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From pathway to products: Canadian achievements in plant specialized metabolism

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Abstract

Canada has made significant contributions to the field of plant biochemistry, with numerous researchers actively focusing on elucidating the biosynthetic pathways of plant specialized metabolites and producing these compounds in heterologous systems, such as bacteria, yeast, or other plant species. The review aims to highlight the strengths of Canadian research in this domain over the last three decades. It will describe advances in pathway elucidation, enzyme characterization, and production of enzymes and metabolites in heterologous systems, particularly in the areas of alkaloids, terpenoids, and phenolic compounds. Canadian researchers have not only made pivotal scientific discoveries but have also ensured the continuity of scientific excellence by mentoring new generations of principal investigators in plant specialized metabolites. These advances warrant recognition and financial support to retain future talent and to maintain Canada's leadership in scientific progress on the global stage.

Key words: biochemical pathways, scientific innovation, biotechnology, metabolic engineering, alkaloids

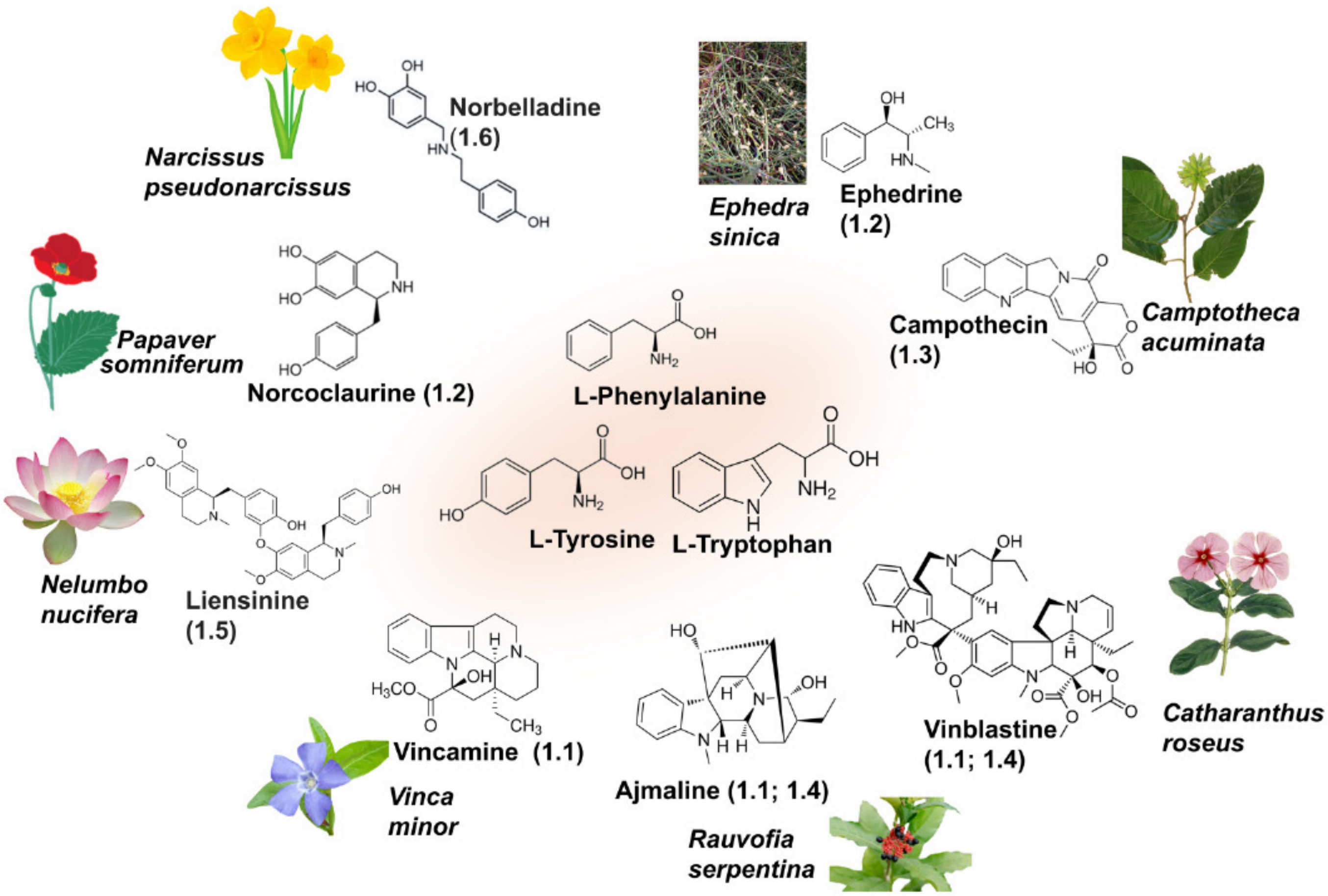
1. Introduction

Plants synthetize a wide arsenal of metabolites to protect themselves against herbivores, pathogens, and parasites, and abiotic stresses, or to attract pollinators. Humans use plants as food and fuel, and exploit plants specialized metabolites for medicines, cosmetics, and nutritional supplements. One notable example of a phytometabolite with pharmaceutical properties is Taxol™ (generic name paclitaxel), a diterpene that was discovered in 1967 from bark extracts of the North American tree *Taxus brevifolia* (Pacific yew) (Weaver 2014). Paclitaxel was first approved by the USA's Food and Drug Administration (FDA) for the treatment of ovarian cancer in 1992, and is now also approved for the treatment of breast and non-small cell lung cancer, as well as Kaposi's sarcoma (Weaver 2014). Another example is capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide), a phenolic alkaloid from *Capsicum* spp. (e.g., chili peppers) native to the American continent (Costa et al. 2022) that brings spiciness to food by causing a burning sensation in the mucous membranes of the mouth. Besides its role in gastronomy, the compound is used in medicine and has been approved for pain relief by both the FDA and the European Medicines Agency (Sharma et al. 2013; Weaver 2014; Chung and Campbell 2016). Both metabolites have biological relevance: paclitaxel acts against parasites and fungal attacks in *T. brevifolia* (Elmer et al. 1994), and capsaicin repels mammal herbivores (Tewksbury and Nabhan 2001).

In Canada, several research groups are dedicated to elucidating how plants produce specialized metabolites of interest. For instance, in 2013, a multi-laboratory effort led to sequencing, de novo assembly, and annotation of the transcriptomes from 20 plant species of medicinal importance, enabling the identification of genes in biosynthetic pathways of specialized metabolites, including valerenic acid, benzylisoquinoline alkaloids (BIAs), and the polyketide hypericin (Xiao et al. 2013). A quick search on Scopus shows that, between 2019 and the first half of 2024, Canada was among the top 10 countries publishing on plant metabolism elucidation and plant metabolic engineering, with Canadian researchers contributing 142 research and review articles among 4538 published worldwide.

In this review, we provide an overview of the advances led by principal investigators (PIs) active in the domain of plant specialized metabolism across Canada. Due to space constraints, we focused on PIs whose research centres on pathway elucidation and/or bioengineering of plant alkaloids, terpenoids, and phenolic compounds, excluding phytohormones. We apologize if we have inadvertently omitted any PIs; our intention was not to offend anyone but to highlight the significant contribution of Canadian researchers. We have done our best to include everyone and would appreciate it if you could inform us of any omissions so we can include them in a future revision of this review. Additionally, we listed researchers with at least three publications in the

Fig. 1. Alkaloids and their plants of origin investigated in Canada, along with their main precursor: aromatic amino acids. Numbers in parenthesis indicate the researchers that investigate the topic: (1.1) Vincenzo De Luca; (1.2) Peter J. Facchini; (1.3) Thu-Thuy T. Dang; (1.4) Yang Qu; (1.5) Vincent JJ Martin; (1.6) Isabel Desgagné-Penix. *Narcissus pseudonarcissus*' drawing was done with Krita 5.2.9. The following images were obtained from Wikimedia Commons: *Camptotheca acuminata*: Auckland Museum (CC BY 4.0) https://commons.wikimedia.org/w/index.php?curid=65765508; *Ephedra sinica*: By alexlomas (Flickr, CC BY 2.0) https://commons.wikimedia.org/w/index.php?curid=6343381; *Papaver somniferum*: By Rachelhs (CC0) https://commons.wikimedia.org/w/index.php?curid=34838409; *Raulwolfia serpentina*: By MAPeFY (CC BY-SA 4.0) https://commons.wikimedia.org/w/index.php?curid=80304394; *Vinca minor*: By Ryan Kaldari, https://commons.wikimedia.org/w/index.php?curid=6369683.



filed within the last 5 years. Major breakthroughs in the field over the past 30 years, as well as synthetic biology innovations for producing plant specialized metabolites in heterologous systems, will be described.

2. Investigating alkaloids

Alkaloids, derived from amino acids such as phenylalanine, tryptophan, and tyrosine, form the one of the largest groups of specialized metabolites. This category includes the neuroactive caffeine (McLellan et al. 2016), the antitumoral vinblastine and vincristine (Dhyani et al. 2022), the anti-gout agent colchicine (Dhyani et al. 2022; Stamp et al. 2024), and the acetylcholinesterase inhibitor galanthamine (Kaur et al. 2022).

Canadian research teams have significantly advanced the understanding of monoterpene indole alkaloids (MIAs) and BIAs. Their work highlights the enzymes involved in biosynthesis, plant defense roles, biological activities, medicinal potential, and heterologous production methods. International efforts have contributed to the elucidation of the MIA pathway, with several reviews providing comprehensive insights (O'Connor and Maresh 2006; St-Pierre et al. 2013; De Luca et al. 2014; Pan et al. 2015; Salim et al. 2023).

Meanwhile, in Canada, BIA research has primarily focused on poppy species and Amaryllidaceae. Global studies predominantly investigate alkaloids from *Papaver somniferum* (opium poppy), but species of other orders have also been investigated, with advances in gene discovery, expression, and protein characterization (Menendez-Perdomo and Facchini 2018; Singh et al. 2019; Georgiev et al. 2020; Desgagné-Penix 2021; Aghaali and Naghavi 2024; Aghaali et al. 2024; Liyanage et al. 2024).

This section reviews advancements in MIA metabolism led by Professors Vincenzo De Luca and Yang Qu, contributions by Professors Peter Facchini and Vincent J.J. Martin on poppy alkaloids, Pr. Isabel Desgagné-Penix on Amaryllidaceae alkaloids, and Pr. Thu-Thuy T. Dang's research on cytochrome P450s in alkaloid biosynthesis pathways (Fig. 1).

2.1. Vincenzo de Luca

The legacy of Pr. Vincenzo de Luca (Brock University) includes his team's major discoveries on alkaloids biosynthesis and training of the next generation of Canadian plant biochemists. His group focused on the elucidation of the biosynthesis pathway of the MIA vindoline and vinblastine, derived from tryptophan and secologanin (Salim et al. 2023), mainly in *Catharanthus roseus* (Madagascar periwinkle). This massive complex pathway of 31 steps was recently elucidated in its entirety, with 17 enzymes being discovered and characterized by Pr. De Luca's team and other three being further characterized by them (Fig. 2; Kulagina et al. 2022).

Pr. de Luca's team also researched MIA biosynthesis in Indian snakeroot (*Rauvolfia serpentina*), characterizing the role of γ-tocopherol-like *N*-methyltransferases (Cazares-Flores et al. 2016; Levac et al. 2016) in ajmaline biosynthesis, and uncovered the transporters involved in the export of vincamine in *Vinca minor* (periwinkle) (Demessie et al. 2017). His group has also reported on grapes and their glucosyltransferases, flavonols, and esters (Wang and De Luca 2005; Hall and De Luca 2007; Hall et al. 2011*a*, 2012).

In addition to the research achievements describe above, the training of a new generation of accomplished researchers in the area is also part of Pr. De Luca's legacy. Several big and emerging names in the plant specialized metabolites research in Canada passed by his laboratory, including Pr. Peter Facchini, Pr. Yang Qu, and Pr. Mehran Dastmalchi, whose research works are discussed below.

2.2. Peter J. Facchini

Pr. Peter J. Facchini's (Calgary University) research on the BIA pathway in *Papaver somniferum* (opium poppy) started with the characterization of tyrosine/dihydroxyphenylalanine decarboxylases (TYDCs) and the profiling of their expression in different tissues (Facchini and De Luca 1994, 1995*a*, 1995*b*; Facchini et al. 1996*a*). In the following years, his group tackled the identification and characterization of enzymes in this pathway, including transporters, as well as the expression profiles of the genes encoding them, including berberine bridge enzyme 1 (Facchini et al. 1996*b*), TYDCs (Facchini et al. 1998), tyramine *N*-(hydroxycinnamoyl)transferase (Yu and Facchini 1999), norcoclaurine synthase (Samanani and Facchini 2001, 2002; Samanani et al. 2004; Luk et al. 2007; Lee and Facchini 2010), and many more (Bird et al. 2003; Liscombe and Facchini 2007; Hagel and Facchini 2010; Lee and Facchini 2011; Dang and Facchini 2012; Hagel et al. 2012; Beaudoin and Facchini 2013; Dang et al. 2015; Chen et al. 2018; Dastmalchi et al. 2019*a*; Li et al. 2020).

Pr. Facchini's team investigated the biosynthesis of BIA in other species as well, including *Thalictrum flavum*, *Eschscholzia californica*, *Papaver bracteatum*, and *Glaucium flavum* (yellow meadow rue, California poppy, Iranian poppy, and yellow horned poppy, respectively), which allowed the study of the evolution of norcoclaurine synthase, berberine-bridge enzyme, and *O*-methyltransferases (Liscombe et al. 2005), and the identification of new *N*-methyltransferases, including the first isolated enzyme in the pavine alkaloid branch pathway (Liscombe et al. 2009; Samanani et al. 2005).

His group also performed a transcriptomic study of *Lophophora williamsii* and elucidated the biosynthetic pathway of tetrahydroisoquinoline and phenethylamine alkaloids, including mescaline and pellotine (Watkins et al. 2023). Facchini's team also characterized aromatic aminotransferase implicated in ephedrine and associated alkaloids from *Ephedra sinica* and *Catha edulis* (ephedra and khat) (Kilpatrick et al. 2016; Morris et al. 2018). Through Pr. Facchini's collaborations with the structural biologist Pr. Kenneth Ng, the crystal structures of *P. somniferum*'s codeine reductase (Carr et al. 2021), *T. flavum*'s pavine *N*-methyltransferase (Torres et al. 2016), and *G. flavum*'s tetrahydroprotoberberine *N*-methyltransferase (Lang et al. 2019) were resolved, contributing to our overall understanding of substrate recognition by methyltransferases and reductases.

Finally, Pr. Facchini also trained recently established researchers in the plant alkaloid research in Canada. For instance, Pr. David Liscombe's (adjunct assistant professor at Brock University, Ontario, and researcher at Vineland Research and Innovation Centre) recent study of the invasive species *Vincetoxicum rossicum* led to an update on the biosynthesis pathway of phenanthroindolizidine alkaloid (Kempthorne et al. 2024). Pr. Mehran Dastmalchi, Pr. Thu-Thuy T. Dang, and Pr. Isabel Desgagné-Penix, who are discussed below, are also among the specialized metabolism experts that were trained by Pr. Facchini.

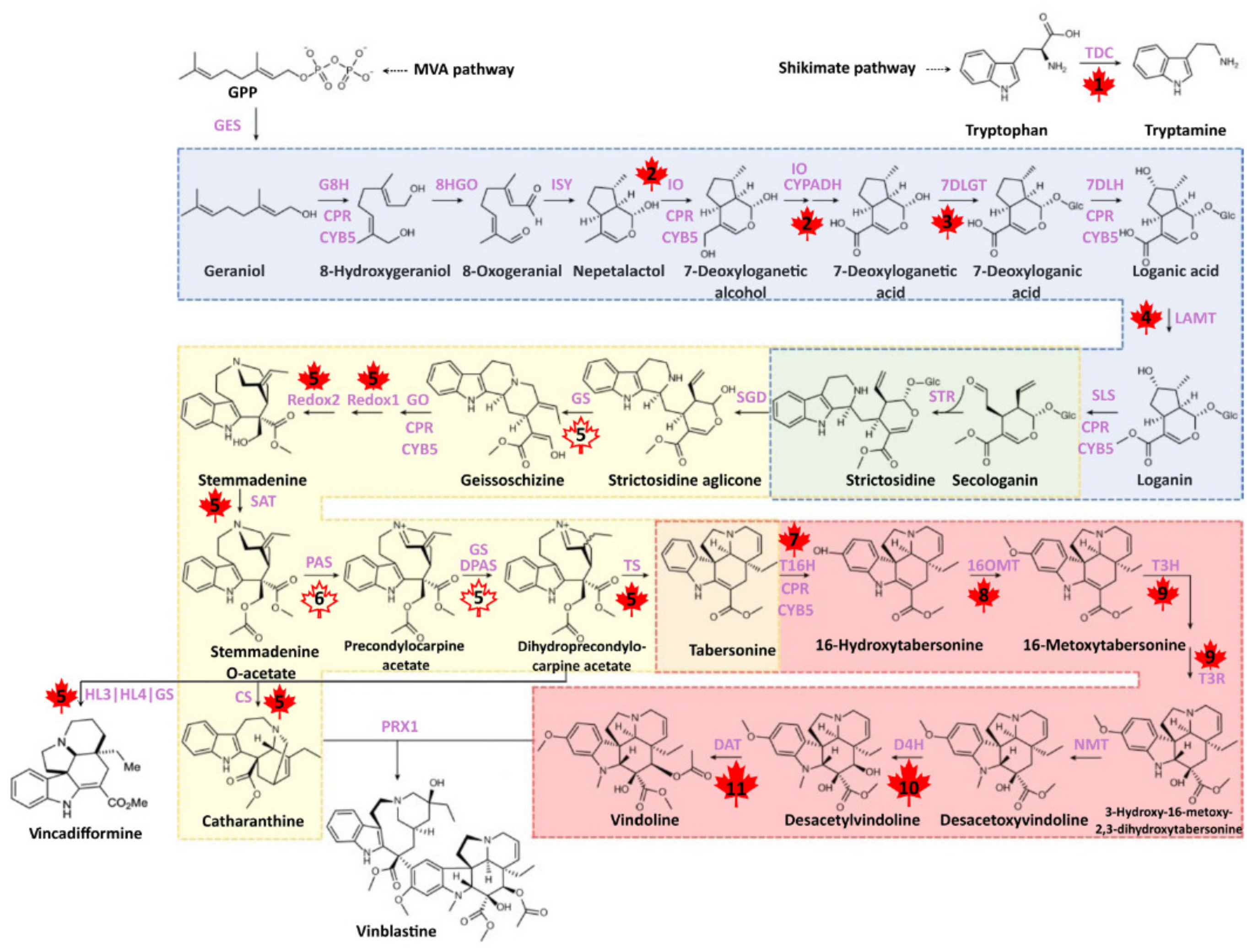
2.3. Thu-Thuy T. Dang

Pr. Thu-Thuy T. Dang recently established her laboratory at University of British Columbia (UBC), where her team uses a combination of genomics and biochemistry to understand plant alkaloid biosynthesis. The group published abundantly on the topic (Bui et al. 2023; Kwan et al. 2023; Nguyen and Dang 2021, 2022; Nunes et al. 2022), as well as with Canadian and international collaborators (Dang et al. 2012, 2017; Tatsis et al. 2017; Stavrinides et al. 2018; Carqueijeiro et al. 2018; Bui et al. 2023). Additionally, Pr. Thu-Thuy T. Dang's team used gene expression analysis to identify CYP encoding genes in *Camptotheca acuminata* (Happy tree), and enzymatic assays to show that the corresponding enzymes were able to oxidize camptothecin, a quinoline alkaloid (Nguyen et al. 2021), resulting in a patent (Dang et al. 2021). The patented innovation highlights isolated cytochrome P450 sequences, as well as synthetic biology application in plants, highlighting the role of specific cytochrome P450s in plant defense and isoprenoid compound synthesis. The group was also the first to identify and characterize CYP responsible for the formation of two spirooxindole alkaloids using comparative transcriptomics and enzymatic assays, namely *Ms*CYP72056 from *Mitragyna speciosa* (kratom) (Nguyen et al. 2023).

2.4. Yang Qu

Pr. Yang Qu previously worked with Pr. Dae-Kyun Ro (University of Calgary) on the biosynthesis of natural rubber in lettuce (Chakrabarty et al. 2015; Qu et al. 2015*b*; Barnes et al. 2021), and with Pr. Vincenzo de Luca on MIA metabolism

Fig. 2. Enzymes from *Catharanthus roseus* monoterpenoid indole alkaloid pathway. Filled maple leaves indicate steps characterized by Pr. De Luca's research teams; hollow maple leaves indicate steps characterized by teams outside Canada, but that were further characterized by Canadian teams. Numbers inside maple leaves indicate studies that characterized the enzymes. (1) De Luca et al. (1989); (2) Salim et al. (2014); (3) Asada et al. (2013); (4) Murata and De Luca (2005); (5) Qu et al. (2018*a*, 2018*b*); (6) Qu et al. (2019); (7) St-Pierre and De Luca (1995); (8) Levac et al. (2008); (9) Qu et al. (2015*a*); (10) De Carolis and De Luca (1993, 1994); De Carolis et al. (1990); Vazquez-Flota et al. (1997); (11) Power et al. (1990). MVA: mevalonic acid; GPP: geraniol pyrophosphate; GES: geraniol synthase; TDC: tryptophan decarboxylase; G8H: geraniol 8-hydroxylase; CPR: cytochrome P450 reductase; CYB5: cytochrome B5; CYPADH: cytochrome P450 alcohol dehydrogenase; 7DLGT: 7-deoxyloganetic acid transferase; 7DLH: 7-deoxyloganic acid hydroxylase; LAMT: loganic acid methyltransferase; SLS: secologanin synthase; STR: strictosidine synthase; SGD: strictosidine 8HGO: 8-hydroxygeraniol oxidoreductase; ISY: iridoid synthase; IO: iridoid oxidase; SGD: strictosidine *β*-d-glucosidase; GS: geissoschizine synthase; GO: geissoschizine oxidase; Redox1/2: protein redox 1/2; SAT: stemmadenine-O-acetyltransferase; PAS: precondylocarpine acetate synthase; DPAS: dehydroprecondylocarpine acetate synthase; CS/TS: catharanthine/tabersonine synthase; T16H: tabersonine 16-hydroxylase; 16OMT: 16-hydroxytabersonine O-methyltransferase; T3O: tabersonine 3–oxygenase; T3R: tabersonine 3-reductase; NMT: 3-hydroxy-16-methoxy-2,3-dihydrotabersonine-N-methyltransferase; D4H: desacetoxyvindoline-4-hydroxylase DAT: deacetylvindoline-4-O-acetyltransferase; PRX1: class III peroxidase. The colored boxes lines indicate strictosidine (blue), tabersonine/catharanthine (yellow) and vindoline (red) modules. Adapted from Zhang et al. (2022).



(Demessie et al. 2017; Kidd et al. 2019; Qu et al. 2018*b*, 2019; Williams et al. 2019). In De Luca's lab, Pr. Qu bioengineered yeast to produce vindoline (Qu et al. 2015*a*). He established his laboratory at the University of New Brunswick (New Brunswick) focusing on natural medicine biosynthesis, including alkaloids and bibenzyls. Among his works on the elucidation of biosynthetic pathways of specialized metabolites is the characterization of vindolinine synthase, which diverts tabersonine from vinblastine metabolism to the formation of 19*S*-vindolinine, 19*R*-vindolinine, and venalstonine (Eng et al. 2022). His group also elucidated the biosynthesis pathway of the analgesic mitragynine, from kratom, through

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the transcriptomic study of the latter and other species of *Rubiaceae*, leading to the identification of reductases and enol methyltransferases that completed the pathway (Kim et al. 2023).

Finally, his team recently identified and characterized the enzymes catalyzing the last two unknown steps of the antiarrhythmic MIA ajmaline biosynthesis in Indian snakeroot, namely vomilenine 1,2(*R*)-reductase and 1,2-dihydrovomilenine 19,20(*S*)-reductase, as well as a new isoform of the sarpagan bridge enzyme and two new isoforms of the 17-*O*-acetylnorajmaline acetyl esterase (Guo et al. 2024). The group succeeded in applying these findings for the de novo biosynthesis of ajmaline in yeast. They also recently bioengineered yeast to produce multiple terpenoids and alkaloids, mainly vinblastine and other *Catharanthus* metabolites (Shahsavarani et al. 2023; Guo et al. 2024).

2.5. Vincent JJ Martin

Pr. Vincent JJ Martin is interested in bioengineering microorganisms to produce compounds of interest such as BIAs at Concordia University. He collaborated with Pr. Facchini on opioids and with Pr. Jay Keasling (University of California) on cannabinoid pathway elucidation and heterologous production. Pr. Martin's recent work includes synthetic biology approaches to optimize microbial platforms, mainly yeast (Pyne et al. 2020, 2023*b*; Dykstra et al. 2023), as well as pathway elucidation efforts for multiple BIA compounds. For instance, his team screened plant *O*-methyltransferase s, enabling de novo synthesis of liensinine (Pyne et al. 2023*a*), and designed an enzyme-coupled biosensor for reticuline upstream intermediate L-3,4-dihydroxyphenylalanine (Fossati et al. 2014). Pr. Martin is also a co-director of Concordia university's Centre for Applied Synthetic Biology, also known as the Concordia Genome Foundry.

2.6. Isabel Desgagné-Penix

Lastly, our lab, at the Université du Québec à Trois-Rivières, has also made strides in medicinal plants specialized metabolism bioactivity and pathway elucidation, focusing on *Amaryllidaceae* alkaloids (AAs), cannabinoids, and vanillin. Early and more recent de novo transcriptomic studies of *Narcissus pseudonarcissus* "King Alfred", *N. papyraceus*, *Leucojum aestivum*, and *Crinum* x *powellii*, led to the identification of candidate genes involved in the biosynthesis of AAs (Singh and Desgagne-Penix 2017; Hotchandani et al. 2019; Tousignant et al. 2022; Koirala et al. 2023). Following identification of candidates, our strategy involves in-depth study of each specific step of the AA pathway. This led to the characterization of norbelladine synthase from *N. pseudonarcissus* (Singh et al. 2018), noroxomaritidine/norcraugsodine reductase in *N. pseudonarcissus* and *L. aestivum* (Majhi et al. 2023), as well as of cytochrome P450s (CYPs) cinnamate 4-hydroxylase, *p*-coumaroyl 3′-hydroxylase, and ascorbate peroxidase/4-coumarate 3-hydroxylase from *L. aestivum* (Karimzadegan et al. 2024). In addition to plants, we also assembled the transcriptome of two fungal species, the plant pathogen *Armillaria sinapina* and the medicinal fungus *Inonotus obliquus*, and identified terpenoid biosynthesis genes, including squalene epoxidase and lupeol synthase (Fradj et al. 2019, 2020).

The research group also made strides in plant metabolite synthesis in heterologous systems. In addition to using yeast and bacteria (Majhi et al. 2023; Karimzadegan et al. 2024), the team bioengineered microalgae as platforms for specialized metabolite production and enzyme characterization. Although the process may be more tedious, it could lead to a more sustainable platform (Slattery et al. 2018; Diamond et al. 2023). The group succeeded in achieving stable expression of different *Cannabis sativa* and bacterial enzymes in the diatom *Phaeodactylum tricornutum* for the production of olivetolic acid, cannabigerolic acid and other cannabinoids (Awwad et al. 2023; Fantino et al. 2024). They have also optimized techniques to bioengineer other microalgae, including *Chlamydomonas reinhardtii* and *Chlorella vulgaris* (Carscallen et al. 2023; Desgagné-Penix et al. 2023; Beauchemin et al. 2024).

3. Investigating terpenes

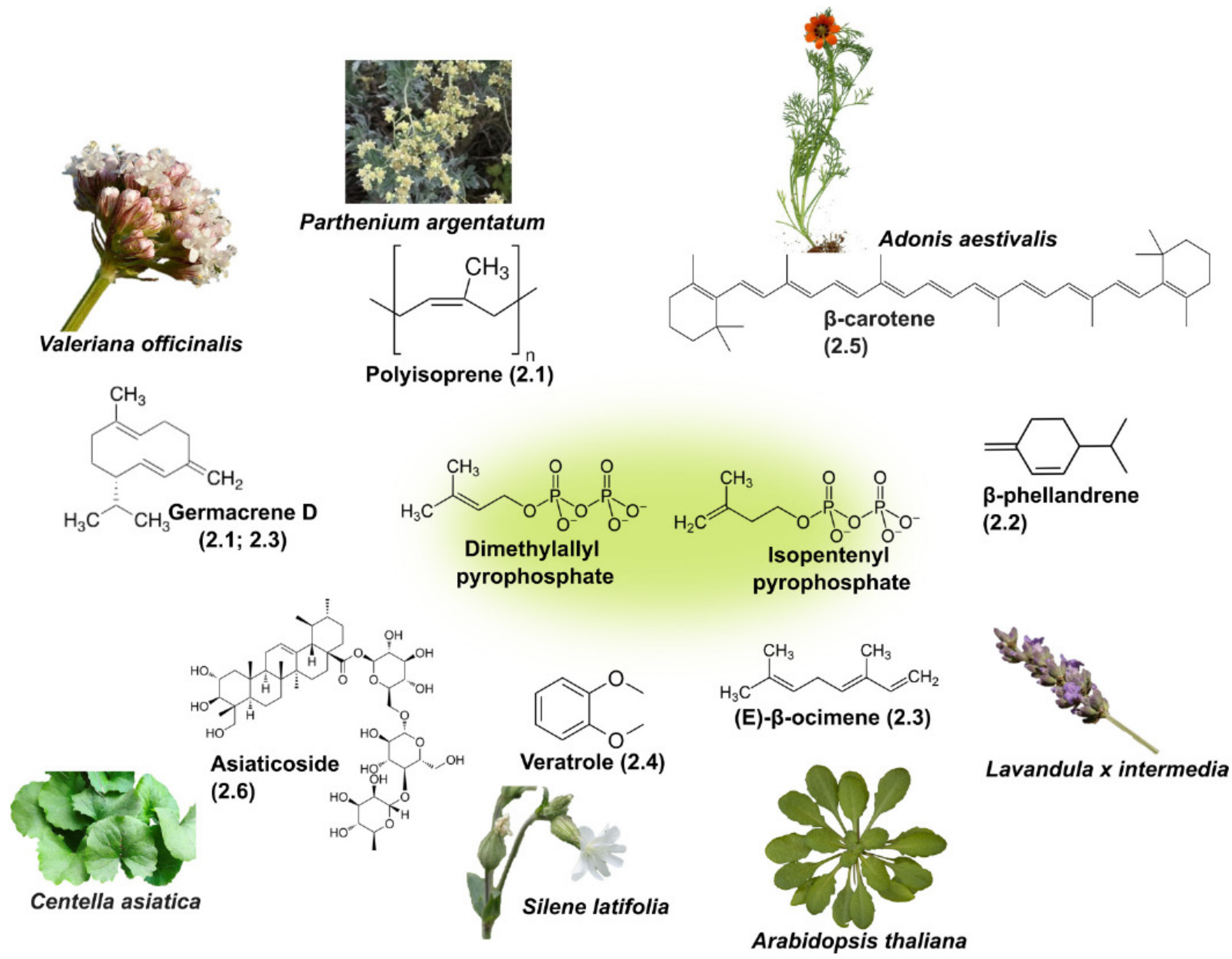
Terpenes, derived from dimethylallyl pyrophosphate and isopentenyl pyrophosphate produced via the mevalonate and methylerythritol phosphate pathways, play critical roles in plant development, stress responses, and pollinator attraction (Singh and Sharma 2015; Pichersky and Raguso 2018; Boncan et al. 2020). Many of these compounds, such as paclitaxel, menthol, and artemisinin, are utilized in the food, cosmetic, and pharmaceutical industries (Wagner and Elmadfa 2003; da Silva-Santosa et al. 2005; Yang et al. 2020). Given the identification of thousands of terpenes and terpenoids, numerous research teams focus on characterizing the enzymes responsible for their synthesis (Kajikawa et al. 2005; Chen et al. 2011; Cornish 2014; Boutanaev et al. 2015; Singh and Sharma 2015; Lau et al. 2016; Huang and Osbourn 2019; Kopaczyk et al. 2020; Zhou and Pichersky 2020; Amerik et al. 2021; Long et al. 2021; Jaramillo-Madrid et al. 2022).

This section details the contributions of professors Dae-Kyun Ro, Soheil Mahmoud, Jörg Bohlmann, Tariq A. Akhtar, and Reinhard Jetter in characterizing terpene synthases in gymnosperms and angiosperms. Additionally, it covers the research by professors Ro, Bohlmann, Akhtar, and Valerie C.A. Ward on the production of terpenoids in heterologous systems, including yeast, microalgae, and plants (Fig. 3).

3.1. Dae-Kyun Ro

At the University of Calgary, Pr. Dae-Kyun Ro studies the biosynthesis of terpenes, proanthocyanidins and natural rubber. His group used transcriptomics to identify *Pisum sativum* anthocyanidin, leucoanthocyanidin, and dihydroflavonol reductases, and characterized these enzymes in vitro, showing that they synthesize *cis*- and *trans*-flavan-3-ols (Ferraro et al. 2014). His research on sesquiterpene biosynthesis led to the identification and characterization of several enzymes in different pathways. In *Lippia dulcis* (Aztec sweet herb), they characterized (+)-epi-α-bisabolol synthase, which catalyzes the first step in the biosynthesis of hernandulcin, and bornyl diphosphate synthase, involved in the formation of camphor (Attia et al. 2012; Hurd et al. 2017). In *Valeriana officinalis* (valerian), the group characterized three sesquiterpene synthases

Fig. 3. Variety of terpenoids, and the plants that produce them, investigated in Canada and their main precursors, dimethylallyl phosphate and isopentenyl phosphate. Numbers in parenthesis indicate the principal investigators that research these topics. (2.1) Dae-Kyun Ro; (2.2) Soheil Mahmoud; (2.3) Jörg Bohlmann; (2.4) Tariq Akhtar; (2.5) Valerie CA Ward; (2.6) Reinhard Jetter. *Partenium argentatum*'s photo was modifed from Rousset et al. (2021). The following images were obtained from Wikimedia commons: *Adonis aestivalis*: By Osnat Ravid Amir (CC BY-SA 4.0) https://commons.wikimedia.org/w/index.php?curid=151799697; Arabidopsis thaliana: By Charles Andrès (CC BY-SA 3.0) https://commons.wikimedia.org/w/index.php?curid=22510218; Centella asiatica: By Md. Siddiq Hasan (CC BY-SA 4.0) https://commons.wikimedia.org/w/index.php?curid=114909062; *Lavandula* x *intermedia*: By Photo by David J. Stang (First published at ZipcodeZoo.com, CC BY-SA 4.0) https://commons.wikimedia.org/w/index.php?curid=61171226; Silena latifolia: By Loz (L. B. Tettenborn, CC BY-SA 3.0) https://commons.wikimedia.org/w/index.php?curid=4506347; Valeriana officinales: By Ivar Leidus (CC BY-SA 4.0) https://commons.wikimedia.org/w/index.php?curid=106650217.



which synthesize germacrene C and D, valerena-4,7(11)-diene and (-)-drimenol (Pyle et al. 2012; Kwon et al. 2014). They also identified and characterized two germacrene A synthases from *Barnadesia spinosa* (*espino santo* or "holy thorn"), and one from *Lactuca sativa* (lettuce) (Nguyen et al. 2016). While studying two sesquiterpene oxidases from *Artemisia annuam*, they showed that germacrene A and amorphadiene oxidases are involved in the biosynthesis of a widespread and species-specific sesquiterpenes (Nguyen et al. 2019). They also identified and characterized a CYP that converts kolavenol to crotonolide G, a savonorin-related compound (Kwon et al. 2022*b*). Finally, they characterized the promoters of *L. sativa*'s *Germacrene A Synthase 1* and *2*, showing that these genes are expressed in parenchyma cells adjacent to laticifers (Kwon et al. 2022*a*).

The group's research on natural rubber biosynthesis includes works with *Parthenium argentatum* (guayule) and *L. sativa*, from which they identified and characterized *cis*-prenyltransferases (CPT) and CPT binding proteins (Lakusta et al. 2019; Barnes et al. 2021). In *L. sativa*, they show that CPT binding protein 2 (*Ls*CBP2, previously named CPTL2) tethers CPT3 to the endoplasmic reticulum and synthesize *cis*-polyisoprenes in vitro (Qu et al. 2015*b*). Additionally, they identified the promoter region of these genes responsible for their laticifer-specific expression (Barnes et al. 2021). Lastly, by expressing CPT3 from *P. argentatum* and *Solidago canadensis* (goldenrod) in natural rubber-deficient lettuce, they showed that these proteins can synthesize better quality natural rubber in the heterologous cell context, suggesting the quality of this compound is not dependent on CPT alone (Kwon et al. 2023).

In addition to the terpenoid pathway elucidation *in planta*, Pr. Ro has made important advances in the metabolic engineering of yeast as a platform to produce SMs during his graduate studies, and as a group leader or a collaborator. For instance, he succeeded in enhancing the carbon flux in mevalonate pathway through the expression of acetyl-CoA synthetase variant from *Salmonella enterica* with the aim of producing amorphadiene, precursor of the high-value sesquiterpene artemesin (Shiba et al. 2007). Pr. Ro's group designed modular multiplex genome-edit-CRISPR platform to enhance feruloyl-CoA pathway in the aim of producing curcumin and other alkaloids in yeast (Utomo et al. 2024). Finally, his team's achievements *in planta* include works in *Nicotiana benthamiana* (a tobacco relative), and pea plants. In *N. benthamiana*, his group was able to increase the yield of sesqui- and triterpenes (α-bisabolol, amorphadiene, valerenadiene and β-amyrin) in tobacco (Lee et al. 2019). This was achieved by discovering enzyme crosstalk and using push–pull strategies between different pathways. They recently targeted the pea plant gene *β-amyrin synthase* with CRISPR/Cas9 system to obtain saponin-free pea products, which are less bitter (Hodgins et al. 2024).

3.2. Soheil Mahmoud

An associate professor at UBC, Pr. Soheil Mahmoud has worked in the elucidation of monoterpene metabolism. From the transcriptome of *Coriandrum sativum* (coriander), his group identified and then characterized two monoterpene synthases, *S*-linalool synthase, and γ-terpinene synthase (Galata et al. 2014). Nevertheless, his research focuses on the biosynthesis of *Lavandula* spp. (lavender) essential oils. His efforts led to the publication of a draft genome for *L. angustifolia*, the first sequenced genome in the genus (Malli et al. 2019). He has used gene expression techniques, including expressed sequence tags, microarray, and RNA sequencing to identify and characterize terpene synthases in *Lavandula* spp. These include *L. angustifolia* β-phellandrene synthase (Demissie et al. 2011), borneol dehydrogenase, an enzyme in camphor biosynthesis pathway (Sarker et al. 2012), 1,8-cineole synthase (*Li*CINS) (Demissie et al. 2012), 9-epi-(E)-caryophyllene synthase (Sarker et al. 2013), lavandulyl diphosphate synthase (Demissie et al. 2013), two BAHD acyltransferases (Sarker and Mahmoud 2015), 3-carene synthase (Adal et al. 2017), S-linalool synthase (*Li*LINS) (Adal et al. 2019), geranyl diphosphate synthase, geranylgeranyl diphosphate synthase and farnesyl diphosphate synthase (Adal and Mahmoud 2020), and (+)-bornyl diphosphate synthase (Adal et al. 2023) from *L.* x *intermedia.* The team also identified and characterized several transcription factors from this hybrid that associate with the promoters of *Li*LINS and/or *Li*CINS (Sarker et al. 2019).

3.3. Jörg Bohlmann

Pr. Jörg Bohlmann started to investigate TPS while he was at the Max Planck Institute for Chemical Ecology in Germany, where he analyzed the expression profile of a *Nicotiana attenuata* gene encoding for a 5-*epi*-aristolochene synthase (an enzyme involved in capsidiol biosynthesis) (Bohlmann et al. 2002). He also identified and characterized a TPS from *Arabidopsis thaliana* (Bohlmann et al. 2000) that synthesizes myrcene, as well as (*E*)-β-ocimene. At UBC, his group performed in silico analysis of predicted TPSs from *A. thaliana* (Aubourg et al. 2002) and later characterized a (*E*)-β-ocimene synthase from this species (Faldt et al. 2003*a*).

Subsequent works of his group focused on terpene synthesis in gymnosperms. In addition to understanding the role of terpenes in conifer defense against pathogens and pests and how this response is affected by methyl jasmonate (Faldt et al. 2003*b*; Huber et al. 2005; Miller et al. 2005; Ro and Bohlmann 2006; Zulak et al. 2009, 2010; Hall et al. 2011*b*), they identified many genes and functionally characterized TPSs in *Pseudotsuga menziesii* (Douglas fir) (Huber et al. 2005), *Pinus taeda* (loblolly pine) (Ro and Bohlmann 2006), *Picea abies* (Norway spruce) (Faldt et al. 2003*b*; Martin et al. 2004; Keeling et al. 2011*a*), *Picea glauca* (white spruce) (Keeling et al. 2010), *Abies balsamea* (balsam fir) (Zerbe et al. 2012), and *Picea sitchensis* (Sitka spruce) (Hamberger et al. 2011; Roach et al. 2014). In a single study, his group identified and functionally characterized 15 monoterpene synthases from spruce, including 4 sesquiterpene synthases and 2 diterpene synthases of Sitka spruce, white spruce, and hybrid white spruce (Keeling et al. 2011*b*). They also characterized and performed evolutionary studies of cytochrome P450s involved in diterpene resin acid biosynthesis in different conifers, including enzymes of the CYP720B, CYP750B, and CYP76AA subfamilies (Ro and Bohlmann 2006; Hamberger et al. 2011; Gesell et al. 2015; Geisler et al. 2016).

Along with his work on conifers, Pr. Bohlmann's team also worked with angiosperms, characterizing (–)-germacrene D synthase from *Populus trichocarpa* x *deltoides* (hybrid poplar) (Arimura et al. 2004); characterizing TPSs from *Vitis vinifera* (grape) (Martin et al. 2010) and evaluating the relationship between wine aroma and terpene biosynthesis (Martin and Bohlmann 2004; Martin et al. 2009, 2012); identifying and characterizing CYPs that synthesize sesquiterpenols of *Santalum album* (sandalwood) oil (Celedon et al. 2016; Diaz-Chavez et al. 2013); and identifying and characterizing TPSs from *C. sativa* (Booth et al. 2017, 2020). Pr. Bohlmann also contributed to plant synthetic biology through the identification of cannabinoid glycosides and participating in reconstruction of pathways in yeast and *N. benthamiana* (Gülck et al. 2020).

Finally, his group elucidated the biosynthesis pathway of MontbretinA, identifying and characterizing several UDP-dependent glycosyltransferases, BAHD-acyltransferases, 4-coumaroyl-CoA ligases, and acyl activating enzyme (Irmisch et al. 2018, 2019, 2020; Sunstrum et al. 2021). They finally reconstructed the whole pathway in *N. benthamiana* (Irmisch et al. 2020).

3.4. Tariq A. Akhtar

Pr. Tariq Akhtar is an associate professor at University of Guelph, where he investigates plant metabolism. His work with specialized metabolism started with Pr. Eran Pichersky (University of Michigan) on the identification of the tomato *CPT* gene family (Akhtar et al. 2013). The investigation of polyprenols led to the characterization of CPT from tomato and *A. thaliana*, both located in the chloroplast stroma, which elongate geranylgeranyl diphosphate (Akhtar et al. 2017; Van Gelder et al. 2018). Furthermore, they showed that the biosynthesis of the polyprenol dolichol requires a CPT and an accessory protein which localizes in the ER and Golgi system in tomato (Brasher et al. 2015) and reconstructed the pathway in *N. benthamiana* (Van Gelder et al. 2021).

His group expanded on his initial work with Pr. Pichersky on veratrole biosynthesis in *Silene latifolia* (white champion) (Akhtar and Pichersky 2013; Gupta et al. 2012), showing that salicylic acid is catabolized into veratrole white champion, with catechol and guaiacol as intermediates (Van Gelder et al. 2020). Finally, his team also proposed the biosynthetic pathway of bibenzyls and cannflavins A and B in *C. sativa* (Boddington et al. 2022; Rea et al. 2019), along with the identification of the enzymes of both pathways.

3.5. Valerie CA Ward

Pr. Valerie CA Ward is an assistant professor at the University of Waterloo at the Chemical Engineering Department. She works on metabolic engineering of microorganisms for isoprenoid production (Edgar et al. 2021) and finding efficient process for high yield extraction from wet biomass. Dr Ward's team bioengineered *E. coli* to produce astaxanthin, expressing genes from the β-carotene pathway of the gram-negative bacteria *Pantoea agglomerans* and genes from the plant *Adonis* aestivalis (summer pheasant's eye) encoding for β-carotene hydroxylase and ketolase (Roth and Ward 2023). Dr Ward, in collaboration with Pr. Gregory Stephanopoulos from the Massachusetts Institute of Technology, has also worked with other organisms to produce fat-soluble isoprenoids, including the lipid-producing yeast *Yarrowia lipolytica* (Stephanopoulos et al. 2019; Edgar et al. 2021) and the microalga *Chlorella vulgaris* (Roushan et al. 2023).

3.6. Reinhard Jetter

Though his main focus is on plant cuticle composition and plant-insect interaction (Greer et al. 2007; Hegebarth et al. 2017; Sun et al. 2020, 2021, 2023), it is important to highlight Pr. Jetter's (UBC) contributions in the triterpenoid biosynthesis research. His group identified and characterized two CYPs from *Centella asiatica* (Indian/Asiatic pennywort), involved in the biosynthesis of the saponin asiaticoside (Kim et al. 2018), as well as oxidosqualene cyclases from *Ricinus communis* (castor bean) (Guhling et al. 2006), *Kalanchoe daigremontiana* (mother of thousands) (Wang et al. 2010), *Solanum lycopersicum* (tomato) (Wang et al. 2011), and *Quercus suber* (cork oak) (Busta et al. 2020).

4. Investigating polyketides and phenolic compounds

Phenolic compounds and polyketides have similar origins, with acyl molecules, from acyl-coenzyme A substrates, as precursors. Phenolic compounds, such as phenolic acids and lignans, are synthesized from the acetate-malonate or the shikimate pathway, with malonyl-coenzyme A, erythrose 4-phosphate, and phosphoenolpyruvate as primary metabolite precursors (Babenko et al. 2019; de la Rosa et al. 2019; Zagoskina et al. 2023). Meanwhile, polyketides, such as cannabinoids and flavonoids, are formed through the extension of an initial acyl molecules (such as acetyl, malonyl, and hexanoyl) by condensation of malonyl units by type III polyketide synthase, followed by the cyclization of the resulting chain (Abe and Morita 2010; Lussier et al. 2012). In plants, these compounds contribute to structure and defense, scavenging of reactive oxygen species, and attraction of pollinators (Di Ferdinando et al. 2012; Dias et al. 2020; Juca et al. 2020). With antioxidant and anti-inflammatory properties, these metabolites are of interest in medicine for targeting cancer, diabetes and other diseases (Al Jitan et al. 2018; Zhang et al. 2018*b*).

From 1983 to 2021, more than 20 chalcone synthase (CHS) genes had been characterized (Niu et al. 2021) and there have been many efforts to understand their evolution and that of CHS-like enzymes across the plant kingdom (Han et al. 2014; Naake et al. 2021; Guo et al. 2022). We described below the contributions of Pr. Dae-Yeon Suh's team to our understanding of polyketide synthase evolution and function in both bryophytes and angiosperms (Fig. 4). On a different front, the research on phytocannabinoid biosynthesis has included transcriptomics of *C. sativa*, evaluating transcription factors and stresses that regulate the production of cannabinoids and other specialized metabolites (Braich et al. 2019; Jalali et al. 2019; Zager et al. 2019; Apicella et al. 2022; Kim et al. 2022); and population studies, which have identified several markers related to morphology and productivity, cannabinoid content (Adamek et al. 2023; de Ronne et al. 2024; Dehnavi et al. 2025). This fundamental research is the basis for improving the production of the desired metabolites through breeding efforts, gene silencing, or synthetic biology (Geissler et al. 2018; Zirpel et al. 2018; Luo et al. 2019; Gülck et al. 2020; Thomas et al. 2020; Matchett-Oates et al. 2021; Ma et al. 2022; Awwad et al. 2023; Desgagné-Penix et al. 2023; Fantino et al. 2024). These studies were made possible by the pioneering contributions of Pr. Page's team on cannabis genomics, which are described below (Fig. 4).

Canadian researchers have identified genes and enzymes involved in the metabolism of phenolic compounds in crops like beans and poplar, focusing on transcription factors controlling their biosynthesis and catabolism. Global research has similarly elucidated mechanisms driving phenolic compound accumulation in these plants, including transcriptomic and genomic studies identifying phenolic compound-associated loci (Kosonen et al. 2012; Cho et al. 2016; James et al. 2017; Perez de Souza et al. 2019; He et al. 2021; Bryant et al. 2023; Campa et al. 2023; Celebioglu et al. 2023; Chen et al. 2023; Li et al. 2023; Ma et al. 2023, 2024; Tian et al.

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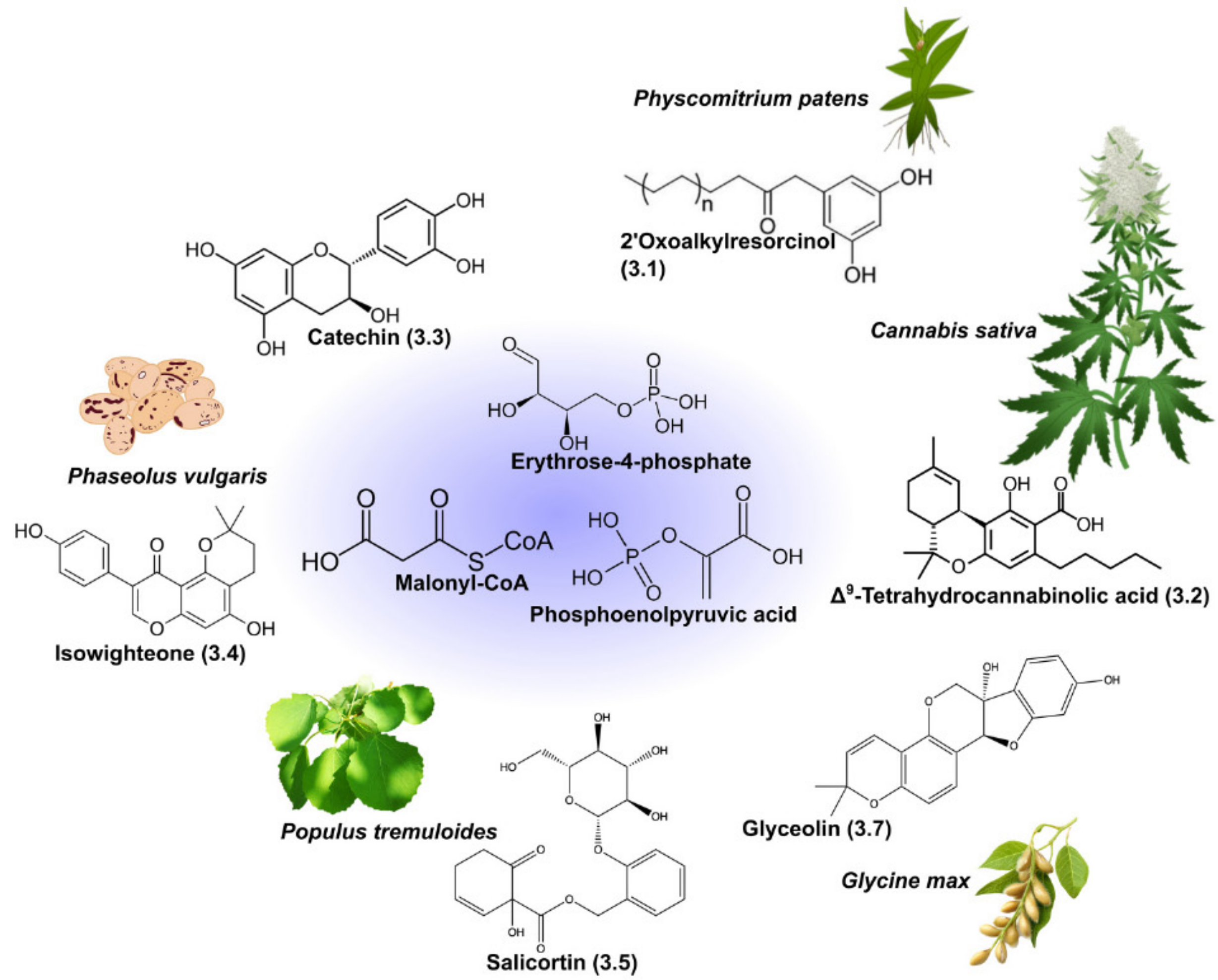
Fig. 4. Polyketides and other phenolic compounds investigated in Canada, along with their precursors and plants that produce them. Numbers in parenthesis indicate principal investigators working in the subject. (3.1) Dae-Yeon Suh; (3.2) Jonathan E. Page; (3.3 and 3.4) Gale G. Bozzo and Sangeeta Dhaubhadel, respectively, who work on isoflavonoids and anthocyanins in beans; (3.5) C. Peter Constabel; (3.7) Nikola Kovinich. *Cannabis sativa*'s drawing was done with Krita 5.2.9. Illustrations for *Glycine max* and *Phaseolus vulgaris* were obtained from Vecteezy; *Physcomitrium patens*'s drawing was obtained from Lang et al. (2018). *Populus tremuloides*' photo was Wikimedia Commons (By I, Hugo.arg (CC BY-SA 3.0) https://commons.wikimedia.org/w/index.php?curid=2268194).



2021; Tapia et al. 2024; Zhang et al. 2018*a*, 2023, 2024). For detailed insights, readers are referred to comprehensive reviews (Pourcel et al. 2007; Cheynier et al. 2013; Corso et al. 2020; Ma and Constabel 2021; Li et al. 2022*a*; Pratyusha and Sarada 2022; Sunil and Shetty 2022; Islam and Dhaubhadel 2023; Trush and Pal'ove-Balang 2023).

This section discusses the efforts of Professors Gale Bozzo, Sangeeta Dhaubhadel, and Mehran Dastmalchi on anthocyanin and flavonoid metabolism, and Professors C. Peter Constabel and Nikola Kovinich on transcription factors in polyphenol metabolism (Fig. 4).

4.1. Dae-Yeon Suh

Having previously worked on chalcone synthases with Pr. Ushio Sankawa in Japan (Kojima et al. 2000; Okada et al. 2001; Suh et al. 2000*a*, 2000*b*, 2000*c*; Yamazaki et al. 2001), Pr. Dae-Yeon Suh established his research team at University of Regina, where they work on both bryophytes and angiosperms and their CHS enzymes. His group performed evolutionary studies on plant enzymes of the thiolase superfamily and CHS family (Jiang et al. 2008), collaborated with Pr. Sankawa in analysing the effects of mutating highly conserved arginine residues in CHS (Fukuma et al. 2007) and characterized a CHS from the spreading earthmoss (*Physcomitrium patens*) (Jiang et al. 2006). Later they used expressed sequence tags from the bryophyte and identified a gene encoding for Anther-Specific CHS-Like Enzyme, which was shown to play a role in sporopollenin biosynthesis, like its ortholog in arabidopsis, which is essential for reproduction (Colpitts et al. 2011; Daku et al. 2016). They also characterized 2-oxoalkylresorcinol synthase in *P. patens*, an enzyme proposed to be similar to ancestral type III polyketide synthases, showing that it plays a role in cuticle formation, and therefore is necessary for resistance to dehydration (Kim et al. 2013; Li et al. 2018; Aslam et al. 2022). His group has also performed genome-wide analysis of spreading earthmoss' class III peroxidase gene family, with 49 members, and CHS gene superfamily, with 17 putative members (Aparato et al. 2024; Koduri et al. 2010). While the CHS gene superfamily's expansion was proposed to be through segmental duplication (Koduri et al. 2010), the group hypothesized that the expansion of class III peroxidase gene family was due to whole-genome duplication (Aparato et al. 2024). Finally, another CHS involved in sporopollenin biosynthesis that the group characterized was *Polyketide Synthase 1*, from the angiosperm St John's wort's (*Hypericum perforatum*), showing that the enzyme uses medium to very-long chain fatty acyl-coenzyme A substrates to produce triketide and tetraketide alkylpyrones and that, in nonanther tissues, it could be involved in the biosynthesis of components of cell wall (Jepson et al. 2014).

4.2. Jonathan E. Page

A professor at the Department of Botany of UBC, Jonathan E. Page, has carried out works on tobacco, *Humulus lupulus* (hop) and *Cannabis* spp., investigating the biosynthesis of alkaloids, flavonoids, and cannabinoids. In *N. benthamiana*, his group analyzed expressed sequence tags from methyl-jasmonate-treated roots, gene silencing, and gene overexpression to identify two basic Helix-Loop-Helix transcription factors acting as positive regulators of nicotine biosynthesis in response to jasmonate (Todd et al. 2010). This work led to two patents, one on the uses of *N*-methylputrescine (Page and Liu 2023), and the other on the transcription factors impacting the production of alkaloids in this plant (Page and Todd 2023). In hop, the group applied expressed sequence tags and transcriptome sequencing for the identification of a methyltransferase that synthesizes xanthohumol (Nagel et al. 2008), and of genes involved in branched-chain amino acid biosynthesis and catabolism (Clark et al. 2013). Pr. Page's team also filed two patents on specialized metabolism of hops plants (Nagel and Page 2010; Page et al. 2013).

Pr. Page's team has contributed significantly to the cannabinoid metabolism research, starting with the draft genome and transcriptome assembly of *C. sativa* "Purple Kush" in 2011 (van Bakel et al. 2011). Later, they generated a genetic map of the species by crossing this strain with hemp "Finola" strain, finding the genes cannabidiolic acid and tetrahydrocannabinolic acid synthases (*CBDAS* and *THCAS*, respectively) in a retrotransposon-rich region. Moreover, studying strains of marijuana and hemp using genotyping-by-sequencing, his group showed the greater heterozygosity in hemp, and the differences in many loci, not only in the *CBDAS/THCAS* genes (Sawler et al. 2015). Finally, they identified and characterized two acyl-activating enzymes able to synthesize hexanoyl-CoA (Stout et al. 2012) and olivetolic acid cyclase (Gagne et al. 2012) from expressed sequence tags obtained from glandular trichomes of cannabis flowers, and identified three transcription factors that regulate THCAS expression (Liu et al. 2021). Pr. Page has three patents related to cannabinoid biosynthesis enzyme characterization (Page et al. 2020; Page and Stout 2020; Page and Gagne 2024). These patents were widely used by companies (including Intrexon, Gingko Bioworks, Hyacinth, and Demetrix) or research institutes to produce cannabinoid compounds in vivo or in vitro (Awwad et al. 2023).

4.3. Gale G. Bozzo

Pr. Gale G. Bozzo is an associate professor at the University of Guelph interested in controlled atmosphere storage and specialized metabolism, mainly phenylpropanoids. His work with cranberry beans (*Phaseolus vulgaris* L.) showed that darkening of seed coat postharvest was associated with increased expression of proanthocyanidins biosynthesis genes, including *Anthocyanidin Reductase 1*, which converts cyanidin to epicatechin and catechin (Freixas Coutin et al. 2017). With common beans, the team showed that expression of isoflavone biosynthetic genes and concentration of isoflavones were up-regulated in a line resistant to common bacterial blight (caused by the bacterium *Xanthomonas axonopodis*), but not in the susceptible line (Cox et al. 2021). In addition, they discovered a β-glucosidase from Arabidopsis (BGLU15) which catabolized flavonol rhamnosides in nitrogen-deprived plants exposed to low temperatures (Roepke and Bozzo 2015), and later they showed that flavonol rhamnosides are also catabolised in radish stored in cold temperature and that this could be associated with the activity of an α-rhamnosidase (Unterlander et al. 2022).

4.4. Sangeeta Dhaubhadel

Pr. Sangeeta Dhaubhadel, a researcher at the Agriculture and Agri-Food Canada and adjunct professor at the University of Western Ontario, works on the metabolism of phenylpropanoids, isoflavonoids, and anthocyanins in legume species, including common bean and soybean (*P. vulgaris* and *Glycine max*, respectively), along with her research on soybean defense (Khatri et al. 2022; Scott et al. 2021, 2022). Her team showed that soybean embryos can synthesize isoflavonoids de novo (Dhaubhadel et al. 2003) and that the genes encoding for chalcone synthases 7 and 8 are more expressed in a cultivar that accumulates more isoflavonoids (Dhaubhadel et al. 2003). Later, they identified the transcription factor *Gm*MYB176, which regulates the expression of *GmCS8* (Anguraj Vadivel et al. 2019; Yi et al. 2010), showing that it interacts with 14-3-3 proteins, affecting its localization in the cell (Li and Dhaubhadel 2012), and with *Gm*bZIP5, involved in isoflavonoid and phytoalexin metabolism and accumulation (Anguraj Vadivel et al. 2021). In another study, they identified two genes encoding flavonoid-metabolizing enzymes, flavonoid 3′-hydroxylase and dihydroflavonol 4-reductase, which compete for substrates with isoflavonoid biosynthesis pathway and were highly down-regulated in isoflavonoid-rich cultivars (Dastmalchi et al. 2017). In addition, her group identified and characterized three soybean genes encoding for cinnamate 4-hydroxylases (Khatri et al. 2023).

Similar to what was shown by Pr. Bozzo's team (Freixas Coutin et al. 2017), her team revealed a correlation between the slow darkening of the seed coat of pinto beans, and the decrease in biosynthesis and accumulation of proanthocyanidins (Duwadi et al. 2018). Later, they found that the vacuolar transporter *Pm*MATE8 is down-regulated in the slow darkening cultivar compared to the regular darkening cultivar, and that there is possibly a feedback regulation between the biosynthesis of proanthocyanidins and their accumulation in the vacuole (Islam et al. 2022).

4.5. C. Peter Constabel

Pr. C. Peter Constabel, from University of Victoria, has performed extensive research on poplar's defense mechanisms against herbivores and fungal pathogens. His group evaluated the impact of wound and herbivory on the expression of a hybrid poplar polyphenol oxidase (Constabel et al. 2000) and later showed, in *Populus tremuloides* (quaking aspen), that this enzyme contributes to plant defense by oxidizing catechol (Haruta et al. 2001). They also identified a UDP-glycosyltransferases, which co-expressed with proanthocyanidin biosynthesis genes, able to glycosylate the flavonols quercetin and kaempferol (Veljanovski and Constabel 2013) and a gene, encoding a dihydroflavonol reductase whose induced expression by herbivory led to increased accumulation of condensed tannins (Peters and Constabel 2002). Moreover, Pr. Constabel's team identified several MYB transcription factors that regulate proanthocyanidin biosynthesis genes, among others such as shikimate pathway genes, including the activators MYB134 (Mellway et al. 2009), which was shown to act mainly in the leaves (Gourlay et al. 2020), MYB115 (James et al. 2017; Liu et al. 2023), MYB117 (Ma et al. 2021), and the repressors MYB182 (Yoshida et al. 2015), MYB165 and MYB194 (Ma et al. 2018). His group also showed that the apple transcription factor MYB9 has a similar function to poplar's MYB134 (Gesell et al. 2014).

Besides his work on flavonoids, he also works on salicinoids, which are phenolic glycosides of the *Salicaceae* family. The team characterized several enzymes involved in the biosynthesis of these metabolites, including: a salicyl benzoate acyltransferase and a benzyl benzoate acyltransferase (Chedgy et al. 2015); two UDP-glycosyltransferases involved in the synthesis of salicortin, tremulacin, tremuloidin, and salicin (Fellenberg et al. 2020); and a sulfotransferase that is able to synthesize these newly identified sulfated salicinoids (Lackus et al. 2020).

4.6. Mehran Dastmalchi

Pr. Mehran Dastmalchi previously worked with Pr. Sangeeta Dhaubhadel on bean flavonoids (Dastmalchi and Dhaubhadel 2015; Dastmalchi et al. 2019*a*), with Pr. Vincenzo de Luca on *Catharanthus* metabolites, and Pr. Peter J. Facchini on BIA metabolism (Morris et al. 2016; Dastmalchi et al. 2018, 2019*a*, 2019*b*). After opening his own laboratory at McGill University focusing on isoflavonoids biosynthesis in *Fabaceae* and *Apocyanaceae*, he published several reviews on his expertise on plant specialized metabolism (Dastmalchi 2020*a*, 2020*b*, 2021*a*, 2021*b*). Furthermore, his team showed that the accumulation of the alkaloid akuammicine (a weak opioid agonist and potential anti-diabetic drug) can be increased in *C. roseus* using methyljasmonate, and that naturally formed lesions in a mutant had more of this alkaloid (Li et al. 2022*b*). Pr. Dastmalchi's team also identified and characterized a transporter Multidrug And Toxic compound Extrusion 1, which imports secologanin (a key intermediate in the synthesis of MIAs) into the vacuole, and revealed that in its absence this monoterpenoid is reduced to secologanol in *C. roseus* (Li et al. 2024).

4.7. Nikola Kovinich

Nikola Kovinich was appointed assistant professor at York University in 2019, where he works on soybean responses to biotic stress. Specifically, Pr. Kovinich is interested in understanding how biotic stresses affect soybean's metabolism (Yousefi-Taemeh et al. 2021) and the regulation of phytoalexin biosynthesis mediated by MYB and NAC transcription factors (Farrell et al. 2017; Kovinich and Durkin 2018; Jahan and Kovinich 2019; Jahan et al. 2020; Lin et al. 2023*b*). In addition, Pr. Kovinich has broadened his research on plant metabolites to include the semi-synthesis of anticancer natural products using soybean seed coats (Gary et al. 2018) and he has contributed with methods for genetic transformation of soybean (Lin et al. 2023*a*) and cannabis (Ahmed et al. 2021).

5. Biofoundries and incubators

In addition to the uplisted research teams, Canada is home to two biofoundries: Centre for Applied Synthetic Biology (Concordia Genome Foundry) and the BioFoundry at UBC. Both offer metabolic and enzyme engineering incubators in an academic environment to achieve more sustainable and profitable pharmaceutical production of molecules of interest. Concordia Genome Foundry allowed companies to use high-throughput genomic techniques and develop metabolic engineering host cells producing isoprenoids and cannabinoids (Keasling et al. 2007; Keasling et al. 2011).

The BioFoundry at UBC is led by Pr. Vikramaditya G. Yadav, an Associate Professor in the Department of Chemical & Biological Engineering, and the School of Biomedical Engineering UBC. The group collaborates with several companies and works on enzyme optimization and drug development. Among the fruits of these collaborations are innovations in the synthesis of cannabinoids (Ayakar et al. 2020; Yadav et al. 2022).

6. Conclusion

Canada is a fertile environment for advancing plant metabolomics and platforms to produce plant specialized compounds due to active researchers and their previous mentors. These include one of the pioneers of the Canadian research on plant specialized metabolism, Pr. G.H. Neil Towers that mentored Pr. Ragai K. Ibrahim, who then trained Pr. Vincenzo de Luca. Though this review focused on researchers directly working on pathway elucidation and metabolic engineering of plant specialized metabolites, many advances have also been supported by interdisciplinary collaborations. Researchers such as Pr. John T. Arnason (Binns et al. 2001), Pr. Jürgen Ehlting (Carrington et al. 2018; Adams et al. 2019; Alber et al. 2019), Pr. Abdelali Hannoufa (Yu et al. 2007, 2008; Bhinu et al. 2009; Ben-Abdallah et al. 2018; Carrington et al. 2018), and Pr. Charles Goulet (Bulot et al. 2022; Liscombe et al. 2022), to name a few, have significantly advanced our understanding of specialized metabolism and its applications across various fields, including plant stress responses, ecological interactions, and agricultural innovations.

Canadian research institutes are offering new insights into plant biochemistry and synthetic biology every year. A pan-Canadian research collaboration could allow major advances in this field and help young researchers to obtain funding, which would help Canada to retain talent of the new scientific generation.

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