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Risk Analysis of Gene Flow from Cultivated, Addictive, Social-Drug Plants to Wild Relatives

L. G. Campbell[1,3] **· C. M. Blanchette**[1] **· E. Small**[2]

[1] Department of Chemistry and Biology, Ryerson University, Toronto, Ontario M5B 2K3, Canada
[2] Ottawa Research and Development Centre, Agriculture and Agri-Food Canada, Central Experimental Farm, Ottawa, Ontario K1A 0C6, Canada
[3] Author for Correspondence; e-mail: lesley.g.campbell@ryerson.ca

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Abstract

Addictive "social drugs" that are derived from plants range from reputable stimulants (e.g., coffee and tea) to stigmatized and dangerous preparations (e.g., ephedrine and cocaine). Both legal and illicit global trade has increased the geographic distribution of plants from which the principal social drugs are obtained. In turn, this range expansion increased opportunities to transfer genes controlling production of high levels of secondary chemicals because of increases in overlapping geographic distributions with sexually compatible domesticated, wild, and weedy relatives. We review the literature for evidence that the introduction of these chemicals into ecosystems could occur through gene flow in ten common, addictive, social drug crops: coca, coffee, cola, ephedra, khat, marijuana, opium poppy, tea, tobacco and yerbe maté. From the published literature of the potential evolutionary and environmental consequences of gene flow from popular social drug crops, we also analyse the subsequent unintended ecological or evolutionary consequences, such as increased weediness, loss of genetic diversity in sexually compatible wild relatives, or health and fitness consequences for herbivores of these crops. Given the rapid industrialization of many of these crops, we identify knowledge gaps and call for renewed attention to the study of their ecology and evolution.

Keywords Crop-wild hybridization · Gene flow · Genetic diversity · Medicinal plants · Secondary metabolites · Social drugs

Introduction

By a considerable margin, most chemical constituents in flowering plants are secondary chemicals – organic compounds produced during metabolism not directly involved in essential biological structures or in normal development or reproduction. Secondary compounds often protect plants against herbivory (Wink, 1988; Maag et al., 2015) or photodamage (Close & McArthur, 2002), act as tools for plant communication (Maag et al., 2015; van Dam & Bouwmeester, 2016) or interspecific competition (Maag et al., 2015), and/or may rarely represent excreted, unwanted metabolic products (Haslam, 1986). Plants that accumulate large amounts of secondary chemicals are often of immense economic significance (Small, 2004; Small, 2006), including culinary herbs and medicinal plants. Accordingly, plants with large concentrations of secondary chemicals are widely cultivated.

Drugs that are consumed for non-medical purposes are often termed “social drugs” or “recreational drugs.” These may be efficacious, useless, or dangerous; legally controlled (sales and/or consumption banned or restricted); employed for spiritual or religious purposes; or consumed alone or in the company of others. As a rule, these drugs are employed to produce a pleasant, satisfying mental state, and, for at least some individuals, the desire for repeated consumption may become addictive. In fact, of all the secondary chemicals produced by plants, among the most employed are those that are addictive. Indeed, most humans consume addictive plant secondary chemicals, often on a daily basis (Van Wyk & Wink, 2017). For instance, caffeine is the world’s most universally employed psychoactive chemical, mostly imbibed as coffee (from *Coffea* spp.), tea (from *Camellia sinensis*), cola (from *Cola* spp.), and maté (from *Ilex paraguariensis*), and eaten as chocolate (from *Theobroma cacao*) (Daly et al., 1998; Mitchell et al., 2014). Therefore, the most popular of the addictive, social plant inebriants are very widely grown and consumed, and thus represent an ideal group for examining the potential effects of gene flow from species with very high concentrations of secondary chemicals to their wild relatives that tend to produce less of such chemicals.

Plants grown for their production of addictive chemicals may be capable of transferring genes responsible for their biosynthesis to related species, which in turn could profoundly affect the ecology and evolution of the latter, as well as associated interacting organisms. Like any other crop trait, genes involved in pharmacological chemical pathways can spread *via* pollen and seed dispersal to populations of related crops, weeds, and wild relatives (Ellstrand, 2003). More so than other crops, gene flow from cultivated, addictive, social-drug plants may have unintended biosafety consequences, given their dramatic effects on vertebrate physiology (e.g., Ankley et al., 2007; Nutt et al., 2010, and later references). Here, we explore the potential ecological risks related to gene flow from cultivated, addictive, social-drug crops, a class of domesticated plants that is becoming increasingly widespread. Our observations are likely applicable to many crops that accumulate very high levels of secondary metabolites (Ellstrand, 2003; FAO, 2004; Snow et al., 2005).

While social-drug plants were historically restricted in distribution, the ranges of many of them are rapidly expanding due to increased cultivation and escape from cultivation through various mechanisms, such as interspecific hybridization and ferality (Plowman, 1979; Plowman, 1980; Hylander & Nemomissa, 2009; Cadena-González et al., 2013). Gene flow from crops or uncultivated populations derived from them can alter the pharmacological status of recipient, non-narcotic populations (e.g., Ellstrand et al., 2014). Domesticated plants often hybridize spontaneously with their sexually compatible crop and wild relatives when they come into contact (e.g., Whitney et al., 2010; Khoury et al., 2013; Ellstrand et al., 2014). Moreover, experimental and descriptive studies, using genetic markers, have demonstrated that crop alleles frequently enter and persist in natural populations (e.g., Snow et al., 2010; Campbell et al., 2016; Jhala et al., 2017).

Ecological consequences of crop-to-wild gene flow may have three consequences: 1) generation of more competitive weeds, 2) altered gene frequencies in wild plant populations, and 3) reduced survival and fecundity of natural herbivores. Here we describe examples of each, especially focusing on examples for which there are potentially negative ecological consequences to explore the possible risks that may arise from gene flow from social drug crops to wild relatives.

Generation of More Competitive Weeds. Gene flow from crops to weeds has commonly resulted in more aggressive or successful weed populations (examples include non-transgenic radish, *Bt* canola, herbicide resistant canola, herbicide resistant rice, insect resistant rice, *Bt* sunflower, weedy radish, wild bird's rape, weedy rice, weedy sunflower, among others; Snow et al., 2003; Campbell et al., 2006; Londo et al., 2010; Hovick et al., 2012; Liu et al., 2014; Sagers et al., 2015; Lu et al., 2016). Mechanisms by which the competitiveness of weeds could increase via crop-wild hybridization have been discussed elsewhere (e.g., Ellstrand & Schierenbeck, 2000; Whitney et al., 2006; Campbell & Snow, 2007) but include hybrid vigour (e.g., radish: Snow et al., 2001) and the transfer of alleles that directly influence relative plant competitiveness (such as associated with reduced susceptibility to herbivory (e.g., Snow et al., 2003) or allelopathy (see coffee example)).

Altered Gene Frequencies in Wild Plant Populations. When crop alleles enter the populations of wild relatives, they may persist for long periods (Snow et al., 2010), reducing genetic diversity while increasing genetic homogeneity (Campbell et al., 2016). This may cause the local extirpation (Hegde et al., 2006) or near extinction of the wild relatives (e.g., *Oryza rufipogon* Griff. subsp. *formasana* Masam. and S. Suzuki [Kiang et al., 1979]), cotton (*Gossypium darwinii* G. Watt and *G. tomentosum* Nutt. [Wendel & Percy, 1990]), and mulberry (*Morus rubra* L. [Burgess et al., 2005]). The loss of these wild relatives limits the genetic diversity of *in situ* or *ex situ* germplasm collections and will thus limit future crop development.

Reduced Survival or Fecundity of Natural Herbivores. When crops produce novel phytochemicals or novel dosages of phytochemicals (e.g., genetically engineered *Bt* crops, etc.), the growth and reproductive success of herbivore consumers may be inadvertently altered (Snow et al., 2003; Raybould et al., 2007), especially when they consume relatively large quantities of these chemicals – an event that might be more likely to occur in large crop fields (Prasifka et al., 2005). These novel chemical traits can be transferred among cultivars and from crop populations to their wild relatives (Snow et al., 2003; Rong et al., 2005). Non-target insect consumers of transgenic plants producing Cry proteins from *Bacillus thuringiensis* have been shown to sometimes experience negative fitness consequences but the consequences depend on the toxicity of the insecticidal proteins and their exposure to the insecticides (Garcia-Alonso et al., 2006, Romeis et al., 2008). For instance, Cry1ab proteins are unlikely to negatively affect non-lepidopteran herbivores (Glare & O'Callaghan, 2000, US Environmental Protection Agency (USEPA), 2001; Wolfenbarger et al., 2008). However, natural lepidopteran herbivores have been documented to ingest and experience negative impacts of the *Bt* toxins while consuming *Bt* genetically engineered plants (e.g., Raybould et al., 2007; Snow et al., 2003). Thus, growing pharmacological plants outdoors, in close proximity to herbivore populations, increases their access and may influence organismal health, depending on the dosage consumed, herbivore species, and the activity of the chemical (Hartmann, 1999; Baldwin, 2001; Wynn-Edwards, 2001; Agrawal & Konno, 2009).

The risk of transferring genes that control the expression of social drugs into wild non-drug plants, may also affect domesticated animals that consume altered plants. In stabilized ecological communities, wild animals typically have learned which poisonous plants and fungi to avoid, and are naturally cautious when they encounter unfamiliar plants (Iason & Villalba, 2006). Nevertheless, conceivably, when social drug genes escape into populations of wild relatives or non-cultivated populations via either crop-wild hybridization or ferality, gene transfer may, at least occasionally, imperil local herbivores. More likely, domesticated animals, whose natural instincts have been dulled, are likely to be affected. It is well known that pets and livestock are susceptible to poisoning by eating deadly plants (e.g., Fowler, 1983). Pet animals are unlikely to consume plants outside of urban areas, but livestock, grazing or foraging in wildlands, might well consume plants expressing introgressed traits.

Case Studies: Ten Globally Important Social Drug Crops

The ten social drug crops chosen for analysis include the plant sources of the most popular caffeine beverages (coffee, tea, cola, and maté) and the most commonly misused plant-derived drugs, as identified by Ashihara & Crozier (2001) and Nutt et al. (2010). Some of the widespread plant drugs are obtained from more than one species; we reviewed as many species as were necessary to account for a substantial majority of the drugs harvested. These case studies represent tropical, subtropical, and temperate species belonging to ten taxonomic families (and are presented in alphabetical order). The sample includes crops grown as annuals (*Cannabis sativa, Papaver somniferum*, *Nicotiana tabacum* – although *Nicotiana* is sometimes perennial) and shrubs (*Catha edulis*, *Ephedra spp.*, *Erythroxylum spp, Coffea spp., Camellia sinensis, Cola spp., and Ilex paraguariensis*). We used several citation indices (Web of Science, Google Scholar, Agricola) for our literature search (April–October, 2017). For each of the ten groups we reviewed: their taxonomy and geography (with particular regard to establishing the extent to which related uncultivated taxa and populations are potentially interfertile with social drug plants); identification of wild taxa or populations that are in danger of gene loss or even population extinction; pollen and seed vectors (the vehicles which transport genes from cultivated to non- cultivated populations); documented evidence of hybridization and gene transfer; information on the inheritance of the drugs (which affects the ability of the determining genes to develop the drug in targeted populations); information pertinent to the harmfulness of the drugs in herbivores; and considerations that endanger particular ecosystems.

Coca – *Erythroxylum coca* Lam., *E. novogranatense* (Morris) Hieron (Erythroxylaceae) [including four infra-specific taxa: *E. coca* var. *coca*, *E. coca* var. *ipadu*, *E. novogranatense* var. *novogranatense*, *E. novogranatense* var. *truxillense*]

Erythroxylum is a genus of about 230 mostly Neotropical species of small trees and shrubs. Cocaine-rich leaves can be obtained from at least 15 species (Bieri et al., 2006) but the primary sources are *E. coca* var. *coca*, *E. coca* var. *ipadu*, *E. novogranatense* var. *novogranatense*, and *E. novogranatense* var. *truxillense* (Ganders, 1979). Perhaps as a result of the U.S. “war on drugs” (Briones et al., 2013) and the associated political instability or the plant's long life-cycle, we could not find any publications describing the inheritance of the tropane-ester alkaloid, cocaine (methylbenzoylecgonine). With a heterostylous mating system, these plants tend to outcross (and may be self-incompatible in some taxa), although hand-crosses have demonstrated that selfing is possible in *E. coca* and *E. novagratense* var. *novagratense* (Ganders, 1979). The taxa differ in floral fragrance. The scent of *E. coca* is foetid, consistent with insect pollination (Ganders, 1979). Fruit may travel long distances since the drupes are dispersed by birds (Ganders, 1979). Finally, *E. coca* var. *coca* is planted as seeds whereas *E. coca* var. *ipadu* is propagated as cuttings, presumably making the latter more genetically homogenous than the former (Plowman, 1979). There are no germplasm collections or formalized breeding programs (Chung & Brink, 1999) which, in conjunction with active attempts to control the illicit market, makes the genetic diversity within these populations vulnerable to loss (Kangas, 1990).

Crop-to-wild gene flow in this group is complicated by a number of factors. Whereas *E. coca* var. *coca* is found as both apparently uncultivated populations and large plantations of cultivated plants, the other three taxa are only found as cultivated plants (and sometimes at smaller scale than the former) (Plowman, 1979). Therefore, gene flow from crops to non-crops is only possible when the recipient is uncultivated *E. coca* var. *coca*. Yet, feral and cultivated plants are perhaps impossible to distinguish – *E. coca* var. *coca* plantations may be abandoned and continue to survive in untended gardens which could be difficult to differentiate from seeds that have unintentionally grown in uncultivated areas (Plowman, 1979). Furthermore, there is little opportunity for varieties and species to exchange genes because their ranges rarely overlap and they have distinct ecological requirements (Plowman, 1979).

When *Erythroxylum* species do share habitats, varieties can interbreed, at least with moderate success (i.e., var. *coca* with var. *ipadu* and *vice versa*; var. *novogranatense* with var. *truxillense* and *vice versa*) (Bohm et al., 1982). Although occasional inter-specific F_1 hybrids can be produced, they appear to be sterile or nearly so (Bohm et al., 1982; Chung & Brink, 1999), suggesting physiological reproductive barriers have evolved (Plowman, 1979; Plowman, 1980). However, in regard to the influence of gene flow on the evolution of uncultivated *Coca* populations, more information is needed about population dynamics (e.g., effective population size, dispersal patterns), the mode of inheritance of key chemical pathways and the genetic variability of these genes, as well as the ecological role of *E. coca* in its natural landscape (summarized in Box 1).

We did not locate studies of the effects of cocaine on the survival and fecundity of natural herbivores of *Erythroxylum*. Yet, several lepidopteran larvae and fungi consume *Erythroxylum* species as food sources, sometimes as obligate herbivores (e.g., Blum et al., 1981; Sands et al., 1997). In fact, the use of lepidopteran and fungal species tolerant of cocaine have been proposed as means of biological control of cocaine plants (U.S. Congress, 1993). Clinical studies of the effects of cocaine (rather than fresh leaves) on laboratory rodents and humans indicate that there are deleterious effects on mammals. In particular, rats fed a low protein and high carbohydrate diet gained less weight if they also consumed coca leaves than controls (Burczynski et al., 1986). This is consistent with results from chronic cocaine administration to female house mice that exhibited slowed growth and development, delayed puberty, and decreased weaning weight of pups, relative to controls (Chen & Vandenbergh, 1994). Cocaine administration also temporarily suppressed the immune system of mice (Ou et al., 1989). That said, in rodents, short-term cocaine administration enhances flexible and goal-directed behavior in ever-changing environments, as well as psychomotor speed, whereas long-term cocaine exposure results in general cognitive impairment across various functions (Spronk et al., 2013).

Toxicity is always related to dosage, and the literature reporting the toxicity of the plants discussed in this review needs to be interpreted with the understanding that many animals, including humans, tolerate certain levels of consumption without exhibiting ill effects. In some cases, people misuse social drugs by consuming large amounts. The concentrations in social drugs can be far greater than in the plants, so herbivores that consume the green plants are less likely to absorb toxic quantities. Indigenous people who have a long history with particular inebriant plants usually use limited dosages for medical or spiritual practices (de Rios & Smith, 1977). For example, coca is used, apparently safely, in South America as a leaf tea or masticatory, but extracted cocaine is clearly a dangerously addictive substance (Nutt et al., 2010).

Box 1: Summary of Risk of Gene Flow from Coca to Wild Relatives.

- Risk of gene transfer to wild relatives:
  - Intraspecific: differences between cultivated and uncultivated plants not well understood, so risk, if any, is unclear.
  - Interspecific: Evidence of interfertility unevaluated for many close *Erythroxylum* relatives, but hybrid sterility suggests very limited risk.
- Risk of toxicity to animals: Laboratory animals often harmed, but risk to natural herbivores unevaluated.
- Risk of genetic swamping: Hybrid sterility suggests very limited risk.
- Risk of generation of invigorated weeds: Negligible.

Coffee – *Coffea arabica* L., *C. canephora* Pierre ex A. Froehner, *C. liberica* Bull. ex Hiern (Rubiaceae)

Coffee is produced from the seeds of *Coffea arabica*, and to a lesser extent, *C. canephora* and *C. liberica* (Davis et al., 2006). Caffeine biosynthesis in coffee is now well understood (Nagai et al., 2008). Caffeine content in *C. arabica* and *C. canephora* is quantitatively inherited and generally controlled by genes with additive effects, with different inheritance mechanisms controlling caffeine content in seeds vs. leaves (Priolli et al., 2008). In addition to the domesticated species, there are several uncultivated species that produce significant amounts of caffeine, primarily in low altitude west and central Africa, where the high-caffeine crops *C. arabica*, *C. canephora*, and *C. liberica* also originate, suggesting caffeine may be protecting these plants against indigenous herbivores in the region (Hamon et al., 2017).

Hybridization among *Coffea* species is well known. The three cultivated *Coffea* species (*C. arabica*, *C. canephora*, and *C. liberica*) hybridize spontaneously and can coexist in the same habitat (Lashermes et al., 2000: Davis et al., 2006: Gomez et al., 2016). Indeed, *C. arabica* is considered to be a naturally occurring species of hybrid origin as a well-known allotetraploid hybrid (Davis et al., 2006). Cultivated *C. liberica* can mate with wild, caffeine-free *C. pseudozanguebariae* and the trait for caffeine production has been documented to be transferred (Barre et al., 1998). However, knowledge is limited about the extent of hybridization in the genus.

None of the caffeine-producing *Coffea* species are considered weedy, so at least with respect to this alkaloid there are no “crop-wild-weed complexes”. However, as noted previously, hybridization has generated crop-wild hybrid offspring that produce caffeine and caffeine is known to possess allelopathic properties (Sugiyama et al., 2016). In fact, given their morphological intermediacy between a cultivated species and another wild species, two coffee “species” have been interpreted as hybrid lineages derived from crop-wild hybridization (*C. affinis* = *C. liberica* x *C. stenophylla*, Chevalier, 1947; Stoffelen, 1998; *C. bakossii* = *C. liberica* x *C. montekupensis*, Davis et al., 2006). Moreover, the cultivated coffee species have even been documented to produce fertile inter-generic hybrids (*Psilanthus ebracteolatus* Hiern × *Coffea arabica* L.; Couturon et al., 1998; Lombello & Pinto-Maglio, 2003; Lombello & Pinto-Maglio, 2004). When *C. liberica* hybridizes with wild, caffeine-free species, including *C. canephora* and *C. pseudozanguebariae*, F_2 offspring express caffeine in their tissues (Barre et al., 1998; Akaffou et al., 2012; Amidou et al., 2007). Although we are not aware of any *Coffea* species that has gone extinct as a result of crop-wild hybridizations (summarized in Box 2), we expect wild *Coffea* species to be relatively vulnerable to this event. Two caffeine-free species (*C. salvatrix* and C. *pseudozanguebariae*) can hybridize with the domesticated coffee species, which may make these wild species particularly vulnerable to genetic swamping. Of 103 *Coffea* species, 72 (ca. 70%) are threatened with extinction due to loss of habitat (Davis et al., 2006). Further, genetic variation within crop populations of (*C. arabica*) is relatively low (Wellman, 1961; Anthony et al., 2002) and this species has been assigned a “vulnerable” extinction threat globally (Davis et al., 2006; IUCN, 2017).

Caffeine biosynthesis occurs in immature leaves (especially those produced while the plant is flowering), upper part of the stem, flowers, and immature fruits (but is absent in cotyledons, lower stem, and root), and it is accumulated in the mature leaves (Kim et al., 2006; Ashihara et al., 2008; Wright et al., 2013). Caffeine can have diverse consequences for organisms that live near or consume the coffee plant and there are two hypotheses as to its adaptive role in coffee plants (Sano et al., 2013). Caffeine has toxic and allelopathic effects, directly restricting the growth and development of bacteria, fungi, arthropods, and plants (Kim et al., 2010) while supporting the establishment of young coffee seedlings (Baumann & Gabriel, 1984; Aerts & Baumann, 1994). Additionally, it has been hypothesized that endogenous plant defenses are indirectly stimulated or primed by caffeine through signaling pathways (Kim & Sano, 2008).

In some animals, at (naturally) low doses, caffeine tends to enhance memory retention and cognitive performance (Nehlig, 1999). For instance, when caffeine occurs in floral nectar, pollinator memories of receiving a reward are enhanced (Wright et al., 2013) and thus these flowers tend to receive more bee pollinator visitation (Thomson et al., 2015). Moreover, some insects (e.g., coffee berry borer, *Hypothenemus hampei*) can metabolize caffeine as a defense (Ceja-Navarro et al., 2015). However, some insects are clearly deterred from feeding on *Coffea* or caffeine. For instance, *Oligonychus ilicis* (Acari: Tetranychidae) is a pest of *Coffea canephora* (Gentianales: Rubiaceae) and *C. canephora* genotypes that are resistant to this mite species actually create resistance through a non-caffeine-related mechanism (instead trypsin-like protease inhibitors seem to differentiate *C. canephora* genotypes that are resistant and susceptible; Silva et al., 2015). Caffeine and other leaf extracts sprayed on a coffee leaf encouraged physical movement of the green scale (*Leucoptera coffeella*, a coffee pest) and reduced their feeding on treated, relative to untreated, coffee leaves (Magalhães et al., 2010; Fernandes et al., 2011; Fernandes et al., 2012). In contrast, caffeine stimulates egg-laying by the coffee leaf miner in coffee leaves (Magalhães et al., 2008). Moreover, when several caffeine biosynthetic pathway genes were expressed in tobacco plants, the leaves were unpalatable to tobacco cutworms (*Spodoptera litura*) (Kim et al., 2006).

Box 2: Summary of Risk of Gene Flow from Coffee to Wild Relatives.

- Risk of gene transfer to wild relatives
  - Intraspecific: classification uncertain, but genetic interchange with some putative ancestors seems very likely
  - Interspecific: Substantial
- Risk of toxicity to animals: Caffeine is a known toxin for many animals, and gene transfer is likely to affect natural herbivores
- Risk of genetic swamping: High
- Risk of generation of invigorated weeds: Low

Cola (kolanut) – *Cola* spp. (Sterculiaceae)

The genus *Cola* comprises about 125 species of evergreen trees of tropical lowland and montane forests of continental Africa. For millennia, people have chewed kolanuts, derived from *C. nitida* and *C. acuminata*, for their stimulating effects, due to the caffeine content (Somorin, 1973; Suzuki & Waller 1987; Atawodi et al., 2007). Occasionally *C. anomala* is also cultivated for similar purposes in the Cameroon highlands. This tree crop is naturally distributed along the west coast of Africa (Bodard, 1955). However, less is known about the ca. ten close wild *Cola* species in West Africa, despite their potential value for the genetic improvement of the crop (Hutchinson & Dalziel, 1958; Adebola, 2011). For instance, wild *C. ballayi* seeds appear to have the same properties as *C. accuminata*, when chewed. When land is cleared for development, *Cola* trees, regardless of the species, are often left standing but are treated as an unmanaged resource (Tachie-Obeng & Brown, 2004). There are also two field-based germplasm collections of the crop, maintained as living trees in Nigeria and Ghana (Adebola et al., 2002; Aburi Botanical Gardens, 2002).

Few papers, to our knowledge, explore the herbivore community of kolanut. The herbivores are diverse and change with developmental stage of the plants, and include seedling-specific pests (*Gryllotalpa africana*, *Brachytrypes membranaceus*, and *Zonocerus variegatus*), stem borers (*Phosphorus virescens* var. *jansoni*, var. nimbatus, and var. *gabonator*) and defoliators (*Sylepta semilugens*, *S. polycymalis*, *S. retractalis*, and *Anaphe venata*) along with frugivores (*Balanogastris kolae*, *Sophrorhinus quadricristatus*, *S. insperatus*, *S. duvenoyi*, *S. kolae*, *S. pujoli*, *S. gbanjaensis*, *Ceratitis colae*) (Daramola, 1974). Although some study of the biology of these pests has occurred and wild *Cola* species may act as a refuge for weevils when the crop plants are unavailable (e.g., Daramola & Taylor, 1975; Daramola, 1981), we did not locate analyses of the effect of *Cola*-derived caffeine on non-human animals of any kind. Caffeine is found in dozens of plant species (including those producing coffee, tea, and maté, discussed in this paper), and probably is a natural anti-herbivore agent (see the discussion for coffee).

The functionally monoecious mating system of the kolanut species is unusual because although it possesses male and hermaphrodite flowers, the viable pollen from the hermaphrodites has been confirmed to be non-functional in self- and cross-pollinations (Opeke, 1984). Cola species appear to be pollinated by animal vectors (Russel, 1955; Bodard, 1962). Flowering times of *C. nitida* and *C. acuminata* partially overlap, allowing for possible pollen transfer between them. *Cola nitida* flowers twice a year with a minor flowering event occurring in January and February and a major flowering event occurring between August–October. *Cola acuminata* only flowers between January and March (Adebola, 2011). The two cultivated species of *Cola* and some wild relatives (*C. lateritia*, *C. ballayi*, *C. verticillata*, *C. gigantea*) possess the same number of chromosomes ($2n = 40$) (Morakinyo, 1978; Adebola & Morakinyo, 2005). Pollinations between the two partially self-incompatible, crop species have been reported (Jacob 1980, Morakinyo & Olorode, 1984). The F_1 offspring were viable but did not produce fruit, possibly due to post-zygotic barriers to genetic exchange (Jacob, 1980). In contrast, *C. nitida* can hybridize with *C. millenii* (a wild species) to produce viable offspring (Morakinyo, 1995). We did not locate publications reporting the caffeine content of inter-specific hybrids (Box 3).

Box 3: Summary of Risk of Gene Flow from Cola to Wild Relatives.

- Risk of gene transfer to wild relatives:
  - Intraspecific: Low
  - Interspecific: Low
- Risk of toxicity to animals: Not measured but potentially possible since caffeine is toxic.
- Risk of genetic swamping: Possible but not measured.
- Risk of generation of invigorated weeds: Unknown

Ephedra – *Ephedra spp.* (Ephedraceae)

Ephedra comprises about three dozen shrubs of arid environments of the northern hemisphere and South America. The genus produces two key alkaloids, ephedrine and pseudoephedrine, which are methamphetamine analogues. A few of the species from Asia (*E. sinica*, *E. equisetina*, and *E. intermedia*) produce moderate to high quantities of ephedrine (Qazilbach, 1971; White et al., 1997; Zhu, 1998) (Other species produce additional secondary metabolites with known neuropharmacological activity; Caveney et al., 2001; Ellis, 2003). The biosynthetic pathway of ephedrine synthesis in *Ephedra* has been partly clarified (Grue-Sørensen & Spenser, 1994) but only the first two steps have been characterized in high-alkaloid producing *E. sinica* (Okada et al., 2008; Krizevski et al., 2010), the species typically grown for commercial purposes (Caveney et al., 2001). Expression of ephedrine appears to be both environmentally dependent (Kondo et al., 1999) and genetically controlled (Krizevski et al., 2010), although the gene(s) responsible for ephedrine production have not been identified.

When *Ephedra* species grow in the same location, they frequently hybridize via wind-dispersed pollen (Huang et al., 2005; Kitani et al., 2011; Wu et al., 2016). However, rates of pollen movement have not been documented and expression of ephedrine in hybrid offspring of high- and low-content species remain unstudied (summarized in Box 4). The seeds of *Ephedra* are dispersed by both small rodents and wind (Meyer, 2008), providing two routes by which volunteer populations could escape cultivation and evolve ferality. The alkaloids present in *Ephedra* provide protection from both UV radiation and herbivory (Caveney et al., 2001) and so may influence fitness, but this has not been studied. Only three species of insects are known to consume *Ephedra* spp. and these feed exclusively on the plant (Qiao & Zhang, 2002; Luo & Wei 2015a, 2015b; Wang et al., 2017), perhaps because of novel detoxification mechanisms that they possess.

Exposure to methamphetamines via breast milk significantly negatively impacted pup development in rats and resulted in poorer maternal care (Sevcikova et al., 2017). More broadly, extracts of *Ephedra spp*. stimulate the central nervous system and influence muscle contraction in vertebrates (Miao et al., 2011). The potential for this plant to influence the food web dynamics of desert ecosystems, by altering nutritional options for herbivores (Janzen et al., 1977; Anderson & Pater, 2000), requires study (Box 4).

Box 4: Summary of Risk of Gene Flow from *Ephedra* to Wild Relatives.

- Risk of gene transfer to wild relatives:
  - Intraspecific: differences between cultivated and wild plants not well documented, so risk of gene exchange is unknown
  - Interspecific: Strong evidence of inter-fertility between some species
- Risk of toxicity to animals: Probable, but effect on wild herbivores not evaluated
- Risk of genetic swamping: Unknown
- Risk of generation of invigorated weeds: Unknown

Khat (or Qat) – *Catha edulis* (Vahl) Forssk. ex Endl. (Celastraceae)

Khat is a slow-growing evergreen shrub or tree of the Horn of Africa and the Arabian Peninsula. Its leaves are harvested for their mildly stimulating effects (Kalix, 1991; Lemessa & Ababa, 2001). Farmers clonally propagate superior strains of khat (Lemessa & Ababa, 2001). Clones are, of course, genetically uniform, and such selections sometimes have reduced seed production (Lemessa & Ababa, 2001). When seeds are produced, the caruncular appendage aids the seed in traveling long distances via wind dispersal (Zhang et al., 2014). Although older reports recognize more than one species of *Catha*, the genus is widely considered today to be monotypic, and presumably hybridization of *C. edulis* with other species is not possible (*Catha* was once classified in *Celastrus*, and, were hybridization possible, it presumably would be with the latter genus). Accordingly, the chief concern, insofar as gene flow is concerned, is that domesticated strains high in cathinone could transfer their enhanced production to wild plants. Despite an extensive search, we did not find reports of hybridization between domesticated and wild khat or descriptions of the inheritance of cathinone, the drug produced by the plant (Box 5). However, most reports noted a paucity of biological information on *C. edulis* (Lemessa & Ababa, 2001; Islam et al., 2006) and a better understanding of its basic biology is required. Although the ecology of khat has not been intensively studied, the plant is important in preventing soil erosion in Ethiopia (Lemessa & Ababa, 2001), and control programs to curb khat production are expected to have a negative impact on soil ecosystems in these communities.

As with all potentially toxic social drugs, there is particular interest in assessing the consequences of vertebrate consumption. In particular, grazing mammals in dryland regions are especially dependent on shrubs such as khat, and cathinone may have evolved in *Catha* as protection against mammalian grazing. Highland goats, which typically consume low to moderate quality forage-based diets, were fed khat biomass leftover after cathinone extraction, and their growth was significantly better than goats that were not fed khat (Waffie et al., 2012). Moreover, when fed leftover khat biomass, Ogaden sheep possessed fewer sperm abnormalities relative to control diet sheep (Mekasha et al., 2008). These observations suggest that *Catha* provides superior nutrition to grazers when cathinone is removed. There is additional evidence of toxicity of cathinone. In mice, low doses of crude khat extract have an immune stimulating property, whereas higher doses lead to suppression of cellular immune response (Ketema et al., 2015a). When mice are administered khat extract, they exhibit more severe malaria complications (Ketema et al., 2015b), thyroid hyperactivity (Zaghloul et al., 2003), enhanced locomotor activity, reduced social interaction and impaired cognitive function (Bogale et al., 2016). Chromosomal aberrations were detected in mice administered khat extract, making them more likely to develop cancer (Al-Zubairi et al., 2008).

Box 5: Summary of Risk of Gene Flow from Domesticated Khat to Wild Khat.

- Risk of gene transfer to wild relatives:
  - Intraspecific: High possibility of transfer from domesticated to wild strains of *Catha edulis*
  - Interspecific: A monotypic genus, probably incapable of exchanging genes with other species
- Risk of toxicity to animals: Slight risk of enhanced toxicity in wild plants
- Risk of genetic swamping: Unknown
- Risk of generation of invigorated weeds: Negligible

Marijuana – *Cannabis sativa* L. (Cannabaceae)

Cannabis is usually recognized as having one species, *C. sativa* (Small, 2015, 2016, 2017). It produces over 100 terpenophenolic compounds called cannabinoids, most notable of which are inebriating Δ^9-tetrahydrocannabinol (THC) and non-inebriating cannabidiol (CBD) (Mechoulam, 1970; Turner et al., 1980; Mechoulam, 2005; Pertwee, 2006). The qualitative inheritance of THC and CBD has been clarified (de Meijer et al., 2003; Sirikantaramas et al., 2004; Marks et al., 2009; Weiblen et al., 2015), and the capacity to produce these chemicals can be readily exchanged among fibre, oilseed and drug cultivars, and wild plants (Box 6). All populations appear capable of interbreeding freely, so genes controlling cannabinoid production can easily be transferred.

Cannabis produces prodigious quantities of pollen, which can be carried vast distances by wind (Small & Antle, 2003). Unfertilized female plants are usually employed for production of marijuana, so males are generally culled from dioecious marijuana populations or female clones are grown in isolation from pollen sources (Ohlsson et al., 1971; Pijlman et al., 2005). Female clones have become the norm for marijuana production in western countries, and these almost never produce seeds, except sometimes under stress or deliberately treated chemically to produce some male flowers (e.g., Mohan Ram & Sett, 1982). Clonal production is a relatively recent cultivation tool and, to date, both cultivated hemp (low-THC *Cannabis*) and marijuana plants have been sources of pollen that could serve to transfer traits from cultivated to uncultivated populations.

Gene flow from cultivated to unmanaged locations may also occur by seed dispersal in *C. sativa* (Small & Antle, 2003). Many hemp cultivars are monoecious (Van der Werf et al., 1996), so a single seed of such a biotype, distributed to an uncultivated area, could self-fertilize and found a new population. However, monoecious *Cannabis* suffers from inbreeding depression (Heslop-Harrison & Heslop-Harrison, 1969), and represents distinctly inferior material for founding a population grown outside of cultivation. Dioecious hemp cultivars and marijuana strains, by definition, produce male and female plants, and so generally both sexes would need to be co-located in the wild to start a new population. Alternatively, a single female plant might receive pollen from quite remote locations. *Cannabis sativa* does not seem to have specialized adaptations for seed dispersal, but animal vectors (particularly humans and birds) and water are known agents of distribution (Small & Antle, 2003). Domesticated seeds of *C. sativa* (whether selected for fiber, oilseed or drugs) have largely lost several critical adaptations that improve survival outside of cultivation: dormancy (to not germinate in the autumn and be killed by frost), shattering (that allows seeds to fall off the infructescence), and camouflage (hiding the fallen seeds from rodents and insects) (Small, 1974). Nevertheless, hemp escapes are estimated to lose their domesticated seed phenotype within 50 generations, re-evolving the adaptations facilitating survival outside of cultivation (Small, 1984).

Cannabis sativa has been domesticated largely for stem fiber in temperate Eurasia. Land races and cultivars from this region exhibit a cannabinoid profile that is dominated by CBD (with very low amounts of THC), a relatively low production of cannabinoids (of the order of 2% dry weight of female inflorescences), and photoperiodic adaptation to flower relatively quickly in response to shortening day length (Small et al., 2003). By contrast, *C. sativa* has been domesticated largely for euphoric qualities in semi-tropical Asia and in Africa; land races from this region exhibit a cannabinoid profile that is dominated by THC (depending on land race, CBD may be absent or present in substantial amounts), a relatively high production of cannabinoids (typically 5% or more dry weight of female inflorescences), and photoperiodic adaptation to flower relatively slowly in response to shortening day length (Small et al., 2003). Worldwide, it appears that unmanaged populations in *C. sativa* are derived from cultivated populations (there is no evidence of persistent, ancestral populations, even within Afghanistan and India, the centres of marijuana domestication) (Small, 2017).

Generally, *Cannabis sativa* is a successional and “weedy” species and, in nature, feral populations are commonly found in disturbed areas, tolerating little competition, perhaps because the species has very high needs for nitrogen-rich, moist (albeit well-drained) soil, and high levels of sunlight (Small et al., 2003). There is some speculation that some constituents of *C. sativa* have possible allelopathic roles (Inam et al., 1989; McPartland, 1997a; McPartland et al., 2000) but this area of study is under-developed. In temperate areas of the world (especially most of Europe, northern Eurasia, and North America north of Mexico) “wild” (i.e., feral) populations are likely escapes from fiber hemp cultivated in recent past centuries when the crop was indispensable for canvas and cordage needed for ships. Indeed, mapped feral populations in North America tend to cluster around historic areas of hemp production (Small et al., 2003; Hillig & Mahlberg, 2004). In temperate Eurasia, where fiber hemp has been cultivated for millennia, feral hemp is extremely widespread and, presumably as a result of the much longer period for adaptation to have evolved, occupies a much greater range of habitats

(Small, 1984). In semitropical Asia and Africa, most feral populations appear to be escapes from domesticated marijuana plants, sharing their high relatively high THC content and photoperiodic adaptation to relatively long seasons (Small & Beckstead, 1973). However, as a rule feral plants have significantly lower THC content by comparison with local marijuana strains (Small & Beckstead, 1973), suggesting that the conditions that support feral populations or natural selection do not favor extremely high THC concentrations.

Since THC and/or CBD can dominate the resin of most plants of *C. sativa*, the transfer of genes to feral populations that increases their presence is of concern, so it is desirable to understand how these cannabinoids can affect herbivores. *Cannabis sativa* foliage and flowering parts are consumed by grazing mammals and a wide diversity of herbivorous invertebrates (Haney & Bazzaz, 1970; Haney & Kutscheid, 1975; McPartland, 1998; McPartland et al., 2000), but are remarkably resistant to significant damage, which is likely the result of anti-herbivorous chemicals, including the cannabinoids (Small, 2016). By contrast, cannabinoids are virtually absent from the seeds, which are subject to extensive bird consumption (Ross et al., 2000, but see Yang et al., 2017). While the cannabinoids are economically valued largely because THC is a euphoriant chemical, it is highly unlikely that inebriation of herbivores occurs when they consume living plant material. In the living plant, the cannabinoids are carboxylated (a –COOH moiety is attached to the molecule), and in this condition THC is not significantly psychoactive (heat, as in smoking or cooking, sunlight or storage decarboxylates the acidic form of THC in marijuana; Taura et al., 2007). Moreover, insects, the primary herbivores of *Cannabis* (McPartland, 1997b, 1998, 1999; McEno, 1998; McPartland et al., 2000), lack endocannabinoid receptors necessary for euphoria in humans (McPartland et al., 2001). Although one hypothesis for their presence in plant populations is that the cannabinoids act as an anti-herbivory mechanism especially against insects (Rothschild & Fairbairn, 1980), exactly how cannabinoids are protective is uncertain – possibly a combination of toxicity, repellent taste, and objectionable stickiness (Small, 2016).

Several studies have demonstrated an apparent ability to detect, indeed prefer, THC by some non-human organisms. Some bacteria that can colonize the interiors of *C. sativa* roots like endomycorrhizal fungi, are capable of discriminating among marijuana genotypes, showing preferences for some over others, based on the cannabinoids possessed (Winston et al., 2014). Ovipositing *Pieris rapae* (cabbage white butterfly) was offered leaves painted with extracts from THC-possessing and THC-absent *C. sativa* plants; the butterflies notably avoided ovipositing on leaves painted with the high-THC extract (Rothschild & Fairbairn, 1980). In contrast, Tiger moths (*Arctia caja*) have a poor ability to discriminate among *C. sativa* that differ in THC concentration. When given a controlled choice of consuming a high-THC, lethal genotype of *C. sativa* or a low-THC, non-lethal genotype, the moths often chose the former, lethal option (Rothschild et al., 1977). Although these experiments suggest that THC is the basis for behavior, it needs to be kept in mind that correlated chemicals, such as terpenes, might actually have been the causative stimulus.

Given the significance of marijuana, there have been very extensive studies of the harm and therapeutic benefits of the cannabinoids, mostly THC and CBD, to humans and laboratory rodents, and depending on state of health, age, individual responses, and other factors, both benefits and harms have been demonstrated (reviewed in Small, 2016). There are numerous reports of companion dogs being poisoned (occasionally fatally) from deliberate or accidental ingestion of high-THC cannabis preparations intended for human recreation (Donaldson, 2002). Swiss physician and alchemist Paracelsus (1493–1541) is famous for his statement “Everything is a poison. The difference between a poison and a medicine depends on the dose.” The concentrations of cannabinoids (indeed, of any secondary compound) that are high enough to have health and ecological consequences for the millions of wild species is of course almost impossible to determine, but as suggested by the following paragraph, there is at least some evidence that *C. sativa* repels many animals.

Powdered material and extracts of *C. sativa* have been used as anti-feedants, repellents and insecticides (Bouquet, 1950; McPartland, 1997a, 1997b). Mukhtar et al. (2013) found that *C. sativa* is effective against nematodes. There are numerous such studies of the effects of crude preparations of cannabis on various classes of noxious organisms, but there is often insufficient evidence to attribute the effects to particular chemicals. “Bhang” is a traditional Asian intoxicating beverage made with chopped *Cannabis* foliage, but the leaves and floral parts are not palatable, and recipe books on preparing cannabis edibles almost never recommend consumption of such tissues. Although small amounts of herbal cannabis (i.e. leaves and stems) can be incorporated in the feed of ruminant livestock and horses, this is not recommended (EFSA Panel, 2011). However, hemp silage is more acceptable (Letniak et al., 2000), the fermentation associated with silage preparation presumably neutralizing harmful constituents. The extent (if any) to which the cannabinoids in the previous examples are acting as a toxin remains undetermined (Box 6; Fig. 1).

Box 6: Summary of Risk of Gene Flow from *Cannabis* to Wild Relatives.

- Risk of gene transfer:
  - Intraspecific: Extremely high risk to ruderal populations; ancestral wild populations, if extant, have not been identified.
  - Interspecific: Wild species of *Cannabis* have not been identified.
- Risk of toxicity to animals: Seeds do not accumulate cannabinoids and are very palatable; foliage is toxic to numerous animals, almost all of which avoid consumption.
- Risk of genetic swamping: Wild relative likely extinct due to genetic swamping.
- Risk of generation of invigorated weeds: High.

Maté (Yerba Maté) – *Ilex paraguariensis* A. St. Hil. (Aquifoliaceae)

A small southern South American tree, *Ilex paraguariensis*, is the basis of a $1-billion beverage industry in Argentina, Brazil and Paraguay (Small & Catling, 2001; FAOSTAT, 2007; Grigioni et al., 2004; USDA ARS National Genetic Resources Program, 2007). *Ilex paraguariensis* leaves are used to prepare a popular hot drink (yerba maté or chimarrão) and in the production of stimulating pharmaceuticals with derivative methylxanthines, including caffeine and theobromine (Ricco et al., 1995). The chief chemical of culinary interest is caffeine, and many of the considerations regarding toxicity discussed for coffee, tea and kolanut apply to maté. However, likely the other chemicals present are ecologically significant. The plant is known to be allelopathic (PIER, 2008).

This dioecious species is outcrossing (Gauer & Cavalli-Molina, 2000), insect-pollinated (Ayub, 1999), and flowers between October and November (Heck & de

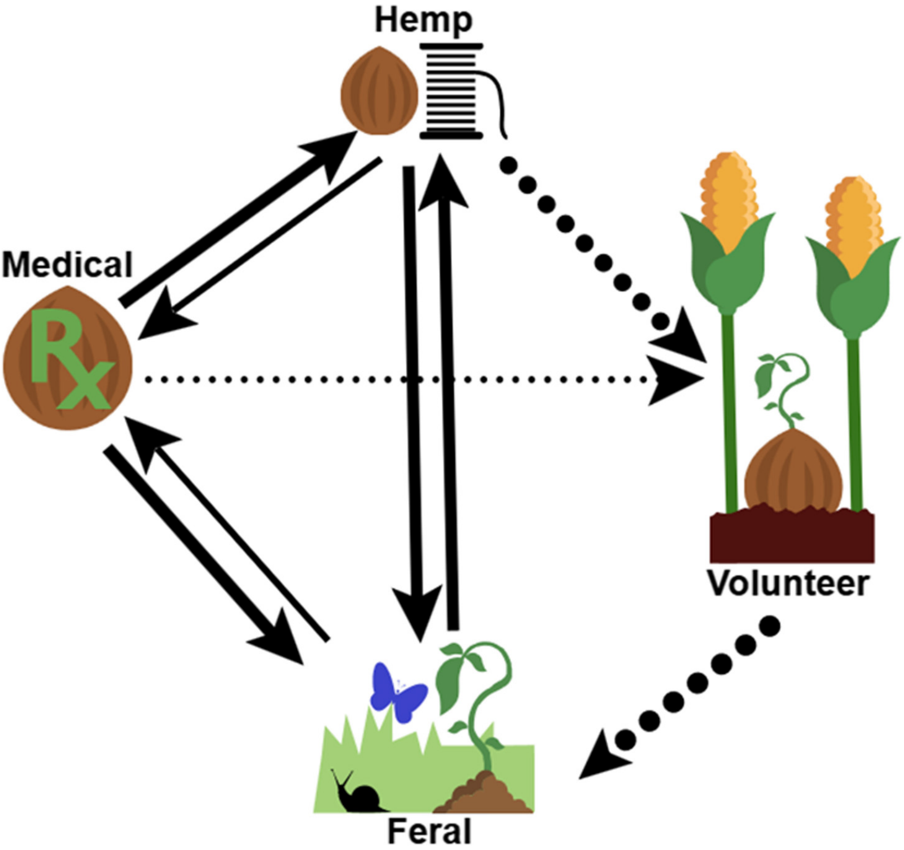

Fig. 1 Pathways of gene flow in crop-feral *Cannabis sativa* meta-populations. Most gene flow can occur by unidirectional pollen flow from fibre and seed hemp to feral populations. Seed dispersal from crop plants results in volunteers that can backcross with feral plants. Seed movement may start from a crop population to start volunteer populations and could result in the introgression of maternally inherited crop alleles whereas pollen movement can occur in both directions. Volunteers may be able to create feral populations

Mejia, 2007). There are 35 relatively close wild relatives (Vincent et al., 2013), Hao et al. (2013) stated "Hybridization and introgression events between distantly related lineages are inferred, indicating weak reproductive barriers between *Ilex* species," but our literature searches did not reveal any publications that tested sexual compatibility with *I. paraguariensis* or described putative hybrids with it. Therefore, we cannot assess the potential for gene flow from cultivated maté to related species. However, since breeding is occurring (discussed in the next paragraph) and cultivation is carried out within the natural wild distribution areas, it is inevitable that intraspecific gene flow will occur from cultivation to the wild. This is highly significant for conservation aspects of the species. IUCN (2017) provides an assessment of "near threatened" for *I. paraguariensis*, suggesting limited concern for the species' conservation status. However, according to PIER (2008), "the risks of genetic erosion are high because the natural forest is gradually giving way to agroforestry and livestock production." Under these circumstances, there should be considerable concern for future effects of introgression from domesticated to wild biotypes (Box 7).

Part of the maté commercial crop is harvested by extractive exploitation of the natural forest, which can result in a radical loss of genetic diversity within populations. Maté is also cultivated (Heck & de Mejia, 2007). Breeding programs are relatively recent and emphasize silvicultural characteristics, including plant architecture and its response to defoliation, leaf weight, and pest and disease resistance (Friedrich et al., 2017; Cardozo et al., 2010; Nakamura et al., 2009; de Resende et al., 2000; Wendt et al., 2007). There is evidence that insect herbivory is partly determined by ecological context (i.e., the local diversity of plant species) and the chemical content of plants (de Avila et al., 2016; Coelho et al., 2010).

Box 7: Summary of Risk of Gene Flow from Maté to Wild Relatives.

- Risk of gene transfer to wild relatives:
  - Intraspecific: high, but, at present, domesticates are scarcely different from wild forms, so gene transfer is likely inconsequential
  - Interspecific: Probable, but occurrence is unknown at present
- Risk of toxicity to animals: Caffeine is a toxin so there is a possibility of increased toxicity in wild plants in the future as cultivars are selected; risk is unmeasured at present
- Risk of genetic swamping: Undetermined
- Risk of generation of invigorated weeds: Negligible

Opium Poppy – *Papaver somniferum* L. (Papaveraceae)

There are about 100 species of *Papaver*, which are native mostly to temperate regions of the Northern Hemisphere (Goldblatt, 1974). *Papaver somniferum*, an annual herb, is believed to be indigenous to the Mediterranean region, from the Canary Isles eastwards (Goldblatt, 1974). It is now found as an escape from cultivation in fields, roadsides, and waste places in scattered localities throughout North America and in other regions of the world (Goldblatt, 1974). *Papaver somniferum* has been treated taxonomically in different ways. According to a popular interpretation, the cultivated phase is placed in subspecies *somniferum* while free-living plants are assigned to Subs*p. setigerum*.

Opium poppies produce the global supply of medical-use morphine and illicit-use heroin, as well as the unharmful culinary poppy seed and some ornamental flowering cultivars (Williams, 2010). In fact, opium poppy (*P. somniferum*) is the predominant source of several medicinal (and potentially toxic) alkaloids, notably morphine, thebaine, papaverine, codeine, narcotine (noscopine) and narceine (although it should be noted that several other species of *Papaver* produce some of the same compounds). Opium poppy produces almost 100 alkaloids (Hagel & Facchini, 2013), but, of these, morphine is infamous as the most deleterious narcotic to human welfare in history (Nutt et al., 2010). Some strains of *P. bracteatum* can produce considerable morphine, but are usually cultivated for codeine and thebaine (Hagel & Facchini, 2013). Crude opium is the hardened latex (milky sap) of the unripe fruit (capsule) of the opium poppy. The drug opium is a mixture of many constituents, but morphine is normally the most abundant alkaloid present; however, there are cultivars in which thebaine or codeine predominates (López et al., 2018). Heroin, which is produced by chemical conversion of morphine, acts relatively rapidly to produce euphoria, and is a chief illegal drug of abuse (Nutt et al., 2010). The plant’s capacity to produce pharmacological compounds is inherited and polygenic, controlled by at least three genetic regions, 4’-OMT (Ziegler et al., 2005), T6ODM (Hagel & Facchini, 2010), and STORR (Winzer et al., 2015). Cultivars of opium poppy differ widely in ability to produce alkaloids; pharmaceutical cultivars produce much higher quantities of alkaloids than do culinary and ornamental varieties (Small, 2010). For instance, the capsules of some ornamental forms have less than 1% opiate alkaloids, while those of narcotic cultivars can have more than 20%. Curiously, although ornamental and ruderal populations contain opiates and are common, they are almost always legally tolerated (Lim, 2013; Meos et al., 2017). In recent times, medicinal cultivars (sometimes known by the oxymoron “low-morphine opium poppy”) have been bred which are virtually devoid of “narcotic” constituents (Small, 2010).

Although generally characterized as self-pollinating (Tetenyi, 1977; Chitty et al., 2003), the outcrossing rate of *P. somniferum* can vary widely in the presence of insect pollen vectors, especially bees (7–71%; Chitty et al., 2003; Kumar & Patra, 2010). Opium poppy seeds are tiny – about 1.25–1.50 mm long – and are distributed by wind, which shakes the seeds out of the capsule through pores at the apex (Small, 2006). Such natural dispersal is usually restricted – up to 15 m (van der Pijl, 1982; Hughes et al., 1994; Vigni & Melati, 1999). The seeds of opium poppy are very nutritious, and because poppy seed is a widespread culinary item that is obtained from a plant which is considered dangerously narcotic, the issue of whether the seeds contain opiate alkaloids has been contentious. Trace amounts of alkaloids have been found in the embryos, but more significantly, since the seeds come from the capsules that are the source of opiates, contamination is almost unavoidable, although quality control can produce seeds with insignificant opiates. In nature, however, herbivores interested only in the seeds are likely to also consume opiates. Seeds can be transported by grazing animals which consume the seed pods and later defecate viable seeds (e.g., red deer (*Cervus elaphus*, Gill & Beardall, 2001), fallow deer (*Dana dama,* Claridge et al., 2016), European rabbit (*Oryctolagus cuniculus,* Fernández & Sáiz, 2007). Even if plant cultivation ceased in a site, the seeds of *P. somniferum* can remain viable yet dormant for up to a decade (Nagel & Börner, 2010). The distribution of feral *P. somniferum* is widespread but sparsely distributed in temperate regions (evidenced by several online floras: Kartesz, 2011; GBIF Secretariat, 2017; NBN, 2017; State Herbarium of South Australia, 2017; USDA-NRCS, 2017; Proto World Flora Online, 2017).

Opium poppy is sexually compatible with four closely related species (in particular, *P. setigerum*, but also *P. bracteatum*, *P. orientale*, and *P. pseudo-orientale*; Fig. 2a) (e.g., Duke, 1973; Ojala & Rousi, 1986; Garnock-Jones & Scholes, 1990). As noted previously, *P. setigerum* is often treated as a subspecies of *P. somniferum* (Small, 2006). Secondary gene transfer (i.e., transmission of genes from a source plant, *via* a bridging species, to a third, recipient species) may also occur since those compatible plants may hybridize with at least four additional species (Fig. 2a). Of course, successful gene flow depends on a shared geographic distribution (Fig. 2b). There are two regions of geographic overlap and thus potential hybridization hotspots (Central and Northern Germany, as well as the Swedish coast along the Baltic Sea in Europe and Turkey, Iran and along the Caucasus in West Asia), with a total of five species sharing a common range within areas of legal, large-scale cultivation (Fig. 2b, Chitty et al., 2003). However, the rate of gene flow and the propensity for secondary gene transfer are undetermined. Of ecological significance, experimental hybridization with *P. somniferum* resulted in increased morphine content in all recipients measured (Bohm

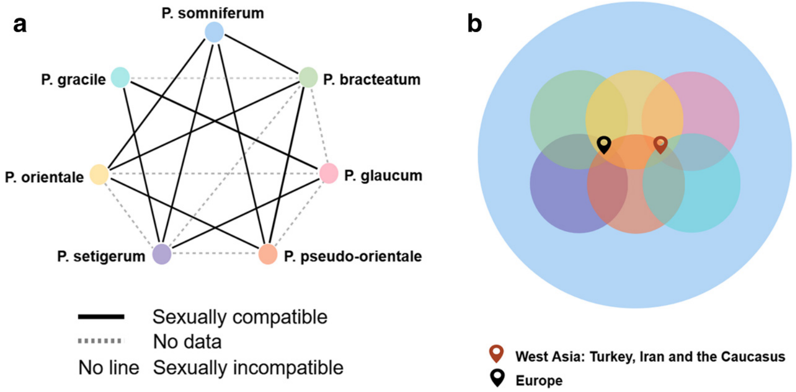

Fig. 2 The capacity for gene flow to result in the transfer genes from opium poppies (*Papaver somniferum*) to other species is influenced by A) the sexual compatibility of *Papaver* species and B) the overlap in geographic distributions of sexually compatible species. In this abstract representation of the geographic distribution of *P. somniferum*, there are two locations where gene flow among five sexually compatible species could occur, West Asia and Europe. Colour coding in B is described in A. Sexual compatibility described in: Goldblatt (1974); Malik et al. (1979); Nyman and Bruhn (1979); Kadereit (1986); Levy and Milo (1991). Geographic distributions described in Chitty et al. (2003)

& Nixdorf, 1983; Ojala & Rousi, 1986; Garnock-Jones & Scholes, 1990). Increased opiate availability can have a diversity of consequences for herbivores, including altering growth, reproductive success, health and cognitive function. Chickens fed 7.5–15% poppy seed meal consumed more food, grew larger, and produced heavier eggs with thicker eggshells but produced equivalent numbers of eggs relative to control-diet chickens (Kucukersan et al., 2009). In contrast, rat pups that were exposed to opiates through breastmilk had decreased body weights at birth and male offspring had persistently reduced body weight (at weaning until 60 d of age) (Siddiqui et al., 1995). Morphine disrupted ovarian cyclicity in female rats and reduced fertilization rates; stillbirths were more common in morphine-exposed female rats (Siddiqui et al., 1995). Morphine-exposed male rats could copulate, but failed to impregnate females (Cicero et al., 2002). Generally, opiates have proved to be central nervous system depressants for most vertebrates assessed. They have increased anxiety in mice (Li et al., 2014) and impaired spatial working memory in rhesus monkeys (Wang et al., 2013). In contrast, horses experience central nervous system stimulation (Kollias-Baker & Sams, 2002). Race horses have been tested worldwide, often revealing low levels of opiate consumption, commonly attributed to environmental contamination of feed stock (Camargo et al., 2005). Occasionally, this contamination can be linked to seeds of *P. somniferum* (sometimes identified as *P. setigerum*) (Camargo et al., 2005). Opiates affect invertebrates in various ways, depending on the species; they suppress aggressive behaviour in crickets (Dyakonova et al., 2002) and immune function in aquatic invertebrates (Stefano et al., 1993). When exposed to morphine, rats exhibit abnormal immune function (Zhang et al., 2012) and rhesus monkeys (rhesus macaques) exhibit reduced immunocompetence (Carr & France, 1993). In nature, the influence of opiates may be transferred to higher trophic levels. Opiates have also been anecdotally reported to accumulate in honey when bees foraged near *P. somniferum* crops (McAlpine, 2002). Risk assessment is needed to establish the effect of increased environmental opiate contamination on ecological communities, and specifically on herbivores of *P. somniferum* and its hybrid offspring. (Figure 2)

Box 8: Summary of Risk of Gene Flow from Opium Poppies to Wild Relatives.

- Risk of gene transfer to wild relatives:
  - Intraspecific: Very High
  - Interspecific: High
- Risk of toxicity to animals: High
- Risk of genetic swamping: Substantial
- Risk of generation of invigorated weeds: Low but not negligible

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Tea – *Camellia sinensis* (L.) Kuntze, *Camellia taliensis* (W.W. Sm.) Melch. (Theaceae)

The genus *Camellia* is estimated to have about 300 species (Mondal, 2011). The tea plant (*C. sinensis*) is a small evergreen tree, usually pruned back to a low shrub in cultivation so that the leaves can be easily harvested. The species is native to the Assam-Burma-Yunnan triangle and has been planted widely in tropical and subtropical areas. Tea and coffee are the world's principal sources of caffeine beverages. Caffeine has been recorded in about 23 species of *Camellia* (Mondal, 2011). The commercial production of tea is largely based on harvesting the leaves of *Camellia sinensis*, although there is also local tea production from *C. taliensis* (Jackson, 1870; Zhao et al., 2014) and other species. Caffeine and several of its degradation products (especially allantoin and allantoate) accumulate in tissues of caffeine-containing plants such as coffee and tea, and in the case of tea these are found principally in the foliage, fruits, seeds, and flowers (Mohanpuria et al., 2009).

Meegahakumbura et al. (2016) stated that "since no wild populations of the tea plant have ever been found, the exact species used for the first domestication of tea plants remains unknown." Nevertheless, they identify China and to a lesser extent India as primary sites of domestication of *C. sinensis*. Many of its wild relatives are native to Southwest China (Yang et al., 2016). Natural intra-generic hybridization among *C. sinensis* and related species is a common occurrence (Sealy, 1958; Kondo, 1977; Takeda, 1990) and although F_1 hybrid offspring often have reduced fertility, it is frequently possible to generate F_2 offspring (Kondo, 1977). Although rarely measured, the capacity for caffeine biosynthesis can be transferred via inter-specific hybridization (e.g., between *C. sinensis* and another non-caffeine producing, horticulturally important plant, *C. japonica*; Fujimori & Ashihara, 1990). However, we did not find any studies describing the prevalence of natural gene flow between the crop and its wild relatives, nor the consequences of such gene flow for the conservation of wild relatives (which are mostly identified as threatened by habitat loss) (e.g., Yang et al., 2011; IUCN, 2017; Box 9).

Feral or escaped tea trees are somewhat common within the geographic range of commercial production, especially when tea plantations are abandoned (Ahmed et al., 2010; SuZhen et al., 2011). However, we could not find significant research that suggested caffeine facilitates the persistence of these plants in unmanaged conditions. Perhaps, plants with higher caffeine may have an ecological advantage because caffeine exuded by tea seeds has been shown to have an allelopathic effect on neighbouring plants (Suzuki & Waller, 1987). Since tea plants can persist outside of cultivation, caffeine is probably frequently encountered in the agricultural landscape by herbivores and yet its impact on these organisms has rarely been measured. Beyond the broad effects of caffeine (described in the coffee section previously), tea caffeine has inhibited oviposition and delayed development in shot-hole borer beetle (*Xyleborus fornicatus*) under laboratory conditions (Hewavitharanage et al., 1999).

Box 9: Summary of Risk of Gene Flow from Tea to Wild Relatives.

- Risk of gene transfer to wild relatives:
  - Intraspecific: very high
  - Interspecific: Medium
- Risk of toxicity to animals: Likely affects a range of susceptible wild species
- Risk of genetic swamping: Wild relative likely extinct
- Risk of generation of invigorated weeds: Negligible

Tobacco – *Nicotiana tabacum* L.; *N. rustica* L. (Solanaceae)

Nicotine is a widespread alkaloid in plants, for example occurring in several cultivated members of the Solanaceae, such as tomato, potato, eggplant and green pepper (Siegmund et al., 1999) and in common milkweed (*Asclepias syriaca*) (Marion, 1939). Nicotine-based insecticides were frequently used worldwide until the 1980s, but have since lost popularity, in part because of concerns about their strong toxicity (Kozlowski et al., 2001). The wide-spectrum toxicity of nicotine coupled with its occurrence in unrelated plants indicates that it is a particularly potent natural deterrent of herbivores (see references later; Box 10).

The genus *Nicotiana* consists of about 44 species native to the Americas and 20 species native to Australia (Ren & Timko, 2000; Wylie et al., 2015). The most economically important species, common tobacco (*Nicotiana tabacum*), is an herbaceous annual (or less commonly a short-lived herb or forb). The species is thought to be a hybrid, the ancestors distributed in the eastern Andes Mountains of South America (Lewis & Nicholson, 2007). Tobacco from *N. tabacum* is produced in most temperate and tropical regions of the world, and is a major crop of many nations, with a global market worth over $112 billion annually (USDA, 2016). *Nicotiana rustica* is South American annual, naturalized in eastern North America (Gunn, 1974). Like *N. tabacum*, *N. rustica* was domesticated for tobacco production, although it is not grown commercially in North America. It is thought to have arisen as a hybrid, probably from ancestral species in Peru (Chase et al., 2003), and was spread northward as a result of cultivation by indigenous people (Gunn, 1974; Delcourt & Delcourt, 2004). Feral plants are rare, and when they are reported, these plants tend to be *N. rustica* which is not typically planted at an industrial scale like *N. tabacum*, von Gernet, 1992; Lim et al., 2004).

In the Solanaceae, nicotine is biosynthesized in the roots and transported to and accumulated in the foliage (Siegmund et al., 1999). The dried leaves of *N. rustica* contain up to 10% nicotine (younger leaves may have higher content), whereas those of *N. tabacum* usually have only 1.5–4% (although up to 8% is possible). Nicotine production is heritable and *N. tabacum* plants possess at least three nicotine demethylase genes that control nicotine production (Lewis et al., 2010). Research has documented inter-specific gene flow and alkaloid transfer, including nicotine, after experimental hybridizations, but success is low, as explained next (Smith, 1965).

Generally described as a self-pollinated plant, estimates of outcrossing rate for *N. tabacum* range from as low as 0.3% (Litton & Stokes, 1964) to as high as 17.2% (Paul et al., 1995). Hand crosses between *N. tabacum* and its closest relative, the ornamental tobacco (*N. sylvestris*) produced F_1 hybrids with extremely low pollen fertility and no seeds whereas back-cross progeny produced a few viable seeds (Al-Ahmad et al., 2006). Transgenic tobacco has become a major platform for pharmaceuticals (Small & Catling, 2006), and so there has been interest in establishing the extent to which gene escape from cultivated *Nicotiana* is possible (e.g., USDA, 2008). There have been limited tests of hybridization potential between *N. tabacum* and other wild relatives, such as *N. tomentosiformis* and *N. otophora* (Khoury et al., 2013), and to our knowledge there are no close weedy relatives. Because of the anti-herbivory properties of nicotine (Steppuhn et al., 2004) and the up-regulation of nicotine production in response to herbivory (Zong & Wang, 2004), it is plausible that the transfer of nicotine genes to low-nicotine *N. tabacum* populations could influence fitness of offspring. However, given the limited tendency to evolve ferality and low gene flow, even in sympatry, this is unlikely.

Increased nicotine consumption is known to have a diversity of consequences for herbivores, including altering growth, reproductive success, health and cognitive function.

Feeding on tobacco can increase the longevity of a phytophagous stilt bug (Jackson & Kester, 1996). In contrast, alcohol extracts of *N. tabacum* act as a repellent and toxicant against *T. castaneum* (red flour beetle) (Sagheer et al., 2013). Although some herbivorous insects (*Myzus persicae*: Cabrera-Brandt et al., 2010; *Globodera tabacum tabacum*: Lamondia, 1995) exhibit slowed or no reproduction on tobacco, others are clearly pests adapted to the crop. Moreover, increased tobacco in the environment may have trophic consequences. For instance, mirid parasitoid (*Macrolophus caliginosus*) exhibited faster maturity and more reproductive success when prey were raised on tobacco than cabbage or brussels sprouts (Hatherly et al., 2009). There also seem to be some health consequences to tobacco leaf exposure. Skin irritation in mice in response to tobacco leaves was attributed largely to the nicotine content of the leaves (Da Silva et al., 2010). Limited consumption of *N. tabacum* leaf did not affect sheep, but had anti-nematicidal effects on their parasitic nematodes (Hamad et al., 2013), and indeed tobacco is commonly employed topically to control ecto-parasites in dogs (Lansa et al., 2000). Although there is no evidence of tobacco-consumption affecting cognitive function in herbivores, there is some intriguing information from trials with nicotine extracts. For instance, nicotine-infused nectar sources, under experimental conditions, enhanced bee flower constancy (Baracchi et al., 2017).

Box 10: Summary of Risk of Gene Flow from Tobacco to Wild Relatives.

- Risk of gene transfer to wild relatives:
  - Intraspecific: limited feral forms exist, with slight possibility of introgression to them
  - Interspecific: Low but possible in regions of South America where ancestral species persist
- Risk of toxicity to animals: Nicotine is very toxic, and there is some possibility of increased nicotine in related wild species
- Risk of genetic swamping: Unlikely, but study of potential target species required for evaluation of risk
- Risk of generation of invigorated weeds: Negligible

Discussion of the Consequences of Gene Flow from Cultivated, Social Drug Plants

Considering the controversy over the health consequences of addictive social drug plants, it seems surprising that no one has yet presented a risk analysis of ecosystem consequences of their cultivation. From our review of the published literature, it is clear this science is in its infancy. Many cultivated, social-drug plants, including coffee, ephedra, khat, marijuana, maté, opium poppy, and tea, can exchange genes with either uncultivated intraspecific ancestors and/or close relatives. In fact, gene flow from cultivated, social drug plants to extant wild relatives is apparently rare only in self-pollinating tobacco and outcrossing kolanut. Although gene flow studies are limited for all of the species examined, further research is particularly required to document and measure gene flow from coca, ephedra and maté which appear to have no published information on this topic. Depending on rates of gene flow, genetic correlations, and adaptive trait values, genes that control social drug production and correlated traits could persist indefinitely in cultivated or free-living populations (Snow et al., 2005). These genes could continue to spread among other plants of the same species, especially if gene flow is maintained from a large source population, like an industrial cropping system.

Three issues regarding gene flow from addictive, social drug crops are of particular concern: (1) gene flow from social drug crops to their compatible plant relatives may increase the relative fitness of hybrid offspring; (2) it may endanger the conservation of genetic material that can be used for crop improvement in the future; (3) and it may influence food webs through altering the health of herbivores. These topics remain scarcely studied. Several of the plants reviewed produce illegal controlled substances, making it difficult to study them (Page & Ware, 2015). Nevertheless, as reviewed in this report, there is appreciable relevant information on the ecological and genetic impact of gene flow of several of the species.

Social drug plants are rarely weedy. Of the species examined, only marijuana expresses significantly weedy tendencies. Coffee and opium poppies show limited tendencies to escape cultivation, but they are not aggressive weeds. We found evidence to suggest that coca, khat, maté, tea, and tobacco do not tend to be weedy. There appear to be no studies on the weediness of kolanut and ephedra. Careful investigation comparing genotypes with and without drug properties would be interesting to determine if the social drug affects the ability of the plant to be more competitive or escape herbivory.

Wild relatives of crops represent invaluable sources of genes for crop improvement. Since *ex situ* conservation collections (gene seedbanks and permanent gardens) can only maintain a small fraction of natural gene pools, wild crop relatives are best maintained *in situ* (Husband & Campbell, 2004; Khoury et al., 2013). For instance, tobacco breeding has benefitted from the conserved germplasm of tobacco relatives that have received very little if any gene flow from crop tobacco. However, wherever crops are cultivated near their sexually compatible wild relatives, there is concern about gene escape from the crop and consequent alteration of gene frequencies in the wild forms (Snow et al., 2005; Campbell et al., 2016; Ellstrand et al., 2014); the most threatening possibilities are extinction of unique genes, extinction of unique populations, extinction of infra-specific taxa, and extinction of species. Additional research to understand the potential implications of gene flow on the conservation of germplasm should be urgently undertaken for coca, kolanut, ephedra, khat, and maté.

Although gene transfer between a crop and distantly-related species can be invaluable for plant breeding, for the most part taxa that are very closely related to a crop are the conventional sources of wild genes (Khoury et al., 2013). Indeed, the ancestor or ancestors of a crop, if extant, are the predominant sources of useful genes. Typically, crops are entirely or substantially inter-fertile with their wild ancestors (Ellstrand, 2003; Ellstrand et al., 2014), and so wherever the crop is grown in the same locality as surviving ancestors, there is a strong possibility of crop genes introgressing and altering altering gene frequencies in the ancestral gene pool (Snow et al., 2005), which is very undesirable from the point of view of gene conservation (Campbell et al., 2016). Genetic swamping has likely occurred in the close relatives of coffee, kolanut, and opium poppy. The ancestors and/or close relatives of marijuana and tea are not identifiable, according to published literature, although nevertheless feral forms likely have unique genes meriting conservation and protection from gene flow.

Future breeding efforts in social drug plants will rely, in part, on the genetic reserves of wild relatives (Ellstrand, 2003). Unfortunately, many natural ecosystems and many of their wild plant species are in severe decline as a result of human activities. Social drug plants are often harvested to the point that natural supplies are threatened (e.g., peyote: Hernandez & Barcenas, 1995), and unfortunately illicit drugs are often cultivated in wild places, endangering the surrounding ecosystem (e.g., McSweeney et al., 2014). While many crops are expanding, particularly the social drug species reviewed in this paper, many of their wild relatives are declining. This means that gene survival of many crop relatives is doubly threatened – by drastic reduction in habitats and population sizes, and also by gene transfer. A third threat applies to several of the social drug plants reviewed in this paper, because they are classified as sources of illegal or controlled narcotics. In this circumstance, the associated stigma has often prevented the collection of *in situ* resources, and indeed has often stimulated programs of destruction of wild-growing populations (Plowman, 1980).

Finally, one possible consequence of gene flow from addictive social drug crops is an increase in exposure of animals to potentially toxic compounds. In this review, a wide array of studies demonstrate the consequences of exposure to and effects of social drug plants on animal health and behavior. Clearly, animals respond strongly to compounds in coffee, marijuana, opium poppy, tea, and tobacco (but seemingly demonstrated few negative responses to khat).

Toxicological and behavioral studies of the effect of leafy material from coca, kolanut, ephedra and maté on animals are particularly limited and need to be undertaken.

Conclusions

Ideally, the industrial-scale cultivation of social drug plants should have been preceded by scientific research on their ecological and evolutionary consequences to susceptible species and ecosystems. Given the scale at which various nations are authorizing or permitting the development of social drug plants (e.g., Potter et al., 2015; UNGASS, 2016), there should be concern about both local and global unintended ecological consequences, which may be profound. In countries that produce social drugs from plants, information about the geographic distribution, population ecology, herbivore dynamics, and reproductive biology of sympatric wild relatives and non-drug crops will be useful for evaluating the potential for gene escape and the ecological effects of these phytochemicals, much as one might proceed with evaluating crops with novel traits that are potentially ecologically harmful (Lu & Snow, 2005; Snow et al., 2005). This knowledge will assist in promoting the further development of plant biotechnology and the safe production of promising plant-based chemicals globally. Given that several of the species we have reviewed here are highly stigmatized, many governments have restricted research so tightly that very few scientists have been able to conduct the required research to assess their possible benefits and harms. Publicly accessible and scientifically rigorous assessments of environmental impact are essential for the long-term success of these emerging industries as an important source of chemicals with valuable pharmaceutical properties.

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