Review

Climate-Affected Australian Tropical Montane Cloud Forest Plants: Metabolomic Profiles, Isolated Phytochemicals, and Bioactivities

Ngawang Gempo , Karma Yeshi * , Darren Crayn , And Phurpa Wangchuk

Posted Date: 11 March 2024

doi: 10.20944/preprints202403.0584.v1

Keywords: wet tropics; climate change; metabolomics; tropical montane cloud forest; Wet Tropics World Heritage Area; plant secondary metabolites

Review

Climate-Affected Australian Tropical Montane Cloud Forest Plants: Metabolomic Profiles, Isolated Phytochemicals, and Bioactivities

Ngawang Gempo [1,2,†], Karma Yeshi [1,2,*,†], Darren Crayn [3] and Phurpa Wangchuk [1,2]

[1] Australian Institute of Tropical Health and Medicine (AITHM), James Cook University, Nguma-bada campus, McGregor Rd, Smithfield, Cairns, QLD 4878, Australia; ngawang.gempo@my.jcu.edu.au; karma.yeshi@jcu.edu.au; phurpa.wangchuk@jcu.edu.au
[2] College of Public Health, Medical, and Veterinary Services (CPHMVS), James Cook University, Nguma-bada campus, McGregor Rd, Smithfield, Cairns, QLD 4878, Australia
[3] Australian Tropical Herbarium (ATH), James Cook University, Nguma-bada campus, McGregor Rd, Smithfield, Cairns, QLD 4878, Australia; darren.crayn@jcu.edu.au
* Correspondence: karma.yeshi@my.jcu.edu.au
† Equally contributed as the first author.

Abstract: The Australian tropical montane cloud forest (TMCF) is home to approximately 18 percent of the nation's total vascular plant species. Over the past century, human activity and industrial development have caused global climate changes, posing a severe and irreversible danger to the entire land-based ecosystem, and WTWHA is no exception. The current average annual temperature of WTWHA in FNQ is 24 °C. However, in the coming years (by 2030), the average annual temperature increase is estimated to be between 0.5 and 1.4 °C compared to the climate observed between 1986 and 2005. Looking further ahead to 2070, the anticipated temperature rise is projected to be between 1.0 and 3.2 °C, with the exact range depending on future emissions. We identified 84 plant species endemic to the WTWHA in FNQ, which are already experiencing climate change threats. Few of these plants are used in herbal medicines. This study comprehensively reviewed metabolomics studies conducted on these 84 plant species until now toward understanding their physiological and metabolomics responses to global climate change. This review also discusses: i) recent developments in plant metabolomics studies that can be applied to study and understand the interactions of wet tropical plants with climatic stress, ii) medicinal plants and isolated phytochemicals with structural diversity, and iii) reported biological activities of crude extracts and isolated compounds.

Keywords: Wet Tropics; climate change; metabolomics; tropical montane cloud forest; Wet Tropics World Heritage Area; plant secondary metabolites

---

1. Introduction

Human activity and industrial development have led to significant and irreversible threats to the entire land-based ecosystem in the last century, primarily due to global climate changes. As the average global annual temperature continues to rise by 1℃ compared to the average temperature during the preindustrial era, and experts have predicted that the temperature will further rise by 3–5 ℃ by the end of this century, owing to the increasing concentration of greenhouse gases (GHGs), such as CO_2 and methane in the atmosphere [1,2]. Looking further ahead to 2070, the anticipated temperature rise ranges from 1.0 to 3.2 °C, based on the intensity of future greenhouse gas emissions [3]. Climate change indirectly impacts species by diminishing the quantity and accessibility of habitat and eliminating species crucial for the survival of the species in question [4]. This impact is significantly felt in the Tropical montane (TM) regions within the evergreen forests that are enveloped in persistent and frequent low-level clouds form unique ecosystems called TM cloud forest (TMCF) [5]. Indeed, recent studies including climate model studies [6–8], predicted higher rates of temperature increase at higher elevations of TMCF regions compared to lower elevations. Furthermore, alterations in reliability and quantity of precipitation in TMCF are anticipated due to reductions in cloud cover [5,9–11]. These factors would bring significant challenges to species in TMCF, leading to shifts in altitudinal ranges, reshuffling of species compositions, and increased risk of extinction [5].

The Australian TMCF situated at or above 900 meters in elevation (Figure 1) across Wet Tropics World Heritage Area (WTWHA) of northeast Queensland, Australia, is no exception. Indeed, the impacts of climate change on Australian TMCF are anticipated to manifest within this century [7,12] as the plant species are particularly vulnerable to climatic stress compared to the lowland species [7,13]. The WTWHA, which is considered the sixth most important protected area globally for conserving biodiversity [14], is home to over 3,300 plant species, of which 700+ are endemic to the region, accounting for 18 percent of the nation’s total vascular plant species [15,16]. The ongoing project on climate-affected TMCF plants, which is led by the Australian Tropical Herbarium at James Cook University, has identified 84 plant species that are vulnerable to the impact of climate change in the WTWHA. Some of these plants are used in traditional medicines, including Aboriginal bush medicines.

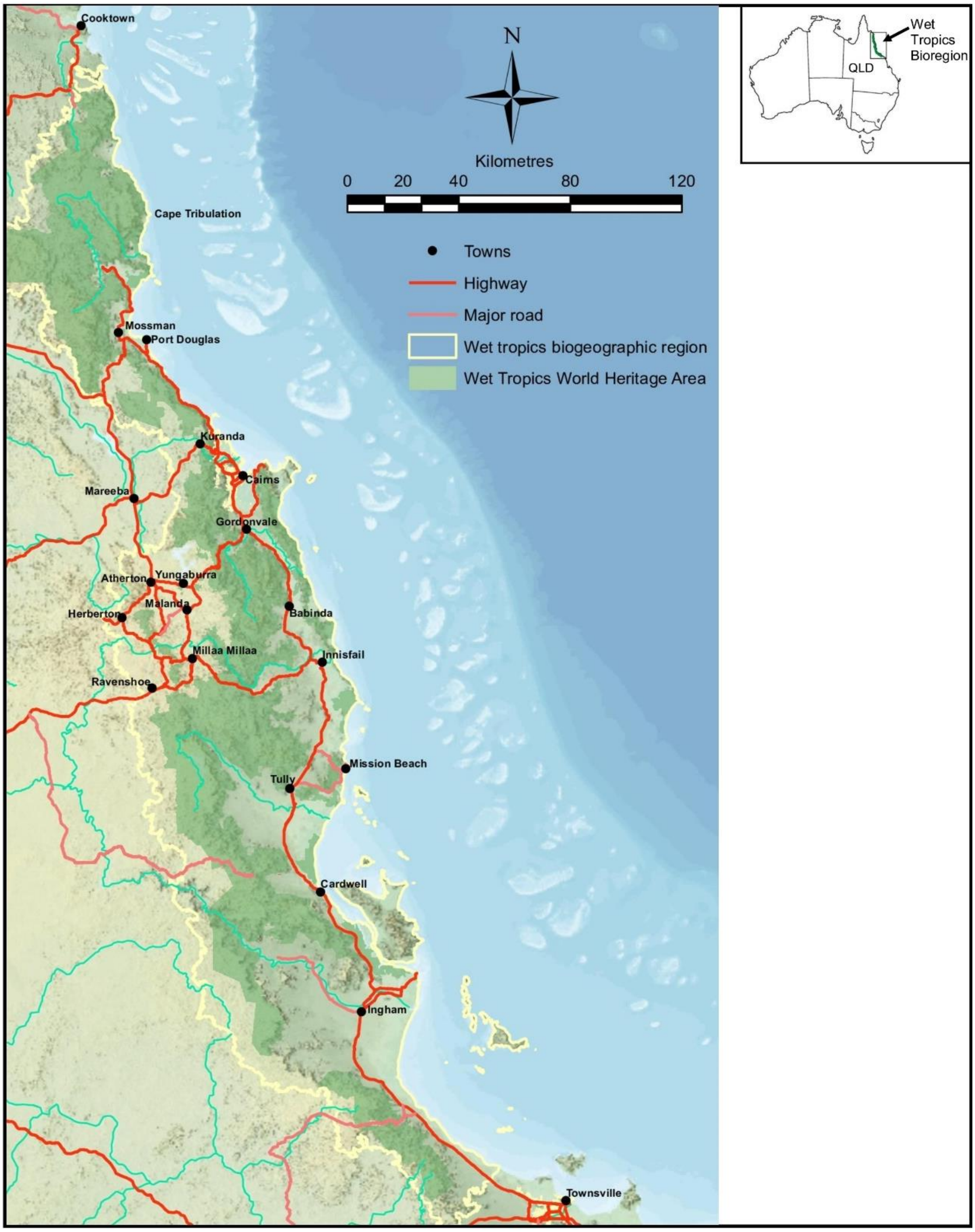

Figure 1. Map of Australia showing the State of Queensland and the Wet Tropics World Heritage Area (WTWHA) shaded in green. Tropical Montane Cloud Forest is restricted to the mountaintops of the WTWHA, typically areas above 900 m above sea level. A map depicting WTWHA was generated from the Wet Tropics Plan zoning map Edition 3.0 with the help of Wet Tropics Management Authority office, Queensland.

These plants that are affected by climate change or biotic stressors exhibit both morphological and physiological plasticity in order to adapt, survive, and thrive [17]. Their adaptability relies on complex genetic or metabolic detection and communication systems that we are just starting to comprehend. Numerous research investigations have been carried out on various plants, for instance, *Arabidopsis*, aiming to unravel the intricate molecular mechanisms that plants exhibit in response to constantly changing environments [18–22]. More recently, technological advancements have enabled

 doi:10.20944/preprints202403.0584.v1

the acquisition of molecular data, including phenomics, epigenomics, transcriptomics, proteomics, and metabolomics data. These multidisciplinary approaches have enabled a better understanding of plants' responses to various environmental changes linked to climate change, including drought and cold [23,24]. The plant produces various biomolecules, which serve different biological roles throughout plant life cycles. These biomolecules can be categorized under two major groups: primary metabolites (PMs) and secondary metabolites (SMs). Primary metabolites, such as proteins, sugars, and organic acids, are widely recognized for their role in essential plant physiological processes, including photosynthesis, photorespiration, and the tricarboxylic acid cycle [25,26]. Secondary metabolites, mainly phenolics, terpenoids, and alkaloids, are produced in response to competitive environmental factors for survival and fulfilling various physiological functions [27]. These SMs do not play a direct role in plants' typical growth and survival; instead, they contribute to plant development and enhance resilience to stress [28]. For example, flavonoids are photo-protectants, shielding plants from damage caused by ultraviolet-B (UV-B) radiation [29,30]. Similarly, some terpenoids or alkaloids might act as antioxidants or osmotic regulators in response to abiotic stresses in plants [31,32]. In contrast, glucosinolates, limited to specific taxonomic groups, are considered essential antitoxins that play a crucial role in enabling plants to resist insect attacks [33].

Understanding the response patterns of these secondary metabolites to potential global climate changes is crucial due to their significance in plant growth, resistance, human health, and conservation efforts. Recently developed powerful omics techniques [34–36] and bioimaging [37] and biosensor tools [38,39] have been widely applied for understanding plant physiology, analyzing the plant metabolome, and discovering novel metabolomic pathways in response to the changing environment [40]. However, there is no comprehensive review that examined recent metabolomic and phytochemical studies on climate-affected plants of Australian TMCF.

This review comprehensively analysed the literature on the available metabolomics studies conducted on the 84 TMCF plant species and discusses i) recent developments in plant metabolomics studies that can be applied to study and understand the interactions of wet tropical plants with climatic stress, ii) medicinal plants and isolated phytochemicals with structural diversity, and iii) reported biological activities of crude extracts and isolated compounds. In doing so, we compiled and listed the plant species largely restricted to TMCF based on Hoyle et al. (2023) [5] and additional information from several sources: i) records in the Atlas of Living Australia [41], ii) the 'Rainforest Key' [42], and 3) expert knowledge [43]. We searched for studies of metabolomic profiles, medicinal plants use, phytochemical contents, and biological activities in Google Scholar, MEDLINE Ovid, Scopus, PubMed, and journal websites using the following keywords: "wet tropics climate-affected plants," "secondary metabolites in plants," "metabolomics studies of plants," "phytochemical analysis of plants affected by climatic impact," "biological activities," and accepted plant name and their synonyms. The information we collected was analyzed and presented in tables and figures. Additionally, we utilized ChewDraw Professional software to create chemical structures, ensuring the accuracy of each structure by cross-referencing them with databases such as PubChem, ChemSpider, and HMDB databases.

2. Climate-Affected Australian Tropical Montane Cloud Forest Plants and Their Medicinal Uses

Using information from Hoyle et al. (2023) [5], expert opinion (botanists from the Australian Tropical Herbarium (ATH) at James Cook University in Cairns), and other literature, we found 84 climate-affected plant species largely restricted to TMCF. The plant names were cross-checked using the Australian Plant Census [44], WFO Plant List [45], and Australian Tropical Rainforest Plants information system [42]. Based on these 84 plant species lists, we generated information on their botanical names, taxonomy, distribution, life form, and medicinal uses of each plant (Table 1).

Of the 84 plant species, 54 were native to the WTWHA, 26 were endemic, and four were non-native (Table 1 and Figure 2A). Four non-native species were *Parapolystichum grayi* (D.J.Jones) J.J.S. Gardner & Nagalingum, *Phlegmariurus creber* (Alderw.) A.R.Field & Bostock, *Oreogrammitis reinwardtii* Blume, and *Mischocarpus montanus* C.T.White. Of 84 plant species, 29 were trees, followed by shrubs (28 species) and ferns (8 species) (Table 1 and Figure 2B). These 84 plant species belonged

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 March 2024 doi:10.20944/preprints202403.0584.v1

to 34 families, and the Orchidaceae family had the maximum number of species (8 species), trailed by the Ericaceae and Myrtaceae (6 species each) and Proteaceae and Rubiaceae (5 species each) (Figure 2C). Most of the families (15 families) had one species. When checked for their plant uses in traditional medicines, we found that most sTWHA plants were not used medicinally. This could be because most plants are endemic to WTWHA, and these endemic species, although used in Aboriginal bush medicines, their medicinal uses are not publicly available. Of 84 species, 43 belong to 29 medicinally important genera (Figure 2D). Of the 43 species, species of *Planchonella, Tasmania,* and *Litsea* were particularly indicated as traditionally used by Australian Aboriginal communities to treat various ailments, such as skin sores, scabies, and sore throat, as an antiseptic for boils, malaria, diarrhea, and cough (Table 1). Most of the genera were found to be used for medicinal purposes in traditional medicine systems of Asian countries, such as China, India, Indonesia, Malaysia, Japan, Taiwan, and Korea.

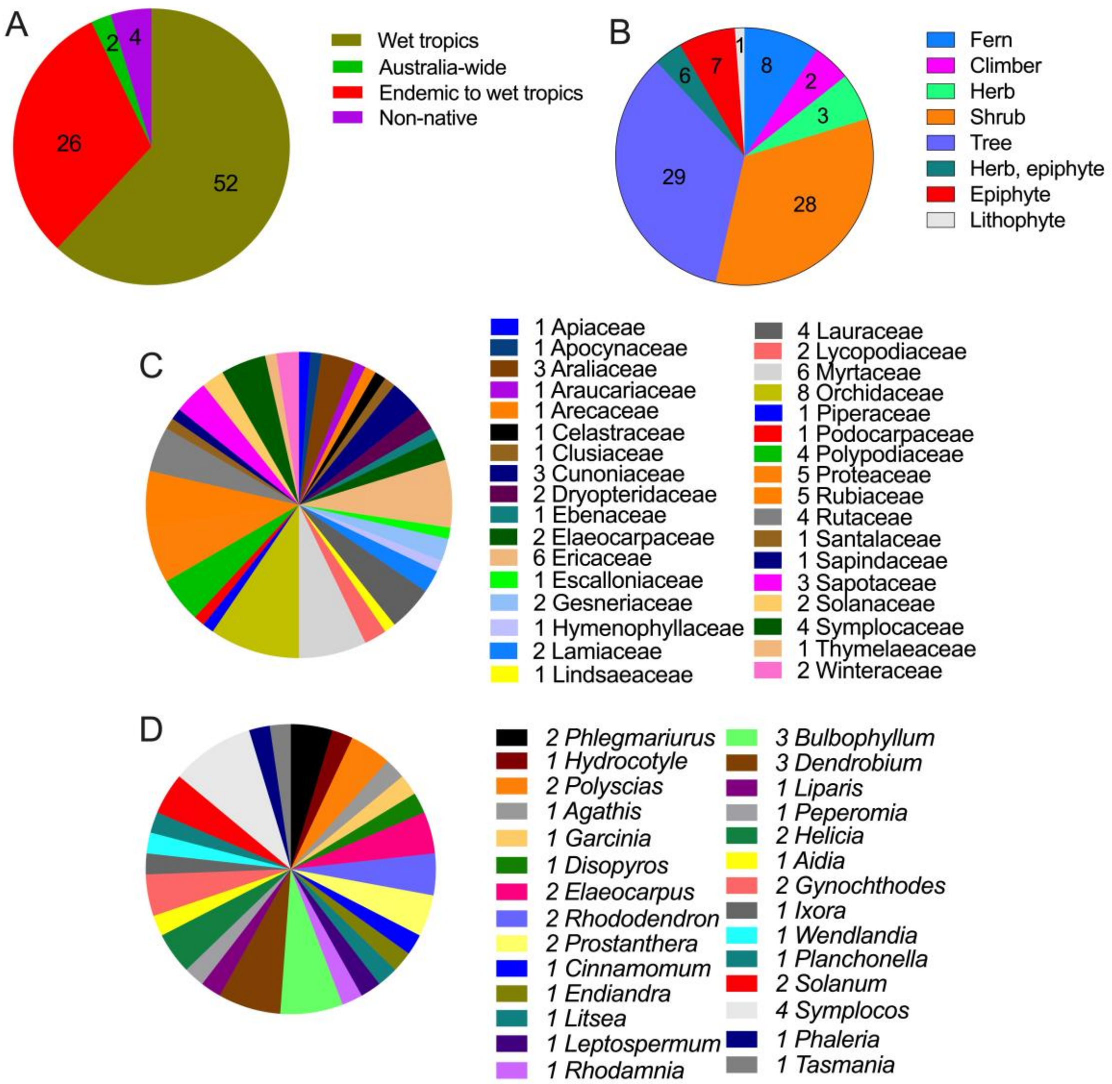

Figure 2. Climate-affected Australian montane cloud forest plants in the Wet Tropics World Heritage Area, Queensland: A) distribution, B) life form, C) family diversity, and D) medicinally important genus with species number.

A report from 2010 by the Commonwealth Scientific and Industrial Research Organization (CSIRO) [46] indicates that numerous tree species are at risk of experiencing mean temperatures that exceed their typical tolerance levels. To illustrate, the recent increase in temperature may already be placing stress on a lowland tree species that has adapted to thrive within a mean annual temperature

 doi:10.20944/preprints202403.0584.v1

range of 23.0 to 24.0 (measured at 200 masl). To survive in a comparable temperature environment, they must relocate more than 1000 m upward by 2080. However, habitat fragmentation will severely constrain their capacity to respond in this way [16]. Figure 4 illustrates the conservation status of 84 Australian TMCF plant species affected by climate change. Of these, nearly half (41 species) are of conservation significance under Queensland State legislation: 21 species are listed as Vulnerable (V, sky blue bar), six are Near Threatened (NT, yellow bar), 3 are Endangered (E, orange bar), and 11 are Critically Endangered (CR, light red bar) (Table 1 and Figure 3). The remainder (43 species) are not currently listed as threatened, i.e., are categorized as Least Concern (LC), Special Least Concern (SL), or no conservation status indicated (No).

Through modelling analysis, Costion et al. [7] projected significant declines in suitable habitat for 19 of the 84 TMCF plant species listed in Table 1, with estimates ranging from 17% to 100% by 2040 and at least 46% by 2080. Roeble [47] further refined these predictions, modeling 37 plant species (including 8 from Costion's study) and predicting a mean habitat loss of 63% by 2085. The study predicted that five out of 37 modelled species (*Acrotriche baileyana, Gynochthodes constipata, Hymenophyllum whitei, Syzygium fratris, Tasmania sp. Mt. Bellenden Ker*) will experience a total loss of their suitable habitat by 2035 and another two species (*Cinnamomum propinquum* and *Leucopogon malayanus*) by 2085 [48]. For only *Bubbia whiteana* was a substantial increase in the suitable habitat through 2085 predicted. Overall, both studies [7,48] suggest that a significant portion of Australian montane cloud forest species is either threatened or vulnerable to climatic stress. Hence, these plants must acclimatize and react swiftly to overcome environmental stresses or face extinction. Therefore, it is crucial to comprehend how plants react and adjust to shifts in their environment, striving to enhance their ability to withstand the challenges posed by climate change.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 March 2024 doi:10.20944/preprints202403.0584.v1

Table 1. List of climate-affected Australian montane cloud forest plants: their distribution, life form, conservation status and medicinal uses.

Botanical name, family, and synonyms	Distribution	Life Form	Medicinal uses	Metabolomics profile studied	Conservation status (QLD)
Pteridophyta					
Dryopteridaceae					
Parapolystichum grayi (D.J.Jones) J.J.S. Gardner & Nagalingum **Syn.** *Lastreopsis grayi* D.L.Jones	Africa, the Neotropics, north-eastern Australia, Madagascar, Pacific Island, and southern Asia	Fern	NU	No	V
Parapolystichum tinarooense (Tindale) Labiak, Sundue & R.C.Moran **Syn.** *Lastreopsis tinarooensis* Tindale	Wet Tropics region (Australia)	Fern	NU	No	V
Hymenophyllaceae					
Hymenophyllum whitei Goy	Wet Tropics region (Australia)	Fern	NU	No	CR
Lindsaeaceae					
Lindsaea terrae-reginae K.U.Kramer	Wet Tropics region (Australia)	Fern	NU	No	E
Lycopodiaceae					
Phlegmariurus creber (Alderw.) A.R.Field & Bostock **Syn.** *Huperzia crebra* (Alderw.) Holub	Wet Tropics region (Australia), PNG, Hawaii	Epiphyte	*Phlegmariurus/Huperzia* species are traditionally used as vermifuge, purgative, and laxative [49].	No	CR
Phlegmariurus delbrueckii (Herter) A.R.Field & Bostock **Syn.** *Huperzia delbrueckii* (Herter) Holub	Wet Tropics region (Australia)	Epiphyte		No	V
Polypodiaceae					
Oreogrammitis albosetosa (F.M.Bailey) Parris **Syn.** *Polypodium albosetosum* F. M.Bailey	Wet Tropics region (Australia)	Fern	NU	No	V
Oreogrammitis leonardii (Parris) Parris **Syn**. *Grammitis leonardii* Parris	Wet Tropics region (Australia)	Fern	NU	No	V
Oreogrammitis reinwardtii Blume	Wet Tropics region (Australia), Sri Lanka, Philippines, Papua New Guinea, Solomon Islands, Malaysia	Fern	NU	No	V
Oreogrammitis wurunuran (Parris) Parris **Syn.** *Grammitis wurunuran* Parris	Wet Tropics region (Australia)	Fern	NU	No	SL
Magnoliophyta					
Apiaceae					
Trachymene geraniifolia F.M.Bailey	Wet Tropics region (Australia)	Herb	NU	No	NT
Apocynaceae					
Parsonsia bartlensis J.B.Williams	Wet Tropics region (Australia)	Climber	NU	No	V

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 March 2024 doi:10.20944/preprints202403.0584.v1

Araliaceae					
Hydrocotyle miranda A.R.Bean & Henwood	Wet Tropics region (Australia)	Herb	*Hydrocotyle* species are used as anti-inflammatory herbs in Taiwanese folk medicines [50].	No	V
Polyscias bellendenkerensis (F.M.Bailey) Philipson	Wet Tropics region (Australia)	Shrub	*Polyscias* species are traditionally used to treat ailments, such as malaria, obesity, and mental disorders [51].	No	V
Polyscias willmottii (F.Muell.) Philipson	Wet Tropics region (Australia)	Tree		No	LC
Araucariaceae					
Agathis atropurpurea B.Hyland	Australia	Tree	*Agathis* species are traditionally used to treat myalgia and headaches [52].	Yes	LC
Arecaceae					
Linospadix apetiolatus Dowe & A.K.Irivine	Wet Tropics region (Australia)	Tree	NU	No	LC
Celastraceae					
Hypsophila halleyana F.Muell.	Wet Tropics region (Australia)	Shrub	NU	No	LC
Clusiaceae					
Garcinia brassii C.T.White	Wet Tropics region (Australia)	Tree	Infusions prepared from fruits of *Garcinia* species are traditionally used to treat dysentery, ulcers, and wounds [53].	No	LC
Cunoniaceae					
Ceratopetalum corymbosum C.T.White	Wet Tropics region (Australia)	Tree	NU	No	V
Ceratopetalum hylandii Rozefelds & R.W.Barnes	Wet Tropics region (Australia)	Tree	NU	No	LC
Eucryphia wilkiei B.Hyland	Wet Tropics region (Australia)	Shrub	NU	Yes	CR
Ebenaceae					
Diospyros granitica Jessup	Wet Tropics region (Australia)	Tree	*Diospyros* species are used traditionally used as sedative, astringent, carminative, febrifuge, anti-hypertensive, vermifuge, antidiuretic, and to relieve constipation [54].	No	NT
Elaeocarpaceae					
Elaeocarpus linsmithii Guymer	Wet Tropics region (Australia)	Tree	*Elaeocarpus* species are the source of popular spiritual beads (known as Rudraksha in Asia), which are used to treat various ailments, including mental/neurological disorders (stress, depression, anxiety, hypertension,	No	LC
Elaeocarpus hylobroma Y.Baba & Crayn	Wet Tropics region (Australia)	Tree		No	LC

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 March 2024 doi:10.20944/preprints202403.0584.v1

			epilepsy, migraine, and neuralgia), asthma, and also used as analgesic [55].		
Ericaceae					
Acrotriche baileyana (Domin) J.M.Powell	Wet Tropics region (Australia)	Shrub	NU	No	NT
Dracophyllum sayeri F.Muell	Wet Tropics region (Australia)	Tree	NU	No	V
Leucopogon malayanus subsp. *novoguineensis* (Sleumer) Pedley **Syn.** *Styphelia malayana* subsp. *novoguineensis* (Sleumer) Hislop, Crayn & Puente-Lel.	Wet Tropics region (Australia)	Shrub	NU	No	No
Rhododendron lochiae F.Muell. **Syn.** *Rhododendron notiale,* Craven	Wet Tropics region (Australia)	Shrub	*Rhododendron* species are used to prevent and treat many ailments, including respiratory disorders like asthma and bronchitis, dysentery, diarrhea, constipation, fever, cardiac disorders, and inflammation [56].	No	No
Rhododendron viriosum Craven	Wet Tropics region (Australia)	Tree		No	LC
Trochocarpa bellendenkerensis Domin	Wet Tropics region (Australia)	Tree	NU	No	LC
Escalloniaceae					
Polyosma reducta F.Muell.	Wet Tropics region (Australia)	Tree	NU	No	LC
Gesneriaceae					
Boea kinneari (F.Muell.) B.L.Burtt	Wet Tropics region (Australia)	Herb	NU	No	E
Lenbrassia australiana (C.T.White) G.W.Gillett	Wet Tropics region (Australia)	Shrub	NU	No	SL
Lamiaceae					
Prostanthera albohirta C.T.White	Mount Emerald, Wet Tropics region (Australia)	Shrub	Some *Prostanthera* species are used for topical applications to treat skin sores and infections [57,58].	No	CR
Prostanthera athertoniana B.J.Conn & T.C.Wilson	Wet Tropics region (Australia)	Shrub		No	CR
Lauraceae					
Cinnamomum propinquum F.M.Bailey	Wet Tropics region (Australia)	Tree	*Cinnamomum* species are most commonly used in traditional Chinese medicines to treat multiple disorders, including indigestion, microbial infections, and cough and cold [59].	Yes	V
Cryptocarya bellendenkerana B.Hyland	Wet Tropics region (Australia)	Tree	NU	Yes	LC
Endiandra jonesii B.Hyland	Wet Tropics region (Australia)	Tree	*Endiandra* species are traditionally used to treat rheumatism, headache, dysentery, pulmonary disorders, and uterine tumors [60].	No	V

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 March 2024 doi:10.20944/preprints202403.0584.v1

Litsea granitica B.Hyland	Wet Tropics region (Australia)	Tree	*Litsea* species are used traditionally by Aboriginal communities to treat skin infections such as sores and scabies, and also used an antiseptic [61].	No	V
Myrtaceae					
Leptospermum wooroonooran F.M.Bailey	Wet Tropics region (Australia)	Tree	*Leptospermum* species are traditionally used in Malaysia to relieve menstrual and stomach disorders [62,63].	Yes	LC
Micromyrtus delicata A.R.Bean	Wet Tropics region (Australia)	Shrub	NU	No	E
Pilidiostigma sessile N.Snow	Wet Tropics region (Australia)	Shrub	NU	No	LC
Rhodamnia longisepala N.Snow & A.J.Ford	Wet Tropics region (Australia)	Shrub	*Rhodamnia* species are used traditionally in Indonesia to treat scars, toothache, and cough [64].	No	CR
Syzygium fratris Craven	Wet Tropic region (Australia)	Shrub	NU	No	CR
Uromyrtus metrosideros (F.M.Bailey) A.J.Scott	Wet Tropics region (Australia)	Shrub	NU	Yes	LC
Orchidaceae					
Bulbophyllum lilianiae Rendle	Wet Tropics region (Australia)	Epiphyte	*Bulbophyllum* species are traditionally used to treat skin diseases, cardiovascular diseases, and rheumatism [65].	No	LC
Bulbophyllum wadsworthii Dockrill **Syn.** *Oxysepala wadsworthii* (Dockrill) D.L.Jones & M.A.Clem.	Australia	Epiphyte		No	SL
Bulbophyllum windsorense B.Gray & D.L.Jones **Syn.** *Oxysepala windsorensis* (B.Gray & D.L.Jones) D.L.Jones & M.A.Clem.	Wet Tropics region (Australia)	Epiphyte		No	V
Dendrobium brevicaudum D.L.Jones & M.A.Clem. **Syn.** *Dockrillia brevicauda* (D.L.Jones & M.A.Clem.) M.A.Clem. & D.L.Jones	Wet Tropics region (Australia)	Herb, Epiphyte	*Dendrobium* species are used in traditional Chinese and Indian medicine systems as a source of tonic for longevity and also as an antipyretic, analgesic, astringent, and anti-inflammatory agent [66].	No	No
Dendrobium carrii Rupp & C.T.White **Syn.** *Australorchis carrii* (Rupp & C.T.White) D.L.Jones & M.A.Clem.	Wet Tropics region (Australia)	Herb, Epiphyte		No	SL
Dendrobium finniganense D.L.Jones **Syn.** *Thelychiton finniganensis* (D.L.Jones) M.A.Clem. & D.L.Jones	Wet Tropics region (Australia)	Herb, Epiphyte		No	SL
Liparis fleckeri Nicholls	Wet Tropics region (Australia)	Lithophyte	*Liparis* species are traditionally used in Chinese medicine to treat inflammatory diseases, including hemoptysis, metrorrhagia, traumatic hemorrhage, and pneumonia; it is also used to stop	No	No

			bleeding from wounds and to detoxify snakebite [67].		
Octarrhena pusilla (F.M.Bailey) M.A.Clem. & D.L.Jones **Syn.** *Octarrhena pusilla* (F.M.Bailey) Dockrill	Wet Tropics region (Australia)	Epiphyte	NU	No	SL
Piperaceae					
Peperomia hunteriana P.I.Forst.	Wet Tropics region (Australia)	Herb	*Peperomia* species are traditionally used for treating pain and inflammation, gastric ulcers, asthma, and bacterial infections [68,69].	No	LC
Podocarpaceae					
Prumnopitys ladei (F.M.Bailey) de Laub **Syn.** *Stachycarpus ladei* (Bailey) Gaussen, *Podocarpus ladei* F.M.Bailey	Endemic to Wet Tropics Australia	Tree	Fruits and bark of *Prunmnopitys* species are considered medicinal [70].	Yes	No
Proteaceae					
Austromuellera valida B.Hyland	Endemic to Wet Tropics region	Tree	NU	No	V
Helicia lewisensis Foreman	Endemic to Wet Tropics region	Tree	*Helicia* species are used for treating mouth and skin sores and also kidney and gastric problems [71–74].	No	V
Helicia recurva Foreman	Endemic to Wet Tropics region	Tree		No	No
Hollandaea porphyrocarpa A.J.Ford & P.H.Weston **Syn.** *Hollandaea sp.* Pinnacle Rock Track (P.I.Forster PIF10714*)*	Endemic to Wet Tropics region	Shrub	NU	No	CR
Nothorites megacarpus (A.S.George & B.Hyland) P.H.Weston & A.R.Mast **Syn.** *Orites megacarpa* A.S.George & B.Hyland	Endemic to Wet Tropics region	Tree	NU	No	LC
Rubiaceae					
Aidia gyropetala A.J.Ford and Halford	Endemic to Wet Tropics region	Tree	*Aidia* species are used for treating body/muscle pains and pains due to gastric disorders [75].	No	LC
Gynochthodes constipata (Halford & A.J.Ford) Razafim. & B.Bremer **Syn.** *Morinda constipata* Halford & A.J.Ford	Endemic to Wet Tropics region	Climber	*Gynochthodes/Morinda* species are traditionally used for treating diabetes, inflammation, cancer, psychiatric disorders, and microbial infections [76].	No	LC
Gynochthodes podistra (Halford & A.J.Ford) Razafim. & B.Bremer **Syn.** *Morinda podistra* Halford & A.J.Ford	Endemic to Wet Tropics region	Climber		No	LC
Ixora orophila C.T.White **Syn.** *Psydrax montigena* S.T.Reynolds & R.J.F.Hend.	Endemic to Wet Tropics region	Shrub	*Ixora* species are used in Ayurvedic medicine against leucorrhoea, dys, hypertension, menstrual irregularities,	No	No

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 March 2024 doi:10.20944/preprints202403.0584.v1

			sprains, bronchitis fever, sores, chronic ulcers, scabies, and skin diseases [77].		
Wendlandia connata C.T.White	Endemic to Wet Tropics region	Shrub	*Wendlandia* species are traditionally used for treating fever, dysentery, cough, hypertension, diabetes, constipation, inflammations, and hyperlipidemia [78].	No	NT
Rutaceae					
Flindersia oppositifolia (F.Muell.) T.G.Hartley & Jessup	Wet Tropics region (Australia)	Tree	NU	Yes	V
Leionema ellipticum Paul G. Wilson	Endemic to Wet Tropics region	Shrub	NU	Yes	V
Zieria alata Duretto & P.I.Forst.	Endemic to Wet Tropics region	Shrub	NU	No	CR
Zieria madida Duretto & P.I.Forst.	Endemic to Wet Tropics region	Shrub	NU	No	CR
Santalaceae					
Korthalsella grayi Barlow	Endemic to Wet Tropics region	Herb		No	LC
Sapindaceae					
Mischocarpus montanus C.T.White **Syn.** *Mischocarpus pyriformis* subsp. *retusus* (Radlk.) R.W.Ham, *Mischocarpus retusus* Radlk.	Wet Tropics region (Australia), New Guinea	Tree	NU	No	LC
Sapotaceae					
Pleioluma singuliflora (C.T.White & W.D.Francis) Swenson **Syn.** *Planchonella singuliflora* (C.T.White & W.D.Francis) P.Royen, *Pouteria singuliflora* (C.T.White & W.D.Francis) **Baehni**	Endemic to Wet Tropic region	Shrub	NU	No	LC
Sersalisia sessiliflora (C.T.White) Aubrév. **Syn.** *Pouteria sylvatica* Baehni, *Lucuma sessiliflora* C.T.White	Endemic to Wet Tropics region	Tree	NU	No	LC
Planchonella sp. Mt. Lewis (B.Hyland 14048) Qld Herbarium	Endemic to Wet Tropics region	Tree	*Planchonella* species have been used by Aboriginal medicine system to treat sores/sore throat and as an antiseptic for boils [61].	No	No
Solanaceae					
Solanum dimorphispinum C.T.White	Endemic to Wet Tropics region	Shrub	*Solanum* species have been traditionally used against infectious diseases and also as anti-microbial agents and insecticidal against mosquitoes [79].	No	LC
Solanum eminens A.R.Bean	Endemic to Wet Tropics region	Climber		No	LC

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 March 2024 doi:10.20944/preprints202403.0584.v1

Symplocaceae					
Symplocos bullata Jessup **Syn.** *Symplocos* sp. North Mary (B. Gray 2543)	Endemic to Wet Tropics region	Shrub	*Symplocos* species are traditionally known for treating diseases such as malaria, ulcers, leprosy, leucorrhea, menorrhagia, and gynecological disorders [80].	No	LC
Symplocos graniticola Jessup	Endemic to Wet Tropics region	Shrub		No	V
Symplocos oresbia Jessup **Syn.** *Symplocos* sp. Mt Finnigan (L.J. Brass 20129)	Endemic to Wet Tropics region	Shrub		No	NT
Symplocos wooroonooran Jessup **Syn.** *Symplocos stawellii* var. *montana* C.T.White, *Symplocos cochinchinensis* var. *montana* (C.T.White) Noot	Endemic to Wet Tropics region	Shrub		No	NT
Thymelaeaceae					
Phaleria biflora (C.T.White) Herber **Syn.** *Oreodendron biflorum* C.T.White	Endemic to Wet Tropics region	Tree	*Phaleria* species are used for treating stomachache, general pain, diarrhea, lowering glucose/cholesterol levels in blood, and also known for anti-cancer properties [81].	No	V
Winteraceae					
Bubbia whiteana A.C.Sm. **Syn.** *Zygogynum semecarpoides* var. *whiteanum* Vink, *Bubbia semecarpoides* var. *whiteana* Vink	Endemic to Wet Tropics region	Shrub	NU	No	CR
Tasmannia sp. Mt Bellenden Ker (J.R.Clarkson 6571)	Wet Tropics region (Australia)	Shrub	*Tasmania* species are traditionally used for treating malaria, diarrhea, and cough [82].	No	LC

 doi:10.20944/preprints202403.0584.v1

The scientific names and plant families follow the Australian Plant Census. Where taxonomy differs in "Plants of the World Online" [83], the synonym is given; Distribution and plant life form were sourced from: Atlas of Living Australia [41], Australian Tropical Rainforest Plants system [42], and Australian Tropical Rainforest Orchids [84]. Conservation status is per the Queensland Nature Conservation Act 1992 [85]: Abbreviations - SL: Special Least Concern; LC: Least Concern; NT: Near Threatened; V: Vulnerable; E: Endangered; CR: Critically Endangered; No: Species for which no conservation status is indicated; NU: Not used medicinally.

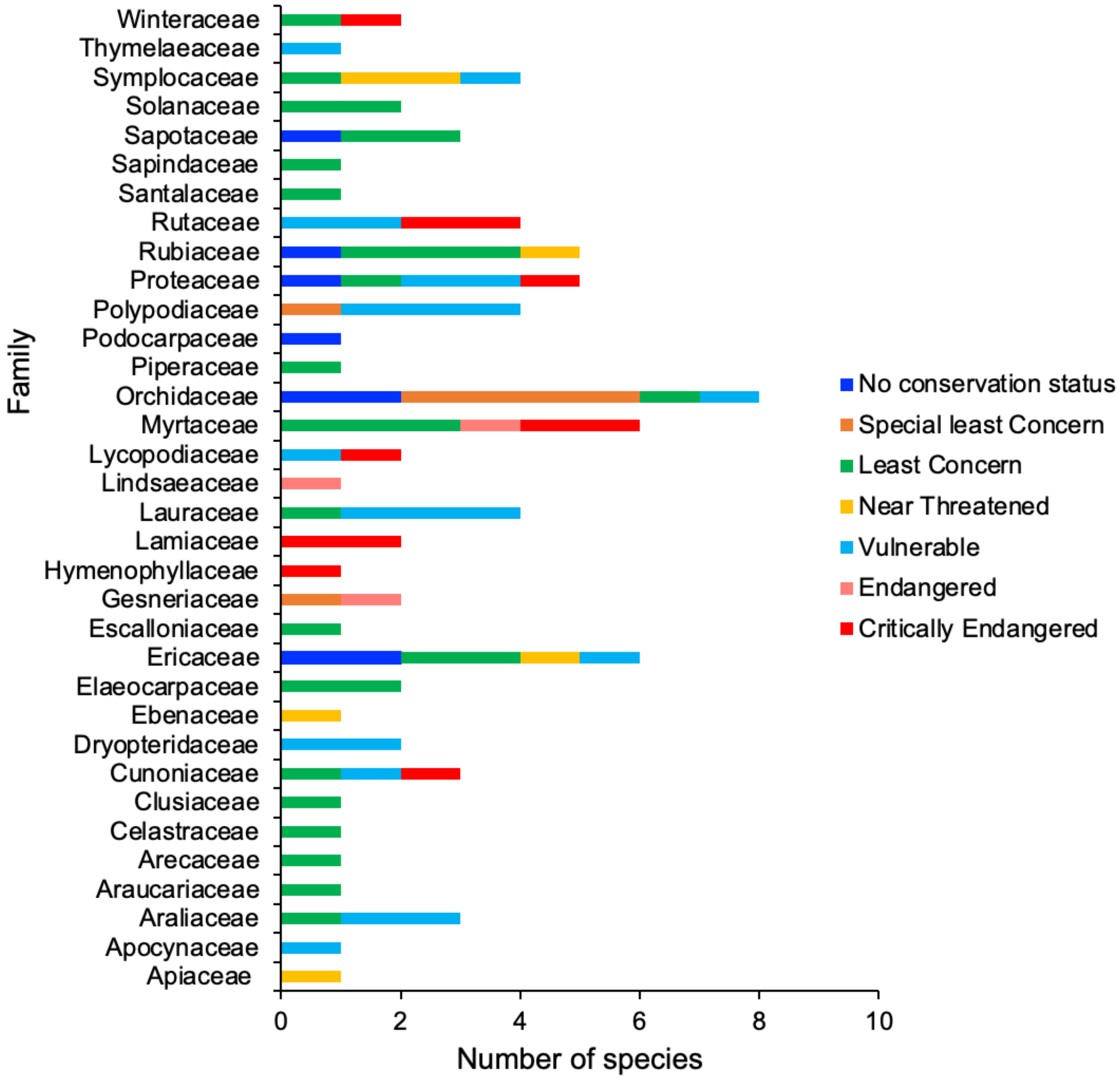

Figure 3. Conservation status of climate-affected Australian montane cloud forest plants in the Wet Tropics World Heritage Area, Queensland. Conservation status are as per the Queensland Nature Conservation Act 1992 [85].

3. Metabolomic Profile of Climate-Affected Plants in WTWHA

The anticipated impact of global climate changes on plant secondary metabolism is significant, but a comprehensive understanding of these effects is currently absent. Changes in the metabolome (defined as the complete set of metabolites found in a biological sample) can occur rapidly in seconds or minutes due to living organisms' responses, acclimation, and adaptation to environmental conditions [86–88]. Investigations into climate effects on plants have shown that plants growing under various climatic stresses in their natural habitat produce various SMs that could potentially have a role in adaptation to the changing environment [89–91]. Studies have also revealed that abiotic stress factors, such as increased temperature and ultraviolet (UV) radiation, stimulate plants to

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 March 2024 doi:10.20944/preprints202403.0584.v1

reprogram their genetic codes for metabolic pathways, leading to the accumulation of new and unique secondary metabolites [92].

For example, it was demonstrated that elevated temperatures can lead to increased production of terpenoids, phenolic acids, and flavonoids in plants [93,94]. These compounds act as protective pigments when trees are exposed to UV-B radiation (wavelengths between 280-315 nm) [95]. Likewise, higher ozone (O_3) concentrations have been linked to heightened production of antioxidant compounds such as glutathione, gamma-aminobutyric acid (GABA), terpenoids, and volatile organic compounds (VOCs) [96]. For example, the production of phenolics in plants plays an integral part in protecting mesophyll tissue from UV radiation and water stress [97,98]. It was discovered that drought conditions enhance plant productivity, leading to increased production of SMs, terpenes, complex phenols, and alkaloids [99–101]. Moreover, secondary metabolites with antioxidant properties, such as phenolic compounds and tocopherols, were known to scavenge the ROS (Reactive Oxygen Species) generated, thus adapting to a new environment [102].

In addition to metabolites, plants store proteins like hydrolases, enzymes for detoxifying reactive oxygen species (ROS), and enzymes for modifying cell walls. These proteins act as regulatory agents, governing plant growth and development [103]. Similarly, salinity also impacts the plant's growth and development. It leads to an abnormal ion composition, causing toxicity, osmotic stress, producing reactive oxygen species (ROS), cellular harm, and degrading membrane lipids, proteins, and nucleic acids [102]. In response to saline soil stress, plants undergo a biochemical process that produces ions that can act against ion toxicity and abnormal osmotic pressure developed from salinity [104]. In addition, when a huge amount of sodium (Na^+) ions prevails, plants respond to an abundance of Na^+ ions by activating a sophisticated defense system, which enables them to regulate cellular and ion balance effectively [105]

These studies enable us to understand the pattern of metabolite/micronutrient changes, including compositions, variations, and biosynthetic pathways resulting from plants' responses to biotic and abiotic stressors is known as the Plant metabolomics [106,107]. It can provide insights into plant phenotypic relations to their physiological and resistance development and biodiversity [108]. More than 200,000 secondary metabolites (SMs) have been identified [109] from over 391,000 plant species known worldwide [110] through metabolomics studies. The projected number for the plant kingdom is expected to surpass 200,000.[111,112]. Hence, plant metabolomics poses a significant hurdle for researchers in plant science. The comprehensive research workflow in plant metabolomics encompasses experimental planning, sample gathering, sample handling, sample preparation, detection and examination, data handling, as well as the analysis of metabolic pathways and networks [113].

From our literature review on 84 plant species affected by climate change in WTWHA of FNQ, only nine species were studied for their metabolomic profiles/phytochemical contents (Table 2). A total of 279 metabolites (251 identified and 18 isolated) were identified/isolated from parts of nine plant species. The identified metabolites were mostly flavonoids, terpenoids, alkaloids, and glucosides (Table 2). However, none of these metabolomics studies included in Table 2 were conducted to investigate their response to climatic stress conditions under in situ or ex-situ conditions. There is a need for this type of study, but the challenge would be to control various factors influencing plant responses, which is why we see most of the studies conducted under controlled conditions in glass houses. Currently, our group is conducting a first-of-its-kind study on selected WTWHA plants, in which we are comparing the metabolome profile and chemical variation between the wild and the domesticated plant population.

4. Phytochemicals Isolated from Climate-Affected Plants in WTWHA

Out of 84 plant species included in this review, phytochemicals were isolated from only three plant species, namely, *Uromyrtus metrosideros, Flindersia oppositifolia*, and *Leionema ellipticum* (Table 2). A total of 19 compounds/secondary metabolites were isolated from these three plant species (Table 2), and these compounds belong to four different chemical groups (alkaloids, flavonoids, benzopyrans, and glucosides). For example, two new galloyl glucosides (galloyl-lawsoniaside A and

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 March 2024 doi:10.20944/preprints202403.0584.v1

uromyrtoside) and four known compounds were isolated from *Uromyrtus metrosideros* [114]. These six compounds were characterised using low and high-resolution mass spectrometry (L/HRMS) and Nuclear Magnetic Resonance (NMR) spectroscopy. All three studies involving three plants were conducted to identify pharmacological drug leads (*U. metrosideros* and *F. oppositifolia*) and solve the taxonomic discrepancies (*L. ellipticum*). They did not suggest their role in response to climatic stress factors.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 March 2024 doi:10.20944/preprints202403.0584.v1

Table 2. List of climate-affected Australian montane cloud forest plants studied for their phytochemical contents and bioactivity.

Botanical name	Medicinal uses	Number and major metabolites identified	Isolated Compounds	Chemical class	Biological Activities of compounds
Agathis atropurpurea	*Agathis* species are traditionally used to treat myalgia and headaches [52].	27 metabolites; major metabolites are α-pinene, α-copaene, bicyclogermacrene, δ-cadinene, phyllocladane, and 16-kaurene [115]	NA	Terpenoid	Antimicrobial, antibacterial, antiviral, anti-cancer activity (α-pinene) [116–118], antioxidant activity (α-copaene) [119]
Eucryphia wilkiei	NU	2 unknown metabolites [120]	NA	Flavonoid	NA
Cinnamomum propinquum	*Cinnamomum* species are most commonly used in traditional Chinese medicines to treat multiple disorders, including indigestion, microbial infections, and cough and cold [59].	40 metabolites; Major metabolites are *p*-cymene, α-pinene, and β-eudesmol [121]	NA	Terpenoid	Anti-cancer activity (*p*-cymene) [122], anti-allergic and anti-angiogenic effect (β-eudesmol) [123,124]
Cryptocarya bellendenkerana	NU	39 metabolites; major metabolites are α-pinene, limonene, β-phellandrene, *p*-cymene, viridiflorene, *E*-β-farnesene, α-copaene, β-and α-selinene, δ-cadinene, bicyclogermacrene, calamenene, and cubeban-11-ol [125].	NA		Antioxidant, antidiabetic, anticancer, anti-inflammatory (limonene) [126,127], anti-fungal (β-phellandrene) [128], antioxidant and antitumour properties (viridiflorene) [129,130], insect repellent (*E*-β-farnesene) [131] antioxidant activity (copaene) [119].
Leptospermum wooroonooran	*Leptospermum* species are traditionally used in Malaysia to relieve	45 metabolites; major metabolitesare α-pinene, β-pinene, sabinene, α-terpinene, γ-	NA		Reduce skeletal muscle atrophy (sabinene) [133], antibacterial and antibiofilm

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 March 2024 doi:10.20944/preprints202403.0584.v1

Botanical name	Medicinal uses	Number and major metabolites identified	Isolated Compounds	Chemical class	Biological Activities of compounds
	menstrual and stomach disorders [62,63].	terpinene, terpinen-4-ol and α-terpineol [132]			activities (terpinene-4-ol) [134]
Uromyrtus metrosideros	NU	27 metabolites; major metabolites are α-pinene, β-pinene, spathulenol and aromadendrene [135]	norbergenin, bergenin, (*6S,9R)*-*r*oseoside, (4*S*)-**α**-terpineol 8-*O*-β-D-(6-*O*-galloyl) glucopyranoside, galloyl-lawsoniaside A, and uromyrtoside [114]	Benzopyran, Glucoside,	Anti-inflammatory (galloyl-lawsoniaside A) [114]; reduced hypertension and allergic reaction (roseoside) [136,137]
Prumnopitys ladei	Fruits and bark of *Prunmnopitys* species are considered medicinal [70].	44-metabolites; major compounds are α-pinene, limonene, verbenone, and p-cymene. β-caryophyllene, caryophyllene oxide, spathulenol, and α-humulene [138]	NA		Antimicrobial, anticarcinogenic, anti-inflammatory, antioxidant, and local anesthetic effects (β-caryophyllene) [139–141]
Flindersia oppositifolia	NU	37 metabolites; major compounds are β-caryophyllene and bicyclogermacrene [142]; Identified 8 alkaloids from leaf [143].	pimentelamine A, pimentelamine B, pimentelamine C, 2-isoprenyl-*N*-*N*-dimethyltryptamine, 4-methylborreverine, borreverine, dimethylisoborreverine, quercitrin, and carpachromene [142]; harmalan, pimentelamine B, isoborreverine, skimmianine, kokusaginine, maculosidine, flindersiamine, 8-methoxy-*N*-methylflindersine [143].	Terpene, Alkaloid	Antiplasmodial (pimentelamine C) [144,145]
Leionema ellipticum	NU		3,4',5-trimethoxyflavone-7-*O*-α-rhamnoside, boropinol-B, and osthol [146]	Flavonoid	Neuroprotective (boropinol-B) [147,148]; anti-inflammatory (osthol) [149,150]

Chemical class for isolated chemicals were referred from human metabolome database (https://hmdb.ca); Abbreviations - NA: Not available; NU: Not used medicinally.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 March 2024 doi:10.20944/preprints202403.0584.v1

5. Pharmacological Activities of Isolated Phytochemicals of Climate-affected Plants in WTWHA

Studies have suggested that SMs, which function as plant defense mechanisms, possess intriguing pharmacological properties, including antioxidant and anti-inflammatory properties [151]. For instance, a novel galloyl-lawsoniaside A isolated from *U. metrosideros* leaf significantly suppressed pro-inflammatory cytokines, such as interferon-gamma and interleukins-17 (IL-17) and IL-18, and thus were identified as new anti-inflammatory drug-lead molecule [114]. Osthol isolated from *Leionema ellipticum* also showed anti-inflammatory activity [149,150]. A study by Yeshi *et al.* [151] analysed crude extracts from leaves of seven plant species endemic to WTWHA of FNQ. Five of seven plant species showed potent antioxidant and anti-inflammatory activities in *in-vitro* human peripheral blood cells (PBMCs) assay [151]. About 30 plant species growing in the WTWHA were reported as medicinal plants used for many years by indigenous communities to treat various diseases and ailments, including inflammation-related diseases [152]. Many metabolites identified through metabolomic studies (Table 2) were also studied for numerous biological properties (Table 2). Some major and bioactive metabolites were α-pinene, *p*-cymene, β-endemol, limonene, viridiflorene, E-β-farnesene, copaene, and β-caryophyllene (Table 2). Figure 6 shows some interesting structures of these isolated compounds. They showed a wide array of pharmacological activities, from anti-microbial to anti-cancer and anti-plasmodial properties. Of nine plant species listed in Table 2, four were tested for anti-inflammatory and anti-cancer properties, three each were tested for anti-microbial and antioxidant activities, two were tested for anti-allergic reactions, and the rest were tested for anti-diabetic, anti-malarial, and neuro-protective properties (one plant species each). For instance, galloyl-lawsoniaside A isolated from *U. metrosideros* leaf showed promising anti-inflammatory activity through significant suppression of pro-inflammatory cytokines, interferon-gamma (IFN-γ), and interleukin-17A (IL-17A) by phorbol myristate acetate/ionomycin (P/I)-activated cells [114]. Moreover, it also significantly suppressed the release of IL-8 by the anti-CD3/anti-CD28-activated cells [114]. There are increasing studies on identifying anti-inflammatory molecules by targeting the 5-lipoxygenase (5-LOX) pathway, as 5-LOX drives inflammation by producing inflammatory mediators, such as leukotrienes [153,154]. Osthol isolated from aerial parts of *Leionema ellipticum* showed selective inhibition of the 5-LOX pathway [146]. The anti-cancer/anti-tumor activity was mainly tested with crude extracts or essential oils by studying their inhibitory effect on tumor growth using tumor cell lines such as sarcoma 180 ascites tumor cells [129]. The anti-cancer activity was attributed to the major metabolite constituents, such as limonene, *p*-cymene, α-pinene, and viridiflorene (Table 2), and was not tested against the single compound. A few isolated compounds also exhibited anti-plasmodial activity. For example, pimentelamine C, isolated from the leaf of *Flindersia pimentaliana* showed moderate anti-plasmodial activity against *Plasmodium falciparum* with IC_{50} values of 3.6 ± 0.7 (against chloroquine-sensitive strain) and 2.7 ± 0.3 (against chloroquine-resistant strains) [144]. Figure 6 shows some interesting structures of these isolated compounds.

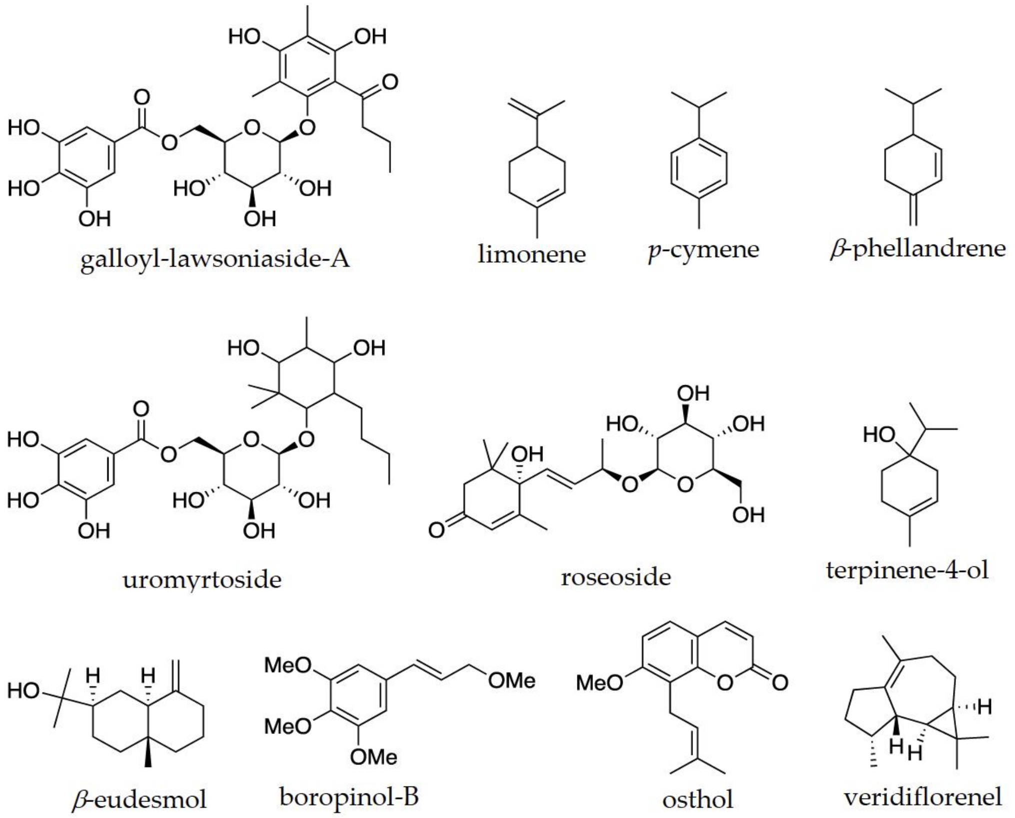

Figure 6. Chemical structure of bioactive compounds isolated/identified from the climate-affected Australian montane cloud forest plants (also used medicinally) in the Wet Tropics World Heritage Area, Queensland.

6. Metabolomics Approaches, Tools, and Techniques Used in Plant Metabolomics

Understanding plants' physiological and metabolomic responses to global change is key to identifying potential traits, including their genetic mutations and changes in their metabolomic pathways. Additionally, it is possible to predict potential changes in the composition of plant communities by assessing the ability of various plant species to adapt to environmental shifts [155,156]. Metabolites from living matters can be identified using i) isolation techniques and ii) metabolomics platforms. Metabolomics platforms, in general, rely on mass spectrometry (MS)-based techniques, namely capillary electrophoresis mass spectrometry (CE-MS), liquid chromatography-mass spectrometry (LC-MS), and gas chromatography-mass spectrometry (GC-MS) [157,158]. Two innovative technological methods that do not require the use of metabolite chromatography include Nuclear Magnetic Resonance (NMR) analysis of unrefined extracts and the direct inspection of unrefined extracts using Mass Spectrometry (MS), specifically either quadrupole (Q) TOF-MS or ultra-high-resolution Fourier transform ion cyclotron MS (FT-MS) [108], which are discussed in-depth in later sections. Compared to conventional methods in the postgenomic era, metabolomics analysis offers numerous advantages and potential applications [158]. It has various steps, as shown in Figure 5, including sample preparation, spectra processing, data analysis, and metabolite identification.

The NMR-based metabolomic analysis offers a potent, non-invasive method, delivering precise structural details about metabolites [159]. While metabolomic analysis using mass spectrometry is inherently destructive, it is highly sensitive and can detect traces of metabolites, and thus, it has gained more popularity [160]. Mass spectrometry (MS) methods are frequently integrated with chromatographic separation methods, including gas chromatography (GC) and liquid chromatography (LC) [160]. Since the metabolome is a complex mixture of many small molecules, chromatographic separation is necessary prior to ion detection, particularly to distinguish isobaric

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 March 2024 doi:10.20944/preprints202403.0584.v1

compounds with a similar mass. Alternatively, the direct-infusion mass spectrometry (DIMS) approach is applied to measure metabolites directly without a prior chromatographic separation [161]. Most of the plant-based metabolomics published studies so far use the Orbitrap or TOF (time-of-flight) equipment [162]. One of the main reasons for using TOF equipment could be due to its mass resolution values (i.e., 30,000–40,000) [163,164], and the resolution power is unaffected by chromatography acquisition rates [165–167]. On the contrary, Orbitrap mass spectrometers can rapidly acquire tandem MS spectra up to 240,000 mass resolution, and thus, they are mainly applied in the shotgun metabolomics [165,168,169].

The DIMS methodology has recently been expanded to swift, high-throughput fingerprinting techniques employing advanced mass spectrometers with high resolution, such as Fourier Transform Ion Cyclotron Resonance (FT-ICR) mass spectrometers (FT-ICR-MS) [165], its extensive usage in plant metabolomics greatly aids in understanding plant development, responses to both biotic and abiotic stresses, and the exploration of novel natural nutraceutical compounds [162,170]. Fourier Transform Ion Cyclotron Resonance mass spectrometers have a higher resolution power (10^5 to $>10^6$), mass accuracy (typically 0.1–2 ppm), and sensitivity [171,172]. For instance, FT-ICR-MS can analyse and evaluate approximately 50,000 molecular formulas in complex samples, such as plant-derived crude oils [173,174]. Another reason for widely using FT-ICR-MS is that this application has a wide range of ionisation sources, including electron spray ionisation (ESI), atmospheric pressure chemical ionization, and photoionization, thus, enabling analyses of different sample types [175]. For example, Shahbazya *et al.* [176] used FT-ICR-MS to study the response of thyme plants (*Thymus vulgaris)* to drought stress. The study identified galactose metabolism as the most significant for drought adaptive response in thyme. Other studies, including metabolomics changes in poplar species in response to salinity stress [177] and UV-B radiation, also applied the same technique [178].

Nevertheless, because metabolites exhibit various chemical properties and are found abundantly in various cells, no single analytical platform can encompass the entire metabolome. Therefore, multi-omics technology has enabled the exploration of genes and metabolites in response to various climatic stress factors, particularly by combining transcriptomics and metabolomics approaches. For instance, Wang *et al.*, [24], in their study about *Poa crymophila*, applied transcriptomics and metabolomics and identified the phenylpropanoid pathway as the main mechanism that facilitates this plant to survive against the unfavourable environment of Qinghai-Tibet Plateau. Liu *et al.*, [23] also applied a combination of transcriptomics with physiological analyses to understand the chilling response in pumpkins and found that α-linolenic acid biosynthesis was one of the key pathways in the response.

These instruments employ three types of approaches to characterize metabolites, namely, (i) targeted analysis, (ii) untargeted analysis, and (iii) metabolic fingerprinting [179]. Unlike the targeted approach (identify a set of targeted metabolites with reference to available standards), the untargeted approach generates a large volume and complex data requiring specialised computational methods, such as artificial intelligence (AI) and machine learning (ML) algorithms, to process and interpret data [179]. In contrast, metabolic fingerprinting or exometabolomics involves characterising extracellular metabolites (i.e., metabolic by-products of organisms produced in response to environmental factors in which they survive) [180,181]. For plant metabolomic profiling, 'ecometabolomics' is a commonly applied technique. The term ''ecometabolomics'' first appeared in the scientific literature in 2009 [34,182]. This study investigates how living organisms respond, acclimate, and adapt to environmental conditions by a nontargeted approach [86–88]. Metabolite identification can be achieved at four different metabolite standard initiative (MSI) levels. Metabolite standard initiative level-1 (MSI-1) is considered the highest level of identification as it identifies metabolites after comparing with their chemical standards [183,184]. Level 2 (MSI-2) and level-3 identifications are only putative, as metabolites (MSI-2) or metabolite class (MSI-3) are not compared to their chemical standards, whereas MSI level-4 (MSI-4) putatively annotates unknown metabolites [183,184].

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 March 2024 doi:10.20944/preprints202403.0584.v1

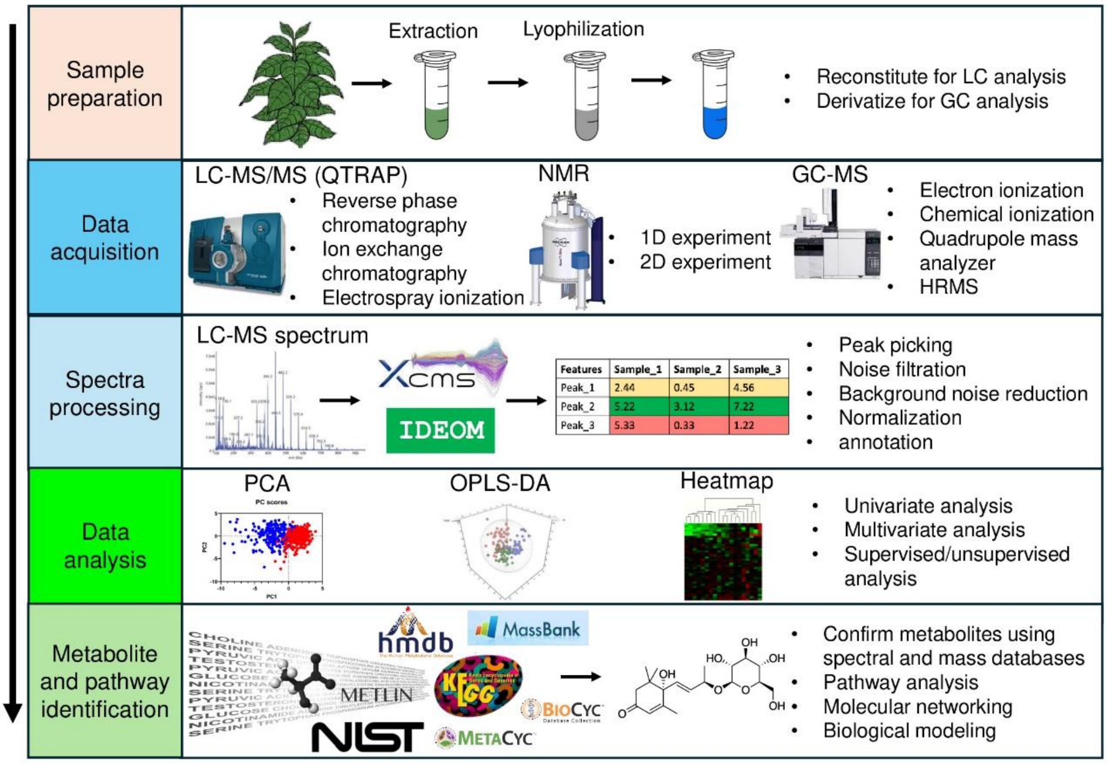

Figure 5. Common metabolomic workflow applied in plant metabolomics studies. The figure was adapted from Xu and Fu [185], and all databases' logos used in this figure were obtained from their respective websites. Abbreviations: - LC-MS: Liquid chromatography-mass spectrometry; NMR: Nuclear magnetic resonance; 1D: one dimensional; 2D: two dimensional; GC-MS: Gas chromatography-mass spectrometry; QTRAP: The Quadrupole Ion Trap; XCMS: eXtensible Computational Mass Spectrometry; HMDB: Human metabolome database; PCA: principal component analysis; OPLS-DA: Orthogonal Partial Least Squares Discriminant Analysis; NIST: National Institute of Standards and Technology; METLIN: Metabolite and chemical entity database. .

7. Conclusions and Future Directions

The Australian Tropical Montane Cloud Forest (TMCF), which lies in the Wet Tropics World Heritage Area in FNQ, has rich and unique biodiversity, with over 700 endemic plant species. The current study identified that 84 plant species were affected by climate change, with some species already being endangered in their natural habitat. Recent studies of 37 of these species predicted total loss of suitable habitat for five species by 2035 and seven species by 2085 if greenhouse gas emission (e.g., CO_2) into the atmosphere continues at the current speed. Recently, many powerful technologies have been developed, including omics techniques, bioimaging, and biosensor tools, which have been widely applied to understanding plants' physiology and metabolome and discovering novel metabolomic pathways in response to global climate change. However, our literature review revealed that these 84 Australian TMCF plants were scarcely studied for their biomolecules, and we understand little about their medicinal uses, chemical profiles, and biological functions. Of 84 species, 43 belong to 29 medicinally important genera with various medical properties, and only seven species were studied for their metabolite compositions. There is an urgent need for enhanced metabolomics studies of these least studied plants, given that they are at risk of significant habitat loss because of climate change. Additionally, it is urgent to understand and identify potential traits in these least studied plants, including possible genetic mutations that may have led to the change in the pattern of secondary metabolite accumulation and their metabolomic pathways in the adaptive response to climatic stress factors. Such studies will produce more data to holistically understand the interactive effect of climate change on the growth and fitness of these plants. This, in turn, would enable us to predict the adaptive response of plants specific to future climatic conditions and, thus, design the appropriate conservation measures to rescue those already identified as endangered and nearly threatened plant species.

Many metabolites reported from those plants that have already been studied have shown numerous pharmacological activities. Studies have also reported that plants produce defensive/protective secondary metabolites in response to climate change. Most of these defensive secondary metabolites are antioxidative/anti-inflammatory. Therefore, Australian TMCF plants also present an exciting avenue to discover novel pharmaceutical leads.

Author Contributions: Conceptualization, P.W., and K.Y.; writing—original draft preparation, N.G., and K.Y; writing—review and editing, P.W. and D.C.; supervision, P.W., and D.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: Not Applicable.

Acknowledgments: We acknowledge funding support from the FNQH grant and the NHMRC Ideas grant (APP1183323) awarded to P.W and the Ian Potter Foundation grant awarded to D.C. Authors sincerely acknowledge the office of Wet Tropics Management Authority office, state of Queensland for generating and allowing us to use a map of the Wet Tropics bioregion depicting WTWHA in this study.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Arnell, N.W.; Lowe, J.A.; Challinor, A.J.; Osborn, T.J. Global and regional impacts of climate change at different levels of global temperature increase. *Climatic Change* **2019**, *155*, 377-391.
2. Cohen, I.; Zandalinas, S.I.; Huck, C.; Fritschi, F.B.; Mittler, R. Meta-analysis of drought and heat stress combination impact on crop yield and yield components. *Physiologia Plantarum* **2021**, *171*, 66-76.
3. QLD. Climate change in the Far North Queensland region. **2019**.
4. Morris, R.J. Anthropogenic impacts on tropical forest biodiversity: a network structure and ecosystem functioning perspective. *Philosophical Transactions of the Royal Society B: Biological Sciences* **2010**, *365*, 3709-3718, doi:doi:10.1098/rstb.2010.0273.
5. Hoyle, G.L.; Sommerville, K.D.; Liyanage, G.S.; Worboys, S.; Guja, L.K.; Stevens, A.V.; Crayn, D.M. Seed banking is more applicable to the preservation of tropical montane flora than previously assumed: A review and cloud forest case study. *Global Ecology and Conservation* **2023**, *47*, doi:10.1016/j.gecco.2023.e02627.
6. Helmer, E.H.; Gerson, E.A.; Baggett, L.S.; Bird, B.J.; Ruzycki, T.S.; Voggesser, S.M. Neotropical cloud forests and páramo to contract and dry from declines in cloud immersion and frost. *PLOS ONE* **2019**, *14*, e0213155, doi:10.1371/journal.pone.0213155.
7. Costion, C.M.; Simpson, L.; Pert, P.L.; Carlsen, M.M.; John Kress, W.; Crayn, D. Will tropical mountaintop plant species survive climate change? Identifying key knowledge gaps using species distribution modelling in Australia. *Biological Conservation* **2015**, *191*, 322-330, doi:10.1016/j.biocon.2015.07.022.
8. Karger, D.N.; Kessler, M.; Lehnert, M.; Jetz, W. Limited protection and ongoing loss of tropical cloud forest biodiversity and ecosystems worldwide. *Nature Ecology & Evolution* **2021**, *5*, 854-862, doi:10.1038/s41559-021-01450-y.
9. Still, C.J.; Foster, P.N.; Schneider, S.H. Simulating the effects of climate change on tropical montane cloud forests. *Nature* **1999**, *398*, 608-610, doi:10.1038/19293.
10. Foster, P. The potential negative impacts of global climate change on tropical montane cloud forests. *Earth-Science Reviews* **2001**, *55*, 73-106, doi:https://doi.org/10.1016/S0012-8252(01)00056-3.
11. Hu, J.; Riveros-Iregui, D.A. Life in the clouds: are tropical montane cloud forests responding to changes in climate? *Oecologia* **2016**, *180*, 1061-1073, doi:10.1007/s00442-015-3533-x.
12. Williams, S.E.; Bolitho, E.E.; Fox, S. Climate change in Australian tropical rainforests: an impending environmental catastrophe. *Proc. R. Soc. B Biol. Sci.* **2003**, *270*, 1887-1892, doi:10.1098/rspb.2003.2464.
13. Williams, S.E.; Bolitho, E.E.; Fox, S. Climate change in Australian tropical rainforests: an impending environmental catastrophe. *Proc Biol Sci* **2003**, *270*, 1887-1892, doi:10.1098/rspb.2003.2464.
14. Le Saout, S.; Hoffmann, M.; Shi, Y.; Hughes, A.; Bernard, C.; Brooks, T.M.; Bertzky, B.; Butchart, S.H.; Stuart, S.N.; Badman, T.; et al. Conservation. Protected areas and effective biodiversity conservation. *Science* **2013**, *342*, 803-805, doi:10.1126/science.1239268.
15. UNESCO World Heritage Convention. Wet Tropics of Queensland. Available online: https://whc.unesco.org/en/list/486/ (accessed on August 6 2023).

16. Weber, E.T.; Catterall, C.P.; Locke, J.; Ota, L.S.; Prideaux, B.; Shirreffs, L.; Talbot, L.; Gordon, I.J. Managing a World Heritage Site in the Face of Climate Change: A Case Study of the Wet Tropics in Northern Queensland. *Earth* **2021**, *2*, 248-271.
17. Grossmann, G.; Krebs, M.; Maizel, A.; Stahl, Y.; Vermeer, J.E.M.; Ott, T. Green light for quantitative live-cell imaging in plants. *Journal of Cell Science* **2018**, *131*, doi:10.1242/jcs.209270.
18. Awlia, M.; Alshareef, N.; Saber, N.; Korte, A.; Oakey, H.; Panzarová, K.; Trtílek, M.; Negrão, S.; Tester, M.; Julkowska, M.M. Genetic mapping of the early responses to salt stress in Arabidopsis thaliana. *The Plant Journal* **2021**, *107*, 544-563.
19. Berg, C.S.; Brown, J.L.; Weber, J.J. An examination of climate-driven flowering-time shifts at large spatial scales over 153 years in a common weedy annual. *American journal of botany* **2019**, *106*, 1435-1443.
20. Cortijo, S.; Charoensawan, V.; Brestovitsky, A.; Buning, R.; Ravarani, C.; Rhodes, D.; van Noort, J.; Jaeger, K.E.; Wigge, P.A. Transcriptional regulation of the ambient temperature response by H2A. Z nucleosomes and HSF1 transcription factors in Arabidopsis. *Molecular plant* **2017**, *10*, 1258-1273.
21. Sriden, N.; Charoensawan, V. Large-scale comparative transcriptomic analysis of temperature-responsive genes in Arabidopsis thaliana. *Plant Molecular Biology* **2022**, *110*, 425-443.
22. Zhao, Y.; Antoniou-Kourounioti, R.L.; Calder, G.; Dean, C.; Howard, M. Temperature-dependent growth contributes to long-term cold sensing. *Nature* **2020**, *583*, 825-829.
23. Liu, W.; Zhang, R.; Xiang, C.; Zhang, R.; Wang, Q.; Wang, T.; Li, X.; Lu, X.; Gao, S.; Liu, Z.; et al. Transcriptomic and Physiological Analysis Reveal That alpha-Linolenic Acid Biosynthesis Responds to Early Chilling Tolerance in Pumpkin Rootstock Varieties. *Front Plant Sci* **2021**, *12*, 669565, doi:10.3389/fpls.2021.669565.
24. Wang, Y.; Li, X.Y.; Li, C.X.; He, Y.; Hou, X.Y.; Ma, X.R. The Regulation of Adaptation to Cold and Drought Stresses in Poa crymophila Keng Revealed by Integrative Transcriptomics and Metabolomics Analysis. *Front Plant Sci* **2021**, *12*, 631117, doi:10.3389/fpls.2021.631117.
25. Sun, Y.; Alseekh, S.; Fernie, A.R. Plant secondary metabolic responses to global climate change: A meta-analysis in medicinal and aromatic plants. *Global Change Biology* **2023**, *29*, 477-504, doi:https://doi.org/10.1111/gcb.16484.
26. Hodges, M.; Dellero, Y.; Keech, O.; Betti, M.; Raghavendra, A.S.; Sage, R.; Zhu, X.-G.; Allen, D.K.; Weber, A.P. Perspectives for a better understanding of the metabolic integration of photorespiration within a complex plant primary metabolism network. *Journal of Experimental Botany* **2016**, *67*, 3015-3026.
27. Ncube, B.; Van Staden, J. Tilting plant metabolism for improved metabolite biosynthesis and enhanced human benefit. *Molecules* **2015**, *20*, 12698-12731.
28. Yang, L.; Wen, K.-S.; Ruan, X.; Zhao, Y.-X.; Wei, F.; Wang, Q. Response of plant secondary metabolites to environmental factors. *Molecules* **2018**, *23*, 762.
29. Peng, M.; Shahzad, R.; Gul, A.; Subthain, H.; Shen, S.; Lei, L.; Zheng, Z.; Zhou, J.; Lu, D.; Wang, S. Differentially evolved glucosyltransferases determine natural variation of rice flavone accumulation and UV-tolerance. *Nature communications* **2017**, *8*, 1975.
30. Tohge, T.; Fernie, A.R. Leveraging natural variance towards enhanced understanding of phytochemical sunscreens. *Trends in plant science* **2017**, *22*, 308-315.
31. Boncan, D.A.T.; Tsang, S.S.; Li, C.; Lee, I.H.; Lam, H.-M.; Chan, T.-F.; Hui, J.H. Terpenes and terpenoids in plants: Interactions with environment and insects. *Int. J. Mol. Sci.* **2020**, *21*, 7382.
32. Matsuura, H.N.; Rau, M.R.; Fett-Neto, A.G. Oxidative stress and production of bioactive monoterpene indole alkaloids: biotechnological implications. *Biotechnology letters* **2014**, *36*, 191-200.
33. Bakhtiari, M.; Rasmann, S. Variation in below-to aboveground systemic induction of glucosinolates mediates plant fitness consequences under herbivore attack. *Journal of chemical ecology* **2020**, *46*, 317-329.
34. Sardans, J.; Gargallo-Garriga, A.; Urban, O.; Klem, K.; Walker, T.W.N.; Holub, P.; Janssens, I.A.; Peñuelas, J. Ecometabolomics for a Better Understanding of Plant Responses and Acclimation to Abiotic Factors Linked to Global Change. *Metabolites* **2020**, *10*, doi:10.3390/metabo10060239.
35. Ma, A.; Qi, X. Mining plant metabolomes: Methods, applications, and perspectives. *Plant Commun* **2021**, *2*, 100238, doi:10.1016/j.xplc.2021.100238.
36. Oh, S.-W.; Imran, M.; Kim, E.-H.; Park, S.-Y.; Lee, S.-G.; Park, H.-M.; Jung, J.-W.; Ryu, T.-H. Approach strategies and application of metabolomics to biotechnology in plants. *Frontiers in Plant Science* **2023**, *14*, doi:10.3389/fpls.2023.1192235.
37. Colin, L.; Martin-Arevalillo, R.; Bovio, S.; Bauer, A.; Vernoux, T.; Caillaud, M.-C.; Landrein, B.; Jaillais, Y. Imaging the living plant cell: From probes to quantification. *The Plant Cell* **2021**, *34*, 247-272, doi:10.1093/plcell/koab237.
38. Hsiao, A.-S.; Huang, J.-Y. Bioimaging tools move plant physiology studies forward. *Frontiers in Plant Science* **2022**, *13*, doi:10.3389/fpls.2022.976627.
39. Uslu, V.V.; Grossmann, G. The biosensor toolbox for plant developmental biology. *Current Opinion in Plant Biology* **2016**, *29*, 138-147, doi:https://doi.org/10.1016/j.pbi.2015.12.001.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 March 2024 doi:10.20944/preprints202403.0584.v1

40. Gamalero, E.; Bona, E.; Glick, B.R. Current Techniques to Study Beneficial Plant-Microbe Interactions. *Microorganisms* **2022**, *10*, doi:10.3390/microorganisms10071380.
41. Belbin, L.; Wallis, E.; Hobern, D.; Zerger, A. The Atlas of Living Australia: History, current state and future directions. Biodiversity Data Journal 9: e65023. Available online: (accessed on September 19).
42. Zich, F.A.; Hyland, B.P.M.; Whiffin, T.; Kerrigan, R.A. Australian Tropical Rainforest Plants, Edition 8. **2020**.
43. Crayn, D.; Worboys, S. Personal communication. **2023**.
44. APC. Australian Plant Census IBIS database, Centre for Australian National Biodiversity Research, Council of Heads of Australasian Herbaria. **2024**.
45. WFO. World Flora Online. Version 2023.03. **2023**, doi:https://doi.org/10.5281/zenodo.7460141.
46. CSIRO. *CSIRO Annual Report 2010-11*; ACT: Australia, 2011; pp. 1-176.
47. E., R. Modelling the vulnerability of endemic montane flora to climate change in the Australian Wet Tropics. MSc thesis. Imperial College London, UK, 2018.
48. Roeble, E. Modelling the vulnerability of endemic montane flora to climate change in the Australian Wet Tropics. Imperial College London, UK, 2018.
49. Armijos, C.; Gilardoni, G.; Amay, L.; Lozano, A.; Bracco, F.; Ramirez, J.; Bec, N.; Larroque, C.; Finzi, P.V.; Vidari, G. Phytochemical and ethnomedicinal study of Huperzia species used in the traditional medicine of Saraguros in Southern Ecuador; AChE and MAO inhibitory activity. *Journal of Ethnopharmacology* **2016**, *193*, 546-554, doi:https://doi.org/10.1016/j.jep.2016.09.049.
50. Hamdy, S.A.; El Hefnawy, H.M.; Azzam, S.M.; Aboutabl, E.A. Botanical and genetic characterization of Hydrocotyle umbellata L. cultivated in Egypt. *Bulletin of Faculty of Pharmacy, Cairo University* **2018**, *56*, 46-53, doi:https://doi.org/10.1016/j.bfopcu.2018.03.006.
51. Śliwińska, A.; Figat, R.; Zgadzaj, A.; Wileńska, B.; Misicka, A.; Nałęcz-Jawecki, G.; Pietrosiuk, A.; Sykłowska-Baranek, K. Polyscias filicifolia (Araliaceae) Hairy Roots with Antigenotoxic and Anti-Photogenotoxic Activity. *Molecules* **2021**, *27*, doi:10.3390/molecules27010186.
52. Ho, Y.T.; Liu, I.H.; Chang, S.T.; Wang, S.Y.; Chang, H.T. In Vitro and In Vivo Antimelanogenesis Effects of Leaf Essential Oil from Agathis dammara. *Pharmaceutics* **2023**, *15*, doi:10.3390/pharmaceutics15092269.
53. Espirito Santo, B.; Santana, L.F.; Kato Junior, W.H.; de Araújo, F.O.; Bogo, D.; Freitas, K.C.; Guimarães, R.C.A.; Hiane, P.A.; Pott, A.; Filiú, W.F.O.; et al. Medicinal Potential of Garcinia Species and Their Compounds. *Molecules* **2020**, *25*, doi:10.3390/molecules25194513.
54. Rauf, A.; Uddin, G.; Patel, S.; Khan, A.; Halim, S.A.; Bawazeer, S.; Ahmad, K.; Muhammad, N.; Mubarak, M.S. Diospyros, an under-utilized, multi-purpose plant genus: A review. *Biomedicine & Pharmacotherapy* **2017**, *91*, 714-730, doi:https://doi.org/10.1016/j.biopha.2017.05.012.
55. Sudradjat, S.E.; Timotius, K.H. Pharmacological properties and phytochemical components of Elaeocarpus: A comparative study. *Phytomedicine Plus* **2022**, *2*, 100365, doi:https://doi.org/10.1016/j.phyplu.2022.100365.
56. Nisar, M.; Ali, S.; Qaisar, M.; Gilani, S.N.; Shah, M.R.; Khan, I.; Ali, G. Antifungal activity of bioactive constituents and bark extracts of Rhododendron arboreum. ||| *Bangladesh Journal of Pharmacology* **2013**, *8*, 218-222.
57. Sadgrove, N.J.; Padilla-González, G.F.; Telford, I.R.H.; Greatrex, B.W.; Jones, G.L.; Andrew, R.; Bruhl, J.J.; Langat, M.K.; Melnikovova, I.; Fernandez-Cusimamani, E. Prostanthera (Lamiaceae) as a 'Cradle of Incense': Chemophenetics of Rare Essential Oils from Both New and Forgotten Australian 'Mint Bush' Species. *Plants (Basel)* **2020**, *9*, doi:10.3390/plants9111570.
58. Lassak, E.V.; McCarthy, T. Australian medicinal plants. *(No Title)* **1983**.
59. Wang, J.; Su, B.; Jiang, H.; Cui, N.; Yu, Z.; Yang, Y.; Sun, Y. Traditional uses, phytochemistry and pharmacological activities of the genus Cinnamomum (Lauraceae): A review. *Fitoterapia* **2020**, *146*, 104675, doi:https://doi.org/10.1016/j.fitote.2020.104675.
60. Salleh, W.M.N.H.W.; Farediah, A.; Khong, H.Y.; Zulkifli, R. A Review of Endiandric Acid Analogues. *International Journal of Pharmacognosy and Phytochemical Research* **2015**, *7*, 844-856.
61. Cock, I.E. Medicinal and aromatic plants—Australia. In Ethnopharmacology Section, Biological, Physiological and Health Sciences, Encyclopedia of Life Support Systems (EOLSS), Developed under the Auspices of the UNESCO; EOLSS Publishers: Oxford, UK, 2011. Available online: http://www.eolss.net (accessed on 30 April 2022).
62. Caputo, L.; Smeriglio, A.; Trombetta, D.; Cornara, L.; Trevena, G.; Valussi, M.; Fratianni, F.; De Feo, V.; Nazzaro, F. Chemical Composition and Biological Activities of the Essential Oils of Leptospermum petersonii and Eucalyptus gunnii. *Front Microbiol* **2020**, *11*, 409, doi:10.3389/fmicb.2020.00409.
63. Riley, M. *Māori healing and herbal: New Zealand ethnobotanical sourcebook*; Viking Sevenseas NZ: 1994.
64. Oktavia, D.; Pratiwi, S.D.; Munawaroh, S.; Hikmat, A.; Hilwan, I. The potential of medicinal plants from heath forest: Local knowledge from Kelubi Village, Belitung Island, Indonesia. *Biodiversitas Journal of Biological Diversity* **2022**, *23*, doi:10.13057/biodiv/d230731.
65. Sharifi-Rad, J.; Quispe, C.; Bouyahya, A.; El Menyiy, N.; El Omari, N.; Shahinozzaman, M.; Ara Haque Ovey, M.; Koirala, N.; Panthi, M.; Ertani, A.; et al. Ethnobotany, Phytochemistry, Biological Activities, and

Health-Promoting Effects of the Genus Bulbophyllum. *Evid Based Complement Alternat Med* **2022**, *2022*, 6727609, doi:10.1155/2022/6727609.
66. Cakova, V.; Bonte, F.; Lobstein, A. Dendrobium: Sources of Active Ingredients to Treat Age-Related Pathologies. *Aging Dis* **2017**, *8*, 827-849, doi:10.14336/ad.2017.0214.
67. Liang, W.; Guo, X.; Nagle, D.G.; Zhang, W.-D.; Tian, X.-H. Genus Liparis: A review of its traditional uses in China, phytochemistry and pharmacology. *Journal of Ethnopharmacology* **2019**, *234*, 154-171, doi:https://doi.org/10.1016/j.jep.2019.01.021.
68. Ware, I.; Franke, K.; Hussain, H.; Morgan, I.; Rennert, R.; Wessjohann, L.A. Bioactive Phenolic Compounds from Peperomia obtusifolia. *Molecules* **2022**, *27*, doi:10.3390/molecules27144363.
69. Al-Madhagi, W.M.; Mohd Hashim, N.; Awad Ali, N.A.; Alhadi, A.A.; Abdul Halim, S.N.; Othman, R. - Chemical profiling and biological activity of Peperomia blanda (Jacq.) Kunth. *PeerJ* **2018**, *6*, e4839, doi:10.7717/peerj.4839.
70. Inostroza-Blancheteau, C.; Sandoval, Y.; Reyes-Díaz, M.; Tighe-Neira, R.; González-Villagra, J. Phytochemical characterization and antioxidant properties of Prumnopitys andina fruits in different ripening stages in southern Chile. *Chilean journal of agricultural research* **2022**, *82*, 285-293, doi:10.4067/s0718-58392022000200285.
71. Tlau, L.; Lalawmpuii, L. Commonly used medicinal plants in N. Mualcheng, Mizoram, India. *Science Vision* **2020**, *20*, 156-161.
72. Ray, S.; Saini, M.K. Impending threats to the plants with medicinal value in the Eastern Himalayas Region: An analysis on the alternatives to its non-availability. *Phytomedicine Plus* **2022**, *2*, 100151.
73. Cock, I.E. Medicinal and aromatic plants–Australia. *Ethnopharmacology, Encyclopedia of Life Support Systems (EOLSS)* **2011**.
74. Palombo, E.A.; Semple, S.J. Antibacterial activity of traditional Australian medicinal plants. *Journal of ethnopharmacology* **2001**, *77*, 151-157.
75. Awang-Jamil, Z.; Basri, A.; Ahmad, N.; Taha, H. Phytochemical analysis, antimicrobial and antioxidant activities of Aidia borneensis leaf extracts. *Journal of Applied Biology & Biotechnology* **2019**, *7*, doi:10.7324/JABB.2019.70515.
76. Singh, B.; Sharma, R.A. Indian Morinda species: A review. *Phytotherapy Research* **2020**, *34*, 924-1007, doi:https://doi.org/10.1002/ptr.6579.
77. Baliga, M.S.; Kurian, P.J. Ixora coccinea Linn.: Traditional uses, phytochemistry and pharmacology. *Chinese Journal of Integrative Medicine* **2012**, *18*, 72-79, doi:10.1007/s11655-011-0881-3.
78. Hossain, M.J.; Maliha, F.; Hawlader, M.B.; Farzana, M.; Rashid, M.A. Ethnomedicinal uses, phytochemistry, pharmacology and toxicological aspects of genus Wendlandia: an overview. *Journal of Bangladesh Academy of Sciences* **2023**.
79. Chidambaram, K.; Alqahtani, T.; Alghazwani, Y.; Aldahish, A.; Annadurai, S.; Venkatesan, K.; Dhandapani, K.; Thilagam, E.; Venkatesan, K.; Paulsamy, P.; et al. Medicinal Plants of Solanum Species: The Promising Sources of Phyto-Insecticidal Compounds. *J Trop Med* **2022**, *2022*, 4952221, doi:10.1155/2022/4952221.
80. Badoni, R.; Semwal, D.K.; Kothiyal, S.K.; Rawat, U. Chemical constituents and biological applications of the genus Symplocos. *J Asian Nat Prod Res* **2010**, *12*, 1069-1080, doi:10.1080/10286020.2010.532789.
81. Ahmad, R.; Khairul Nizam Mazlan, M.; Firdaus Abdul Aziz, A.; Mohd Gazzali, A.; Amir Rawa, M.S.; Wahab, H.A. Phaleria macrocarpa (Scheff.) Boerl.: An updated review of pharmacological effects, toxicity studies, and separation techniques. *Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society* **2023**, *31*, 874-888, doi:10.1016/j.jsps.2023.04.006.
82. Mohanty, S. Bioactive properties of Australian native fruits, *Tasmannia lanceolata* and *Terminalia ferdinandiana*: The Characterization of their Active Compounds. Griffith University Australia 2016.
83. POWO. Plants of the World Online. Facilitated by the Royal Botanic Gardens, Kew. Published on the Internet; http://www.plantsoftheworldonline.org/. **2023**.
84. Jones, D.L.; Hopley, T.; Duffy, S.M. Australian Tropical Rainforest Orchids. **2010**.
85. QLD. Nature Conservation Act 1992. **2017**.
86. Rivas-Ubach, A.; Pérez-Trujillo, M.; Sardans, J.; Gargallo-Garriga, A.; Parella, T.; Peñuelas, J. Ecometabolomics: optimized NMR-based method. Methods Ecol. Evol. 4, 464–473. **2013**.
87. Rivas-Ubach, A.; Peñuelas, J.; Hódar, J.A.; Oravec, M.; Paša-Tolić, L.; Urban, O.; Sardans, J. We are what we eat: A stoichiometric and ecometabolomic study of caterpillars feeding on two pine subspecies of Pinus sylvestris. *Int. J. Mol. Sci.* **2018**, *20*, 59.
88. Allevato, D.M.; Kiyota, E.; Mazzafera, P.; Nixon, K.C. Ecometabolomic analysis of wild populations of Pilocarpus pennatifolius (Rutaceae) using unimodal analyses. *Frontiers in plant science* **2019**, *10*, 258.
89. Berini, J.L.; Brockman, S.A.; Hegeman, A.D.; Reich, P.B.; Muthukrishnan, R.; Montgomery, R.A.; Forester, J.D. Combinations of abiotic factors differentially alter production of plant secondary metabolites in five woody plant species in the boreal-temperate transition zone. *Frontiers in plant science* **2018**, *9*, 1257.

90. Steinbauer, M.J.; Grytnes, J.-A.; Jurasinski, G.; Kulonen, A.; Lenoir, J.; Pauli, H.; Rixen, C.; Winkler, M.; Bardy-Durchhalter, M.; Barni, E. Accelerated increase in plant species richness on mountain summits is linked to warming. *Nature* **2018**, *556*, 231-234.
91. Lavola, A.; Julkunen-Tiitto, R.; Aphalo, P.; de la Rosa, T.; Lehto, T. The effect of UV-B radiation on UV-absorbing secondary metabolites in birch seedlings grown under simulated forest soil conditions. *The New Phytologist* **1997**, *137*, 617-621.
92. Salam, U.; Ullah, S.; Tang, Z.H.; Elateeq, A.A.; Khan, Y.; Khan, J.; Khan, A.; Ali, S. Plant Metabolomics: An Overview of the Role of Primary and Secondary Metabolites against Different Environmental Stress Factors. *Life (Basel)* **2023**, *13*, doi:10.3390/life13030706.
93. Sallas, L.; Luomala, E.-M.; Utriainen, J.; Kainulainen, P.; Holopainen, J.K. Contrasting effects of elevated carbon dioxide concentration and temperature on Rubisco activity, chlorophyll fluorescence, needle ultrastructure and secondary metabolites in conifer seedlings. *Tree Physiology* **2003**, *23*, 97-108.
94. Večeřová, K.; Klem, K.; Veselá, B.; Holub, P.; Grace, J.; Urban, O. Combined Effect of Altitude, Season and Light on the Accumulation of Extractable Terpenes in Norway Spruce Needles. *Forests* **2021**, *12*, doi:10.3390/f12121737.
95. Yeshi, K.; Crayn, D.; Ritmejeryte, E.; Wangchuk, P. Plant Secondary Metabolites Produced in Response to Abiotic Stresses Has Potential Application in Pharmaceutical Product Development. *Molecules* **2022**, *27*, doi:10.3390/molecules27010313.
96. Pinto, D.M.; Blande, J.D.; Souza, S.R.; Nerg, A.M.; Holopainen, J.K. Plant volatile organic compounds (VOCs) in ozone (O3) polluted atmospheres: the ecological effects. *J Chem Ecol* **2010**, *36*, 22-34, doi:10.1007/s10886-009-9732-3.
97. Schneider, G.F.; Coley, P.D.; Younkin, G.C.; Forrister, D.L.; Mills, A.G.; Kursar, T.A. Phenolics lie at the centre of functional versatility in the responses of two phytochemically diverse tropical trees to canopy thinning. *J Exp Bot* **2019**, *70*, 5853-5864, doi:10.1093/jxb/erz308.
98. Pinasseau, L.; Vallverdu-Queralt, A.; Verbaere, A.; Roques, M.; Meudec, E.; Le Cunff, L.; Peros, J.P.; Ageorges, A.; Sommerer, N.; Boulet, J.C.; et al. Cultivar Diversity of Grape Skin Polyphenol Composition and Changes in Response to Drought Investigated by LC-MS Based Metabolomics. *Front Plant Sci* **2017**, *8*, 1826, doi:10.3389/fpls.2017.01826.
99. Sampaio, B.L.; Edrada-Ebel, R.; Da Costa, F.B. Effect of the environment on the secondary metabolic profile of Tithonia diversifolia: a model for environmental metabolomics of plants. *Sci* **2016**, *6*, 29265.
100. Niinemets, Ü. Uncovering the hidden facets of drought stress: secondary metabolites make the difference. *Tree Physiology* **2016**, *36*, 129-132.
101. Afzal, S.F.; Yar, A.K.; Ullah, R.H.; Ali, B.G.; Ali, J.S.; Ahmad, J.S.; Fu, S. Impact of drought stress on active secondary metabolite production in Cichorium intybus roots. *J Appl Environ Biol Sci* **2017**, *7*, 39-43.
102. Punia, H.; Tokas, J.; Malik, A.; Bajguz, A.; El-Sheikh, M.A.; Ahmad, P. Ascorbate-Glutathione Oxidant Scavengers, Metabolome Analysis and Adaptation Mechanisms of Ion Exclusion in Sorghum under Salt Stress. *Int J Mol Sci* **2021**, *22*, doi:10.3390/ijms222413249.
103. Singiri, J.R.; Swetha, B.; Sikron-persi, N.; Grafi, G. Differential response to single and combined salt and heat stresses: Impact on accumulation of proteins and metabolites in dead pericarps of Brassica juncea. *Int. J. Mol. Sci.* **2021**, *22*, doi:10.3390/ijms22137076.
104. Munns, R.; Gilliham, M. Salinity tolerance of crops–what is the cost? *New phytologist* **2015**, *208*, 668-673.
105. Goche, T.; Shargie, N.G.; Cummins, I.; Brown, A.P.; Chivasa, S.; Ngara, R. Comparative physiological and root proteome analyses of two sorghum varieties responding to water limitation. *Sci. Rep.* **2020**, *10*, 11835.
106. Xiao, Q.; Mu, X.; Liu, J.; Li, B.; Liu, H.; Zhang, B.; Xiao, P. Plant metabolomics: a new strategy and tool for quality evaluation of Chinese medicinal materials. *Chinese Medicine* **2022**, *17*, 45, doi:10.1186/s13020-022-00601-y.
107. Guy, C.; Kopka, J.; Moritz, T. Plant metabolomics coming of age. *Physiol Plant* **2008**, *132*, 113-116, doi:10.1111/j.1399-3054.2007.01020.x.
108. Hall, R.; Beale, M.; Fiehn, O.; Hardy, N.; Sumner, L.; Bino, R. Plant metabolomics: the missing link in functional genomics strategies. *Plant Cell* **2002**, *14*, 1437-1440, doi:10.1105/tpc.140720.
109. Neilson, E.H.; Goodger, J.Q.; Woodrow, I.E.; Møller, B.L. Plant chemical defense: at what cost? *Trends in plant science* **2013**, *18*, 250-258.
110. Kesselmeier, J.; Staudt, M. Biogenic volatile organic compounds (VOC): an overview on emission, physiology and ecology. *Journal of atmospheric chemistry* **1999**, *33*, 23-88.
111. Pichersky, E.; Gang, D.R. Genetics and biochemistry of secondary metabolites in plants: an evolutionary perspective. *Trends Plant Sci* **2000**, *5*, 439-445, doi:10.1016/s1360-1385(00)01741-6.
112. Fiehn, O. Combining genomics, metabolome analysis, and biochemical modelling to understand metabolic networks. *Comp Funct Genomics* **2001**, *2*, 155-168, doi:10.1002/cfg.82.
113. Kim, H.K.; Verpoorte, R. Sample preparation for plant metabolomics. *Phytochem Anal* **2010**, *21*, 4-13, doi:10.1002/pca.1188.

114. Ritmejeryte, E.; Ryan, R.Y.M.; Byatt, B.J.; Peck, Y.; Yeshi, K.; Daly, N.L.; Zhao, G.; Crayn, D.; Loukas, A.; Pyne, S.G.; et al. Anti-inflammatory properties of novel galloyl glucosides isolated from the Australian tropical plant Uromyrtus metrosideros. *Chem Biol Interact* **2022**, *368*, 110124, doi:10.1016/j.cbi.2022.110124.
115. Garrison, M.S.; Irvine, A.K.; Setzer, W.N. Chemical composition of the resin essential oil from Agathis atropurpurea from North Queensland, Australia. *Am. J. Essent. Oils Nat. Prod* **2016**, *4*, 4-5.
116. Risner, D.; Marco, M.L.; Pace, S.A.; Spang, E.S. The Potential Production of the Bioactive Compound Pinene Using Whey Permeate. *Processes* **2020**, *8*, 263.
117. Salehi, B.; Upadhyay, S.; Erdogan Orhan, I.; Kumar Jugran, A.; S, L.D.J.; D, A.D.; Sharopov, F.; Taheri, Y.; Martins, N.; Baghalpour, N.; et al. Therapeutic Potential of α- and β-Pinene: A Miracle Gift of Nature. *Biomolecules* **2019**, *9*, doi:10.3390/biom9110738.
118. Rivas da Silva, A.C.; Lopes, P.M.; Barros de Azevedo, M.M.; Costa, D.C.; Alviano, C.S.; Alviano, D.S. Biological activities of α-pinene and β-pinene enantiomers. *Molecules* **2012**, *17*, 6305-6316, doi:10.3390/molecules17066305.
119. Türkez, H.; Celik, K.; Toğar, B. Effects of copaene, a tricyclic sesquiterpene, on human lymphocytes cells in vitro. *Cytotechnology* **2014**, *66*, 597-603, doi:10.1007/s10616-013-9611-1.
120. Wollenweber, E.; Dörr, M.; Rozefelds, A.C.; Minchin, P.; Forster, P.I. Variation in flavonoid exudates in Eucryphia species from Australia and South America. *Biochemical Systematics and Ecology* **2000**, *28*, 111-118.
121. Brophy, J.J.; Goldsack, R.J.; Forster, P.I. The Leaf Oils of the Australian Species ofCinnamomum(Lauraceae). *Journal of Essential Oil Research* **2001**, *13*, 332-335, doi:10.1080/10412905.2001.9712225.
122. Balahbib, A.; El Omari, N.; Hachlafi, N.E.L.; Lakhdar, F.; El Menyiy, N.; Salhi, N.; Mrabti, H.N.; Bakrim, S.; Zengin, G.; Bouyahya, A. Health beneficial and pharmacological properties of p-cymene. *Food and Chemical Toxicology* **2021**, *153*, 112259, doi:https://doi.org/10.1016/j.fct.2021.112259.
123. Han, N.R.; Moon, P.D.; Ryu, K.J.; Jang, J.B.; Kim, H.M.; Jeong, H.J. β-eudesmol suppresses allergic reactions via inhibiting mast cell degranulation. *Clin Exp Pharmacol Physiol* **2017**, *44*, 257-265, doi:10.1111/1440-1681.12698.
124. Tshering, G.; Pimtong, W.; Plengsuriyakarn, T.; Na-Bangchang, K. Anti-angiogenic effects of beta-eudesmol and atractylodin in developing zebrafish embryos. *Comp Biochem Physiol C Toxicol Pharmacol* **2021**, *243*, 108980, doi:10.1016/j.cbpc.2021.108980.
125. Brophy, J.J.; Forster, P.I.; Goldsack, R.J. Coconut Laurels: The Leaf Essential Oils from Four Endemic Australian Cryptocarya Species: C. bellendenkerana, C. cocosoides, C. cunninghamii and C. lividula (Lauraceae). *Nat Prod Commun* **2016**, *11*, 255-258.
126. Anandakumar, P.; Kamaraj, S.; Vanitha, M.K. D-limonene: A multifunctional compound with potent therapeutic effects. *J Food Biochem* **2021**, *45*, e13566, doi:10.1111/jfbc.13566.
127. Vieira, A.J.; Beserra, F.P.; Souza, M.C.; Totti, B.M.; Rozza, A.L. Limonene: Aroma of innovation in health and disease. *Chem Biol Interact* **2018**, *283*, 97-106, doi:10.1016/j.cbi.2018.02.007.
128. Thangaleela, S.; Sivamaruthi, B.S.; Kesika, P.; Tiyajamorn, T.; Bharathi, M.; Chaiyasut, C. A Narrative Review on the Bioactivity and Health Benefits of Alpha-Phellandrene. *Scientia Pharmaceutica* **2022**, *90*, 57.
129. Ferraz, R.P.; Cardoso, G.M.; da Silva, T.B.; Fontes, J.E.; Prata, A.P.; Carvalho, A.A.; Moraes, M.O.; Pessoa, C.; Costa, E.V.; Bezerra, D.P. Antitumour properties of the leaf essential oil of Xylopia frutescens Aubl. (Annonaceae). *Food Chem* **2013**, *141*, 196-200, doi:10.1016/j.foodchem.2013.02.114.
130. Minh, P.T.H.; Tuan, N.T.; Van, N.T.H.; Bich, H.T.; Lam, D.T. Chemical Composition and Biological Activities of Essential Oils of Four Asarum Species Growing in Vietnam. *Molecules* **2023**, *28*, doi:10.3390/molecules28062580.
131. Qin, Y.; Zhang, J.; Song, D.; Duan, H.; Li, W.; Yang, X. Novel (E)-β-Farnesene Analogues Containing 2-Nitroiminohexahydro-1,3,5-triazine: Synthesis and Biological Activity Evaluation. *Molecules* **2016**, *21*, 825.
132. brophy2000.pdf.
133. Ryu, Y.; Lee, D.; Jung, S.H.; Lee, K.J.; Jin, H.; Kim, S.J.; Lee, H.M.; Kim, B.; Won, K.J. Sabinene Prevents Skeletal Muscle Atrophy by Inhibiting the MAPK-MuRF-1 Pathway in Rats. *Int J Mol Sci* **2019**, *20*, doi:10.3390/ijms20194955.
134. Cordeiro, L.; Figueiredo, P.; Souza, H.; Sousa, A.; Andrade-Júnior, F.; Medeiros, D.; Nóbrega, J.; Silva, D.; Martins, E.; Barbosa-Filho, J.; et al. Terpinen-4-ol as an Antibacterial and Antibiofilm Agent against Staphylococcus aureus. *Int J Mol Sci* **2020**, *21*, doi:10.3390/ijms21124531.
135. Brophy, J.J.; Goldsack, R.J.; Forster, P.I. The Essential Oils of the Australian Species of Uromyrtus (Myrtaceae). *Flavour and Fragrance Journal* **1996**, *11*, 133-138, doi:https://doi.org/10.1002/(SICI)1099-1026(199603)11:2<133::AID-FFJ564>3.0.CO;2-2.
136. Hong, E.Y.; Kim, T.Y.; Hong, G.U.; Kang, H.; Lee, J.Y.; Park, J.Y.; Kim, S.C.; Kim, Y.H.; Chung, M.H.; Kwon, Y.I.; et al. Inhibitory Effects of Roseoside and Icariside E4 Isolated from a Natural Product Mixture (No-ap) on the Expression of Angiotensin II Receptor 1 and Oxidative Stress in Angiotensin II-Stimulated H9C2 Cells. *Molecules* **2019**, *24*, doi:10.3390/molecules24030414.

137. Yajima, A.; Oono, Y.; Nakagawa, R.; Nukada, T.; Yabuta, G. A simple synthesis of four stereoisomers of roseoside and their inhibitory activity on leukotriene release from mice bone marrow-derived cultured mast cells. *Bioorg Med Chem* **2009**, *17*, 189-194, doi:10.1016/j.bmc.2008.11.002.
138. Brophy, J.J.; Goldsack, R.J.; Forster, P.I. Chemistry of the Australian Gymnosperms Part VIII. The Leaf Oil ofPrumnopitys ladei(Podocarpaceae). *Journal of Essential Oil Research* **2006**, *18*, 212-214, doi:10.1080/10412905.2006.9699068.
139. Dahham, S.S.; Tabana, Y.M.; Iqbal, M.A.; Ahamed, M.B.; Ezzat, M.O.; Majid, A.S.; Majid, A.M. The Anticancer, Antioxidant and Antimicrobial Properties of the Sesquiterpene β-Caryophyllene from the Essential Oil of Aquilaria crassna. *Molecules* **2015**, *20*, 11808-11829, doi:10.3390/molecules200711808.
140. Francomano, F.; Caruso, A.; Barbarossa, A.; Fazio, A.; La Torre, C.; Ceramella, J.; Mallamaci, R.; Saturnino, C.; Iacopetta, D.; Sinicropi, M.S. β-Caryophyllene: A Sesquiterpene with Countless Biological Properties. *Applied Sciences* **2019**, *9*, 5420.
141. Fidyt, K.; Fiedorowicz, A.; Strządała, L.; Szumny, A. β-caryophyllene and β-caryophyllene oxide-natural compounds of anticancer and analgesic properties. *Cancer Med* **2016**, *5*, 3007-3017, doi:10.1002/cam4.816.
142. Brophy, J.J.; Goldsack, R.J.; Forster, P.I. The Leaf Oils of the Australian Species of Flindersia (Rutaceae). *Journal of Essential Oil Research* **2005**, *17*, 388-395, doi:10.1080/10412905.2005.9698939.
143. Robertson, L.P.; Hall, C.R.; Forster, P.I.; Carroll, A.R. Alkaloid diversity in the leaves of Australian Flindersia (Rutaceae) species driven by adaptation to aridity. *Phytochemistry* **2018**, *152*, 71-81, doi:https://doi.org/10.1016/j.phytochem.2018.04.011.
144. Robertson, L.P.; Duffy, S.; Wang, Y.; Wang, D.; Avery, V.M.; Carroll, A.R. Pimentelamines A-C, Indole Alkaloids Isolated from the Leaves of the Australian Tree Flindersia pimenteliana. *J Nat Prod* **2017**, *80*, 3211-3217, doi:10.1021/acs.jnatprod.7b00587.
145. Robertson, L.P.; Lucantoni, L.; Avery, V.M.; Carroll, A.R. Antiplasmodial Bis-Indole Alkaloids from the Bark of Flindersia pimenteliana. *Planta Med* **2020**, *86*, 19-25, doi:10.1055/a-1028-7786.
146. Resch, M.; Steigel, A.; Chen, Z.-l.; Bauer, R. 5-Lipoxygenase and Cyclooxygenase-1 Inhibitory Active Compounds from Atractylodes lancea. *J. Nat. Prod.* **1998**, *61*, 347-350, doi:10.1021/np970430b.
147. Mu, K.; Zhang, J.; Feng, X.; Zhang, D.; Li, K.; Li, R.; Yang, P.; Mao, S. Sedative-hypnotic effects of Boropinol-B on mice via activation of GABAA receptors. *J Pharm Pharmacol* **2023**, *75*, 57-65, doi:10.1093/jpp/rgac077.
148. Hu, Q.; Luo, L.; Yang, P.; Mu, K.; Yang, H.; Mao, S. Neuroprotection of boropinol-B in cerebral ischemia-reperfusion injury by inhibiting inflammation and apoptosis. *Brain Research* **2023**, *1798*, 148132, doi:https://doi.org/10.1016/j.brainres.2022.148132.
149. Liu, J.H.; Zschocke, S.; Reininger, E.; Bauer, R. Inhibitory effects of Angelica pubescens f. biserrata on 5-lipoxygenase and cyclooxygenase. *Planta Med* **1998**, *64*, 525-529, doi:10.1055/s-2006-957507.
150. Resch, M.; Steigel, A.; Chen, Z.L.; Bauer, R. 5-Lipoxygenase and cyclooxygenase-1 inhibitory active compounds from Atractylodes lancea. *J Nat Prod* **1998**, *61*, 347-350, doi:10.1021/np970430b.
151. Yeshi, K.; Ruscher, R.; Miles, K.; Crayn, D.; Liddell, M.; Wangchuk, P. Antioxidant and Anti-Inflammatory Activities of Endemic Plants of the Australian Wet Tropics. *Plants (Basel)* **2022**, *11*, doi:10.3390/plants11192519.
152. Yeshi, K.; Wangchuk, P. Bush Medicinal Plants of the Australian Wet Tropics and Their Biodiscovery Potential. In *Bioprospecting of Tropical Medicinal Plants*, Arunachalam, K., Yang, X., Puthanpura Sasidharan, S., Eds.; Springer Nature Switzerland: Cham, 2023; pp. 357-379.
153. Giménez-Bastida, J.A.; González-Sarrías, A.; Laparra-Llopis, J.M.; Schneider, C.; Espín, J.C. Targeting Mammalian 5-Lipoxygenase by Dietary Phenolics as an Anti-Inflammatory Mechanism: A Systematic Review. *Int J Mol Sci* **2021**, *22*, doi:10.3390/ijms22157937.
154. Rådmark, O.; Samuelsson, B. 5-Lipoxygenase: mechanisms of regulation1. *J. Lipid Res.* **2009**, *50*, S40-S45, doi:https://doi.org/10.1194/jlr.R800062-JLR200.
155. Barbier de Reuille, P.; Routier-Kierzkowska, A.-L.; Kierzkowski, D.; Bassel, G.W.; Schüpbach, T.; Tauriello, G.; Bajpai, N.; Strauss, S.; Weber, A.; Kiss, A.; et al. MorphoGraphX: A platform for quantifying morphogenesis in 4D. *eLife* **2015**, *4*, e05864, doi:10.7554/eLife.05864.
156. Fernandez, R.; Das, P.; Mirabet, V.; Moscardi, E.; Traas, J.; Verdeil, J.-L.; Malandain, G.; Godin, C. Imaging plant growth in 4D: robust tissue reconstruction and lineaging at cell resolution. *Nature Methods* **2010**, *7*, 547-553, doi:10.1038/nmeth.1472.
157. Perez de Souza, L.; Alseekh, S.; Scossa, F.; Fernie, A.R. Ultra-high-performance liquid chromatography high-resolution mass spectrometry variants for metabolomics research. *Nat Methods* **2021**, *18*, 733-746, doi:10.1038/s41592-021-01116-4.
158. Jamtsho, T.; Yeshi, K.; Perry, M.J.; Loukas, A.; Wangchuk, P. Approaches, Strategies and Procedures for Identifying Anti-Inflammatory Drug Lead Molecules from Natural Products. *Pharmaceuticals* **2024**, *17*, 283.
159. Markley, J.L.; Brüschweiler, R.; Edison, A.S.; Eghbalnia, H.R.; Powers, R.; Raftery, D.; Wishart, D.S. The future of NMR-based metabolomics. *Curr Opin Biotechnol* **2017**, *43*, 34-40.
160. Dunn, W.B.; Bailey, N.J.; Johnson, H.E. Measuring the metabolome: current analytical technologies. *Analyst* **2005**, *130*, 606-625.

161. Castrillo, J.I.; Hayes, A.; Mohammed, S.; Gaskell, S.J.; Oliver, S.G. An optimized protocol for metabolome analysis in yeast using direct infusion electrospray mass spectrometry. *Phytochemistry* **2003**, *62*, 929-937.
162. Maia, M.; Figueiredo, A.; Cordeiro, C.; Sousa Silva, M. FT-ICR-MS-based metabolomics: A deep dive into plant metabolism. *Mass Spectrometry Reviews* **2023**, *42*, 1535-1556, doi:https://doi.org/10.1002/mas.21731.
163. Andrews, G.L.; Simons, B.L.; Young, J.B.; Hawkridge, A.M.; Muddiman, D.C. Performance characteristics of a new hybrid quadrupole time-of-flight tandem mass spectrometer (TripleTOF 5600). *Analytical chemistry* **2011**, *83*, 5442-5446.
164. Pelander, A.; Decker, P.; Baessmann, C.; Ojanperä, I. Evaluation of a high resolving power time-of-flight mass spectrometer for drug analysis in terms of resolving power and acquisition rate. *Journal of the American Society for Mass Spectrometry* **2011**, *22*, 379-385.
165. Ghaste, M.; Mistrik, R.; Shulaev, V. Applications of fourier transform ion cyclotron resonance (FT-ICR) and orbitrap based high resolution mass spectrometry in metabolomics and lipidomics. *Int. J. Mol. Sci.* **2016**, *17*, 816.
166. Glauser, G.; Veyrat, N.; Rochat, B.; Wolfender, J.-L.; Turlings, T.C. Ultra-high pressure liquid chromatography–mass spectrometry for plant metabolomics: A systematic comparison of high-resolution quadrupole-time-of-flight and single stage Orbitrap mass spectrometers. *Journal of chromatography A* **2013**, *1292*, 151-159.
167. Park, S.-G.; Mohr, J.P.; Anderson, G.A.; Bruce, J.E. Application of frequency multiple FT-ICR MS signal acquisition for improved proteome research. *International journal of mass spectrometry* **2021**, *465*, 116578.
168. Schuhmann, K.; Herzog, R.; Schwudke, D.; Metelmann-Strupat, W.; Bornstein, S.R.; Shevchenko, A. Bottom-up shotgun lipidomics by higher energy collisional dissociation on LTQ Orbitrap mass spectrometers. *Analytical chemistry* **2011**, *83*, 5480-5487.
169. Schuhmann, K.; Almeida, R.; Baumert, M.; Herzog, R.; Bornstein, S.R.; Shevchenko, A. Shotgun lipidomics on a LTQ Orbitrap mass spectrometer by successive switching between acquisition polarity modes. *Journal of Mass Spectrometry* **2012**, *47*, 96-104.
170. Allwood, J.W.; Parker, D.; Beckmann, M.; Draper, J.; Goodacre, R. Fourier Transform Ion Cyclotron Resonance mass spectrometry for plant metabolite profiling and metabolite identification. *Methods Mol Biol* **2012**, *860*, 157-176, doi:10.1007/978-1-61779-594-7_11.
171. Barrow, M.P.; Burkitt, W.I.; Derrick, P.J. Principles of Fourier transform ion cyclotron resonance mass spectrometry and its application in structural biology. *Analyst* **2005**, *130*, 18-28.
172. Hiraoka, K. *Fundamentals of mass spectrometry*; Springer: 2013; Volume 8.
173. Folli, G.S.; Souza, L.M.; Araújo, B.Q.; Romão, W.; Filgueiras, P.R. Estimating the intermediate precision in petroleum analysis by (±) electrospray ionization Fourier transform ion cyclotron resonance mass spectrometry. *Rapid Communications in Mass Spectrometry* **2020**, *34*, e8861.
174. Hughey, C.A.; Rodgers, R.P.; Marshall, A.G. Resolution of 11 000 compositionally distinct components in a single electrospray ionization Fourier transform ion cyclotron resonance mass spectrum of crude oil. *Analytical Chemistry* **2002**, *74*, 4145-4149.
175. Allwood, J.W.; De Vos, R.C.; Moing, A.; Deborde, C.; Erban, A.; Kopka, J.; Goodacre, R.; Hall, R.D. Plant metabolomics and its potential for systems biology research: Background concepts, technology, and methodology. *Methods in enzymology* **2011**, *500*, 299-336.
176. Shahbazy, M.; Moradi, P.; Ertaylan, G.; Zahraei, A.; Kompany-Zareh, M. FTICR mass spectrometry-based multivariate analysis to explore distinctive metabolites and metabolic pathways: A comprehensive bioanalytical strategy toward time-course metabolic profiling of Thymus vulgaris plants responding to drought stress. *Plant Science* **2020**, *290*, 110257.
177. Janz, D.; Behnke, K.; Schnitzler, J.-P.; Kanawati, B.; Schmitt-Kopplin, P.; Polle, A. Pathway analysis of the transcriptome and metabolome of salt sensitive and tolerant poplar species reveals evolutionary adaption of stress tolerance mechanisms. *BMC Plant Biology* **2010**, *10*, 1-17.
178. Kaling, M.; Kanawati, B.; Ghirardo, A.; Albert, A.; Winkler, J.B.; Heller, W.; Barta, C.; Loreto, F.; SCHMITT-KOPPLIN, P.; SCHNITZLER, J.P. UV-B mediated metabolic rearrangements in poplar revealed by non-targeted metabolomics. *Plant, cell & environment* **2015**, *38*, 892-904.
179. Fiehn, O. Metabolomics—The link between genotypes and phenotypes. *Plant Mol Biol* **2002**, *48*, 155–171.
180. Silva, L.P.; Northen, T.R. Exometabolomics and MSI: deconstructing how cells interact to transform their small molecule environment. *Curr Opin Biotechnol* **2015**, *34*, 209-216, doi:https://doi.org/10.1016/j.copbio.2015.03.015.
181. Mapelli, V.; Olsson, L.; Nielsen, J. Metabolic footprinting in microbiology: methods and applications in functional genomics and biotechnology. *Trends in Biotechnology* **2008**, *26*, 490-497, doi:10.1016/j.tibtech.2008.05.008.
182. Kuzina, V.; Ekstrøm, C.T.; Andersen, S.B.; Nielsen, J.K.; Olsen, C.E.; Bak, S. Identification of defense compounds in Barbarea vulgaris against the herbivore Phyllotreta nemorum by an ecometabolomic approach. *Plant physiology* **2009**, *151*, 1977-1990.

183. Salek, R.M.; Steinbeck, C.; Viant, M.R.; Goodacre, R.; Dunn, W.B. The role of reporting standards for metabolite annotation and identification in metabolomic studies. *GigaScience* **2013**, *2*, 13, doi:10.1186/2047-217X-2-13.
184. Sumner, L.W.; Amberg, A.; Barrett, D.; Beale, M.H.; Beger, R.; Daykin, C.A.; Fan, T.W.; Fiehn, O.; Goodacre, R.; Griffin, J.L.; et al. Proposed minimum reporting standards for chemical analysis Chemical Analysis Working Group (CAWG) Metabolomics Standards Initiative (MSI). *Metabolomics* **2007**, *3*, 211-221, doi:10.1007/s11306-007-0082-2.
185. Xu, Y.; Fu, X. Reprogramming of Plant Central Metabolism in Response to Abiotic Stresses: A Metabolomics View. *Int. J. Mol. Sci.* **2022**, *23*, 5716.