International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 12, Issue 4, 2020

Review Article

A REVIEW ON NICOTINE FOR HEALTH: INSIGHT FOR "PRO-HEALTH" NICOTINE USAGE

FLORENCE PRIBADI[1], RAHAJOE IMAM SANTOSA[2], ARIEF GUNAWAN DARMANTO[1]

[1]Pharmacology, [2]Clinical Pathologist, Faculty of Medicine, Universitas Ciputra Surabaya, Citraland CBD Boulevard, Made, Kec Sambikerep, Surabaya 60219, East Java, Indonesia
Email: florence.pribadi@ciputra.ac.id

Received: 17 Mar 2020, Revised and Accepted: 19 May 2020

ABSTRACT

Nicotine is a major chemical of tobacco that makes smokers having difficulties to stop consuming cigarette. That chemical is an alkaloid-based plant and known for one of the major compound of cigarette. Many researches showed the negative side of nicotine. In contrast, a recent study showed the benefits of nicotine. Some researches proved that nicotine has high possibility to improve the depressive behavior both in animal models and human subject. In addition, more research also proved that nicotine has cognitive-enhancing effects, which means it has the ability to improve the function of working memory, episodic memory, attention, and fine motor function. The current review deliberates about the good side and the diversity usage of nicotine, particularly in medicine, as novel therapeutics for neurodegenerative diseases.

Keywords: Nicotine, Cigarette, Tobacco, Cognitive-enhancing effects

DOI: http://dx.doi.org/10.22159/ijcpr.2020v12i4.39081. Journal homepage: https://innovareacademics.in/journals/index.php/ijcpr

INTRODUCTION

Nicotine is an alkaloid-based plant famous for being an active ingredient of cigarette smoke. It is additive and has been related to several diseases but, as a coin nicotine, has another side that has been understudied. Recent research results reveal the health benefits of nicotine [1]; hence, it deserves a throughout review for better understanding to bring insight for pro-health nicotine usage.

Does nicotine all bad? Nicotine is always associated with tobacco, smoking and harm for health when tomatoes and black tea are also sources of nicotine but they are considered healthy food and not carcinogenic [2]. Smoking is listed as a carcinogen in IARC monograph [3], along with drinking hot coffee [4] and DDT [5], but nicotine is not. Cigarette smokes contain 69 carcinogenic chemicals, other than nicotine [6, 7].

Smoking also a risk factor for metabolic syndrome, yet smoking cessation is also causing weight gain which lead to obesity and diabetes, but nicotine is associated to appetite control; hence, nicotine is used in weight loss research [8–13]. Other doubt raised from cardiovascular department, where smoking paradox is found. Acute myocardial infarction has lower mortality rate in smokers and also recanalization and reperfusion therapy is more effective in smokers [14-19].

Nicotine has also been widely researched for medicinal purposes, especially in Parkinson and other neurodegenerative disorders [20–24]. All of the positive points above are obscured from the hazards of smoking. How did human first encounter nicotine from tobacco?

Bitter sweet relationship with tobacco

Tobacco plant (*Nicotiana tobacum*) is a cross between *Nicotiana sylvestris* and *Nicotiana tomensiformis*,a nightshade family along with bell peppers and eggplant, but *N. tobacum* has the highest nicotine content of all plants [25]. Tobacco farming is still farmer favorite plant as it brings higher revenue compared to chili, hybrid corn or soy [26]. Tobacco product industry also brings 96.65% of exercise duty in 2016 and absorb more than 4 million workers in industry sector and about 1.7 million farmers [27]. On the other side of the high employment rate and revenue for people, and also government tax income, there is health sector protest. Smokers starting age gets younger, and there are more and more diseases are attributable to smoking [28, 29].

As exercise duty, health concern and vape popularity increases, cigarette sales decreases [30–32]. A leading cigarette industry is developing heat not burn cigarette, as a method for smokers to continue on enjoying cigarette without the smoke [33]. Government farming, industry and health sector, should aware of this shift and be prepared for future change. Another alternative is to bring product diversity to from tobacco leaves and industry waste. The love and hate situation with tobacco been around since Christopher Columbus era. He brought the gift of tobacco back from San Salvador, and Sir Walter Raleigh began tobacco farming in Virginia, until now, Virginia tobacco dominate 40% of world tobacco population [34].

King James I first wrote the famous "A Counterblast to Tobacco" in 1604, an-eight-sections long essay describing his resentment to tobacco, and exercise high tax for tobacco, yet he was addicted to the revenue stream and even monopolies the importation and sales of tobacco [35]. Tough by time health concern for smoking is rising, it has hooked and rooted deep hence unavoidable.

During wars times, smoking was considered as a "comfort" and lighten the hardships, when the soldiers didn't know if they will be still alive in the next 20 min, long term health havoc of nicotine usage is a minor concern [36]. Why people smoke and why tobacco leaves is the chosen one for smoking it is down to the main content that is nicotine.

History of tobacco use for health

Tobacco has been used since the Mayan empire at first for religious purposes, along with other mixture of herbs, considered sacred and have medicinal use [37, 38]. The odor of fresh green leaves was used to relieve persistent headaches by Catherine de' Medici and her son Francis II, hence tobacco leaves was called the Queen's herb [39].

The powdered leaves used to treat cough and cold and as toothpaste, the leaves can be applied topically to heal wounds and burns; believed to improve respiratory diseases and in desperate cases, until it was regarded as penicillin of the seventeenth century [38, 40, 41]. The dispute of tobacco usage also occurs among physicians, tough no one questions tobacco's effectiveness to ward of outbreak of plaque and outbreak, kills germs and ward of diseases, all concurs that it also brings constitutional effects [40].

As scientist manage to isolate nicotine from tobacco leaves, the usage grows The use of nicotine as pesticide was vastly popular until in 1940s when new and cheaper pesticide is invented, along with more and more health hazard awareness' campaign [42].

Research on nicotine

Nicotinic receptors are responsible not only for pleasure and reward system but also muscle contraction, motor control, learning and memory, arousal and analgesia, hence nicotine can be related to aforementioned effect [43, 44]. Among nine α subunits composing nAChRs complex, α-7 recently gained attention as it is recently discovered to have important physiologic and pharmacologic role in neurodegenerative diseases [22, 45]. Nicotine through alpha 7 nAChRs also proven to reduce inflammation which is the basis of many diseases [46].

Cognition

Nicotine is proven to enhance parietal cortex associated with attention for both smokers and non-smokers. Neural nicotine receptors are known has major role in cognitive function in rodents and also primates including rhesus monkeys and humans. Past studies showed that treatment of nicotine and nicotinic agonist, both acute and chronic treatment, could improve the working memory of rats while the antagonist such as mecamylamine showed the opposite result. Working memory function involves nicotinic receptor α4β2 and α7 nicotinic receptors in the ventral hippocampus [47].

Nicotinic receptors of α4β2 and α7 have been shown to be involved in working of memory function and have a role in the release of acetylcholine. The ventral hippocampus and amygdala are known to have key role for nicotinic involvement in memory activity. The nicotinic antagonist methyllycaconitine (MLA) and dihydro-β-erythrodine (DHβE) can block the α7 and α4β2 nicotinic receptors, respectively in basolateral amygdala and the ventral hippocampus. Those blocking could impair the memory function in brain [47, 48].

Normally, the high doses of MLA and DHβE could also increasing the latencies and caused preconvulsant responses such as piloerection, head bobbing, tremor, and teeth chattering which may give an effect for memory. However, previous research proved that MLA and DHβE could harm the memory withoutany preconvulsant effects showed up and the latencies remaining steady. In addition, only DHβE was known to give an effect on the reference memory in ventral hippocampus [47–49].

The antagonist of MLA and DHβE have displayed that the receptor α4β2 and α7 are really important in memory function in the ventral hippocampus and basolateral amygdala of mammals. Moreover, more investigation also shown that the cortical area is also prominent for cognitive functions. Unfortunately, the significant result of research regarding the memory α4β2 and α7 in the dorsal hippocampus still need improvement [47, 48, 50].

The loss of nicotinic receptor has been demonstrated in Alzheimer disease (AD) patients and related to the hallmark plaques and tangles and cognitive impairment. One of the best therapeutic effect on nicotine that has been established is cognitive improvement. In previous clinical studies, memory improvement spotted in AD subjects with IV nicotine. Others discover that the administration of nicotine by transdermal patch or subcutaneous injection could enhance the cognitive function in AD [51].

Study conducted by Newhouse *et al.* [51] showed that the administered of transdermal nicotine to nonsmoking subjects with mild cognitive impairment over 6 mo will not cause any harm. In fact, the result shown the improvement in primary and secondary cognitive measures of memory, mental processing, and attention, but not in rank of clinician-rated global impression. Transdermal administration method may have a contribution to increase tolerability, especially minimize the rate of gastrointestinal side effects.

Those researches are related with another research that reveal the importance of nicotinic receptors in dorsal hippocampus in working memory function. Some previous studies, assess the function of nicotinic receptors in the dorsal hippocampus as a whole is connected in reference and working memory. The nicotinic α7 and α4β2 receptors give a mutual attenuation effects on part of memory in the dorsal hippocampus, that effects could be seen in basolateral amygdala. That event indicates the importance of interaction between the two receptors in memory function [47, 52].

The stimulation of nicotinic receptors is recognized have an effect in the efflux of downstream neurotransmitters that could be as an inhibitory, such as GABA, or excitatory such as glutamate. The blockade of the two receptors may interrupt the fragile balance of transmitter release which is affecting the downstream of neural activity. The infusion of the correct ratio antagonist, could make the blockade of both subtypes, it would bring back the neural activity to its native level. In spite of the fact that each nicotinic antagonist, MLA and DHβE, itself was considered to impair the working memory function, they were found to attenuate each other's effects. Thus, at the same time, the entry of antagonist with the correct ratio could produce an attenuated effect [47, 52].

Some of data showed that administrated of nicotine since adolescent demonstrate more major impairment of working memory and weaken the verbal memory during periods when they decided to stop, comparing it to non-smokers. Additionally, animal studies disclose that nicotine administration during young age can induce everlasting changes in brain region, such as nucleus accumbens, amygdala, and prefrontal cortex. Those changes also influence the reward-related manifestation and drug sensitivity in adulthood. However, last human and preclinical models' studies have demonstrated that nicotine has the ability to improve the function of working memory, episodic memory, attention, and fine motor function. It showed cognitive-enhancing effects [50, 53].

Although the information about the usage of nicotine on teenagers can trigger long-lasting changes in neural signaling and emotional changes, and cognitive in juvenile, is important to be spread. However, a diversity of novel ligands for nicotinic receptors are being developed by many researches for cognitive impairment treatment, for example subject with Alzheimer's disease, schizophrenia, and attention deficit hyperactivity disorder (ADHD). The cognitive-enhancing effects by nicotine might be critical factor in vulnerability to tobacco use disorder, particularly in someone with cognitive deficits [50, 53].

The α7 subunit has possibility to modulate a sensory filtering function corresponding with schizophrenia and the β2 subunit may to mediate working memory, attention, and behavioral flexibility function. Furthermore, the neurotransmitter that contribute to nicotine's cognitive effects are DA, GABA, norepinephrine, acetylcholine, glutamate, and serotonin. It is a required to enrich the knowledge of the role of receptor activation facing to desensitization and the circuit basis of the way nicotinic receptors dealings with related neural system in cognitive function [50, 52].

Further researches about nicotinic acetylcholine receptor (nAChr) agonist are interesting to be done because nicotine has high possibility to use as a novel therapeutic. Moreover, research about determination of which type from nicotine agonist that could improve the memory and the interaction of nicotinic receptor system with the wider neural circuits as fundamental studies of cognitive function and the action from nicotinic receptors in specific brain areas. The agonist of nAChR also assume to have benefits as unique therapeutic for late life depression (LLD). LLD or major depressive disorder usually happen in 60 y old person or more [52, 54].

Both previous preclinical and clinical studies are in agreement that nicotine and other nAChr agonist can boost the mood, depressive behavior, and cognitive performance. The nAChr agonist may also enhance the ability of emotional regulation, improve cognitive deficits, andreduce depressive symptoms that are usually found in LLD patients. Past clinical trial also proved that nicotine gives effects on cognition, network dynamics, and mood in someone with LLD [54].

Late-life depression

The late-life depression (LLD) usually can be found in elderly age around more than 60 y old. Recently, LLD becomes one of public health issue as the number of incidence and prevalence are rising. This disease has high risk of suicide and high cost for the healthcare. LLD is also describe as cognitive impairment disease. Depression at

any age is corresponding with cognitive impairment [54, 55]. Impairment to those cognition in elderly are serious problem because it becomes a burden for normal cognitive aging and structural brain pathology [55].

Mostly, people with LLD also showed mood dysfunction beside brain structural integrity and impairment in cognition. LLD appears to be a cognitive and mood syndrome. Cognitive disorder usually could happen in any age but in LLD it could be a major problem because the impairment may be followed by presence of normal aging processes and depressive disorder [55].

Patients with LLD also showed poor performance of various cognitive domain. Even without dementia as co-morbid, individual with LLD performs poor executive function, episodic memory, visuospatial, and processing speed ability. LLD become one of the biggest risk factors for dementia as it has two times risk than the normal cause of dementia. On individual whose showed response against antidepressants, it could be seen that there is improvement in cognitive deficits. However, the level of cognitive performance never goes back into normal [54–57].

LLD patients have worse effect to cognition, greater impairment than young adults with depression and non-depressed elderly. Additionally, severe cognitive impairment in depressed elderly are connected with lower remission rates and more severe symptoms of depression. LLD also associated with extensive volumetric differences in temporal, frontal, and cingulate regions. Furthermore, patients with LLD is also related with bigger severity of hyperintense lesions (leukoariasosis) in subcortical gray matter (thalamus, putamen, caudate), subcortical white matter, temporal and frontal lobes compared to non-depressed elderly [55, 58–62].

The destruction of neuronal integrity in LLD patients showed many disorder affecting various brain region that are important for cognition and mood, propose an area of overlap in neural mechanism based on mood dysfunction and cognitive impairment. Previous studies reported some new solution to improve the condition of individual that has LLD. Last review study suggested cholinergic system as one of potential therapeutic target to improve cognitive performance in LLD. Another study proposed nAChr agonist as potential novel treatment for LLD [54, 55, 57].

Last study reported that nicotine reduces self-referential negativity bias in LLD. The reduction in negativity bias are early predictors of antidepressant response and probably became basis to the mechanism of conventional antidepressants. Activity at nAChRs nicotine modulate dopamine, serotonin, and norepinephrine. Previous study also proposed nAChR agonist as potential novel treatment for the cognitive symptoms and mood of LLD because recent therapeutic still can't show changes in cognitive performance [54, 57].

The most popular treatment program for stimulating cognition in neurodegenerative diseases is by stimulating cholinergic system with acetylcholinesterase inhibitors. Unfortunately, acetylcholinesterase inhibitors are not ideal for cognitive impairment treatment in LLD. Nicotine manipulation has shown various effects on mood disorders, mostly because of the plasticity of nicotinic receptors and smoking history of subjects. One of the effects from treatment with nicotine is improving the mood in non-smoking depressed patients [55, 63].

Previous review study suggested that LLD should be treated with both cognitive enhancer and antidepressant. In addition, further research about the optimal dose of nicotine as therapeutic is important to do. Past study proposed that further trials examining transdermal nicotine as therapeutic for LLD should have a slower dose titration. Not only that, the detail information about measurement of plasma metabolites to assess bioavailability will be essential to be known [55, 57].

Further researches regarding nicotine for LLD patient's treatment are important to be conducted. Nicotine administration results a changes of brain activity during memory, attentional. And cognitive control tasks. Thus, people with LLD or people with suboptimal cognitive performance are possibly get benefit from drug targeting nicotinic stimulation. Previous study also propose that nicotinic agonist will increase task related with activity of brain in frontal regions [55, 64, 65].

Nicotinic stimulation is known to have enhanced the performance of test of attention, processing speed, memory, and executive function in depressed patients. In addition, studies are also needed to spot novel nicotine agonist that can be added to antidepressant treatment for enhancement of mood and cognition in LLD. Thus, further research of seeking the nicotine benefit is important to do. Moreover, separate treatment of cognitive impairment may be needed to enhance the outcome in LLD patients [55, 66].

Inflammation

Inflammation process is a self-defense mechanism from noxious stimuli, but prolonged inflammation proven to be hazardous. One anti-inflammation pathway is cholinergic anti-inflammation pathway (CAP). Acetylcholine produced by T lymphocyte binds with α-7 nAChRs which is ubiquitous in the body and has many functions, including for memory and learning. In central nervous system, astrocytes produce both pro-inflammatory cytokines such as IL-6, and IL-1β, and also anti-inflammatory cytokines namely TGF β, which will slows microglia in inflammation process [67]. Astrocytes cells in central nervous system produces IL-1 and IL-6,

Parkinson disease

Parkinson is a neurodegenerative disease marked with inflammation in neurons, and death of dopamine producing neurons. Basal ganglia function depends on the equilibrium between midbrain dopaminergic and striatal cholinergic systems. The hypothesis of nicotine patch of this disease is increasing theMangan and Iron levels. Nicotine protects dopaminergic cells by binding with cholinergic receptors in cell SH-SY5Y.

Alzheimer

Alzheimer is a neurodegenerative disease marked with memory, cognitive and behavior deterioration. In murine models, continuous nicotine exposure increases cognitive and memory, the two things that are decreasing in Alzheimer [68]. The main culprit for this disease is senile plaque formed by β-amyloid peptide (Aβ), causing synaptic dysfunction, disrupting neural connectivity and association with neuronal death [69]. Aβ has high affinity with nAChR, so does nicotine [70]. Aβ also induced microglial activation (M1 state) to secretes inflammatory cytokines, including tumor necrosis factor α (TNF-α), interleukin-(IL-) 1β, and IL-6 [71].

Further research shows microglial cells can be activated not only to M1 state but also as M2 state which is neuroprotective and produces anti-inflammatory factor IL-10 and Brain-Derived neurotrophic factor (BDNF) [72, 73], in result, TNF-α and IL-6 level are decreased, furthermore, nicotine binds with cannabinoid CB2 and attenuated iNOS expression and upregulates Arg-1 expression in the Aβ-treated microglia, indicates inflammation at microglia exposed by beta amyloid by binding with protein and blocks Protein Kinase C [74]. Nicotine also activates $ERK_{1/2}$, that will active EGR1 to increase cell repair [75].

Nicotine metabolites, cotinine and 6 hydoxy L also has beneficial effects. Cotinine prevents GSK-3β and prevents further aggregation of beta amyloid and increases pro-survival enzymes [76]. The 6HLN proven to reduce oxidative stress and increases antioxidant in mice hippocampus [77].

CONCLUSION

Tobacco farming is still farmer favorite plant as it brings higher revenue compared to chili, hybrid corn or soy. Tobacco product industry high number of exercise duty and absorb more than millions farmer and workers in industry sector. However, in health sector, tobacco not give good impact in users life. Smokers starting age gets younger, and there are more and more diseases are attributable to smoking.

Furthermore, as exercise duty, health concern and vape popularity increases, cigarette sales decreases and make cigarette industry developing heat not burn cigarette, as a method for smokers to

continue on enjoying cigarette without the smoke. Government farming, industry and health sector, should aware of this shift and be prepared for future change. Another alternative is to bring product diversity from tobacco leaves and industry waste. In addition, more research about nicotine as novel therapeutic in depressed and neurodegenerative disease is really needed.

ACKNOWLEDGMENT

Author would like to thank the rector of Ciputra University and all staffs for all support and facilities that were given.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

Author have contributed equally

CONFLICT OF INTERESTS

Author declare that there is no conflict of interest. I am alone responsible for writing the content of this article.

REFERENCES

1. Malczewska Jaskoła K, Jasiewicz B, Mrowczynska L. Nicotine alkaloids as antioxidant and potential protective agents against *in vitro* oxidative haemolysis. Chem Biol Interact 2016;243:62–71.
2. Davis RA, Stiles MF, deBethizy JD, Reynolds JH. Dietary nicotine: a source of urinary cotinine. Food Chem Toxicol 1991;29:821–7.
3. International Agency for Research on Cancer (IARC), World Health Organization. Tobacco smoke and involuntary smoking IARC Monographs on the evaluation of carcinogenic risks to humans Vol. 83. Lyon: IARCPress; 2004. Available from: https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Tobacco-Smoke-And-Involuntary-Smoking-2004 [Last accessed on 10 Feb 2020]
4. International Agency for Research on Cancer (IARC), World Health Organization. Drinking coffee, mate, and very hot beverages IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 116. Lyon: IARCPress; 2018. Available from: https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Drinking-Coffee-Mate-And-Very-Hot-Beverages-2018 [Last accessed on 10 Feb 2020]
5. International Agency for Research on Cancer (IARC) World Health Organization. DDT, lindane, and 2,4-D IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 113. Lyon: IARCPress; 2018. Available from: https://monographs.iarc.fr/wp-content/uploads/2018/07/mono113.pdf [Last accessed on 10 Feb 2020]
6. World Health Organization. A guide for tobacco users to quit. Geneva: World Health Organization; 2014. Available from: https://www.who.int/tobacco/publications/smoking_cessation/9789241506939/en/ [Last accessed on 10 Feb 2020]
7. Cogliano VJ, Baan R, Straif K, Grosse Y, Lauby Secretan B, El Ghissassi F, *et al.* Preventable exposures associated with human cancers. J Natl Cancer Inst 2011;103:1827–39.
8. Aubin HJ, Farley A, Lycett D, Lahmek P, Aveyard P. Weight gain in smokers after quitting cigarettes: meta-analysis. Br Med J 2012;345:4439.
9. Audrain Mcgovern J, Benowitz NL. Cigarette smoking, nicotine, and body weight. Clin Pharmacol Ther 2011;90:164–8.
10. Bush T, Lovejoy JC, Deprey M, Carpenter KM. The effect of tobacco cessation on weight gain, obesity and diabetes risk. Obesity 2016;24:1834–41.
11. Kryfti M, Dimakou K, Toumbis M, Daniil Z, Hatzoglou C, Gourgoulianis KI. Effects of smoking cessation on serum leptin and adiponectin levels. Tob Induc Dis 2015;13:30.
12. Bunneu PE, Hansen M, LeSage M. Effects of isolated tobacco alkaloids and tobacco products on deprivation induced food intake and meal patterns in rats. Pharmacol Biochem Behav 2018;165:45–55.
13. Hu Y, Zong G, Liu G, Wang M, Rosner B, Pan A, *et al.* Smoking cessation, weight change, type 2 diabetes, and mortality. N Engl J Med 2018;379:623–32.
14. Liu R, Gao Z, Wang H, Tang X, Gao L, Song Y, *et al.* Association of baseline smoking status with long-term prognosis in patients who underwent percutaneous coronary intervention: large single-center data. J Interv Cardiol 2019. https://doi.org/10.1155/2019/3503876
15. Kufner A, Nolte CH, Galinovic I, Brunecker P, Kufner GM, Endres M, *et al.* Smoking-thrombolysis paradox: recanalization and reperfusion rates after intravenous tissue plasminogen activator in smokers with ischemic stroke. Stroke 2013;44:407–13.
16. Gupta T, Kolte D, Khera S, Harikrishnan P, Mujib M, Aronow WS, *et al.* Smoker's paradox in patients with st-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. J Am Hear Assoc 2016;5:1–10.
17. Venkatason P, Salleh NM, Zubairi Y, Hafidz I, Ahmad WAW, Han SK, *et al.* The bizzare phenomenon of smokers' paradox in the immediate outcome post acute myocardial infarction: an insight into the Malaysian national cardiovascular database-acute coronary syndrome (NCVD-ACS) registry year 2006–2013. Springerplus 2016;5:534.
18. Aune E, Røislien J, Mathisen M, Thelle DS, Otterstad JE. The "smoker's paradox" in patients with acute coronary syndrome: a systematic review. BMC Med 2011;9:97.
19. Bell TM, Bayt DR, Zarzaur BL. "Smoker's paradox" in patients treated for severe injuries: lower risk of mortality after trauma observed in current smokers. Nicotine Tob Res 2015;17:1499–504.
20. Aaseth J, Dusek P, Roos MP. Prevention of progression in Parkinson's disease. BioMetals 2018;31:737–47.
21. Barreto GE, Iarkov A, Moran VE. Beneficial effects of nicotine, cotinine and its metabolites as potential agents for Parkinson's disease. Front Aging Neurosci 2015;6:340.
22. Budzianowski J. [Tobacco--once a medicinal plant. does it contain substances with medicinal properties?]. Przegl Lek 2013;70:865–8.
23. Getachew B, Csoka AB, Aschner M, Tizabi Y. Nicotine protects against manganese and iron-induced toxicity in SH-SY5Y cells: implication for Parkinson's disease. Neurochem Int 2019;124:19–24.
24. Tizabi Y, Getachew B. Nicotinic receptor intervention in parkinson's disease: future directions. Clin Pharmacol Transl Med 2017;1:14–9.
25. Lewis RS, Nicholson JS. Aspects of the evolution of *Nicotiana tabacum* L. and the status of the United States nicotiana germplasm collection. Genet Resour Crop Evol 2007;54:727–40.
26. Djajadi D. Tobacco diversity in Indonesia. J Biol Res 2015;20:27–32.
27. Commission Secretariat VII Indonesian House of people's. Kunjungan spesifik komisi VII DPR RI ke Provinsi Jawa Timur pengelolaan limbah di perusahaan rokok PT. HM Sampoerna; 2018. Available from: http://www.dpr.go.id/dokakd/dokumen/K7-12-2639ccef7ca140a729a6aa350afbf03c.pdf [Last accessed on 10 Feb 2020]
28. Tobacco Control Support Center. Fakta tembakau dan permasalahannya di Indonesia. Kemenkes. Jakarta: Tobacco Control and Support Center-IAKMI; 2014. Available from: http://www.tcsc-indonesia.org/wp-content/uploads/2016/06/Buku-Fakta-Tembakau-2014__Web-Version.pdf [Last accessed on 10 Feb 2020]
29. Kosen S, Thabrany H, Kusumawardani N, Martini S. Review of evidence series: health and economic costs of tobacco in Indonesia. Kementerian Kesehatan Republik Indonesia. Jakarta: Lembaga Penerbit Badan Penelitian dan Pengembangan Kesehatan (LPB); 2017. Available from: https://www.litbang.kemkes.go.id/review-of-evidence-series-health-and-economic-costs-of-tobacco-in-indonesia [Last accessed on 10 Feb 2020]
30. Hamdani T. Cukai rokok naik, pengusaha prediksi penjualan di 2020 anjlok. Detik Finance; 2019. Available from: https://finance.detik.com/industri/d-4731454/cukai-rokok-naik-pengusaha-prediksi-penjualan-di-2020-anjlok [Last accessed on 10 Feb 2020].

31. Qolbi N. Laba bersih mayoritas emiten rokok meningkat tapi penjualan turun, begini rekomendasi. Kontan.co.id; 2019. Available from: https://investasi.kontan. co.id/news/laba-bersih-mayoritas-emiten-rokok-meningkat-tapi-penjualan-turun-begini-rekomendasi?page=all [Last accessed on 10 Feb 2020]
32. Indonesian Directorate General of Customs and Excise. Dialog interaktif di udara, bea cukai Ambon sosialisasikan pengenaan cukai cairan rokok elektrik (vape). Indonesian Directorate General of Customs and Excise; 2018. Available from: https://www.beacukai.go.id/berita/dialog-interaktif-di-udara-bea-cukai-ambon-sosialisasikan-pengenaan-cukai-cairan-rokok-elektrik-vape-.html [Last accessed on 10 Feb 2020]
33. Philip Moris International. Delivering a smoke-free future | PMI-Philip Morris International. Philip Moris International (PMI); 2019. Available from: https://www.pmi.com/our-transformation/delivering-a-smoke-free-future [Last accessed on 10 Feb 2020].
34. Geiss O, Kotzias D. Tobacco, cigarettes and cigarette smoke an overview. European Commission Directorate General Joint Research Centre. Luxembourg: European Commission Directorate-General Joint Research Centre Institute for Health and Consumer Protection; 2007. Available from: https://ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/tobacco-cigarettes-and-cigarette-smoke-overview [Last accessed on 10 Feb 2020]
35. Butler T. Power in smoke: the language of tobacco and authority in caroline England. Studies Philol 2009;106:100–18.
36. Smith EA, Malone RE. "Everywhere the soldier will be": wartime tobacco promotion in the us military. Am J Public Health 2009;99:1595–602.
37. Hanafin J, Clancy L. History of tobacco production and use. Prog Respir Res 2015;42:1–18.
38. Routh HB, Bhowmik KR, Parish JL, Parish LC. Historical aspects of tobacco use and smoking. Clin Dermatol 1998;16:539–44.
39. Laccourreye O, Werner A, Laccourreye H, Bonfils P. Tobacco and otorhinolaryngology: Epic and disaster. Eur Ann Otorhinolaryngol Head Neck Dis 2014;131:183–8.
40. Charlton A. Medicinal uses of tobacco in history. JRSM 2004;97:292–6.
41. Hajdu SI, Vadmal MS. The use of tobacco. Ann Clin Lab Sci Spring 2010;40:178–81.
42. Fusetto R, O'Hair RA. Nicotine as an insecticide in Australia: a short history. Chemistry 2015;38:18–21.
43. Wu J. Understanding of nicotinic acetylcholine receptors. Acta Pharmacol Sin 2009;30:653–5.
44. Gotti C, Clementi F. Neuronal nicotinic receptors: from structure to pathology. Prog Neurobiol 2004;74:363–96.
45. Bertrand D, Lee CHL, Flood D, Marger F, Donnelly Roberts D. Therapeutic potential of α7 nicotinic acetylcholine receptors. Pharmacol Rev 2015;67:1025–73.
46. Yamada Nomoto K, Yoshino O, Akiyama I, Ushijima A, Ono Y, Shima T, et al. Alpha-7 nicotinic acetylcholine receptor (nAChR) agonist inhibits the development of endometriosis by regulating inflammation. Am J Reprod Immunol 2016;76:491–8.
47. Nott A, Levin ED. Dorsal hippocampal α7 and α4β2 nicotinic receptors and memory. Brain Res 2006;1081:72–8.
48. Levin E, Bradley A, Addy N, Sigurani N. Hippocampal α7 and α4β2 nicotinic receptors and working memory. Neuroscience 2002;109:757–65.
49. Levin ED. Nicotinic receptor subtypes and cognitive function. J Neurobiol 2002;53:633–40.
50. Valentine G, Sofuoglu M. Cognitive effects of nicotine: recent progress. Curr Neuropharmacol 2018;16:403–14.
51. Newhouse P, Kellar K, Aisen P, White H, Wesnes K, Coderre E, et al. Nicotine treatment of mild cognitive impairment: A 6-month double-blind pilot clinical trial. Neurology 2012;78:91–101.
52. Levin ED. Complex relationships of nicotinic receptor actions and cognitive functions. Biochem Pharmacol 2013;86:1145–52.
53. Salmanzadeh H, Ahmadi Soleimani SM, Pachenari N, Azadi M, Halliwell RF, Rubino T, *et al.* Adolescent drug exposure: a review of evidence for the development of persistent changes in brain function. Brain Res Bull 2020;156:105–17.
54. Gandelman JA, Newhouse P, Taylor WD. Nicotine and networks: potential for enhancement of mood and cognition in late-life depression. Neurosci Biobehav Rev 2018;84:289–98.
55. Zurkovsky L, Taylor WD, Newhouse PA. Cognition as a therapeutic target in late-life depression: potential for nicotinic therapeutics. Biochem Pharmacol 2013;86:1133–44.
56. Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. Br J Psychiatry 2013;202:329–35.
57. Gandelman JA, Kang H, Antal A, Albert K, Boyd BD, Conley AC, *et al.* Transdermal nicotine for the treatment of mood and cognitive symptoms in nonsmokers with late-life depression. J Clin Psychiatry 2018;79:18m12137.
58. Taylor WD, Steffens DC, McQuoid DR, Payne ME, Lee SH, Lai TJ, *et al.* Smaller orbital frontal cortex volumes associated with functional disability in depressed elders. Biol Psychiatry 2003;53:144–9.
59. Burke J, McQuoid DR, Payne ME, Steffens DC, Krishnan RR, Taylor WD. Amygdala volume in late-life depression: relationship with age of onset. Am J Geriatr Psychiatry 2011;19:771–6.
60. Zhao Z, Taylor WD, Styner M, Steffens DC, Krishnan KRR, MacFall JR. Hippocampus shape analysis and late-life depression. PLoS One 2008;3:e1837.
61. Taylor WD, MacFall JR, Payne ME, McQuoid DR, Steffens DC, Provenzale JM, *et al.* Greater MRI lesion volumes in elderly depressed subjects than in control subjects. Psychiatry Res Neuroimaging 2005;139:1–7.
62. MacFall JR, Taylor WD, Rex DE, Pieper S, Payne ME, McQuoid DR, *et al.* Lobar distribution of lesion volumes in late-life depression: the biomedical informatics research network (BIRN). Neuropsychopharmacology 2006;31:1500–7.
63. Salin Pascual RJ, Rosas M, Jimenez Genchi A, Rivera Meza BL, Delgado Parra V. Antidepressant effect of transdermal nicotine patches in nonsmoking patients with major depression. J Clin Psychiatry 1996;57:387–9.
64. Newhouse P. Effects of nicotinic stimulation on cognitive performance. Curr Opin Pharmacol 2004;4:36–46.
65. Jansari AS, Froggatt D, Edginton T, Dawkins L. Investigating the impact of nicotine on executive functions using a novel virtual reality assessment. Addiction 2013;108:977–84.
66. Butters MA, Becker JT, Nebes RD, Zmuda MD, Mulsant BH, Pollock BG, *et al.* Changes in cognitive functioning following treatment of late-life depression. Am J Psychiatry 2000;157:1949–54.
67. Revathikumar P, Bergqvist F, Gopalakrishnan S, Korotkova M, Jakobsson P, Lampa J, *et al.* Immunomodulatory effects of nicotine on interleukin 1β activated human astrocytes and the role of cyclooxygenase 2 in the underlying mechanism. J Neuroinflammation 2016;13:256.
68. Noshita T, Murayama N, Nakamura S. Effect of nicotine on neuronal dysfunction induced by intracerebroventricular infusion of amyloid-β peptide in rats. Eur Rev Med Pharmacol Sci 2015;19:334–43.
69. Murphy MP, LeVine H. Alzheimer's disease and the amyloid-β peptide. J Alzheimer's Dis 2010;19:311–23.
70. Lombardo S, Maskos U. Role of the nicotinic acetylcholine receptor in Alzheimer's disease pathology and treatment. Neuropharmacology 2015;96:255–62.
71. Wang WY, Tan MS, Yu JT, Tan L. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. Ann Transl Med 2015;3:136.
72. Benson FE, Nierkens V, Willemsen MC, Stronks K. Smoking cessation behavioural therapy in disadvantaged neighbourhoods: an explorative analysis of recruitment channels. Subst Abuse Treat Prev Policy 2015;10:28.
73. Cherry KE, Blanchard B, Walker EJ, Smitherman EA, Lyon BA. Knowledge of memory aging across the lifespan. J Genet Psychol 2014;175:547–53.
74. Jia J, Peng J, Li Z, Wu Y, Wu Q, Tu W, *et al.* Cannabinoid CB2 receptor mediates nicotine-induced anti-inflammation in n9 microglial cells exposed to β amyloid via protein kinase C. Mediators Inflamm 2016;8:1-10.
75. Xue M, Zhu L, Zhang J, Qiu J, Du G, Qiao Z, *et al.* Low dose nicotine attenuates Aβ neurotoxicity through activation early

growth response gene 1 pathway. PLoS One 2015; 10:e0120267.

76. Ng YP, Or TCT, Ip NY. Plant alkaloids as drug leads for Alzheimer's disease. Neurochem Int 2015;89:260–70.
77. Hritcu L, Stefan M, Brandsch R, Mihasan M. Enhanced behavioral response by decreasing brain oxidative stress to 6-hydroxy-l-nicotine in Alzheimer's disease rat model. Neurosci Lett 2015;591:41–7.