SOCIETY FOR EXPERIMENTAL BIOLOGY

Journal of Experimental Botany, Vol. 76, No. 1 pp. 1–4, 2025
https://doi.org/10.1093/jxb/erae463

eXtra Botany

Special Issue Editorial

Improving medicinal plant cultivation through in-depth understanding of environmental, physiological, metabolic, and genetic constraints

Traditional herbal medicines are intricately linked to advancing human societies, and there has been a renewed interest in isolating specific secondary metabolites for pharmaceutical use. Amongst the most prominent examples are alkaloids such as the chemotherapy agent paclitaxel (brand name Taxol®) isolated from cambium cells of the Pacific yew tree (*Taxus brevifolia*), the *Amaryllidaceae* alkaloid galanthamine used to treat symptoms of Alzheimer's disease, and opium alkaloids produced by opium poppy (*Papaver somniferum* L.) used as sedatives and in management of severe pain. Meroterpenoids derived from phytocannabinoids found in glandular trichomes of female flowers of *Cannabis sativa* L. are being assessed for treating chronic pain and treatment-resistant epilepsy.

To standardize production of these phytoceuticals by the respective plant species, it is paramount to understand the biological context in which they are produced, the cells or tissues in which they accumulate, as well as metabolic pathways and biochemical constraints for their synthesis. Many secondary metabolites are serving ecological functions, such as protection of plants from extreme temperatures, high light intensity, as well as pathogen or insect attack. Using alkaloids as an example for plant chemical defences against herbivorous insects, Leite Dias and D'Auria (2025) illustrate how an evolutionary arms race leads to structural diversification of toxic alkaloids and strategic compartmentalization in host plant tissues, while insects often display a narrow host plant range to optimize survival strategies such as detoxification by cytochrome P450 enzymes and glutathione *S*-transferases, excretion via their digestive system (Malpighian tubules), sequestration in fat bodies or haemolymph, or recruitment of specialized gut microorganisms to break down toxins. The authors also discuss the impact of this arms race on beneficial insects, and in particular pollinators, that must be able to metabolize alkaloids found in nectar or pollen. Chemical diversity of alkaloids in host plants is exemplified in *Amaryllidaceae* that produce >650 of these secondary metabolites including phytoceuticals such as galanthamine, lycorine, and crinamine (Liyanage *et al.*, 2025). These compounds are derived from phenylalanine and tyrosine, and share a benzopyridine heterocyclic group; however, a universal classification system based on the structural attributes is still lacking. Common precursors tyramine and 3,4-dihydroxybenzaldehyde undergo condensation to norbelladine followed by methylation to 4'-*O*-methylnorbelladine which is required for oxidative phenol coupling catalysed by highly diverse cytochrome P450 enzymes. Identifying individual enzymes in a given species through recent technical advances will help to understand their promiscuous nature and to elucidate evolutionary relationships with synthetic pathways for non-alkaloid defence compounds such as lignans, flavonoids, and coumarins.

Another key aspect for pharmaceutical production is a better understanding of subcellular and cell- or organ-specific sequestration, transport, and storage of the end products. Alkaloids are often secreted into the apoplast of leaf scales or vascular tissues, as well as mucilage. The benzylisoquinoline alkaloids in opium poppy (*Papaver somniferum*) can be found in specialized laticifers which form a tube-like network in the phloem to produce and store latex (Hong *et al.*, 2025). Enzymes involved in benzylisoquinoline alkaloid synthesis have been functionally characterized and are produced in phloem companion cells. Enzymes are then transported into sieve elements where pathway intermediates salutaridine and thebaine are produced for predominantly apoplastic transport to laticifer cells where the enzymes required for the synthesis of end products morphine, codeine, papaverine, and noscapine are localized. Open questions for all alkaloid synthetic pathways are how gene expression is regulated to confer organ- or cell-specific expression and its activation by elicitors or phytohormones. Genes encoding individual enzymes in the metabolic pathway are often found in clusters. Pangenomes of a given plant species can elucidate how major structural variations such as copy number variants and chromosomal rearrangements enabled diversification of metabolic pathways and provide new targets for increasing yield or alkaloid composition.

Paclitaxel found in *Taxus*—as well as other tree and endophytic fungal—species is widely used as an anti-cancer drug and is one of the most successful examples of a phytoceutical. It is produced from substrates geranylgeranyl diphosphate and phenylalanine by a series of >20 enzymes including two cytochrome P450 proteins as a jasmonate-dependent defence response against fungal pathogens (Coombe-Tennant *et al.*, 2025). Synthesis of this alkaloid is highly compartmentalized as it predominantly accumulates in the phloem and dead bark of yew trees. Tissue-specific expression of pathway genes is mediated by the phloem-specific MYB domain transcription factor MYB3 in *Taxus marei*. Induction by fungal elicitors involves *Taxus chinensis* WRKY1. Gene clusters for the precusor taxadiene as well as paclitaxel synthesis have been identified in chromosome-scale genomic studies. For pharmaceutical production, high-yielding *Taxus* cell culture systems have been developed and pathway engineering deployed to introduce metabolic modules into heterologous hosts such as *Nicotiana benthamiana* or microbial production systems. *Taxus* cell cultures are currently the preferred way to produce high amounts of commercial grade product; however, further work needs to investigate more potent elicitors, inhibitors of competing pathways such as phenylpropanoid synthesis, as well as reversing the effects of DNA methylation in ageing cell cultures.

As indicated for *Taxus* cell cultures above, the recalcitrance of many medicinal plant explants or cell lines to sustain productivity and pluripotency through repeated cycles of tissue culture poses challenges for establishing sustainable *in vitro* production systems (Bennur *et al.*, 2025). While genome editing to manipulate entire pathways as outlined for paclitaxel above can boost target metabolite concentration, there are genotype-specific challenges such as transformation recalcitrance and loss of vigour through cycles of clonal propagation to overcome. These pose larger obstacles for medicinal plants due to the limited size of donor populations. The choice of germplasm, target tissues used as explants, use of growth regulators, and morphogenic genes may boost dedifferentiation capacity and help to address regeneration recalcitrance. For medicinal plants, tissues that harbour undifferentiated cells such as zygotic embryos, shoot apical meristems, or haploid gametophytes are preferential targets for tissue culture explants. The latter can be used in microspore cultures to generate double haploids—a technique particularly useful in outcrossing medicinal plant species with a high level of genomic heterogeneity. Aside from manipulating auxin to cytokinin ratios, the use of synthetic phytohormones such as thidiazuron, picloram, meta-topolin, or ethylene inhibitors has boosted tissue culture performance in some medicinal plant species. Genes encoding transcriptional regulators of stem cell identity and maintenance such as WUSCHEL, KNOTTED1, BABYBOOM, LEAFY COTYLEDON, and GROWTH-REGULATING FACTORS can be transformed into tissue culture cells via nano particles which, aside from delivering cargo into cells, may also exhibit antimicrobial and elicitor activities to enhance target secondary metabolite production.

Apart from alkaloids, terpenoids and meroterpenoids such as phytocannabinoids are another class of plant secondary metabolites with great potential for pharmaceutical use. In dioecious drug-type *Cannabis sativa* L., these metabolites accumulate preferentially in the apoplastic space of glandular trichomes in the flowers and bracts of female inflorescences. As discussed for alkaloids before, their synthesis from precursor cannabigerolic acid (CBGA) derived from polyketide and methylerythritol 4-phosphate pathways can be elicited by methyl jasmonate and salicylic acid treatment. Here, Dimopoulos *et al.* (2025) investigate the diurnal control of metabolites and enzymes of this well-characterized pathway. They found a close link between cannabinoid accumulation and increased availability of photoassimilates—in particular sucrose—during the day, as reflected by increased abundance of enzymes associated with cytosolic glycolysis. The strongest increase in cannabinoid concentrations over the course of the day was seen for the CBGA precursor. Similar to the reported decrease in transcript and protein abundance with flower maturity, the authors report a decline in key cannabinoid biosynthetic enzymes with daytime progression. They conclude that the rate-limiting factor for cannabinoid synthesis is likely to be precursor synthesis from primary metabolism.

Given that metabolic, light, and other environmental factors are key determinants of product yield, protected cropping or controlled environments are preferred by growers of medicinal plants. Dsouza *et al.* (2025) provide an overview of how existing systems help to boost product yield in target medicinal corps. The authors also propose strategies on how to further improve photosynthetic carbon assimilation as well as light quality, diurnal and elicitor responses in a commercial setting whilst ensuring current good manufacturing practice.

Successful introduction of a medicinal plant species into a protected cropping environment requires a deeper understanding of its natural habitat, geographic distribution, and—if applicable—its domestication history. The plant's response to changes in nutrient supply, especially that of macro elements nitrogen and phosphorus, relies heavily on ecological constraints that limit plant productivity. Adaptive traits include root-to-shoot biomass ratio, root system architecture, repression or induction of selective nutrient transporters to maintain overall nutrient balance, as well as genetic determinants of plant development that promote the transition from vegetative to reproductive stage. Wee *et al.* (2025) illustrate anthropogenic effects on these traits through selective breeding of *Cannabis sativa* L. for seed and fibre versus cannabinoid production. Domestication of hemp- and drug-type *Cannabis* has led to great diversity in plant morphology (tall plants with long stems versus compact plants with large female inflorescences), plant development (late versus early flowering), and nutrient use (low versus high fertilizer requirement). For a C_3 species, nitrogen and phosphate requirements of fibre or dual-purpose hemp tend to be low, with a narrow optimal range. Flowering hemp as well as medicinal or drug-type *Cannabis*

tend to require higher nitrogen and phosphate supply, with substantial genotypic diversity in their nutrient response. A case study of how introgression of hemp- into drug-type *Cannabis* impacts nutrient response and sink strength of female inflorescences—and ultimately cannabinoid yield—illustrates how profound differences in key agronomic traits between usage groups are (Jost *et al.*, 2025). This study identified transcriptional regulators of nutrient assimilation and flower development that are differentially expressed in the two contrasting drug type chemovars. Low expression of genes encoding members of GROWTH REGULATING FACTOR and SQUAMOSA PROMOTER BINDING PROTEIN-LIKE transcription factor families in flowers of the cannabidiol (CBD)-dominant chemovar and misregulation of genes encoding key regulators of phosphate and nitrate assimilation pathways, such as SPX DOMAIN GENE1 (SPX1), SPX3, and NITRATE REGULATORY GENE2, are associated with reduced flower, and ultimately cannabinoid, yield.

Making use of the most recent genomic tools and genetic resources is critically important for *Cannabis* crop improvement (Pancaldi *et al.*, 2025). Identified target traits are cannabinoid and terpenoid profiles in female flowers, seed oil content and composition, fibre quality, flowering time control, and sex determination in this dioecious species. The authors summarize efforts to manipulate underlying metabolic and regulatory pathways and highlight current knowledge gaps. Sex determination in *Cannabis* is particularly complex as it is highly heritable, yet very sensitive to environmental as well as endogenous—in particular hormonal—signals. Identifying genetic determinants is further complicated due to observed linkage with both sex and autosomal chromosomes. Tracking differential gene expression in male and female hemp plants across development followed by weighted gene co-expression network analysis led to the identification of *Cannabis* homologues of a B3-domain [REPRODUCTIVE MERISTEM16 (REM16)] and a bZIP transcription factor [BZIP14/FLOWERING LOCUS D1 (FD-1)] (Shi *et al.*, 2025). In *Cannabis*, the REM16 homologue is encoded on the non-recombining region of the X chromosome, while the gene encoding the FD-1 homologue is located on the Y chromosome and may well be responsible for the early flowering phenotype reported for male hemp plants. Transcripts encoding these two flowering time regulators already display differential expression between the sexes at early vegetative stages. Differential expression of genes associated with sex tends to increase as male and female plants start to flower. However, these are largely associated with autosomes rather than sex chromosomes. Further research will be needed to ascertain which of these genes specifies the sex of the plant itself and which are involved in the underlying developmental programmes and associated metabolic and hormonal pathways.

The reviews and research articles presented in this Special Issue highlight the importance of generating genomic resources and molecular breeding tools for medicinal plants to ensure sustainable production of phytoceuticals and herbal medicines. Many of the plant species highlighted here can be regarded as orphan or underimproved crops in urgent need of further attention from agricultural research, breeders, and the protected cropping industry. From the work featured here, one can easily see how these plants offer unique opportunities to expand our current 'classical' crop models through greater diversity of morphological, physiological, and biochemical traits as a consequence of their adaptation to a distinct ecological niche and often challenging environments. Not only are they a great resource for alternative medicines, but knowledge gained can also contribute to more sustainable, low-input, and climate-resilient cropping systems.

Acknowledgements

This special issue is dedicated to Professor Gary Loake, in memoriam.

Conflict of interest

The authors declare no conflicts of interest.

Funding

RJ was funded by the ARC Industrial Transformation Hub for Medicinal Agriculture (grant ID IH180100006). Research in RM's lab is supported by the Irish Research Council (grant ID IRCLA/2022/3294). Research in SS's lab is supported by the HEA North South Programme (Project: ÉIREhemp).

Keywords: Alkaloids, *Amaryllidaceae*, *Cannabis sativa*, diurnal regulation, galanthamine, glandular trichomes, hemp, insects, meristems, multi-purpose crops, nitrogen, paclitaxel, *Papaver somniferum*, phosphorus, phytocannabinoids, plant defence, plant nutrient use, protected cropping, secondary metabolism, sex determination, *Taxus* species, tissue culture.

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