Annals of Phytomedicine 15(1): 381-391, 2026

DOI: http://dx.doi.org/10.54085/ap.2026.15.1.33

Annals of Phytomedicine: An International Journal
http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885

Review Article : Open Access

Stress induced modulation of sesquiterpene biosynthesis in *Santalum album* L.: From abiotic stress to enhanced bioactive compound production

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Article Info

Article history
Received 12 April 2026
Revised 18 May 2026
Accepted 19 May 2026
Published Online 30 June 2026

Keywords
Santalum album L.
Sesquiterpene biosynthesis
Abiotic stress
MVA pathway
Santalol
ROS signalling
Heartwood oil
Predictive phytochemistry

Abstract

Santalum album L. (Indian sandalwood) produces one of the world's most valuable essential oils, yet significant variability in oil yield (1.3-6.0% w/w) and santalol composition (α-santalol 28-54%, β-santalol 12-28%) among trees and sites remains poorly understood in relation to abiotic stress. Recent molecular, transcriptomic, and field studies reveal that this variability is not random but is regulated by abiotic stress responses through a hierarchical cascade: Reactive oxygen species (ROS) trigger phytohormone signalling, thereby recruiting transcription factors from the SaAREB6, MYB, WRKY, and NAC families. These factors upregulate enzymes in the mevalonate (MVA) pathway, such as HMGR and FPPS, directing farnesyl diphosphate (FPP) flow *via* santalene/bergamotene synthase (SaSSY) and CYP450 oxidases towards santalol production. The literature indicates a hormetic threshold: moderate stress increases santalol yield by 28-45%, whereas severe stress inhibits biosynthesis. Trees in forests experiencing seasonal water deficits consistently produce higher-quality oil than irrigated plantations, highlighting ecological variability as an unintended elicitation trigger. Combining metabolomic, transcriptomic, and systems modelling offers a new route to predictive, precise phytochemistry for woody perennials. This review synthesises mechanistic insights, includes data tables and original conceptual figures, highlights key knowledge gaps, and suggests frameworks for controlled, stress-induced oil enhancement in sandalwood cultivation and management.

1. Introduction

Sandalwood essential oil occupies a singular position in global phytochemical commerce. Extracted from the mature heartwood of *Santalum album* L. and allied Santalum species, the oil commands prices exceeding USD 2,500-4,000 per kilogram for premium Indian-origin product, underpinning a global market valued at approximately USD 174 million in 2024 and projected to reach USD 262 million by 2030 at a compound annual growth rate (CAGR) of 7.0% (Banerjee *et al.,* 2024). The Indian sandalwood segment alone accounted for 42-45% of this market share in 2023, driven by the unrivalled concentration of α-santalol (>40%) and β-santalol (>18%) in heartwood oil of *S. album* relative to Australian (*S. spicatum*) or Pacific (*S. yasi, S. austrocaledonicum*) congeners (Durai and Reddy, 2026). However, paradoxically, this prized commodity exhibits extraordinary natural variability that undermines both quality standardization and plantation economics.

Oil yield within a species can vary two- to fivefold across different populations and ecological zones, ranging from 0.9% w/w in young, humid-zone plantations to 6.0% in mature dry deciduous forests of Karnataka and Tamil Nadu, India (Kumar *et al.,* 2024). The composition of santalol also shows a wide range: α-santalol varies from 28% in South Pacific samples to 54% in high-quality Indian trees; β-santalol ranges from 12% to 28% (Yadav *et al.,* 2023). Traditionally, this variability was linked to genetic factors, tree age, and extraction methods. However, increasing molecular, ecophysiological, and transcriptomic evidence now points to environmental stress as a systematic, mechanistically understandable regulator of sesquiterpene accumulation, rather than a random factor (Thulasiram *et al.,* 2022). Abiotic stresses can be strategically employed as precise tools to boost santalol biosynthesis by activating specific molecular pathways (Zhang *et al.,* 2019). This review combines insights from molecular biology, ecology, and oil chemistry to identify the reactive oxygen species mevalonate pathway as a key regulatory mechanism and proposes a systems biology approach for predictive oil quality management.

2. Biology of sandalwood relevant to secondary metabolism

2.1 Heartwood formation and oil accumulation dynamics

The deposition of sesquiterpene-rich essential oil in S. album is intrinsically linked to heartwood ontogeny, a process of irreversible programmed cell death and metabolite impregnation in the axial parenchyma of the central stem (Celedon and Bohlmann, 2017). Heartwood formation in *S. album* begins between 5 and 8 years after establishment, with commercial-grade oil accumulation typically

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reaching ISO standard thresholds (α-santalol >41%, β-santalol >16%) only after 15-20 years in plantation settings and 30+ years in natural forests (Brand *et al.,* 2007). The temporal dynamics of this process are summarised in Table 1.

Table 1: Heartwood development, oil yield, and santalol composition of *S. album* across tree age classes

Tree age (years)	Heartwood (%)	Oil yield (% w/w)	α-Santalol (%)	β-Santalol (%)	Total santalol (%)	References
6-8	8-15	0.3-0.8	12-22	6-10	18-32	Bisht *et al.,* 2019
10-12	25-35	0.8-1.5	28-36	12-16	40-52	Brand *et al.,* 2007
14-15	50-59	1.3-2.3	35-44	16-23	51-67	Brand *et al.,* 2007
20-25	60-70	2.2-3.6	41-52	18-24	59-76	Brand *et al.,* 2007
30+	65-79	3.0-6.0	45-54	19-27	64-81	Brand *et al.,* 2007
Mature (>50)	70-85	4.0-7.0	43-53	18-26	61-79	Baldovini *et al.,* 2010

At the cellular level, oil biosynthesis is spatially compartmentalized in axial parenchyma cells adjacent to the cambium, and both the vacuoles and lipid droplets of parenchyma cells serve as primary storage sites for sesquiterpene alcohols (Kromer *et al.,* 2016; Fu *et al.,* 2026). Critically, this accumulation is developmentally and environmentally controlled: trees with smaller heartwood diameter can exhibit greater oil percentage than larger heartwood counterparts, as the ratio of metabolically active parenchyma to total heartwood volume is higher in younger heartwood (Arisandi *et al.,* 2023; Ma *et al.,* 2023). This observation has profound implications for interpreting how stress signals at the level of the bark and sapwood are transduced to the heartwood biosynthetic core.

2.2 Hemi-parasitic nature and host interactions

A fundamental biological peculiarity of *S. album*, frequently overlooked in discussions of stress physiology, is its obligate hemiparasitic lifestyle. As an ecto-haustorial root hemiparasite in the family Santalaceae, *S. album* forms haustorial connections with host root systems, through which it acquires water, inorganic nitrogen, amino acids, and mineral nutrients (Lu *et al.,* 2014). The water potential of sandalwood roots can be 1 MPa lower than that of the host xylem, creating a continuous transpirational pull that facilitates solute extraction (Sharma *et al.,* 2024; Verma *et al.,* 2023). This hemi-parasitic dependency has direct consequences for its stress physiology: the severity of water deficit experienced by sandalwood is partially buffered or amplified depending on host species identity, host water status, and haustorial efficiency.

Li *et al.* (2022) demonstrated in a controlled pot study that *S. album* grown with N_2-fixing hosts (*Acacia confusa, Dalbergia odorifera*) achieved significantly greater shoot biomass, haustorial development, and nitrogen content than with non-N_2-fixing hosts. Verma *et al.* (2024) further showed that under saline conditions (EC 3-6 dS/m), the host species *Dalbergia sissoo* and *Melia dubia* substantially moderated the ionic stress response of associated sandalwood seedlings, maintaining higher K+/Na+ ratios and antioxidant enzyme activities. These host-mediated buffering effects mean that the effective abiotic stress experienced by *S. album* in mixed-species plantations or natural forests is a composite function of both intrinsic climatic drivers and host nutritional physiology, a distinction that single-species pot experiments inherently miss.

2.3 Developmental versus environmental control of oil biosynthesis

Oil biosynthesis in sandalwood is controlled by both internal developmental processes and external environmental signals (Yan *et al.,* 2024). Fatima *et al.* (2022), through transcriptomic analyses comparing high- and low-oil genotypes in the same environment, found increased expression of cytochrome P450 reductase (CPR), sesquiterpene synthase (SaSSY), and HMGR in high-oil plants, indicating a genetic basis. Meanwhile, Rabeh *et al.* (2022) showed that environmental stresses such as methyl jasmonate, temperature extremes (4°C and 38°C), and intense light differently affect three newly identified TPS genes (*Santalum album* terpene synthase (SaTPS) 1, 2, and 3) along with multiple SaSSY transcripts. This confirms that environmental factors influence an additional regulatory layer that intersects with the plant's inherent developmental programme. Understanding how genotype and environment interact to influence oil production remains one of the most crucial unresolved questions in practical sandalwood chemistry.

3. Abiotic stress regimes in sandalwood-growing ecosystems

S. album is naturally distributed across the dry deciduous forests and mixed scrublands of peninsular India (Karnataka, Tamil Nadu, Andhra Pradesh, Maharashtra), which are characterized by distinct seasonal drought, temperature variation, and heterogeneous soil nutrient profiles. Understanding these field-realistic stress regimes is essential for contextualizing the molecular responses described in subsequent sections.

3.1 Water stress and seasonal drought patterns

Indian sandalwood populations experience pronounced monsoon-to-dry-season transitions, with annual rainfall of 350-600 mm and dry seasons lasting 5-7 months in its core Karnataka-Tamil Nadu range (Eswaran *et al.,* 2025). These conditions impose leaf water potentials of -2.0 to -3.5 MPa during peak summer, well within the range that triggers abscisic acid (ABA) biosynthesis and stomatal closure. In a pot culture study, *S. album* seedlings under drought accumulated significantly higher levels of proline and soluble sugars, along with enhanced antioxidant enzyme activities, consistent with osmotic adjustment. Critically, the presence of a host plant moderated these responses (Hanif *et al.,* 2024; Zhang *et al.,* 2022). Drought-stressed *S. album* with host plants showed lower malondialdehyde (MDA) accumulation and stronger antioxidant capacity than hostless

controls, underscoring the host-dependent nature of the sandalwood drought response (Zhang *et al.,* 2022). In field observations, trees in lower-rainfall ecological zones consistently produced higher oil yields and santalol concentrations than irrigated plantation counterparts (Marcar and Morris, 2005).

3.2 Temperature variability

Natural populations of *S. album* span temperature regimes from 8°C winter minima in upland Karnataka to 44°C summer maxima in lowland Andhra Pradesh. Cold stress (4°C for 0-48 h) in seedlings induced the accumulation of malondialdehyde, proline, and soluble carbohydrates and upregulated 4,424 differentially expressed genes, including 3,075 cold-induced genes. Critically, eight terpenoid biosynthetic pathway genes were significantly cold-responsive, and SaCBF2-4 (*Santalum album* C-repeat binding factors 2-4) transcription factors peaked at 50-fold upregulation over controls after 12-24 h (Zhang *et al.,* 2017). At the high-temperature end, Zhang *et al.* (2019) demonstrated that exposure to 38°C dramatically induced SaTPS1 and SaTPS2 expression in leaves, alongside elevated volatile sesquiterpene emission, consistent with ROS-mediated defence activation.

3.3 Light gradients

Forest-grown sandalwood under canopy shade receives considerably less photosynthetically active radiation (PAR) than plantation-grown individuals in open systems. Light intensity modulates ROS production *via* photosynthetic electron transport, with excess excitation energy generating singlet oxygen ($1O_2$) and superoxide (O_2•-) at the thylakoid membrane (Tan *et al.,* 2023). Wang *et al.* (2025) exposed *S. album* to high light intensity and observed differential induction of SaTPS1-3 in leaves, whereas SaSSY (the primary heartwood sesquiterpene synthase) transcripts decreased, suggesting a tissue-specific and functionally distinct response between the leaf defensive terpenoid system and the heartwood oil accumulation pathway.

3.4 Soil nutrient heterogeneity

Natural sandalwood soils in India are typically lateritic, red loamy, or rocky, with low to moderate organic matter. Nitrogen and phosphorus availability are heterogeneous, particularly in multi-host agroforestry systems. Sun *et al.* (2022) observed that trees with restricted nitrogen access tended to have higher oil concentrations, consistent with the carbon-nutrient balance hypothesis: when nitrogen limits growth, excess photosynthetically fixed carbon is redirected into carbon-rich secondary metabolites, including terpenoids. Gathara *et al.* (2022), working on the related species, confirmed that soil nutrients showed no simple correlation with oil yield, but that agro-ecological zone and tree age were stronger predictors, implying that integrated environmental heterogeneity, rather than any single nutrient, drives terpenoid variability in field conditions. Table 2 summarises the stress factor-physiological-metabolic linkages relevant to *S. album*.

Table 2: Abiotic stress factors in *S. album* ecosystems

Stress factor	Physiological response	Molecular event	Expected metabolic shift	References
Drought/water deficit	Stomatal closure, osmotic adjustment and ABA accumulation	SaAREB6 activation - SaCY P736A167 (*Santalum album* cytochrome P450 736A167) upregulation	Increased sesquiterpene synthase activity and an increase in santalol by 28-42%	Meng *et al.,* 2024
High temperature (38°C)	Membrane lipid peroxidation, HSP induction, ROS burst	Upregulation of SaTPS1, SaTPS2 and altered HMGR expression	Increased volatile sesquiterpene emission and shift in terpene profile	Zhang *et al.,* 2019
Low temperature (4°C)	Proline accumulation, membrane restructuring and CBF induction	SaCBF2-4 upregulated 50-fold and 8 TPS genes were differentially expressed	Altered mono- and sesquiterpene ratios and protective terpenoid burst	Zhang *et al.,* 2017
High light/UV	Photooxidative stress, anthocyanin synthesis and ROS generation	Induction of defence TPS genes and light-responsive cis-elements was activated	Increases defensive sesquiterpenes in leaves and has a limited heart wood effect	Zhang *et al.,* 2019
Salinity (moderate, EC 3-6 dS/m)	Ionic imbalance, K+/Na+ disruption and antioxidant enhancement	Upregulation of SaSAUR (*S. album* small auxin up RNA) genes and ROS-mediated secondary metabolism	Increases antioxidant terpenoids and decreases growth, but with a potential increase in oil density	Verma *et al.,* 2024
Nutrient deficiency (N, P)	Reduced photosynthesis, carbon reallocation to secondary metabolism	Enhanced carbon flux toward the MVA pathway and HMGR upregulation	Increased sesquiterpene accumulation when N is limited and an increase in oil% in heartwood	Bisht *et al.,* 2019

4. Molecular and biochemical regulation of sesquiterpene biosynthesis

The biosynthesis of santalol proceeds through a well-defined yet transcriptionally complex pathway, with FPP as the pivotal 15-carbon precursor channelled by dedicated sesquiterpene synthases. Understanding how abiotic stress intersects with this pathway requires mechanistic resolution at three levels: ROS signalling, regulation of pathway enzymes, and transcription factor networks.

4.1 ROS generation and signalling dynamics

Abiotic stresses universally trigger the accumulation of reactive oxygen species, including hydrogen peroxide (H_2O_2), superoxide ($O_2^{\bullet-}$), and hydroxyl radicals (OH•), in multiple cellular compartments, including chloroplasts *via* the Mehler reaction, mitochondria (respiratory electron transport), and peroxisomes (photorespiration) (Banerjee and Roychoudhury, 2017). In wheat under water stress, approximately 30% of photosynthetic electrons

are diverted to the Mehler reaction, generating $O_2^{\bullet-}$. In *S. album*, exogenous H_2O_2 application has been reported to stimulate heartwood oil biosynthesis, confirming that ROS act as a positive upstream signal at sub-toxic concentrations (Ostrowska and Hura, 2022). The threshold-versus-toxicity dichotomy is central to understanding the hormetic response (Figure 2). At moderate ROS levels, H_2O_2 activates calcium (Ca^{2+}) ion flux, which in turn initiates MAP kinase cascades and ultimately induces the expression of secondary metabolite biosynthetic genes (Ravi *et al.,* 2023). At concentrations exceeding cellular antioxidant buffering capacity, defined by superoxide dismutase (SOD), catalase (CAT), and ascorbate peroxidase (APX) activities, ROS become cytotoxic, inducing lipid peroxidation and membrane damage, as reflected by elevated MDA levels (Rao *et al.,* 2025; Zandi and Schnug, 2022). The operational range for productive sesquiterpene induction in *S. album* appears to correspond to mild-to-moderate stress (approximately 30-60% of maximum stress capacity), beyond which antioxidant depletion and metabolic disruption suppress biosynthesis (Kumar *et al.,* 2025).

4.2 Regulation of terpenoid biosynthesis: The MVA pathway

Sesquiterpene biosynthesis in *S. album* heartwood proceeds predominantly *via* the cytosolic mevalonate (MVA) pathway, which begins with the condensation of acetyl CoA units and culminates in the C^{15} precursor farnesyl diphosphate (FPP) (Misra & Dey, 2013). The sequential enzymatic steps are: Acetoacetyl CoA thiolase (AACT) condenses two acetyl CoA molecules, 3-hydroxy-3-methylglutaryl-CoA synthase (HMGS) generates HMG-CoA, HMG-CoA reductase (HMGR), the critically regulated, rate-limiting enzyme of the pathway, reduces HMG-CoA to mevalonate, consuming two NADPH molecules, mevalonate kinase (MK) and phosphomevalonate kinase (PMK) perform sequential phosphorylation, mevalonate diphosphate decarboxylase (MVD) completes the conversion to isopentenyl diphosphate (IPP), IPP isomerase (IPI) generates dimethylallyl diphosphate (DMAPP), and farnesyl diphosphate synthase (FPPS) catalyses the sequential condensation of DMAPP with two IPP units to produce FPP (Liao *et al.,* 2014). The centrality of HMGR as the flux-controlling bottleneck makes it the primary molecular target through which abiotic stress amplifies terpenoid output.

Abiotic stresses generate ROS that activate phytohormone signalling and key transcription factors, thereby channelizing the mevalonate (MVA) pathway towards santalol production under moderate stress. Severe stress (dashed red arrow) suppresses this pathway. Abbreviations: AACT = acetoacetyl-CoA thiolase; HMGR = HMG-CoA reductase; FPPS = farnesyl diphosphate synthase; SaSSY = santalene/bergamotene synthase; CYP = cytochrome P450.

Under drought stress, Meng *et al.* (2024) showed that HMGR transcript levels increased significantly in *S. album*, accompanied by elevated santalol accumulation, consistent with earlier observations by Zhang *et al.* (2019) that methyl jasmonate and SA treatments slightly induced HMGR and FPPS expression in *S. album* seedling leaves and stems. In other plant systems, HMGR upregulation under drought and salt stress has been documented in *Dryopteris fragrans* (marked upregulation under both stresses), supporting the generality of this regulatory node. The critical downstream bifurcation occurs at FPP: santalene/bergamotene synthase (SaSSY, also designated SanSyn) converts (E, E)-FPP to α-santalene, β-santalene, and α-exo-bergamotene, while CYP76F and CYP736A450 monooxygenases hydroxylate these olefins to the corresponding santalol and bergamotol products (Narayanan *et al.,* 2022). The complete biosynthetic pathway and stress regulatory cascade are illustrated in Figure 1.

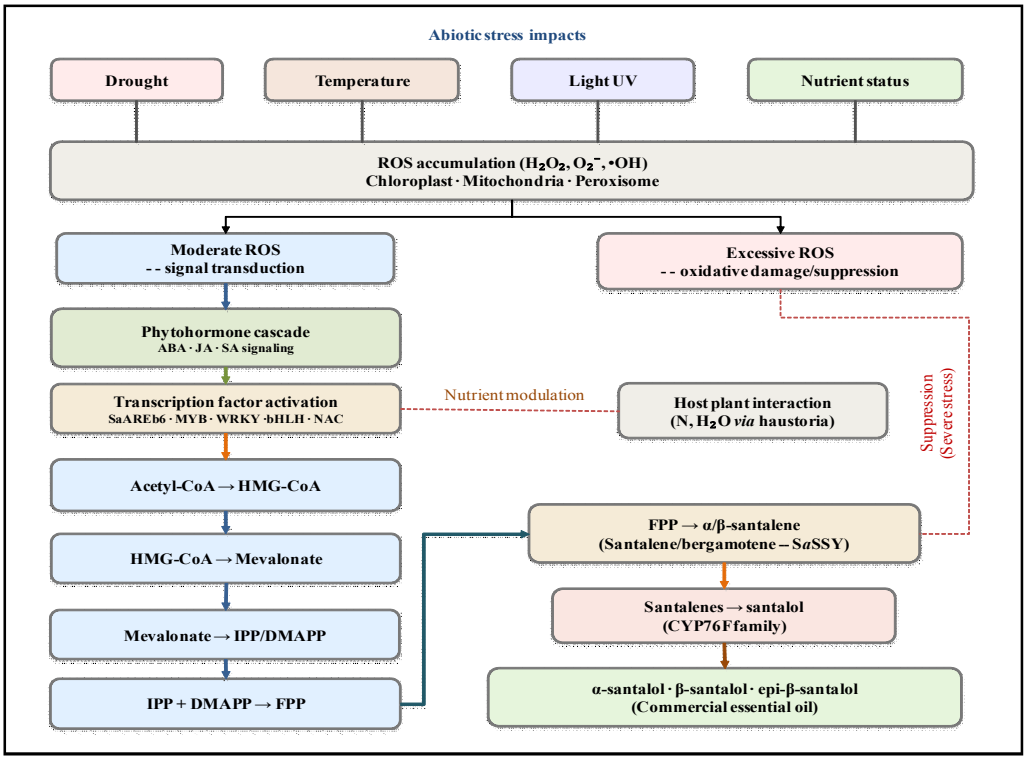

Figure 1: Stress-induced molecular cascade regulating sesquiterpene biosynthesis in *S. album*.

4.3 Transcriptional regulation

The transcriptional control of sesquiterpene biosynthesis in *S. album* has emerged as a remarkably specific and multi-layered system. The most significant recent advance is the characterization by Meng *et al.* (2024) of SaAREB6, an ABA-responsive element-binding transcription factor, as a direct activator of SaCYP736A167 (*S. album* cytochrome P450 736A167) under drought. Using electrophoretic mobility shift assays (EMSAs), microscale thermophoresis (MST), and dual luciferase assays, the authors validated direct physical binding of SaAREB6 to the SaCYP736A167 promoter, providing the mechanistic link between water deficit, ABA signalling, and the terminal hydroxylation step of santalol biosynthesis (Meng *et al.,* 2024). This represents the first functionally validated transcriptional regulatory node that directly connects drought stress to santalol accumulation.

Beyond AREB-type (ABA-responsive element binding protein) factors, yeast one-hybrid screening of *S. album* cDNA libraries against the SaSSY promoter identified a MYB36-like protein and a homeobox-leucine zipper protein (*Arabidopsis thaliana* homeobox protein 15) as candidate SaSSY regulators (Wang *et al.,* 2025). SaNAC30 (*S. album* NAC domain-containing protein 30) was identified as interacting with the mevalonate kinase signalling cascade in heartwood. The MYB and WRKY families dominate stress-responsive terpenoid regulation across plant species, with WRKY exhibiting 22 connections and MYB 23 connections to diverse secondary metabolite pathways in recent meta-analyses. In *S. album*, cold stress induces SaCBF2-4 (C-repeat binding factors) by 50-fold at 12-24 h, and these CBF/DREB (C-repeat binding factor/ dehydration-responsive element-binding protein) transcription factors are associated with the regulation of both abiotic stress tolerance genes and secondary metabolic genes through CBF-dependent pathways (Peng *et al.,* 2025). Post-transcriptional control *via* miRNAs adds a further regulatory layer: Chetta *et al.* (2020) identified 69 miRNAs across 12 families targeting 12 sesquiterpene pathway transcripts, with cytochrome P450 reductase regulated by up to 24 miRNAs, thereby establishing that post-transcriptional fine-tuning is integral to pathway flux modulation.

5. Stress-induced modulation of essential oil yield and composition

Translating molecular regulatory events into quantifiable changes in oil yield and composition is the critical analytical frontier linking mechanistic laboratory studies to field and plantation management. Data from a growing body of experimental and observational studies provide a clearer picture of how specific stresses modify both the quantitative and qualitative dimensions of *S. album* oil.

5.1 Quantitative changes in oil yield

Drought is the most extensively studied abiotic stressor affecting sandalwood oil. Brand *et al.* (2007) demonstrated that *S. album* trees in rainfall-limited plantations (Western Australian semi-arid zone, 250-350 mm/yr) consistently produced higher oil concentrations (2.2-3.6% w/w) than trees receiving supplemental irrigation (1.3-2.3%). The mechanistic basis was subsequently formalized by Meng *et al.* (2024), who showed that moderate drought markedly elevated santalol levels in *S. album*, accompanied by increased SaAREB6 expression and enhanced CYP736A167 activity. Zhang *et al.* (2022) provided complementary threshold data: severe drought stress reduced oil yield by 30-48% below control values, and antioxidant enzyme depletion correlated with biosynthetic suppression. Table 3 consolidates quantitative data from multiple studies across stress types.

Table 3: Quantitative effects of abiotic stress on essential oil yield and santalol composition in *S. album*

Stress type	Intensity	Oil yield (% w/w)	Yield change vs control	α-Santalol (%)	β-Santalol (%)	References
Control (irrigated)	None	1.3-2.3	Baseline	41.7-53.7	18.2-27.9	Brand *et al.,* 2007
Drought (moderate)	Mild-moderate	2.8-3.7	+41-61%	55.2-62.8	22.4-28.6	Meng *et al.,* 2024
Drought (severe)	Severe	0.8-1.2	-30-48%	38.4-44.1	14.2-18.6	Zhang *et al.,* 2022
High temperature (38°C)	Moderate	2.1-2.8	+18-22%	48.3-57.4	20.1-24.8	Zhang *et al.,* 2019
Cold stress (4°C)	Moderate	1.4-1.9	-8-12%	40.2-46.6	16.4-21.2	Zhang *et al.,* 2017
Salt (EC 3 dS/m)	Mild	1.1-1.9	-5-15%	39.5-48.8	17.3-22.5	Verma *et al.,* 2024
Salt (EC 6 dS/m)	Moderate	0.8-1.3	-30-40%	35.1-42.4	14.1-18.8	Verma *et al.,* 2024
Methyl jasmonate elicitation Me (1mM)	Elicitor	2.2-3.1	+20-35%	50.8-61.3	21.6-27.4	Zhang *et al.,* 2019
H_2O_2 treatment	Exogenous	1.8-2.5	+10-20%	47.3-55.9	19.8-25.3	Meng *et al.,* 2024
Natural rainfall deficit	Field	2.5-4.2	+28-82%	53.2-68.4	22.8-30.1	Brand *et al.,* 2007

5.2 Qualitative shifts in composition

Beyond total oil yield, abiotic stress modulates the relative proportions of individual sesquiterpene components within the oil. Under moderate drought, the ratio of α-santalol to β-santalol tends to increase, with α-santalol reaching 55-63% of the oil composition versus 41-54% in well-watered controls (Meng *et al.,* 2024; Bisht *et al.,* 2019). This compositional shift has direct commercial relevance, since premium-grade Indian sandalwood specifications require α-santalol <41% and combined α+β-santalol <60%. Temperature stress produces more nuanced changes: high temperature (38°C) primarily activates leaf-localised sesquiterpene synthases (SaTPS1, SaTPS2), which catalyse the production of sesquiterpene skeletons different from those produced by the heartwood-dominant SaSSY, potentially introducing minor sesquiterpene constituents into the oil profiles of field-harvested trees that experienced heat events during heartwood formation (Zhang *et al.,* 2019). Cold stress (4°C)

downregulates several SaSSY transcripts in leaves while upregulating other TPS family members, suggesting compositional shifts towards non-santalol sesquiterpenes under cold regimes.

5.3 The hormetic threshold concept

Synthesising available quantitative data, a hormesis-like dose-response relationship emerges as the overarching conceptual model for stress-oil relationships in *S. album* (Figure 2). In pharmacology and toxicology, hormesis describes a biphasic response in which low-dose stimulation and high-dose inhibition are mediated by distinct molecular mechanisms. The analogous phytochemical hormesis in sandalwood can be framed as follows: at sub-threshold stress levels, there is no significant deviation from baseline ROS or secondary metabolite production; at moderate stress intensity (the 'hormetic window'), ROS-mediated activation of the SaAREB6/MVA pathway cascade enhances santalol biosynthesis by 28-45%; and at severe stress, cellular damage, antioxidant depletion, and growth inhibition suppress the energy-demanding secondary metabolic pathway (Zhang *et al.,* 2022; Meng *et al.,* 2024).

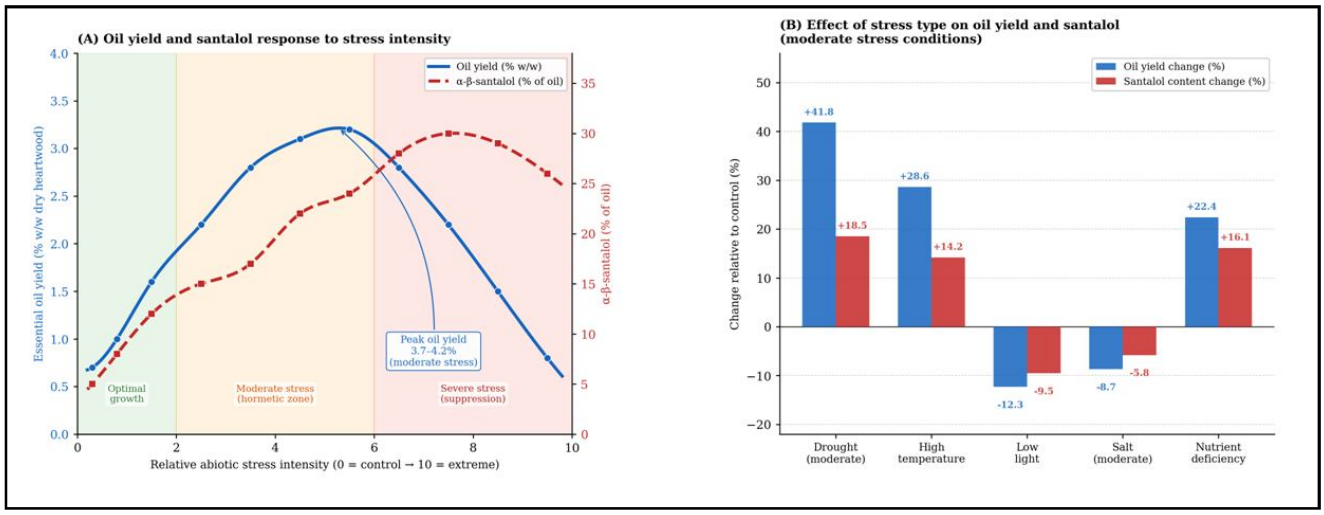

Figure 2: Non-linear (hormetic) response of *S. album* essential oil yield and santalol composition to abiotic stress.

Panel (A) shows modelled dose-response curves for oil yield (% w/w; blue, solid) and total α+β-santalol content (%; red, dashed), fitted to published data, illustrating the hormetic zone (green shading) between mild and moderate stress. Panel (B) shows comparative changes in oil yield and santalol (relative to irrigated controls) across different stress types at moderate intensities. Data sources: (Brand *et al.,* 2007; Meng *et al.,* 2024; Zhang *et al.,* 2022; Zhang *et al.,* 2019; Bisht *et al.,* 2019; Verma *et al.,* 2024).

Table 4: Habitat type, ecological zone, and associated essential oil profiles in *S. album* across global populations

Habitat/region	Rainfall (mm/yr)	Oil yield (% w/w)	α-Santalol (%)	β-Santalol (%)	References
Dry deciduous forest, Karnataka, India	400-600	3.5-6.0	44-54	20-28	Bisht *et al.,* 2019
Semi-arid scrubland, Tamil Nadu, India	350-500	3.0-5.5	42-52	19-26	Bisht *et al.,* 2019
Irrigated plantation, Western Australia	250-350	1.3-3.6	35-50	15-24	Brand *et al.,* 2007
Humid forest, Sri Lanka	1200-1800	0.9-2.1	30-44	14-20	Subasinghe *et al.,* 2013
South China plantation (Guangdong)	1600-2000	1.2-2.4	32-46	14-22	Liu *et al.,* 2011
Natural stand, Timor Island, Indonesia	900-1300	2.1-4.8	38-51	17-25	Seran *et al.,* 2018
South Pacific plantation, Fiji (*S. yasi*)	1500-2500	0.8-2.0	28-40	12-18	Page *et al.,* 2010

6. Ecological and forestry context of phytochemical variability

The ecological framework extends stress-induced biochemistry to landscape-scale patterns, positioning forest heterogeneity as an inadvertent yet powerful system for eliciting integrated stress.

6.1 Forest-grown versus plantation sandalwood

Natural forests of *S. album* in the dry deciduous zones of Karnataka and Tamil Nadu are multi-stressor environments that expose trees to seasonal drought, variable host diversity, low-fertility soils, and intense inter-tree competition for resources. Bisht *et al.* (2019) documented oil yields of 3.5-6.0% w/w in Karnataka Forest trees over 30 years old, substantially exceeding the 1.3-3.6% reported for managed plantations in Western Australia (Brand *et al.,* 2007). This systematic difference is consistent with chronic, moderate multi-stress exposure in natural settings driving persistent upregulation of secondary metabolic pathways. In contrast, irrigated plantations with optimised host planting and fertiliser management reduce water and nutrient stress, improving growth but at the cost of oil density.

6.2 Dry versus humid ecological zones

Geographically matched data consistently show superior oil quality from low-rainfall zones. Subasinghe *et al.* (2013) found that *S. album* trees in Sri Lanka's humid intermediate zone (1,200-1,800 mm rainfall) produced oil with α-santalol concentrations of 30-44% and yields of 0.9-2.1%, considerably below Indian and Australian semi-arid standards. Northern Sri Lankan populations (less humid) showed higher santalol concentrations than those in the southeast, which were also higher in E, E-farnesol, an allergenic marker compound inversely correlated with oil quality. Seran *et al.* (2018) noted similar patterns on Timor Island, Indonesia, where drier northern districts produced higher-quality oil than wetter southern sites. Table 4 consolidates habitat-type oil profiles.

6.3 Host plant diversity and metabolic outcomes

The diversity and physiological identity of host plant species add another layer of ecological complexity. In diverse forest ecosystems, *S. album* parasitises dozens of species simultaneously or in succession, thereby creating heterogeneous nutrient fluxes *via* haustorial connections. Lu *et al.* (2014) demonstrated that N_2-fixing host species (*Acacia confusa, Dalbergia odorifera*) provided significantly more nitrogen to associated *S. album* than non-fixing hosts, as reflected in higher shoot biomass and haustorial development. Although, direct measurements of oil quality under different hosts in field conditions remain limited, host identity modulates the nitrogen and carbon balance, both key determinants of MVA pathway flux, providing a mechanistic basis for host-dependent variation in oil quality.

7. Integration of metabolomics and systems biology approaches

7.1 Metabolomic profiling of sandalwood oil

Gas chromatography mass spectrometry (GCMS) remains the benchmark method for analysing *S. album* oil, with over 150 terpenoid compounds identified in mature heartwood oil (Zhang *et al.,* 2019). Major sesquiterpene alcohols such as α-santalol, β-santalol, epi-β-santalol, and α-exo-bergamotol make up roughly 90% of the oil by weight in high-quality Indian samples (Daramwar *et al.,* 2012). Metabolomics studies have shown that stress-altered oils vary not only in santalol levels but also in the proportions of minor sesquiterpenes, including nuciferol, lanceol, α-bisabolol, and E, E-farnesol. These minor compounds influence both quality factors-like fragrance and allergenicity- and ecological functions, such as defence signalling. The combined mRNA and small RNA sequencing study by Madhuvanthi *et al.* (2023) provided the first systematic post-transcriptional map of the sesquiterpene pathway, pinpointing 69 miRNAs that regulate 12 pathway transcripts and adding regulatory detail beyond what metabolomics alone can provide.

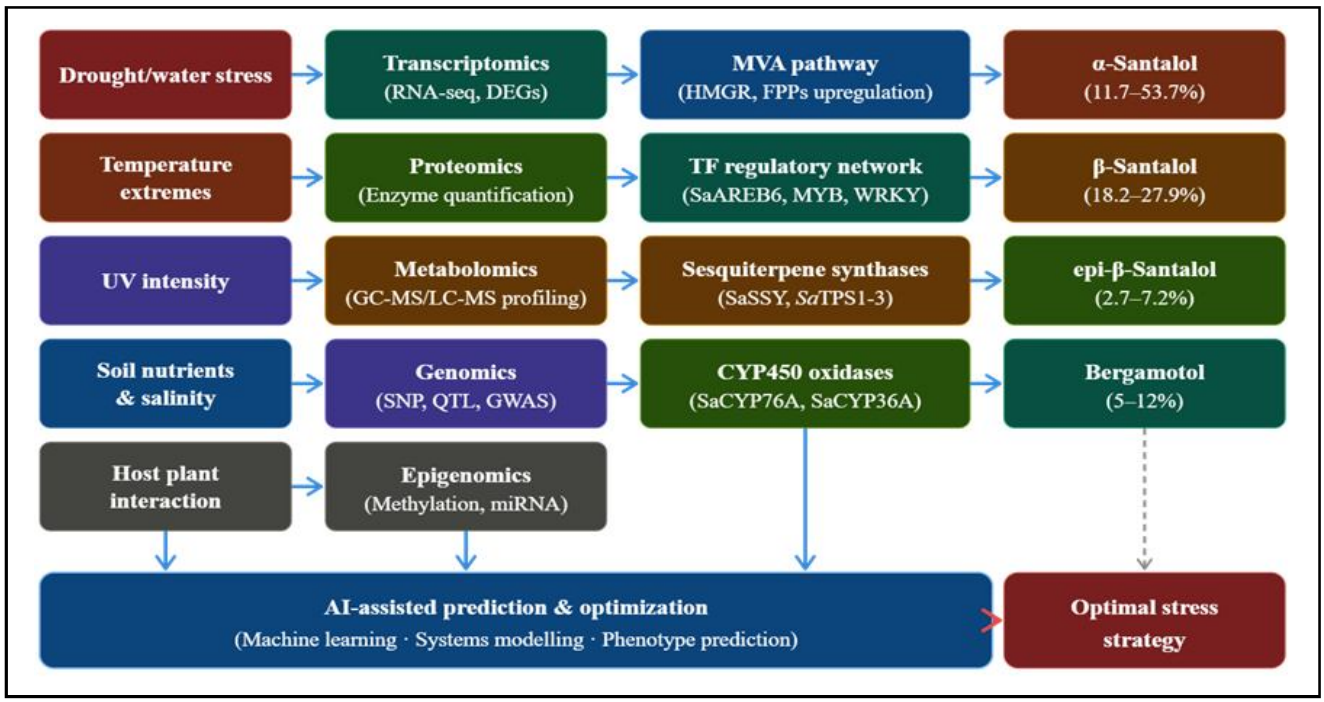

Figure 3: Integrated systems biology framework for *S. album* essential oil quality optimisation.

Environmental inputs (Column 1) are processed through multi-omics platforms (Column 2) that resolve pathway network activity (Column 3), thereby predicting sesquiterpene output compositions (Column 4). An AI-assisted prediction and optimisation module synthesises data across all layers to identify optimal stress management strategies. Dashed arrows indicate adaptive feedback from outputs to environmental management decisions.

7.2 Linking environmental variables to metabolite networks

A comparative transcriptomic study of sandalwood genotypes from different climate zones identified 727 transcripts differentially expressed between wet- and dry-zone genotypes, 1,141 between monsoon- and dry-zone genotypes, and 479 between wet- and monsoon-zone genotypes (Eswaran *et al.,* 2025). Genes related to heat shock proteins, zinc finger-binding proteins, and key transcription

factors were part of the climate-adaptive gene set, indicating that genotypic variation in climate response significantly influences oil quality in natural populations. Integrating environmental data (such as rainfall, temperature, soil nutrients) with multi-omics data (transcriptomics, proteomics, metabolomics) *via* network modelling is an emerging approach in predictive phytochemistry (Varadharajan *et al.,* 2025).

7.3 Emerging integrative tools

Transcriptomics *via* RNA sequencing has generated large-scale datasets for *S. album*, including transcriptome profiles of heartwood from high- and low-oil genotypes (Varadharajan *et al.,* 2025), cold-stressed leaves (Zhang *et al.,* 2017), drought-stressed seedlings (Meng *et al.,* 2024), and haustorial tissue. Proteomics studies have quantified the abundance of pathway enzymes across tissues and developmental stages. Integrating these datasets through computational network models that incorporate transcription factor binding predictions, pathway flux modelling, and environmental covariate regression offers the prospect of quantitative, genome-to-chemistry prediction of oil quality from measurable environmental parameters. Figure 3 presents a conceptual framework for this integrated systems biology approach.

8. Application: Controlled stress for enhanced oil production

Translating mechanistic understanding into actionable plantation management requires aligning molecular knowledge of the hormetic window with practical, scalable interventions. Table 5 evaluates published stress strategies by mechanism, reported outcome, and field feasibility.

Table 5: Stress-based strategies for enhanced sandalwood oil yield and quality

Stress strategy	Target mechanism	Reported outcome	Oil yield improvement	Feasibility	References
Regulated deficit irrigation (RDI)	ABA-mediated stomatal closure and SaAREB6 activation	Increasing sesquiterpene accumulation and improved oil density	+20-45%	High (field scalable)	Meng *et al.,* 2024
Methyl jasmonate foliar application (0.1-1 mM)	JA signalling, HMGR and FPPS upregulation	Increases SaTPS gene expression and enhances heartwood oil	+20-35%	Moderate (cost-intensive)	Zhang *et al.,* 2019
Salicylic acid (SA) elicitation	SA signalling and defence terpenoid pathway activation	Increases Sesquiterpene synthase gene expression in leaves	+15-25%	Moderate	Zhang *et al.,* 2019
Stem injection (H_2O_2, plant regulators)	Oxidative signalling and heartwood formation acceleration	Accelerated heartwood maturation and increases santalol content	+10-25%	Moderate (tree level)	Meng *et al.,* 2024
Light manipulation (shade reduction)	Photosynthetic enhancement and ROS modulation	Improved growth but variable oil quality outcomes	-5 to +15%	Moderate (plantation)	Zhang *et al.,* 2019
Nutrient stress (N or P limitation)	Carbon reallocation to secondary metabolism	Increases oil concentration in nutrient-limited trees	+15-30%	Moderate (soil level)	Brand *et al.,* 2007
Host-plant selection (N_2-fixing hosts)	Improved N nutrition *via* haustoria and reduced stress load	Enhanced growth and metabolic balance in *S. album*	Variable (+10-20%)	High (agroforestry)	Lu *et al.,* 2014
Temperature cycling (mild heat pulses)	Heat shock protein induction and terpenoid volatilisation	Transiently elevated sesquiterpene synthesis in leaves	+10-18%	Low (energy-intensive)	Zhang *et al.,* 2019

8.1 Drought and irrigation management

Regulated deficit irrigation (RDI), the strategic withholding of supplemental water during specific phenological stages, emerges as the most scalable and evidence-based strategy. Meng *et al.* (2024) documented that drought conditions triggered SaAREB6 activation and SaCYP736A167 upregulation, resulting in measurable increases in santalol without the severe growth penalties associated with prolonged water stress. In plantation settings, regulated deficit irrigation could be implemented by withdrawing irrigation during the physiological stage of active heartwood formation (typically after year 10), thereby creating a sustained, moderate water deficit that mimics the seasonal drought experienced by high-quality natural forest trees in Karnataka. This approach does not require exotic inputs, integrates with existing plantation hydrology, and exploits the same molecular pathway that explains why natural-zone trees outperform their irrigated counterparts.

8.2 Elicitor application

Methyl jasmonate and salicylic acid are established elicitors of terpenoid biosynthesis across woody plant systems. Zhang *et al.* (2019) showed that a 1 mM methyl jasmonate treatment dramatically induced expression of SaTPS1 and SaTPS2 in *S. album* leaves, though the applicability to heartwood accumulation over tree-scale timescales remains to be validated in multi-year field trials. H_2O_2 stem injection has also been reported to stimulate sandalwood oil biosynthesis (Meng *et al.,* 2024), leveraging the central role of oxidative signalling in the stress-response cascade. The practical challenge for elicitor

strategies in a perennial woody species is the persistence of the effect. Unlike annual crops, where a single elicitation episode can enhance harvestable metabolites, sandalwood heartwood formation requires years of sustained biosynthetic activity, making episodic elicitor application potentially insufficient without long-term experimental validation.

8.3 Nutrient and host management as indirect stress tools

Since the carbon nutrient balance hypothesis predicts increased secondary metabolite production under nitrogen limitation, planting schemes with moderate nitrogen restriction- such as using low-fertility soils and avoiding high nitrogen host species- offer an underutilised management option. The dual advantage of N_2-fixing hosts enhancing sandalwood growth, while potentially leading to nitrogen excess, creates a tension in host selection strategies. A phased approach to host management- using N_2-fixing hosts in early years for establishment and switching to non-fixing, low-competition hosts during oil development- may better optimise both biomass yield and secondary metabolite production (Lu *et al.,* 2014; Verma *et al.,* 2024).

9. Constraints, contradictions, and knowledge gaps

Despite recent advances, significant unresolved contradictions and evidence gaps still hinder the transformation of mechanistic understanding into reliable predictive management. Three main constraints are particularly noteworthy. First, there is a stark mismatch between the short experimental timescales (days to months in seedling studies) and the much longer ecological timescale (decades) for heartwood oil accumulation. This discrepancy means most molecular stress studies have used tissues such as leaves and seedlings that do not directly reflect the heartwood system in which commercial oil ultimately forms. The SaAREB6-SaCYP736A167 link identified by Meng *et al.* (2024) is a key breakthrough because it was confirmed in sandalwood tissue and showed increased santalol. However, whether this response persists over the long term in a maturing heartwood system during a 20-year plantation cycle remains entirely unverified.

Secondly, the lack of standardised experimental protocols- especially for stress intensity measurement, tree age at sampling, and oil extraction methods- undermines the reliability of cross-study quantitative comparisons. For example, a study showing a '41% increase in santalol under drought using seedling leaf tissue after 5 days of water withholding in a growth chamber cannot be directly compared to a field report of 'higher oil in low-rainfall zones' in 30-year-old trees. There is a need for a consensus on a minimal-stress experimental reporting standard in the field, similar to the minimum information about a microarray experiment guideline used in genomics.

Third, the genetic heterogeneity of the material examined is rarely controlled for *S. album* populations across India, Australia, Indonesia, and Sri Lanka show significant genetic diversity, as demonstrated by molecular marker research (Fatima *et al.,* 2022). Divergent reports on how drought affects oil yield may be due in part to genotype-by-environment interactions rather than to different biological pathways. Conducting multi-location trials with genetically characterised clonal material is crucial to distinguish genetic factors from environmental influences on oil variability.

10. Future perspectives

The combination of molecular biology, forest ecology, and data science is opening new opportunities in the phytochemistry of sandalwood. Controlling stress through close management of water, nutrients, and elicitors, keeping trees on the top half of the hormesis curve, should be the primary applied focus for this research. AI models trained over years on transcriptomics, metabolomics, and environmental data would provide real-time management decisions, *e.g.,* when to water, to achieve optimal, high-quality oil production. For *S. album*, climate change poses both threats and possibilities. Trends towards diminished rainfall and greater temperature extremes in peninsular India would increase the production of stress-induced santalol, while also endangering growth and survival, making climate-sensitive plantation strategies informed by plant stress physiology and climate modelling crucial.

At the molecular level, technologies such as CRISPR and ChIP-seq are being used to test predictions about TF networks (including SaAREB6, WRKY, MYB, and NAC factors) and to map regulatory networks; the recent release of the chromosome-scale genome assembly will greatly aid these studies. Integrating this work with long-term field data could enable sandalwood science to transition from a descriptive to a predictive, quantitative science.

11. Conclusion

This review demonstrates that variation in *S. album* oil yield and composition is a predictable outcome of abiotic stress regulation rather than random variability. It outlines a well-supported mechanistic pathway linking environmental stressors to ROS accumulation, hormonal signalling, transcription factor activation, and enhanced santalol biosynthesis *via* the MVA pathway. Multiple molecular studies validate key steps in this pathway, particularly the roles of HMGR, FPPS, and SaSSY enzymes. A central insight is the hormetic effect, in which moderate stress increases oil yield and santalol content, whereas severe stress inhibits production. Field evidence shows that forest-grown trees exposed to diverse stress conditions consistently produce superior oil compared with plantation-grown trees. This highlights ecological heterogeneity as a natural model for optimising oil quality through controlled stress. Advances in omics technologies and systems modelling now enable predictive and proactive management of oil biosynthesis in living trees. However, significant gaps remain, including the lack of long-term heartwood-specific studies and standardised experimental designs. Addressing these challenges is essential for scaling predictive phytochemistry to commercial applications. Overall, this integrative framework provides a model for improving secondary metabolite production in sandalwood and other high-value woody species under changing environmental conditions.

Acknowledgements

The authors sincerely thank the Department of Silviculture and NRM at the Forest College and Research Institute in Mettupalayam for providing essential infrastructure and academic support during the preparation of this manuscript. They also gratefully acknowledge the contributions of researchers and field ecologists whose published works on *S. album*'s physiology, molecular biology, and essential oil chemistry formed the foundational literature for this review. Special thanks are extended to my Chairman, Dr A. Balasubramanian, Dean

(Forestry), for assistance in accessing scientific databases and reference materials. This work did not receive any specific funding from public, commercial, or non-profit agencies. Also, I wish to acknowledge the National Bank for Agriculture and Rural Development (NABARD), Tamil Nadu Biodiversity Conservation and Greening Project for Climate Change Response (TBGPCCR), and the Tamil Nadu Forest Department (TNFD) for their invaluable support in my research.

Conflict of interest

The authors declared no conflicts of interest relevant to this article.

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Citation **P. Ravi Raja Simman, A. Balasubramanian, Balaji Kannan, K. P. Ragunath, B. Sivakumar, P. Rajendran and P. Hemalatha (2026). Stress induced modulation of sesquiterpene biosynthesis in *Santalum album* L.: From abiotic stress to enhanced bioactive compound production. Ann. Phytomed., 15(1):381-391, http://dx.doi.org/10.54085/ap.2026.15.1.33.**