study by Osibogun et al. (2020) found youth e-cigarette initiation was associated with reduced odds of progressing to established cigarette smoking relative to non-use (adjusted odds ratio 0.74, 95% CI 0.59–0.93) (Osibogun et al. 2020). While cautioning that youth should not be encouraged to vape, the authors suggest e-cigarettes may divert some adolescents from smoking escalation. But another U.S. high school survey identified concurrent e-cigarette and cigarette use as the primary driver of increased youth nicotine addiction prevalence from 2017 to 2019 (Leung et al. 2023). This complex interrelationship between vaping and smoking among adolescents requires ongoing surveillance. For adults, a recent systematic review of over 15 randomized controlled trials encompassing 12,000 participants found e-cigarette users had significantly higher smoking abstinence rates relative to recipients of nicotine replacement therapy or placebo controls at 6–12 months follow-up (Marques et al. 2021).

However, most studies were limited to 1 year, with only 3 trials following participants beyond 12 months. Population-based surveys also indicate many adult e-cigarette users persist with dual use rather than completely switching from cigarettes. For example, analysis of U.S. national survey data found 47.1% of e-cigarette users continued smoking cigarettes in 2016, with dual use highest among young adults aged 18–24 (Temourian et al. 2022). While e-cigarettes show promise for cessation, uncertainty remains around long-term abstinence and population patterns of dual use (Kelsh et al. 2023b). In summary, statistical evidence indicates e-cigarette adoption is rising among youth and adults, but the long-term individual and public health impacts remain ambiguous due to limited longitudinal data and complex dual use relationships with conventional smoking.

Mechanisms of smoking-induced disease

Combustible cigarettes release thousands of chemicals, including carcinogens and oxidants that can initiate inflammatory pathways and lead to respiratory, cardiovascular, and other diseases. COPD, lung cancers, atherosclerosis, and stroke exemplify smoking-related illnesses. At the cellular level, cigarette smoke triggers oxidative stress through reactive ROS, causing DNA damage, lipid peroxidation, and activation of DAMPs (Travis et al. 2023). This provokes inflammatory signaling via receptors like RAGE and TLRs, inducing downstream cytokines through MAPK and NF-κB pathways. Smoking also impairs apoptosis and autophagic mechanisms, including mitophagy, contributing to cellular senescence. In the lungs, oxidative stress and inflammation from smoking are central in COPD pathogenesis (Zhang et al. 2023). MMPs, RAGE, NOX, and Nrf2 all play roles in emphysema and COPD progression. New treatments like metformin and astaxanthin targeting oxidative stress show promise. For cancers, carcinogens in smoke can directly mutate oncogenes like p53 while also fueling tumor growth through oxidative stress (Cha et al. 2023a). Targeted therapies, immunotherapies, and emerging tools like nanocarriers and gene editing may improve cancer outcomes. Smoking likely worsens outcomes in ARDS and COPD exacerbations by heightening inflammation. For cardiovascular disease, smoking impairs endothelial function, reduces nitric oxide, and promotes atherosclerosis through oxidized LDL and effects on adhesion molecules (Kuśnierczyk 2023). As illustrated in Fig. 1, cigarette smoke (CS) exposure activates multiple pathological pathways in cells, leading to chronic inflammation, fibrosis, premature cellular senescence, and dysregulated autophagy. Specifically, cigarette smoke initiates inflammatory signaling cascades that recruit immune cells to the lungs and stimulate the release of pro-inflammatory cytokines. Prolonged cigarette smoke exposure also switches on pro-fibrotic pathways that cause excessive extracellular matrix deposition and scar tissue formation (fibrosis) in the lungs. Additionally, cigarette smoke exposure can expedite cellular senescence, a state of irreversible growth arrest that contributes to aging-related disease (Cha et al. 2023b).

Cigarette smoke exposure activates inflammatory signaling pathways and increases oxidative stress in alveolar epithelial cells of the lungs. As shown in Fig. 2, cigarette smoke can stimulate kinases like ERK and JNK, as well as transcription factors like NF-κB. This leads to enhanced expression of proinflammatory cytokines like interleukin-1β, interleukin-6, interleukin-8, and tumor

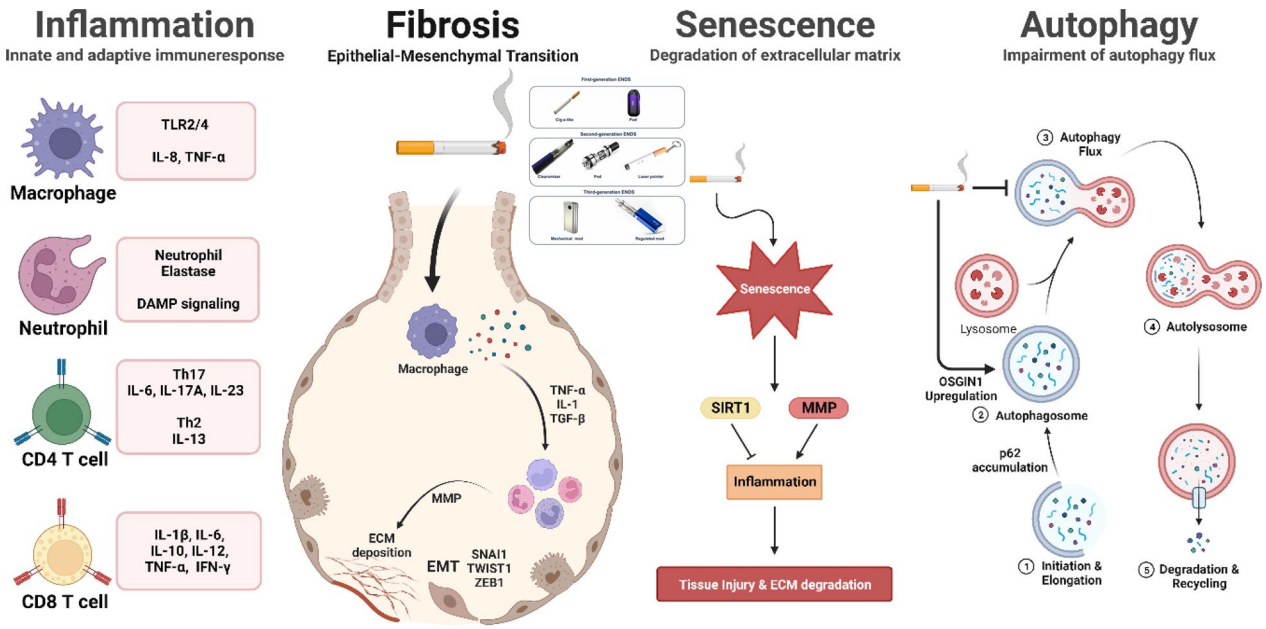

Fig. 1 Cigarette smoke-induced pathological pathways driving cellular dysfunction (Cha et al. 2023b)

necrosis factor alpha. Elevated inflammation can in turn further increase oxidative stress, creating a positive feedback loop that sustains damaging levels of both inflammation and oxidative stress in lung tissue. This helps explain the decreases in lung function parameters like forced expiratory volume in one second (FEV1) seen in smokers (Dailah 2022). Several therapeutic strategies targeting mechanisms disrupted by (CS) exposure have shown promise for treating major CS-induced lung diseases like COPD, pulmonary fibrosis, lung cancer, and acute respiratory distress syndrome (ARDS) (Fairley et al. 2023). For COPD, metformin inhibits CS-triggered apoptosis by regulating AMP kinase, while astaxanthin suppresses CS-induced oxidative stress and inflammation by modulating Nrf2 and NF-κB pathways. Stem cell-derived extracellular vesicles and nanoparticles alleviate CS-induced damage and inflammation in COPD models (Aruldas et al. 2023). For pulmonary fibrosis, N-acetylcysteine replenishes antioxidant glutathione and reduces CS-induced inflammation, and PDE4B inhibitors prevent inflammation and fibrosis by blocking cAMP degradation (Cha et al. 2023a). In lung cancer, PD-1/PD-L1 checkpoint inhibitors boost anti-tumor immunity, trastuzumab targets HER2 mutations, rituximab depletes CD20 + B cells, and CRISPR-Cas9 corrects disease-causing mutations. CAR-T cell therapy and mesenchymal stem cell exosomes also show efficacy (Mokra et al. 2023). Finally, vitamin C inhibits CS-induced neutrophil extracellular traps in ARDS, while ICAM nanoparticles reduce inflammatory cytokines. In summary, therapies targeting CS-disrupted pathways like oxidative stress, inflammation, apoptosis, and immunity may provide clinical benefit across CS-related lung diseases (Wang et al. 2023).

One major mechanistic pathway involves oxidative stress induced by ROS and reactive nitrogen species (RNS) present in cigarette smoke. ROS can directly damage DNA, proteins, and lipids within cells. Chronic oxidative stress can overwhelm endogenous antioxidant systems, leading to necrotic cell death, tissue dysfunction, and DNA mutations that can promote carcinogenesis. Cigarette smoke contains high concentrations of ROS-generating substances like superoxide radicals, nitric oxide, and peroxynitrite. Inhalation of cigarette smoke has been shown to quickly deplete circulating antioxidant reserves in smokers as well (Seo et al. 2023). Carcinogens in cigarette smoke also drive the formation of reactive DNA aldehydes like formaldehyde that can interfere with DNA repair pathways. The cumulative DNA damage caused by repeated exposure to cigarette smoke carcinogens promotes cell cycle dysregulation and malignant transformations. There are also important epigenetic effects of cigarette smoke exposure mediated by aberrant microRNA expression and DNA methylation patterns in target tissues. Dysregulated microRNAs in smokers can interfere with normal cell cycle control and apoptosis. Altered DNA methylation can silence tumor suppressor genes and activate oncogenic pathways. These heritable epigenetic changes represent another pathway promoting malignant degeneration (Emma et al. 2022). In addition to direct genotoxicity, cigarette smoke

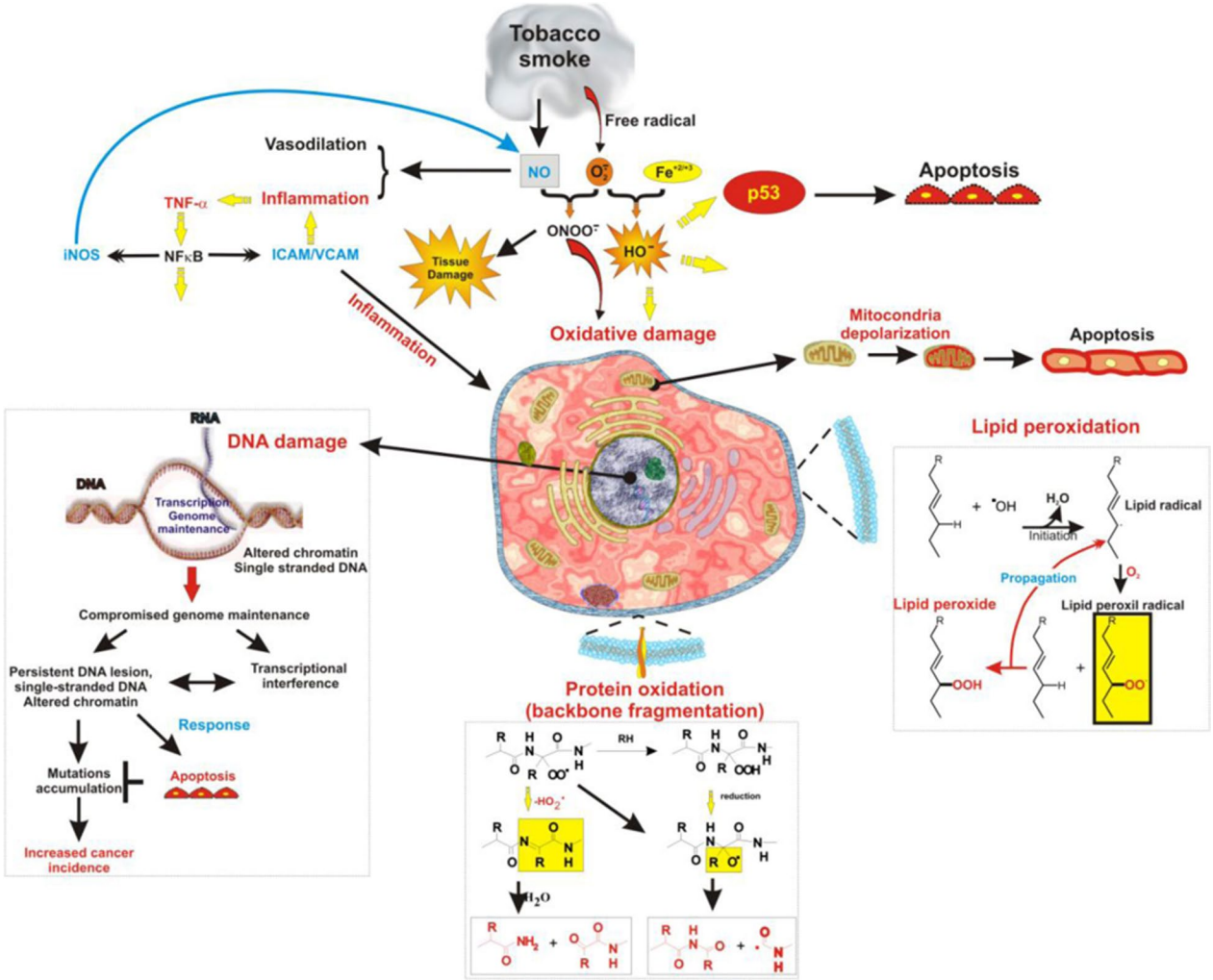

Fig. 2 Cigarette smoke-induced oxidative stress and inflammation in cells and tissues (Dailah 2022)

activates inflammatory pathways that contribute to organ damage and tumor promotion microenvironments. For example, smoking can induce activation of NF-kB, a key pro-inflammatory transcription factor. This perpetuates the release of cytokines like IL-6 and TNF-a that foster continuing inflammation, impair apoptosis, and enable cancer cell proliferation and survival (Wang et al. 2022). The specific manifestation of smoking-induced injury and molecular aberrations varies across affected organ systems. In the lungs, direct DNA damage and inflammation lead to disruptions in bronchial epithelial barrier function. Repeated tissue injury creates proliferative niches and release of growth factors that favor development of lung cancer. In the heart and vasculature, ROS inflict oxidative damage on LDL particles, while inflammation accelerates atherosclerotic plaque formation. In reproductive tissues, carcinogens in cigarette smoke penetrate cervical mucus and are absorbed systemically, contributing to cancers of the lung, cervix, bladder and pancreas (Kotlyarov 2023).

Respiratory effects

COPD, lung cancer, respiratory infections, and impaired lung development in infants of smoking mothers exemplify the diverse negative impacts of cigarette smoke exposure on respiratory health as shown in Table 1. As emerging tobacco products like e-cigarettes increase in popularity, a key public health question involves how the respiratory effects of these alternatives compare to traditional cigarette smoking. Extensive epidemiologic evidence clearly links cigarette smoking to increased risks of COPD, including emphysema and chronic bronchitis (Leroue et al. 2023). Cigarette smoke induces chronic inflammation and oxidative stress that damages alveoli, impairs mucociliary clearance, and disrupts normal lung architecture over time. COPD pathogenesis is related

Table 1 Respiratory effects of cigarette smoking

Disease	Key mechanisms	Epidemiological evidence
COPD	Oxidative stress, inflammation, protease imbalance	Clear dose-dependent association
Lung Cancer	Carcinogens, chronic inflammation, DNA damage	90% of cases attributable to smoking
Impaired Lung Development	In utero smoke exposure, oxidative injury	Lower birth weight, reduced lung function

to direct toxicity of inhaled irritants, pro-inflammatory effects of ROS, protease/anti-protease imbalance, and impaired immune function in the lungs of smokers. Dose-dependent reductions in forced expiratory volume (FEV1) and airflow limitation make COPD a leading cause of morbidity and mortality in smokers. Cessation of smoking is the most effective way to prevent COPD progression (Czarnecka-Chrebelska et al. 2023). Lung cancer is also causally associated with cigarette smoking, accounting for around 90% of lung cancer cases (Addissouky and Khalil 2020).

Carcinogens in cigarette smoke can directly mutate tumor suppressor genes and oncogenes, while cigarette smoke-induced inflammation creates a tumor-promoting microenvironment in the lungs. The relationship is dose-dependent, with lung cancer risk and mortality higher with greater smoking intensity and pack-years (Adler et al. 2023; Voskarides and Giannopoulou 2023; Feng et al. 2006). Smoking cessation decreases risk, but former smokers remain at elevated lifetime risk compared to never smokers. In comparison, emerging data on the respiratory effects of e-cigarette use has yielded a more complex picture without long-term prospective evidence. Some studies suggest switching from cigarettes to e-cigarettes can improve lung function and reduce asthma exacerbations in smokers with pre-existing respiratory disease (Qureshi et al. 2023; Roxlau et al. 2023). This is likely due to the elimination of direct smoke inhalation. However, concerns remain about long-term risks, especially for youth. E-cigarette vapor contains particulates, solvents, and flavorings that may negatively impact the delicate respiratory epithelium, especially during development. Use of e-cigarettes has been associated with increased cough, asthma exacerbations, and fibrosis markers in some studies (Addissouky et al. 2023a; Song et al. 2023; White et al. 2023).

E-cigarette vapor also induces immune and inflammatory responses in lung epithelial cells distinct from cigarette smoke. More research is required to definitively characterize the long-term respiratory impact of e-cigarettes relative to traditional smoking. Additionally, while e-cigarettes may confer harm reduction for individual smokers, population-level lung health impacts depend on usage patterns. If most e-cigarette use comes from youth and former smokers who initiate nicotine use with e-cigarettes, any intrinsic harm from e-cigarette vapor could outweigh benefits from cigarette smokers switching products. Monitoring respiratory outcomes as the e-cigarette market evolves will be important, especially since long-term cancer risk associated with these products remains essentially unknown (Mir et al. 2022).

Cardiovascular effects

Beyond pulmonary illness, smoking represents a foremost coronary malady and stroke element alongside other vascular conditions (Okorare et al. 2023). Smoking contributes plaque progression, thrombogenicity, and accelerated aging mechanisms involving systemic inflammation, endothelial dysfunction, hypercoagulability, and oxidative stress as shown in Table 2. Chemicals implicated in atherogenesis comprise oxidizing real factors triggering endothelial injury, nicotine enhancing adrenergic activity, and carbon monoxide diminishing oxygen tissue accessibility. Even minimal smoking relates increased mortality (Addissouky et al. 2024a; Morrison et al. 2023; Mallah et al. 2023). Quitting rapidly cuts risk. Smoking links heightened bleeding and ischemic stroke probabilities attributable to platelet triggering and coagulation alterations propelling embolism. Cessation significantly lowers this jeopardy. Similar links exist between smoking and peripheral, aortic, and atherosclerotic advancement. Switching to e-cigarettes potentially

Table 2 Cardiovascular effects of cigarette smoking

Effect	Mechanisms	Evidence
Atherosclerosis	Endothelial dysfunction, lipid oxidation, inflammation	Dose-dependent ↑ MI risk
Hypercoagulability	Platelet activation, ↓ antithrombotics	↑ Risk of ischemic stroke, DVT
Hypertension	Sympathetic activation, vascular stiffness	↑ Systolic and diastolic BP

mitigates cardiovascular impacts hypothetically through toxic smoke elimination, though e-cigarette impacts stay restricted with certain investigations showing biomarker bettering yet others finding no oxidative, endothelial, or structural modifications (Salehi et al. 2021).

Cancer risks

In addition to cardiovascular and respiratory diseases, cigarette smoking represents one of the most significant preventable risk factors for cancer worldwide as depicted in Table 3. Tobacco smoke constituents promote inflammatory glomerular microvascular damage via complement activation, macrophage accumulation, and dysregulated matrix remodeling (Addissouky et al. 2023b; Al-Fayez and El-Metwally 2023). Tobacco smoke contains a mixture of carcinogens that can drive mutagenesis through direct DNA damage as well as indirect mechanisms including oxidative stress, chronic inflammation, and immune modulation. Chronic tobacco smoke exposure exacerbates hepatic inflammatory mediators and reactive oxygen species, precipitating fibro proliferative remodeling through hepatic stellate cell activation and matrix metalloproteinase dysregulation (Addissouky 2019; Addissouky et al. 2019, 2021; Marti-Aguado et al. 2022). Epidemiological studies have identified dose-dependent causal links between cigarette smoking and increased risk of lung cancer as well as at least 14 other cancer types. Assessing the potential carcinogenic effects of emerging nicotine products like e-cigarettes represents an important area of ongoing research. Lung cancer is the cancer most conclusively linked to cigarette smoking, with around 80–90% of lung cancer deaths attributable to smoking. Mutagens in cigarette smoke can directly damage oncogenes and tumor suppressor genes like p53, driving malignant transformation of lung epithelial cells (Darmon et al. 2022). Smoking is linked in a dose-dependent manner with all major histological types of lung cancer. Smoking cessation reduces risk, but former smokers remain at elevated lifetime risk compared to never smokers. Beyond lung cancers, epidemiological associations and biological plausibility link cigarette smoking to increased risk of cancers all along the aerodigestive tract including oral, pharyngeal, laryngeal, Breast, esophageal, stomach, pancreatic, bladder, cervical, kidney, and colorectal cancers. Smoking has been linked to an increased risk of developing colorectal cancer. Several studies have shown a correlation between tobacco consumption and colorectal cancer occurrence. The carcinogens in tobacco smoke can damage the DNA of cells in the colon and rectum (Addissouky et al. 2023c). Smoke exposure likely facilitates carcinogenesis through direct contact with exposed tissues as well as systemic absorption of carcinogens. Tobacco smoking also increases risk of acute myeloid leukemia, likely through carcinogen-induced mutation of genes important for hematopoiesis (Yang et al. 2021).

Table 3 Cancer risks associated with cigarette smoking

Cancer site	Evidence of increased risk	Potential mechanisms
Lung	Very strong	Local carcinogens, inflammation
Oral Cavity	Strong	Local irritation, carcinogens
Bladder	Strong	Excreted carcinogens
Kidney	Moderate	Excreted carcinogens
Stomach	Moderate	Systemic effects
Cervix	Moderate	Absorbed carcinogens

Other health effects

Smoking compromises wound healing, increases susceptibility to infections, and disrupts reproductive health across the lifespan. Secondhand and thirdhand exposure to tobacco smoke also poses significant health risks, especially for vulnerable child populations. With regard to wound healing, numerous studies have outlined mechanisms by which cigarette smoke delays and impairs healing steps including inflammation, new tissue formation, and remodeling (Hergesell et al. 2023). Vasoconstrictive effects of smoking reduce local blood flow to wounds while nicotine limits oxygen delivery and nutrient supply for repair processes. Smoking also increases risk of wound infections, likely linked to systemic immune suppression and local microbial contamination from nicotine and tar deposition (Guo and DiPietro 2010). Patients undergoing surgical procedures heal slower and have higher postoperative complication rates if they smoke. Dental implant failure rates are also increased with smoking. Smoking cessation for as little as 4 weeks prior to surgery can significantly improve outcomes. Beyond wound healing, smoking increases severity of both bacterial and viral infections, especially in the lungs and respiratory tract. Alterations in mucociliary clearance, secretory immunoglobulin levels, and salivary antimicrobial proteins in smokers impair first-line defenses against inhaled pathogens. Smoking also suppresses systemic cell-mediated immunity by effects on lymphocyte counts and activity. The immunosuppressive effects of smoking are thought to account for the increased incidence, disease severity, and mortality attributed to conditions like pneumonia, tuberculosis, meningitis, and hepatitis in smokers (Addissouky et al. 2024b; Okada and Matsuo 2023; Mahmoudzadeh et al. 2023).

Reproductive health across the lifespan is similarly impacted by tobacco exposure. In adolescents, smoking is associated with earlier menarche in girls and reduced sperm counts and motility in young boys. In adults,

smoking reduces fertility in both men and women. Mechanisms include ovarian dysfunction, altered hormone levels, direct gonadotoxic effects, and genetic damage to sperm from cigarette mutagens (He and Wan 2023; Osadchuk et al. 2023). During pregnancy, smoking is linked to increased risks of miscarriage, pregnancy complications, and negative fetal health outcomes like low birth weight. Infants exposed to secondhand smoke have higher rates of respiratory infections, asthma exacerbations, and sudden infant death syndrome. Secondhand and thirdhand tobacco smoke pose appreciable health risks, especially to children. Secondhand smoke refers to the inhalation of smoke from others actively smoking, while thirdhand smoke refers to contact with surfaces where smoke has adsorbed and deposited residual chemicals (Kaur et al. 2023; Tatton and Lloyd 2023). Children are most vulnerable given their higher respiratory rates and developing immune systems. Parental smoking increases risk of ear infections, asthma, respiratory symptoms, and impaired lung function. The developing brains of children are also sensitive to chemicals from tobacco smoke absorbed during critical windows of growth. Public smoking bans help reduce population-level health impacts of secondhand smoke (Buisman et al. 2021).

Screening and diagnostics

Research has helped delineate optimal protocols for lung cancer screening in high risk smokers. Guidelines also exist for diagnostic spirometry and assessment of COPD severity to guide treatment. Implementation of evidence-based guidelines into clinical practice can enhance detection of smoking-related diseases at earlier, more treatable stages. Lung cancer often presents at an advanced stage after metastasis has already occurred, contributing to the high mortality rate. However, low-dose CT screening in smokers has been shown to detect smaller, early stage lesions leading to reduced lung cancer mortality (Guo et al. 2023). Following accumulation of evidence from controlled trials like the National Lung Screening Trial, major health organizations now recommend annual low-dose CT scanning for lung cancer screening in high risk groups including adults aged 50–80 with ≥ 20 pack-year smoking history who currently smoke or quit within the past 15 years. Radiologic criteria for positive scans and follow-up diagnostic workups have been established. While false positives remain an issue with low-dose CT screening, this approach provides a means for early detection of lung cancer in appropriate candidates (Hunger et al. 2021). Beyond cancer, objective pulmonary function testing for COPD diagnosis and monitoring has also been optimized. Spirometry measuring forced expiratory volume in 1 s (FEV1) and the FEV1/forced vital capacity (FVC) ratio helps quantify airflow limitation indicative of obstructive lung diseases. Reduced FEV1/FVC confirms obstruction, while lower FEV1 correlates with COPD severity. Post-bronchodilator spirometry improves diagnostic specificity (Shlomi et al. 2023). Underuse of spirometry leads to missed COPD cases, while only a fraction of eligible patients receive lung cancer screening. Lack of provider awareness, time constraints, cost barriers and limited access contribute to low adoption of recommended protocols. Efforts to improve guideline-concordant screening and diagnostics for smoking-related illness could enable earlier detection, inform smoking cessation efforts with objective lung data, and reduce morbidity and mortality through expanded access to evidence-based protocols (López et al. 2023).

Smoking cessation

Combining counseling with social support through peer groups or talklines improves efficacy. There is a dose–response where more intensive behavioral interventions lead to higher prolonged abstinence rates. However, real-world utilization of behavioral cessation resources remains low due to barriers like cost and accessibility. Pharmacotherapy represents another efficacious facet of traditional smoking cessation programs. Nicotine replacement therapy (NRT) through gum, lozenges, patches, sprays and inhalers doubles long-term quit rates compared to placebo. The choice of NRT format can be tailored to individual needs and preferences (Theodoulou et al. 2023a). Beyond nicotine delivery, the antidepressant bupropion and the nicotinic receptor partial agonist varenicline also improve cessation outcomes. Combining behavioral counseling with pharmacotherapy leads to the highest abstinence rates clinically. However, high relapse rates remain an issue even with traditional interventions. Electronic cigarettes have rapidly grown in popularity as an alternative nicotine delivery system and purported smoking cessation aid. E-cigarettes aim to provide users with inhaled nicotine and smoking-related sensory cues while eliminating toxic combustion products responsible for the majority of smoking-related disease risks. This has led to considerable interest in evaluating whether e-cigarettes may represent a reduced harm nicotine product that can effectively promote smoking cessation (Theodoulou et al. 2023b).

Early randomized controlled trials of first generation "cig-a-like" e-cigarette devices showed mixed or minimal benefit compared to traditional nicotine replacement therapy. However, studies employing newer generation devices with improved nicotine delivery have found e-cigarettes can improve quit rates over NRT. For example, one recent trial using refillable e-cigarettes with free choice of liquid nicotine strengths reported

roughly double the abstinence rates with vaping compared to nicotine patches (Tillery et al. 2023). However, other studies using regulated low-nicotine e-cigarettes have found comparable efficacy between vaping and NRT. Device characteristics and user puffing behaviors appear to impact nicotine exposure and associated cessation potential. While clinical trials show promise, real-world observational data on e-cigarette patterns of use and effectiveness for quitting remains limited. Some population data indicate a majority of smokers who try e-cigarettes continue smoking combustibles long-term rather than fully switching, highlighting concerns about dual use. Surveys also indicate many e-cigarette users eventually discontinue vaping as well. More research is needed on long-term trajectories of e-cigarette use and correlations with permanently quitting smoking (Pajai et al. 2023). Given the limited long-term efficacy of existing approaches, investigation into the potential role of electronic cigarettes as cessation devices has intensified over the past decade. E-cigarettes deliver inhaled nicotine without combustion products, aiming to mitigate the health consequences of smoking while maintaining nicotine pharmacology that facilitates switching. Several randomized controlled trials have compared e-cigarettes to NRT for smoking cessation. While results are mixed, a number of studies have found comparable or even superior quit rates with e-cigarettes. However, real-world observational data on the efficacy and patterns of e-cigarette use for quitting remain limited. Concerns also remain about dual use and unknown long-term health effects (Sivasankari et al. 2023).

Tobacco product regulation

By manipulating variables like cigarette fiber packing, filter ventilation, and paper porosity, the industry honed products to provide optimized nicotine uptake. Adding ammonia compounds and acetaldehyde also enhanced nicotine delivery through free base nicotine generation and MAO inhibition. These changes increased addictiveness while making cigarettes smoother and less harsh to inhale. The industry further exploited minimal regulation through decades of targeted youth marketing and product claims implying reduced harm which kept smoking rates high (Goud 2023). While combustible cigarettes contain thousands of chemicals that can cause smoking-related diseases, newer non-combustible nicotine delivery systems like heated tobacco products (HTPs) and electronic nicotine delivery systems (ENDS) have emerged as potentially less harmful alternatives (Goniewicz 2023). ENDS, known colloquially as e-cigarettes or vapes, work by heating a liquid solution containing nicotine, flavors, solvents like propylene glycol (PG) and vegetable glycerin (VG), and other additives to generate an inhalable aerosol. ENDS may aid smoking cessation but health effects with long-term use are still debated (Zhang and Wen 2023). Acute ENDS use can deliver less nicotine than cigarettes, but newer generation devices offer more customization of nicotine concentrations and delivery profiles. Besides nicotine, studies show ENDS aerosols contain compounds like metals, volatile organic chemicals, polycyclic aromatic hydrocarbons (PAHs), and favoring agents at much lower levels than conventional cigarettes. However, thermal decomposition of solvents like PG/VG during heating can produce toxic aldehydes. Flavorings may also enhance palatability and abuse liability, especially in youth (Krishnan-Sarin et al. 2019). Some animal and clinical studies report ENDS use induces oxidative stress, inflammation, and cardiovascular or respiratory effects, but the long-term disease risks in humans remain uncertain. For cessation, pharmacotherapies like nicotine replacement therapy (NRT), varenicline, or cytisine are first-line options, with behavioral counseling also effective alone or in combination. While clinical trials suggest ENDS may increase smoking abstinence over NRT, real-world effectiveness and long-term safety require further study. Appropriate regulation balancing potential ENDS benefits for adult smokers with population risks remains complex and debated. Overall, ENDS likely confer lower individual health risk compared to continued smoking, but impacts on youth uptake, dual-use, and implications for population health outcomes need ongoing investigation (Sala and Gotti 2023).

Tobacco harm reduction philosophies advocate for risk-proportionate regulation where novel nicotine products with lower toxicity like e-cigarettes or heated tobacco are made accessible to inveterate adult smokers while preventing youth initiation. But some public health experts argue this may sustain nicotine addiction at a population level. There are also environmental impacts of discarded tobacco and e-cigarette waste to consider. These complex tradeoffs inherent to tobacco regulatory policy will require ongoing re-evaluation as products and consumption patterns evolve (Su et al. 2022).

Recent advances in understanding and managing smoking-attributable disease

As depicted in Fig. 3, ROS from cigarette smoke lead to lipid peroxidation of cell membranes, oxidation of proteins, DNA strand breaks, and mitochondrial dysfunction. This overwhelms endogenous antioxidant systems like superoxide dismutase, catalase, and glutathione peroxidase. Oxidative stress from cigarette smoke has been linked to endothelial injury, atherosclerosis, lung disease, and cancer. Smoke components activate cytokine release (e.g., IL-1β, TNF-α) and expression of adhesion factors like selectins, VCAM-1, and ICAM-1. This promotes

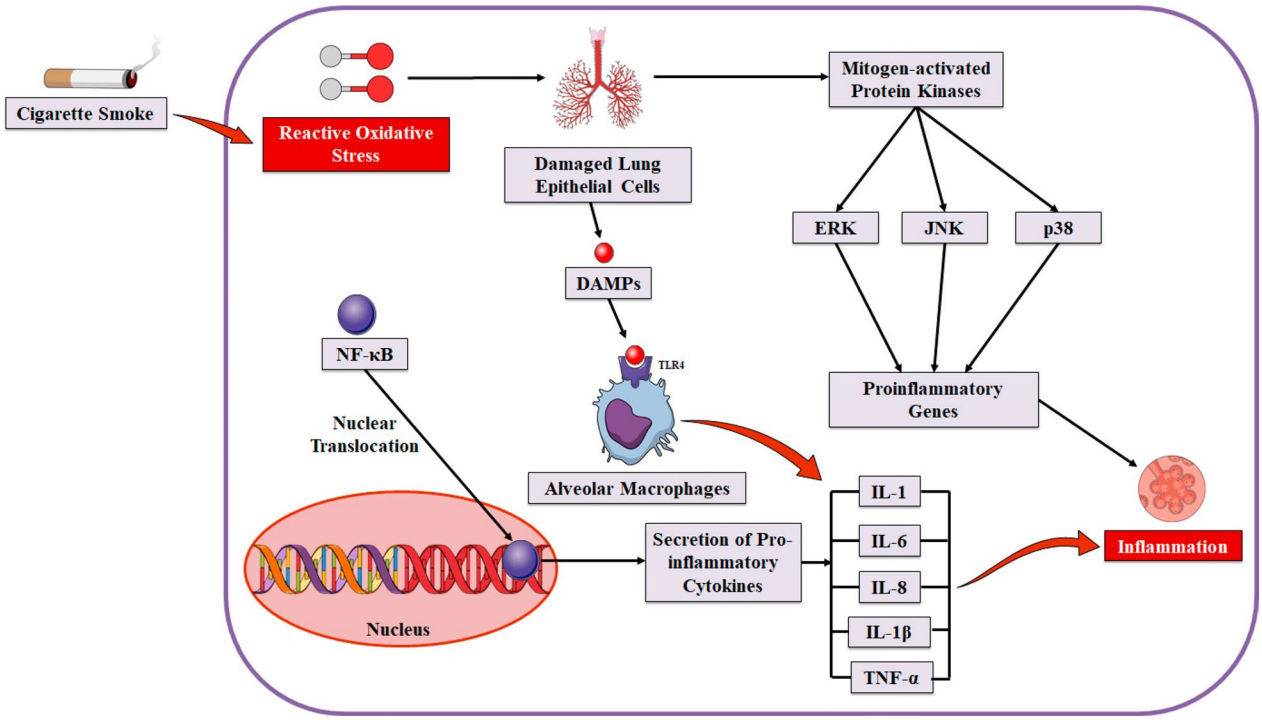

Fig. 3 Cigarette smoke triggers inflammatory signaling in lung cells (Mazzone et al. 2010)

immune cell recruitment, especially of neutrophils and monocytes. These immune cells secrete proteases like MMPs that further propagate inflammation and tissue damage (Mazzone et al. 2010). Advanced profiling techniques have characterized antioxidant depletion and free radical damage from cigarette smoke with higher precision in human samples. Studies utilizing single-cell RNA sequencing have mapped out cell-specific inflammatory responses to smoking across multiple organ systems. This includes delineating unique cytokine signatures and pathway activations in relevant cell populations like alveolar macrophages in the lungs. Mapping the effects of smoking on cellular oxidative and inflammatory processes through sophisticated omics approaches provides new targets for therapeutic intervention (Tu et al. 2022). Recent clinical advances have also improved management of common smoking-related diseases. Tobacco smoke suppresses immune responses, attenuating vaccine efficacy in smokers (Addissouky et al. 2023d). For lung cancer, checkpoint inhibitor immunotherapies like pembrolizumab and nivolumab have become integral to treatment paradigms, demonstrating superior survival over chemotherapy alone. Novel targeted agents are also emerging, including TRK, RET, and NTRK1 inhibitors for cancers driven by fusions in these growth factor genes. Non-pharmacological innovations like tumor ablation by irreversible electroporation represent additional progress (Ham et al. 2023). For cardiovascular disease, PCSK9 inhibitors have proven effective at lowering LDL cholesterol, while canakinumab reduces inflammation implicated in atherogenesis (Addissouky et al. 2023e). Technological enhancements like bioresorbable stents and 3D-printed heart valves continue improving smoking-accelerated cardiovascular pathology. Leveraging new understandings of disease biology and technical advances shows promise for mitigating the diverse manifestations of smoking-induced illness (Barungi et al. 2023).

Traditional and herbal medicine approaches for smoking cessation

Traditional medicine systems encompass long-standing practices, beliefs, and natural remedies used for health promotion and treatment of illness (Addissouky et al. 2023f). Several therapeutic modalities originating from traditional healing frameworks like traditional Chinese medicine (TCM), Ayurvedic medicine, Mastic gum and Native American medicine have shown preliminary promise for aiding smoking cessation and mitigating smoking-related diseases (Pradipta et al. 2023; Addissouky et al. 2023g). TCM utilizes a holistic approach emphasizing balance between mind, body and environment. Acupuncture is a key TCM technique involving insertion of small needles into defined body points to

modulate energy flow. Moxibustion is another technique applying heat to acupoints, usually via burning of mugwort herb. Studies suggest moxibustion alleviates nicotine withdrawal symptoms and reduces smoking urge at specific acupoints. Beyond acupuncture, TCM herbal formulations such as mixture of olive oil and figs may also benefit smoking cessation efforts (Plaut 2023; Addissouky et al. 2020). A TCM formula containing ingredients like licorice, Fructus aurantii, and Semen vaccariae segetalis was found comparable to nicotine replacement therapy for relieving withdrawal symptoms during quit attempts. Ayurveda is a traditional Indian whole-body healing system using natural remedies tailored to an individual's specific doshas or mind–body types. Butea frondosa and Bacopa monnieri are two Ayurvedic herbs that demonstrate therapeutic effects for smoking addiction (Pourova et al. 2023). Animal research found B. frondosa inhibited nicotine absorption and conditioned place preference behaviors through effects on mu opioid and dopamine pathways in the reward circuitry. B. monnieri also reduced nicotine withdrawal signs in rodents, with proposed mechanisms involving modulation of neurotransmitters like GABA, serotonin and glutamate. An Ayurvedic polyherbal formulation decreased nicotine cravings and affective withdrawal symptoms in a small clinical trial (Shukla et al. 2024). Several Native American traditional medicines have also shown preliminary potential for smoking cessation. Kinnikinnick, an herbal mixture frequently used in sacred pipe ceremonies, contains antioxidants that may mitigate tobacco smoke toxicity. Studies identified ceremonies incorporating kinnikinnick served as smoking cessation rituals supporting quitting among Northern Plains tribes (Berlowitz et al. 2023). Lobelia, a plant used medicinally by Cherokee, Iroquois and other tribes, contains lobeline compound chemically similar to nicotine. Lobeline binds nicotinic receptors as a partial agonist, which may aid smoking cessation through reducing cravings and withdrawal while avoiding risks of tobacco toxicity. St. John's Wort was traditionally used across North American tribes for respiratory ailments; some evidence suggests it may alleviate tobacco withdrawal symptoms through monoamine reuptake inhibition effects. While clinical evidence remains limited, these and other traditional medicine approaches represent promising areas for novel smoking cessation treatment development (Zheng et al. 2021).

Future research directions

Emerging directions like computational methods and traditional Chinese medicine approaches may complement continued progress in established domains like cessation pharmacotherapy and public policy (Bickel et al. 2023). Artificial intelligence and machine learning show great promise for advancing tobacco and nicotine research (Bendotti et al. 2023). Neural networks could integrate diverse variables to build predictive models forecasting individual disease risk under different smoking cessation interventions, potentially uncovering personalized strategies. Machine learning may also facilitate optimal treatment matching based on previous outcomes data. Thoughtfully applied, AI could significantly enhance tobacco research (Issabakhsh et al. 2023). Innovative technologies like nanomedicine also hold potential for smoking cessation (Addissouky et al. 2023h). Polymeric nanoparticles loaded with nicotine and antidepressants could enable sustained pharmacotherapy and improved brain uptake. Magnetic nanoparticles may allow external regulation of nicotine delivery through magnetic fields. Recent research found cigarette smoke extract dramatically boosted anti-inflammatory effects of peptide-gold nanoparticles, enabling new therapeutic targeting (Yuan et al. 2023; Yau et al. 2023; Gao et al. 2019). The nanoparticles accumulate inside cells, enhancing Toll-like receptor 4 inhibition, which requires endosomal acidification. CSE-treated nanoparticles also stimulated antioxidant protein expression through autophagy as depicted in Fig. 4 (Gao et al. 2019). Proteomic profiling of biological samples can identify smoking-related disease biomarkers for earlier diagnosis and personalized interventions (Lung Cancer Cohort Consortium (LC3) 2023). Machine learning analysis of proteomic data has already identified protein signatures predicting smoking status with 85–90% accuracy (Lung Cancer Cohort Consortium (LC3) 2023). Ongoing proteomics research aims to elucidate mechanisms of smoking-induced injury for targeting. Translating emerging science into individualized cessation plans accounting for genetic, biomarker, psychosocial, and product preference data shows great potential to improve outcomes (Cobos-Campos et al. 2023). While most patients currently receive generic recommendations, personalized medicine approaches tailored to biological and behavioral profiles hold enormous promise. Well-designed trials like the WeChat smoking cessation study will provide vital evidence on innovative interventions like integrated mobile cessation modalities (Roosan et al. 2023; Chu et al. 2023). Findings from emerging directions can inform continued optimization of established cessation approaches.

Conclusions

Tobacco smoking remains one of the foremost preventable causes of morbidity and mortality worldwide, despite unequivocal evidence of health risks. Comprehensive efforts encompassing prevention, screening, treatment innovation, harm reduction, and policy reform focused on improving cessation outcomes must continue

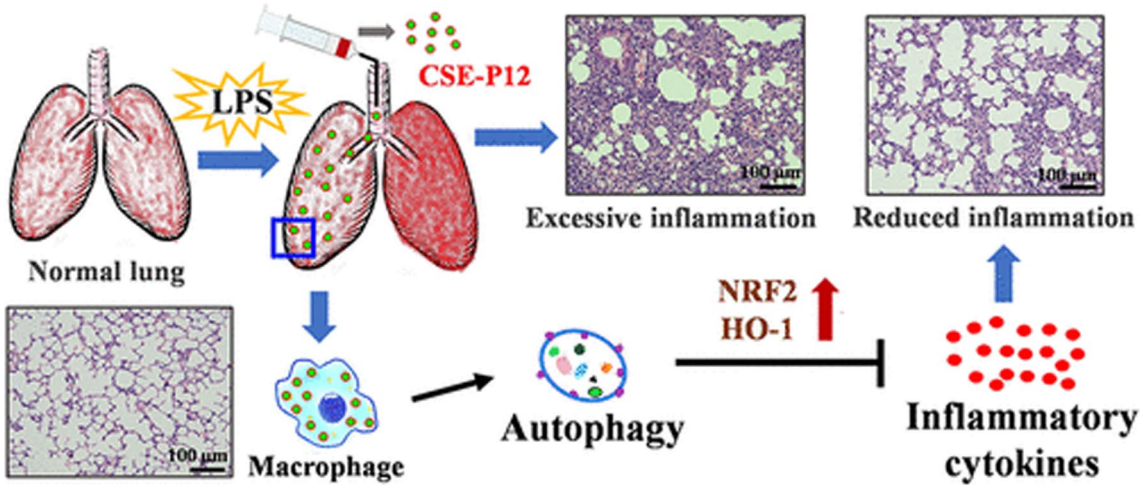

Fig. 4 Enhanced anti-inflammatory effects of peptide-gold nanoparticles with cigarette smoke extract (Gao et al. 2019)

advancing to curb smoking-attributable disease. At the basic science level, research has characterized pathological mechanisms of smoking-induced injury like oxidative stress, inflammation, and cellular senescence across organ systems. Translation of emerging science into clinical and public health interventions is critical for tangible improvements in population-level disease endpoints. Population data reveal marked disparities in smoking prevalence and risks, highlighting needs for culturally-informed prevention and cessation initiatives promoting health equity. Screening of at-risk groups and earlier diagnosis of smoking-related illness should also be expanded through increased adoption of evidence-based guidelines. Future directions like computational models, harm reduction approaches, and traditional medicine warrant exploration to improve cessation outcomes.

Recommendations

Several priorities emerge for ongoing research and clinical efforts to curb the substantial preventable harms of cigarette smoking:

1. Public health initiatives aimed at smoking prevention should continue targeting youth and adolescents, emphasizing both short and long-term health risks. School-based programs, mass media campaigns, and regulations limiting youth-oriented tobacco marketing could help reduce smoking initiation.
2. Healthcare providers should adhere to screening guidelines for early lung cancer detection with low-dose CT in high-risk smokers, which evidence shows reduces mortality. Annual spirometry assessment for COPD in smokers over 40 is also recommended but underutilized currently.
3. Smoking cessation counseling and pharmacotherapy should be offered routinely in primary care. Combination nicotine replacement therapy, varenicline, and bupropion all have proven efficacy. Behavioral interventions and mobile apps utilizing cognitive behavioral techniques can further boost quit rates.
4. E-cigarettes require ongoing surveillance to elucidate long-term cardiovascular and respiratory health impacts. Their population-level effects on cessation versus sustaining nicotine addiction across age groups remain uncertain. Further research can help guide evidence-based policies on these emerging products.
5. Disparities in smoking prevalence and access to cessation resources among disadvantaged populations must be addressed through culturally-informed interventions. Community health worker models may aid engagement. Policy initiatives promoting smoke-free public housing and tobacco taxation are also warranted.
6. Funding support for tobacco/nicotine research should continue across domains from basic science elucidating smoking-induced disease mechanisms to clinical trials improving cessation outcomes. Especially promising areas include pharmacogenetics, immune therapies, harm reduction approaches, and computational models forecasting risks.

In summary, reducing the health burdens of tobacco smoking will require diverse, collaborative efforts scaling up prevention, screening, treatment, harm reduction, and social equity initiatives worldwide. Ongoing

innovation and implementation research will be key to translating proven interventions into tangible improvements in population health endpoints.

Abbreviations

COPD	Chronic obstructive pulmonary disease
ROS	Reactive oxygen species
DAMPs	Damage-associated molecular patterns
RAGE	Receptor for advanced glycation end products
TLRs	Toll-like receptors
MAPK	Mitogen-activated protein kinase
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
MMPs	Matrix metalloproteinases
LDL	Low-density lipoprotein
NO	Nitric oxide
WHO	World Health Organization
SES	Socioeconomic status
LGBTQ+	Lesbian, gay, bisexual, transgender, queer/questioning, and others
NRT	Nicotine replacement therapy
ENDS	Electronic nicotine delivery systems
HTPs	Heated tobacco products
PG	Propylene glycol
VG	Vegetable glycerin
PAHs	Polycyclic aromatic hydrocarbons
FEV1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
CT	Computed tomography
ARDS	Acute respiratory distress syndrome

Acknowledgements
The authors thank all the researchers, editors, reviewers, and the supported universities that have done great efforts on their studies. Moreover, we are grateful to the editors, reviewers, and reader of this journal.

Author contributions
The authors completed the study protocol and were the primary organizers of data collection and the manuscript's draft and revision process. TAA wrote the article and ensured its accuracy. All authors (TA, IE, MA, YW, AE, NE, AK) contributed to the discussion, assisted in designing the study and protocol and engaged in critical discussions of the draft manuscript. Lastly, the authors reviewed and confirmed the final version of the manuscript.

Funding
Corresponding author supplied all study materials. There was no further funding for this study.

Availability of data and materials
All data are available and sharing is available as well as publication.

Declarations

Ethics approval and consent to participate
Not Applicable.

Consent for publication
Not Applicable.

Competing interests
The authors hereby that they have no competing interests.

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Received: 13 December 2023 Accepted: 14 January 2024
Published online: 22 January 2024

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