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REVIEW PAPER

Same, yet different: towards understanding nutrient use in hemp- and drug-type *Cannabis*

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Abstract

***Cannabis sativa* L., one of the oldest cultivated crops, has a complex domestication history due to its diverse uses for fibre, seed, oil, and drugs, and its wide geographic distribution. This review explores how human selection has shaped the biology of hemp and drug-type *Cannabis*, focusing on acquisition and utilization of nitrogen and phosphorus, and how resulting changes in source–sink relations shape their contrasting phenology. Hemp has been optimized for rapid, slender growth and nutrient efficiency, whereas drug-type cultivars have been selected for compact growth with large phytocannabinoid-producing female inflorescences. Understanding these nutrient use and ontogenetic differences will enhance our general understanding of resource allocation in plants. Knowledge gained in comparison with other model species, such as tomato, rice, or Arabidopsis can help inform crop improvement and sustainability in the cannabis industry.**

Keywords: *Cannabis sativa* L., domestication, fibre, flowering, hemp, medicinal, nitrogen, nutrient use, phosphorus, sink, source.

Introduction

Cannabis sativa L. (hereafter *Cannabis*) has a long domestication history dating back at least 12 000 years (Clarke and Merlin, 2016; Ren *et al.*, 2021). A unique feature of *Cannabis* plants is their production of secondary metabolites called cannabinoids within the glandular trichomes of their female flowers, with the major ones being cannabidiolic acid (CBDA) and Δ^9-tetrahydrocannabinolic acid (THCA). Decarboxylation during the processing of flowers leads to their pharmacologically active forms, with tetrahydrocannabinol (THC) having psychoactive and intoxicating properties, while cannabidiol (CBD) has pharmaceutical uses as an anti-convulsant and anti-inflammatory drug (Lu and Mackie, 2016). In living plant tissues, the decarboxylated THC or CBD usually represents less than 2% the total (carboxylated plus decarboxylated) pools (Happyana *et al.*, 2013).

The wide geographic distribution of *Cannabis* led to genetic and phenotypic variation in local varieties and its subsequent domestication throughout most of Eurasia. Complex genetic diversity within the species is likely attributed to a successive blend of human selection, escapees, and outcrossing leading

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to unique feral landraces, and their subsequent reintroduction into domesticated germplasm (Clarke and Merlin, 2016; Barcaccia *et al.*, 2020; Ren *et al.*, 2021). Extensive targeted selection produced two divergent usage types with distinct genetics and contrasting plant architecture: hemp-type (aka hemp or industrial hemp for fibre and seed) and drug-type *Cannabis* (aka marijuana or weed for female flowers and cannabinoids) (Fig. 1) (Small, 2015; Clarke and Merlin, 2016). The tall-growing hemp type was selected for fibre production and contains high concentrations of CBDA and very little THCA. By contrast, drug-type *Cannabis* was selected for recreational and ceremonial purposes due to high amounts of the acid precursor of hallucinogenic THC and prolific production of female flowers. Recent heightened interest in CBDA accumulating drug-type chemovars for pharmaceuticals has instigated re-introgression of hemp- into drug-type cultivars (Grassa *et al.*, 2021). The term 'chemovar' refers to *Cannabis* germplasm categorized either as THCA dominant, or CBDA dominant, or balanced (approximately equal levels of THCA and CBDA) with further differentiation according to terpenoid profiles (Hazekamp *et al.*, 2016; Reimann-Philipp *et al.*, 2020). It is often used instead of the more rigorous botanical term of 'cultivar', which implies that the progeny of those plants retains traits of interest—which due to the heterogeneous nature of *Cannabis* is often not the case for seed stock.

The difference in specific usage of hemp- and drug-type *Cannabis* is reflected in their cultivation. Hemp types are grown in field conditions across a divergent range of environments and regions, often on marginal lands, and following traditional agricultural practise in broad acre systems with moderate inputs of fertilizer (Struik *et al.*, 2000; Tang *et al.*, 2017; Landi *et al.*, 2019; Wylie *et al.*, 2020; Blandinières and Amaducci, 2022). By contrast, drug types are largely grown in high-input, cost-intensive protected cropping or indoor environments due to their substantial value and quality standards imposed on pharmaceutical production (Madhusoodanan, 2019; Wartenberg *et al.*, 2021; Velechovsky *et al.*, 2024). Hence,

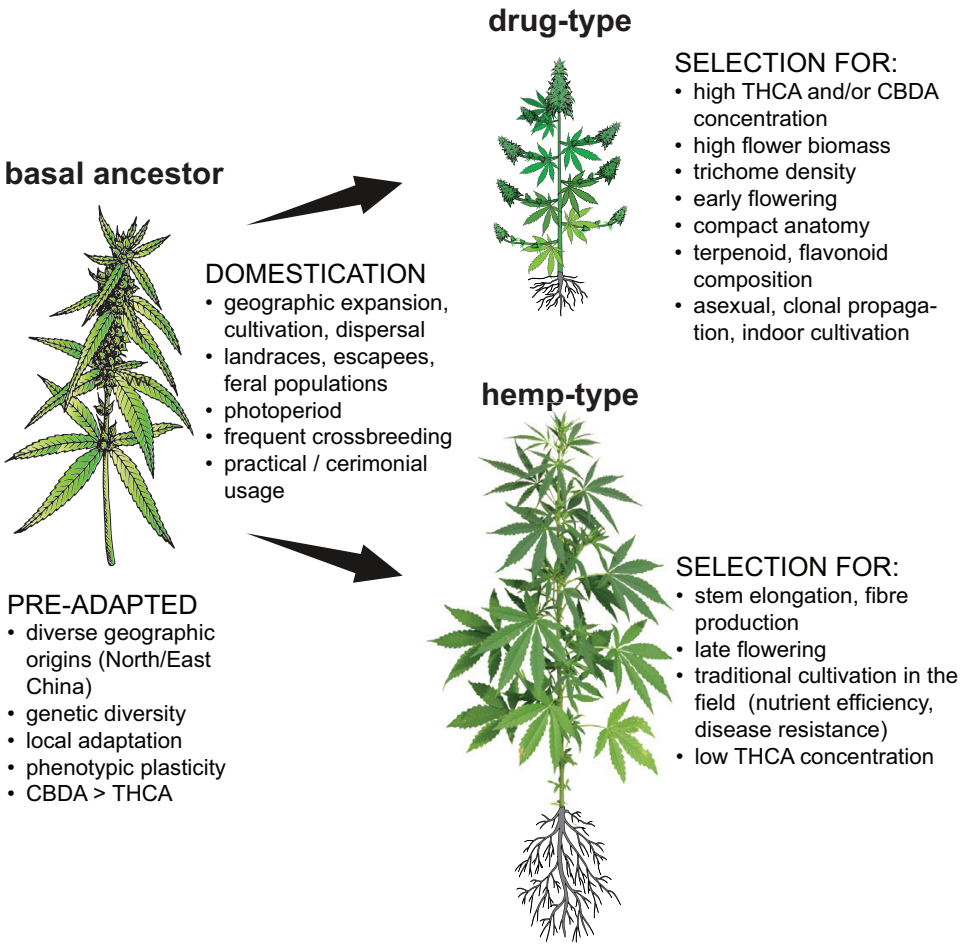

Fig. 1. Divergent positive trait selection in *Cannabis* led to two distinct usage types. Illustrated are processes accompanying *Cannabis* domestication and the subsequent split into the two main usage types (drug- and hemp type). Major selected traits are cannabinoid content, plant architecture (tall versus compact stature, compound highly branched female inflorescence), biomass allocation (flower versus stem/fibre), flowering (early/late) as well as cultivation (indoors/field). See text for details. Abbreviations: CBDA, cannabidiolic acid; THCA, Δ^9-tetrahydrocannabinolic acid.

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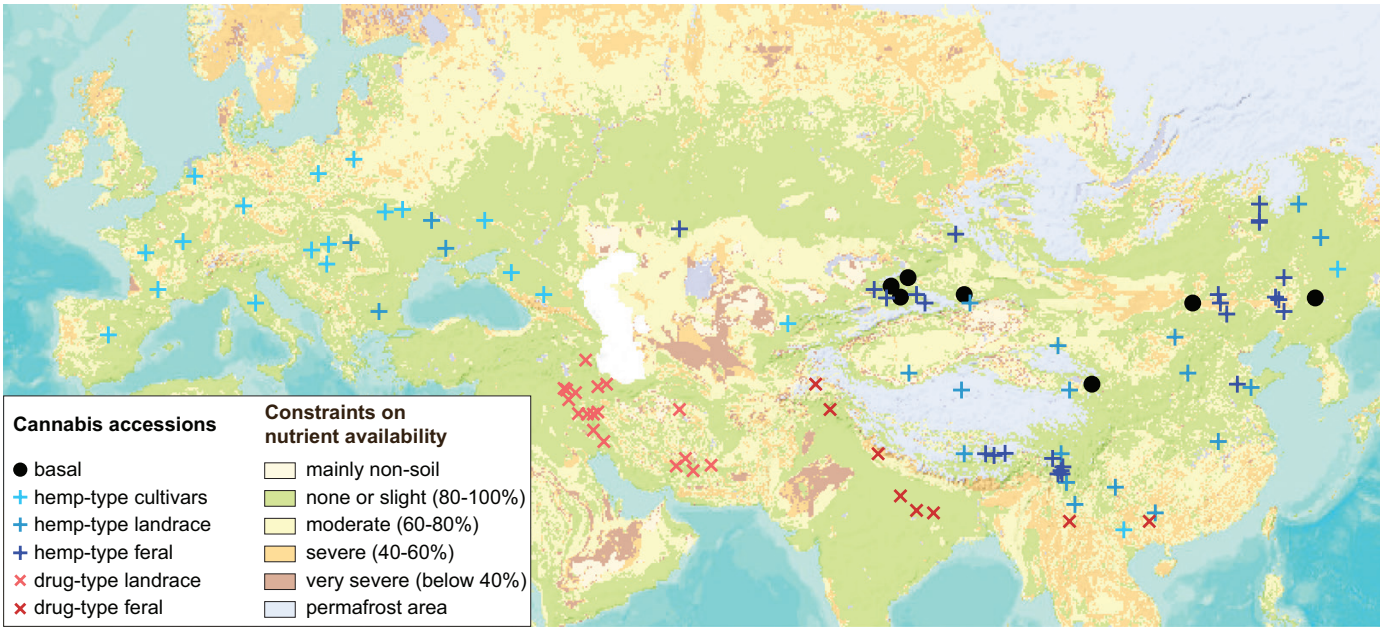

Fig. 2. *Cannabis* accessions originate from diverse regions with contrasting soil nutrient availabilities. Geographic distribution of accessions included in the determination of *Cannabis* domestication history was overlaid with soil nutrient availability constraints. Although the exact origin of *Cannabis* is unknown, accessions genetically close to the progenitor (basal accessions) originate from regions of northern China with constraints on nutrient availability ranging from none/slight to severe (percentages indicate ratings of growth potential). This wide ancestral adaptation to various soil types enabled subsequent worldwide domestication and local selection of hemp- and drug-type landraces with diverse trait combinations at least partially linked to agronomic constraints of their ancestral origin. Data for *Cannabis* accessions are based on field or seed bank collections (Zhang *et al.*, 2018; Ren *et al.*, 2021; Mostafaei Dehnavi *et al.*, 2022). Soil nutrient availability data were downloaded from the FAO Global Soil Partnership website (https://www.fao.org/global-soil-partnership) and visualized using Data Basin (https://databasin.org).

growth regimes vary greatly for both *Cannabis* usage types, with human mitigation efforts being strongly influenced by abiotic and biotic stresses inherent to each type (Small, 2015; Clarke and Merlin, 2016; Wylie *et al.*, 2020; Blandinières and Amaducci, 2022; Llewellyn *et al.*, 2023). Inherent differences in nutrient requirements pose a challenge towards optimizing fertilizer input, which is an important factor for plant biomass production and product yield in commercial settings as well as for reducing the detrimental impact on local environments (Tilman *et al.*, 2002).

In this respect, *Cannabis* presents an interesting case study to investigate how human selection and natural genetic diversity influence each other, and how these, advertently or inadvertently, influence nutrient use and its effects on plant development. While recent advances in next-generation sequencing have led to increased understanding of *Cannabis* genetic diversity to enable functional genomics (Kovalchuk *et al.*, 2020; Grassa *et al.*, 2021; Hurgobin *et al.*, 2021; Lynch *et al.*, 2024, Preprint), building on these resources to gain a better insight into the physiology of *Cannabis* plants is still lacking. Our review will focus on current knowledge of nutrient use, that is, the acquisition and utilization of the two macronutrients nitrogen (N) and phosphorus (P) and how these may influence growth and development in *Cannabis*. We will also highlight knowledge gaps that need to be addressed to optimize fertilizer application for *Cannabis* cultivation.

The domestication history of *Cannabis* is reflected in current cultivation practices

Although the true ancestor will likely remain unknown, recent genomic studies suggest that current *Cannabis* cultivars originate from a small number of domestication events (Kovalchuk *et al.*, 2020; Ren *et al.*, 2021). Their origins can be traced back to a few locations across northeast China with a subsequent geographic expansion and scattered distribution of genetically diverse landraces, escapees, and feral populations (Fig. 2). These early diverse geographic origins ensured development of trait combinations within subpopulations that made *Cannabis* 'pre-adapted' for human cultivation in divergent locations with contrasting temperature zones, photoperiods, water availabilities, and/or soil types with distinct nutrient availabilities (Clarke and Merlin, 2016). This allowed a wide distribution of *Cannabis* throughout Eurasia driven by the close co-evolutionary relationship of *Cannabis* and humans. Early selection led to cultivars with specialized purposes with frequent outcrossing and re-introduction enhancing genetic diversity, while recent hybridization led to the modern commercial

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cultivars (Clarke and Merlin, 2016). These processes resulted in *Cannabis* cultivars with greatly varying architectures, morphology, and biochemistry, but the underlying molecular processes, trait associations or genes driving these variations are not well understood (Ren *et al.*, 2021). Analysis is further complicated because certain trait combinations might have been unknowingly selected for or may have been lost over time, while some genetic features neutral in certain growth conditions or locations became beneficial or detrimental in others. In addition, traits might have purposefully or inadvertently been re-introduced from wild populations at various stages over thousands of years of domestication.

About 12 000 years ago, the two usage types of *Cannabis* diverged from the basal ancestors by human targeted selection, and from these a limited number of domesticated accessions expanded to the current hemp- and drug-type *Cannabis* cultivars about 4000 years ago (Clarke and Merlin, 2016; Kovalchuk *et al.*, 2020; Ren *et al.*, 2021). Hemp was selected for bast fibre production and constituted the main and most wide-spread usage type of *Cannabis* for millennia. Selection of hemp types favoured late flowering to maximize vegetative growth, and for not well-understood reasons this also led to a preferential biosynthesis of CBDA over THCA. Decreasing concentrations of THCA in feral drug types suggest its accumulation has no adaptive significance in wild populations, and in hemp-type cultivars extensive flower development and high THCA concentrations were not desired (Clarke and Merlin, 2016). More recently, strict requirements by regulatory bodies for low total THC concentrations have resulted in hemp types almost devoid of any THCA.

By contrast, for drug-type *Cannabis* the aim of obtaining high THCA concentrations and flower biomass led to narrow, targeted selection, which started about 1000 years ago in Afghanistan and India due to more widespread ceremonial usage (Small, 2015). This included preference for a short photoperiod to induce flower production, short stature, and quick flower maturation. Introduction of Afghan cultivars into existing North American and European drug-type chemovars over the last decades produced the modern asexually propagated 'sensimilla' or seedless/unpollinated female accessions (Small, 2015; Clarke and Merlin, 2016). This further facilitated extensive indoor cultivation, initially largely in concealed growth spaces due to their illicit status. However, narrow selection under high-input, protected cropping conditions and inbreeding between already significantly related individuals for extremely high THC-yielding drug-type chemovars led to 'spoiled' cultivars with limited genetic diversity. These founder effects created genetic bottlenecks that constrained subsequent breeding efforts. They also resulted in the loss of beneficial traits such as pathogen resistance or nutrient efficiency that have become key determinants for modern cost-efficient, environmentally sustainable, and large-scale horticulture (McKernan *et al.*, 2020, Preprint). For example, the dense, racemose flower structure introduced from Afghan cultivars is highly beneficial for commercial production but also increases susceptibility to fungal infections (Clarke and Merlin, 2016).

In contrast to hemp, very little is known about the nutrient efficiency of drug-type *Cannabis* and differences between cultivars or accessions. While drug-type *Cannabis* is often described as a neutrophile (Small, 2015), it is not clear if this reflects requirement or tolerance of high nitrogen supply. Overlaying the geographic origin with data on nutrient availability indicates some ancestral *Cannabis* progenitors originated on soils constraining growth by as much as 60% or more, while others evolved under non-limiting conditions (Fig. 2). This implies that the genetic diversity for nutrient-related traits was extensive even before domestication began. The contrasting selection of hemp- and drug-type *Cannabis* suggests varying degrees of conservation of the ancestral genetics. Traditional cultivation of hemp on diverse soil types across a wide geographical range suggests that traits related to the root uptake and organ distribution of important nutrients such as N and P were retained. In addition, common cultivation of hemp on marginal soils and its use in phytoremediation demonstrate its ability to grow with limited fertilizer inputs and its efficient heavy metal absorption and tolerance (Struik *et al.*, 2000; Blandinières and Amaducci, 2022). For drug-type *Cannabis*, preferential growth in protected cropping environments with a 'more is better' attitude to increasing product yield together with a general (mis) interpretation of generic stress symptoms as nutrient limitation has likely led to an overestimation of the optimal fertilizer range (Westmoreland and Bugbee, 2022). Inadvertently, this may have also led to selection of drug-type cultivars able to tolerate, or even require, elevated nutrient input for biomass production. In this respect, drug-type *Cannabis* might be considered an extreme example for the genetic erosion observed in other crop species during the course of their domestication (Khoury *et al.*, 2022).

Differences in nutrient response between *Cannabis* usage types: current knowledge

Macronutrients N and P are examples for factors constraining establishment of a more sustainable crop production. While increasing N and P fertilizer use in agricultural soils accompanying the 'green revolution' has resulted in increasing crop yields over the last century (Khush, 1999), a recent push to decrease fertilizer inputs to ensure sustainability and reduce environmental impact is hampered by limited genetic diversity in high-yielding varieties and their stagnating N and P use efficiencies (Hirel *et al.*, 2007; Han *et al.*, 2015). Thus, understanding the differences in the usage of these two nutrients between hemp and drug type might not only improve cultivation outcomes for *Cannabis*, but also provide valuable clues for the sustainability of other crops. As discussed in the previous section, the selection of basal *Cannabis* led to distinct usage types with divergent traits and resulted in a high degree

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of heterogeneity in phenotypic and genotypic representation. The nutrient requirements for optimal growth for each usage type, and indeed across cultivars within respective types, will hence be different (Bernstein *et al.*, 2019a; Cockson *et al.*, 2020; Yep *et al.*, 2020; Bevan *et al.*, 2021; Dilena *et al.*, 2023).

Understanding the physiological traits that are responsive to nutrient supply, as well as the molecular mechanisms underlying traits associated with nutrient use, is key for the selection of nutrient-efficient genotypes in any crop breeding program (Ferrante *et al.*, 2017). Complementing this approach with molecular tools to determine the genetic basis of these traits allows for the identification and/or development of nutrient-efficient cultivars in other crop species (van de Wiel *et al.*, 2015; Tiwari *et al.*, 2017; Goel *et al.*, 2018). For *Cannabis*, this approach has so far been limited to morphological and physiological traits within a small number of cultivars that are not representing the full and divergent phenotypic range in the existing germplasm (Cockson *et al.*, 2020; Anderson *et al.*, 2021; Bevan *et al.*, 2021; Saloner and Bernstein, 2021, 2022, 2023; Shiponi and Bernstein, 2021a; Dilena *et al.*, 2023; Farnisa *et al.*, 2023; Massuela *et al.*, 2023). It is therefore necessary to evaluate our current knowledge base to identify gaps and how to address them. Given the long-standing illicit legal status of drug-type *Cannabis*, the underground 'hobbyist' nature of its cultivation has led to many myths penetrating commercial growing practices which go against the horticultural science behind the cultivation of other commercial crops such as tomato, cabbage, or lettuce (Rengel *et al.*, 2022). Building a mechanistic understanding of the regulation of nutrient acquisition and utilization in *Cannabis* will thus be critical for improving its yield potential and product quality. Here, we will focus on current knowledge on the response to supply of two macronutrients, nitrogen (N) and phosphorus (P), which are of high importance for the sustainability of *Cannabis* cultivation, and will highlight the potential of knowledge transfer from other crops.

Usage types differ in their nitrogen acquisition and utilization

N is critical for plant growth and development as an integral component of DNA, RNA, proteins, and free amino acids. Leaf biomass is tightly linked to available N in growth substrates, as N is also a structural component of chlorophyll and hence critical for carbon fixation through photosynthesis (Rengel *et al.*, 2022). In angiosperms, N is present at an average 6% of total dry matter (n=62 species) and 18% of total protein (n=74) (Yeoh and Wee, 1994; Broadley *et al.*, 2004). While it can be taken up as mineral N (nitrate and ammonium), oxides of nitrogen (NO_x), as well as amino acids and peptides, N acquisition through nitrate (NO_3^-) is typically the preferred pathway for most plants and tightly coupled to photosynthetic activity (Lejay *et al.*, 2008; O'Brien *et al.*, 2016). Due to the high energetic cost of nitrate reduction, a mixture of nitrate and ammonium is considered beneficial in plant cultivation as compared with either source of mineral N alone (Hachiya and Sakakibara, 2017). A ratio of 1 part ammonium to 3 or 4 parts nitrate is considered optimal for most plants with some benefits of higher ammonium levels reported for secondary metabolites such as vitamin C, carotenoids, flavonoids, and phenolic compounds (Shilpha *et al.*, 2023). *Cannabis* appears to be quite sensitive to ammonium with a nitrate-to-ammonium supply ratio of more than 3 to 1 at 15 mM total N supply considered optimal to balance flower biomass and cannabinoid concentrations in one drug-type *Cannabis* cultivar (Saloner and Bernstein, 2022). However, some species like rice, onion, and blueberry are more tolerant to ammonium (Britto and Kronzucker, 2002). This is linked to the environment these plants have evolved in, that is, the presence of biological nitrogen fixation and whether soil N, P, or both are limiting plant productivity (Britto and Kronzucker, 2013; Prodhan *et al.*, 2019; Shilpha *et al.*, 2023).

Most research suggests that whilst human selection has driven cannabinoid concentrations in female inflorescences of drug-type *Cannabis* to near maximum metabolic capacity, flower architecture and overall biomass are key targets for further increasing yield potential (Saloner and Bernstein, 2021; Shiponi and Bernstein, 2021a; Massuela *et al.*, 2023; Stack *et al.*, 2023; Wei *et al.*, 2023). This highlights the importance of understanding sink–source relationships and their response to nutrient supply for yield improvement (Smith *et al.*, 2018; Tegeder and Masclaux-Daubresse, 2018; Burnett, 2019). In rice and tomato, modern hybrids already feature increased spikelet/fruit number and higher spikelet/fruit to leaf biomass ratios (Li *et al.*, 2015; Li *et al.*, 2023). Having a larger sink size, rice hybrids also have higher leaf N content, pre-flowering biomass, and efficient resource translocation during grain filling (Li *et al.*, 2023). However, these properties are highly dependent on soil fertility with source–sink relations in need of optimization for specific cultivation conditions, in particularly for more sustainable low nutrient input systems. In tomato, sink–source relationships are responsive to nutrient supply (de Groot *et al.*, 2003; Kanai *et al.*, 2007) as well as environmental stress factors (drought, light intensity, CO_2 levels, salt) (Matsuda *et al.*, 2011; Osorio *et al.*, 2014; Ji *et al.*, 2020) and vary between cultivars (Matsuda *et al.*, 2011; Li *et al.*, 2015). Genetic manipulation may be needed given that modern crop varieties rarely surpass the trait boundaries of their wild progenitors. The latter were domesticated precisely because they already featured desired traits as adaptations to environmental conditions in their natural habitat (Gómez-Fernández *et al.*, 2024).

The diverse response of hemp- and drug-type *Cannabis* to N supply can be viewed as a case in point. Industrial hemp is bred for vegetative (fibre) biomass—and to some degree seed production—and features relatively weak sink strength in female flowers. In general, flower biomass of industrial/fibre hemp makes up less than 10% of total plant dry matter (Tang *et al.*, 2018; Wei *et al.*, 2023). By contrast, drug types are

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selected based on cannabinoid content, flower architecture, and flower biomass and grown in the presence of excess nutrients (Llewellyn *et al.*, 2023). Female flowers of drug types as well as many 'floral' hemp types are strong sinks and make up between 30% and 50% of total plant biomass (Bernstein *et al.*, 2019b; Anderson *et al.*, 2021; Rodriguez-Morrison *et al.*, 2021; Farnisa *et al.*, 2023).

Comparing inflorescence biomass in response to increasing N supply across both usage types grown in controlled environments (Fig. 3A) highlights their different nutrient requirements for optimal growth, as well as differences in what constitutes limiting levels of N supply. While it is difficult to compare the absolute values of flower yield with N supply due to differences in growing conditions between the studies in terms of light quality/intensity and growth environment (e.g. open versus closed greenhouses), the trends observed suggest differences in nutrient use and flower yield across usage types and cultivars. In hemp, flower biomass initially increases with higher N supply, reaching a cultivar-dependent optimum, after which increased N supply becomes detrimental (Fig. 3A). In comparison with drug-type *Cannabis*, this optimum is reached at lower N supply. There also appears to be a higher tolerance in drug types, whereby what would be a toxic N supply and detrimental to growth in hemp or other species is instead accepted as luxury supply without growth benefit (e.g. accumulation of N without increasing flower yield). However, drug types are sensitive to N limitation of net photosynthesis as leaf chlorophyll concentration starts to decline at a total N supply of less than 11 mM (Saloner and Bernstein, 2021). By contrast, despite substantial variations in biomass, there are no significant differences in leaf chlorophyll concentrations of hemp cultivars grown at between 4 mM and 32 mM total N (Anderson *et al.*, 2021). Regulatory differences in N acquisition and translocation between drug- and hemp-type *Cannabis* are also apparent (Fig. 3B). In hemp, N concentration in inflorescences increases with N supply despite overall reduction in flower biomass due to toxicity (Fig. 3A) and is higher than that in drug types at similar levels of N supply. Together, these data confirm a higher N use efficiency of hemp (Tang *et al.*, 2018; Landi *et al.*, 2019).

In higher plants, there is a strong effect of nutrient supply on secondary metabolism (Amtmann and Armengaud, 2009). In tomato, nitrogen and phosphorus supply impact sink strength and fruit quality—especially in terms of carbohydrate, carotenoid, amino acid, and polyamine composition (Sung *et al.*, 2015; Vallarino *et al.*, 2020; Weinert *et al.*, 2021). Excess N supply often has a negative or no impact on the metabolite profile of tomato fruit (Truffault *et al.*, 2019; Schmidt and Zinkernagel, 2021). In *Cannabis*, the impact of nutrient supply on the synthesis of cannabinoids and terpenes in floral organs is of key concern. Consistent with impacts on secondary metabolite profiles in tomato, increasing N supply decreases cannabinoid concentrations in inflorescences across usage types: total content of CBD and its precursor cannabigerol decrease with increasing N supply in five hemp cultivars, and a relatively low N supply of about 4 mM was considered optimal for both cannabinoid concentration and total yield (Anderson *et al.*, 2021). Similar trends were obtained for another hemp cultivar that showed a broader optimal N supply range of between 2 and 15 mM (Dilena *et al.*, 2023). In a balanced drug-type chemovar, however, there was no effect of N supply on total CBD and THC content in dried and cured female inflorescences (Saloner and Bernstein, 2021). In a later study using the same chemovar, total cannabinoid content determined in fresh-frozen inflorescence material decreased with increasing N supply while terpenoid concentration remained unchanged (Song *et al.*, 2023). N-containing compounds such as chlorophylls and amino acids increased, while hexose and pentose sugars (fructose, glucose, and xylose), phenols, and flavonoids as well as total carbon content decreased. A decrease of phosphate and hexose phosphates furthermore indicates that with increasing N supply, P becomes limiting, which may explain the increase in nicotinic acid, proline, ornithine, lysine, and polyamines such as putrescine (Morcuende *et al.*, 2007; Huang *et al.*, 2008; Aleksza *et al.*, 2017).

In summary, while industrial and floral hemp seem to be more N efficient with high growth rates at low levels of N supply, meta-analysis of different studies indicates that they have a lower threshold for N toxicity as compared with drug types. In contrast to hemp and tomato, many drug types require high N inputs of >11 mM total N to reach maximum photosynthetic rates and flower biomass. Drug-type *Cannabis* seems to also tolerate higher N supply with no discernible effects on either performance or metabolic profile (Saloner and Bernstein, 2021; Song *et al.*, 2023). The complex breeding history involving frequent introgression of hemp- into drug-type *Cannabis* means that the N response of each cultivar or genotype needs to be assessed for optimal cannabinoid yield. It remains to be seen whether a more sustainable N use is achievable through selective introgression of desired hemp traits into drug-type *Cannabis* without affecting yield.

Phosphorus requirements vary between hemp and drug-types

In most rhizosphere environments, P is one of the least plant-available nutrients, with inorganic phosphate (P_i) often tightly adsorbed onto metal-based complexes (Hinsinger *et al.*, 2005). Therefore, field crops are heavily dependent not only on external fertilizer applications but also root exudation of P_i-releasing enzymes such as nucleases and phosphatases as well as of organic (carboxylic) acids such as malate, oxalate, and citrate, which induce localized soil acidification to encourage P_i mobilization (Vance *et al.*, 2003; Richardson *et al.*, 2011; Gerke, 2015). Further root adaptations include auxin-dependent lateral root and root hair formation and increasing P_i uptake and xylem loading (Peret *et al.*, 2011; Zhang *et al.*, 2014). All these adaptations are critical as P itself is a major

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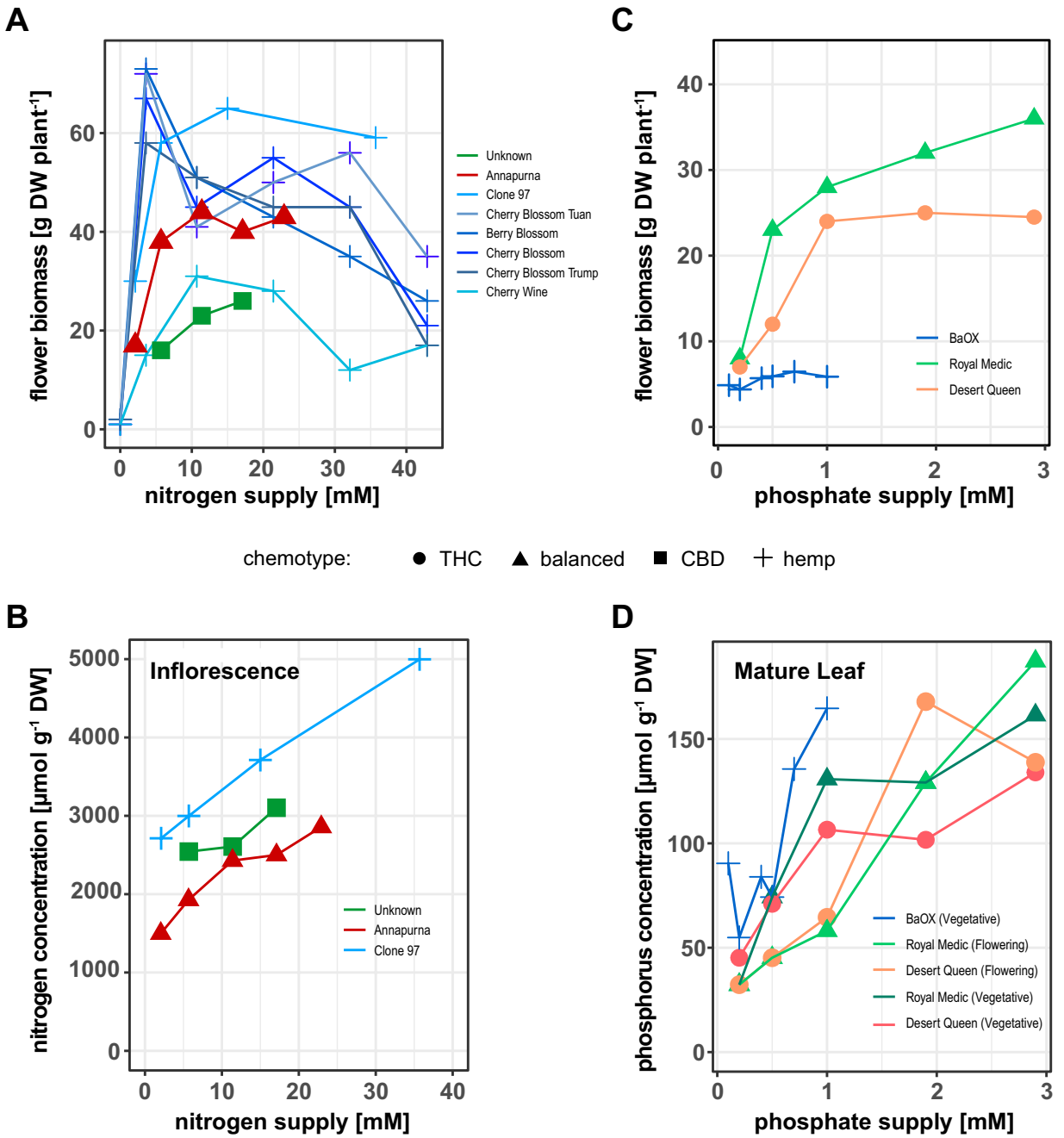

Fig. 3. Response of hemp- and drug-type cultivars to variation in N or P supply. (A, C) In hemp types, flower biomass increases with higher N or P_i supply, reaching a cultivar-dependent optimum, after which additional supply becomes detrimental. By contrast, drug-type *Cannabis* tolerates higher N and P_i supplies without impacting flower biomass. (B) Total nitrogen concentration in flowers continuously increases with increasing N supply in hemp, while it tends to level off in flowers of drug-type cultivars. (D) At any given level of supply during vegetative growth, total P concentration of fan leaves is higher in hemp- than drug-type cultivars, and accumulation in response to supply is exponential in the former. At flowering stage, cultivar specific responses are observed in the latter as P accumulation is either up- or down-regulated with P_i supply. Data points shown are replotted with averages (n=4–10) from Anderson *et al.* (2021), Cockson *et al.* (2020), Massuela *et al.* (2023), Saloner and Bernstein (2020, 2021), and Shiponi and Bernstein (2021b). For Cockson *et al.* (2020), fresh weights were converted to approximate dry weights assuming 85% moisture content. Abbreviations: CBD, cannabidiol; DW, dry weight; THC, tetrahydrocannabinol.

macronutrient required for essential plant processes such as photosynthesis, respiration, protein activity regulation, and the synthesis of nucleic acids and membrane lipids (Veneklaas *et al.*, 2012). In mature legume and cereal seed, the main P storage compound, phytate, accounts for 1–5% by weight, representing 65–85% of total P (Oo *et al.*, 2023). P_i is also

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tightly linked to both sucrose and starch synthesis through the Calvin–Benson cycle, an integral process for plant development that requires triose phosphates and releases P_i in a tightly regulated process (McClain and Sharkey, 2019). Due to its strong impact on carbon flows and feedback regulation of N assimilation, cytosolic levels of P_i are tightly controlled in most crop and model plants, and once plant P status is sufficient, transporters involved in P_i uptake and translocation are rapidly suppressed on both transcriptional and post-translational levels (Aung *et al.*, 2006; Bari *et al.*, 2006; Franco-Zorrilla *et al.*, 2007). During development, plastid P_i translocators are critically important for the translocation of photoassimilates from source to sink tissues, and trehalose-6-phosphate is an important signal for coordination of carbon and nitrogen assimilation to provide the building blocks for organ growth (Fluegge, 1995; Hammond and White, 2008; Griffiths *et al.*, 2016). P_i supply is therefore critical for plant metabolism and growth, with strong links to flower development and reproduction.

In *Cannabis*, despite the effect of P on plant development, there are even fewer studies on the impact of P than that of N supply for both usage types. An impact of P_i on cannabinoid biosynthesis might be expected given cannabigerolic acid and cannabigerovarinic acid, the common precursors of phytocannabinoids, require geranyl pyrophosphate to be synthesized (Gülck and Møller, 2020). Geranyl pyrophosphate is in turn synthesized by the plastidial methylerythritol phosphate pathway, of which P_i is a key component and regulator through triose phosphate utilization in the Calvin–Benson cycle (McClain and Sharkey, 2019). Early studies point towards cannabinoid content being positively correlated with soil P content in drug types of Afghan origin (Coffman and Gentner, 1977). In a recent study of a balanced and a THC-dominant drug type, the highest cannabinoid concentrations were reported under the lowest P_i supply of 0.16 mM, which severely limited plant growth and total flower biomass, while there were no changes in total cannabinoid concentrations with P_i supply levels greater than 0.5 mM (Shiponi and Bernstein, 2021a). In a hemp cultivar, cannabinoid concentrations, predominantly total CBD, increased up to 0.36 mM P_i supply, after which concentrations remained relatively unchanged (Cockson *et al.*, 2020). The CBD-dominant hemp-type cultivar BaOx reached an optimal level of P_i supply for flower production much earlier than the two drug types (Fig. 3C). Higher P_i supply had a negative impact on flower biomass, while there was no response in plant height, total above-ground biomass or root-to-shoot ratio (Cockson *et al.*, 2020). In drug types, P_i supply above the hemp optimum did not affect flower or total plant dry matter, which was fairly constant between 1 mM and 3 mM P_i supply, with female flowers also strong P sinks accumulating about 80% of total organ P (Fig. 3C) (Shiponi and Bernstein, 2021a). Within drug types, there are cultivar-specific differences in their P_i response: the THC-dominant chemovar was slower growing, and as a consequence, had a more compact stature with reduced branching, while, due to stronger vegetative growth that was evident at the two lowest P_i supply levels, leaves and stems of the THC/CBD-balanced chemovar became N-limited at P_i supplies of 1 mM and above. This was accompanied by increased translocation of N to reduced leaves in the inflorescence helping to maintain sink strength (Shiponi and Bernstein, 2021a). N-limited growth in the balanced chemovar may also explain lower net photosynthetic rates compared with the THC-dominant chemovar across treatments. Total P accumulation in flowers reached a maximum of about 400 μmol g^{-1} dry weight at the high P_i supplies across chemovars. Total P content also plateaued in roots of the balanced chemovar, while P content kept increasing in roots of the THC-dominant chemovar, which resulted in higher P acquisition efficiency with increasing P_i supply. Despite its higher P acquisition efficiency, the THC-dominant chemovar had a lower root-to-shoot biomass ratio (Shiponi and Bernstein, 2021a).

These data may indicate repression of P_i uptake in the balanced chemovar because of N-limitation at higher P_i supplies. It is of note that at limiting P_i supply, the balanced chemovar experienced only an approximate 15% flower yield loss while the THC-dominant chemovar incurred nearly 50%, relative to the proposed 'optimal' 1 mM P_i supply (Fig. 3C) (Shiponi and Bernstein, 2021a). The higher yield under P limiting conditions in the balanced chemovar could be due to its higher root-to-shoot ratio most likely in combination with molecular traits such as increased expression of high-affinity phosphate transporters in roots, as well as more efficient remobilization of P_i from source to sink tissues (Akhtar *et al.*, 2008; Julia *et al.*, 2016). Interestingly, the studied hemp cultivar had a 3-fold higher root-to-shoot biomass ratio at the lowest P_i supply in the vegetative phase and it did not change its biomass allocation with increasing P_i supply (Cockson *et al.*, 2020). For hemp, uninhibited P accumulation in leaves would suggest a constitutive phosphate starvation response with sustained P_i uptake as observed in plant species adapted to P limited environments (Shane *et al.*, 2004). At higher P_i supply to hemp in the reproductive phase, reductions in N and microelement pools in source leaves together with a lack of increase in flower biomass, premature senescence, and browning of mature fan leaves indicate that plants are becoming increasingly P toxic and/or N limited (Shukla *et al.*, 2017; Cockson *et al.*, 2020). P accumulation in hemp leaves is much stronger than in the two drug types, as a critical toxicity level of 160 μmol total P g^{-1} dry weight is already reached at an external P_i supply of 1 mM, while such levels are only reached at between 2 and 3 mM P_i in drug types (Fig. 3D) (Shane *et al.*, 2004). This again supports the notion that hemp types are more nutrient efficient than drug-type *Cannabis*, with higher yield at relatively lower levels of fertilizer input (Tang *et al.*, 2018; Stack *et al.*, 2023).

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Integrating molecular approaches for improvements in understanding nutrient regulation in *Cannabis*

The available data suggest that drug types have a higher tolerance for excessive or luxurious nutrient supply than hemp-type *Cannabis*. Within usage types, cultivar specific differences in nutrient response and sink strength are also evident (Wylie *et al.*, 2020). Recent introgression of hemp (Grassa *et al.*, 2021), coupling a functional *CANNABIDIOLIC ACID SYNTHASE* gene with the capacity of modern drug-type cultivars to produce high cannabinoid concentrations and flower biomass, has resulted in progeny with high allelic diversity, especially since drug-type parental lines are not homozygous to begin with (Barcaccia *et al.*, 2020). These more recent introgressions led to complex segregation of associated nutrient efficiency traits that were relatively fixed in hemp- and drug-type *Cannabis* with restricted gene flow between domesticated populations (Small, 2015; Ren *et al.*, 2021).

However, these progenies also provide a rich genetic resource for the analysis and interaction of such traits. Assessing the genetic basis of selected traits of interest will rely on both traditional and molecular techniques to uncover quantitative trait loci and/or molecular markers (Platten *et al.*, 2019; Li *et al.*, 2022). Such approaches are advantageous as conventional breeding through crossing and selection is highly impractical due to the dioecious nature of *Cannabis* and the unclear lineage and heterozygosity of drug types (Sawler *et al.*, 2015; Ingvardsen and Brinch-Pedersen, 2023). As proof-of-concept, desirable domestication traits relating to plant anatomy, fruit shape, fruit size, fruit number, and nutritional quality were transferred to wild tomato by CRISPR–Cas9 genome editing to improve agronomical value (Zsögön *et al.*, 2018). Extensive knowledge of carbon and nitrogen fluxes across different plant model species has allowed an increase in fruit yield in tomato through multi-gene metabolic engineering (Vallarino *et al.*, 2020). In *Cannabis*, marker-assisted methods have been employed successfully for cannabinoid profiling (Weiblen *et al.*, 2015; Laverty *et al.*, 2019; Jin *et al.*, 2021; Welling *et al.*, 2022), sex determination (Toth *et al.*, 2020), and usage type distinction (Cascini *et al.*, 2019; Barbaric and Bezbradica, 2023). However, the fidelity of these markers is reliant on high quality and continuous improvement of well-annotated reference genomes (Barcaccia *et al.*, 2020; Ingvardsen and Brinch-Pedersen, 2023). The creation of a *Cannabis* pangenome in combination with phased genomes is likely to help bridge the high heterogeneity present in current germplasm, facilitating breeding via identification of elite and stable markers conserved across the variable *Cannabis* genomes (Hurgobin *et al.*, 2021).

Optimizing for nutrient efficiency and sink strength

Nutrient-efficient *Cannabis* cultivars are key to meeting industry sustainability goals (Landi *et al.*, 2019; Velechovsky *et al.*, 2024). The commercialization of *Cannabis* of both usage types into pharmaceutical products also requires good manufacturing practices to be consistently met by growers to ensure product quality standards (Craven *et al.*, 2019; Montoya *et al.*, 2020; Jameson *et al.*, 2022). Hemp is well known for its phytoremediation potential due to its high uptake capacity for heavy metals and other soil contaminants (Testa *et al.*, 2023). These traits may become detrimental if cultivation conditions are not well defined and constantly monitored. For example, arsenic is taken up by high-affinity phosphate transporters (Navarro *et al.*, 2021), and thus selecting lines with high P_i acquisition efficiency may lead to higher tissue accumulation of heavy metals in field-grown produce (Blandinières and Amaducci, 2022). The nutritional value of some hemp products could also be compromised by the hyperaccumulation of phosphate in flowers and phytate in seed—given that phosphate toxicity is an issue for both human and animal health (Razzaque, 2011; Lei *et al.*, 2013; Alexander *et al.*, 2022). Nutrient management, and by extension how nutrient status is regulated across different cultivars and usage types, is necessary for uniform plant growth, secondary metabolite synthesis, and flower development, as well as maintaining plant health through decreasing susceptibility towards opportunistic pathogens detrimental to harvest quality (Dordas, 2008; Punja, 2021). For these purposes, cannabinoid production at an industrial scale is largely indoors under controlled environmental conditions, which also maximizes the number of crop cycles per year (Chandra *et al.*, 2020).

Several studies have emphasized the importance of flower biomass for overall cannabinoid yield in both hemp- and drug-type *Cannabis* (Naim-Feil *et al.*, 2021; Wei *et al.*, 2023). By contrast, cannabinoid concentrations are relatively stable across moderate changes in nutrient supply and/or composition (Saloner and Bernstein, 2021; Shiponi and Bernstein, 2021a; Massuela *et al.*, 2023; Stack *et al.*, 2023; Wei *et al.*, 2023). This recapitulates findings in tomato that emphasize the importance of source–sink interactions for fruit quality and yield (Osorio *et al.*, 2014; Smith *et al.*, 2018). A high N-to-P ratio is known to promote vegetative growth with a negative impact on sink strength and thus fruit harvest index and fruit quality (Schauer *et al.*, 2006; Tegeder and Masclaux-Daubresse, 2018). High N levels suppress circadian clock and flowering genes in Arabidopsis whilst low N supply accelerates flowering either through promoting the expression of genes for transcriptional regulators CONSTANS (CO) and SUPPRESSOR OF OVEREXPRESSION OF CONSTANS1 (SOC1), altering the phosphorylation state of transcription factor FLOWERING BHLH4, and/or inhibiting expression of transcription factors GATA, NITRATE-INDUCIBLE, CARBON-METABOLISM INVOLVED (GNC), and GNC-LIKE (Cho *et al.*, 2017; Lin and Tsay, 2017; Olas *et al.*, 2019; Y. Zhang *et al.*, 2023). By contrast, high P_i supply promotes flower initiation and development, whilst P limitation delays flowering (Nord and Lynch, 2008; Y. Zhang *et al.*, 2023). This

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is mediated through altered expression of flowering genes such as *CO* and *SOC1*; however, effects seen for mutants with altered shoot P status support a metabolic control over trehalose-6-phosphate, an important flowering signal (Kant *et al.*, 2011; Wahl *et al.*, 2013). In *Cannabis*, orthologues for these key flowering genes have been identified pending further functional characterization (Steel *et al.*, 2023; Dowling *et al.*, 2024). The emergence of inositol pyrophosphates as important signals of plant nutrient status and associated sensor proteins that coordinate nitrate and phosphate acquisition as well as developmental programs will provide new targets for metabolic engineering (Poza-Carrion and Paz-Ares, 2019; Z. Zhang *et al.*, 2023). These sensors and their regulatory networks are yet to be explored in plant species that differ in their nutrient efficiencies and breeding history. Hemp- and drug-type *Cannabis* provide an excellent opportunity to study these. Significant differences in sink strength within the two usage types provides valuable insight into the impact of N and/or P redistribution on C balance during the reproductive stage (Veneklaas *et al.*, 2012). Vegetative plants largely rely on P_i uptake by roots during early growth stages, with a shift to P remobilization from shaded, older to young, growing leaves occurring in the later stages (Han *et al.*, 2022). After the shift to flowering, plants depend much more heavily on P_i translocation from source organs—and drug-type *Cannabis* plants allocate a large proportion of dry mass to female unpollinated flowers (see above). It remains to be seen how increasing P use efficiency in drug types grown indoors will affect cannabinoid and terpene concentrations and their profiles given the importance of P for photosynthesis, carbon flux, and source–sink interactions in field grown crops (Wissuwa *et al.*, 2005).

Understanding the molecular regulation of plant nutrient status and source–sink interactions will be crucial towards the development of nutrient-efficient cultivars and sustainable crop management and will tie into optimizing crop quality and yield whilst reducing agrochemical inputs and therefore costs and environmental pollution (Zheng *et al.*, 2021).

Towards community standards in *Cannabis* nutrient research

In *Cannabis*, trends in growth responses to various environmental factors such as nutrient supply, daylength, light intensity, or light quality are emerging from recent published data (Shukla *et al.*, 2017; Magagnini *et al.*, 2018; Saloner *et al.*, 2019; Anderson *et al.*, 2021; Bevan *et al.*, 2021; Rodriguez-Morrison *et al.*, 2021; Shiponi and Bernstein, 2021a; Llewellyn *et al.*, 2022, 2023; Reichel *et al.*, 2022; Saloner and Bernstein, 2022; Westmoreland and Bugbee, 2022; Dilena *et al.*, 2023; Massuela *et al.*, 2023; Peterswald *et al.*, 2023; Song *et al.*, 2023). However, a lack of community standards presently impedes straight-forward comparison of results and their interpretation. Currently, hemp- and drug-type *Cannabis* cultivars are often independently tested under different ranges of P or N supply (Fig. 3), making it difficult to determine where actual limitations to their performance lie across the entire genetic range. Determination of the mass balance between nutrients supplied, nutrients taken up by the plant, and their partitioning into downstream metabolites requires accurate description of tissue concentrations, nutrient quantities supplied, and frequency of application, and sensible information on nutrient formulations (Lambers and Barrow, 2021). For comparative analyses, a greater number of genetically well-defined hemp- and drug-type *Cannabis* grown in parallel under standardized cultivation conditions is needed to identify traits of interest and obtain a functional understanding. Furthermore, accurate identifiers and terms are needed to describe morphological and physiological features, especially around flowering time and flower maturity, for both hemp- and drug-type *Cannabis* (Mediavilla *et al.*, 1998; Brym *et al.*, 2023). This will help to detect differences in the timing of developmental transitions caused by changes in nutrient supply ratios and resource allocation. It is also important to study organs that respond quickly to environmental conditions, given that in many species individual reproductive organs are protected against fluctuations in nutrient status whilst photosynthetically active source leaves along the main stem quickly display signs of nutrient stress (Veneklaas *et al.*, 2012).

Systematic analysis of the metabolomic and transcriptomic response to nutrient limitation or excess will help to define key metabolites and marker genes for cultivar selection (Watanabe *et al.*, 2010; Cobb *et al.*, 2013; Vallarino *et al.*, 2020; Cuyas *et al.*, 2023). In this respect, determination of cannabinoid profiles and concentrations often lacks standardization of methodology and preparation of the plant materials before analysis (Welling *et al.*, 2019; Kim *et al.*, 2022). The current practice of trimming reduced leaves from flowers and drying harvested materials over long periods of time (up to several weeks) at temperatures ranging from 15 °C to 60 °C introduces artifacts and reduces reproducibility between studies with information on residual water content often lacking. Shock-freezing plant materials on-site and storage at below −70 °C until further processing, tissue homogenization under liquid N_2 or on dry ice, and the use of internal standards improve cannabinoid preservation to reflect the actual profile and concentrations of individual cannabinoids *in planta* at harvest.

While the common practice of clonal propagation is eliminating some of the phenotypic variation, comparison of experimental results between growth facilities is still difficult, even if the same seed source is used. Highly heterozygous plants and the lack of true *Cannabis* F_1 hybrids in most breeding programs lead to a high degree of genetic diversity, even in 'all-female' or sinsemilla cultivars (Barcaccia *et al.*, 2020). For research purposes, it would be desirable to generate suitable representations of hemp- and drug-type *Cannabis* that are genetically fixed as much as possible and create near-homozygous parental clones that serve as stable reference populations.

Optimizing nutrient use is highly dependent on cultivation practices. Soil-grown crops are often nutrient or water limited for at least some part of their growth cycle, so that boosting

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soil health through increasing organic matter and fostering the soil microbiome have dramatic effect on yields (Qiao *et al.*, 2022; Suman *et al.*, 2022). Plants grown in protected cropping systems, on the other hand, often benefit from inorganic fertilizer formulations without competition from microbes (Sanjuan-Delmás *et al.*, 2020; Chavan *et al.*, 2022). Breeding programs therefore must generate a diverse range of cultivars that cater for these very different growth environments.

Concluding remarks and future perspectives

Cannabis sativa L. is a monotypic genus with highly polymorphic, heterogeneous accessions, varieties, and chemovars. Human selection for divergent purposes has resulted in two very distinct usage types—hemp-type (fibre or industrial hemp) and psychoactive compound-producing drug-type (marijuana) *Cannabis*. In contrast to other crop plants, very little research has gone into exploring the genetic basis for the very strong contrasts in growth habit, flowering control, and nutrient use between the two main usage types. This review has highlighted differences in nutrient use based on the analysis of relevant *Cannabis* literature, as well as the knowledge gaps that still exist between observed physiological responses to nutrient supply and the underlying genetic factors. There is great potential to increase our understanding of source–sink interactions as *Cannabis* displays stronger contrasts in developmental programs, nutrient use, and metabolic fluxes than many current model plants such as *Brassicaceae*, cereals, and tomato. While progress in this area is encouraging, employing available genetic resources and 'omics' tools towards understanding the complex breeding history and biology of *Cannabis* will further boost genetic improvement. As has been the case for tomato breeding, scientific research and methodological advances for *Cannabis* will generate more resilient germplasm for different purposes and growth environments. Preserving a diverse gene pool that includes wild accessions and landraces will furthermore provide genetic resources for future demands on pharmaceuticals, food products, clothing, biofuels, and building materials that this highly adaptable species can no doubt cater for.

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Conflict of interest

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