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Review Article

Medicinal Plants and Natural-Derived Compounds for Smoking Cessation: Is There a Real Potential?

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ABSTRACT

Nicotine use disorders, which are typically acquired through tobacco smoking, are a global problem and a leading cause of preventable deaths. Unfortunately, the available therapies intended for tobacco smoking cessation have varying efficacy among smokers in addition to some adverse effects observed. These factors, alongside the cost of such therapies deemed as a financial burden by some, contribute to the failure to meet patients' needs. This necessitates the many studies being conducted on the possible use of natural products in the treatment of nicotine use disorders to address such issues. Therefore, this review aims to discuss published data documenting the effects of plant extracts and bioactive compounds on nicotine-induced reactions and nicotine use disorders by looking into the different effects, possible mechanisms, and the putative targets of these selected natural products. A total of 21 natural products and bioactive compounds were obtained from searches across PubMed, Ovid Medline and Scopus databases which comprised of studies performed *in vitro* and *in vivo* as well as human trials. These data suggest that these natural products may have the potential to be utilized to treat nicotine use disorders. Undoubtedly, more detailed studies are still required to resolve conflicting or inconclusive outcomes from these investigations before clinical use is warranted.

***Keywords*:** Natural product, Nicotine, Phytotherapy, Smoking.

Introduction

Smoking is a significant public health issue that affects people all over the world due to its firsthand and secondhand smoke nature. It greatly increases the risk of major non-communicable diseases such as lung cancer, chronic respiratory disorders, and cardiovascular diseases, all of which can lead to mortality. Thousands of chemical compounds in tobacco smoke contribute to smoking toxicity,[1,2] among them is nicotine which is the principal psychoactive component that leads to and sustains addictive tobacco usage.[3,4] Nicotine, through various cellular pathways, influences cell proliferation, oxidative stress, apoptosis, and DNA mutation, all of which can lead to cancer and even promote metastasis; also causes resistance to chemotherapy and radiotherapeutic treatments.[5-7] Tobacco and tobacco smoke also contain tobacco-specific procarcinogenic nitrosamines such as N-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), which have been linked to an elevated risk of esophageal and lung cancer.[8] Nicotine has also been linked to reproductive system injury and osteoporosis, in addition to its reported carcinogenicity.[9-11] Many efforts have been made to tackle the problem of tobacco use disorder in the form of smoking taxation, mass media advertising campaigns, tobacco products health warnings, public smoking prohibitions and notably the behavioural interventions such as counselling.[12-14] Despite all these initiatives and policy changes, the cessation rate remains unsatisfactory due to the complex nature of human psychology and behaviour.

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For instance, teenagers will still opt to smoke rather than quitting despite being aware of the health concerns associated with smoking.[15] Several pharmacological interventions which include nicotine replacement therapy (NRT; patch, gum, spray, inhaler and lozenge), bupropion and varenicline are available for smoking cessation treatment. Unfortunately, long-term abstinence is difficult to achieve, and relapse remains a big issue for many trying to quit smoking. Smoking cessation aids also produce side effects such as nausea, dry mouth, weight gain and sedation.[16,17] The current smoking cessation medicines are said to have limited effectiveness in real-life situations, thus need to be combined with behavioural therapies for better success rates. Another contributing factor to low success rate of smoking cessation is the financial aspect as majority of smokers are from low- and middle-income nations where pharmacotherapy cessation aids are regarded as expensive.[12] In order to make treatments of nicotine use disorder more desirable to all smokers, a more effective yet affordable treatment options are required. Natural products may therefore become a potential source for the treatment of nicotine use disorder, either as monotherapy or in combination with NRT. For centuries, plants and herbs have been used as remedies for various ailments and conditions. The widespread use of traditional medicine is reported globally in both Western and Asian countries with varying local prevalence which ranges from 11% up to 60% of the studied population.[18-21] There is not much conclusive data available regarding the use of natural products in nicotine use disorders, but they may play an equally important role as a potential pharmacological agent for cessation of smoking. In fact, a considerably great amount of research has been conducted on the effects of natural products in nicotine use disorder. This review was conducted to identify the extent of potential that natural products have for use in the treatment of nicotine use disorder. Although interesting, it is noteworthy that this review does not cover the studies of natural products on nicotine-induced toxicity and carcinogenicity; it is acknowledged that such studies are available which include for instance, effects of natural products on nicotine-induced cardiotoxicity, osteoporosis, fertility as well as carcinogenesis.[10,22-25] The current review rather focuses on natural products which can assist towards smoking cessation as it is seen as a primary strategy to prevent all other related toxicity and carcinogenicity in the first place.

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Methodology

Selection of Plant Extracts And Compounds Studied For Treatment Of Nicotine Use Disorders

In searching for the potential natural products for smoking cessation, this review employs a search strategy across PubMed, Ovid Medline and Scopus databases by using keywords such as "natural product", "phytotherapy", "herbal remedies", "smoking", "nicotine use disorder", "tobacco use disorder", "nicotine dependence" and "nicotine addiction", where the Boolean operators 'AND' and 'OR' were used to join the keywords as required. Data were extracted from *in vitro* studies, animal studies and human-controlled trials. In this review, a total of 14 plants and 7 bioactive compounds, as listed in Table 1 and Table 2 respectively, have been previously investigated for their potential values in the treatment of nicotine use disorders. One of the bioactive compounds listed, which is desformylflustrabromine, is extracted from marine source while others are of plant origin. In the following sub-section, only 5 plants and 4 bioactive compounds are discussed further in terms of their effectiveness in either *in vitro*, *in vivo* or human studies and their potential use in the treatment of nicotine use disorders. The remaining plants and compounds which were only reported by not more than 3 studies are considered inadequately proven thus not described in detailed herein, but are included in the summary tables in the Appendix (Table A1, A2 and A3).

Results and Discussion

Vernonia cinerea

Recent study reported that *Vernonia cinerea* tea showed a trend of reduced cigarette cravings among Thailand smokers aged 15-65 years.[38] The Smoking Urge Score of *Vernonia cinerea* was 36.25±7.41 at the beginning of the study and was reduced to 16.50±4.12 at week 1 and 14.25±4.19 at week 2. The number of cigarettes smoked also decreased from 1.00±1.15 (week 1) to 0.50±0.58 (week 2). An earlier study in northern Thailand using *Vernonia cinerea* juice presented similar outcome which showed reduction in smoking rate for light-cigarette and self-rolling cigarettes by 59.52 % and 54.47 %, respectively.[39] In addition, the blood oxidative stress conditions of the smokers also showed improvement when the levels of malondialdehyde, protein hydroperoxide, nitric oxide and total antioxidant capacity were analysed. Adverse events such as tongue bitter or numbness, nausea and headache did not seem to persist after the first week of treatment.[39] Another study reported that a 14-day *Vernonia cinerea* supplementation program with tea prepared using the whole plant scored a higher continuous abstinence rate (CAR) (28.1 %) compared to placebo (12.5 %), while after 24 weeks of treatment, CAR was 18.8 % with *Vernonia cinerea* and 9.4 % with placebo. Meanwhile, the seven-day point prevalence abstinence rate (PAR) also showed a similar trend; 43.8 % for *Vernonia cinerea* and 21.9% for placebo in week 12, then reduced to 34.4% for *Vernonia cinerea*, and 15.6 % for placebo in week 24. It is noted that these results were not statistically significant, presumably due to the relatively small sample size in detecting the effect of at least 9.4-22.0 % CAR or PAR difference between *Vernonia cinerea* and the placebo group. Nevertheless, it is worthy to note that the study did not reveal any serious adverse events.[40]

Another study aims to help young smokers to stop smoking by giving cookies containing 1.2 g of *Vernonia cinerea*, five cookies a day for six months. When compared to control group who received plain cookies, the CAR at 1-, 3-, and 6-month periods in the study group were significantly higher. The research also revealed that those consuming cookies containing *Vernonia cinerea* smoked less cigarettes as indicated by the measured carbon-monoxide (CO) level within the 6-month period where the average CO level of the study group was significantly lower compared to the control group. Additionally, the relationship between the cookies containing the plant extract and smoking cessation was significant, showing a 20.38 times higher chances of smokers consuming the cookies to quit smoking.[41] Meanwhile, another approach using *Vernonia cinerea* candy was developed and showed a higher number of participants gave up smoking within the 6-months period of consuming the candy. However, several side effects were reported which include dry mouth and throat, headache and insomnia but were resolved after the study was concluded.[41,42] It was proposed that nitrates in *Vernonia cinerea* may be the direct cause of tongue numbness and therefore made the subjects less favored to cigarette smell and taste. However, this needs to be investigated further. In summary, these studies support the use of *Vernonia cinerea* as an alternative smoking cessation agent due to its efficacy and safety. Furthermore, it is considered cost-effective as the daily cost of *Vernonia cinerea* is much more cheaper than bupropion and nicotine replacement therapy.[40] Nevertheless, future studies to include more volunteers are warranted to achieve a more accurate and statistically significant result. Investigations on long term efficacy and safety of *V. cinerea* alone or in combination with conventional therapies are also required to further support its use as an alternative.

Hypericum perforatum

Hypericum perforatum, or commonly known as St. John's wort, is used as an adjunct treatment to manage mild to moderate depression due to its antidepressant activity. It was proposed that it may be helpful to overcome cravings after nicotine withdrawal by avoiding a rapid reduction in synaptosomal dopamine concentration by dopamine re-uptake inhibition. A study using a standardized form of the Hypericum extract known as Ze 117 was shown to cause dose-dependent dopamine reuptake inhibition (100 to 750 µg/mL) in an *in vitro* study, which paved the way to further explore the potential use of *Hypericum* extract Ze 117 in smoking cessation treatments.[43] Having gone through extensive safety and efficacy testing, clinical trials have provided convincing evidence on Ze 117 being a potent and well-tolerated antidepressant thus strengthening its potential to be repurposed for smoking cessation.[44] In animal studies, *Hypericum perforatum* extract has been observed to decrease the signs of nicotine withdrawal by significantly increasing locomotor activity and decreasing the total nicotine abstinence signs score in mice where nicotine dependency has been experimentally induced.[45, 46] This was attributed to changes in serotonergic system where high dose of the extract shown to restore the reduction in cortical 5-HT, concomitant with restoration of 5-HT_{1A} receptor expression, evaluated 30 days after nicotine withdrawal.[46] Furthermore, a pilot human study showed that *Hypericum* extract Ze 117 was effective in improving cognitive deficits associated with nicotine withdrawal and reduced the number of smokers over the course of the study, however it was not significantly different from NRT.[44] The smoking status of the participants was measured by CO criteria where participants with CO value of less than 6 ppm were classified as non-smokers.

Table 1: Plants studied for their potential role in the treatment of nicotine use disorders

Plants
Hypericum perforatum (St. John's wort)
Panax ginseng (Asian ginseng)
Rhodiola rosea (Golden root)
Tabernanthe iboga (Iboga)
Vernonia cinerea (Little ironweed)
Citrus aurantifolia (Lime)[a]
Passiflora incarnata (Purple passion flower)[a]
Piper nigrum (Black pepper)[b]
Angelica archangelica (Angelica)[c]
Angelica gigas NAKAI (Korean Angelica)[c]
Coptidis rhizome (Huanglian)[c]
Glycyrrhizae radix (Licorice root)[c]
*Paecilomyces japonica (*Chinese mushroom*)*[c]
Ixeris dentata (Sowthistle)[c]

[a]reported by three studies; [b]reported by two studies; [c]reported only by one study

Another extended study on 60 individuals also implied that Ze 117 is as effective as transdermal NRT in smoking cessation because there was no significant difference in the mean number of smokers at 10 weeks following the quit date between the treatment groups.[47] It is noted that the study also reported that Ze 117 treatment alone significantly reduced craving towards smoking compared to NRT alone or a combined therapy of NRT and Ze 117.[47] However, in an earlier randomized, blinded, placebo-controlled, three-arm, parallel group, dose-ranging clinical trial it was observed that there were no significant effects in smoking abstinence rates and withdrawal signs among abstinent subjects.[48] Another similar finding was also reported which demonstrated that St. John's wort was safe and well tolerated but it did not increase smoking cessation rates with no significant differences in the urge to smoke, tobacco withdrawal symptom composite score, or composite provisional withdrawal symptom score between St. John's wort active and St. John's wort placebo groups.[49]

Overall, current evidences on efficacy of *Hypericum perforatum* in smoking cessation are conflicting. This may be attributed to the use of extracts which is generally known to be biologically variable to some extent. However, having noted that the preliminary evidence demonstrated the efficacy of Hypericum extract Ze 117 is comparable to NRT, it is worth to further investigate which requires larger randomized double-blind study to support its potential use in smoking cessation.

Panax ginseng

Panax ginseng is commonly referred to as ginseng or Korean ginseng. It is used to treat acute alcohol poisoning in China.[50] *Panax ginseng* contains saponins, which prevent the behavioural hyperactivity caused by psychomotor stimulants. Ginseng total saponin (GTS), inhibited both nicotine-induced hyperactivity by approximately 40-55% and nicotine-precipitated conditioned place preference (CPP) by 45-65 % when administered 1 hour prior to nicotine injection[51, 52] It was shown that GTS inhibited the development of postsynaptic dopamine (DA) receptor supersensitivity in nicotine-induced CPP by inhibiting apomorphine (a DA receptor agonist) ambulatory activity by almost 30% when compared to control group. In addition to that, the development of nicotine-induced reverse tolerance was also inhibited.[52] Meanwhile, an *in vivo* microdialysis demonstrated that maximum DA release induced by intra-striatal nicotine infusion at milimolar concentration could be inhibited by systemic GTS pre-treatment up to almost 60 %.[53] A different study reported an increase in DA release in nucleus accumbens produced by systemic nicotine injection was clearly attenuated by GTS while pre-administration with GTS abolished nicotine-induced tyrosine hydroxylase mRNA elevations. GTS also further enhanced nicotine-induced c-fos and c-jun mRNA levels at both ventral tegmental area and nucleus accumben regions.[54] However, Kim et al. [55] showed that GTS inhibited nicotine-induced enhancement of dopaminergic transmission by decreasing the expression of nicotine-induced Fos protein in the nucleus accumbens and striatum by 32% and 36% , respectively. Therefore, further studies are required to study the mechanism of GTS in the regulation of nicotine-induced immediate early gene. Furthermore, the same group also demonstrated that systemic pre-treatment with GTS can dose-dependently inhibit nicotine-induced hyperactivity and the release of DA from the striatum. GTS administered intraperitoneally at a dose of 100 and 400 mg/kg was able to decrease the nicotine-induced maximal locomotor activity by 37 % and 58 %, respectively.[55] The same GTS doses inhibit nicotine-induced maximal DA response by up to 76 %. In summary, data from animal studies have shown the potential of GTS in the treatment of nicotine use disorder through which can be further expanded to future translational research.

Tabernanthe iboga

Tabernanthe iboga (family Apocynaceae) is a West African shrub that contains ibogaine, a naturally occurring psychoactive indole alkaloid found in the root and bark. The efficacy of ibogaine has been claimed in the treatment of cocaine and opioid use disorders.[56] A study carried out by Benwell *et al*.[57] demonstrated that ibogaine can significantly reduce nicotine-induced dopamine release but not nicotine-induced hyperlocomotion in rats. However, ibogaine did not decrease sensitized locomotor responses to nicotine [58]. Additionally, the primary human metabolite of ibogaine, noribogaine attenuated nicotine drug taking behaviour in a dose-dependent manner by significantly reducing nicotine infusion and decreasing nicotine self-administration in rats by 13 % at 12.5 mg/kg. Meanwhile, higher concentration of noribogaine (50 mg/kg) was comparable to varenicline, which was equi-effective to 1.7 mg/kg intraperitoneal varenicline.[59] It was proposed that the ibogaine treatment effects seen in human for inpatient detoxification of cocaine and heroin may be due to the action of noribogaine as the pharmacokinetic clearance rate of noribogaine is slow.[60]

At molecular level, a study showed a significant decrease in nicotine-induced extracellular dopamine levels when pre-treated with ibogaine prior to nicotine infusion, suggesting that ibogaine may help to reduce the nicotine rewarding effect.[61] However, the reported effects of ibogaine on the dopamine metabolite, 3, 4-Dihydroxyphenylacetic acid (DOPAC) were conflicting; one reported that ibogaine pre-treatment attenuated the increase in DOPAC induced by nicotine[61] while in another study DOPAC level was significantly enhanced by a single ibogaine pre-treatment.[57] It was suggested that the divergence of the results may be due to differences in the schedule of nicotine administration, probe implantation protocols or preparation of ibogaine solution. Pre-treatment of cultured chromaffin cells with 10μM ibogaine inhibited catecholamine release induced by acetylcholine up to 70 %; release of mesolimbic catecholamine is one of the causes of drug addiction. The authors suggested that the site of action of ibogaine is the nicotinic receptor, because the primary pathway of acetylcholine stimulation in bovine chromaffin cells is through nicotinic acetylcholine receptors.[62] However, there were reports of cardiotoxicity and neurotoxicity associated with *Tabernanthe iboga*.[63, 64] Nevertheless, if its anti-addictive properties are potentially effective, future studies should consider to modify the chemical composition of ibogaine in order to reduce its toxicity and enhance its safety.

Rhodiola rosea

Rhodiola rosea,also known as golden root or roseroot, is one of the members of family Crassulaccae, which grows in arctic regions of Europe and Asia. . *Rhodiola rosea* has been used for centuries in traditional folk medicine to stimulate the central nervous system, improve physical and mental performance, longevity and resistance to high altitude sickness, and to restore from fatigue and symptoms of asthenia following intense physical and psychological stress.[65] Furthermore, it has anxiolytic, anti-depressant and anti-stress properties.[66,67] Flavonoids, monoterpenes, triterpenes, phenolic acids, phenylethanol derivatives (salidroside and tyrosol) and phenylpropanoid glycosides such as rosin, rosavin and rosin are present in the rhizomes of *Rhodiola rosea*, but the most pharmacoactive compound of rhizome is salidroside, a component with known therapeutic activity.[68] *R. rosea* L. extract (RHO), a hydroalcoholic extract of *R. rosea* L. and salidroside were tested in both the acquisition and expression of conditioned place preference (CPP) induced by nicotine to investigate the effects on nicotine rewarding properties. The results demonstrated the ability of RHO extract and salidroside to significantly decrease the rewarding properties of nicotine at different concentrations. The researchers also showed that both priming- and stress-induced reinstatements of CPP were abolished by RHO extract and salidroside.[69] In addition to that, they have shown that RHO (10, 15, 20 mg/kg) was also able to prevent and counteract somatic signs such as head shaking, paw tremors, body tremors, ptosis, jumping, piloerection and chewing induced by nicotine withdrawal in a dose-dependent manner.[70] The RHO treatment given before the induction of nicotine dependence also prevented the nicotine withdrawal anxiety-like behaviour characterised by increasing light time, latency time and entries in the light/dark box test, as well as increasing distance travelled and ambulation time concomitantly with decreased immobility time when measured for locomotor activity by open-field test. Similar acute effects were also observed when high dose of RHO extract was given twice during 20-hour nicotine withdrawal period.[70]

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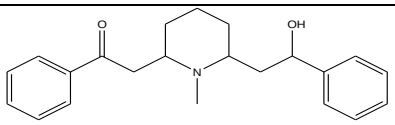
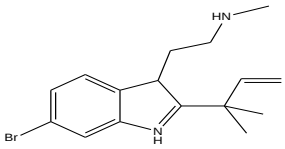
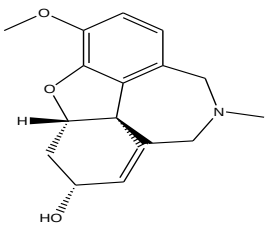
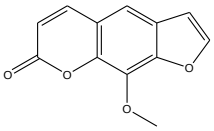
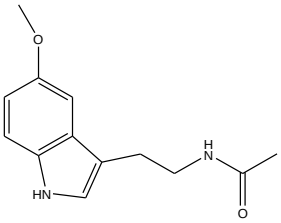
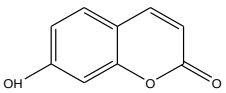
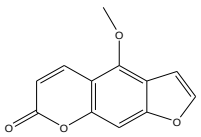
Table 2: Bioactive compounds reported for their potential in the treatment of nicotine use disorders

Bioactive compounds	Biological sources[d]	Chemical structures
Lobeline	*Lobelia inflata* [26]	
Desformylflustrabromine	*Flustra foliacea* [27]	
Galantamine	*Galanthus nivalis* [28]	
Methoxsalen	*Ammi majus* [29], *Psoralea corylifolia* [30], *Pastinaca sativa* [31]	
Melatonin[a]	*Coffea arabica (L.), Brassica hirta* [32-34]	
Umbelliferone[c]	*Coronilla varia L., Ruta chalepensis*[35, 36]	
Bergapten[c]	*Heracleum sibiricum, Heracleum verticillatum*[37]	

[a]*reported by three studies;* [c]*reported only by one study*

[d]*examples of sources reported to have the bioactive compounds*

All these results indicate not only that RHO administration after nicotine discontinuation can attenuate signs of abstinence withdrawal, but can also influence the development of nicotine dependence when administered with nicotine. Moreover, progressive reduction in 5-HT and diencephalic 5-HT_{1A} expression was observed in animals in which nicotine dependence was experimentally induced and oral treatment with *Rhodiola rosea* resulted in a significant increase of 5-HT level and diencephalic 5-HT_{1A} expression, which indicates the role of the serotonergic system in mediating the effects of *Rhodiola rosea*.[71] The evidence from these animal studies suggest that *Rhodiola rosea* extracts have the ability to counteract nicotine withdrawal syndrome, reduce craving and prevent smokers from relapse. In the future, studies such as elucidating the mechanism of action of *Rhodiola rosea* on changes of neurotransmitter levels in the brain and evaluating the effects of other active compounds such as tyrosol, rosin, rosavin and rosarin may have on nicotine use disorder should be carried out.[68] In contrast to suggestion made by a study[71] that the effects of *Rhodiola rosea* do not involve monoamine oxidase, another study[70] proposed that *Rhodiola rosea* might inhibit monoamine oxidase to help in smoking cessation, and therefore further investigations can help to clarify this contradiction. Most importantly, more data is required on whether *Rhodiola rosea* will be effective as a smoking cessation aid in human as observed by the positive results seen in animal models.

Bioactive Compounds

Galantamine

Galantamine, an Amaryllidaceae type alkaloid, is a long acting, selective, reversible and competitive inhibitor of acetylcholinesterase, an enzyme that breaks down acetylcholine and hence increases synaptic acetylcholine levels. It can be obtained from the genera *Amaryllis*[72], *Hymenocallis*[73] *Galanthus*,[74] *Hippeastrum*,[75] *Lycoris*,[76,77] *Haemanthus*[78], *Ungernia*,[79] *Leucojum*,[80,81] *Zephyranthes*[82] and *Narcissus*.[78,83,84] Galantamine has been approved by the Food and Drug Administration (FDA) to alleviate cognitive deficits associated with Alzheimer's disease[85, 86] and also has potential efficacy in the treatment of cocaine use disorder.[87] Recently, galantamine has been suggested as an effective strategy to facilitate smoking cessation and abstinence by enhancing endogenous cholinergic transmission. This has been supported by several studies that showed attenuation of nicotine self-administration and preventing reinstatement of nicotine-seeking behaviour in rodents.[88-90] However, human studies showed mixed results.[90-92] It was shown that pre-treatment with galantamine can significantly reduce the number of nicotine infusions in rat but also significantly decrease food self-administration compared to saline control.[88] In another animal study, repeated administration of galantamine significantly attenuated the self-administration of nicotine compared to saline-treated controls of the 10-day treatment phase.[90] Another study showed that nicotine self-administration was attenuated by acute galantamine administration,[89] while nicotine reinstatement was reduced. Furthermore galantamine produced a significant partial generalization nicotine discriminative stimulus in rats[93] and monkeys[94] like those observed for partial nicotinic acetylcholine receptor (nAChR) agonists cytisine or varenicline.[95] Recently, a study has investigated the effects of two weeks of galantamine on smoking behaviour in 30 healthy, treatment-seeking smokers who smoke more than ten cigarettes per day.[90] Relative to placebo, galantamine intake showed a 12% reduction of cigarettes per day as opposed to 7% reduction in placebo. Compared to baseline, smokers taking galantamine reported less satisfaction and rewarding with smoking after two weeks. However, in another study which involved 60 participants, it was found that galantamine extended-release (8 or 16 mg/day) decreased smoking in a laboratory choice task and reduced urine cotinine levels but the researchers did not observe decreased daily cigarette consumption or smoking pleasure associated with galantamine administration in either laboratory or ecological momentary assessment data (EMA).[92] EMA is considered a powerful assessment tool because it is a real-time measurement which can assess participants' drug dependency in one's natural environment and daily activities.[96] The authors concluded that galantamine was unlikely to improve cognitive performance in the laboratory or during EMA as most of the parameters studied did not show significant interaction with treatments. The effect of galantamine on cognitive performance was also tested in twelve participants in a different study using the Go/No-Go task, where there was no decrease in performance; the results even showed that the performance of the No-Go trials was improved.[97] The findings are consistent with a separate study in which 1mg/kg galantamine administration was able to reverse nicotine withdrawal-induced cognitive deficits in mice.[98] Moreover, another study also showed that a 4-day treatment period with galantamine (8 mg/day) reduced the self-reported ratings of "like the drug effects", "good drug effects", "bad drug effects" and "stimulated" in response to intravenous nicotine. In addition to that, galantamine also reduced the diastolic blood pressure.[97] However, the limitation of the above human-controlled trials is small sample size. Therefore, larger randomised clinical trials should be carried out to determine if galantamine can improve smoking cessation outcomes. Based on these findings, enhancing cognitive function by galantamine can be a potential treatment strategy for smokers who are trying to quit smoking.

Methoxsalen

Methoxsalen is a natural furocoumarin that can be obtained from several plant species, including *Ammi majus*,[29] *Psoralea corylifolia*[30] and *Pastinaca sativa*.[30, 31, 99, 100] It is also known as xanthotoxin and is a pigmentation agent used in the treatment of psoriasis cutaneous, T-cell lymphoma, and vitiligo.[101-103] Methoxsalen is a potent inhibitor of CYP2A6 nicotine metabolism in the liver microsomes of adult male ICR mouse with a K_i of 0.32±0.03 μM.[104] An animal study demonstrated that the administration of methoxsalen intraperitoneally significantly enhanced C_{max} of nicotine, prolonged the plasma half-life of nicotine and increased its area under the curve compared to intraperitoneal vehicle treatment.[105] Similarly, the mean plasma nicotine and mean nicotine area under the curve were increased by methoxsalen by 47% and 63%; and nicotine clearance was decreased by 39%, compared to placebo in a study involving 7 abstinent smokers receiving oral methoxsalen (30-50 mg) one-half hour before three subcutaneous nicotine injections (31 μg/kg) given at hourly intervals.[106] In addition, *in vivo* studies have shown that methoxsalen can modulate nicotine-induced behavioural effects. A significant improvement in cognitive processes in the mice treated with xanthotoxin (an alternative name to methoxsalen) and nicotine in the passive avoidance test was revealed as compared to xanthotoxin-treated mice or nicotine-treated mice. In addition to that, the immobility time in the forced swimming test used to evaluate antidepressant activity was reduced when xanthotoxin (15 mg/kg) and nicotine (0.2 mg/kg) were administered together compared to monotherapy of either xanthotoxin or nicotine.[107] Using CPP as a standard preclinical behavioural model used to study the rewarding and aversive effects of nicotine, methoxsalen (15 and 30 mg/kg) pre-treatment was seen to produce a significant increase of nicotine-induced place preference in mice; however this was attenuated at the highest dose of methoxsalen (45 mg/kg)[108] possibly due to the gradual development of aversive properties at higher nicotine concentrations[109] as inhibition of methoxsalen on mouse CYP2A5 (ortholog to human CYP2A6) increased bioavailibility of nicotine. In rats that were spontaneously withdrawn from chronic nicotine infusion, low dose nicotine (0.05mg/kg) was seen to be able to reverse withdrawal symptoms and this effect was more pronounced in rats also receiving methoxsalen. These results suggest that methoxsalen can potentially be given concomitantly with low dose nicotine replacement therapy (NRT) in the treatment of nicotine use disorder to improve the efficacy of NRT.[108] Neither abuse potential nor clinical side effects were detected, suggesting that methoxsalen alone or in combination with NRT is safe.[110] Furthermore, pre-treatment of methoxsalen (15 mg/kg, i.p.) in mice prolonged the duration of nicotine-induced antinociception and hypothermia.[105] This observation provided supporting evidence of the enhanced nicotine-induced antinociception and hypothermia effects by methoxsalen in mice in a dose-dependent manner.[104] It was demonstrated in human study that oral methoxsalen attenuated nicotine clearance and thus increased its plasma level, resulting in decreased cigarette smoking and breath carbon monoxide by 24% and 47% respectively, compared to placebo. In addition, the

same dose of methoxsalen also decreased participants' current self-rated desire to smoke, as measured by visual analogue scale.[110]
Interestingly, the same research group later furthered the investigation and reported that concomitant to a higher plasma nicotine/expired-air CO (number of cigarettes smoked maintained during 3 days) upon methoxsalen treatment, it also significantly converted more of the tobacco potent procarcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) to its inactive form.[106] NNK is normally converted to a mutagenic reactive metabolite catalysed by CYP2A6; this study shows that by inhibiting CYP2A6, methoxsalen has a dual effect, which is reducing tobacco smoking and also its procarcinogen. Taken together, these studies shed new light on methoxsalen as a potentially helpful adjunct therapeutic agent in the process of tapering down cigarette consumption with the aim of complete cessation. A larger cohort in future clinical studies can help confirm the efficacy or safety of methoxsalen as smoking cessation treatment. Nevertheless, future studies should also consider the toxicity of methoxsalen as this has been reported in several studies, for example on ocular as well as reproductive systems.[111, 112]

Lobeline
Lobeline is an alkaloid compound extracted from the leaves of the Indian tobacco plant, *Lobelia inflata*.[113] Its proposed therapeutic uses include on spasmodic asthma, as a respiratory stimulant, relaxant and emetic.[114] Lobeline interacted with nicotinic receptors in a concentration-dependent manner and inhibited the effects of nicotine in voltage-clamped *Xenopus* oocytes expressing α4β2 nAChRs.[115] Lobeline was shown to significantly reduce mice immobility time in the forced swim test, which is a measure of nicotine withdrawal-induced depression-like behaviour, suggesting that lobeline produced antidepressant-like effects.[116] The behavioural change was accompanied by a reduction of nicotine withdrawal-induced norepinephrine elevation in prefrontal cortex and hippocampus.[116] Furthermore, another study[117] demonstrated that lobeline (3 mg/kg) attenuated nicotine-induced hyperactivity and sensitization following repeated administration of nicotine. In a multicentre phase III trial which tested the efficacy of sublingual lobeline sulphate in smoking cessation, it was shown that there was no statistical significance between the placebo group and the lobeline sulphate group.[118] DIPSTOP™, a liquid form of lobeline, had no effect on craving and nicotine withdrawal over 48 hrs of deprivation in smokeless tobacco users. Nevertheless participants reported significantly lower problems of concentration (assessed by The Minnesota Nicotine Withdrawal Scale) in the presence of DIPSTOP™.[119] In a much earlier study, Davidson et. al. carried out a 4-week study and failed to show that 0.5 mg lobeline troches has better effect than placebo.[120] Importantly, a systematic review has reported that it is not evident that lobeline is useful for long-term effects in smoking cessation.[121]
Although lobeline has shown reasonable efficacy in preclinical investigations, all three clinical studies have shown no significant efficacy of lobeline in the treatment of nicotine use disorder. The conflicting results may possibly be due to the different aspects of nicotine withdrawal investigated where the *in vivo* studies focused on depression-like behaviour while the clinical studies looked at more holistic indicators of smoking. It may be worthwhile to pursue investigation on the usefulness of lobeline on smokers experiencing depression or mental illness, as this subset of smokers is less supported by the currently available smoking cessation treatment regimen.

Desformylflustrabromine
Desformylflustrabromine (dFBr) is an alkaloid isolated from marine bryozoan *Flustra foliacea*.[122] It is a positive allosteric modulator (PAM) of nAChR with higher selectivity to the α4β2 nAChR.

Table 3: Summary of effects of reported plants/bioactive compounds used to study nicotine use disorders

Plants/Bioactive compounds	Type of studies	Effects	References
Hypericum perforatum	human	Ameliorate cognitive deficits associated with nicotine withdrawal by modulating serotonergic and/or dopaminergic function in the brain.	44
	in vitro	Inhibit dopamine reuptake.	43
	in vivo	Decrease the signs of nicotine withdrawal by normalizing the level of serotonin.	46
Panax ginseng	*in vivo*	Inhibit nicotine-induced dopaminergic activation.	51-55
Rhodiola rosea	*in vivo*	Counteract nicotine withdrawal symptoms by normalizing serotonin decrease caused by nicotine withdrawal.	70, 71
Tabernanthe iboga	*in vivo*	Decrease nicotine-induced dopamine release and inhibit self-administration of nicotine in the rats.	57, 59, 61
	in vitro	Inhibit catecholamine release (cause of drug addiction)	62
Vernonia cinerea	human	Improve smoking abstinence rates.	38-42
Desformylflustrabromine	*in vivo*	Reverse nicotine withdrawal signs and reduce nicotine self-administration by prolonging the response of nicotinic acetylcholine receptors.	88, 125
Galantamine	*in vivo*	Reduce nicotine self-administration by acting as acetylcholinesterase inhibitor and prolonging the effects of nicotinic acetylcholine receptors	89, 90, 93, 98
	human	Reduce smoking rate, satisfaction and reward.	90, 92, 97
Methoxsalen	human, *in vivo*	Decrease plasma nicotine by inhibiting its metabolism.	105, 107, 108, 110
Lobeline	*in vivo*	Reduce nicotine-induced hyperactivity.	116, 117
	human	Not effective as a smoking cessation agent.	118-120

This binding greatly enhances the affinity for ligands, the intrinsic efficacy of the receptors and the likelihood of nicotine and acetylcholine-induced channel opening.[123, 124]
Therefore, PAMs can significantly improve and prolong the nicotine-induced and endogenous acetylcholine-induced responses of nAChRs; smokers experience the same nicotine reinforcing effects while consuming less nicotine. *In vivo* study showed that 0.02, 0.1, and 1 mg/kg dFBr injected subcutaneously reversed nicotine withdrawal symptoms dose-dependently after chronic nicotine infusion in a well-established male mouse model of spontaneous nicotine withdrawal. Spontaneous signs of nicotine withdrawal were tested in anxiety-like behaviours, somatic signs and hyperalgesia. Nicotine withdrawal anxiety-related behaviour was significantly reversed by high dose of dFBr. For somatic signs of nicotine withdrawal, significant dFBr effect was observed at both 0.1 and 1mg/kg. When the mice were evaluated for hyperalgesia signs of nicotine withdrawal using the hot-plate test, lower concentrations of dFBr in nicotine minipump mice produced a reversal of 50-100%.[125] In another study, dFBr pre-treatment attenuated the behaviour of nicotine self-administration but not the behaviour of food self-administration. In contrast to nAChR agonists, α4β2 PAMs that do not activate the receptor directly may have little liability for abuse and dependence because they lack of self-reinforcing action. This was also demonstrated in the study, in which nicotine substitution with dFBr, similar to saline substitution, does not support self-administration behaviour.[88] Both studies suggest that dFBr may be used in the future as a smoking cessation agent. Moving forward, perhaps more natural products of marine origin can be discovered and may potentially be utilized for therapeutic purposes.

Conclusion

In conclusion, the reported plant extracts and active compounds derived from natural sources may inhibit nicotine-induced reactions and nicotine-use disorders by targeting various metabolic and signaling pathways of nicotine such as cholinergic, dopaminergic and serotonergic systems (Table 3). Therefore, these plants and active compounds may have great potential to be developed as smoking cessation agents. However, further studies, which include quality control and standardization, as well as large-scale clinical trials, are required. It is also of importance to note that the toxicity and safety profiles of these medicinal plants and natural products as smoking cessation therapies are somewhat still lacking in current reports and therefore need to be adequately addressed to avoid serious harmful effects.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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