

Adverse Effects and Therapeutic Potential of Nicotine: A Review

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Abstract Nicotine, a potent alkaloid present in tobacco, is well-known for its highly addictive nature and significant health hazards, such as cancer, heart disease, and respiratory diseases. This review delves into nicotine's comprehensive impact on various biological systems and overall health. It provides a detailed examination of nicotine's detrimental effects on the brain, cardiovascular, respiratory, immune, and reproductive systems, alongside its profound implications for mental health. Despite its well-documented adverse effects, emerging research highlights potential cognitive benefits of nicotine in neurodegenerative conditions such as Parkinson's and Alzheimer's diseases. Specifically, nicotine has demonstrated promise in improving cognitive function in Alzheimer's disease and alleviating dyskinesia and memory problems in Parkinson's disease. These therapeutic effects are thought to be mediated through mechanisms involving Sirtuin 6 inhibition, enhanced protein kinase B activity, and stimulation of phosphoinositide 3-kinase/Akt signaling pathways. Furthermore, this review explores the dual nature of nicotine's impact, emphasizing both its severe health risks and its potential therapeutic benefits, particularly in the context of cognitive disorders. The analysis aims to provide a balanced perspective on nicotine, acknowledging its harmful consequences while also considering its possible utility in specific medical scenarios.

Understanding these complex dynamics is crucial for developing effective public health strategies and therapeutic interventions that can mitigate nicotine's risks while potentially harnessing its benefits for treating neurodegenerative diseases. Such a nuanced approach is essential for informing public health policies and advancing therapeutic research, ultimately contributing to improved health outcomes.

Keywords Addiction, Cognitive Function, Dopamine, Nicotine, Nicotinic Acetylcholine Receptors, Oxidative Stress, Synaptic Plasticity

1. Introduction

Pharmacology has undergone rapid advancements in recent decades, improving our understanding of drug mechanisms, aiding the discovery of new therapeutic agents, and enhancing our ability to treat various diseases. These advancements have revolutionized areas such as drug discovery, personalized medicine, and pharmacogenomics [1]. High-throughput screening and molecular biology techniques now allow for personalized

medicine, tailoring treatments to individual genetic profiles, which has significantly improved patient outcomes. One of the most impactful innovations in modern pharmacology is the development of biologics, such as monoclonal antibodies. These biologics have transformed the treatment landscape for diseases like cancer, autoimmune disorders, and infectious diseases by offering highly targeted therapies with improved efficacy and fewer adverse effects in comparison to traditional small-molecule medications [2]. Additionally, advancements in drug delivery systems, including nanoparticles, have allowed for more precise targeting of drugs to specific tissues or cells, further improving therapeutic outcomes and minimizing toxicity.

This review focuses on nicotine, a well-known psychoactive compound found primarily in the leaves of the tobacco plant, as well as in other members of the Solanaceae family like tomatoes and potatoes [3]. The chemical formula of nicotine is $C_{10}H_{14}N_2$, with a molecular weight of 162.23 g/mol. Despite being highly addictive, nicotine is also a subject of interest for its therapeutic potential, particularly in smoking cessation and cognitive enhancement. However, nicotine addiction remains a major public health concern, contributing to a variety of health problems, such as cancer, heart disease, and respiratory disorders [4]. The complex biological mechanisms that drive nicotine addiction continue to be an area of extensive research.

Nicotine primarily affects the central nervous system by activating nicotinic acetylcholine receptors (nAChRs), which triggers the release of dopamine and other neurotransmitters linked to pleasure and reward. This process contributes to nicotine's addictive properties. Moreover, nicotine impacts various bodily systems, including the cardiovascular and immune systems. While its addictive potential is clear, numerous animal and human studies have also explored nicotine's effects on cognition, with findings indicating that nicotine can enhance attention, memory, and cognitive flexibility, especially in individuals with cognitive impairments or neurodegenerative conditions [5]. Chronic nicotine exposure, however, is linked to cognitive decline, indicating that its effects may vary depending on usage patterns.

Tobacco smoking, however, is more than just nicotine addiction. The severe health risks associated with smoking arise from the thousands of other harmful chemicals in tobacco products, including carcinogens, toxicants, and carbon monoxide. These substances, rather than nicotine itself, are primarily responsible for the heightened risk of cancer, cardiovascular disorders, chronic obstructive pulmonary disease (COPD), and stroke [6]. Smoking is also particularly dangerous during pregnancy, as it increases the risk of adverse outcomes such as ectopic pregnancy, low birth weight, and premature birth. Children exposed to secondhand smoke face elevated risks of respiratory diseases, cognitive and behavioral problems, and sudden infant death syndrome (SIDS) [7].

Nicotine, when isolated from the harmful chemicals in

tobacco, plays a significant role in smoking cessation therapies. Nicotine replacement therapies (NRTs), such as patches, gum, and lozenges, have been proven effective in helping smokers quit by reducing withdrawal symptoms. Additionally, electronic nicotine delivery systems (ENDS), such as e-cigarettes, are newer alternatives that may help reduce the harms of traditional smoking by delivering nicotine without the toxic byproducts of combustion [8]. However, the long-term safety and efficacy of ENDS remain subjects of ongoing research and debate.

In this review, we will provide a comprehensive exploration of nicotine, including its adverse health effects, its role in addiction, and its potential therapeutic benefits. We will also delve into the historical context of nicotine use and discuss the complex interplay between its harmful and beneficial effects on cognition and health.

2. Nicotine Sources and Consumption

Nicotine is consumed in diverse forms, reflecting the range of products derived from the tobacco plant and the emergence of alternative nicotine delivery systems. Traditional combustible cigarettes remain the most prevalent form of nicotine consumption, exposing users to nicotine through inhaled tobacco smoke [9]. Smokeless tobacco products, such as chewing tobacco and snuff, offer an alternative route of absorption through the oral mucosa, albeit with associated health risks, including an elevated risk of oral cancers and gum diseases [10]. Electronic cigarettes (e-cigarettes) have gained popularity as a smoke-free alternative, heating a liquid (often containing nicotine) into an inhalable aerosol, although the long-term health effects are still under investigation [11]. Nicotine Replacement Therapies (NRTs), such as patches, gum, lozenges, inhalers, and nasal sprays, are designed to help people stop smoking by delivering regulated amounts of nicotine without the dangerous chemicals present in tobacco smoke [12]. Each form of nicotine consumption has unique pharmacokinetic profiles and health implications, reflecting ongoing efforts to address both nicotine addiction and associated health risks.

Trends in nicotine consumption have evolved significantly, shaped by cultural, social, economic, and regulatory factors. Historically, traditional tobacco use, such as cigarettes, cigars, and smokeless tobacco, dominated. Recently, there has been a notable shift towards electronic cigarettes (e-cigarettes) and other vaping devices, particularly among younger people, sparking concerns about a new generation of nicotine users [13]. Nicotine replacement therapies (NRTs), including patches, gum, lozenges, inhalers, and nasal sprays, have become key tools in smoking cessation efforts. These trends are continuously influenced by scientific advancements, public health initiatives, and regulatory measures, highlighting the importance of monitoring for effective interventions and policies to reduce nicotine use and its health risks.

3. Pharmacokinetics of Nicotine

Nicotine enters the body quickly through various methods, like inhaling smoke from cigarettes or using smokeless tobacco. Once absorbed, it travels throughout the body and reaches the brain quickly [14]. The liver breaks down nicotine, with cotinine as a main byproduct [15]. This breakdown can vary depending on a person's genes. Finally, the body gets rid of nicotine and its waste products mainly through urine [16]. Knowing how nicotine moves through the body (pharmacokinetics) is important to understand its effects, design ways to help people quit smoking, and predict how individuals will react to nicotine products.

Nicotine pharmacokinetics are influenced by various factors, contributing to the considerable inter-individual variability in responses to nicotine-containing products. Age-related changes, such as altered metabolism and clearance, can impact nicotine kinetics, with older individuals potentially experiencing slower nicotine elimination. Gender differences also play a role, with

women generally metabolizing nicotine more rapidly than men, influenced by hormonal fluctuations. Genetic factors, particularly variations in cytochrome P450 enzymes, notably CYP2A6, contribute significantly to individual differences in nicotine metabolism [17]. Liver and renal functions are critical determinants, affecting the metabolism and elimination of nicotine. Individuals with impaired liver or renal function may experience altered nicotine clearance, influencing overall pharmacokinetics.

4. Impacts of Nicotine on Health

The effects of nicotine on biology are complex, which shows effects on different parts of the body like brain, cardiovascular system, respiratory system, and immune system. Figure 1 depicts the effect of nicotine on health. This review will explore the impact of nicotine on biology, highlighting the current understanding of the mechanisms underlying its harmful effects. The impacts of Nicotine on various biological systems were reported below.

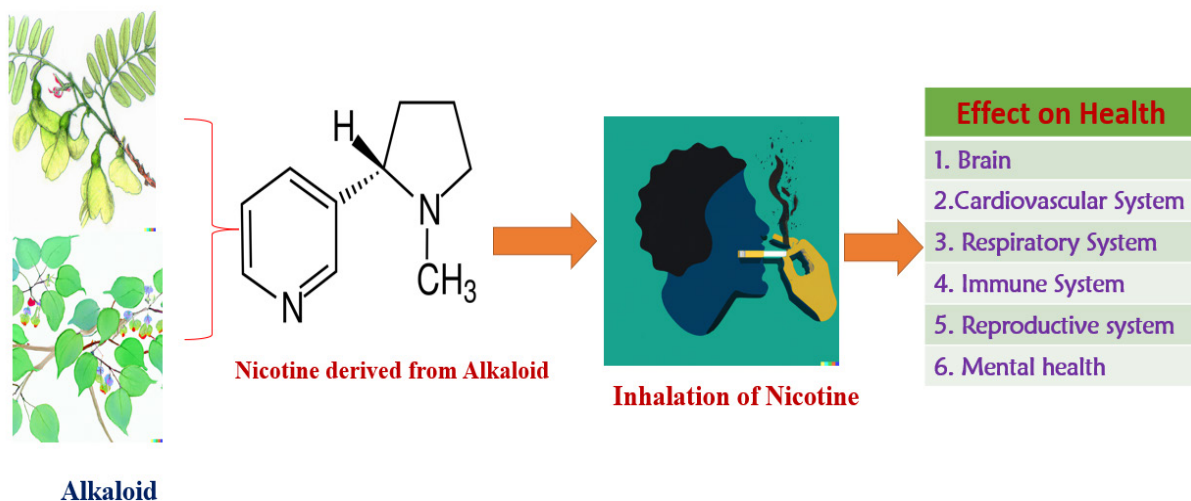


Figure 1. Effects of Nicotine on human health

4.1. Effect on the Brain

Nicotine is a psychoactive substance that can have various effects on the brain. When nicotine is ingested through smoking or other means, it rapidly enters the bloodstream and passes through the blood-brain barrier. Once it reaches the brain, nicotine binds to nicotinic acetylcholine receptors (nAChRs), leading to the release of several neurotransmitters, including dopamine, norepinephrine, and acetylcholine, which can affect mood, attention, and cognition. Studies show that structure and function of the brain change when continuing use of nicotine, including alterations in the density and circulation of nAChRs and changes in synaptic plasticity [18]. Nicotine absorption occurs as it travels from the lungs to the brain via arterial circulation, where it binds to nicotinic cholinergic receptors-ligand-gated ion channels that normally interact with acetylcholine. The development of nicotine dependence is mainly triggered by nicotine binding to the junction between two receptor subunits [19]. When the gene for the 2 subunits is disrupted in mice, nicotine's behavioural effects are lost; however, when the gene is put back into the ventral tegmental region, the behavioural effects of nicotine are recovered.

Additionally, nicotine can increase the activity of different parts of brain regions, such as the prefrontal cortex and hippocampus, which are involved in learning and memory. However, the effects of nicotine can also be negative, including addiction, increased heart rate, and elevated blood pressure. Some studies revealed the effects of nicotine on the brain and found that nicotine administration can improve cognitive performance in tasks requiring attention and working memory [20]. Palmatier et al [21] reported that smokers had less activity in the prefrontal cortex during a working memory task compared to non-smokers, suggesting that chronic nicotine use may lead to changes in brain function. These findings suggest the effects of nicotine on the brain may vary depending on the age of the individual and the duration of nicotine use.

4.2. Effect on the Cardiovascular System

Nicotine is a potent vasoconstrictor, which means it narrows the blood vessels and can increase blood pressure. Smoking and other forms of nicotine use can increase the risk of cardiovascular disease, heart attacks, and strokes [22]. Nicotine causes the release of adrenaline, which can increase heart rate and blood pressure, and also increases the risk of blood clots by making blood stickier [23]. Moreover, nicotine can harm the inner lining of blood vessels, facilitating the accumulation of fatty deposits and contributing to atherosclerosis, a condition characterized by the hardening and narrowing of the arteries. The negative cardiovascular effects of nicotine can be seen even in occasional smokers and users of other nicotine products.

Kaur et al. [24] investigated the impact of nicotine on the

cardiovascular system and discovered that smoking a single cigarette can cause instant harm to the blood vessel lining, resulting in decreased blood flow and a heightened risk of heart attack and stroke. Heiss et al [25] found that smoking and other forms of nicotine use can lead to an increased risk of atherosclerosis and cardiovascular disease, even in individuals who do not have traditional risk factors such as high blood pressure or high cholesterol. These findings suggest that the negative cardiovascular effects of nicotine are not limited to heavy smokers, but can also affect occasional smokers and other users of nicotine products.

Nicotine use can have a significant negative impact on the cardiovascular system, increasing the risk of cardiovascular disease, heart attacks, and strokes. Nicotine causes vasoconstriction, elevated blood pressure, and increased heart rate, as well as damaging the inner lining of blood vessels and leading to atherosclerosis. These effects can be seen even in occasional smokers and users of other nicotine products. The best way to protect the cardiovascular system from the negative effects of nicotine is to quit smoking and other forms of nicotine use altogether.

4.3. Effect on the Respiratory System

Nicotine can cause damage to the lining of the lungs, leading to inflammation, scarring, and an increased risk of lung cancer [26]. It can also cause increases in mucus production and airway resistance, leading to breathing difficulties. Nicotine is a potent respiratory stimulant, which means that it can cause an increase in breathing rate and depth. However, despite its respiratory stimulant properties, nicotine is also a harmful substance that can have negative effects on the respiratory system. Inhalation of nicotine, whether through smoking or other forms of nicotine use, can cause damage to the lungs and airways, leading to a range of respiratory problems [27]. Nicotine use has been linked to chronic bronchitis, emphysema, asthma, and other respiratory disorders.

The negative effects of nicotine on the respiratory system are not limited to smokers. Secondhand smoke and other forms of exposure to nicotine can also have harmful effects on lung function and respiratory health. Eisner et al [28] found that exposure to secondhand smoke in childhood was associated with an increased risk of developing chronic obstructive pulmonary disease (COPD) in adulthood. Jaakkola et al [29] reported that even short-term exposure to secondhand smoke can cause significant damage to the respiratory system, increasing the risk of respiratory infections and exacerbating existing respiratory conditions.

Nicotine use can negatively impact the respiratory system, contributing to various respiratory issues such as chronic bronchitis, emphysema, and asthma. These effects can be seen not only in smokers but also in individuals

exposed to secondhand smoke and other forms of nicotine use. The best way to protect the respiratory system from the negative effects of nicotine is to quit smoking and other forms of nicotine use altogether.

4.4. Effect on the Immune System

Nicotine use has been linked to adverse effects on the immune system, increasing the risk of infections and autoimmune diseases. Nicotine can cause alterations in immune cell function, leading to decreased immune responses to pathogens and increased inflammation. Nicotine has been shown to have a complex effect on the immune system, with both immunosuppressive and immunostimulatory effects [30]. Jin et al [31] revealed that nicotine can modulate the immune response in various ways, such as altering cytokine production, affecting immune cell function, and suppressing the adaptive immune response. Sopori et al found that nicotine may have potential therapeutic applications for autoimmune disorders, such as multiple sclerosis, while other studies have found that nicotine can impair immune function and increase susceptibility to infections [32].

Nicotine use has been shown to increase the risk of respiratory infections, such as pneumonia, and to impair the immune response to viral infections such as influenza. Additionally, nicotine use has been linked to an increased risk of certain types of cancer, which may be related to its effect on the immune system [33]. Overall, the effect of nicotine on the immune system is complex and depends on many factors, including the dose and duration of exposure. While nicotine may have potential therapeutic applications, its negative effects on the immune system highlight the importance of reducing nicotine use to promote overall health and well-being.

4.5. Effect on the Reproductive System

Nicotine use can adversely affect the reproductive system in both men and women. In women, smoking during pregnancy can result in complications like premature birth, low birth weight, stillbirth, and miscarriage. Exposure to nicotine can also harm fetal development, including brain development, and increase the risk of sudden infant death syndrome (SIDS) [34]. In men, nicotine use has been shown to reduce sperm count and affect sperm quality, leading to infertility. Nicotine use has also been linked to erectile dysfunction and impotence in men. Quitting nicotine use can improve reproductive health and increase the chances of a healthy pregnancy and successful conception.

4.6. Effect on Mental Health

Nicotine has been shown to have significant effects on mental health, particularly in individuals with pre-existing mental health conditions [35]. Studies have found that nicotine use can worsen symptoms of anxiety and depression, increase the risk of developing psychiatric disorders such as schizophrenia, and decrease overall cognitive function. Nicotine use has also been linked to increased stress levels and decreased ability to cope with stress [36,37]. However, some individuals report that nicotine use can temporarily improve mood and alleviate symptoms of anxiety or depression, which may contribute to its addictive properties. Individuals with mental health conditions should be mindful of the potential harmful effects of nicotine use and seek treatment for addiction when needed.

4.7. Changes in Drug Metabolism and Addiction Liability

Research suggests that early exposure to nicotine can increase the risk of nicotine addiction and related disorders later in life. This heightened sensitivity may be due, in part, to changes in nicotine metabolism caused by prenatal exposure to cigarette smoke or nicotine. Studies on mice have found that those exposed to nicotine prenatally, either through cigarette smoke or directly, had elevated levels of nicotine metabolism enzymes in their livers, both as adults and as neonates. These elevated levels could contribute to increased susceptibility to nicotine addiction [38]. Neonatal and adult mice exposed to nicotine prenatally through cigarette smoke exhibited elevated liver Cyp2a5 mRNA expression, higher DNA methylation in the Cyp2a5 promoter region, and reduced levels of the DNA methyltransferase Dnmt1. In a similar study, male mice exposed to nicotine before birth also showed increased Cyp2a5 mRNA expression. Postnatal treatment further increased the conversion of nicotine to cotinine [39]. Nicotine metabolism involves Cyp2a5 [40]. While the connection between increased Cyp2a5 expression and DNA methylation of the Cyp2a5 promoter region is unidentified it is well known that higher nicotine metabolism is linked to a higher risk of nicotine addiction [41]. So, it would stand to reason that prenatal nicotine exposure would raise the likelihood of subsequently acquiring a nicotine addiction. To support this claim, prenatal nicotine exposure was linked to a 5.5-fold higher risk of youth tobacco use [42], a risk that was not significantly impacted by mother cigarette use at the time of the study's completion.

Table 1. Biological impacts induced by Nicotine

System Affected	Impact	Reference
Brain	<ul style="list-style-type: none"> Addiction and dependence Increased alertness and focus (short-term) Altered mood and reward processing Impaired memory and learning 	[45, 46]
Cardiovascular system	<ul style="list-style-type: none"> Increased heart rate and blood pressure Risk of arrhythmias Increased risk of heart attack and stroke 	[47]
Respiratory System	<ul style="list-style-type: none"> Irritation of airways Increased risk of chronic obstructive pulmonary disease 	[48]
Digestive System	<ul style="list-style-type: none"> Increased stomach acid secretion Ulcers 	[49]
Reproductive System	<ul style="list-style-type: none"> Decreased fertility in men and women Increased risk of miscarriage and premature birth 	[46, 50, 51]
Cancer	<ul style="list-style-type: none"> Increased risk of various cancers, including lung, esophagus, and pancreatic cancer 	[52,53]
Immune System	<ul style="list-style-type: none"> Suppressed immune function Increased susceptibility to infection Impaired wound healing 	[46]
Mental Health	<ul style="list-style-type: none"> Increased anxiety and stress Symptoms of depression Difficulty concentrating 	[46,47]
Endocrine System	<ul style="list-style-type: none"> Disrupting hormonal balance and altering the function of glands such as the adrenal, pituitary, and thyroid. Increased secretion of stress hormones like cortisol and adrenaline, 	[45,46]

4.8. Diabetes Susceptibility

As previously mentioned, prenatal nicotine exposure is linked to lower birth weight, which is a marker for an elevated risk of diseases such as diabetes. To explore the potential impact of prenatal nicotine exposure on pancreatic function, pregnant rats were given daily nicotine doses, and the pancreatic tissue of the newborn rats was analyzed for alterations in gene expression and histone methylation [43]. Prenatal nicotine exposure elevated p66shc expression in the pancreas in neonates. Apoptosis and reactive oxygen species are regulated by p66shc. The expression of the lysine demethylase Kdm4c was upregulated along with the expression of p66shc, while histone H3 methylation was downregulated in the pancreas. Nicotine exposure during pregnancy and in the newborn period caused pancreatic cell malfunction and mitochondrial damage, both of which are linked to type2 diabetes [44]. This suggests that nicotine exposure during pregnancy may increase children's susceptibility to type 2 diabetes and pancreatic disorders, potentially leading to epigenetic modifications associated with oxidative damage in the pancreas. Nicotine elicits a range of biological effects, which are detailed in Table 1.

5. Therapeutic Effects of Nicotine

Nicotine, despite its well-known addictive properties

and health risks, has shown potential therapeutic benefits in the treatment methods of neurodegenerative diseases like Parkinson's disease and Alzheimer's disease. These therapeutic effects are primarily due to nicotine's interaction with neurotransmitter systems in the brain and its neuroprotective properties.

5.1. Therapeutic Effects of Nicotine on Alzheimer's Disease

Despite negative effects of nicotine, recent research suggests a potential therapeutic effects of nicotine in treating Alzheimer's disease (AD) [46]. In AD, the loss of cholinergic neurons and abnormal nAChR function contribute to cognitive decline. The $\alpha 7$ -nAChR subtype plays a critical role in cholinergic anti-inflammatory activity, which is crucial for brain health. Theoretically, nicotine agonists that target these receptors could improve cognition by stimulating cholinergic pathways, modulating inflammation, and mitigating the negative effects of amyloid-beta plaques, all of which contribute to AD progression. However, clinical trials have shown mixed results, with some observing minimal cognitive improvement and others reporting adverse effects [45]. Nicotine administration may improve cognitive impairment in AD patients, and acute nicotine administration during electroencephalography can shift electroencephalography (EEG) readings towards normal

levels. Given the established health risks of nicotine, further research is necessary to determine if the potential benefits outweigh the risks for treating AD.

5.2. Therapeutic Effects of Nicotine on Parkinson's Disease

Parkinson's disease (PD), is a common neurological disturbance that basically impacts old-aged individuals. This condition results from the degeneration of neurons that produce dopamine in a specified region of brain. This loss of dopamine leads to motor symptoms like tremors, stiffness, and difficulty moving. Nicotine has been shown to protect neurons and decrease the likelihood of developing Parkinson's disease. It may also help improve symptoms like dyskinesia and memory impairments. Nicotine activates pro-survival signalling pathways and inhibits SIRT6, an NAD⁺-dependent class III deacetylase, slowing PD progression [54]. Further investigation is needed to understand its downstream effects on SIRT6 in PD.

6. Mechanism of Action of Nicotine

Nicotine, the primary addictive component of tobacco, has a complex mechanism of action on human health. When nicotine enters the body, it binds to nAChRs i.e., Nicotinic acetylcholine receptors of the brain, resulting in the release of dopamine, norepinephrine, and serotonin etc., that act as neurotransmitters. This release of neurotransmitters creates a pleasurable sensation, leading to the reinforcing effects of nicotine and the development of addiction.

Three main methods by which nicotine works to affect various organ systems physiologically and pathologically are described [55,56].

- 1 Ganglion related transmission.
- 2 Catecholamines effect on nAChRs of chromaffin cells.
- 3 nAChRs mediated stimulation of Central nervous system (CNS).

Research has shown that nicotine can show a profound impact on brain function, particularly in the regions of prefrontal cortex and visual systems. This is due to the release of neurotransmitters, which play a crucial role in associated response for drug use. Additionally, nicotine has been found to increase of oxidative stress, peroxidation of lipids, and DNA damage, which results in the cell damage and apoptosis. Furthermore, studies have revealed that nicotinic receptors are not limited to neuronal cells, but are also present in non-neuronal tissues. While previous research suggested that nicotinic receptors (nAChRs) were primarily found in the nervous system, more recent studies have identified functional receptors in various tissues throughout the body. The activation of these receptors can have both short-term and long-term effects on organ

systems, cell division, and apoptosis. Overall, nicotine's impact on the body is complex and multifaceted, with both positive and negative effects on various physiological processes.

7. Conclusions

Nicotine, a major active component in tobacco, significantly impacts various physiological systems and presents both risks and therapeutic potentials. This comprehensive review outlines nicotine's pharmacokinetics, detailing its absorption, distribution, metabolism, and excretion. We have explored nicotine's interactions with neurotransmitters and its consequential effects on cardiovascular, respiratory, immune, reproductive, and mental health. Notably, nicotine's role in cognitive function and its potential implications for neurodegenerative diseases such as Alzheimer's and Parkinson's disease have been highlighted, with a particular emphasis on its interaction with cholinergic neurons and nAChRs. Therapeutic applications of nicotine, particularly in NRT and ENDS, offer promising avenues for smoking cessation and harm reduction. However, the health risks associated with nicotine, including its contribution to cardiovascular diseases, respiratory issues, immune system dysfunctions, and negative reproductive and developmental outcomes, underscore the need for cautious application of these therapies.

Moreover, the emerging understanding of nicotine's impact on metabolic pathways, such as the Sirtuin 6 and Protein kinase B signaling, suggests a complex interplay between nicotine use and metabolic diseases like diabetes. The potential epigenetic changes induced by nicotine also warrant further investigation, particularly concerning prenatal exposure and long-term health effects. In conclusion, while nicotine's addictive properties and health risks are well-documented, ongoing research into its molecular mechanisms and therapeutic potential continues to offer new insights. Future studies should aim to balance the benefits of nicotine-based therapies with their potential health risks, ensuring informed and safe usage. The development of targeted interventions and public health policies will be crucial in managing nicotine's impact on health globally.

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