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Ways to Reduce the Health Risks of Cigarettes in the Next Decade

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Abstract:

In modern life, people are always troubled by various stresses, and many people think that smoking is a good way to relieve stress, so whenever they feel tired or encounter difficulties, they choose to smoke to relieve stress. It is one of the major public health issues worldwide. People are more likely to develop various cancers as the amount of cigarettes they smoke increases. Smoking affects our respiratory system (chronic bronchitis, emphysema), digestive system (overproduction of gastric juice and saliva), and nervous system (mental decline, stroke). Over the past two decades, a series of measures have been taken at the national and scientific levels to address the impact of smoking on human health. In 2004, scientists developed e-cigarettes as an alternative to traditional cigarettes. Later, at the biological level, scientists conducted research on drug treatment and reducing the nicotine content of tobacco leaves, and both made significant discoveries.

Keywords: *health, tobacco, nicotine*

1. Introduction

Smoking remains the leading cause of preventable disease and premature death in most countries. In the United States, approximately 435,000 people die prematurely each year from smoking-related diseases. All in all, smoking kills 1/5 of the number of people who die each year. Lifelong smokers have about a 50% chance of dying prematurely from complications caused by smoking [1]. Cigarettes, which contain nicotine, tar and other ingredients, are still one of the most popular products in the present life. Hundreds of ingredients are harmful to the human body, for instance, many carcinogens in tobacco leaves. Nicotine is the main ingredient in smoking addiction. Because of its existence, people cannot control smoking. Reducing nicotine intake can not only reduce peoples' demand for cigarette products but also help peoples' physical health. Smoking has serious effects on the human respiratory system (chronic bronchitis, emphysema), digestive system (excessive secretion of gastric juice and saliva), and nervous system (mental decline, stroke). SDG3 (Sustainable Development Goals) involves achieving human health and well-being. The impact of smoking on human health is a sub-goal of the Sustainable Development Goals, so solving this problem is also an important step in achieving sustainable development.

2. Smoking Status

According to Forouzanfar et al., the article tells about the problems caused by smoking, which is one of the major public health problems worldwide [2]. In modern life, people are always troubled by all kinds of pressure, and many people think that smoking is a good way to release pressure, so whenever they feel tired or meet difficulties, they choose smoking to release the pressure [3]. However, long-term smoking will make people's nerves under the influence of the influence of cigarette use and smoking behavior becomes difficult to control. When people try to stop smoking, smokers will feel uncomfortable because they have not smoked for a long time, and a condition called withdrawal syndrome will occur, which usually makes people anxious. Attention loss, mood depression and other symptoms [4]. Excessive use of cigarettes will make people prone to serious diseases. Lung cancer, as one of the diseases caused by smoking, is also one of the cancers with the highest risk. As smoking increases, people are more likely to suffer from various types of cancer [5]. Based on knowledge related to biology, biological solutions can start from three directions: animals, plants and microorganisms. Next, the article will discuss and evaluate botanical experiments (reducing the synthesis of nicotine in tobacco leaves) and zoological experiments (drugs that reduce nicotine levels in the blood). This article shows the scientific research results on tobacco leaves and drugs in the past 20 years, as well as the investigation on the use of e-cigarettes. Demonstrate effective results in reducing the use of traditional cigarettes from these three aspects.

3. Statistics on E-cigarette Therapy

E-cigarettes are one of the must-have items for many smokers in their lives now. Because of its particularity: it can be used on many occasions. Therefore, many smoking enthusiasts choose to buy and use them. The initial purpose of the birth of e-cigarettes was to reduce the use of traditional cigarettes and achieve the result of smoking cessation. Although the current quality of the evidence is low, e-cigarettes may help smokers quit [6,7]. The statistics are given in a 2018 article titled Electronic Cigarette: a longitudinal study of regular vapers. A total of 3868 regular e-cigarette users registered on the Internet between 2012 and 2015 were surveyed for one month (n = 1631, 42%), three months (n = 1337, 35%), six months (n = 1148, 30 %) and 12 months (n = 893, 23%). The results obtained were as follows: the median time of participants vaping was five months. The majority (77%) were former smokers who had not smoked for an average of three months. Over a 12-month period, the most frequently cited reason for vaping was enjoyment (93%), while the number of people vaping in order to reduce the need for tobacco fell from 87% to 56%. In e-cigarette-only users, the nicotine concentration in the e-liquid decreased from 12 mg/ml to 9 mg/ml over time, but the number of puffs per day remained stable at 200 puffs per day. After 12 months, 9% of 687 ex-smokers relapsed and 64 of 28 daily smokers (dual users). After 12 months, when participants stopped vaping, they tended to smoke again. When ex-smokers return to smoking, they tend to stop vaping. Therefore, enjoyment and prevention of relapse are the most important reasons for vaping. Previous smokers have a lower rate of relapse, while current smokers have a higher rate of quitting. Stopping vaping is associated with re-smoking. E-cigarettes are not a good solution to the problem of smoking, and more effective solutions should continue to be found [6].

3.1 . NtARF6: Addressing Nicotine Synthesis at the Plant Level

An article published in 2021 titled Transcriptomic Analysis provides insights into the AUXIN RESPONSE FACTOR 6 mediated repression of nicotine biosynthesis in tobacco. This article mainly mentions that activating the oxylipin biosynthetic pathway can achieve the production of different forms of JA molecules. Increasing evidence suggests that the basic molecular components of the JA signaling cascade may be conserved, or at least highly similar, in several species-specific metabolic pathways [8]. For example: contains at least 7 clusters. The tobacco NIC2 locus transcription factors of ERF genes (such as NtERF189, NtERF221) can activate the expression of a group of nicotine pathway genes, thereby enhancing the accumulation of pyridine alkaloids in tobacco roots [9]. In this study, the authors characterized the molecular function of NtARF6 (an ortholog of NbARF1) in tobacco and found that this TF also acts as a repressor, conferring a reduction in alkaloid accumulation in tobacco due to overexpression of NtARF6. Transcriptome analysis suggests that NtARF6-mediated inhibition of alkaloid accumulation may be achieved through inhibition of JA biosynthesis combined with activation of antagonistic interactions between JA and other signaling pathways, such as ETH, ABA, and SA. The authors propose that ARF family TFs serve as regulatory mediators linking auxin signaling with other phytohormone signaling pathways to balance elicitor-triggered transcriptional reprogramming in various specialized metabolic pathways in tobacco. The main experimental methods in this article mainly include RNA extraction, gene cloning and vector construction, reverse transcription quantitative PCR analysis (RT-qPCR), subcellular localization of NtARF6, yeast one-hybrid assay and dual-luciferase transient assay, library preparation and transcriptome Sequencing, read assembly and differential gene expression, alkaloid extraction and quantification.

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in N. benthamiana was due to virus-induced NbARF1 gene silencing (VIGS) [13]. NtARF6 overexpression resulted in the downregulation of structural gene expression in the nicotine biosynthetic pathway, thereby reducing alkaloid accumulation. Transcriptome analysis: Equal amounts of each three libraries were pooled for RNA-seq using the Illumina platform. The quality of sequencing data was initially checked by FastQC [14]. Transcriptome analysis was performed on NtARF6 overexpression transgenic lines and thousands of differentially expressed genes (DEGs) were identified. These DEGs are involved in multiple biological processes and pathways, including hormone signal transduction, secondary metabolic pathways, etc. Potential regulatory model: Overexpression of the NtPYL6 homolog NtPLY4 leads to reduced alkaloid accumulation in tobacco hairy roots [15]. This article proposes that NtARF6 may serve as a mediator that integrates different plant hormone signaling pathways to regulate the accumulation of alkalis in tobacco by antagonizing JA synthesis and attenuating JA-induced nicotine alkaloid synthesis. The combined results of the study provide new insights into the regulatory mechanism of NtARF6 in tobacco nicotine synthesis.

3.2 . NicA2: A Major Breakthrough in Drug Therapy

Another article, the nicotine-degrading enzyme NicA2 reduces nicotine levels in the blood, nicotine distribution to the brain, and nicotine discrimination and reinforcement in rats, is based on bacterial nicotine-degrading enzymes NicA2 was isolated from Pseudomonas putina to evaluate its potential use in the treatment of tobacco dependence. Scientists came up with two experimental protocols, the first of which is to use a nicotine vaccine to bind nicotine in the blood and reduce its distribution in the brain [16]. Another pharmacokinetic strategy being investigated is nicotine-degrading enzymes, which can rapidly reduce nicotine concentration in the blood and delivery of nicotine to the brain [17].

In a recent report, these preliminary findings were indicated, suggesting that the albumin-binding domain (NicA2-J1) fuses to a truncated form of 50 residues at the N-terminus of NicA2, showing a long half-life. Pretreatment of rats with this enzyme revealed a significant reduction in the distribution of nicotine to the brain. To further explore the therapeutic potential of nicotine enzymatic degradation, NicA2 was injected into rats to determine its effect on nicotine concentrations in the blood and brain within the NicA2 dose range of single and repeated doses of nicotine. When given as a high-dose intravenous bolus of nicotine, NicA2 significantly blocks the distribution of nicotine to the brain or its behavioral effects. This nicotine delivery method mimics the rapid nicotine absorption kinetics of smoking [18]. The results obtained included purity and endotoxin levels: the final purity of NicA2-ABD was greater than 95% according to SDS-PAGE. Endotoxin levels below 0.25 EU/mg.

In vitro activity: The in vitro activity of NicA2-ABD in the Amplex Red assay is indistinguishable from that of NicA2. NicA2 in vitro selectivity: NicA2 has 40-49% activity against nicotine-1'-N-oxide and trace amounts of tobacco alkaloids nornicotine and neonicotine compared to nicotine. No measurable activity was observed for the remaining test compounds. Integrity of MeOH in vitro quenching of NicA2 activity: The addition of methanol (MeOH) prior to mixing NicA2 and nicotine effectively quenched NicA2 activity. Delayed addition of MeOH after mixing results in a large degradation of nicotine. Comparison of quenching methods: There was no significant difference in the concentration of nicotine in the measured brain between immediate homogenization with methanol and flash freezing followed by the addition of methanol. NicA2 and NicA2-ABD pharmacokinetics: NicA2 has a serum half-life of 9.1 ± 0.7 h, clearance of 0.083 ± 0.015 ml/min/kg, and a steady-state volume of distribution of 0.057 ± 0.005 L/kg. NicA2-ABD exhibits a longer half-life (60.9 ± 7.2 h) and lower clearance (0.009 ± 0.002 ml/min/kg) compared to NicA2. Effect of NicA2 on Nicotine Levels in Blood and Brain: Single Dose: NicA2 dose-dependently reduces nicotine concentrations in blood and brain, with significant effects observed at 1, 3, and 5 minutes. When the NicA2 dose $\geq$ 1.25 mg/kg, blood nicotine levels were significantly reduced at all sampling times. When the NicA2 dose $\geq$ 0.31 mg/kg, there was a significant reduction in intracerebral nicotine levels after 5 minutes. Effect of NicA2 on Blood and Brain Nicotine Levels: Multiple Doses: Nicotine concentrations in the blood and brain were significantly reduced in rats treated with NicA2 who received a single nicotine dose or 5 consecutive nicotine doses. NicA2 attenuates nicotine discrimination: NicA2 pretreatment reduces the percentage of response with appropriate nicotine levels in a 0.1 mg/kg nicotine replacement test. NicA2 and NicA2-ABD attenuation of nicotine self-administration (NSA): NicA2 treatment resulted in a dichotomous NSA response, with some rats showing a decrease (reducer) and others a compensatory increase (compensator). NicA2-ABD pretreatment significantly reduced NSA in six consecutive tests. The main findings of the current assessment of NicA2 in vivo activity are that rats pretreated with NicA2: when nicotine is administered as a single rapid intravenous bolus dose, the amount of nicotine distributed early to the brain is significantly reduced, the distribution of nicotine to the brain is reduced when intravenous nicotine is repeated

at a dose comparable to that of heavy smoking, and the attenuation of nicotine discrimination and nicotine intensification, which predict the efficacy of smoking cessation medications. The results were consistent with the brain-to-brain distribution of nicotine by NicA2, in which NicA2 attenuated nicotine discrimination and reduced nicotine enhancement, but it had no effect on sucrose, i.e., NicA2 only acted on nicotine. Although the nicotine enhancement effect was attenuated in all rats, it manifested itself in two different patterns. At the 20 mg/kg NicA2 dose, most rats exhibited a moderate increase in NSA followed by a drop to extinction-like levels on Day 4, while other rats showed only a compensatory increase in NSA, possibly to overcome brain decline nicotine content. However, this compensatory response can be avoided by increasing the NicA2 dose. These data suggest that 20 mg/kg is an effective dose close to the threshold. The longer half-life of the NicA2-ABD fusion construct allows it to be evaluated in a 23-h/day NSA model where the nicotine dose is closer to the nicotine exposure of smokers and confirms the attenuation of nicotine fortification [19]. In addition to nicotine, it is also discussed that components of tobacco or tobacco smoke are also behaviorally active in various animal models [20-22]. In contrast, however, there is substantial evidence that the nicotine content in cigarettes can lead to tobacco addiction [23,24]. There is a good reason to use enzymes such as NicA2 to reduce smoker exposure to nicotine to achieve smoking cessation goals. Overall, NicA2 was able to rapidly reduce blood and brain nicotine concentrations when single or multiple rats were administered nicotine doses related to smoker nicotine intake. In a rat model of nicotine self-administration, NicA2 also reduced the potency of nicotine enhancement. These data make NicA2 a promising starting point for further optimization and development of tobacco use disorder therapeutics and novel treatment strategies.

4. Results

This article mainly introduces the control of smoking through three solutions to achieve the purpose of human health development. Nicotine is the addictive ingredient in tobacco. It is recognized that only by reducing the amount of nicotine to zero can the effect of quitting smoking be achieved. The first one to be discovered was electronic cigarettes. Electronic cigarettes are defined as alternatives to traditional cigarettes. They can achieve better results initially, but in the end, they still fail to achieve the purpose of keeping smokers away from traditional cigarettes. Only a small number of people can quit smoking. Effect. Most smokers will also relapse. So later came more reliable biological solutions. The first is the discovery of NtARF6. The starting point of this experiment is at the plant level, achieving the goal of reducing nicotine synthesis in tobacco leaves. Effect of NtARF6 overexpression on alkaloid accumulation. NtARF6 overexpression leads to the down-regulation of structural gene expression in the nicotine biosynthetic pathway, thereby reducing alkaloid accumulation. The last solution is to use drugs to reduce the amount of nicotine in smokers' bodies entering their brains through blood circulation. There are good reasons for using enzymes like NicA2 to reduce smokers' exposure to nicotine for the purpose of quitting smoking. Overall, NicA2 was able to rapidly reduce blood and brain nicotine concentrations when rats were administered single or multiple doses of nicotine that were relevant to the nicotine intake of smokers. NicA2 also reduced the reinforcing potency of nicotine in a rat model of nicotine self-administration.

5. Conclusion

In conclusion, tobacco is now loved by the majority of consumers, and the reason why smokers find it difficult to quit smoking is because of the nicotine content in tobacco. Nicotine is the addictive ingredient in cigarettes. Through the disdainful efforts of scientists, major breakthroughs have been made in medicines and in the plants themselves. It will bring great help to future smokers to quit smoking and also lay a solid foundation for achieving the sustainable goal of human health and well-being in the future.

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