**Int. j. adv. multidisc. res. stud.** 2025; 5(3):1337-1345

**Received:** 27-04-2025
**Accepted:** 07-06-2025

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

# A Review: Cigarettes Trigger Chronic Inflammation in the Body

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**DOI:** https://doi.org/10.62225/2583049X.2025.5.3.4455
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**Abstract**

**Background**

Cigarettes are a controversial product with the highest smoking rate in Indonesia, which contain harmful substances like nicotine and tar that can cause chronic inflammation, as shown by increased levels of IL-8, TNF-α, and ROS in saliva. Even though people are aware of the dangers, most still smoke without paying attention to the impact on health. Long-term smoking can weaken the immune system and increase Non-communicable illness risks including cancer.

**Objective**

To explain how smoking can trigger chronic inflammation in the body.

**Discussion**

Cigarettes are a combination of chemicals. When cigarettes are inhaled, incomplete combustion can be deposited in the body. Generally speaking, there are two major categories of cigarette components: Gas components (92%) and solid components or particles (8%). The gas elements of cigarette smoke consist of oxides, carbon monoxide, ammonia, hydrogen cyanide, carbon dioxide, and hydrocarbons. Cigarette particles consist of nicotine, tar, benzopyrene, cadmium, benzanthracene, indole, henol, carbarzol and cresol. These chemicals are poisonous and unpleasant, and they can also raise the release of salivary ROS and pro-inflammatory cytokines like TNF-a and IL-8.

**Conclusion**

Cigarettes increase salivary ROS, TNF-α, and IL-8 production, which can cause chronic inflammation in the body.

**Keywords:** Cigarettes, Chronic Inflammation, IL-8, TNF-α, ROS, Good Health and Well Being

## Introduction

Cigarettes are one of the controversial products widely circulated in society that have pros and cons in their use. Indonesia is the country with the third-highest smoking prevalence worldwide [1]. The prevalence of smokers in Indonesia according to the 2018 Riskesdas data was (33.8%), with a prevalence of men (62.9%) and women (4.8%). Based on the survey, Indonesian people already know the dangers contained in cigarette content but people still smoke without caring about their health [2]. The cigarette smoke consumed consists of a mixture of chemicals, both in the form of gas and particles that have been decomposed, and almost all of these compounds are toxic to the human body [3].

Toxic substances contained in cigarette smoke can be chemicals such as formaldehyde, nitrosamine, carbon monoxide, nitrogen oxides, and hydrogen cyanide. Cigarettes also contain toxic nicotine, tar that produces excess free radicals, and benzopyrene

which induces inflammation [3]. The combustion of organic compounds in cigarettes can produce highly reactive and unstable radical compounds such as superoxide and hydroxyl radicals, which are members of reactive oxygen species (ROS). Excess ROS formation outcome in oxidative stress, a dangerous process that can have a negative impact on a number of cellular structures, such as lipids, membranes, lipoproteins, DNA, and proteins [4].

Studies on smoking activity state that smokers usually start their habit at a young age and it will be difficult to stop [5]. Prolonged cigarette consumption can affect the immune-inflammatory system and cause various diseases related to chronic inflammation. Globally, chronic inflammation is a major cause of mortality. According to the World Health Organization (WHO), chronic diseases such as cardiovascular conditions, cancer, diabetes, respiratory disorders, stroke, and obesity account for the deaths of three out of every five people worldwide. Inflammation-related diseases represent among today's biggest risks to human health.

Smoking causes chronic inflammation by releasing inflammatory cells into the circulation and increasing inflammatory mediators such as acute phase proteins and pro-inflammatory cytokines [6]. Inflammation is an essential component of normal tissue repair and is fundamental to the body's defenses. The inflammatory response is usually limited to a short period of time when there is a threat and resolves after the threat has passed [7]. However, the presence of other factors such as smoking can cause inflammation to shift from acute or short-term to chronic or long-term. This change raises the risk of several chronic inflammatory disorders by causing significant alterations in tissues and organs, a reduction in immunological tolerance, and modifications to normal cellular physiology [8].

Smoking can result in pathological conditions or lesions in the oral cavity, including periodontal disease, precancerous lesions, caries, and even oral cancer. Chronic inflammation can trigger an excessive reaction of IL-8 and TNF-α which causes DNA damage, triggers cell death, and angiogenesis [9]. Inadequate management of the angiogenesis process, which produces new blood vessels from preexisting ones, can result in chronic inflammation. The angiogenesis process is stimulated by various types of cells, including mast cells, fibroblasts, and macrophages. Macrophages can start angiogenesis by releasing cytokines and angiogenic factors including TNF-a and IL-8. The increased amount of secretion of proinflammatory mediators around the tissue triggers activated macrophages to damage the tissue massively, which ultimately results in chronic inflammation [10].

## Chronic Inflammation

One of the body's defense mechanisms, inflammation can be either acute or chronic. The inflammatory process begins when the body's immune system recognizes and eliminates foreign and harmful stimuli to begin recovery process [11]. A protracted, slowly progressing inflammatory reaction that might last for months or even years is referred to as chronic inflammation. The impact varies based on the underlying cause and the body’s capacity to heal and manage the resulting harm. This type of long-term inflammation is a key contributor to many chronic illnesses and represents a significant health risk. Numerous illnesses have been connected to it, such as inflammatory bowel disease, cancer, diabetes, asthma, Alzheimer's disease, chronic kidney disease, cardiovascular disorders, and chronic obstructive pulmonary disease (COPD) [12]. The following are some causes of chronic inflammation [13]:

1. The immune system's inability to fully remove pathogens responsible for acute inflammation, such as protozoa, fungi, *Mycobacterium tuberculosis* can lead to chronic inflammation.
2. Prolonged exposure to specific irritants or foreign materials may trigger a sustained inflammatory response.
3. In autoimmune diseases, the body's own tissues are erroneously attacked by the immune system as though they were alien, which may result in chronic inflammation and sustained tissue damage.
4. Malfunctions in cells involved in the inflammatory response can lead to ongoing or repeated inflammation.
5. A number of biochemical processes, including elevated free radical production and buildup of advanced glycation end products (AGEs), presence of oxidized lipoproteins, uric acid crystals, and elevated homocysteine levels, can contribute to chronic inflammation by causing oxidative stress and impairing mitochondrial function.

Some predisposing factors that encourage chronic inflammation include [14]:

1. Elevated levels of certain inflammatory chemicals are linked to aging. The buildup of free radicals over time or mitochondrial malfunction can be the cause of the age-related rise in inflammatory chemicals.
2. Obesity, as fat tissue is an endocrine organ that releases a lot of inflammatory mediators and adipokines. Numerous studies have demonstrated a correlation between an individual's body mass index and the quantity of proinflammatory cytokines they release.
3. Increased synthesis of pro-inflammatory chemicals has been connected to diets high in trans fats, saturated fats, and refined sweets, especially in individuals with diabetes or obesity.
4. Smoking contributes to inflammation by reducing the release of anti-inflammatory substances and promoting inflammatory responses.
5. Reduced concentrations of sex hormones, including testosterone and estrogen, may lead to increased inflammation, as these hormones normally help block the produce of certain pro-inflammatory cytokines.
6. Chronic stress and poor sleep quality are both linked to increased pro-inflammatory cytokine levels, with sleep disturbances being recognized as an independent risk factor for chronic inflammation.

## Smoking

Smoking involves inhaling the smoke produced by burning tobacco contained in cigarettes. It is a harmful habit that negatively impacts the body. World Health Organization (WHO) reports that exposure to cigarette smoke, whether directly through active smoking or indirectly through passive smoking can lead to numerous diseases and has severe consequences for both Environmental factors and human health [15]. Smoking has negative impacts on more than only systemic health; it also significantly affects oral health. Particularly at risk are the soft tissues and teeth in the oral cavity, with potential damage including periodontal disease, dental caries, tooth loss, gingival recession, precancerous changes, and oral cancer [16].

**Contents of Cigarettes**

Cigarettes contain a mixture of various chemical substances. When smoked, they undergo incomplete combustion, resulting in harmful residues that can accumulate in the body. Cigarette smoke mainly consists of two key elements: Gases (92%) and solid particles (8%). The gaseous part contains substances like carbon monoxide, hydrogen cyanide, carbon dioxide, ammonia, different oxides, and hydrocarbons. The particulate matter contains harmful substances such as cresol, carbazole, cadmium, benzopyrene, phenol, tar, nicotine, benzanthracene, and indole. These compounds are known to be poisonous and irritating to the body [17].

Tar, nicotine, and benzopyrene are considered the most hazardous substances found in cigarette smoke. When a cigarette is smoked, tar enters the mouth in vapor form and solidifies upon cooling, leaving brown stains on the teeth, respiratory tract, and lungs. Tar contains free radicals, which have been connected to a higher danger of causing cancer [18]. Nicotine, a toxic and addictive natural alkaloid, is a colorless, volatile liquid that turns brown and emits a tobacco-like odor when exposed to air [19, 20]. It interferes with the attachment and proliferation of periodontal ligament fibroblast cells, lowers fibroblast protein levels, and damages cell membranes. Benzopyrene is another harmful compound in cigarette smoke, known for its inflammatory and carcinogenic properties, which contribute to the development of various cancers [21].

Cigarettes also contain other harmful chemicals, such as carbon monoxide, which can elevate blood pressure and interfere with the oxygen transport system by affecting hemoglobin function [22]. Carbon monoxide shows a strong affinity for hemoglobin approximately 200 times greater than that of oxygen, significantly reducing oxygen delivery to body tissues. Another highly toxic substance found in cigarettes is lead (Pb), which poses serious health risks. These particles are contained in cigarettes as much as 0.5 µg. The threshold for lead in the body is 20 milligrams per day. These elements' components undoubtedly have a variety of impacts that vary depending on how many cigarettes are consumed, how long one smokes, and what kind of cigarette one smokes [21].

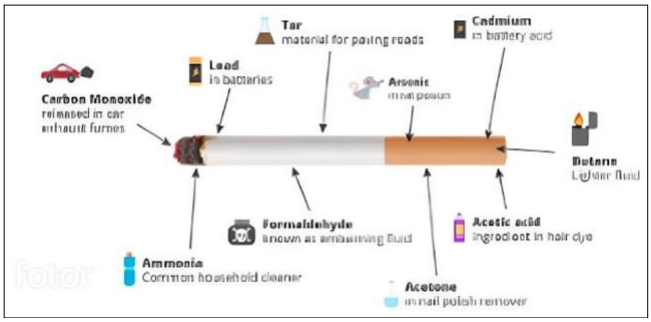


**Fig 1:** Component of cigarettes

**Benzopyrene**

Benzopyrene (BaP) is a member of the polycyclic aromatic hydrocarbon (PAH) group formed from carbon and hydrogen structures that arise from the incomplete combustion process. Benzopyrene is one of the most carcinogenic members of the PAH family, which is usually found in cigarette smoke and tobacco [23]. This substance can cause genetic changes in body cells and repeated exposure to benzopyrene will cause DNA mutations in cells in the oral cavity [24]. These genetic mutations can potentially initiate and promote the growth of cancer cells. In addition, cigarette smoke containing benzopyrene can also irritate tissues in the oral cavity, including the gums, lips, and tongue [25].

A higher risk of chronic inflammation has been associated with cigarette smoking, specifically exposure to benzopyrene in cigarette smoke. Research indicates that benzopyrene disrupts redox balance and contributes to oxidative stress [26]. Findings reveal a reduction in the activity of key antioxidant enzymes, like glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD). Moreover, benzopyrene lowers levels of crucial antioxidants such vitamin E, vitamin C, and reduced glutathione (GSH). It also elevates lipid peroxidation, promotes protein carbonyl formation, and stimulates the produce of proinflammatory cytokines [23].

**The Effect of Cigarettes on the Oral Cavity**

Smoking can cause a number of dangerous illnesses and has a significant detrimental impact on dental health. The toxic substances in cigarette smoke can directly affect both the soft and hard tissues within the oral cavity [27], increasing the risk of oral diseases. The chemicals in tobacco can trigger inflammation and impair blood flow and nutrient delivery to the gums, resulting in symptoms such as swelling, bleeding, and, in more severe cases, periodontitis. The tissues supporting the teeth are harmed by this degenerative disorder, which might ultimately lead to tooth loss [28].

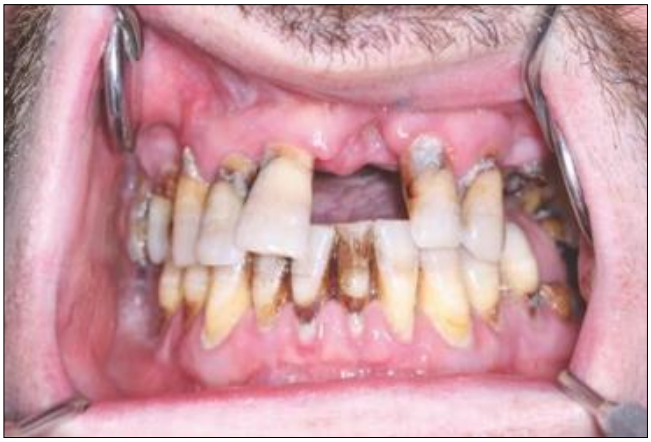

**Fig 2:** Chronic periodontitis within active smokers [58]

In further pathogenesis of the disease, smoking can increase the risk of oral cancer. Cigarette smoke contains various carcinogenic substances that can damage cells in the oral cavity. Oral cancer has a high rate of death and is often difficult to detect in the early stages [29]. In addition, smoking can affect the aesthetics of teeth and mouth. Nicotine and other substances in cigarettes can cause tooth discoloration, bad breath, and other things that can affect a person's social interaction and self-confidence. Not only that, smoking can also slow down the healing process after medical intervention in the oral cavity [30].

**Immune Response to Pathogens**

Smoking can cause exposure to pathogens that trigger the body's immune response. The immune response involves four key components: (1) endogenous or exogenous stimuli, including damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs), and cellular injury; (2) Cell receptors, especially pattern

recognition receptors (PRRs) like toll-like receptors (TLRs), had a crucial role; (3) proinflammatory mediators like cytokines and chemokines; and (4) the target cells or tissues [31]. The harmful substances or combustion products found in cigarette smoke can function as PAMPs, which are detected by TLRs located on cell membranes. Structurally, TLRs are made up of an ectodomain, a membrane-spanning region, and a toll/interleukin-1 receptor (TIR) domain within the cytoplasm [32].

Polycyclic aromatic hydrocarbons will bind to TLR4, which is one type of PRR that is able to identify pathogens. Myeloid differentiation primary response 88 (MyD88) and TIR-domain–containing adaptor-inducing interferon-β (TRIF) are adaptor proteins that become activated when a pathogen-associated molecular pattern (PAMP) binds to TLR4, triggering the receptor to form a dimer. The interleukin-1 receptor-associated kinase (IRAK) family is activated via the MyD88-dependent pathway, which is the main source of TLR4 signaling. Tumor necrosis factor receptor-associated factor 6 (TRAF6) is activated following the phosphorylation of IRAK1 by IRAK4. TRAF6 then activates inhibitor kappa B kinases (IKK) via stimulating transforming growth factor-β-activated protein kinase 1 (TAK1). The production and nuclear translocation of NF-κB, which can start the transcription of proinflammatory genes, are caused by IKK's phosphorylation of IκB [33, 34].

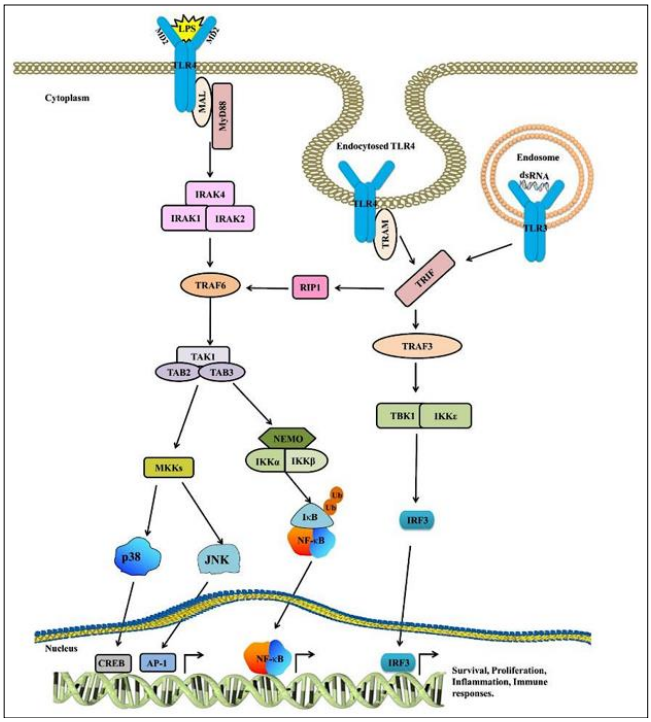


**Fig 3:** Signaling pathway of TLR4[32]

### Interleukin-8 (IL-8)

The transcription of several immune-related genes, including TNF-α and IL-8, is activated by the migration of NF-κB into the nucleus. As a crucial mediator, IL-8 orchestrates various immune and inflammatory activities within the body. This cytokine is released by many different cell types, such as leukocytes, fibroblasts, endothelial cells, and malignant cells. In non-immune cells, the IL-8 gene first encodes a precursor protein consisting of ninety-nine amino acids, which is subsequently converted into its active form by seventy-seven amino acids, and in monocytes and macrophages, by seventy-two amino acids. IL-8 carries out its biological functions by binding to two G protein-coupled receptors: CXCR1 and CXCR2. Upon ligand binding, these receptors undergo processes such as phosphorylation, desensitization, and internalization [35, 36].

When IL-8 binds to CXCR1 or CXCR2, it triggers the activation of several intracellular signaling pathways, including Mitogen-Activated Protein Kinase (MAPK), Phosphoinositide 3-Kinase (PI3K), Protein Kinase C (PKC), and Focal Adhesion Kinase (FAK). These pathways, in turn, lead to the activation of key transcription factors such as NF-κB, Activator Protein-1 (AP-1), Hypoxia-Inducible Factor 1 (HIF-1), and Signal Transducer and Activator of Transcription 3 (STAT3). The signaling mechanisms of IL-8, particularly through CXCR1/2, are typically tightly regulated under normal physiological conditions, but their activation can enhance inflammatory responses [35].

### TUMOR NECROSIS FACTOR ALPHA (TNF-α)

Tumor Necrosis Factor Alpha (TNF-α) is a vital cytokine that orchestrates immune and inflammatory responses within the body. It belongs to the tumor necrosis factor superfamily (TNFSF), which includes over twenty structurally and functionally related molecules, such as Fas Ligand (FasL) and CD40 Ligand (CD40L). Primarily produced by macrophages, TNF-α contributes to numerous cellular mechanisms, including cell division, tissue invasion, cellular migration, and the promotion of blood vessel growth (angiogenesis) [37]. This cytokine exists in two bioactive forms: A 26 kilodalton membrane-bound trimer and a 17 kilodalton soluble version, which enters the circulation after being cleaved by TNF-α converting enzyme (TACE). TNF-α exerts its signaling effects primarily through two receptors, TNFR1 and TNFR2, each of which triggers different intracellular signaling pathways [38].

TNFR1 is ubiquitously expressed on nearly all cell types, whereas TNFR2 expression is more limited, primarily observed on neurons, immune cells, and endothelial cells. TNFR2 has a higher affinity for the membrane-bound form of TNF-α and can enhance TNF-α signaling through TNFR1 by facilitating its more efficient presentation. Both TNFR1 and TNFR2 can be cleaved by TACE, resulting in soluble receptor forms that function as natural antagonists to TNF-α. Functionally, TNF-α serves a dual purpose: Under physiological conditions, it helps maintain cellular equilibrium, but under pathological states, particularly through TNFR1, it can promote inflammation and tissue damage. On the other hand, TNFR2 is more commonly associated with beneficial effects, including immune regulation, wound healing, epithelial-to-mesenchymal transition, and stimulation of cell proliferation. Therefore, the contrasting effects of TNF-α depend largely on how its two receptors are regulated and activated [38].

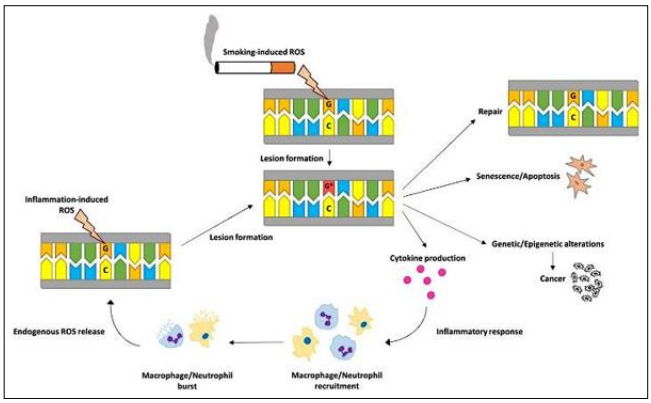


**Fig 4:** The cycle of oxidative damage and inflammation due to smoking[8]

## Formation of Reactive Oxygen Species

Cigarette smoke is composed of two main phases based on the size of its ingridients: The tar (particulate) phase and the gas phase. The tar phase contains particles ranging from 0.1 to 1 micrometer (µm) in diameter, with an average size of about 0.2 µm, while the gas phase consists of chemicals smaller than 0.1 µm. Both phases generate significant amounts of reactive oxygen species [8]. Reactive oxygen species (ROS) is a term often encountered in biology and medicine. This term is simply defined as a group of oxygen free radicals.

ROS as molecules are able to survive independently and contain a single oxygen atom along with one or more unpaired electrons. ROS contain various molecules like superoxide anion radicals, hydrogen peroxide, hydroxyl radicals, hydroperoxyl radicals, peroxyl radicals, peroxyl radicals, alkyl radicals, lipid hydroperoxides, peroxynitrite, hypochlorous acid, singlet oxygen, and free nitrogen radicals. Both in healthy and diseased circumstances, mitochondria produce ROS [39, 40, 41].

During the combustion of tobacco, various reactive oxygen species (ROS) form in the gaseous phase and are directly inhaled by smokers through the cigarette filter into their mouths and further into the respiratory tract. This gaseous phase contains several oxygen- and carbon-centered radicals, including alkoxy, phenoxy, aryloxy, carbonyl, alkylperoxy, and alkyl aminocarbonyl radicals. In contrast, the tar phase composes more stable free radicals, including the quinone/hydroquinone ($Q/QH_2$) complex. The $Q/QH_2$ complex acts as a redox-active agent that facilitates oxygen reduction in the lungs, triggering the synthesis of superoxide ($O_2^{\bullet -}$) and promoting the formation of additional reactive molecules like hydrogen peroxide ($H_2O_2$) and hydroxyl radicals (•OH) obtained from cigarette smoke [8].

Oxidative stress arises when the generation of reactive oxygen species (ROS) surpasses the body's ability to neutralize them, resulting in damage to cells and tissues [42]. This oxidative burden can impair various cellular constituents, including proteins, lipids, membranes, DNA, and lipoproteins, through chemical alterations. Unrepaired oxidative damage to DNA may promote cell dysfunction, trigger mutations, destabilize the genome, and potentially initiate cancer development [4]. Additionally, reactive oxygen species (ROS) act as molecular signals that activate pathways like NF-κB, a key transcription factor responsible for regulating genes involved in immune responses. Kinases such as NF-κB-inducing kinase (NIK) and protein kinase Akt initiate this pathway by phosphorylating components of the IκB kinase (IKK) complex. This complex includes the subunits IKKα (also called IKK1), IKKβ (IKK2), and IKKγ. Phosphorylation of the inhibitor protein IκB by IKKα and IKKβ results in its breakdown, releasing NF-κB dimers such as RelA. These dimers then move into the nucleus to start the transcription of immune-related genes [43, 34].

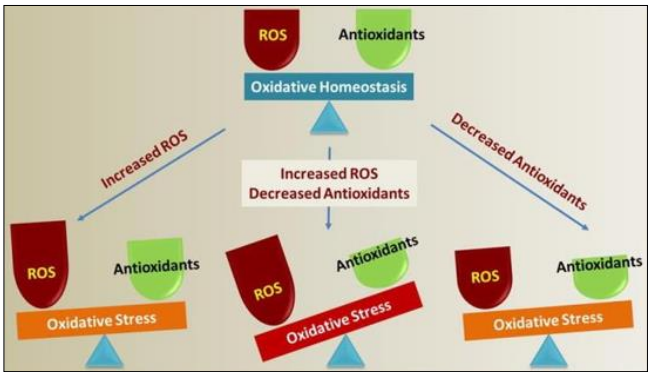


**Fig 5:** Correlation between ROS, antioxidant, and oxidative stress [59]

## Antioxidant

Antioxidants are a group of compounds that function to neutralize free radicals in cells, by donating electrons to reactive free radicals so that they can neutralize the free radicals. Because of their small molecular weight, antioxidants can readily interact with free radicals and halt chain reactions before they cause harm to essential components. Protection against free radical damage serves a vital role in preventing several chronic diseases like anemia, cardiovascular disease, heart disease, cancer, aging, and chronic inflammation (Zehirogl*u et al*., 2019).

Based on their source, antioxidants are grouped into three, namely [45]:

1. Endogenous antioxidants or antioxidant enzymes, namely antioxidants produced in the human body, for example the enzyme superoxide dismutase (SOD), *catalase* (CAT), and glutathione peroxidase (GPx).
2. Synthetic antioxidants, namely antioxidants found in food products such as butyl hydroxy anisole (BHA), propyl gallate and tert-butyl hydroxy quinone (TBHQ), butyl hydroxy toluene (BHT).
3. Natural antioxidants, or antioxidants derived from plant parts that include phenolic compounds (flavonoids) and vitamins A, C, and E, such as wood, bark, roots, leaves, fruit, flowers, seeds, and pollen.

Based on their working mechanism, antioxidants are divided into three, namely [46]:

1. Primary antioxidants, namely antioxidant enzymes produced by the body and function as the body's most powerful safeguarding from free radicals.

There are only 3 primary antioxidants, namely glutathione peroxidase (GPx), superoxide dismutase (SOD), and *catalase* (CAT).

2. Secondary antioxidants, which are hydroperoxide decomposers that play a role in converting hydroperoxides into non-radical and non-reactive products. To produce a synergistic stabilization effect, these compounds are often combined with primary antioxidants. *Glutathione reductase, Glucose-6-phosphate dehydrogenase, ubiquinone* And *glutathione-s-transferase*, is a secondary antioxidant.

3. Tertiary antioxidants, namely antioxidants that function to repair oxidized molecules (several DNA enzymes, proteolytic enzymes, etc.) through sources such as antioxidant supplementation or food.

**SUPEROXIDE DISMUTASE (SOD)**

Superoxide dismutase (SOD) is an enzyme that facilitates the conversion of superoxide into hydrogen peroxide through dismutation:

$$O2^{-} + O2^{-} + 2H^{+} \rightarrow H2O2 + O2$$

This enzyme is sensitive to heat but relatively stable under alkaline conditions, and it can retain its enzymatic activity even after being stored for five years at a temperature of 5°C. Superoxide dismutase (SOD) exhibits its highest activity in organs such as the kidneys, liver, adrenal glands, spleen, brain, blood, ovaries, lungs, stomach, pancreas, intestines, and thymus. The activity of SOD is influenced by the presence of metal cofactors like Cu, Fe, Zn, and Mn, which form the basis for its classification into Cu/Zn-SOD, Mn-SOD, and Fe-SOD types [45].

**Catalase (CAT)**

Catalase is an enzyme that uses iron as a cofactor to initiate the transformation of hydrogen peroxide into water and oxygen. During this process, the iron in catalase is initially oxidized by one hydrogen peroxide molecule to form compound I, and then it returns to its original state through moving the bound oxygen to another hydrogen peroxide molecule [47].

The reactions are as follows:

$$\text{Catalase–Fe(III)} + H_2O_2 \rightarrow \text{Compound I}$$
$$\text{Compound I} + H_2O_2 \rightarrow \text{Catalase–Fe(III)} + 2H_2O + O_2$$

Catalase composed of four protein subunits, each of which contains a heme group and an NADPH molecule. This enzyme is mainly found in peroxisomes, which are organelles that also house enzymes involved in producing hydrogen peroxide. Although catalase is present in all body tissues, it is most abundantly found in the liver and red blood cells [47].

**Glutathione Peroxidase (GPx)**

Glutathione peroxidase is a celloprotein consisting of four protein subunits that catalyze the reduction reaction of H2O2 into organic hydroperoxide compounds (ROOH). Glutathione is predominantly located in the cytosol of liver cells. Within cells, it exists mainly in its reduced form, known as GSH, and to a lesser extent in its oxidized form, referred to as glutathione disulfide (GSSG). The ratio of GSH to GSSG serves as a sensitive marker for assessing oxidative stress levels. GSH with the enzyme glutathione peroxidase (GPx) can catalyze the process of reducing hydrogen peroxide to water [47, 45].

$$Fe^{2+} + H2O2 \longrightarrow Fe^{3+} + OH + OH$$
$$GSH + OH \longrightarrow GS + H2O$$
$$GS + GS \longrightarrow GSSG$$
$$2\ GSH + ROOH \Rightarrow GSSG + ROH + H2O$$

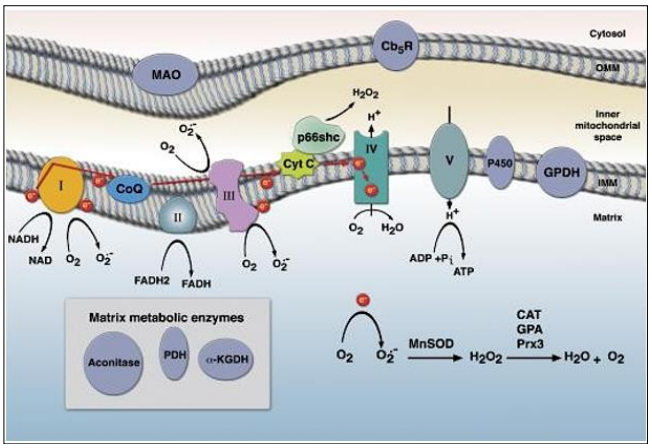


**Fig 6:** Mechanism of action of enzymatic antioxidants [60]

**Discussion**

Smoking has become part of everyday activities for Indonesian people. Based on the Central Statistics Agency (2023), smoking in adolescence or young adulthood in Indonesia in 2022 was quite high with a higher percentage of men than women. Adolescence is a vulnerable age because of the high level of curiosity and search for identity and the tendency to be easily influenced by the surroundings around. Numerous studies have demonstrated that smoking typically starts in adolescence, namely between the ages of 15 and 19. Cigarettes contain toxins that have an effect on immune modulation and increase morbidity and mortality for the body due to cancer induction. Cigarette consumption causes chronic inflammation on the mucosal surface, changes the host response to exogenous antigens, and on immunity can be in the form of pro-inflammatory induction or suppressive effects and interfere with the response. Innate body against pathogens, modulation of antigen presentation, and autoimmune induction. The effect of smoking on inflammatory conditions can be observed, one of which is through IL-8 secretion. IL-8 acts as a regulator in the acute inflammatory response by attracting and activating neuthrophils and monocytes at the inflammation site.

IL-8 is a chemokine from the CXC group that is actively produced by monocytes, endothelium, epithelium, and smooth muscle in the respiratory tract. The production of IL-8 in the human system that smokes can be induced by several factors, namely stress, environment, chemicals, inflammatory signals, and steroids. The increase in IL-8 secretion in smokers is due to oxidative stress induced together with pro-inflammatory conditions, this causes the IL-8 secretion rate to be greater in smokers than in non-smokers [49]. The pro-inflammatory properties of IL-8 cause growth suppression in normal cells, but in cancer cells IL-8 causes division, alteration, and invasion. Tumor suppression with the Nf-κB pathway.

Another research by Sahibzada *et al* [49] showed that smokers' saliva had higher levels of IL-8, which found that tobacco use in any form can induce oxidative stress in cells, as indicated by elevated malondialdehyde (MDA) levels. This oxidative stress triggers a pro-inflammatory cycle, leading to higher cytokine production. The study also found a correlation between the quantity of cigarettes smoked daily and increased MDA levels, reinforcing the link between tobacco exposure, oxidative stress, and inflammation.

Cigarette smoke is recognized by the body as a harmful toxin, which triggers an inflammatory response. This response

involves enhanced secretion of IL-8, stimulated by activation of the NF-κB pathway through IKK. IL-8 is released in reaction to diverse signals, including stress, environmental factors, steroids, and inflammatory signals. These stimuli activate the NF-κB signaling pathway, leading to elevated IL-8 release. This highlights the key role of NF-κB in mediating the inflammatory effects of cigarette smoke, which not only enhances IL-8 secretion but also increases the levels of other chemokines, like monocyte chemotactic protein-1 (MCP-1).

IL-8 is also produced locally in muscle tissue during physical activity, particularly noticeable after exercises involving eccentric contractions. IL-8 functions through two receptors—CXCR1 and CXCR2—which share structural similarities but differ in their antigenic properties (Rezai *et al*., 2019). When IL-8 binds to CXCR1 and CXCR2, it activates signaling pathways involving STAT3 and β-catenin, promoting cell proliferation and angiogenesis. Angiogenesis, or the development of new blood vessels from current vasculature, is promoted by various cells including mast cells, fibroblasts, and macrophages. Macrophages contribute by releasing cytokines and angiogenic factors that strongly support this process. The angiogenic function of IL-8 is distinct from its pro-inflammatory role. Specifically, CXCR2, expressed on microvascular endothelial cells, mediates IL-8-driven angiogenesis. Additionally, Exercise has been shown to enhance the expression of CXCR2 mRNA and protein in the vascular endothelial cells of muscles, suggesting the IL-8 generated in muscle primarily promotes angiogenesis locally [50].

Innate immune system cells and macrophages create the pro-inflammatory cytokine TNF-α. Most of them are Antigen Presenting Cells (APCs) that participate in directing cell movement and triggering the activation of adaptive immunity together with interleukins, like IL-1β, IL-6, IL-1α, and IL-8, to integrate innate and adaptive immunity. TNF-α secretion is found in both chronic and acute inflammatory conditions. Smoking can stimulate TNF-α secretion which causes chronic inflammation that triggers tissue damage. With this inflammation, APC will respond by moving towards damaged tissue and producing TNF-α. Therefore, TNF-α in subjects who smoke will be higher compared to non-smokers. The important function of TNF-α is to initiate immunological responses. TNF-α affects almost all types of cells and is involved in blood clotting, metabolism, growth, differentiation, and cell death. The cytokine TNF-α is trimeric and exists in two forms, namely trans membrane (mTNF) and soluble (sTNF) [51]. The two TNF receptors, TNF receptor 1 (TNFR-1) and 2 (TNFR-2) have different ligands and are activated by TNF isoforms in different ways. However, their actions and pathways may seem counter-intuitive. All TNFR-1 cell types have a death domain with a signaling protein that links them to cytotoxic pathways and activates MAP kinases and nuclear factor kappa B (NFkB) [52]. By suppressing cytotoxic signals, TNFR-1 activation can lead to cell survival processes. TNFR-2 can activate several kinases and NFkB signals, but does not have a death domain [53]. Although it may also be expressed by non-immune cells like fibroblasts, TNFR-2 is mostly found in immune cells where it functions to regulate inflammation and immune responses [54].

Inhalation of cigarette smoke in the body is considered an irritant component that can stimulate inflammatory responses, ROS activation, and apoptosis. Toxins in cigarettes directly affect the decrease in antioxidant levels in serum, resulting in oxidative stress, increased lipid peroxidation products, atherogenesis, and platelet aggregation. Oxidative stress is caused by an unequal distribution of pro-oxidants and antioxidants, due to excessive ROS production. Fitness level plays a big role inover release of ROS and antioxidant enzyme activity. Antioxidant capacity, which rises to counteract ROS and shield bodily cells, is frequently employed as a gauge of oxidative stress. Different antioxidant enzymes and antioxidant systems are developed by body cells to defend against attacks by free radicals.

The main defense mechanism against free radicals created from oxygen is superoxide dismutase (SOD). SOD is a muscle antioxidant that increases during exercise [55]. By accelerating the transformation of superoxide anions into hydrogen peroxide (H2O2), SOD directly degrades superoxide in the extracellular matrix of the lungs. SOD activity will increase in the group given exercise treatment. The decomposition of superoxide can reduce fibroblast stimulation and reduce the recruitment of inflammatory cells so that it can reduce damage to lung tissue [56, 57].

Superoxide dismutase (SOD) is essential for protecting the body from oxidative stress, as are other muscle antioxidants like glutathione reductase (GR) and glutathione peroxidase (GPx). By lowering hydrogen peroxide ($H_2O_2$) levels, GPx specifically protects the lungs and aids in maintaining the balance of oxidative and antioxidative systems in lung tissue. The metabolism of vital trace elements, including iron, which is required for catalase (CAT) function, and copper and zinc, which are cofactors for SOD, is disturbed by cigarette smoke. As a result, cigarette smoke can decrease the effectiveness of these antioxidant enzymes. Both catalase and GPx contribute to antioxidant defense by breaking down H2O2 into water and oxygen. GPx primarily eliminates organic peroxides at low concentrations, while CAT handles the detoxification of higher concentrations of H2O2.

## Conclusion

Cigarettes can trigger chronic inflammation in the body by increasing the production of IL-8, TNF-α, and salivary ROS.

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