

# The Impact of High Temperature Stress on the Immune System and Mitigation of Nutrients

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**Abstract:** Heat waves have become a widespread environmental concern worldwide and have had a serious impact on human health. Among them, the impact of high temperature on the immune system has become one of the focus of global attention. High temperature and heat wave can reduce the antioxidant performance of living organisms, produce heat stress, damage the immunoreactivity, intestinal histomorphology and microbiota, and aggravate autoimmune diseases. Nutrients such as resveratrol may strengthen the immune response and prevent disease, thus alleviating or reversing the immune damage caused by high temperature. This review summarizes the effects of high temperature on the biological immune system and the latest findings of nutrients that alleviate this phenomenon, to provide a theoretical basis for the development of effective nutritional intervention strategies and provide new ideas for the prevention of biological immune damage by high temperature and heat wave.

**Keywords:** High Temperature; Immune System; Nutritional Products; Influence; Mechanism

## 1. Introduction

An acute short-term rise in environmental temperature from hours to days called heat waves can have adverse effects on the ecosystems worldwide, with consequences including terrestrial forest fires and marine coral bleaching[1]. The human immune system is one of the important systems to maintain the body. It can recognize and eliminate pathogens invading the body and maintain the body's immune homeostasis. However, high temperature stress not only affects the physiological function of living organisms, but also has a non-negligible impact on the immune system of living

organisms, such as affecting the proliferation and differentiation of T lymphocytes and B lymphocytes, affecting the synthesis and secretion of immune molecules, and interfering with the immune response of the body. At present, some studies have found that oral nutrition may alleviate the adverse effects of high temperature on the immune system of organisms, which helps to reveal the complex relationship between the high temperature environment and the immune system, so as to reduce the adverse effects of high temperature stress on the health of organisms, and improve the quality of life and immune function of organisms in the high temperature environment.

## 2. Effect of High Temperature on the Organisms Immune System

### 2.1 Effect on the Antioxidant Properties of Living Organisms

Under thermoneutral conditions, the antioxidant system balances the production and elimination of free radicals (such as ROS). Enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) scavenge reactive oxygen species (ROS) and can be neutralized by the antioxidant defense system. While high temperature can destroy the redox balance, resulting to elevated ROS and oxidative stress response[2]. We found that heat waves along the South Pacific coast induced heat stress in native fish, and found that gill cortisol levels significantly increased and produced oxidative damage manifested by the production of protein carbonylation and lipid peroxidation[3]. Through transcriptome analysis and detection of antioxidant markers, some studies found that high temperature stress causes oxidative damage by reducing the antioxidant capacity of wide-body thread, suppresses the activation of immune capacity, and damages the intestinal function of leeches[4].

## 2.2 Effect on the Organisms Immunoreactivity

Animal experiments have shown that the environmental temperature affects the immune responses of the animals. The lower IgM 10 but higher PHA 12h and PLT were found in hamsters in a 32°C environment, indicating that high temperature reduced humoral immunity but enhanced cellular immunity and coagulability[5]. The high mortality of shellfish at high temperatures was found to be mainly associated with pro-inflammatory-related unsaturated fatty acid metabolism and oxidative damage, and found that the immune response of shellfish at high temperatures was diminished in TNF signaling, and reduced membrane transport efficiency in SLC proteins[6]. We have shown that adaptation to 20°C air temperature during early development would impair the immune competence of the developing lake sturgeon and inhibit its activation of molecular pathways involved in immunity, stress and fatty acid responses[7].

## 2.3 Effects on the Intestinal Function of an Organism

It was found that high temperature stress damages the intestinal integrity of cold-water fish and affects their growth and immunity. Metabolic analysis found that the abundance of glutathione, synthesized by glutamate and glycine, and the levels of adenosine, inosine, xanthine, guanosine, and deoxyguanosine, critical for DNA / RNA synthesis, were significantly reduced in fish at high temperatures[8]. Establish animal model to observe the influence of high humidity and high temperature environment on mice infected with influenza virus, and found that the intestinal flora of 16 srDNA cultured in high humidity and high temperature environment changed, intestinal mucosal permeability increased, the expression of pIgR, sIgA and IgA in intestinal mucosal immune system decreased, NLR immune recognition signaling pathway NOD 1 was activated, NOD 2, NF- $\kappa$ B and pIgR increased, resulting in increased related inflammatory factors near the intestine and aggravated local inflammation. High humidity and high temperature environment can also cause the increased expression of inflammatory cytokines, cause Th17 / Treg immune imbalance, inhibit Treg mature differentiation, increase the

expression of cytokines such as IL-2, IL-6, and reduce the expression of IFN- $\gamma$  and IL-17A. This condition is worsened after influenza virus infection. In general, high humidity and high temperature environment affect the immune status of the intestinal flora and the body, thus aggravating the status of influenza virus infection[9].

## 2.4 Agacerate Autoimmune Diseases

The results of animal experiments showed that EAU mice at high temperature showed more severe histopathological findings of uveitis compared with mice at normal temperature. The frequency of Th1 and Th17 cells in splenic lymphocytes and retina was significantly increased in hot EAU mice, and the expression of IFN- $\gamma$  and IL-17A mRNA was upregulated. The expression of NETs was significantly increased in the serum and neutrophil supernatants of EAU mice maintained at high temperature as compared to the normal temperature group. The metabolites fumarate and succinate in the plasma of EAU mice were significantly increased in the heat group and could induce the production of NETs through the NADPH oxidase-dependent pathway, but did not affect the frequency of Th1 and Th17 cells. In conclusion, elevated ambient temperature is a risk factor for the development of uveitis associated with the induction of Th 1 and Th 17 cells and the production of NETs that can be mediated by the NADPH oxidase-dependent pathway[10].

## 3. Combined Effect with High Temperature

Studies have observed the combined effects of increased seawater temperature and bacteria (luminobacter) on the survival, blood cells and biochemical responses of adult mussels, and found that infected mussels die at 20°C and 24°C, and immune system damage may occur, but the immune signaling pathway is activated after removal of bacteria. Higher oxidative stress responses were found in gill tissue, suggesting that mussels are more susceptible to bacterial pathogens at elevated temperatures[11]. A study of the effects of cadmium exposure and temperature stress on the immune function of blood cells in the Philippines found that blood cell mortality, reactive oxygen species (ROS) and superoxide dismutase (SOD) activity increased, with significant synergistic effect between high temperature and high

concentration of cadmium[12]. Compound stress of high temperature and *Vibrio* infection caused significantly higher clam mortality, and found that the synergistic effect of high temperature and *Vibrio* infection triggered a stronger antibacterial immune response[13].

#### 4. Protective Effects of Drugs Against High-Temperature Injury

**Resveratrol:** Studies have found that resveratrol supplementation during the summer heat can promote the intestinal health of sows and improve the growth of piglets, which may be related to the immunoglobulin and exosome-derived miRNA in the colostrum of sows[14]. Maternal resveratrol supplementation was found to improve the growth performance, antioxidant capacity and intestinal health of piglets at high temperatures, which may be related to increased immunoglobulin secretion in colostrum[15].

**Lipids:** studies have found that high temperature environment can affect the physiological health of fish, feeding the best lipid (12.3%) can improve the antioxidant enzyme activity, reduce malondialdehyde levels and upregulate oxidation related genes (SOD 1, SOD 2, CAT, GPX and HO-1) to reduce oxidative damage, in addition the best lipid can reduce the serum activity, down pro-inflammatory genes and upregulate anti-inflammatory genes, improve immunity. Optimal lipids will also reduce the phosphorylation levels of p38, JNK, and ERK proteins in the liver to inhibit the MAPK signaling pathway. In conclusion, optimal dietary lipid levels contribute to better growth of turbot under heat stress[16].

**Probiotics:** An experiment investigating the effects of dry probiotics on immunity and liver function of laying hens in high temperature areas showed that the addition of 4% dry probiotics in the diet optimized immunity and liver function[17].

**Gatechin gallate (EGCG):** it is the main component of green tea extract and has a variety of biological activities. Animal experiments found that 300 mg / kg diet EGCG had a protective effect in high-temperature laying ducks by improving immune and antioxidant capacity, and helped to improve egg production performance. The potential mechanism may be that EGCG regulates the synthesis of key metabolites and related metabolic pathways[18].

**Essential oil:** It is found that heat stress can

suppress the immunity and increase the morbidity of rabbits. The addition of cardamom essential oil nanoemulsion (NCEO) (300mg / kg) can improve the growth index, feed efficiency, redox balance and immunity, and reduce the inflammatory response of rabbits in summer[19]. It is found that dietary supplementation with thyme essential oil (TEO) reduces the damage effect of heat stress on female rabbits by enhancing antioxidant capacity and immune parameters. TEO significantly improved immune indicators, milk yield, ovulation rate, and decreased MDA and increased protein and its components, hemoglobin and total antioxidant capacity (TAC)[20].

**Zinc:** Studies have found that optimal dietary zinc levels relieve heat stress in spotted bass by enhancing immunity, antioxidant capacity and gut health[21]. It was found that zinc increased the antioxidant capacity and immune response of ewes under heat stress conditions, and dietary supplementation of 30 mg / kg zinc was the most effective dose, but zinc supplementation did not significantly up-regulate IL-4 and downregulate IL-6[22].

**Selenium:** Studies have found that selenium supplementation can improve the antioxidant capacity of ewes, reduce IL-2 and improve the expression of IFN- $\gamma$  gene, indicating that selenium supplementation can reverse the decline of antioxidant capacity and immune function caused by heat stress, and 0.3 mg Se / kg is the optimal dose[22].

**Seaweed halic acid:** Animal experiments have shown that AOS, as a new biological feed additive, can regulate inflammatory cytokines by enhancing immunity and antioxidant defense system, and effectively reduce the adverse effects of heat stress on rabbits[23].

**Riboflavin:** Studies have shown that arsenic contamination and high temperatures reduce the growth performance, antioxidant status and immunity of fish, but the dietary diet riboflavin (RF) reduces this effect[24].

**Curcumin:** Studies have shown that laying hens supplemented with curcumin at high temperature reduce the H / L ratio, serum corticosterone level, inflammatory cytokine response, and liver enzyme activity (ALT), and enhance the immunity of laying hens under thermal climate conditions. Therefore we concluded that curcumin has the ability to fight harsh environmental conditions and can be used as an anti-inflammatory immune-enhanced feed

additive in poultry nutrition[25].

## 5. Conclusion

In conclusion, high temperature stress is an important environmental problem that humans need to face, and it has an important impact on the immune system of living organisms. The supplement of dietary nutrients can repair the immune damage caused by high temperature. Therefore, we should avoid long-term exposure to high temperature environment and take reasonable diet to improve the body's immunity.

## References

- [1] DAI Q, SUSKI C D. Differing physiological performance of coexisting cool- and warmwater fish species under heatwaves in the Midwestern United States [J]. *PLoS one*, 2024, 19(3): e0301130-e.
- [2] EBEID T A, ZEWEIL H S, BASYONY M M, et al. Fortification of rabbit diets with vitamin E or selenium affects growth performance, lipid peroxidation, oxidative status and immune response in growing rabbits [J]. *Livestock Science*, 2013, 155(2-3): 323-31.
- [3] DETTLEFF P, TOLOZA C, FUENTES M, et al. Gills de novo assembly reveals oxidative stress, unfolded protein, and immune response on red cusk-eel (*Genypterus chilensis*) under thermal stress [J]. *Marine Environmental Research*, 2024, 196(106440-).
- [4] XIONG L, ZHENG X, ZHENG Y, et al. Transcriptome analysis reveals the oxidative damage and immune-suppression of leech (*Whitmania pigra* Whitman) intestine induced by high-temperature stress [J]. *Aquaculture Reports*, 2024, 35(102026-).
- [5] LI X D, YUHUI W. Effect of gradual increase and decrease in temperature on innate, cellular and humoral immunity in striped hamsters [J]. *Mammalian Biology*, 2023, 103(3): 265-76.
- [6] DONG L, YU J, WANG H, et al. Transcriptomic insights into vibrio-induced mortality in the clam *Meretrix petechialis* under high temperature [J]. *Comparative Biochemistry and Physiology Part D, Genomics & proteomics*, 2024, 50(101226-).
- [7] S B W, R Y G, N S A, et al. Elevated temperatures dampen the innate immune capacity of developing lake sturgeon (*Acipenser fulvescens*) [J]. *The Journal of experimental biology*, 2023, 226(10):
- [8] M F, Z L, M R, et al. High temperature stress induced oxidative stress, gut inflammation and disordered metabolome and microbiome in tsinling lenok trout [J]. *Ecotoxicology and environmental safety*, 2023, 266(115607-).
- [9] LI D, HUACHONG X, PEI L, et al. Prolonged exposure to high humidity and high temperature environment can aggravate influenza virus infection through intestinal flora and Nod/RIP2/NF- $\kappa$ B signaling pathway [J]. *Veterinary Microbiology*, 2020, 251(108896-).
- [10] SU P, HANDAN T, RUI C, et al. High Ambient Temperature Aggravates Experimental Autoimmune Uveitis Symptoms&#13 [J]. *Frontiers in Cell and Developmental Biology*, 2021, 9(629306-).
- [11] AZIZAN A, VENTER L, ZHANG J, et al. Interactive effects of elevated temperature and *Photobacterium swingsii* infection on the survival and immune response of marine mussels (*Perna canaliculus*): A summer mortality scenario [J]. *Marine environmental research*, 2024, 196(106392-).
- [12] REN J, LIU S, ZHANG Q, et al. Effects of cadmium exposure on haemocyte immune function of clam *Ruditapes philippinarum* at different temperatures [J]. *Marine Environmental Research*, 2024, 195(106375-).
- [13] TIAN J, WANG D, WANG H, et al. The combination of high temperature and *Vibrio* infection worsens summer mortality in the clam *Meretrix petechialis* by increasing apoptosis and oxidative stress [J]. *Fish & shellfish immunology*, 2024, 149(109542-).
- [14] HONG C, HUANG Y, YANG G, et al. Maternal resveratrol improves the intestinal health and weight gain of suckling piglets during high summer temperatures: The involvement of exosome-derived microRNAs and immunoglobulin in colostrum [J]. *Animal Nutrition*, 2024, 17(36-48).
- [15] YI Z, YUJIAN H, KAIGUO G, et al. Maternal resveratrol regulates the growth performance, antioxidant capacity, and intestinal health of suckling piglets through intestinal microorganisms at high summer temperatures&#13 [J]. *Frontiers in Nutrition*, 2022, 9(971496-).
- [16] ZHANG W, DAN Z, ZHENG J, et al. Optimal dietary lipid levels alleviated adverse effects of high temperature on

- growth, lipid metabolism, antioxidant and immune responses in juvenile turbot (*Scophthalmus maximus* L.) [J]. *Comparative biochemistry and physiology Part B, Biochemistry & molecular biology*, 2024, 272(110962-).
- [17] ADRIANI L, PERMANA R, LATIPUDIN D. Dried probiotics enhances immunity and liver function of final production laying hens maintained at upper temperatures zone [J]. *IOP Conference Series: Earth and Environmental Science*, 2024, 1292(1):
- [18] YANG L, XU Z, YALING Y, et al. The effect of epigallocatechin gallate on laying performance, egg quality, immune status, antioxidant capacity, and hepatic metabolome of laying ducks reared in high temperature condition [J]. *The veterinary quarterly*, 2023, 43(1): 41-.
- [19] ISMAIL R F S A, HASSAN M A E, MOUSTAFA M, et al. The Influence of a Nanoemulsion of Cardamom Essential Oil on the Growth Performance, Feed Utilization, Carcass Characteristics, and Health Status of Growing Rabbits under a High Ambient Temperature [J]. *Animals*, 2023, 13(18): 2990-.
- [20] A. A S, T. E R I, I. P S, et al. Effects of dietary thyme essential oil on blood haematobiochemical, redox status, immunological and reproductive variables of rabbit does exposed to high environmental temperature [J]. *Italian Journal of Animal Science*, 2022, 21(1): 51-61.
- [21] JUN Y, XIAO L, KAI S, et al. Effects of dietary zinc levels on growth, intestinal health, antioxidant and non-specific immunity of spotted seabass (*Lateolabrax maculatus*) reared at two temperatures [J]. *Aquaculture*, 2023, 577(
- [22] HAMID A, ASGHAR S A, MOHAMMAD C. Effect of Organic Selenium Supplementation on the Antioxidant Status, Immune Response, and the Relative Expression of IL-2 and IFN- $\gamma$  Genes in Ewes During the Hot Season [J]. *Biological trace element research*, 2023, 202(5): 2052-61.
- [23] A.M. S S, M. A H A, A. M K, et al. Effects of alginates on the growth, haematological, immunity, antioxidant and pro-inflammatory responses of rabbits under high temperature [J]. *Research in Veterinary Science*, 2023, 155(36-43).
- [24] NEERAJ K. Dietary riboflavin enhances immunity and anti-oxidative status against arsenic and high temperature in *Pangasianodon hypophthalmus* [J]. *Aquaculture*, 2021, 533(736209-).
- [25] NAWAB A, TANG S, LI G, et al. Dietary curcumin supplementation effects on blood immunological profile and liver enzymatic activity of laying hens after exposure to high temperature conditions [J]. *Journal of Thermal Biology*, 2020, 90(prepublish): 102573.