Climate-Driven Modulation of Plant Secondary Metabolites: Implications for Medicinal Quality, Standardization, and Therapeutic Efficacy */İklim Kaynaklı Bitkisel Sekonder Metabolit Değişimleri: Tıbbi Kalite, Standardizasyon ve Terapötik Etkinlik Üzerine Etkileri*

ABSTRACT

Background: Secondary metabolites are key biochemical compounds that mediate plant defense, ecological interactions, and environmental adaptation. Major classes—including terpenoids, phenolics, alkaloids, and polyketides—play critical roles in plant–microbe and plant–herbivore interactions while also providing pharmacologically important compounds for human health. **However, global climate change factors substantially influence the biosynthesis and accumulation of these metabolites. Climate change refers to the long-term shifts in global temperatures, precipitation patterns, atmospheric CO_2 concentrations, and UV-B radiation levels driven primarily by anthropogenic greenhouse gas emissions, collectively altering the abiotic environment in which plants evolve, grow, and synthesize their secondary metabolites.** **Aim:** This narrative review synthesizes current evidence on climate-driven modulation of plant secondary metabolism and evaluates the molecular and biochemical mechanisms underlying climate-induced phytochemical variation. **Methods:** Relevant literature published between 2015 and 2025 was systematically surveyed using PubMed, Web of Science, and Scopus, prioritizing experimental, metabolomic, and multi-omics studies investigating climate–metabolite interactions. **Results:** Elevated CO_2 generally enhances carbon-based metabolites, particularly phenolics and flavonoids, through increased carbon flux toward the shikimate pathway. In contrast, heat and drought stress stimulate terpenoid and alkaloid biosynthesis via **reactive oxygen species (ROS)**-mediated signaling and activation of transcription factors such as **myeloblastosis (MYB), basic helix-loop-helix (bHLH), WRKY (named after the conserved WRKYGQK peptide), and NAC (NAM/ATAF/CUC)**. UV-B exposure consistently promotes flavonoid accumulation as a photoprotective response. **Conclusion:** Understanding climate–metabolite interactions is essential for maintaining phytochemical diversity, ensuring pharmaceutical standardization, and developing climate-resilient medicinal plant production systems.

Keywords; Secondary metabolites, Climate change, Phytochemical standardization, Medicinal plants, Abiotic stress

Öz

Giriş: Sekonder metabolitler, bitkilerin savunma mekanizmalarını, ekolojik etkileşimlerini ve çevresel adaptasyon süreçlerini düzenleyen önemli biyokimyasal bileşiklerdir. Terpenoidler, fenolikler, alkaloidler ve poliketidler gibi metabolit sınıfları, bitki–mikroorganizma ve bitki–otçul etkileşimlerinde kritik rol oynarken aynı zamanda farmakolojik açıdan değerli doğal ürünlerin kaynağını oluşturur. Ancak küresel iklim değişikliği faktörleri bu metabolitlerin biyosentezini ve birikimini önemli ölçüde etkilemektedir. **İklim değişikliği; başta antropojenik sera gazı emisyonlarından kaynaklanan küresel sıcaklık artışları, yağış düzeni bozulmaları, atmosferik CO_2 konsantrasyonlarındaki yükseliş ve UV-B radyasyon değişimleri gibi uzun vadeli çevresel dönüşümleri kapsayan ve bitkilerin evrimleştiği, büyüdüğü ve sekonder metabolitlerini sentezlediği abiyotik ortamı köklü biçimde dönüştüren çok boyutlu bir süreçtir.** **Amaç:** Bu derleme, iklim değişikliğinin bitkisel sekonder metabolizma üzerindeki etkilerini sentezlemeyi ve çevresel stres faktörlerinin fitokimyasal profilleri nasıl değiştirdiğini moleküler ve biyokimyasal düzeyde değerlendirmeyi amaçlamaktadır. **Yöntem:** 2015–2025 yılları arasında yayımlanan çalışmalar PubMed, Web of Science ve Scopus veri tabanlarında taranmış; özellikle deneysel, metabolomik ve multi-omik yaklaşımlara dayanan çalışmalar değerlendirilmiştir. **Bulgular:** Yükselen CO_2 seviyeleri karbon temelli metabolitlerin, özellikle fenolikler ve flavonoidlerin, şikimat yoluna artan karbon akışı ile yükselmesine yol açmaktadır. Buna karşılık sıcaklık ve kuraklık stresi, ROS aracılı sinyalleşme ve MYB, bHLH, WRKY ve NAC gibi transkripsiyon faktörleri üzerinden terpenoid ve alkaloid biyosentezini artırmaktadır. UV-B maruziyeti flavonoid birikimini fotoprotektif bir yanıt olarak güçlendirmektedir. **Sonuç:** Sekonder metabolit biyosentezi iklim parametrelerine oldukça duyarlıdır ve bu etkileşimlerin anlaşılması tıbbi bitkilerin sürdürülebilir üretimi ve farmasötik standardizasyon açısından kritik önem taşımaktadır.

Anahtar Kelimeler: Sekonder metabolitler, İklim değişikliği, Fitokimyasal standardizasyon, Tıbbi bitkiler, Abiyotik stres

INTRODUCTION

Plants have developed remarkable chemical diversity over approximately 450 million years of evolutionary history in response to fluctuating ecological pressures. A major component of this diversity is represented by secondary metabolites, which, although not essential for primary metabolic functions, play critical roles in plant survival by contributing to stress tolerance, herbivore deterrence, pathogen resistance, protection against UV radiation, and allelopathic interactions (Michael & Tomczyk, n.d.; Science & 1959, 1959; Khan et al., 2025). As emphasized by chemical ecology studies, interactions between plants and both herbivores and microorganisms have been among the primary selective forces driving the diversification and functional optimization of these metabolites (Ehrlich et al., 1964a; van der Linden et al., 2021). The evolutionary trajectory of secondary metabolism is further supported by paleobotanical evidence. For instance, increased UV-B exposure during the Cretaceous period is believed to have promoted the expansion of flavonoid-based photoprotective compounds, whereas the rising diversity of insect herbivores strengthened the selective pressure for terpenoid- and alkaloid-derived chemical defenses (Xu, S., & Gaquerel, E., 2025; Fernie et al., 2020). These cumulative evolutionary adaptations now underpin thousands of molecules of high therapeutic value in modern pharmacology, phytotherapy, and plant biotechnology.

Over the past decade, global climate change has emerged as one of the most influential environmental drivers shaping the future of plant metabolism. Rising atmospheric CO_2 concentrations, elevated temperatures, irregular precipitation and drought cycles, increased soil salinity, and fluctuations in UV radiation collectively modulate secondary metabolite biosynthetic pathways at both transcriptional and metabolic levels (Sun et al., 2023; Zandalinas et al., 2022). Elevated CO_2 tends to redirect carbon flux toward the shikimate pathway, enhancing phenolic compound production, whereas drought and heat stress frequently stimulate terpenoid and alkaloid biosynthesis through the accumulation of reactive oxygen species (ROS) (Foyer et al., n.d.; Y. Li et al., 2021). UV-B exposure further induces the synthesis of photoprotective flavonoids, regulated primarily through transcription factors such as MYB, bHLH, and WRKY (Meraj et al., 2020).

In medicinal and aromatic plants, climate-induced metabolic shifts have profound consequences for the quantity, chemical composition, and pharmacological potency of bioactive compounds. Levels of artemisinin in *Artemisia annua*, parthenolide in *Tanacetum parthenium*, sesquiterpene lactones in *Ferula* species, and essential oil constituents in *Mentha* species are all strongly influenced by environmental stress conditions (Ge et al., 2022.; Khorasaninejad et al., 2011; Qaderi et al., 2023). Such variability introduces major challenges for both agricultural production and the standardization of phytotherapeutic formulations.

This review synthesizes the evolutionary origins of secondary metabolites and critically examines how climate change alters their biosynthetic pathways at molecular, biochemical, and ecophysiological scales. Particular attention is given to the implications of these shifts for quality control, standardization, and the broader industrial and therapeutic relevance of medicinal plants.

METHODS

This narrative review was grounded in an extensive literature exploration aimed at synthesizing current knowledge on how climate change influences the biosynthesis and regulation of plant secondary metabolites. A broad, non-systematic search was conducted across major scientific databases, including PubMed, Web of Science, Scopus, and Google Scholar. The search covered studies published up to January 2025 and employed a wide range of keyword combinations such as: “secondary metabolites,” “specialized metabolism,” “phenylpropanoids,” “terpenoids,” “alkaloids,” “climate change,” “global warming,” “elevated CO_2,” “heat stress,” “drought stress,” “UV-B exposure,” “salinity stress,” “oxidative stress,” “biosynthetic pathways,” “transcriptional regulation,” and “medicinal plants.”

Eligible publications included in vivo, in vitro, transcriptomic, metabolomic, and physiological studies that directly investigated secondary metabolite biosynthesis, environmental stress responses, or climate-driven metabolic reprogramming. Only English-language articles were included. Studies focusing exclusively on primary metabolism, agricultural yield without biochemical context, or environmental observations lacking mechanistic relevance were excluded.

Priority was given to peer-reviewed articles published in recognized international journals, as well as authoritative reports and high-quality reviews in plant physiology, ecophysiology, phytochemistry, and climate-related biosciences.

All eligible studies were analyzed qualitatively and categorized into thematic domains based on content relevance. These domains included:

1. evolutionary foundations of secondary metabolism;
2. major abiotic stressors associated with climate change;
3. molecular, transcriptional, and biosynthetic regulatory mechanisms;
4. species-specific metabolic shifts and chemical variability;
5. implications for phytotherapeutic quality control and industrial applications; and

6. emerging biotechnological and agronomic strategies for resilient metabolite production.

This methodological framework enabled the integration of data derived from multiple disciplines and provided a holistic basis for interpreting the multi-layered metabolic responses that plants exhibit under changing climate conditions. By combining evolutionary, mechanistic, and applied perspectives, the review establishes a rigorous foundation for understanding both the scientific and practical implications of climate-induced metabolic modulation.

LITERATURE REVIEW AND THEORETICAL FRAMEWORK

Evolutionary Perspectives on Secondary Metabolites

The concept of secondary metabolites originates from classical ecological inquiries into the question: *"Why do plants produce such a vast and peculiar diversity of chemicals?"* Fraenkel's seminal 1959 essay, "The raison d'être of secondary plant substances," proposed that these compounds primarily evolved as defense agents against herbivores and as determinants of feeding preferences, thereby establishing the foundation for the allelochemical framework(York et al., 1959). Subsequently, the pioneering work of Ehrlich and Raven on butterfly–plant associations highlighted the co-evolutionary dynamics between phytophagous insects and their host plants (Ehrlich et al., 1964b), demonstrating that secondary metabolite diversity is shaped by reciprocal selective pressures.

Contemporary reviews portray the evolution of plant metabolism not as a static repertoire of defensive compounds but as a dynamic continuum driven by genome duplications, gene family expansions, and modular biosynthetic networks. Maeda (2021), in a comprehensive overview of metabolic evolution, emphasizes that secondary metabolism constitutes an adaptive layer built upon primary metabolic pathways, largely expanded through gene duplication and neofunctionalization (Maeda & Fernie, 2021). More recent contributions by Fernie and colleagues conceptualize specialized metabolism as a "design space" governed by environmental pressures but constrained by intrinsic genetic and biochemical limitations.

Taken together, the historical and theoretical literature frames the evolution of secondary metabolites along three major axes: (i) ecological functions, including herbivore and pathogen defense, allelopathy, and signaling; (Assunção et al., 2021; Mithöfer et al., 2012), (ii) photoprotective and redox-regulatory roles, particularly involving phenolics and flavonoids; (Agati & Tattini, 2010), (iii) domestication-driven shifts, wherein agricultural selection can reduce or restructure chemical diversity (Challa, 2018). This framework provides the conceptual foundation for understanding how climate change reshapes metabolic networks today.

Climate Change and Secondary Metabolism: Insights From Recent Reviews

Over the past decade, numerous review articles have examined the impacts of global climate change on plant secondary metabolism. Reshi et al. (2023) synthesize how the major biosynthetic pathways of secondary metabolites are reconfigured under various abiotic stressors—including heat, drought, salinity, light regimes (Reshi et al., n.d.), UV radiation, and heavy metals—highlighting the roles of phenolics, terpenoids, and alkaloids in ROS detoxification, membrane stabilization, and stress signaling.

A comprehensive review by Sun et al. (2024) in *Trends in Plant Science* identifies secondary metabolism as a central component of plant adaptation to fluctuating climatic conditions (Sun & Fernie, 2024). Their analysis emphasizes that climate-induced metabolic responses vary according to metabolite class, stress severity, and species-specific traits, often producing complex or even contradictory outcomes. Similarly, Jamloki et al. (2021) report that elevated CO_2 and high temperature generally promote the synthesis of carbon-based metabolites (phenolics, flavonoids, certain terpenoids), but may also cause shifts in yield and chemical composition due to growth–defense trade-offs (Jamloki et al., n.d.).

Focusing on medicinal and aromatic plants, Jangpangi et al. (2025) and Neto et al. (2021) describe heterogeneous yet substantial effects of climate change on the production of bioactive metabolites, marker compounds, and pharmacopoeial quality parameters.(Jangpangi et al., 2025a; Neto et al., 2021) Increased temperature and evapotranspiration intensify soil drying and exacerbate drought stress, leading to shifts in phenolic profiles, increases in certain volatile compounds, and reductions in others.

Collectively, these reviews underscore that secondary metabolite biosynthesis exhibits high sensitivity yet strongly nonlinear responses to climatic variables, with outcomes depending on plant species, tissue type, developmental stage, and the combination of stress factors involved.

Secondary Metabolite Responses to Major Abiotic Stressors

Elevated CO_2 and Temperature

Elevated atmospheric CO_2 concentrations have been widely shown to enhance the accumulation of carbon-based metabolites. In *Zingiber officinale*, increasing CO_2 from 400 to 800 µmol mol^{-1} significantly increased total phenolic and flavonoid contents, with **high-performance liquid chromatography (HPLC) analyses identifying quercetin and gallic acid as dominant compounds. Similar responses are reported in** *Populus* species, where CO_2 enrichment elevates phenolic levels and associated antioxidant capacity.

In their review, Jamloki et al. (2021) indicate that CO_2 elevation generally stimulates phenolic and flavonoid biosynthesis across plant taxa, although high temperatures can produce either stimulatory or inhibitory effects depending on stress thresholds (Athanasiadou & Theriou, 2021). Dobhal et al. (2024) further note that heat stress induces increases in terpenoids and certain alkaloids while causing species-specific shifts in essential oil composition (Dobhal et al., n.d.).

Drought and Water Deficit

Drought is among the strongest abiotic triggers of secondary metabolite production. Pant et al. (2021) demonstrate that drought stress enhances the biosynthesis of phenolics, flavonoids, terpenoids, and several alkaloids, which contribute to drought tolerance through ROS scavenging, lipid peroxidation mitigation, and membrane protection (Pant et al., 2021). More recent syntheses confirm that drought commonly promotes the accumulation of phenolic and flavonoid compounds, reinforcing their essential role in stress adaptation.

Nicolas-Espinosa et al. (2023) evaluated phenolics and glucosinolates under drought, salinity, and heat stress, revealing their close association with root water uptake and oxidative stress regulation (Nicolas-Espinosa et al., n.d.). These findings indicate that phenolic metabolism will remain critical for both physiological adaptation and phytochemical quality under future drought scenarios driven by climate change.

UV-B Radiation

Although UV-B radiation can damage DNA, proteins, and membrane structures, it also acts as a potent inducer of secondary metabolism through photomorphogenic signaling. Li et al. (2024) showed that UV-B exposure in blue-grain wheat enhanced flavonoid accumulation and upregulated key biosynthetic genes such as *FLS*, *DFR*, and *ANR* (L. Li et al., 2024). Tian et al. (2024) reported significant increases in total flavonoids and antioxidant capacity in buckwheat sprouts subjected to UV-B, thereby enhancing their nutritional and functional value (Tian et al., n.d.).

Recent syntheses highlight that UV-B defense strategies depend heavily on the production of flavonoids, phenylpropanoids, and other UV-absorbing metabolites—diversity shaped by gene duplication and long-term environmental adaptation. Changes in UV regimes are thus expected to significantly influence the metabolic profiles of flavonoid-rich plants of pharmacological relevance.

Salinity and Osmotic Stress

Salinity imposes osmotic imbalance and ion toxicity, yet many species respond by increasing secondary metabolite production. In *Silybum marianum*, rising NaCl concentrations enhanced total phenolic content and antioxidant activity, and exogenous ascorbic acid or biostimulants further amplified these responses (Manafi et al., 2024). Broader evidence suggests that salinity can stimulate the accumulation of tannins, alkaloids, flavonoids, phenolics, anthocyanins, and saponins, although the magnitude of responses varies markedly across species and tissues (Chougule et al., 2022).

These observations indicate that salinity stress—expected to intensify in many agricultural regions—poses dual challenges for medicinal plants: maintaining stress tolerance while preserving phytochemical standardization(Bistgani et al., 2019).

PHYTOTHERAPEUTIC AND INDUSTRIAL IMPLICATIONS

Global climate change induces substantial alterations in the quantity, chemical composition, and biological activity of secondary metabolites in medicinal plants, thereby generating significant quality-related challenges in phytotherapy. Fluctuations in therapeutically important metabolites—such as essential oils, flavonoids, sesquiterpene lactones, phenylpropanoids, and alkaloids—under environmental stress complicate standardization processes and create batch-to-batch variability that can influence pharmacological efficacy (Fernandes et al., n.d.; Jain et al., n.d.).

Standardization and Pharmacopoeial Consequences

According to the European Pharmacopoeia and **European Medicines Agency (EMA)**-Herbal Monograph criteria, the quality of a medicinal plant is defined by its drug identity, macro- and microscopic characteristics, ash values, chromatographic fingerprints **high-performance thin-layer chromatography/high-performance liquid chromatography** (**HPTLC/HPLC**), quantification of marker compounds, and pesticide/heavy metal limits. However, climate-driven metabolic fluctuations can induce 20–60% variations in marker compound levels, posing a major barrier to consistent product quality (Jangpangi et al., 2025b).

Phytotherapeutic Efficacy and Safety Considerations

An increase in secondary metabolites induced by stress should not always be interpreted as beneficial.

For example: Excessive UV or drought conditions can induce oxidative modifications in phenolics, potentially increasing genotoxicity risks (Xu et al., 2025). Stress-induced accumulation of alkaloids may elevate hepatotoxic potential in certain taxa, particularly those containing pyrrolizidine alkaloids (Moreira et al., 2018).

Accordingly, climate-induced metabolic changes affect not only agricultural production but also the safety and pharmacological profile of herbal medicines (A & 2011, 2011).

Future Perspectives

Escalating climate variability underscores the need for advanced technological and biotechnological innovations to ensure the sustainable production of secondary metabolites.

Controlled Environment Agriculture (CEA) and Vertical Farming

CEA eliminates environmental fluctuation by fully regulating growth conditions, thereby optimizing metabolite production. Applications include:

- **light-emitting diode (LED)**-based spectral modulation to enhance flavonoid/anthocyanin biosynthesis
- CO_2 enrichment to stimulate phenolic and terpenoid pathways
- Precise control of photoperiod, humidity, and temperature regimes

CEA has demonstrated substantial improvements in standardization for species such as Artemisia, Mentha, Ocimum, Hypericum, and Curcuma (G. Li et al., 2024). It represents a strategic technology capable of making medicinal-plant cultivation largely climate-independent.

CRISPR/Cas9-Based Genetic Engineering

Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein 9 (CRISPR/Cas9) enables targeted modification of secondary metabolite biosynthesis at multiple regulatory nodes: Upregulation of biosynthetic enzymes (e.g., **chalcone synthase (CHS), 1-deoxy-D-xylulose-5-phosphate synthase (DXS), 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR)**), Modification of transcription factors controlling metabolic flux (e.g., MYB, bHLH families), Optimization of hormonal regulatory pathways (**jasmonic acid (JA), salicylic acid (SA), abscisic acid (ABA)** signaling). For instance, CRISPR-mediated overexpression of DXS can enhance monoterpene production via the **methylerythritol phosphate (MEP)** pathway, whereas editing of CHS/CHI may reduce UV-B sensitivity and stabilize flavonoid biosynthesis under environmental stress (Gao et al., 2024). Such strategies may facilitate the development of climate-resilient, high-metabolite-yielding medicinal plant cultivars.

Artificial Intelligence for Climate–Metabolite Interaction Modeling

Machine learning and artificial intelligence have recently emerged as powerful tools for predicting climate-driven shifts in metabolite profiles. Models leveraging environmental inputs (temperature, CO_2, UV-B, humidity) have shown high predictive accuracy using: Random Forest, XGBoost, Artificial Neural Networks (ANN), Deep Neural Networks (DNN) and

Convolutional Neural Networks (CNN). These tools can support the identification of stress thresholds, metabolite optimization strategies, and production planning under future climate scenarios (Anas et al., 2026).

Epigenetic and Priming-Based Strategies

Stress factors such as drought, UV-B, and salinity are known to induce epigenetic memory. Thus, epigenetic priming offers a potential approach for stabilizing metabolite biosynthesis through: persistent histone modifications, DNA methylation patterns,, long-term stress-memory pathways (Springer & Schmitz, 2017). Such approaches may enable the development of cultivars with enhanced and stable metabolite production.

Biotechnological Production Platforms: Cell and Callus Cultures

In vitro production systems—including plant cell suspension cultures, hairy root cultures induced by *Agrobacterium rhizogenes*, and dedifferentiated callus tissues—are widely employed for the large-scale biosynthesis of high-value secondary metabolites. These platforms have already been successfully commercialized or experimentally optimized for key phytochemicals such as artemisinin ("Artemisinin Production in Artemisia Annua: Studies in Planta and Results of a Novel Delivery Method for Treating Malaria and Other Neglected Diseases," n.d.), paclitaxel (taxol) (biotechnology & 2007, n.d.; Degl'Innocenti et al., 2009), and podophyllotoxin (Murthy et al., 2014), demonstrating their utility for controlled, sustainable, and high-yield metabolite production. Because in vitro production systems operate independently of external climate variability, they provide highly reproducible conditions and enable robust standardization of metabolite profiles. The use of biochemical elicitors—including jasmonic acid (JA), salicylic acid (SA), melatonin, and chitosan—is well documented to enhance secondary metabolite biosynthesis, often increasing yields by 100–300% depending on the species and culture type. These elicitation strategies significantly improve productivity, making in vitro platforms scalable and industrially viable (Gadzovska et al., 2013; Zhao et al., n.d.).

CONCLUSION

Plant secondary metabolites constitute one of the most dynamic biochemical interfaces between plants and their environment, shaped by millions of years of evolutionary pressures. Contemporary climate change—characterized by rising temperatures, elevated atmospheric CO_2, fluctuating UV-B radiation, increasing drought frequency, and soil salinization—has emerged as a major driver reshaping these metabolic pathways at molecular, biochemical and ecological levels. Evidence indicates that climate variables induce highly non-linear, species-specific shifts in metabolite profiles through ROS-mediated signaling, **mitogen-activated protein kinase (MAPK)** activation, transcription factor networks (MYB, bHLH, WRKY, NAC), and epigenetic remodeling of biosynthetic genes.

These mechanistic adjustments, while adaptive for plant survival, have direct implications for pharmacological potency, standardization, and safety of medicinal plants. Variability in marker compounds—such as artemisinin, parthenolide, sesquiterpene lactones, flavonoids, and alkaloids—poses growing challenges for **Good Agricultural and Collection Practices/Good Manufacturing Practices (GACP/GMP) frameworks and global herbal medicine markets. As climate instability intensifies, ensuring metabolic consistency will require a transition from climate-dependent to climate-controlled production systems.**

Future strategies must therefore integrate controlled-environment agriculture (CEA), genome editing (CRISPR/Cas), metabolic engineering, epigenetic priming, and **artificial intelligence (AI)-based predictive modelling, enabling stable and scalable production of bioactive metabolites regardless of external environmental fluctuations. A holistic understanding of climate–metabolite interactions will not only safeguard phytochemical diversity but also strengthen the scientific reliability, therapeutic efficacy, and industrial sustainability of natural product-based medicines.**

Ultimately, addressing the biochemical consequences of climate change on plant secondary metabolism represents a critical frontier for plant biology, pharmacognosy, and global health, demanding coordinated research efforts and technologically advanced cultivation systems.

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