

Review

Overlap in Interactions of Cadmium and Endocannabinoid Receptors in Downstream Pathways of the Human Immune System

Gersham Joseph Rainone ^{1,*}, Phillip Mitchell Johansen ¹, Hewitt Kardis ², Kunal Vakharia ¹, Peter Pressman ³ and Andrew Wallace Hayes ⁴

¹ Department of Neurosurgery and Brain Repair, University of South Florida, Tampa, FL 33620, USA; johansenp@usf.edu (P.M.J.); kvakharia@usf.edu (K.V.)

² Department of Biology, Florida College, Tampa, FL 33620, USA; kardish@floridacollege.edu (H.K.)

³ Institute of Medicine & Department of Sociology, University of Maine, Orono, ME 04469, USA; peter.pressman@maine.edu (P.P.)

⁴ Center for Environmental/Occupational Risk Analysis & Management, College of Public Health, University of South Florida, Tampa, FL 33620, USA; awallacehayes@usf.edu (A.W.H.)

* Corresponding author. E-mail: gersham@usf.edu (G.J.R.)

Received: 8 May 2026; Revised: 22 June 2026; Accepted: 7 August 2026; Available online: 23 October 2026

ABSTRACT: Cadmium, a toxic heavy metal with no physiological role in the human body, is encountered mainly through inhalation or ingestion and accumulates due to its slow excretion rate. It negatively impacts health by causing oxidative stress, cellular damage, and apoptosis, especially affecting the kidneys, lungs, and immune system. The endocannabinoid system (ECS), comprising compounds, receptors (CB1, CB2), and enzymes (FAAH, MAGL), regulates immune cell function and homeostasis. The ECS influences various immune cells—including T and B lymphocytes, macrophages, mast cells, dendritic cells, and natural killer cells—mainly by modulating cell proliferation, apoptosis, cytokine secretion, and inflammatory responses. Cadmium disrupts innate immunity by impairing macrophage, neutrophil, mast cell, and NK cell functions, largely through oxidative stress and altered signaling, leading to diminished inflammatory responses and reduced ability to recognize and eliminate threats. In adaptive immunity, cadmium exposure inhibits B and T cell activation and proliferation, induces apoptosis, alters immune memory, and disrupts the balance of helper and cytotoxic T cells, weakening the body's defense mechanisms. While there is ample evidence for cadmium's detrimental effects on immune cells and for the ECS's regulatory role in immunity, direct research on how cadmium affects the ECS specifically is lacking. Current literature suggests possible overlap in the pathways affected by cadmium toxicity and ECS signaling—particularly in the induction of apoptosis and the suppression of immune function—raising the hypothesis that cadmium may modulate immune responses by interacting with endocannabinoid receptors. Further research is needed to clarify these interactions and their implications for immunity.

Keywords: Cadmium; Cannabinoid; Receptors; Biochemistry; Toxicology



1. Introduction

Cadmium is an omnipresent environmental and occupational contaminant with no established physiological function in humans. It is widely used in batteries, pigments, and metal coatings, and enters the environment through mining, smelting, battery disposal, and vehicular emissions. Recognized as a Group 1 human carcinogen, cadmium predominantly accumulates in the kidney and liver and exhibits an exceptionally prolonged biological half-life, estimated at 10 to 35 years before notable elimination [1]. Human exposure occurs primarily through inhalation of polluted air or tobacco smoke and ingestion of contaminated food and water; staple foods such as vegetables and starches (e.g., potatoes) become significant dietary sources when cultivated in cadmium-contaminated soils [1].

Cadmium exposure has been associated with a spectrum of chronic diseases, including renal impairment, pulmonary disorders, malignancy, and well-documented immunotoxic effects. The mechanistic foundation of cadmium toxicity involves the generation of reactive oxygen species [2] and other free radicals, disruption of redox homeostasis, and upregulation of molecular indicators of cellular stress and DNA damage [2,3]. These mechanisms may result in cell-cycle dysregulation and apoptosis across multiple cell types, including those essential for immune surveillance and regulation, ultimately leading to compromised immune function and persistent inflammation.

The immune system depends on precisely regulated networks of cellular communication, partly mediated by receptor-driven signaling pathways that orchestrate the development, activation, and effector functions of various immune cell populations [2]. Notably, the endocannabinoid system has emerged as a key regulator of immune homeostasis. This system consists of endogenous lipid mediators (such as anandamide and 2-arachidonoylglycerol), related biosynthetic and degradative enzymes, and G protein-coupled cannabinoid receptors, which are mainly Gi/o-coupled inhibitory receptors. Through these elements, endocannabinoid signaling modulates the activities of B and T lymphocytes, macrophages, mast cells, natural killer cells, and hematopoietic progenitors, thereby influencing both innate and adaptive immunity [3,4].

Although extensive literature exists on cadmium-induced toxicity and on endocannabinoid regulation of immune responses, research exploring their intersection at the cellular and molecular levels remains limited [3]. Specifically, interactions between cadmium-provoked oxidative and inflammatory signaling and endocannabinoid receptor-mediated modulation of immune cell activation, survival, and effector function have not been thoroughly characterized [4]. This review aims to integrate current knowledge regarding cadmium toxicity and endocannabinoid signaling within the immune system, identify potential mechanisms of interaction, and highlight critical gaps to inform future investigations [3,4].

2. Endocannabinoids and the Immune System

The endocannabinoid system (ECS) is a complex, widely distributed signaling network that regulates a variety of physiological processes to maintain homeostasis. This system responds dynamically to both internal and environmental changes, thereby influencing metabolic, neurological, and immune functions [5]. The ECS comprises endogenous cannabinoid ligands, their associated receptors, and enzymes, all of which work together to enable adaptive responses to pathophysiological stress and disease states.

The primary endogenous cannabinoids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), serve as key signaling molecules within the ECS [6]. These molecules mainly exert their effects through two G protein-coupled receptors: cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2). CB1 is predominantly expressed in the central and peripheral nervous systems, whereas CB2 is primarily expressed on immune cells, including lymphocytes, macrophages, dendritic cells, and mast cells [7]. Enzymes, including fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), hydrolyze and inactivate AEA and 2-AG, respectively [8]. Additionally, biosynthetic enzymes such as N-acyl

phosphatidylethanolamine phospholipase D (NAPE-PLD) and diacylglycerol lipase (DAGL) regulate endocannabinoid production and ECS tone in immune tissues [9].

2.1. ECS Components in the Immune System

Within the immune system, various cell types—including T and B lymphocytes, macrophages, mast cells, dendritic cells, and natural killer (NK) cells—utilize ECS signaling to modulate both innate and adaptive immune responses. Changes in CB2 receptor activation can influence T-cell proliferation, apoptosis, cytokine production, and lineage polarization [10,11]. These mechanisms ultimately impact cytotoxic T-cell activity and the formation of immunological memory. Similarly, activation of CB1 and CB2 receptors in B cells affects proliferation, immunoglobulin synthesis, and antibody structure, thus shaping the humoral immune response [12].

Macrophage function is also modulated by CB2 receptor expression. When this receptor is activated, it suppresses the release of inflammatory cytokines, inhibits antigen presentation, and reduces phagocytosis. These actions contribute to the development of a more anti-inflammatory phenotype in macrophages [13,14]. In mast cells, signaling through CB1 and CB2 receptors can downregulate degranulation, limit angiogenesis, and suppress tumor necrosis factor-alpha (TNF- α) production, thereby mitigating chronic inflammatory activity [15]. Dendritic cells following repeated activation of CB1 and CB2 receptors may exhibit reduced antigen-presenting capacity and undergo apoptosis [16]. Natural killer cells, which serve as the first line of defense against cancerous or virally infected cells, respond mainly to CB2 receptor stimulation. This leads to modulation of cytokine and chemokine production during immune activation [17].

2.2. Immunoregulatory Roles of the ECS

Overall, the ECS primarily exerts immunosuppressive effects, fine-tuning immune activities to maintain physiological balance. This modulation is advantageous for controlling autoimmune and hyperinflammatory conditions. However, if dysregulated, it may also weaken host defenses against infections or malignancies [18,19]. Thus, the ECS represents a critical regulatory axis that connects the neuroendocrine and immune systems through context-dependent signaling mechanisms [5].

The ECS has deep roots in the human immune system and can significantly influence responses to both innate and external pathological threats. Up-regulation of these receptors has varying effects on different parts of the immune system. Overall, it diminishes immune response and function, which can be helpful in conditions of autoimmune disease; in pathologic states, it may have a detrimental effect.

2.3. Dose-Dependent Effects of the ECS

Although the ECS predominantly functions as an immunosuppressive system in most conditions, there are instances in which it can have pro-inflammatory effects. This occurs mainly through CB2 receptor signaling. This can be seen in retinal epithelial cells, where elevated ligand levels can activate CB2 receptor signaling cascades, triggering intracellular calcium elevation and MAPK/ERK phosphorylation [20]. This then induces a pro-inflammatory state in the retinal epithelium, leading to cell death. This should be kept in mind in the context of the overlap between cadmium and its potential effects on the ECS and immune system.

3. Cadmium's Effects on Innate Immunity

Innate immunity refers to the body's immediate and regular response to non-self-identities that are perceived as threats. These threats are identified using methods such as specific molecular patterns and pathogen detection. Once accumulated in a cell, Cd disrupts cell function by displacing essential metals from enzymes and by inhibiting the maintenance of cellular function. This is seen in macrophages exposed to Cd. Abnormal levels of the Fc-gamma receptor, an immune-protective receptor on the surface of

macrophages, were found to inhibit macrophage phagocytic activity. Aside from inhibiting certain macrophage functions, Cd has been found to activate protein kinase B, thereby inducing macrophages to promote inflammation. Overall, Cd has been shown to diminish the inflammatory response that macrophages mediate in the innate immune system [21].

Cadmium has also been shown to affect other cells within the innate immune system, including NK cells, neutrophils, and mast cells—but overall, these effects are not as well studied as cadmium's effects on macrophages. In mast cells, cadmium exposure has been shown to deplete essential molecular components required for cytotoxicity and to make mast cells more sensitive to oxidative stress, which is common in most pathologies. In neutrophils, cadmium has been shown to induce apoptosis and diminish the response to oxidative stress. Regarding NK cells, cadmium exposure has been shown to decrease cytotoxicity against foreign cells by dampening IL-2 signaling, an important cytokine in the immune response and predominantly associated with NK cell function. Cd exposure in NK cells has also been tied to decreased ability to proliferate and effectively recognize threats [21].

4. Cadmium's Effects on Adaptive Immunity

Adaptive immunity, also known as acquired immunity, is the body's defense mechanism that helps support the innate immune system by enabling further recognition of foreign invaders and pathogens, which are processed and acted upon predominantly by B-lymphocytes and T-lymphocytes. Cadmium has similarly been shown to have a detrimental effect on the function of these cell types, much like the cellular components of innate immunity. Both *in vitro* and *in vivo* studies have been conducted to further our understanding of cadmium toxicity on immune system cells. Adaptive immunity is typically considered a more complex extension of the immune system that involves recognition, environmental adaptation, and the body's ability to recall previous pathogens (the concept of memory) [17,21–23].

Regarding B cells, cadmium exposure inhibits their activation in immune responses. Also, it diminishes their production and recognition of IgE (an immunoglobulin implicated in parasitic and allergic responses). Overall viability of B-cells in medium containing cadmium was also drastically reduced. In multiple studies, cadmium exposure has been shown to selectively induce apoptosis of B cells. Interestingly, at lower (albeit still toxic) cadmium concentrations, B-cell number was decreased overall. Still, with increasing parts per million exposure to much more toxic levels, the overall number of B-cells actually increased, potentially implying that at higher cadmium concentrations, a greater number of ineffective B-cells circulate through the immune system [22,23].

With regard to T-cells, a complex subset of the adaptive immune system, cadmium exposure also impairs their proper function, their ability to recognize threats, and the production of properly oriented and effective cell lines. Cadmium exposure has been shown not only to induce apoptosis in T cells but also to do so selectively, altering the CD4:CD8 cell ratio. This is an interesting phenomenon, as CD4 helper cells and CD8 cytotoxic cells have very different functions, and cadmium exposure has been shown to diminish the effects of CD4 helper cells more, suggesting it has a greater effect on the immune system's ability to recognize threats than to neutralize them. Overall, these studies show that both cell lines were affected in proliferation, though more so in CD4 cells [21,23].

Overall, regardless of cell type, cadmium exposure creates an environment of oxidative stress and cellular disorganization that diminishes not only the body's ability to effectively deal with and neutralize pathophysiological cells and processes, but also its ability to recognize them in the first place.

Cadmium and the endocannabinoid system both influence immune function primarily by modulating oxidative stress, inflammatory signaling pathways (notably NF- κ B/MAPK), and alterations in the cytokine profile. Although direct evidence regarding cadmium–CB1/CB2 receptor interactions in immune cells remains limited, mechanistic convergence is apparent. Most intersections can be deduced by superimposing

established cadmium-activated pathways in immune cells onto the documented actions of endocannabinoid receptors within the same networks [21].

5. Cadmium Toxicity in Immune Cells

Cadmium accumulates in immune cells, including macrophages, lymphocytes, and dendritic cells, inducing apoptosis in a dose-dependent manner—primarily through mitochondrial ROS generation and disruption of antioxidant defenses. In macrophages and other leukocytes, cadmium activates NF- κ B and MAPK pathways, elevates reactive oxygen species (ROS), triggers endoplasmic reticulum stress, and modifies cytokine expression (including IL-1 β , IL-6, TNF- α , IFN- γ , IL-10). These actions contribute to both inflammatory and immunosuppressive outcomes, influenced by the degree and timing of exposure [21]. Cadmium also affects innate immunity by altering cell numbers and functions, including reduced phagocytosis and NK cell activity, as well as shifts in neutrophil and macrophage phenotypes. Furthermore, it perturbs adaptive immunity by modifying the balance of CD⁴⁺/CD⁸⁺ T-cell subsets and B-cell function [17,22,23].

6. Endocannabinoid Receptors in the Immune System

CB2 receptors are abundantly expressed on various immune cells, whereas CB1 receptors are expressed at lower yet detectable levels in select subsets; both predominantly couple to Gi/o proteins, thereby inhibiting adenylyl cyclase and influencing downstream kinases. Activation of these receptors generally suppresses pro-inflammatory signaling by reducing NF- κ B activation, limiting ROS generation, and regulating cytokine production. This modulation often fosters regulatory or tolerogenic macrophage and T-cell phenotypes, though CB1/CB2 effects may vary depending on the context. Additionally, CB2 signaling frequently influences the Th1/Th2 balance, modulates B-cell antibody production, and governs leukocyte trafficking, providing mechanisms that may counterbalance toxicant-induced inflammation [4,24,25].

6.1. Mechanistic Overlap at Signaling Pathways

Both cadmium and endocannabinoid receptors converge mechanistically at several key signaling nodes, including NF- κ B. Cadmium can stimulate and, later, inhibit NF- κ B activity in immune cells, eliciting inflammatory responses or dysfunction. In contrast, CB1/CB2 signaling commonly exerts negative regulation over NF- κ B and related transcriptional programs. Cadmium-induced oxidative stress overlaps with endocannabinoid-mediated modulation of redox states, in which CB1/CB2 activation tends to reduce oxidative injury and ER stress responses. Both systems have been shown to interact with MAPK family members (ERK, JNK, p38) and PI3K/Akt: cadmium activates these kinases to promote inflammatory gene expression and apoptosis, whereas CB receptor activation can attenuate or fine-tune these signals, depending on the cellular context [24].

6.2. Functional Overlap in Immune Outcomes

Cadmium biases macrophage activation toward persistent M1-like phenotypes and augments tissue inflammation, predominantly via ROS-driven NF- κ B and HIF-1 α pathways. Conversely, CB2 receptor signaling typically supports a regulatory macrophage state and constrains excessive M1-type inflammation. Therefore, it is possible that there is potential antagonism at the level of macrophage polarization. In T cells, cadmium disrupts the equilibrium between subsets and cytokine profiles, resulting in both immunostimulatory and immunosuppressive effects. Endocannabinoid receptors similarly regulate T-cell activation and differentiation, suggesting that cadmium-driven shifts may occur within a milieu already shaped by endocannabinoid activity. Regarding B cells, cadmium induces dose-dependent variations in cell number and function, while CB2 expression is crucial for proper B-cell migration and response,

highlighting overlapping roles in humoral immunity [4,24,25]. Overall, from the literature, the most likely points of overlap would be NF- κ B, followed by ROS, HIF-1 α , MAPK, and ER-stress.

6.3. Evidence from Cannabinoid Protection Against Cadmium *In Vivo*

In vivo studies have demonstrated that cannabidiol (CBD)—an indirect modulator of CB1/CB2 and other molecular targets—attenuates cadmium-induced hepatic and renal toxicity in mice, normalizes oxidative stress biomarkers, and reduces pro-inflammatory responses [26]. It is therefore possible that enhancement of cannabinoid-associated pathways may mitigate cadmium toxicity through antioxidant, anti-inflammatory, and anti-apoptotic mechanisms that intersect with cadmium's principal toxic routes in both immune and parenchymal cells, although this would need to be explored further with *in vivo* studies.

7. Conceptual Model of Overlap

Cadmium drives immune cell dysfunction by increasing oxidative stress, deregulating NF- κ B/MAPK signaling, and provoking maladaptive cytokine responses. In contrast, endocannabinoid receptors, especially CB2, are strategically positioned on these cells and pathways to modulate—and potentially restrain—these adverse outcomes. The intersection of their actions is best depicted as shared signaling nodes (e.g., ROS, NF- κ B, MAPKs, PI3K/Akt, ER stress, and cytokine networks), in which cadmium serves as a pro-toxic, largely pro-inflammatory agent, and endocannabinoid receptors may provide a modulatory counterbalance (Figure 1).

Currently, no studies have quantified endogenous endocannabinoid levels (such as anandamide or 2-AG) in immune tissues specifically after cadmium exposure. Research on cadmium immunotoxicity focuses on its effects on immune cell viability, cytokine patterns, oxidative status, and intracellular signaling, but lacks direct measurement of endocannabinoids in these contexts [21]. Likewise, current reviews of endocannabinoid function in immunity do not cite cadmium or other heavy metals as modifiers of endocannabinoid levels in immune organs [4]. This gap highlights an unexplored area regarding how cadmium exposure might influence endocannabinoid tone in immune compartments, necessitating further investigation beyond indirect inference from their overlapping signaling pathways.

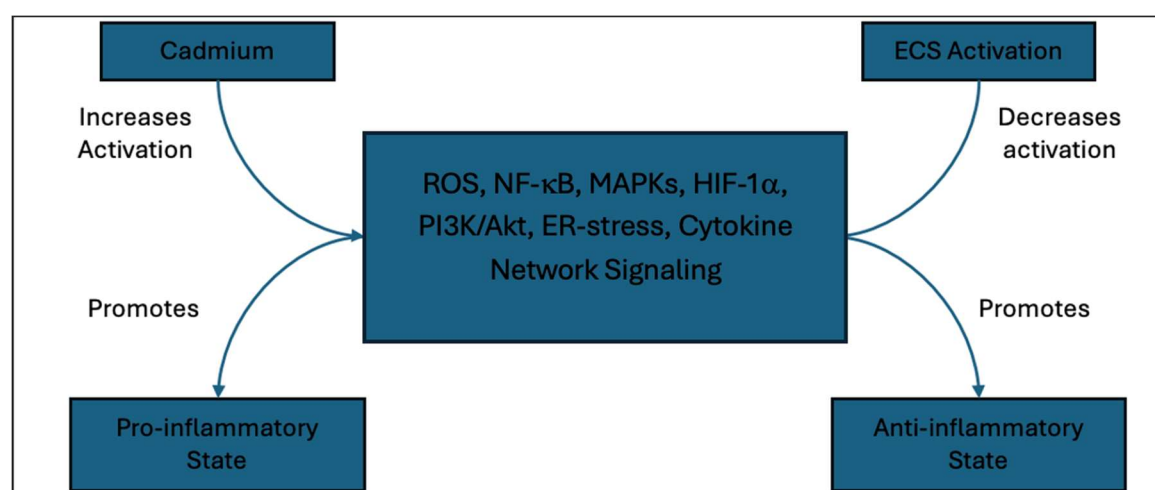


Figure 1. Conceptual overlap of cadmium and ECS.

8. Overlap Between Cadmium Toxicity and Endocannabinoid Receptors in the Immune System

The above studies and literature delineate relatively clearly the effects of cadmium on the immune system (adaptive and innate) and how the endocannabinoid system interacts with it. However, there is no strong evidence on the overlap between cadmium's effects on the endocannabinoid system and its overall

effects on the immune system. The data provided above can open the door to scientific investigations and hypotheses about how cadmium can affect the endocannabinoid system and, in turn, the overall immune response [21]. There is significant overlap between the apoptotic effects and the diminished overall immune response in the setting of upregulation of endocannabinoid receptors, and between the apoptotic effects and the diminished immune recognition pathways when immune cells are exposed to cadmium. One can hypothesize, but would need to investigate, that cadmium may selectively interact with CB1 and CB2 receptors and upregulate their function, thereby diminishing the overall function of immune cells. There should be further investigation into how cadmium directly interacts with endocannabinoid receptors, enzymes, and precursor molecules, as this could help us better delineate how cadmium toxicity influences the endocannabinoid system and, in turn, immunity in both *in vivo* and *in vitro* studies [21].

9. Mechanistic Insights into Cadmium Immunotoxicity

The central mechanism underlying cadmium's immunotoxic effects involves oxidative stress and disturbance of essential metal balance (Table 1) within cells [21]:

- Metal substitution: Cd replaces Zn^{2+} and Cu^{2+} in metalloproteins such as superoxide dismutase (SOD) and catalase, resulting in reduced antioxidant defense.
- Mitochondrial and ER stress: Cd induces stress in these organelles, leading to activation of caspases and apoptosis in immune cells.
- Signal interference: Cd disrupts signaling cascades involving NF- κ B, MAPK, and Ca^{2+} , thereby impairing cytokine production and immune cell activation.
- Epigenetic modulation: Recent studies [27,28] suggests that chronic Cd exposure leads to hypermethylation of immune-related gene loci.

Table 1. Effects of cadmium on immune cells.

Immune Cell Type	Primary Cd-Induced Effect	Mechanistic Pathway	Immunological Consequence
Macrophage	↓ FcγR expression; Akt activation	Metal displacement; oxidative stress	Impaired phagocytosis, dysregulated inflammation
Neutrophil	↑ Apoptosis	Mitochondrial disruption	Reduced bacterial clearance
Mast cell	↓ Cytotoxic mediators	ROS accumulation	Heightened oxidative sensitivity
NK cell	↓ IL-2 signaling	JAK/STAT inhibition	Decreased cytotoxicity
B lymphocyte	Apoptosis; biphasic proliferation	ER stress, ROS	Reduced Ig production
T lymphocyte	Skewed CD ⁴⁺ /CD ⁸⁺ ratio	NF- κ B/Nrf2 disruption	Impaired immune coordination

10. Conclusions and Future Directions

Cadmium remains a persistent threat to immune balance by disrupting pathogen detection and the resolution of inflammation through redox changes and signaling interference. Macrophages and T-lymphocytes are especially vulnerable, underscoring cadmium's broad effects on immune function. Future research should prioritize dose-response studies, epigenetic analysis, and human biomonitoring to establish exposure limits and guide public health action. While substantial evidence exists for cadmium's harmful effects on immune cells and the ECS's regulatory role, direct research on cadmium's impact on the ECS is limited. The current literature suggests overlapping pathways—particularly in apoptosis and immune suppression—raising the hypothesis that cadmium may modulate immune responses by interacting with endocannabinoid receptors. Further research is required to clarify these mechanisms and their implications for immunity.

Author Contributions

Conceptualization, G.J.R., P.M.J., K.V., P.P., H.K. and A.W.H.; Methodology, G.J.R. and A.W.H.; Formal Analysis, G.J.R., P.M.J., K.V., P.P., H.K. and A.W.H.; Investigation, G.J.R., P.M.J., K.V., P.P., H.K. and A.W.H.; Data Curation G.J.R. and A.W.H.; Writing—Original Draft Preparation G.J.R., P.M.J., K.V., P.P., H.K. and A.W.H.; Writing—Review & Editing, G.J.R., P.M.J., K.V., P.P., H.K. and A.W.H.; Supervision, A.W.H.

Ethics Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

All relevant data is openly available.

Funding

This project received no outside funding.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Munisamy R, Ismail SNS, Praveena SM. Cadmium Exposure Via Food Crops: A Case Study of Intensive Farming Area. *Am. J. Appl. Sci.* **2013**, *10*, 1252–1262. DOI:10.3844/ajassp.2013.1252.1262
2. Rafati Rahimzadeh M, Rafati Rahimzadeh M, Kazemi S, Moghadamnia AA. Cadmium toxicity and treatment: An update. *Caspian J. Intern. Med.* **2017**, *8*, 135–145. DOI:10.22088/cjim.8.3.135
3. Rockwell CE, Raman P, Kaplan BLF, Kaminski NE. A COX-2 metabolite of the endogenous cannabinoid, 2-arachidonyl glycerol, mediates suppression of IL-2 secretion in activated Jurkat T cells. *Biochem. Pharmacol.* **2008**, *76*, 353–361. DOI:10.1016/j.bcp.2008.05.005
4. Pandey R, Mousawy K, Nagarkatti M, Nagarkatti P. Endocannabinoids and immune regulation. *Pharmacol. Res.* **2009**, *60*, 85–92. DOI:10.1016/j.phrs.2009.03.019
5. Lu HC, Mackie K. An Introduction to the Endogenous Cannabinoid System. *Biol. Psychiatry* **2016**, *79*, 516–525. DOI:10.1016/j.biopsych.2015.07.028
6. Di Marzo V, Stella N, Zimmer A. Endocannabinoid signalling and the deteriorating brain. *Nat. Rev. Neurosci.* **2015**, *16*, 30–42. DOI:10.1038/nrn3876
7. Pertwee RG. The diverse CB₁ and CB₂ receptor pharmacology of three plant cannabinoids: Δ^9 -tetrahydrocannabinol, cannabidiol and Δ^9 -tetrahydrocannabivarin. *Br. J. Pharmacol.* **2008**, *153*, 199–215. DOI:10.1038/sj.bjp.0707442
8. Dinh TP, Carpenter D, Leslie FM, Freund TF, Katona I, Sensi SL, et al. Brain monoglyceride lipase participating in endocannabinoid inactivation. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 10819–10824. DOI:10.1073/pnas.152334899
9. Cravatt BF, Demarest K, Patricelli MP, Bracey MH, Giang DK, Martin BR, et al. Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling in mice lacking fatty acid amide hydrolase. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 9371–9376. DOI:10.1073/pnas.161191698
10. Klein TW, Newton C, Larsen K, Lu L, Perkins I, Nong L, et al. The cannabinoid system and immune modulation. *J. Leukoc. Biol.* **2003**, *74*, 486–496. DOI:10.1189/jlb.0303101
11. Nagarkatti P, Pandey R, Rieder SA, Hegde VL, Nagarkatti M. Cannabinoids as Novel Anti-Inflammatory Drugs. *Future Med. Chem.* **2009**, *1*, 1333–1349. DOI:10.4155/fmc.09.93

12. Derocq JM, Ségui M, Marchand J, Le Fur G, Casellas P. Cannabinoids enhance human B-cell growth at low nanomolar concentrations. *FEBS Lett.* **1995**, *369*, 177–182. DOI:10.1016/0014-5793(95)00746-v
13. Cabral GA, Griffin-Thomas L. Emerging role of the cannabinoid receptor CB₂ in immune regulation: Therapeutic prospects for neuroinflammation. *Expert Rev. Mol. Med.* **2009**, *11*, e3. DOI:10.1017/S1462399409000957
14. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* **1993**, *365*, 61–65. DOI:10.1038/365061a0
15. Samson MT, Small-Howard A, Shimoda LMN, Koblan-Huberson M, Stokes AJ, Turner H. Differential Roles of CB₁ and CB₂ Cannabinoid Receptors in Mast Cells. *J. Immunol.* **2003**, *170*, 4953–4962. DOI:10.4049/jimmunol.170.10.4953
16. Do Y, McKallip RJ, Nagarkatti M, Nagarkatti PS. Activation through Cannabinoid Receptors 1 and 2 on Dendritic Cells Triggers NF- κ B-Dependent Apoptosis: Novel Role for Endogenous and Exogenous Cannabinoids in Immunoregulation. *J. Immunol.* **2004**, *173*, 2373–2382. DOI:10.4049/jimmunol.173.4.2373
17. Slukvin II, Jerrells TR. Different pathways of *in vitro* ethanol-induced apoptosis in thymocytes and splenic T and B lymphocytes. *Immunopharmacology* **1995**, *31*, 43–57. DOI:10.1016/0162-3109(95)00032-4
18. Galiègue S, Mary S, Marchand J, Dussossoy D, Carrière D, Carayon P, et al. Expression of Central and Peripheral Cannabinoid Receptors in Human Immune Tissues and Leukocyte Subpopulations. *Eur. J. Biochem.* **1995**, *232*, 54–61. DOI:10.1111/j.1432-1033.1995.tb20780.x
19. Klein TW. Cannabinoid-based drugs as anti-inflammatory therapeutics. *Nat. Rev. Immunol.* **2005**, *5*, 400–411. DOI:10.1038/nri1602
20. Hytti M, Andjelic S, Josifovska N, Piippo N, Korhonen E, Hawlina M, et al. CB₂ receptor activation causes an ERK1/2-dependent inflammatory response in human RPE cells. *Sci. Rep.* **2017**, *7*, 16169. DOI:10.1038/s41598-017-16524-w
21. Wang Z, Sun Y, Yao W, Ba Q, Wang H. Effects of Cadmium Exposure on the Immune System and Immunoregulation. *Front. Immunol.* **2021**, *12*, 695484. DOI:10.3389/fimmu.2021.695484
22. Pathak N, Khandelwal S. Oxidative stress and apoptotic changes in murine splenocytes exposed to cadmium. *Toxicology* **2006**, *220*, 26–36. DOI:10.1016/j.tox.2005.11.027
23. Brzóska MM, Moniuszko-Jakoniuk J. Interactions between cadmium and zinc in the organism. *Food Chem. Toxicol.* **2001**, *39*, 967–980. DOI:10.1016/S0278-6915(01)00048-5
24. Kozak KR, Marnett LJ. Oxidative metabolism of endocannabinoids. *Prostaglandins Leukot. Essent. Fat. Acids (PLEFA)* **2002**, *66*, 211–220. DOI:10.1054/plef.2001.0359
25. Pestonjamasp VK, Burstein SH. Anandamide synthesis is induced by arachidonate mobilizing agonists in cells of the immune system. *Biochim. Et Biophys. Acta (BBA) Lipids Lipid Metab.* **1998**, *1394*, 249–260. DOI:10.1016/S0005-2760(98)00110-6
26. Sahin S, Mortas T, Muderrisoglu A, Turksoy VA. Investigation of Cannabidiol's Protective Effects on Cadmium-Induced Toxicity in Mice. *Basic Clin. Pharmacol. Toxicol.* **2025**, *136*, e14131. DOI:10.1111/bcpt.14131
27. Wang B, Li Y, Shao C, Tan Y, Cai L. Cadmium and Its Epigenetic Effects. *Curr. Med. Chem.* **2012**, *19*, 2611–2620. DOI:10.2174/092986712800492913
28. Vilahur N, Vahter M, Broberg K. The Epigenetic Effects of Prenatal Cadmium Exposure. *Curr. Environ. Health Rep.* **2015**, *2*, 195–203. DOI:10.1007/s40572-015-0049-9