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The Effects of Global Climate Change on Gene Expression in Honey Bees *(Apis mellifera)*

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Abstract

Global climate change is reshaping the abiotic environment of honey bees and triggering molecular responses that underlie colony health and resilience. This review synthesizes research from the 2000s to the present, summarizing gene expression responses of *Apis mellifera* to climate-related stressors. The principal drivers include temperature extremes, altered seasonal regimes, elevated atmospheric CO_2, drought, and their interactions. Heat stress induces the expression of heat shock proteins (HSP70/90), antioxidant defenses, and detoxification genes, while suppressing the expression of glandular proteins (MRJPs). Cold stress downregulates genes involved in the peroxisomal and glutathione pathways, thereby increasing oxidative damage. Rising CO_2 levels reduce pollen protein content and indirectly alter the expression of vitellogenin and immune genes. Drought, nutritional scarcity, and pathogen pressure reprogram immune effectors such as defensin-1. Subspecies adapted to hot climates (*A. m. jemenetica*) exhibit strong HSP responses, although increasing extremes may exceed their adaptive thresholds. Recent studies suggest that epigenetic mechanisms, including DNA methylation and histone modification, play a role in the persistence of these responses. Collectively, the findings provide an integrative framework for selective breeding of stress-tolerant colonies and for omics-based research addressing the complex interplay among multiple climatic stressors.

Keywords: Honeybee, Gene expression, Climate change, Heat shock proteins, Immunity

Küresel İklim Değişikliğinin Bal Arısı *(Apis mellifera)* Gen Ekspresyonuna Etkileri

Öz

Küresel iklim değişikliği, bal arılarının abiyotik çevresini yeniden şekillendirmekte ve koloni sağlığını belirleyen moleküler yanıtları tetiklemektedir. Bu derleme, 2000'li yıllardan günümüze *Apis mellifera*'nın iklimle ilişkili stres faktörlerine verdiği gen ekspresyonu tepkilerini özetlemektedir. Başlıca stresörler arasında sıcaklık aşırılıkları, değişen mevsimsel düzenler, artan atmosferik CO_2, kuraklık ve bunların etkileşimleri yer almaktadır. Isı stresi, ısı şok proteinleri (HSP70/90), antioksidan savunmalar ve detoksifikasyon genlerini indüklerken; salgı bezi proteinlerinin (MRJP'ler) ekspresyonunu baskılar. Soğuk stresi, peroksizom ve glutatyon yolak genlerini aşağı regüle ederek oksidatif hasarı artırır. CO_2 artışı, polen protein içeriğini azaltır ve dolaylı olarak vitellogenin ve bağışıklık genlerinde değişime yol açar. Kuraklık, besin kıtlığı ve patojen baskısı bağışıklık efektörlerini (defensin-1) yeniden düzenler. Sıcak iklimlere adapte alt türler (*A. m. jemenetica*) güçlü HSP yanıtları sergilese de aşırı koşullar adaptif sınırları zorlamaktadır. Son yıllarda epigenetik mekanizmaların (DNA metilasyonu, histon modifikasyonu) bu yanıtların sürekliliğinde rol oynadığı belirlenmiştir. Bulgular, stres toleranslı kolonilerin ıslahı ve çoklu stres etkileşimlerine odaklanan omik tabanlı çalışmalar için önemli bir çerçeve sunmaktadır.

Anahtar kelimeler: Bal arısı, Gen ifadesi, İklim değişikliği, Isı şok proteinleri, Bağışıklık

Genişletilmiş Özet

Amaç: Bu çalışma, küresel iklim değişikliğiyle ilişkili faktörlerin, aşırı sıcaklıklar, sıcaklık dalgalanmaları, değişen kış koşulları, yükselen atmosferik karbondioksit (CO_2) seviyeleri, kuraklık ve bunların etkileşimleri, bal arısı (*Apis mellifera*) gen ekspresyonu üzerindeki etkilerine dair kanıtları bir araya getirmeyi amaçlamaktadır. Aynı zamanda, koloni dayanıklılığıyla ilişkili ortak moleküler imzaları tanımlamayı ve bu yanıtların fizyolojik sonuçlarını değerlendirmeyi hedeflemektedir. 2000–2025 yılları arasında yayınlanmış, özellikle açık erişimli ve yüksek etki faktörlü dergilerde yer alan hedeflenmiş gen çalışmaları ve transkriptomik (RNA-seq, DGE, qPCR tabanlı) araştırmalar titizlikle gözden geçirilmiştir. Bulgular, stres faktörü sınıflarına göre düzenlenmiş ve gen düzeyindeki tepkiler; protein homeostazı, oksidatif stres yanıtı, bağışıklık regülasyonu, detoksifikasyon ve besin metabolizması gibi fonksiyonel yollarla eşleştirilmiş, ayrıca yaşam evresi (larva, pupa, ergin) ve doku özgüllüğü dikkate alınmıştır.

Tartışma: Isı stresi, bal arılarında moleküler düzeyde en güçlü yanıtları tetikleyen çevresel faktörlerden biridir. Yüksek sıcaklıklar, ısı şok proteinlerini (HSP70/90 ve küçük HSP'ler), moleküler şaperonları ve oksidatif stres savunmalarını (örneğin SOD, CAT, GST) hızla aktive eder. Aynı zamanda sitokrom P450 gibi detoksifikasyon enzimleri de bu yanıtın bir parçasıdır. Hipofarinks bezlerinde aşırı sıcaklık, MRJP genlerinin ekspresyonunu baskılayarak arı sütü üretimini azaltır ve koloni besleme dengesini bozar. Çöl iklimine adapte olmuş alt türler (*A. m. jemenetica*) daha yüksek HSP düzeyleri ve geniş termal tolerans sergilese de artan sıcaklık dalgaları bu adaptif sınırların aşılabileceğini göstermektedir. Öte yandan, soğuk stresine maruz kalan yavrularda glutatyon ve peroksizom yolu genleri baskılanmakta, oksidatif hasar riski artmaktadır. Ilıman geçen kışlarda diyapoz benzeri durgunluk bozulur, vitellogenin rezervleri azalır ve antimikrobiyal peptitlerin (örneğin defensin-1, abaecin) aşırı ekspresyonu, enerji–bağışıklık dengesinde bozulmaya neden olur.

Atmosferik CO_2 artışı ve kuraklık, bal arılarında beslenme aracılı stresin en önemli bileşenleridir. Yükselen CO_2, polen protein oranını düşürerek besin kalitesini azaltır; bu da vitellogenin düzeylerinde azalma, bağışıklık genlerinde düzensizlik ve artan duyarlılıkla ilişkilidir. Kuraklık, polen ve nektar miktarını azaltarak arılarda savunma mekanizmalarının yeniden düzenlenmesine yol açar; kısa süreli açlıkta defensin-1 gibi genlerin hızla indüklendiği görülmüştür. Son yıllarda yapılan çalışmalar, ısı, beslenme, pestisit ve patojen gibi stresörlerin birleşik etkilerinin homeostaz, bağışıklık ve metabolizma üzerinde sinerjistik sonuçlar doğurduğunu, buna karşın çoklu stres ve kronik maruziyetleri inceleyen uzun dönemli çalışmalarda ciddi bir eksiklik bulunduğunu ortaya koymaktadır. Bu bulgular, bal arılarının iklim değişikliğine verdiği yanıtların sadece tekil faktörlerle değil, etkileşimli stres ağlarıyla anlaşılması gerektiğini vurgulamaktadır.

Sonuç: İklimle ilişkili stres faktörleri, yaşam evresi, doku tipi ve alt tür farklılıklarına bağlı olarak şaperonlar, antioksidan sistemler, antimikrobiyal peptitler, detoksifikasyon enzimleri ve besin depolama genleri üzerinde ortak bir gen ekspresyon desenine yol açmaktadır. Bu genetik ve moleküler imzalar, koloni düzeyinde yavru yetiştirme, bağışıklık dengesi ve kışlama başarısı gibi temel işlevlerin düzenlenmesinde merkezi bir rol oynar. İklim değişikliğinin hızlandığı bu dönemde, koloni işlevlerinin sürdürülebilirliğini sağlamak için çok faktörlü ve uzun vadeli omik yaklaşımlara dayanan deneysel çalışmalara, besin kıtlığı dönemlerinde protein kalitesi yüksek beslenme stratejilerinin uygulanmasına ve stres dayanıklılığına ait moleküler belirteçlerin (örneğin HSP'ler, vitellogenin, defensin-1, glutatyon yolak genleri) ıslah programlarına entegre edilmesine ihtiyaç vardır. Bu bütüncül yaklaşım, bal arılarında iklime dayanıklı genetik hatların tanımlanması, koloni sağlığının izlenmesi ve sürdürülebilir arıcılık yönetimi açısından kritik öneme sahiptir. Ayrıca, arıcılar açısından bakıldığında; yüksek proteinli ve çeşitli polen kaynaklarına erişimin sağlanması, kolonilerin aşırı sıcak ve kuraklık dönemlerinde gölgelik–su desteğiyle korunması ve pestisit uygulamalarının sıcaklık/arı açlığı dönemleriyle çakışmamasına dikkat edilmesi, iklim değişikliğinin moleküler düzeyde artırdığı stres yükünü azaltmak için uygulanabilir temel adımlardır.

INTRODUCTION

Pollinators-particularly the western honey bee, *Apis mellifera*-provide essential pollination services that sustain both wild plant reproduction and agricultural productivity, thereby supporting ecosystem functionality (Feketéné Ferenczi et al. 2023; Ostwald et al. 2024). Accelerating global climate change is reshaping the abiotic environment of honey bee colonies by altering temperature regimes, precipitation dynamics, and plant phenology, while intersecting with pervasive anthropogenic stressors, including pathogens, pesticides, and habitat fragmentation (Zapata-Hernández et al. 2024; Sagastume et al., 2025). At the molecular level, shifts in gene expression represent some of the earliest organismal responses to environmental perturbations, regulating downstream physiological and colony-level outcomes (Cameron et al. 2013). Consequently, deciphering the transcriptomic responses of *A. mellifera* to climate-related stressors provides valuable early indicators of resilience or vulnerability within changing environments.

Over the past two decades, research has documented robust heat-shock responses, modulation of oxidative stress pathways, reprogramming of immune-related genes, and alterations in nutrition- and gland-associated gene networks in honey bees (Anderson and Maes 2022; Alghamdi et al. 2023). Such molecular adjustments have been observed in *Apis mellifera* workers exposed to elevated ambient temperatures, nutritional deprivation, and shifting overwintering conditions (Li 2024; Maigoro et al. 2025). However, despite this growing body of work, critical knowledge gaps remain. Most studies have focused on single stressors and short-term exposures, whereas colonies in natural environments experience continuous, fluctuating, and interacting stress factors (Zapata-Hernández et al. 2024). Consequently, the extent to which molecular responses are amplified under realistic multi-stressor climate scenarios-and how these responses translate into colony-level performance outcomes-remains largely underexplored.

This review synthesizes evidence from the past two decades to examine how *Apis mellifera* responds at the gene-expression level to climate-related stressors. The discussion is structured around four major axes: (1) temperature stress and heat-shock responses; (2) cold stress and antioxidant/winter gene regulation; (3) elevated CO_2, altered pollen and nectar quality, and nutritional stress; and (4) drought, food scarcity, and immune–metabolic gene adjustments. It further explores the interactions among these stress factors, subspecies differences in adaptive capacity, and emerging research and management priorities. By focusing on key molecular indicators-such as heat-shock proteins, antioxidant defense enzymes, immune effectors, and nutrient-storage/glandular genes- this review aims to provide an integrative framework for incorporating gene-expression biomarkers into climate-resilient beekeeping and selective breeding programs.

LITERATURE SEARCH AND STUDY SELECTION

This review was developed through a structured literature survey aimed at synthesizing gene-expression responses of *Apis mellifera* to climate-related stressors. Publications were retrieved from Web of Science, Scopus, PubMed, and Google Scholar between 2000 and 2025, using search terms such as "*Apis mellifera*", "gene expression", "transcriptome", "heat stress", "cold stress", "climate change", "CO_2", "drought", "nutritional stress", "vitellogenin", "HSP", and "immune gene".

Studies were included if they (i) focused on *Apis mellifera*, (ii) reported molecular or gene-expression outcomes (qPCR, RNA-seq, microarray, proteomics) in response to at least one climate-related abiotic stressor, and (iii) were published in peer-reviewed journals. Experimental studies evaluating nutrition, pesticides, or pathogens within thermal or seasonal contexts, and reporting changes in stress-related pathways such as heat-shock proteins, antioxidant enzymes, immune effectors, vitellogenin, and MRJP families, were also retained. Broader reviews addressing climate change, colony resilience, and pollination ecology were consulted as complementary sources to contextualize molecular findings within ecological frameworks.

During screening, duplicate records, studies on non-Apis species, ecological studies lacking molecular data, and non-peer-reviewed material were excluded. Eligible studies were categorized according to the predominant stress factor (heat, cold/winter, elevated CO_2, pollen quality, drought, and forage scarcity) and the molecular pathways affected (heat-shock response, antioxidant and redox homeostasis, immune regulation, detoxification, and nutrition-related gene networks). This classification provided the structural basis for the thematic organization of the review.

Temperature stress and heat shock proteins

Heat waves and sharp diurnal temperature spikes pose acute threats to the proteome integrity of *Apis mellifera* workers, triggering the rapid induction of heat-shock protein (HSP) genes that refold or remove damaged proteins to stabilize cellular protein homeostasis (proteostasis) (Shih et al. 2021; Sagastume et al. 2025).

Field and laboratory studies have consistently reported increased expression of the major HSP families-HSP70, HSP90, and small HSPs-in *Apis mellifera* workers exposed to high ambient temperatures, often accompanied by the activation of oxidative defense pathways (e.g. SOD1) and the upregulation of certain detoxification genes (Zhang et al. 2023; Abou-Shaara 2024).

In the hypopharyngeal glands (HPGs) of worker bees, heat stress reduces the size of acini, suppresses endoplasmic reticulum (ER) protein-processing mechanisms, and downregulates the transcription of major royal jelly protein (MRJP) genes-effects that are associated with reduced brood-food production and altered nurse physiology (Feng et al. 2009; Jianke et al. 2010). These changes are consistent with recently reported transcriptomic signatures in HPG tissues under heat stress (Maigoro et al. 2025).

Comparative studies among subspecies reveal adaptive divergence in heat-stress responses: the desert-adapted *Apis mellifera jemenetica* exhibits significantly higher basal and inducible transcription of HSP genes, as well as broader thermotolerance, compared to the temperate A. m. carnica (Alghamdi et al., 2023). However, recent analyses warn that extreme summer conditions characterized by concurrent heat and drought may exceed even the adaptive limits of thermotolerant subspecies (Alghamdi et al. 2023; Hernández-Rivera et al.

2025).

Mild winters or late-season temperatures higher than expected can partially disrupt the normal "energy-saving and immune-suppression" program of winter bees, leading to off-season activation of both immune and metabolic genes. Steinmann et al. (2015) demonstrated that immune genes (e.g., defensin-1) and certain cellular response pathways are naturally downregulated in overwintering workers as part of an energy-conservation strategy. However, as reported by Döke et al. (2015) and later by Ricigliano et al. (2018), warmer winters sustain colony activity, leading to faster depletion of vitellogenin (Vg), continued flight and foraging behavior during winter, and renewed upregulation of immune genes due to prolonged exposure to microbes. Similarly, Prado et al. (2022) found that warming winters slow the decline of Vg and protective metabolites (e.g. glycerol), though these shifts occur in parallel with altered viral dynamics.

Thus, it becomes evident that not only peak temperatures but also shifts in the winter thermal regime reshape molecular stress programming in *Apis mellifera*. At the core of these adjustments, heat-shock proteins (HSPs) exhibit consistent and repeatable responses across various climatic contexts, positioning them as the most reliable molecular markers of adaptive heat-stress responses in honey bees.

Cold stress and antioxidant gene regulation

Sudden cold snaps during brood development can markedly reduce the antioxidant capacity of developing bees and downregulate genes associated with glutathione metabolism and peroxisome function-particularly in pupal brain tissue. Consequently, measurable declines in glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) activities occur, accompanied by increased susceptibility to oxidative damage (Zhu et al. 2025). This cold-induced suppression is problematic because pupae and newly emerged workers require a stable redox homeostasis for proper neural development and sensory maturation; disruptions at this stage may later manifest as impaired adult performance, shortened lifespan, or learning deficits (Bryś et al. 2025).

Seasonal context is an important regulator of these molecular responses. During cold and stable winters, worker bees typically maintain high and relatively constant levels of Vg, with only controlled, gradual decreases in the expression of key immune and antimicrobial genes (e.g., defensin-1, glucose oxidase). This pattern is interpreted as an energy-conservation strategy within winter clusters where pathogen pressure is low (Alaux et al. 2011; Steinmann et al. 2015). Since Vg in honey bees possesses antioxidant and immunoregulatory properties, maintaining Vg levels during overwintering supports both longevity and resistance to opportunistic infections (Sagastume et al. 2025).

In contrast, under the increasingly frequent mild or erratic winters reported in climate-change scenarios, colonies remain active for longer periods, with worker bees flying on more days and experiencing elevated metabolic rates and pathogen exposure. Under these conditions, Vg reserves deplete more rapidly, and antimicrobial peptides such as abaecin and hymenoptaecin become upregulated out of season, indicating continuous microbial pressure and immune activation during a period when colonies should physiologically conserve energy (Alaux et al. 2011; Hurychová et al. 2024). Such winter activity produces a higher oxidative load combined with lower basal antioxidant and Vg levels, which can increase winter–spring mortality, particularly when nutrition is simultaneously limited. Indeed, protein supplementation during winter has been shown to partially buffer colonies against these oxidative and immune costs, confirming a strong linkage between diet quality, antioxidant enzyme activities (SOD, CAT, and glutathione S-transferase-GST), and overwintering success (García-Vicente et al. 2024; Tawfik et al. 2020; Gajger and Cvetkovikj 2025).

Taken together, these findings indicate that altered winter climates are linked to overwintering phenotypes through gene-expression regulation operating across three interconnected molecular modules: (i) antioxidant and redox homeostasis genes (SOD, CAT, GST, the GSH pathway, thioredoxin/peroxiredoxin systems); (ii) immune and antimicrobial peptides (defensin-1 abaecin, apidaecin, glucose oxidase); and (iii) storage and anti-aging factors such as Vg. This tripartite framework highlights that cold stress in honey bees is not merely a matter of low temperature but rather the combined outcome of temperature fluctuation, nutrition, and pathogen pressure-three drivers expected to intensify or become increasingly unpredictable under ongoing climate change.

Elevated CO_2, pollen quality and nutritional stress

Rising atmospheric CO_2 alters the carbon–nitrogen balance of plants, generally increasing non-structural carbohydrates while diluting nitrogenous compounds; this shift reduces the crude protein content of pollen in several bee-visited plant species (Loladze 2014; Silva et al. 2015). Historical herbarium samples and experimental analyses of Solidago (goldenrod) pollen-a critical late-season resource-have documented an approximately 30% decline in pollen protein concentration concurrent with increasing atmospheric CO_2, a trend projected to continue through the end of this century (Ziska et al. 2016). More recent multi-species assessments indicate that this effect is not uniform across taxa but confirm measurable CO_2-driven reductions in pollen protein and altered amino acid profiles in a subset of flowering plants-findings with direct implications for pollinators such as honey bees that rely on high-quality pollen to produce long-lived winter workers (McMenamin and Ricigliano 2025; Braglia et al. 2025).

For *Apis mellifera*, protein-deficient or nutritionally unbalanced pollen diets have been repeatedly associated with reduced Vg levels, impaired hypopharyngeal gland development, and transcriptional reprogramming of immune and detoxification genes-typically characterized by the upregulation of immune effectors and stress-response genes, coupled with the downregulation of storage and glandular programs (Alaux et al. 2011; Di Pasquale et al. 2013; Sarioğlu-Bozkurt et al. 2022). These declines in Vg shorten worker lifespan, accelerate the transition to foraging, and increase susceptibility to viral and microsporidian pathogens, particularly when other stressors, such as heat, pesticides, or Nosema infection, are present (Kim et al., 2022; Zapata-Hernández et al. 2024). Both field and cage experiments with pollen substitutes corroborate this mechanism: diets with higher total protein content elevated vg and mrjp1 expression while reducing DWV viral loads, confirming that nutrition-sensitive genes can serve as biomarkers of dietary quality in honey bees (Kim et al. 2022; García-Vicente et al. 2024; Güneşdoğdu et al. 2024).

Taken together, these findings demonstrate that the effects of elevated CO_2 on honey bees are largely indirect and plant-mediated: by reducing pollen protein content, rising CO_2 levels drive colonies to invest more heavily in foraging and immune defense rather than in nutrient storage, brood-food synthesis, and the production of long-lived worker phenotypes. This metabolic shift is particularly critical during the pre-overwintering period, when colonies rely on late-summer and early-autumn pollen to produce fat, Vg-rich winter bees. If available pollen becomes diluted under elevated CO_2 and floral resources simultaneously decline due to drought or phenological mismatches, bee transcriptomes may be reprogrammed toward stress and immune investment at the expense of storage and glandular gene expression, linking a global driver (atmospheric CO_2) to colony-level overwintering risk (Ziska et al. 2016; Zapata-Hernández et al. 2024; Sagastume et al. 2025).

Drought, food scarcity and immune gene expression

Drought events reduce floral abundance, shorten blooming periods, and decrease nectar and pollen yields, creating prolonged forage scarcity for colonies (Waser and Price 2016; Phillips et al. 2018). Under these conditions, colonies respond on two levels: behaviorally, by increasing recruitment and expanding foraging ranges; and molecularly, by upregulating immune effectors and stress-response genes to compensate for greater pathogen exposure under nutritional stress (Corona et al. 2023; Wu et al. 2024). In an experiment where honey and pollen reserves were experimentally reduced, the expression of the antimicrobial peptide defensin-1, a predictor of overwintering success and social immunity, was significantly upregulated, while body fat metrics showed little short-term change. This suggests that, under resource limitations, colonies prioritize immunocompetence over energy gain (Wu et al. 2024).

In chronically arid or semi-desert regions, local bees-such as *Apis mellifera jemenetica*-mitigate forage dearth through a combination of behavioral (early foraging onset, heat-tolerant foraging schedules, higher recruitment) and physiological traits (smaller body size, increased cuticular pigmentation, and stronger expression of heat- and stress-responsive genes) (Alghamdi et al. 2023; Alattal 2024). These populations maintain a “primed” stress–immune state in the field, expressing higher levels of essential-for-life-like (l(2)efl) and other stress-marker genes under hot–dry conditions. However, recent reports from the Arabian Peninsula and East Africa indicate that emerging compound extremes-extended heat waves coinciding with severe drought-are now challenging even these thermotolerant genotypes, leading to reduced brood production and increased adult mortality (Alattal 2024; Sagastume et al. 2025).

Nutritional limitation also interacts with the gut–immune axis. Reduced pollen diversity and quantity resulting from drought and landscape homogenization are associated with shifts in the honey bee gut microbiota, accompanied by higher or more prolonged expression of antimicrobial peptides such as abaecin, hymenoptaecin, and defensin-1, suggesting that the host attempts to stabilize its microbial community under low-quality dietary conditions (Mojgani et al. 2025). This pattern aligns with studies showing that improved or supplemented nutrition (e.g. pollen patties, microalgae, or plant-extract additives) can partially buffer drought-induced immune costs and restore a more balanced expression of nutrition-sensitive genes (Nichols and Ricigliano, 2022; Ferraz et al. 2025).

Taken together, these findings indicate that drought and forage scarcity trigger an immune–metabolic rebalancing at the gene-expression level: antimicrobial peptides and social-immunity enzymes (defensin-1, glucose oxidase) are upregulated, while lipid and body-reserve parameters may appear relatively stable in the short term. In parallel, thermal-stress pathways are also activated, as drought rarely occurs independently of heat. This suggests that in an increasingly warm and arid climate, honey bee colonies will more frequently operate in a “high-immunity, low-resource” molecular state- a condition that may be adaptively beneficial in the short term but energetically costly and unsustainable across multiple seasons (Sagastume et al. 2025).

Interactions of multiple stress factors

Honey bee colonies are rarely exposed to a single stressor; instead, they experience concurrent combinations of climatic and anthropogenic pressures, including increased temperature, drought, nutritional limitation, pesticide exposure, and pathogen infections (e.g. Nosema, viruses, bacteria) (Branchiccela et al. 2019; Dequenne et al. 2022; Yıldız et al. 2025). These stressors act upon overlapping physiological and molecular networks, generating nonlinear interactions that exceed the sum of their individual effects (Neov et al. 2019; Berenbaum and Liao 2019; Sagastume et al. 2025).

At the molecular level, transcriptomic and proteomic data indicate that the combined exposure to heat stress and pesticides suppresses detoxification (cytochrome P450, GST) and immune pathways (defensin-1, hymenoptaecin), while concurrently overstimulating oxidative stress markers such as SOD and CAT (Chmiel et al. 2020; Kim et al. 2022; Wu et al. 2024). Nutritional restriction can attenuate the induction of key heat-shock proteins (HSP70, HSP90) and alter Vg-mediated antioxidant capacity, thereby diminishing cellular homeostasis under combined stress (McMenamin and Ricigliano, 2025). When *Nosema ceranae* or deformed wing virus (DWV) infections coincide with pesticide residues, honey bees exhibit an initial hyperactivation of immune genes followed by exhaustion, oxidative imbalance, and reduced lifespan (Alaux et al. 2010).

Recent controlled experiments have confirmed these synergistic effects: combined exposure to imidacloprid and heat stress significantly increased worker mortality and downregulated *hsp* genes (Kim et al. 2022); co-exposure to Nosema infection and poor diet disrupted midgut metabolism and antioxidant defenses (García-Vicente et al. 2024); and bees reared under combined pesticide–heat–nutrition stress exhibited accelerated aging and reduced hypopharyngeal gland size (Roitberg 2025). Epigenetic profiling further suggests that DNA methylation and histone acetylation changes induced by one stressor can modulate transcriptional sensitivity to another, providing a potential mechanism for stress “carry-over” effects (Sagastume et al. 2025).

Despite these advances, truly integrated multi-stressor experiments-combining multiple stressor types, ecologically realistic exposure durations, and full omics coverage-remain rare. Most studies isolate a single stress factor, limiting ecological realism and predictive power. Future research should employ factorial designs that integrate thermal variation, pathogen exposure, and dietary quality, ideally spanning full seasons to map the cumulative and reversible components of stress at the molecular level. Such studies are crucial for developing predictive biomarkers and breeding or management strategies that aim to create climate-resilient colonies.

Conclusion

Global climate change exposes *Apis mellifera* to intersecting thermal, nutritional, drought-related, and chemical stressors that converge on shared molecular pathways. Across these stress classes, honey bees display recurrent gene expression signatures involving heat shock proteins, antioxidant defenses (SOD, CAT, GST, GSH), antimicrobial peptides, detoxification enzymes (cytochrome P450s), and nutrient-storage/secretion genes (Vg, MRJP), which collectively regulate brood rearing, immune homeostasis, and seasonal colony resilience. Our synthesis highlights the need for integrated multi-stressor omics studies, targeted nutritional interventions, stress-tolerance-based selective breeding, and standardized molecular biomarker panels to strengthen predictive frameworks for colony health under global change. Likewise, practical management strategies-ensuring access to diverse, protein-rich pollen, mitigating heat stress through shading and water availability, providing supplemental feeding during drought-driven forage gaps, reducing combined stress exposures, and favoring locally adapted or stress-tolerant lineages-can reduce physiological burden and enhance colony robustness. Together, these research- and management-oriented approaches support a transition from descriptive stress biology toward predictive resilience genomics, forming a foundation for climate-smart apiculture and the long-term sustainability of pollination services.

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