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Mini-review

# Adulteration of cannabis with tobacco, calamus, and other cholinergic compounds

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## Abstract

A shifting demographic of people admix cannabis with cholinergic agents, intent upon enhancing cannabimimetic effects or reducing adverse effects. Augmentation of cannabimimetic effects with tobacco (or nicotine) has been corroborated by in vitro mechanistic studies, animal behaviour studies, anecdotes from patients, and one clinical trial. The mechanism may be pharmacokinetic and pharmacodynamic. This trend of adultering cannabis with tobacco poses a problem because of the adverse effects of tobacco; solutions are suggested. The grey literature also reports admixtures of cannabis and calamus root, with the intent of reducing adverse effects of cannabis. At least one compound in calamus root (beta-asarone) blocks acetylcholinesterase (AChE). Contrary to expectations, AChE blockade diminishes cannabimimetic effects. Obviously more research needs to be done.

**Key words:** Cannabis, endocannabinoid, Nicotiana tabacum, Acorus calamus, nicotinic acetylcholine receptor, muscarinic ACh receptor, acetylcholinesterase



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## Introduction

Black market cannabis (marijuana, hashish) has a chequered history of contamination and adulteration. Contamination largely consists of fungi, bacteria, and pesticide residues. Contamination and adulteration differ by intent. Adulteration is volitional. Cannabis may be adulterated with other psychoactive compounds, for primarily two reasons: the adulterant may enhance efficacy in low-quality cannabis, or the adulterant may mitigate the side effects of cannabis.

This article enlarges upon a case series by McPartland et al. [1], who described cannabis adulterated with a variety of compounds that share a common trait—cholinergic modulation. This trend is not new. In India, cannabis has long been adulterated with cholinergic dhatura (Datura metal), henbane (Hyoscyamus niger), betel nut (Areca catechu), and it was mixed with tobacco (Nicotiana tabacum) shortly after the Portuguese imported tobacco to India from Brazil [2]. Cholinergic compounds may substitute for endogenous acetylcholine (ACh) at nicotinic acetylcholine receptors (nAChRs) or at muscarinic ACh receptors (mAChRs), or block acetylcholinesterase (AChE), the enzyme that breaks down ACh. This article will focus upon two cholinergic compounds: ubiquitous tobacco, and enigmatic calamus (Acorus calamus).

## Tobacco and nicotine

The case series by McPartland et al. [1] was not the first to report that tobacco augments the „cannabimimetic" effects of cannabis. The English prohibitionist Whitelaw Ainslie [3] stated tobacco enhanced cannabis intoxication. From a different perspective, O'Shaughnessy [4] noted that dhatura, another cholinergic herb, increased the effects of cannabis. Fishbein [5] described patients who „dipped" tobacco cigarettes in fluid extracts of pharmaceutical-grade cannabis available in the early 1900s. A recent comparison of canna-

bis-using chronic pain patients versus recreational cannabis users revealed a higher rate of admixing cannabis and tobacco in the chronic pain patients [6]. An independent chi square analysis of that data shows the higher rate in chronic pain patients approached statistical significance ($p = 0.14$).

Demographic trends regarding the admixture of cannabis and tobacco seem to be shifting. Fewer people in some European countries including Germany may add tobacco to cannabis, as hashish consumption has been replaced by marijuana consumption (F. Grotenhermen, pers. commun., 2008). Currently, up to 80% of cannabis is mixed with tobacco in England [7]. Within the past 15 years in the US, tobacco has gained a reputation for enhancing the cannabis „high" amongst urban youth [8]. This belief and the practice of admixing tobacco and cannabis has grown into a cross-cultural phenomenon. In a recent survey of US university students, 40.5% of respondents admitted to mixing cannabis and tobacco, and 18.9% reported that they smoked tobacco to prolong and sustain the effects of cannabis [9]. This phenomenon has been verified in animal studies that show nicotine enhances tetrahydrocannabinol (THC) discrimination [10], and enhances some of the effects of THC or synthetic cannabinoids [11-17]. On balance, a few studies report no interactions or negative interactions (e.g., [18]). One human clinical trial reported that nicotine enhanced the cannabis „high" in all subjects, but caused greater stimulation in male subjects and greater sedation in female subjects [19].

## Tobacco pharmacokinetics

The mechanisms underlying this phenomenon remain unknown. The literature is full of mechanistic studies regarding the effects of cannabis upon tobacco, but rarely the reverse. Several authors have proposed a pharmacokinetic mechanism; the four facets of pharmacokinetic mechanisms are drug absorption, distribution, biotransformation, and elimination [20].

1. Absorption of THC may be improved by mixing hashish with tobacco. The tobacco enables hashish to remain lit, serves as filler, and smoothes the inhalation of poor quality hashish [21]. An improvement in burning efficiency (amount of THC released per gram of cannabis in a smoking machine) was documented by van der Kooy et al. [22], who concluded that mixing cannabis with 50% of tobacco might lead to inhaling a similar amount of THC as a 100% cannabis cigarette.
2. Distribution of THC in the blood and brain may be altered by compounds in tobacco (nicotine and polyaromatic hydrocarbons) by competing for available lipoproteins and albumin in plasma. Furthermore, tobacco compounds may alter blood-brain barrier permeability [1].
3. A biotransformation mechanism was proposed by Starks [24], who suggested tobacco transformed cannabidiol into THC, which seems unlikely. Two cytochrome P450 enzymes, CYP2C9 and CYP3A4, biotransform THC into the active 11-OH-THC metabolite and the inactive THC-COOH metabolite [20]. Nicotine likely does not alter these enzymes (CYP2B6 is the main enzyme that metabolizes nicotine), but other compounds in tobacco might alter CYP2C9 and CYP3A4. In support of this hypothesis, smoking a joint containing THC 29 mg plus tobacco produced a peak THC-COOH / 11-OH-THC ratio of 3.4 (data from [23]), whereas smoking a joint with approximately the same amount of THC but no tobacco produced a peak THC-COOH / 11-OH-THC ratio of 6.4 (data from [25]) — nearly twice the amount of inactive metabolite.
4. Elimination of THC via the faeces and via the urine might be affected by tobacco, by an unknown mechanism.

## Tobacco pharmacodynamics

Instead of pharmacokinetics, McPartland et al. [1] proposed that tobacco altered the pharmacodynamics of THC (its targets and mechanism of action). Valjent et al. [12] argued that the effects of nicotine plus THC were not merely additive effects, instead the researchers proposed a synergistic interaction between the endocannabinoid and nicotinic systems. Synergistic effects are implied in studies where cannabinoids and nicotine are simultaneously administered, whereas sensitising effects are implied in studies where previous administration of nicotine alters the effects of cannabinoids. Sources of synergy between these systems include the following:

- upregulation of receptors and ligands;
- interplay and dimerisation at the receptor level;
- release of third-party neurotransmitters, such as nitric oxide;
- intertwining downstream signal transduction.

Nicotine may upregulate the density of cannabinoid receptors in the brain, sensitising individuals to the effects of cannabinoids [26, 27]. Nicotine may augment the levels of endocannabinoid ligands (AEA and 2-AG) in some brain regions [28, 29]. Endocannabinoids substitute for THC in animal drug- discrimination studies [29, 30]. Given the ability of the cannabinoid receptor (CB1) to cross-talk with other receptors [31, 32], it is tempting to speculate that CB1 and nAChR form a heterodimer. The combination of cannabinoid and nicotinic drugs have been shown to release third-party neurotransmitters (e.g., nitric oxide), and possibly involve downstream second-messenger mechanisms [12, 18]. The interaction of cannabis, endocannabinoids, and nicotine no doubt varies by species, gender, age, and brain region. The multifaceted effects of nicotine may be due to the heterogeneity of nAChR subunit compositions, and single nucleotide polymorphisms (SNPs) expressed in the population. This heterogeneity is ramified by nAChR downregulation, agonist trafficking, and exogenous cholinergic agents modulating the synthesis of endogenous ACh [33].

## Acetylcholinesterase inhibition

Acetylcholinesterase (AChE) is an enzyme that catabolises ACh. Compounds that block AChE (anti-AChE) will augment synaptic ACh and therefore enhance nAChR signalling. AChE blockade also enhances signalling at muscarinic ACh receptors (mAChRs). Eight in vitro studies demonstrated that mAChR agonists such as ACh, pilocarpine, carbachol, and oxotremorine reliably augmented endocannabinoid release and consequential CB1 signalling (see review in [1]). Animal studies have shown that pilocarpine and oxotremorine increased the effects of THC [10, 34].

Based on the evidence that nAChR and mAChR agonists augment the effects of cannabinoids, we would predict that anti-AChE compounds do the same. But they apparently do not. In animals studies, physostigmine (anti-AChE as well as a mixed nAChR and mAChR agonist and a nAChR allosteric agonist) enigmatically decreased THC discrimination [35], THC sedation [36], and THC memory deficits [37, 38]. In one clinical report, physostigmine decreased the THC „high," tachycardia, red eye, and dry mouth, although the patient experienced greater sedation [39].

Calamus root (Acorus calamus) contains beta-asarone, an anti-AChE compound [40]. Reports in the grey literature describe calamus diminishing cannabimimetic effects (e.g., [41]). Adding a „pinch" of dried, powdered calamus per pipe bowl of cannabis provides „mental clarity and memory enhancement" [42, 43]. Adding calamus to cannabis dates to ancient India; according to Ayurvedic medical texts, calamus „balances" and „neutralizes the toxic side effects" of cannabis [44]. The Ayurvedic usage of calamus as a sedative contradicts its traditional use by North American Cree Indians as a stimulant; the discrepancy may be due to pharmacological differences between Asian and American A. calamus [45].

## Conclusions

Animal studies [17] and human anecdotes [1] indicate that tobacco augments the medicinal benefits of cannabis. Physicians must discourage this practice. The use of cannabis by itself carries risks, but adding tobacco massively augments adverse effects. By mixing cannabis with tobacco, cannabis may be regarded as a „gateway" to tobacco dependence, a reversal of the typical developmental sequence for substance-use initiation [46].

Providing patients with better quality cannabis might serve as an alternative to adulteration; a legal and regulated supply might solve the problem. Legal breeders of Cannabis could modulate the cholinergic effects of Cannabis itself; the plant naturally produces many anti-AChE compounds, such as limonene, limonene oxide, α-terpinene, γ-terpinene, terpinen-4-ol, carvacrol, l-carvone, d-carvone, 1,8-cineole, p-cymene, fenchone, pulegone, and pulegone-1,2-epoxide [47-50].

**Conflict of interest statement**

The author previously served as a consultant for GW Pharmaceuticals (www.gwpharm.com/).

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