Review Article

The Expanding Landscape of Aryl Hydrocarbon Receptor Ligands and Signaling Pathways: Implications for Immune Regulation and Disease

Ghadeer S Bustani[1*], Mohamed A Zarka[2], Alaa Sabeeh Alkhazali[3], Qassim Alfaham[4], Estabraq Hayder Khayoon[5]

1. Department of Anesthesia Techniques, College of Medical Techniques, The Islamic University, Najaf, Iraq.
2. Department of Pharmacognosy and Phytochemistry, College of Pharmacy, The Islamic University, Najaf, Iraq.
3. Department of Nursing, College of Nursing, Al-Zahrawi University, Karbala, Iraq.
4. Department of Medical Laboratory Techniques, College of Health and Medical Techniques, University of Alkafeel. Najaf, Iraq.
5. Department of Optics Techniques, College of Health and Medical Technologies, Al-Turath University, Baghdad, Iraq.

Use your device to scan and read the article online

How to Cite This Article Bustani, G. S., Zarka, M. A., Alkhazali, A. S., Alfaham, G., & Khayoon, E. H. (2026). The Expanding Landscape of Aryl Hydrocarbon Receptor Ligands and Signaling Pathways: Implications for Immune Regulation and Disease. *Iranian Journal of Veterinary Medicine, 20*(5), 859-876. http://dx.doi.org/10.22034/ijvm.20.5.1005914

http://dx.doi.org/10.22034/ijvm.20.5.1005914

ABSTRACT

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor first identified as a sensor of halogenated and polycyclic aromatic hydrocarbons but now recognized as a wide-ranging regulator of development, metabolism, and immunity. In its resting state, it forms a cytosolic chaperone complex; ligand binding prompts nuclear translocation, dimerization with the AhR nuclear translocator, and induction of detoxifying genes, while non-genomic signaling via tyrosine kinases and ubiquitin ligase activity further broadens its influence. Yet AhR is not solely a xenobiotic receptor: its ligand landscape now spans endogenous tryptophan metabolites, lipid mediators, bile pigments, and a host of dietary- and microbiota-derived compounds, such as polyphenols, glucosinolates, and terpenoids. A growing body of evidence demonstrates that variations in ligand origin, binding affinity, and metabolic stability directly determine the direction and magnitude of AhR-mediated signaling. For example, the high-affinity xenobiotic TCDD produces sustained AhR activation leading to toxic dysregulation of CYP1A1, whereas the endogenous metabolite FICZ induces only transient activation due to rapid degradation by CYP1A1. Similarly, microbiota-derived indole derivatives have been shown to enhance mucosal tolerance by increasing IL-22 production. These findings highlight that AhR integrates signals across TGF-β/BMP, Notch, Wnt/β-catenin, and NF-κB pathways in a context-dependent manner, and that dietary and microbial sources of ligands play a measurable role in shaping immune and metabolic outcomes. Establishing these mechanistic relationships will help guide the development of selective AhR modulators (SAhRMs) that maximize therapeutic benefit while minimizing the toxicities associated with classical ligands. The current review revealed the AhR role as a key regulator linking ligand diversity to context-dependent immune and disease outcomes, with important implications for therapeutic targeting.

Keywords: Aryl hydrocarbon receptor (AhR), Ligand diversity, Tryptophan metabolites, Dietary compounds, Immune signaling

Article info:
Received: 14 Dec 2025
Accepted: 21 Feb 2026
Publish: 01 Sep 2026

*** Corresponding Author:**
Ghadeer S Bustani, Associate Professor.
Address: *Department of Anesthesia Techniques, College of Medical Techniques, The Islamic University, Najaf, Iraq.*
Phone: *+964 (77) 28299090*
E-mail: *bustani@iunajaf.edu.iq*

Copyright © 2026 The Author(s);
This is an open access article distributed under the terms of the Creative Commons Attribution License (CC-By-NC: https://creativecommons.org/licenses/by-nc/4.0/legalcode.en), which permits use, distribution, and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Introduction

The aryl hydrocarbon receptor (AhR) is an evolutionarily conserved transcription factor that belongs to the basic helix–loop–helix/Per–ARNT–SIM family (Bustani et al., 2025). Originally identified as an environmental sensor for xenobiotic toxins, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and polycyclic aromatic hydrocarbons, AhR has since emerged as a pleiotropic regulator of development, metabolism, and immunity (Al-Ghezi et al., 2019; Motta et al., 2023). In its resting state, AhR resides in the cytoplasm bound to a chaperone complex consisting of HSP90, p23, and XAP2. Ligand binding induces a conformational change, leading to the receptor's release from this complex and its translocation to the nucleus, where it heterodimerizes with the AhR nuclear translocator (ARNT) and binds dioxin-responsive elements to modulate target gene expression (Bustani et al., 2025; Li et al., 2022). Canonical AhR signaling activates cytochrome P450 enzymes (e.g. CYP1A1, CYP1A2, and CYP1B1), which mediate xenobiotic detoxification, but the receptor also participates in non-genomic signaling: the release of c-Src from the cytosolic complex stimulates receptor tyrosine kinase pathways (EGFR, PI3K/AKT, and MAPK), and AhR can act as an E3 ubiquitin ligase, underscoring the breadth of its cellular functions (Beedanagari et al., 2010; Manzella et al., 2020).

Beyond its classical role in toxicology, AhR influences barrier-organ homeostasis and immune balance; high receptor expression in tissues, such as gut, skin, and lungs links environmental cues to mucosal immunity and inflammatory responses. A defining feature of AhR biology is the diversity of ligands that activate it (Coelho et al., 2022). The receptor was initially known to bind xenobiotic, "exogenous synthetic" ligands—halogenated and polycyclic aromatic hydrocarbons, such as TCDD, 3-methylcholanthrene, and benzo[a]pyrene—which exhibit high affinity but also considerable toxicity (Griffiths et al., 2017; Huang et al., 2021). The subsequent discovery of numerous naturally occurring agonists expanded the ligand repertoire. Dietary polyphenols, such as quercetin and resveratrol, and indole-3-carbinol from cruciferous vegetables are low-affinity AhR activators that may act as either agonists or antagonists. The endogenous ligand landscape is equally rich: tryptophan metabolites, including tryptamine, kynurenine, and indole derivatives, such as indole-3-acetic acid and the photoproduct formylindolo [3,2-b] carbazole; lipid mediators, such as lipoxin A4 and certain prostaglandins; and heme breakdown products, including bilirubin and biliverdin, all engage the receptor. Emerging evidence shows that many of these metabolites are generated by the host microbiota and that their availability depends on gut microbial composition (Huang et al., 2020; Wang et al., 2020). Thus, AhR integrates signals from environmental toxins, dietary constituents, and microbial metabolism to regulate both innate and adaptive immunity. Ligand origin, affinity, and half-life profoundly influence downstream responses; the same receptor can drive pro-inflammatory or tolerogenic programmed depending on the activating ligand and cellular context (Cannon et al., 2022). Toxicity associated with synthetic ligands limits their therapeutic use, which has prompted interest in identifying non-toxic natural and microbiota-derived agonists.

AhR does not operate in isolation. It interacts with multiple signaling networks, including transforming growth factor-β/bone morphogenetic protein (TGFβ/BMP), receptor tyrosine kinases (KGFR, VEGFR, and EGFR), the Notch pathway, and the Wnt/β-catenin cascade. Crosstalk with the Wnt pathway is particularly intriguing: Wnt ligands regulate cell fate and tissue homeostasis via β-catenin–dependent transcription, and recent studies highlight mutual modulation between AhR and Wnt components (Liang et al., 2019; Motta et al., 2023). AhR also collaborates with transcription factors such as STAT3, NF-κB, and hypoxia-inducible factor-1α and can activate nongenomic pathways through c-Src and EGFR, illustrating how the receptor links environmental and metabolic signals to broad cellular programs. The combined effects of ligand diversity and pathway crosstalk create an expansive, context-dependent AhR signaling landscape that influences development, tissue homeostasis, immunity, and disease (Diao et al., 2025; Tkachenko et al., 2016).

This review synthesized recent advances on AhR ligands and signaling. By examining the categories and sources of known ligands, the molecular mechanisms governing canonical and non-canonical AhR signaling, and the receptor's interactions with other pathways, we highlighted why AhR is a central integrator of environmental and endogenous cues. A better understanding of this expanding ligand repertoire and of the contextual factors that shape signaling outcomes will be essential to harness AhR therapeutically, particularly through the development of safe, natural agonists or antagonists that can modulate immune responses without the toxicity associated with classical xenobiotic ligands.

Therefore, this review aimed to comprehensively summarize the expanding spectrum of AhR ligands, delineate the canonical and non-canonical signaling pathways engaged by the receptor, and highlight how ligand- and

context-dependent signaling shapes immune regulation and disease processes. By integrating recent mechanistic and structural insights, we also discussed the therapeutic potential of selectively targeting AhR with natural and synthetic modulators.

AhR biology

AhR is a ligand-activated transcription factor that acts as a cellular sensor for a variety of environmental and endogenous molecules (Bustani et al., 2025). Historically recognized for mediating toxic effects of dioxins and other pollutants, AhR is recognized as an important regulator of immune and inflammatory processes (Bustani et al., 2025). It belongs to the basic helix-loop-helix Per-Arnt-Sim (bHLH-PAS) family of proteins and is expressed in many cell types, including immune cells (T cells, dendritic cells, and macrophages) and barrier tissues (skin, gut, and lung) (Bustani et al., 2024; Gargaro et al., 2016).

Molecular structure of AhR

AhR is a ~96 kDa protein with several distinct domains responsible for its function. It contains an N-terminal basic helix-loop-helix (bHLH) DNA-binding domain, which allows it to bind specific DNA sequences, and two PAS domains (PAS-A and PAS-B), which are involved in sensing ligands and interacting with partner proteins. The PAS-B domain forms the ligand-binding pocket of AhR. AhR also has a C-terminal transactivation domain that interacts with coactivators and the transcriptional machinery. The PAS family name comes from its homology to period (Per), AhR nuclear translocator (Arnt), and single-minded (Sim) proteins (Bustani et al., 2025; Hahn, 2002; Schulte et al., 2017). In its resting (unliganded) state, AhR resides in the cytoplasm as part of a multi-protein complex: HSP90 (heat shock protein 90), p23 (a co-chaperone), XAP2 (also known as AIP, AhR-interacting protein), and sometimes the tyrosine kinase c-Src all bind AhR and stabilise it in the cytosol. This complex keeps AhR inactive but "primed" for activation. The chaperones (HSP90/p23) maintain AhR's proper conformation and prevent its degradation. This molecular setup ensures that AhR can rapidly respond when an appropriate ligand enters the cell (Oikawa et al., 2001).

AhR ligands and activation

AhR ligands are remarkably diverse, ranging from environmental toxins to dietary metabolites and endogenous signals. The binding of a ligand to AhR's PAS-B domain induces a conformational change that initiates AhR activation. AhR ligands can be categorized as endogenous or exogenous and, within these categories, according to their sources, including dietary, microbiome-derived, synthetic, and chemical sources (Oikawa et al., 2001).

Endogenous ligands

The discovery of endogenous AhR ligands revealed that AhR is not merely a toxin receptor but also responds to normal metabolic cues. A major source of endogenous ligands is the amino acid tryptophan metabolism pathway (Sun et al., 2020a).

Kynurenine, generated via host IDO/TDO activity, represents a major endogenous AhR ligand involved in immune and metabolic regulation (Amobi-Mccloud, 2019). AhR regulates IDO/TDO expression, creating a feedback loop because Kynurenine itself activates AhR (Wang et al., 2020). Furthermore, FICZ, a UV-derived photoproduct of tryptophan, is among the highest-affinity physiological AhR ligands. (Wincent et al., 2012). FICZ plays a critical role in skin homeostasis and immunity by transiently activating AhR after UVB irradiation (Cano-Sánchez et al., 2023; Farmahin et al., 2014). Several indole derivatives also bind AhR, although their physiological relevance varies according to their source and metabolic context.

Beyond tryptophan metabolites, other endogenous ligands include lipids and fatty acid derivatives, such as oxidized lipids and eicosanoids, which modulate AhR. Moreover, lauric acid derivatives or prostaglandin metabolites weakly bind AhR, although AhR's role in lipid sensing is less defined than its role in xenobiotic sensing (Hankinson, 2016). On the other hand, bilirubin and biliverdin bind AhR at high concentrations, suggesting a link between oxidative stress and AhR (Togawa et al., 2008).

Dietary

Dietary intake makes a substantial contribution to the pool of endogenous AhR agonists by supplying a wide variety of compounds with diverse chemical structures and biological functions that originate from plants and other natural sources. These diet-derived molecules interact with AhR and have been linked to numerous physiological effects. Within this framework, multiple classes of endogenous AhR agonists have been identified, each characterized by unique chemical profiles and specific roles in receptor activation (Busbee et al., 2013; Safe et al., 2012; Safe et al., 2020; Shaito et al., 2020). Many endogenous AhR agonists have dietary origins, with several well-known examples obtained directly from food sources, including, polyphenols.

Polyphenolic compounds

Polyphenols represent a broad class of naturally occurring secondary metabolites in plants, abundantly found in fruits, vegetables, tea, coffee, and numerous other plant-derived foods. These compounds possess notable relevance across synthetic, medicinal, and industrial applications. Naturally occurring polyphenols exhibit a wide spectrum of biological activities, underpinning their well-documented health-promoting properties. Of particular interest is their interaction with the AhR (Handique et al., 2002; Ly et al., 2015). Although the pleiotropic effects of dietary polyphenols have been widely studied, increasing attention has been directed toward their role in modulating AhR activity. Metabolites derived from dietary polyphenols through gut metabolism are emerging as important modulators of AhR. These metabolites can navigate the intracellular environment, influencing AhR function not only within the gut but also in distal organs. This intricate relationship highlights the complex influence of polyphenolic compounds on AhR-mediated signaling pathways (Pinto et al., 2023; Xue et al., 2017). This group encompasses several subclasses, including flavonoids, phenolic acids, and stilbenes.

Tryptophan derivatives

Tryptophan derivatives comprise a class of bioactive compounds originating from the essential amino acid tryptophan (Palego et al., 2016). Through multiple metabolic pathways, tryptophan can generate a variety of AhR ligands. Upon binding to AhR, these ligands induce the transcription of downstream target genes, including interleukin-22 (*IL-22*) and interleukin-17 (*IL-17*) (MacEachern et al., 2018). The tryptophan–AhR axis has attracted growing attention for its critical role in maintaining reproductive system homeostasis. Although its physiological importance is increasingly recognized, strategies for targeted modulation of this pathway to achieve beneficial clinical outcomes remain underexplored. Emerging evidence highlights the indispensable role of tryptophan and its metabolites in mammalian pregnancy. As a metabolic precursor, tryptophan contributes to the biosynthesis of key neurotransmitters, such as serotonin, melatonin, and kynurenine. Kynurenine, in particular, serves as an AhR ligand and functions as a transcriptional regulator in various physiological contexts. This complex biochemical interplay underscores the profound influence of the tryptophan–AhR pathway on reproductive health, reinforcing the need for further investigation into its therapeutic potential (Sun et al., 2020b; Wang et al., 2020). Beyond reproduction, tryptophan metabolism is implicated in diverse physiological and pathological processes, including growth regulation, metabolic control, emotional regulation, spermatogenesis, and immune responses (Liu et al., 2023; Wang et al., 2020). The kynurenine pathway represents a major branch of tryptophan catabolism, initiated primarily by the enzymatic actions of indoleamine-2,3-dioxygenase (IDO) or tryptophan-2,3-dioxygenase (TDO). This pathway is of particular relevance because it produces a spectrum of metabolites with intrinsic AhR-binding capacity. The regulation of these enzymatic steps is therefore pivotal in determining the generation of AhR-active tryptophan derivatives, ultimately shaping downstream physiological processes mediated by AhR signaling.

Fatty acids

Both saturated and unsaturated fatty acids are capable of interacting with AhR. Omega-3 fatty acids, in particular, influence AhR activity by modulating the metabolism of polyunsaturated fatty acids (PUFAs), such as α-linolenic acid, eicosatetraenoic acid, and docosahexaenoic acid. These PUFAs are essential precursors in the production of bioactive metabolites, including epoxides (Huerta-Yepez et al., 2020), which can subsequently modulate AhR activation. Evidence indicates that diets enriched in omega-3 fatty acids, by altering PUFA metabolism, can influence the generation of AhR ligands, thereby modifying downstream receptor responses. Such modulation has been associated with potential inhibitory effects on tumor growth and metastasis, underscoring the complex interplay between dietary lipids, PUFA-derived metabolites, and AhR signaling in cancer biology (Wiest et al., 2015). Short-chain fatty acids (SCFAs), particularly butyrate, also serve as important modulators of AhR activity. Upon binding to AhR, SCFAs trigger downstream signaling cascades that can modulate immune cell differentiation and functionality, contributing to the maintenance of gut homeostasis and the regulation of immune responses. This relationship highlights the intricate nexus between diet, microbial metabolism, and host immunity, with SCFAs playing a pivotal role in AhR-mediated immunomodulation.

Glucosinolates

Glucosinolates, naturally occurring in cruciferous vegetables, such as broccoli and Brussels sprouts, are notable dietary components with the capacity to modulate AhR activity (Tang et al., 2023). Following ingestion, glucosinolates undergo enzymatic hydrolysis, yielding bioactive metabolites, including isothiocyanates and nitriles, both of which can influence AhR signaling pathways. Isothiocyanates, with phenethyl isothiocyanate as

a prominent example, act primarily as AhR antagonists. Their mechanism of action involves blocking the binding of carcinogenic ligands to AhR, thereby attenuating receptor-mediated toxic responses. Experimental findings further demonstrate that isothiocyanates can antagonize AhR activation induced by potent ligands, such as benzo[a]pyrene, mitigating its deleterious effects. Additionally, isothiocyanates may interact with cysteine residues on the AhR protein, inducing conformational changes that impair receptor functionality and contribute to their anti-carcinogenic properties (Abdull Razis et al., 2012). In contrast, nitriles exhibit a more complex relationship with AhR activity. Certain nitriles have been shown to function as AhR agonists, promoting receptor activation, while others exert inhibitory effects, highlighting the structural and functional diversity of these glucosinolate-derived metabolites (Baker et al., 2018).

Terpenoids

Terpenoids, or isoprenoids, constitute a large and diverse group of organic compounds derived from repeating isoprene units. They are widely distributed in nature and are synthesized by plants, fungi, and certain bacterial species (Ludwiczuk et al., 2017). Terpenoids fulfill essential biological functions and are often responsible for the distinctive aromas and flavors characteristic of many plant species. Among them, celastrol—a triterpenoid isolated from the Thunder God vine—has been shown to downregulate AhR expression. This suppression of AhR subsequently reduces the transactivation of cytochrome P450 enzymes CYP1A1 and CYP1B1, both of which are involved in converting polycyclic aromatic hydrocarbons (PAHs) into toxic metabolites. This effect suggests celastrol's potential as a chemo-preventive agent against PAH-induced carcinogenesis (Yang et al., 2010).

Therapeutic strategies targeting AhR have also explored the use of dietary AhR-active terpenoids, such as limonene, which is a representative compound in this category. Limonene has been reported to activate AhR, highlighting its potential role in cancer prevention through receptor modulation. This underscores the promise of naturally occurring terpenoids as candidates for dietary-based chemo preventive interventions (Ondrová et al., 2023).

Coumarins

Coumarins are a class of naturally occurring organic compounds characterized by a benzene ring fused to a -pyrone ring. Found in various plant species, they are often associated with a distinctive sweet fragrance. Coumarins possess a wide range of biological activities, including anticoagulants, anti-inflammatory, and antioxidant effects (Hussain et al., 2019). Synthetic coumarin derivatives have been shown to inhibit the upregulation of the AhR induced by 7,12-dimethylbenz[a]anthracene (DMBA), a potent carcinogen. By suppressing AhR overexpression and reducing proliferating cell nuclear antigen (PCNA) production, synthetic coumarin effectively decreases tumor formation (Foroozesh et al., 2019).

Angelicin, a member of the furocoumarin subclass, has demonstrated anticancer activity against multiple cancer cell lines. Notably, it can bind directly to AhR, thereby blocking its nucleocytoplasmic translocation from the cytoplasm to the nucleus. Given that AhR functions as a negative regulator of osteogenic differentiation and instead promotes bone resorption, angelicin's modulation of AhR signaling suggests potential therapeutic applications in both oncology and bone metabolism (Mahendra et al., 2020).

Dietary sources from beverages

Coffee and tea are notable dietary sources of AhR activators because they contain caffeic acid and its derivatives, which can directly bind to and activate the receptor (Chapkin et al., 2021). These compounds are often present alongside other polyphenols, such as chlorogenic acid in coffee and catechins in tea, creating a synergistic profile of bioactive molecules. Activation of AhR by these plant-derived compounds can influence detoxification pathways, particularly through upregulation of phase I and phase II metabolizing enzymes, such as cytochrome P450 family members (CYP1A1, CYP1B1) and glutathione S-transferases. In moderate amounts, this activation is thought to contribute to antioxidant defense, modulation of inflammatory responses, and maintenance of gut barrier integrity, although its effects can be context-dependent depending on dose and metabolic background (Huang et al., 2021). Wine, beyond its well-known resveratrol content, also contains quercetin and other flavonoids that modulate AhR activity. Quercetin has been reported to act both as an AhR agonist and as a selective AhR modulator (SAhRM), meaning that it can activate certain AhR-dependent pathways while suppressing others. For example, in hepatic cells, quercetin can alter the expression of AhR-regulated enzymes involved in xenobiotic metabolism, thereby influencing how the liver processes not only dietary components but also environmental toxins and pharmaceuticals. Additionally, wine polyphenols can exert indirect effects by modifying gut microbiota composition, which in turn influences the production of microbial metabolites, such as indole derivatives, that are themselves potent AhR ligands (Goya-Jorge et al., 2022; Liu et al., 2024).

Host–microbiome co-metabolism of AhR ligands

The gut microbiota plays a pivotal role in transforming dietary constituents into a variety of bioactive metabolites, including tryptophan-derived compounds that act as endogenous ligands for AhR. In addition, activation of the kynurenine pathway within host intestinal cells—mediated by IDO and TDO—leads to the generation of kynurenine metabolites, several of which are potent activators of AhR signaling (Salminen, 2023; Szelest et al., 2021; Torti et al., 2021; Walczak et al., 2020).

Host metabolic processes, particularly the catabolism of tryptophan via the kynurenine pathway, generate metabolites that function as AhR agonists. AhR activation relies on ligands originating from environmental exposure, dietary intake, and metabolic activities of both the host and its microbiome (Cheng et al., 2015; Wang et al., 2020). Several bacterial taxa—including *Escherichia coli*, *Clostridium* spp., *Bacteroides* spp., *Clostridium sporogenes*, *Peptostreptococcus* spp., Pepto*streptococcus russellii*, *Peptostreptococcus anaerobius, Peptostreptococcus stomatitis*, *Clostridium botulinum*, *Lactobacillus* spp., *Ruminococcus gnavus*, *Clostridium bartlettii*, and *Bifidobacterium* spp.—are capable of synthesizing indole propionic acid (IPA), indoleacetic acid (IAA), and indolelactic acid (ILA) (Roager et al., 2018; Zelante et al., 2013). Other species, such as *Bacteroides* spp. and *Clostridium* spp., can produce 3-methylindole (skatole) via the decarboxylation of IAA (Cervantes-Barragan et al., 2017; Zelante et al., 2013).

These microbial transformations contribute to the diversification of tryptophan metabolic pathways, yielding a wide spectrum of bioactive metabolites. Compounds, such as indole, IPA, and IAA have been reported to support intestinal integrity, although some may disrupt mucosal homeostasis under certain conditions. Furthermore, specific tryptophan catabolites—including IAA, indoleacrylic acid (IA), indole-3-aldehyde (IAld), ILA, tryptamine, and skatole—act as endogenous AhR ligands, thereby modulating both innate and adaptive immune responses within intestinal immune cells (Abdulla et al., 2021; Ahmed et al., 2022; Ahmed et al., 2022; Alghetaa et al., 2021, Alghetaa et al., 2023; Alharris et al., 2022; Al-Khaqani et al., 2024; Bustani et al., 2024; Elias et al., 2024; Neamah et al., 2020). Additionally, metabolites, such as IPA, indole-ethanol (IE), and IA can be absorbed through the intestinal epithelium into systemic circulation, where they exert antioxidant and anti-inflammatory effects. This intricate interplay between gut microbiota-driven tryptophan metabolism and AhR signaling underscores their pivotal role in regulating immune function and sustaining intestinal homeostasis (Cervantes-Barragan et al., 2017; Cheng et al., 2015; Hubbard et al., 2015; Roager et al., 2018; Zelante et al., 2013).

Yeast/Fungi

Although the specific role of yeast and fungi in regulating the AhR pathway has not been comprehensively characterized, evidence indicates that microbial metabolites— including those produced by these organisms—can activate AhR. As members of the gut microbiota, fungi are capable of producing a range of AhR ligands, such as tryptophan-derived metabolites, indole-3-carbinol, and certain mycotoxins (Dong et al., 2020) Activation of AhR by these fungal metabolites has been associated with anti-inflammatory effects, the promotion of immune tolerance, and the enhancement of xenobiotic detoxification processes (Chen et al., 2023).

Exogenous

Exogenous factors are external agents originating from outside the organism. Within the context of AhR biology, these encompass a broad spectrum of environmental contaminants and synthetic chemicals.

Polycyclic/ halogenated aryl hydrocarbon (PAH/ HAH) pollutant

Exogenous AhR ligands include a wide range of environmental pollutants and synthetic compounds. Among these are polycyclic aromatic hydrocarbons (PAHs) and halogenated aromatic hydrocarbons (HAHs), which are prevalent in industrial waste and can enter the body via ingestion, inhalation, or dermal absorption. Dioxins represent another class of highly toxic environmental contaminants, while specific PAHs, such as benzo[a] pyrene—a potent carcinogen—are capable of binding to AhR and initiating its signaling cascade. In addition, synthetic organic chemicals, such as polychlorinated biphenyls (PCBs), historically used in electrical equipment, as well as various synthetic AhR ligands—including certain pharmaceuticals and experimental compounds—can modulate receptor activity. Upon activation by these exogenous agents, AhR translocates to the nucleus, where it regulates the transcription of numerous target genes (Al-Kinany et al., 2021; Banerjee et al., 2016; Chan et al., 2006; Faiad et al., 2022; O'Driscoll et al., 2018; Revel et al., 2001).

Synthetic exogenous

Synthetic exogenous factors that influence AhR include man-made compounds specifically designed to

bind to the receptor and modulate its activity. These include both pharmaceuticals and experimental agents (Safe et al., 2020). For example, researchers at Bayer have been developing a novel cancer therapy strategy that targets AhR. Their approach involves an orally administered AhR inhibitor with the potential to restore immune function and suppress tumor progression (Gutcher, 2023). In contrast, omeprazole, which is commonly used as a proton pump inhibitor and an antiallergy drug, has been identified as a synthetic compound capable of activating AhR and inducing CYP1A1. Leflunomide, which is used as an immunosuppressant in rheumatoid arthritis, has also been identified as a synthetic compound capable of activating AhR and inducing CYP1A1 (Jin et al., 2014). On the other hand, synthetic AhR antagonists, unlike naturally occurring dietary antagonists, are purposefully engineered to selectively inhibit AhR signaling. Such compounds are frequently designed for research applications or to explore therapeutic potential. Their synthetic origin allows for structural optimization to achieve greater potency and specificity. Ongoing research aims to identify and refine these agents to regulate AhR activity for diverse biomedical uses, including the management of inflammatory diseases, such as GNF-351, StemRegenin 1, CH-223191BAY-13-9006, and GNF-351 (Sa et al., 2021; su Jang et al., 2023).

Environmental xenobiotics

In addition to polycyclic aromatic hydrocarbons and halogenated aromatic hydrocarbons, numerous environmental chemicals from diverse classes are capable of modulating AhR activity (Holme et al., 2022; Xi et al., 2022; Yu et al., 2022). Certain pesticides, including auxin-based herbicides and specific organochlorine compounds, have been identified as AhR agonists. Phthalates and other plasticizers may exhibit weak AhR-binding capacity, potentially contributing to endocrine-disrupting effects. Dietary contaminants, such as benzo(k)fluoranthene and dibenzo-anthracene—frequently originating from charred meats or polluted air—are also recognized as AhR ligands (Mohammadi et al., 2021; Parejo et al., 2000; Shi et al., 2023). Moreover, tobacco smoke contains multiple AhR agonists, including both PAHs and aromatic amines. Additional industrial and environmental sources include dioxin-like compounds from industrial waste, flame retardants, such as polybrominated diphenyl ethers, and other structurally related pollutants, all of which can engage AhR to varying extents and thereby influence immune regulation and disease susceptibility.

Within the context of RA, epidemiological evidence has demonstrated a significant association between exposure to cigarette smoke or air pollution—both of which are rich in PAHs—and an increased risk and severity of RA, particularly in genetically predisposed populations [5, 6]. It is plausible that AhR activation by these exogenous agents, especially within the lungs or other peripheral tissues, may disrupt immune tolerance and promote persistent inflammation—mechanistic pathways that are central to RA pathogenesis.

AhR signaling pathways

AhR signaling is pivotal in xenobiotic metabolism, immune modulation, and cross-communication with multiple cellular pathways. The canonical pathway follows a sequential activation process beginning in the cytoplasm and culminating in gene transcription, while noncanonical signaling extends its influence on other transcriptional and signaling systems.

Cytoplasmic complex components (HSP90, XAP2, p23)

In the absence of a ligand or in an inactive state, AhR resides in the cytoplasm as part of a multiprotein chaperone complex (Grishanova et al., 2023, Grishanova & Perepechaeva, 2024). HSP90 dimers bind AhR's PAS domains, stabilizing it and preventing premature nuclear localization. Moreover, HSP90 keeps AhR's ligand-binding pocket in an open conformation receptive to ligands while p23 binds the HSP90–AhR complex and further aids stability (Bustani et al., 2025). XAP2 associates with HSP90 and AhR and is believed to prevent AhR from translocating to the nucleus prematurely and to protect it from ubiquitin-mediated degradation. Additionally, c-Src kinase associates with this complex. In this cytosolic state, AhR is inactive but ready—the complex essentially "preloads" AhR for activation (Gonzalez et al., 1998).

Ligand binding and conformational change (ligand-induced activation)

The transition of AhR from its inactive to active state is initiated by ligand binding, for which a diverse range of molecules, including endogenous metabolites, xenobiotics such as dioxins and polycyclic aromatic hydrocarbons, as well as dietary compounds, can function as ligands (Safe et al., 2020). Upon diffusion into the cell, the ligand interacts with the PAS-B domain of AhR, inducing pronounced conformational rearrangements. These structural modifications expose previously con-

cealed nuclear localization signals (NLS), which were masked within the HSP90 complex, thereby enabling recognition by importin-β (Chong et al., 2023; Miyamoto et al., 2016; Puga et al., 2002). This ligand-driven conformational shift destabilizes the cytoplasmic chaperone assembly, resulting in the partial dissociation of AhR from HSP90, XAP2, and p23 (Wu et al., 2024). Such a rearrangement represents a critical checkpoint that ensures only ligand-bound AhR proceeds to nuclear translocation, thereby safeguarding against aberrant or unregulated gene activation. Importantly, HSP90 often remains associated with AhR during this process and may accompany it into the nucleus. With the NLS now accessible, the ligand–AhR complex is rapidly imported into the nucleus through the cellular transport machinery, marking the next stage in AhR signaling (Lamas et al., 2018; Schultz et al., 2003).

Nuclear translocation and dimerization with ARNT

Upon ligand activation, AhR translocates from the cytoplasm into the nucleus. This process requires the unmasking of the NLSs and their subsequent recognition by the nuclear import machinery. Once inside the nucleus, AhR dissociates from most of its remaining chaperones and forms a heterodimer with its obligatory partner, the AhR nuclear translocator (ARNT) (Ramadoss et al., 2005; Vazquez-Rivera et al., 2022).

ARNT, also known as hypoxia-inducible factor-1β (HIF-1β) due to its role as a common subunit of the hypoxia-inducible factor (HIF) complex, is a constitutively expressed nuclear protein. The dimerization between AhR and ARNT occurs through their PAS domains, highlighting the potential for competitive crosstalk between hypoxia- and xenobiotic-responsive signaling pathways. Within this interaction, the PAS-A and PAS-B domains of AhR are particularly critical, as they confer structural compatibility and ensure transcriptional competence (Sun et al., 2022; Swedenborg et al., 2010; Zhang et al., 2022).

The AhR–ARNT heterodimer functions as the active transcription factor complex. It binds to specific DNA regulatory sequences within target genes, known as xenobiotic response elements (XREs) or dioxin response elements (DREs). The consensus sequence of the XRE is 5′-GCGTG-3′ (or its complement 5′-CACGC-3′). Within this complex, ARNT contributes a portion of the DNA-binding domain and stabilizes AhR's interaction with the promoter regions of responsive genes, thereby enabling precise transcriptional regulation (DeGroot & Denison, 2014; Diao et al., 2025; Motta et al., 2023).

Binding to XREs and target gene activation

The AhR–ARNT heterodimer binds to XREs sequences in the promoters/enhancer's regions of AhR-responsive target genes and recruits transcriptional co-activators or co-repressors to modulate gene transcription. These elements typically contain the consensus sequence 5′-TNGCGTG-3′, in which AhR recognizes the TNGC half-site and ARNT binds to the GTG motif. This DNA-binding event recruits transcriptional coactivators such as CBP/p300 and SRC-1, which remodel chromatin and facilitate the recruitment of RNA polymerase II. The resulting gene induction primarily upregulates phase I and phase II xenobiotic-metabolizing enzymes, including CYP1A1, CYP1A2, CYP1B1, UGT1A1/1A6, GSTA1/2, and ABC transporters (DeGroot et al., 2014; Nebert, 2017; Rzemieniec et al., 2016). These enzymes orchestrate the detoxification of xenobiotics and metabolic by-products. Beyond detoxification, XRE-driven transcription also extends to immunomodulatory and proliferative genes, such as IL-10 and amphiregulin, demonstrating the pathway's integration into both toxicological defenses and physiological regulation (Zhang et al., 2022; Aldhalemi et al., 2019).

Upon binding to DNA, the AhR/ARNT complex initiates the transcription of these genes, leading to mRNA and protein synthesis and increasing levels of enzymes such as CYP1A1. The functional outcome is often enhanced ligand metabolism. Moreover, classic negative feedback mechanisms limit AhR activation; for example, FICZ is rapidly degraded by induced CYP1A1. The canonical AhR pathway described above is the best-understood mechanism of AhR action. It connects an environmental signal (a ligand) to changes in gene expression that help cells adapt, such as through ligand detoxification. However, AhR's influence extends beyond xenobiotic metabolism. In particular, AhR activation in immune cells alters the expression of cytokines, surface receptors, and other immunoregulatory genes (Manzella et al., 2020; Stejskalova et al., 2013; Vogel et al., 2016).

In contrast, the AhR repressor (AhRR) functions as a feedback inhibitor that is itself induced by AhR activation. The AhRR protein attenuates AhR signaling by competing either for ARNT binding or directly for XRE occupancy, thereby limiting the transcriptional activity of the AhR–ARNT complex and dampening downstream responses. Another key component of negative feedback regulation is TCDD-inducible poly(ADP-ribose) polymerase (TIPARP), which contributes to the repression of AhR activity through ADP-ribosylation–mediated mechanisms (Grunewald et al., 2020; Vogel et al., 2019,

2017; Yang et al., 2018). In parallel, AhR activation also promotes the transcription of phase II detoxification enzymes. Among these, NAD(P)H quinone dehydrogenase 1 (NQO1) and various UDP-glucuronosyltransferases (UGTs) are prominent targets. While many of these enzymes are directly upregulated via XRE binding, others can be induced indirectly through cross-talk with the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, thereby broadening the spectrum of AhR-mediated transcriptional regulation (Mohammadi et al., 2021; Silva-Palacios et al., 2019; Zhang et al., 2016).

Non-canonical AhR signaling

In addition to the classical genomic pathway, AhR can engage in non-canonical signaling modes, affecting cellular processes without directly binding to XREs as a transcriptional activator (Chen et al., 2020). The signaling interplay between the AhR and NF-κB (p65/RelA) pathways is highly dynamic, as their intersection occurs at multiple regulatory levels (Carlucci et al., 2023; Mohammadi et al., 2021). Upon ligand activation, AhR physically interacts with NF-κB subunits or competes for shared coactivators, a mechanism that, in many contexts, suppresses NF-κB–driven gene transcription (Attafi et al., 2022; Wang et al., 2022). However, this interaction does not uniformly result in inhibition. Under certain conditions, AhR activation can actually amplify NF-κB activity (Attafi et al., 2022; Carlucci et al., 2023). A notable example is the shared epitope–AhR synergy observed in rheumatoid arthritis, where NF-κB activation contributed to an increase in Th17 cytokine production (Fu et al., 2018). Consequently, the functional outcome of AhR–NF-κB crosstalk is context-dependent, manifesting as either anti-inflammatory or pro-inflammatory depending on the ligand involved and the cellular environment. Moreover, AhR activation has been shown to counteract NF-κB–inducing stimuli, such as lipopolysaccharide. In dendritic cells, for instance, AhR stimulation resulted in a marked reduction of IL-6 levels through the modulation of both NF-κB and STAT3 phosphorylation. Beyond cytokine regulation, AhR also exerts control over the NLRP3 inflammasome via NF-κB-linked mechanisms, as demonstrated in several inflammatory disease models (Nazari-Khanamiri et al., 2022a; Nazari-Khanamiri et al., 2022b; Zhang et al., 2023).

Crosstalk with NF-κB, MAPK, STAT, and PI3K/Akt

AhR can rapidly activate kinases such as p38, ERK, and JNK, even before changes in gene transcription occur, through noncanonical actions. For example, ligand-bound AhR can release c-Src kinase, which then triggers the Ras/MAPK cascade. Additionally, AhR can influence gene expression in the mitogen-activated protein kinase (MAPK) pathway. An experimental study showed that AhR deficiency leads to altered baseline MAPK activity. In the context of immune activation, AhR agonists have been shown to inhibit the phosphorylation of ERK1/2, JNK, and p38 in activated neutrophils and macrophages, thereby dampening the production of inflammatory mediators. This is one mechanism by which AhR ligands, such as resveratrol and its derivatives, exert anti-inflammatory effects: by blocking MAPK activation and downstream cytokine production, including TNF and IL-1, as well as the production of enzymes such as COX-2 and iNOS (Mohammadi et al., 2021; Parejo et al., 2000; Shi et al., 2023).

STAT (signal transducer and activator of transcription) pathways: AhR cross-talks with STAT proteins, especially STAT1 and STAT3. One study illustrated that AhR can sequester phospho-STAT1 or alter its phosphorylation state (Liu et al., 2024). Furthermore, AhR was shown to regulate STAT1 activation and IL-22 production in T helper 17 cells. TCDD-induced AhR activation also leads to the upregulation of the immunosuppressive cytokine IL-10 through an interaction with STAT3 in T cells, thereby promoting regulatory Tr1 cells. In RA models, an AhR agonist might enhance STAT3 phosphorylation in a manner that induces anti-inflammatory genes, such as those encoding the IL-6 receptor antagonist or IL-10 (Holme et al., 2022; Eslammanesh et al., 2025).

On the other hand, if STAT3 drives pathogenic Th17 differentiation, AhR can sometimes promote this process, as FICZ-driven AhR activation increases STAT3-dependent Th17 differentiation. Thus, AhR–STAT interplay is ligand-specific. AhR also influences STAT-dependent pathways, like JAK/STAT. A previous study found that resveratrol inhibited JAK/STAT/RANKL signaling in arthritic rats, thereby reducing osteoclast activation (Nazari-Khanamiri et al., 2022a; Nazari-Khanamiri et al., 2022b).

There is evidence that AhR activation modulates the PI3K/Akt pathway: in some contexts, AhR ligands activate PI3K/Akt signaling, while in others, they inhibit it. For instance, one study showed that resveratrol reduced Akt phosphorylation in RA fibroblast-like synoviocytes. Moreover, by inhibiting Akt and downstream mTOR signaling, AhR activation can induce a more quiescent or tolerogenic immune-cell phenotype. Additionally, PI3K activity can provide feedback that influences AhR, contributing to dynamic crosstalk relevant to dendritic cell maturation and T-cell differentiation.

AhR as a transcriptional repressor in certain contexts

Beyond activating gene transcription via XREs, AhR can also repress the transcription of certain genes by protein–protein interactions (tethering) or competition. Ligand-bound AhR binds transcription factors, like the estrogen receptor (ER), retinoic acid receptor (RAR), or RelA (NF-κB p65) and prevents them from accessing their own response elements. One study illustrated that AhR forms a complex with ERα and recruits corepressors to estrogen-responsive genes, thereby downregulating estrogenic activity as one proposed mechanism underlying dioxin's antiestrogenic effects. Similarly, AhR interacts with the retinoblastoma protein (Rb), which affects cell-cycle gene expression. Unliganded AhR bound to Rb in the nucleus can sequester Rb, leading to improper cell-cycle progression, whereas certain ligand-induced activations release Rb but subsequently interfere with E2F transcription factors (DeGroot et al., 2014; Nebert, 2017; Ali et al., 2025).

In T-cells, AhR was reported to bind the transcription factor T-bet, reducing IFN-γ production, which shows a repressor function in Th1 differentiation. As noted, AhR activation decreases effector T-cell cytokines, especially IL-17, by promoting suppressive Treg/Tr1 pathways. In a ligand-specific manner, AhR signaling has been observed to decrease the frequency of Th17 cells and their cytokines (IL-17, IL-22) while increasing regulatory cytokines (IL-10) thereby effectively repressing the pro-inflammatory gene program (Xi et al., 2022; Yu et al., 2022).

AhR can recruit enzymes that modify chromatin. During Th17 versus Treg differentiation, AhR binds different ligands and recruits coactivator or corepressor complexes to the *IL17* or *FoxP3* gene loci (Zedan et al., 2023; Ahmady et al., 2024). TCDD-bound AhR in Tregs recruits histone deacetylases (HDACs) to the IL17 promoter, silencing it, whereas FICZ-bound AhR might recruit coactivators to IL17, increasing its expression. Thus, AhR acts as either a repressor or an activator depending on the ligand context (Goya-Jorge et al., 2022; Liu et al., 2024).

AhR shares ARNT with the HIF-1α complex. Under conditions of simultaneous HIF-1 activation, such as hypoxia or high levels of inflammation, HIF-1α can compete with AhR for ARNT, thereby reducing AhR's ability to function. Conversely, constitutive AhR activation can sequester ARNT and repress HIF-1α target genes, such as *VEGF* (Aldhalemi et al., 2025). This interplay means that AhR activation could repress hypoxia-induced genes, including those involved in angiogenesis, which could potentially be beneficial in the often-hypoxic RA synovium. one study showed that high CRP levels induced HIF-1α, which interfered with AhR–ARNT signaling, whereas blocking HIF-1α restored AhR-mediated repression of CRP and bone erosion. This exemplifies how AhR might normally repress certain genes, such as *CRP* and *VEGF*, via competition, whereas inflammation can relieve that repression by occupying ARNT with HIF-1 (Liu et al., 2024).

Non-genomic actions (rapid cytoplasmic signaling)

Apart from influencing gene transcription, AhR can exert fast, non-genomic effects in the cytoplasm. The association of c-Src kinase with the AhR complex is one mechanism for non-genomic signaling. Upon ligand binding, a conformational change in AhR leads to the activation or release of Src. Active Src then phosphorylates downstream targets, including components of the EGF receptor/MAPK pathways. Indeed, TCDD has been shown to rapidly activate Src kinase, leading to EGFR phosphorylation and the activation of ERK and p38 MAPK in certain cells. These events occur within minutes, which is too quickly for them to result from gene transcription. This process alters cell migration, adhesion, or secretion in immune cells. AhR ligands cause rapid changes in intracellular Ca^{2+} levels through the AhR-mediated release of intracellular stores or the modulation of membrane channels. In the cytosol, AhR binds to and affects the stability of proteins such as cyclin-dependent kinase inhibitors. Before any transcription occurs, ligand-bound AhR might induce the proteasomal degradation of some cell-cycle regulators; however, the exact mechanisms are still being elucidated (Mohammadi et al., 2021; Parejo et al., 2000; Shi et al., 2023).

In T cells, evidence suggests that AhR might localize to the immune synapse upon TCR activation and influence signaling molecules there, possibly through direct binding or via Src family kinases, thereby affecting the T-cell activation threshold before any new gene induction (Holme et al., 2022; Yu et al., 2022)

These non-genomic pathways allow AhR to fine-tune cellular responses rapidly. Interestingly, when a dendritic cell encounters a bacterial product and also an AhR ligand from microbes, AhR might quickly dampen excessive inflammatory signaling through the modulation of Src/MAPK/NF-κB pathways, even before upregulating genes, such as IDO or IL-10. In RA, non-genomic effects

of AhR could influence how synovial cells or leukocytes respond immediately to stress or cytokines. AhR blockade prevented hydroquinone, a smoke-derived AhR ligand, from inducing excessive synoviocyte proliferation and the release of inflammatory cytokines. This suggests that part of hydroquinone's deleterious effect involves an AhR-mediated rapid signaling event that drives cell activation and could be prevented by an AhR antagonist.

Conclusion

AhR functions as a ligand-responsive transcription factor whose biological outcomes are determined by ligand origin, affinity, metabolic stability, and cellular context. The evidence reviewed here demonstrates that endogenous metabolites, dietary compounds, microbiota-derived products, and environmental xenobiotics differentially engage canonical and non-canonical AhR signaling pathways, thereby shaping immune regulation and disease processes. Importantly, non-toxic natural ligands and selective modulators offer opportunities to fine-tune AhR activity without the adverse effects associated with persistent xenobiotic activation. Future research should focus on defining tissue-specific signaling networks, ligand-dependent transcriptional programs, and translational strategies for selectively targeting AhR in inflammatory, metabolic, and immune-mediated disorders.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors would like to express their sincere gratitude to the Islamic University of Najaf, Iraq, for its academic support and encouragement. The authors also extend their appreciation to all colleagues, researchers, and individuals who provided valuable assistance, guidance, and encouragement throughout the preparation of this review article. Their contributions and support are gratefully acknowledged.

References

Abdull Razis, A. F., Konsue, N., Dervetzoglou, M., Plant, K. E., Plant, N., & Ioannides, C. (2012). Phenethyl isothiocyanate, a naturally occurring phytochemical, is an antagonist of the aryl hydrocarbon receptor. *Molecular Nutrition & Food Research, 56*(3), 425-434. [DOI:10.1002/mnfr.201100548] [PMID]

Abdulla, O. A., Neamah, W., Sultan, M. H. K., Singh, N., Busbee, P. B., & Nagarkatti, M., et al. (2021). The ability of AHR ligands to attenuate delayed type hypersensitivity reaction is associated with alterations in the gut microbiota. *Frontiers in Immunology, 12*, 684727. [DOI:10.3389/fimmu.2021.684727] [PMID] [PMCID]

Ahmady, H., Afrand, M., Motaqi, M., & Meftahi, G. H. (2024). Utilizing sertoli cell transplantation as a therapeutic technique for the management of neurodegenerative diseases. *Archives of Razi Institute, 79*(4), 701. [DOI:10.32592/ARI.2024.79.4.701] [PMID] [PMCID]

Ahmed, Rusal M, & Mohammed, A. K. (2022). Role of sodium butyrate supplement on reducing hepatotoxicity induced by lead acetate in rats. *The Iraqi Journal of Veterinary Medicine, 46*(2), 29-35. [DOI:10.30539/ijvm.v46i2.1408]

Ahmed, Rusul Mowaffaq, & Mohammed, A. K. (2022). Amelioration of hepatotoxicity by sodium butyrate administration in rats. *World's Veterinary Journal, 3*, 323-329. [DOI:10.54203/scil.2022.wvj41]

Aldhalemi, A. A., Aldhalemi, M. A., Alneamah, S. J. A., Almaghanichy, M. M. J., & Bustani, G. S. (2025). Mentha leaf extracts and oils: A novel approach to enhance the flavor and shelf life of soft cheese. *Iranian Journal of Veterinary Medicine, 19*(1), 105–120. [Link]

Aldhalemi, M. A., Aldhalemi, A. A., & Al-Mosawi, R. S. (2019). The fatty acids determination in breast milk and in infant formula milk. *IOP Conference Series: Earth and Environmental Science, 388*(1), Article 012065. [DOI:10.1088/1755-1315/388/1/012065]

Alghetaa, H., Mohammed, A., Singh, N. P., Bloomquist, R. F., Chatzistamou, I., & Nagarkatti, M., et al. (2023). Estrobolome dysregulation is associated with altered immunometabolism in a mouse model of endometriosis. *Frontiers in Endocrinology, 14*, 1261781. [DOI:10.3389/fendo.2023.1261781] [PMID] [PMCID]

Alghetaa, H., Mohammed, A., Zhou, J., Singh, N., Nagarkatti, M., & Nagarkatti, P. (2021). Resveratrol-mediated attenuation of superantigen-driven acute respiratory distress syndrome is mediated by microbiota in the lungs and gut. *Pharmacological Research, 167*, 105548. [DOI:10.1016/j.phrs.2021.105548] [PMID] [PMCID]

Al-Ghezi, Z. Z., Singh, N., Mehrpouya-Bahrami, P., Busbee, P. B., Nagarkatti, M., & Nagarkatti, P. S. (2019). AHR activation by TCDD (2, 3, 7, 8-Tetrachlorodibenzo-p-dioxin) attenuates pertussis toxin-induced inflammatory responses by differential regulation of tregs and Th17 cells through specific targeting by microRNA. *Frontiers in Microbiology, 10*, 2349. [DOI:10.3389/fmicb.2019.02349] [PMID] [PMCID]

Alharris, E., Mohammed, A., Alghetaa, H., Zhou, J., Nagarkatti, M., & Nagarkatti, P. (2022). The ability of resveratrol to attenuate ovalbumin-mediated allergic asthma is associated with changes in microbiota involving the gut-lung axis, enhanced barrier function and decreased inflammation in the lungs. *Frontiers in Immunology, 13*, 805770. [DOI:10.3389/fimmu.2022.805770] [PMID] [PMCID]

Ali, A., Naeem, M. Y., Selamoglu, Z., & Naqvi, M. R. (2025). Exploring quantum in cancer biology: A comprehensive review of nontrivial quantum events. *Archives of Razi Institute, 80*(2), 395-400. [DOI:10.32592/ARI.2025.80.2.295] [PMID]

Al-Khaqani, B., & Mohammed, A. (2024). Ovalbumin-induced asthma in rats is alleviated by resveratrol treatment. *Journal of Animal Health and Production, 12*(2), 121-127. [DOI:10.17582/journal.jahp/2024/12.2.121.127]

Al-Kinany, Q. S. H., & Enayah, S. H. (2021). The effect of polycyclic aromatic hydrocarbons on AHR and Cyp450 enzymes in oil field workers in south of Iraq. *Iranian Journal of Ichthyology, 8*, 359-363. [Link]

Amobi-Mccloud, A. E. (2019). Indoleamine 2,3-dioxygenase regulates PD-1 expression on CD8 + T cells via kynurenine activation of the aryl hydrocarbon receptor [doctoral dissertation]. New York: University at Buffalo. [Link]

Attafi, I. M., Bakheet, S. A., Ahmad, S. F., Belali, O. M., Alanazi, F. E., & Aljarboa, S. A., et al. (2022). Lead nitrate induces inflammation and apoptosis in rat lungs through the activation of NF-κB and AHR signaling pathways. *Environmental Science and Pollution Research. 29*, 64959–64970. [DOI:10.1007/s11356-022-19980-8]

Baker, J. R., Gilbert, J., Paula, S., Zhu, X., Sakoff, J. A., & McCluskey, A. (2018). Dichlorophenylacrylonitriles as AHR ligands that display selective breast cancer cytotoxicity in vitro. *ChemMedChem, 13*(14), 1447-1458. [DOI:10.1002/cmdc.201800256] [PMID]

Banerjee, B., Chakraborty, S., Ghosh, D., Raha, S., Sen, P. C., & Jana, K. (2016). Benzo (a) pyrene induced p53 mediated male germ cell apoptosis: Synergistic protective effects of curcumin and resveratrol. *Frontiers in Pharmacology, 7*, 245. [DOI:10.3389/fphar.2016.00245] [PMID] [PMCID]

Beedanagari, S. R., Taylor, R. T., Bui, P., Wang, F., Nickerson, D. W., & Hankinson, O. (2010). Role of epigenetic mechanisms in differential regulation of the dioxin-inducible human CYP1A1 and CYP1B1 genes. *Molecular Pharmacology, 78*(4), 608-616. [DOI:10.1124/mol.110.064899] [PMID] [PMCID]

Busbee, P. B., Rouse, M., Nagarkatti, M., & Nagarkatti, P. S. (2013). Use of natural AHR ligands as potential therapeutic modalities against inflammatory disorders. *Nutrition Reviews, 71*(6), 353-369. [DOI:10.1111/nure.12024] [PMID] [PMCID]

Bustani, G. S., & Alghetaa, H. F. K. (2025). Aryl hydrocarbon receptor signaling in male fertility: Protective role of resveratrol and disruptive effects of CH223191 in adult male rats. *Veterinary World, 18*(4), 1274-1287. [DOI:10.14202/vetworld.2025.1274-1287] [PMID] [PMCID]

Bustani, G. S., & Alghetaa, H. (2025). Aryl hydrocarbon receptor modulation impacts on the blood-testis barrier integrity via TJP1 function. *Iranian Journal of Veterinary Medicine, 19*(3), 415. [DOI:10.32598/ijvm.19.3.1005541]

Bustani, G., Alghetaa, H., Mohammed, A., Nagarkatti, M., & Nagarkatti, P. (2025). The aryl hydrocarbon receptor: a new frontier in male reproductive system. *Reproductive Biology and Endocrinology, 23*(1), 1-25. [DOI:10.1186/s12958-025-01401-3] [PMID] [PMCID]

Bustani, G., Al-Humadi, N., & Alghetaa, H. (2024). Aryl Hydrocarbon receptor modulation and resveratrol influence on dnah1 expression: Implications for male reproductive health. *The Iraqi Journal of Veterinary Medicine, 48*(1), 15-24. [DOI:10.30539/p5wv8002]

Cannon, A. S., Nagarkatti, P. S., & Nagarkatti, M. (2022). Targeting AHR as a novel therapeutic modality against inflammatory diseases. *International Journal of Molecular Sciences, 23*(1), 288. [DOI:10.3390/ijms23010288] [PMID] [PMCID]

Cano-Sánchez, J., Murillo-González, F. E., de Jesús-Aguilar, J., Cabañas-Cortés, M. A., Tirado-Garibay, A. C., & Elizondo, G. (2023). The aryl hydrocarbon receptor ligand 6-formylindolo (3, 2-b) carbazole promotes estrogen receptor alpha and c-fos protein degradation and inhibits MCF-7 cell proliferation and migration. *Pharmacology, 108*(2), 157-165. [DOI:10.1159/000527993] [PMID]

Carlucci, C. D., Hui, Y., Chumanevich, A. P., Robida, P. A., Fuseler, J. W., & Sajish, M., et al. (2023). Resveratrol protects against skin inflammation through inhibition of mast cell, sphingosine kinase-1, Stat3 and NF-κB p65 signaling activation in mice. *International Journal of Molecular Sciences, 24*(7), 6707. [DOI:10.3390/ijms24076707] [PMID] [PMCID]

Cervantes-Barragan, L., Chai, J. N., Tianero, M. D., Di Luccia, B., Ahern, P. P.,& Merriman, J., et al. (2017). Lactobacillus reuteri induces gut intraepithelial CD4+ CD8αα+ T cells. *Science, 357*(6353), 806-810. [DOI:10.1126/science.aah5825] [PMID] [PMCID]

Chan, N. L. S., Wang, H., Wang, Y., Leung, H. Y., & Leung, L. K. (2006). Polycyclic aromatic hydrocarbon-induced CYP1B1 activity is suppressed by perillyl alcohol in MCF-7 cells. *Toxicology and Applied Pharmacology, 213*(2), 98-104. [DOI:10.1016/j.taap.2005.10.002] [PMID]

Chapkin, R. S., Davidson, L. A., Park, H., Jin, U., Fan, Y., & Cheng, Y., et al. (2021). Role of the aryl hydrocarbon receptor (AHR) in mediating the effects of coffee in the colon. *Molecular Nutrition & Food Research, 65*(20), 2100539. [DOI:10.1002/mnfr.202100539] [PMID] [PMCID]

Chen, Yangsheng, Xie, H. Q., Sha, R., Xu, T., Zhang, S., Fu, H., & Xia, Y., et al. (2020). 2, 3, 7, 8-Tetrachlorodibenzo-p-dioxin and up-regulation of neurofilament expression in neuronal cells: Evaluation of AHR and MAPK pathways. *Environment International, 134*, 105193. [DOI:10.1016/j.envint.2019.105193] [PMID]

Chen, Yue, Wang, Y., Fu, Y., Yin, Y., & Xu, K. (2023). Modulating AHR function offers exciting therapeutic potential in gut immunity and inflammation. *Cell & Bioscience, 13*(1), 1-26. [DOI:10.1186/s13578-023-01046-y] [PMID] [PMCID]

Cheng, Y., Jin, U. H., Allred, C. D., Jayaraman, A., Chapkin, R. S., & Safe, S. (2015). Aryl hydrocarbon receptor activity of tryptophan metabolites in young adult mouse colonocytes. *Drug Metabolism and Disposition, 43*(10), 1536-1543. [DOI:10.1124/dmd.115.063677] [PMID] [PMCID]

Chong, Z. X., Yong, C. Y., Ong, A. H. K., Yeap, S. K., & Ho, W. Y. (2023). Deciphering the roles of aryl hydrocarbon receptor (AHR) in regulating carcinogenesis. *Toxicology, 495*, 153596. [DOI:10.1016/j.tox.2023.153596] [PMID]

Coelho, N. R., Pimpão, A. B., Correia, M. J., Rodrigues, T. C., Monteiro, E. C., & Morello, J., et al. (2022). Pharmacological blockage of the AHR-CYP1A1 axis: A call for in vivo evidence. *Journal of Molecular Medicine, 100*(2), 215-243. [DOI:10.1007/s00109-021-02163-2] [PMID] [PMCID]

Dai, X., & Zhu, B. T. (2010). Indoleamine 2, 3-dioxygenase tissue distribution and cellular localization in mice: Implications for its biological functions. *Journal of Histochemistry & Cytochemistry, 58*(1), 17-28. [DOI:10.1369/jhc.2009.953604] [PMID] [PMCID]

DeGroot, D. E., & Denison, M. S. (2014). Nucleotide specificity of DNA binding of the aryl hydrocarbon receptor: ARNT complex is unaffected by ligand structure. *Toxicological Sciences, 137*(1), 102-113. [DOI:10.1093/toxsci/kft234] [PMID] [PMCID]

Diao, X., Shang, Q., Guo, M., Huang, Y., Zhang, M., & Chen, X., et al. (2025). Structural basis for the ligand-dependent activation of heterodimeric AHR-ARNT complex. *Nature Communications, 16*(1), 1282. [DOI:10.1038/s41467-025-56574-7] [PMID] [PMCID]

Dong, F., Hao, F., Murray, I. A., Smith, P. B., Koo, I., & Tindall, A. M., et al. (2020). Intestinal microbiota-derived tryptophan metabolites are predictive of Ah receptor activity. *Gut Microbes, 12*(1), 1788899. [DOI:10.1080/19490976.2020.1788899] [PMID] [PMCID]

Elias, F., & Mohammed, A. (2024). Sodium Butyrate's Antioxidant Effects Alleviate DSS-Induced Colitis in Rats. *Azerbaijan Pharmaceutical and Pharmacotherapy Journal, 23*(3), 1-5. [DOI:10.61336/appj/23-03-04]

Eslammanesh, T., Mirshekari, A., Dahmardeh, N., Ghafari, M., Mahmoodi, F., & Jahantigh, M., et al. (2025). Mechanisms of miRNAs (MicroRNAs) and their expression in gastric cancer. *Archives of Razi Institute, 80*(1), 217–224. [DOI:10.32592/ARI.2025.80.1.217] [PMID]

Faiad, W., Soukkarieh, C., Murphy, D. J., & Hanano, A. (2022). Effects of dioxins on animal spermatogenesis: A state-of-the-art review. *Frontiers in Reproductive Health, 4*, 1009090. [DOI:10.3389/frph.2022.1009090] [PMID] [PMCID]

Farmahin, R., Crump, D., & Kennedy, S. W. (2014). Sensitivity of avian species to the aryl hydrocarbon receptor ligand 6-formylindolo [3,2-b] carbazole (FICZ). *Chemico-Biological Interactions, 221*, 61–69. [DOI:10.1016/j.cbi.2014.07.009] [PMID]

Foroozesh, M., Sridhar, J., Goyal, N., & Liu, J. (2019). Coumarins and P450s, studies reported to-date. *Molecules, 24*(8), 1620. [DOI:10.3390/molecules24081620] [PMID] [PMCID]

Fu, J., Nogueira, S. V., van Drongelen, V., Coit, P., Ling, S., & Rosloniec, E. F., et al. (2018). Shared epitope-aryl hydrocarbon receptor crosstalk underlies the mechanism of gene-environment interaction in autoimmune arthritis. *Proceedings of the National Academy of Sciences of the United States of America, 115*(18), 4755-4760. [DOI:10.1073/pnas.1722124115] [PMID] [PMCID]

Gargaro, M., Pirro, M., Romani, R., Zelante, T., & Fallarino, F. (2016). Aryl Hydrocarbon Receptor-Dependent Pathways in Immune Regulation. *American Journal of Transplantation, 16*(8), 2270–2276. [DOI:10.1111/ajt.13716] [PMID]

Gonzalez, F. J., & Fernandez-Salguero, P. (1998). The aryl hydrocarbon receptor: Studies using the AHR-null mice. *Drug Metabolism and Disposition, 26*(12), 1194-1198. [DOI:10.1124/dmd.26.12.1194]

Goya-Jorge, E., Gonza, I., Bondue, P., Douny, C., Taminiau, B., & Daube, G., et al. (2022). Human adult microbiota in a static colon model: AHR transcriptional activity at the crossroads of host-microbe interaction. *Foods, 11*(13), 1946. [DOI:10.3390/foods11131946] [PMID] [PMCID]

Griffiths, A. L., & Schroeder, J. C. (2017). Effects of resveratrol on AhR activity in cells treated with benzo [A] pyrene or indigo. *Georgia Journal of Science, 75*(1), 44. [Link]

Grishanova, A. Y., & Perepechaeva, M. L. (2024). Kynurenic Acid/AhR signaling at the junction of inflammation and cardiovascular diseases. *International Journal of Molecular Sciences, 25*(13), 6933. [DOI:10.3390/ijms25136933] [PMID] [PMCID]

Grishanova, A. Y., Klyushova, L. S., & Perepechaeva, M. L. (2023). AhR and Wnt/β-catenin signaling pathways and their interplay. *Current Issues in Molecular Biology, 45*(5), 3848–3876. [DOI:10.3390/cimb45050248] [PMID] [PMCID]

Grunewald, M. E., Shaban, M. G., Mackin, S. R., Fehr, A. R., & Perlman, S. (2020). Murine coronavirus infection activates the aryl hydrocarbon receptor in an indoleamine 2, 3-dioxygenase-independent manner, contributing to cytokine modulation and proviral TCDD-inducible-PARP expression. *Journal of Virology, 94*(3), e01743-19. [DOI:10.1128/JVI.01743-19] [PMID] [PMCID]

Hahn, M. E. (2002). Aryl hydrocarbon receptors: Diversity and evolution. *Chemico-Biological Interactions, 141*(1-2), 131-160. [DOI:10.1016/S0009-2797(02)00070-4]

Handique, J. G., & Baruah, J. B. (2002). Polyphenolic compounds: an overview. *Reactive and Functional Polymers, 52*(3), 163-188. [DOI:10.1016/S1381-5148(02)00091-3]

Hankinson, O. (2016). The role of AHR-inducible cytochrome P450s in metabolism of polyunsaturated fatty acids. *Drug Metabolism Reviews, 48*(3), 342-350. [DOI:10.1080/03602532.2016.1197240] [PMID] [PMCID]

Holme, J. A., Valen, H., Brinchmann, B. C., Vist, G. E., Grimsrud, T. K., & Becher, R., et al. (2022). Polycyclic aromatic hydrocarbons (PAHs) may explain the paradoxical effects of cigarette use on preeclampsia (PE). *Toxicology, 473*, 153206. [DOI:10.1016/j.tox.2022.153206] [PMID]

Huang, X. X., Xu, S., Yu, L. J., Zhou, Y. F., Zhou, Y., & Liu, Z. H. (2021). Eurotium cristatum fermented loose dark tea ameliorates cigarette smoke-induced lung injury by MAPK pathway and enhances hepatic metabolic detoxification by PXR/AhR pathway in mice. *Oxidative Medicine and Cellular Longevity, 2021*(1), 6635080. [DOI:10.1155/2021/6635080] [PMID] [PMCID]

Huang, Y. S., Ogbechi, J., Clanchy, F. I., Williams, R. O., & Stone, T. W. (2020). IDO and kynurenine metabolites in peripheral and CNS disorders. *Frontiers in Immunology, 11*, 388. [DOI:10.3389/fimmu.2020.00388] [PMID] [PMCID]

Huang, Y., Zhang, J., Tao, Y., Ji, C., Aniagu, S., Jiang, Y., & Chen, T. (2021). AHR/ROS-mediated mitochondria apoptosis contributes to benzo [a] pyrene-induced heart defects and the protective effects of resveratrol. *Toxicology, 462*, 152965. [DOI:10.1016/j.tox.2021.152965] [PMID]

Hubbard, T. D., Murray, I. A., Bisson, W. H., Lahoti, T. S., Gowda, K., & Amin, S. G., et al. (2015). Adaptation of the human aryl hydrocarbon receptor to sense microbiota-derived indoles. *Scientific Reports, 5*(1), 12689. [DOI:10.1038/srep12689] [PMID] [PMCID]

Huerta-Yepez, S., Tirado-Rodriguez, A., Montecillo-Aguado, M. R., Yang, J., Hammock, B. D., & Hankinson, O. (2020). Aryl hydrocarbon receptor-dependent inductions of omega-3 and omega-6 polyunsaturated fatty acid metabolism act inversely on tumor progression. *Scientific Reports, 10*(1), 7843 [DOI:10.1038/s41598-020-64146-6] [PMID] [PMCID]

Hussain, M. I., Syed, Q. A., Khattak, M. N. K., Hafez, B., Reigosa, M. J., & El-Keblawy, A. (2019). Natural product coumarins: Biological and pharmacological perspectives. *Biologia, 74*, 863-888. [DOI:10.2478/s11756-019-00242-x]

Jin, U. H., Lee, S. O., Pfent, C., & Safe, S. (2014). The aryl hydrocarbon receptor ligand omeprazole inhibits breast cancer cell invasion and metastasis. *BMC Cancer, 14*(1), 1-14. [DOI:10.1186/1471-2407-14-498] [PMID] [PMCID]

Lamas, B., Natividad, J. M., & Sokol, H. (2018). Aryl hydrocarbon receptor and intestinal immunity. *Mucosal Immunology, 11*(4), 1024-1038. [DOI:10.1038/s41385-018-0019-2] [PMID]

Li, Y., Wang, X., Su, Y., Wang, Q., Huang, S., Pan, Z., Chen, Y., Liang, J., Zhang, M., & Xie, X. (2022). Baicalein ameliorates ulcerative colitis by improving intestinal epithelial barrier via AhR/IL-22 pathway in ILC3s. *Acta Pharmacologica Sinica, 43*(6), 1495-1507. [DOI:10.1038/s41401-021-00781-7] [PMID] [PMCID]

Liang, C., Li, J., Lu, C., Xie, D., Liu, J., & Zhong, C., et al. (2019). HIF1α inhibition facilitates Leflunomide-AHR-CRP signaling to attenuate bone erosion in CRP-aberrant rheumatoid arthritis. *Nature Communications, 10*(1), 4579. [DOI:10.1038/s41467-019-12163-z] [PMID]

Liu, N., Fan, X., Shao, Y., Chen, S., Wang, T., Yao, T., & Chen, X. (2024). Resveratrol attenuates inflammation and fibrosis in rheumatoid arthritis-associated interstitial lung disease via the AKT/TMEM175 pathway. *Journal of Translational Medicine, 22*(1), 457. [DOI:10.1186/s12967-024-05228-1] [PMID] [PMCID]

Liu, X., Liu, X., Wang, X., Shang, K., Li, J., Lan, Y., Wang, J., Li, J., Yue, B., & He, M. (2023). Multi-omics analysis reveals changes in tryptophan and cholesterol metabolism before and after sexual maturation in captive macaques. *BMC Genomics, 24*(1), 1-12. [DOI:10.1186/s12864-023-09404-3]

Ludwiczuk, A., Skalicka-Woźniak, K., & Georgiev, M. I. (2017). Terpenoids. In S. Badal., & R. Delgoda (Eds.) Pharmacognosy (pp. 233-266). Amsterdam: Elsevier. [DOI:10.1016/B978-0-12-802104-0.00011-1]

Ly, C., Yockell-Lelievre, J., Ferraro, Z. M., Arnason, J. T., Ferrier, J., & Gruslin, A. (2015). The effects of dietary polyphenols on reproductive health and early development. *Human Reproduction Update, 21*(2), 228-248. [DOI:10.1093/humupd/dmu058] [PMID]

MacEachern, S. J., Keenan, C. M., Papakonstantinou, E., Sharkey, K. A., & Patel, B. A. (2018). Alterations in melatonin and 5-HT signalling in the colonic mucosa of mice with dextran-sodium sulfate-induced colitis. *British Journal of Pharmacology, 175*(9), 1535-1547. [DOI:10.1111/bph.14163] [PMID] [PMCID]

Mahendra, C. K., Tan, L. T. H., Lee, W. L., Yap, W. H., Pusparajah, P., & Low, L. E., et al. (2020). Angelicin-A furocoumarin compound with vast biological potential. *Frontiers in Pharmacology, 11*, 366. [DOI:10.3389/fphar.2020.00366] [PMID] [PMCID]

Manzella, C. R., Ackerman, M., Singhal, M., Ticho, A. L., Ceh, J., & Alrefai, W. A., et al. (2020). Serotonin modulates AhR activation by interfering with CYP1A1-mediated clearance of AhR ligands. *Cellular Physiology and Biochemistry, 54*(1), 126. [DOI:10.33594/000000209] [PMID]

Miyamoto, Y., Yamada, K., & Yoneda, Y. (2016). Importin α: a key molecule in nuclear transport and non-transport functions. *The Journal of Biochemistry, 160*(2), 69-75. [DOI:10.1093/jb/mvw036] [PMID]

Mohammadi, H., & Ashari, S. (2021). Mechanistic insight into toxicity of phthalates, the involved receptors, and the role of Nrf2, NF-κB, and PI3K/AKT signaling pathways. *Environmental Science and Pollution Research, 28*(27), 35488-35527. [DOI:10.1007/s11356-021-14466-5] [PMID]

Motta, S., & Bonati, L. (2023). TCDD-induced allosteric perturbation of the AhR: ARNT binding to DNA. *International Journal of Molecular Sciences, 24*(11), 9339. [DOI:10.3390/ijms24119339] [PMID] [PMCID]

Nazari-Khanamiri, F., & Ghasemnejad-Berenji, M. (2022). Resveratrol may ameliorate rheumatoid arthritis via the STAT3/HIF-1/VEGF molecular pathway. *Journal of Food Biochemistry, 46*(8), e14182. [DOI:10.1111/jfbc.14182] [PMID]

Nazari-Khanamiri, F., & Ghasemnejad-Berenji, M. (2022). Resveratrol may ameliorate rheumatoid arthritis via the STAT3/HIF-1/VEGF molecular pathway. *Journal of Food Biochemistry, 46*(8), e14182. [DOI:10.1111/jfbc.14182] [PMID]

Neamah, W. H., Busbee, P. B., Alghetaa, H., Abdulla, O. A., Nagarkatti, M., & Nagarkatti, P. (2020). Ahr activation leads to alterations in the gut microbiome with consequent effect on induction of myeloid derived suppressor cells in a CXCR2-dependent manner. *International Journal of Molecular Sciences, 21*(24), 9613. [DOI:10.3390/ijms21249613] [PMID] [PMCID]

Nebert, D. W. (2017). Aryl hydrocarbon receptor (AHR):"pioneer member" of the basic-helix/loop/helix per-Arnt-sim (bHLH/PAS) family of "sensors" of foreign and endogenous signals. *Progress in Lipid Research, 67*, 38-57. [DOI:10.1016/j.plipres.2017.06.001] [PMID] [PMCID]

O'Driscoll, C. A., Gallo, M. E., Hoffmann, E. J., Fechner, J. H., Schauer, J. J., & Bradfield, C. A., et al. (2018). Polycyclic aromatic hydrocarbons (PAHs) present in ambient urban dust drive pro-inflammatory T cell and dendritic cell responses via the aryl hydrocarbon receptor (AHR) in vitro. *Plos One, 13*(12), e0209690. [DOI:10.1371/journal.pone.0209690] [PMID] [PMCID]

Oikawa, K., Ohbayashi, T., Mimura, J., Iwata, R., Kameta, A., & Evine, K., et al. (2001). Dioxin suppresses the checkpoint protein, MAD2, by an aryl hydrocarbon receptor-independent pathway. *Cancer Research, 61*(15), 5707-5709. [PMID]

Ondrová, K., Zůvalová, I., Vyhlídalová, B., Krasulová, K., Mikoová, E., & Vrzal, R., et al. (2023). Monoterpenoid aryl hydrocarbon receptor allosteric antagonists protect against ultraviolet skin damage in female mice. *Nature Communications, 14*(1), 2728. [DOI:10.1038/s41467-023-38478-6] [PMID] [PMCID]

Palego, L., Betti, L., Rossi, A., & Giannaccini, G. (2016). Tryptophan biochemistry: Structural, nutritional, metabolic, and medical aspects in humans. *Journal of Amino Acids, 2016*, 8952520. [DOI:10.1155/2016/8952520] [PMID] [PMCID]

Parejo, I., Codina, C., Petrakis, C., & Kefalas, P. (2000). Evaluation of scavenging activity assessed by Co (II)/EDTA-induced luminol chemiluminescence and DPPH (2, 2-diphenyl-1-picrylhydrazyl) free radical assay. *Journal of Pharmacological and Toxicological Methods, 44*(3), 507-512. [DOI:10.1016/S1056-8719(01)00110-1] [PMID]

Pinto, C. G., Ávila-Gálvez, M. Á., Lian, Y., Moura-Alves, P., & Dos Santos, C. N. (2023). Targeting the aryl hydrocarbon receptor by gut phenolic metabolites: A strategy towards gut inflammation. *Redox Biology*, 102622. [DOI:10.1016/j.redox.2023.102622] [PMID] [PMCID]

Puga, A., Xia, Y., & Elferink, C. (2002). Role of the aryl hydrocarbon receptor in cell cycle regulation. *Chemico-Biological Interactions, 141*(1-2), 117-130. [DOI:10.1016/S0009-2797(02)00069-8]

Ramadoss, P., Marcus, C., & Perdew, G. H. (2005). Role of the aryl hydrocarbon receptor in drug metabolism. *Expert Opinion on Drug Metabolism & Toxicology, 1*(1), 9-21. [DOI:10.1517/17425255.1.1.9] [PMID]

Revel, A., Raanani, H., Younglai, E., Xu, J., Han, R., & Savouret, J. F., et al. (2001). Resveratrol, a natural aryl hydrocarbon receptor antagonist, protects sperm from DNA damage and apoptosis caused by benzo (a) pyrene. *Reproductive Toxicology, 15*(5), 479-486. [DOI:10.1016/S0890-6238(01)00149-6] [PMID]

Roager, H. M., & Licht, T. R. (2018). Microbial tryptophan catabolites in health and disease. *Nature Communications, 9*(1), 3294. [DOI:10.1038/s41467-018-05470-4] [PMID]

Rzemieniec, J., Litwa, E., Wnuk, A., Lason, W., Krzeptowski, W., & Kajta, M. (2016). Selective aryl hydrocarbon receptor modulator 3, 3′-diindolylmethane impairs AhR and ARNT signaling and protects mouse neuronal cells against hypoxia. *Molecular Neurobiology, 53*, 5591-5606. [DOI:10.1007/s12035-015-9471-0] [PMID]

Sa, R., Guo, M., Liu, D., & Guan, F. (2021). AhR antagonist promotes differentiation of papillary thyroid cancer via regulating circSH2B3/miR-4640-5P/IGF2BP2 Axis. *Frontiers in Pharmacology, 12*, 795386. [DOI:10.3389/fphar.2021.795386] [PMID] [PMCID]

Safe, S., Chadalapaka, G., & Jutooru, I. (2012). AHR-active compounds in the human diet. In R. Pohjanvirta (Ed.) *The AH receptor in biology and toxicology* (pp. 331-342). Hoboken: John Wiley & Sons. [DOI:10.1002/9781118140574.ch24]

Safe, S., Jin, U., Park, H., Chapkin, R. S., & Jayaraman, A. (2020). Aryl hydrocarbon receptor (AHR) ligands as selective AHR modulators (SAhRMs). *International Journal of Molecular Sciences, 21*(18), 6654. [DOI:10.3390/ijms21186654] [PMID] [PMCID]

Salminen, A. (2023). Activation of aryl hydrocarbon receptor (AhR) in Alzheimer's disease: Role of tryptophan metabolites generated by gut host-microbiota. *Journal of Molecular Medicine, 101*(3), 201-222. [DOI:10.1007/s00109-023-02289-5] [PMID] [PMCID]

Schulte, K. W., Green, E., Wilz, A., Platten, M., & Daumke, O. (2017). Structural basis for aryl hydrocarbon receptor-mediated gene activation. *Structure, 25*(7), 1025-1033. [DOI:10.1016/j.str.2017.05.008] [PMID]

Schultz, R., Suominen, J., Värre, T., Hakovirta, H., Parvinen, M., Toppari, J., & Pelto-Huikko, M. (2003). Expression of aryl hydrocarbon receptor and aryl hydrocarbon receptor nuclear translocator messenger ribonucleic acids and proteins in rat and human testis. *Endocrinology, 144*(3), 767-776. [DOI:10.1210/en.2002-220642] [PMID]

Shaito, A., Posadino, A. M., Younes, N., Hasan, H., Halabi, S., Alhababi, D., Al-Mohannadi, A., Abdel-Rahman, W. M., Eid, A. H., Nasrallah, G. K., & Pintus, G. (2020). Potential adverse effects of resveratrol: A literature review. *International Journal of Molecular Sciences, 21*(6), 2084. [DOI:10.3390/ijms21062084] [PMID] [PMCID]

Shi, C., Han, F., Jiang, X., Zhang, Z., Li, Y., & Wang, J., J. (2023). Benzo [b] fluoranthene induces male reproductive toxicity and apoptosis via Akt-Mdm2-p53 signaling axis in mouse Leydig cells: Integrating computational toxicology and experimental approaches. *Food and Chemical Toxicology, 179*, 113941. [DOI:10.1016/j.fct.2023.113941] [PMID]

Silva-Palacios, A., Ostolga-Chavarría, M., Sánchez-Garibay, C., Rojas-Morales, P., Galván-Arzate, S., & Buelna-Chontal, M., et al. (2019). Sulforaphane protects from myocardial ischemia-reperfusion damage through the balanced activation of Nrf2/AhR. *Free Radical Biology and Medicine, 143*, 331-340. [DOI:10.1016/j.freeradbiomed.2019.08.012] [PMID]

Stejskalova, L., Rulcova, A., Vrzal, R., Dvorak, Z., & Pavek, P. (2013). Dexamethasone accelerates degradation of aryl hydrocarbon receptor (AHR) and suppresses CYP1A1 induction in placental JEG-3 cell line. *Toxicology Letters, 223*(2), 183-191. [DOI:10.1016/j.toxlet.2013.09.014] [PMID]

su Jang, Y., Jeong, S., Mok, B. R., Son, S. J., Ryu, J., & Son, W. S., et al. (2023). Cannabidiol mediates epidermal terminal differentiation and redox homeostasis through aryl hydrocarbon receptor (AhR)-dependent signaling. *Journal of Dermatological Science, 109*(2), 61-70. [DOI:10.1016/j.jdermsci.2023.01.008] [PMID]

Sun, M., Ma, N., He, T., Johnston, L. J., & Ma, X. (2020). Tryptophan (Trp) modulates gut homeostasis via aryl hydrocarbon receptor (AhR). *Critical Reviews in Food Science and Nutrition, 60*(10), 1760–1768. [DOI:10.1080/10408398.2019.1598334] [PMID]

Sun, M., Ma, N., He, T., Johnston, L. J., & Ma, X. (2020). Tryptophan (Trp) modulates gut homeostasis via aryl hydrocarbon receptor (AhR). *Critical Reviews in Food Science and Nutrition, 60*(10), 1760–1768. [DOI:10.1080/10408398.2019.1598334] [PMID]

Sun, X., Jing, L., Li, F., Zhang, M., Diao, X., & Zhuang, J., et al. (2022). Structures of NPAS4-ARNT and NPAS4-ARNT2 heterodimers reveal new dimerization modalities in the bHLH-PAS transcription factor family. *Proceedings of the National Academy of Sciences, 119*(46), e2208804119. [DOI:10.1073/pnas.2208804119] [PMID] [PMCID]

Swedenborg, E., & Pongratz, I. (2010). AhR and ARNT modulate ER signaling. *Toxicology, 268*(3), 132-138. [DOI:10.1016/j.tox.2009.09.007] [PMID]

Szelest, M., Walczak, K., & Plech, T. (2021). A new insight into the potential role of tryptophan-derived AhR ligands in skin physiological and pathological processes. *International Journal of Molecular Sciences, 22*(3), 1104. [DOI:10.3390/ijms22031104] [PMID] [PMCID]

Tang, J. S., Stephens, R., Li, Y., Cait, A., Gell, K., & Faulkner, S., et al. (2023). Polyphenol and glucosinolate-derived AhR modulators regulate GPR15 expression on human CD4+ T cells. *The Journal of Nutritional Biochemistry, 122*, 109456. [DOI:10.1016/j.jnutbio.2023.109456] [PMID]

Tkachenko, A., Henkler, F., Brinkmann, J., Sowada, J., Genkinger, D., & Kern, C., et al. (2016). The Q-rich/PST domain of the AHR regulates both ligand-induced nuclear transport and nucleocytoplasmic shuttling. *Scientific Reports, 6*(1), 32009. [DOI:10.1038/srep32009] [PMID] [PMCID]

Togawa, H., Shinkai, S., & Mizutani, T. (2008). Induction of human UGT1A1 by bilirubin through AhR dependent pathway. *Drug Metabolism Letters, 2*(4), 231-237. [DOI:10.2174/187231208786734120] [PMID]

Torti, M. F., Giovannoni, F., Quintana, F. J., & García, C. C. (2021). The aryl hydrocarbon receptor as a modulator of anti-viral immunity. *Frontiers in Immunology, 12*, 624293. [DOI:10.3389/fimmu.2021.624293] [PMID] [PMCID]

Vazquez-Rivera, E., Rojas, B., Parrott, J. C., Shen, A. L., Xing, Y., & Carney, P. R., et al. (2021). The aryl hydrocarbon receptor as a model PAS sensor. *Toxicology Reports, 9*, 1–11. [DOI:10.1016/j.toxrep.2021.11.017] [PMID] [PMCID]

Vogel, C. F. A., & Haarmann-Stemmann, T. (2017). The aryl hydrocarbon receptor repressor-more than a simple feedback inhibitor of AhR signaling: clues for its role in inflammation and cancer. *Current Opinion in Toxicology, 2*, 109-119. [DOI:10.1016/j.cotox.2017.02.004] [PMID] [PMCID]

Vogel, C. F. A., Chang, W. L. W., Kado, S., McCulloh, K., Vogel, H., & Wu, D., et al. (2016). Transgenic overexpression of aryl hydrocarbon receptor repressor (AhRR) and AhR-mediated induction of CYP1A1, cytokines, and acute toxicity. *Environmental Health Perspectives, 124*(7), 1071-1083. [DOI:10.1289/ehp.1510194] [PMID] [PMCID]

Vogel, C. F. A., Ishihara, Y., Campbell, C. E., Kado, S. Y., Nguyen-Chi, A., & Sweeney, C., et al. (2019). A protective role of aryl hydrocarbon receptor repressor in inflammation and tumor growth. *Cancers, 11*(5), 589. [DOI:10.3390/cancers11050589] [PMID] [PMCID]

Walczak, K., Langner, E., Makuch-Kocka, A., Szelest, M., Szalast, K., & Marciniak, S., et al. (2020). Effect of tryptophan-derived AhR ligands, kynurenine, kynurenic acid and FICZ, on proliferation, cell cycle regulation and cell death of melanoma cells-in vitro studies. *International Journal of Molecular Sciences, 21*(21), 7946. [DOI:10.3390/ijms21217946] [PMID] [PMCID]

Wang, K., Huang, D., Zhou, P., Su, X., Yang, R., & Shao, C., et al. (2022). Individual and combined effect of bisphenol A and bisphenol AF on prostate cell proliferation through NF-κB signaling pathway. *International Journal of Molecular Sciences, 23*(20), 12283. [DOI:10.3390/ijms232012283] [PMID] [PMCID]

Wang, P. C., Chen, S. T., Hong, Z. K., Li, S. Y., Yang, Z. S., & Quan, S., et al. (2020). Tryptophan and kynurenine stimulate human decidualization via activating Aryl hydrocarbon receptor: Short title: Kynurenine action on human decidualization. *Reproductive Toxicology, 96*, 282-292. [DOI:10.1016/j.reprotox.2020.07.011] [PMID]

Wang, X. S., Cao, F., Zhang, Y., & Pan, H. F. (2020). Therapeutic potential of aryl hydrocarbon receptor in autoimmunity. *Inflammopharmacology, 28*, 63-81. [DOI:10.1007/s10787-019-00651-z] [PMID]

Wiest, E. F., Warneke, A., Walsh, M. T., Langsfeld, M., Anderson, J., & Walker, M. K. (2015). Association of serum aryl hydrocarbon receptor activity and RBC omega-3 polyunsaturated fatty acids with flow-mediated dilation in healthy, young Hispanic cigarette smokers. Toxicology *Letters, 232*(2), 422-428. [DOI:10.1016/j.toxlet.2014.12.002] [PMID] [PMCID]

Wincent, E., Bengtsson, J., Bardbori, A. M., Alsberg, T., Luecke, S., & Rannug, U., et al. (2012). Inhibition of cytochrome P4501-dependent clearance of the endogenous agonist FICZ as a mechanism for activation of the aryl hydrocarbon receptor. *Proceedings of the National Academy of Sciences, 109*(12), 4479-4484. [DOI:10.1073/pnas.1118467109] [PMID] [PMCID]

Wu, L., Li, X., Li, J., Wang, Y., Yang, C., & Zhao, C., et al. (2024). The role of aryl hydrocarbon receptor in the occurrence and development of periodontitis. *Frontiers in Immunology, 15*, 1494570. [DOI:10.3389/fimmu.2024.1494570] [PMID] [PMCID]

Xi, X., Ye, Q., Fan, D., Cao, X., Wang, Q., & Wang, X., et al. (2022). Polycyclic aromatic hydrocarbons affect rheumatoid arthritis pathogenesis via aryl hydrocarbon receptor. *Frontiers in Immunology, 13*, 797815. [DOI:10.3389/fimmu.2022.797815] [PMID] [PMCID]

Xue, Z., Li, D., Yu, W., Zhang, Q., Hou, X., He, Y., & Kou, X. (2017). Mechanisms and therapeutic prospects of polyphenols as modulators of the aryl hydrocarbon receptor. *Food & Function, 8*(4), 1414-1437. [DOI:10.1039/C6FO01810F] [PMID]

Yang, H., & Ping Dou, Q. (2010). Targeting apoptosis pathway with natural terpenoids: Implications for treatment of breast and prostate cancer. *Current Drug Targets, 11*(6), 733-744. [DOI:10.2174/138945010791170842] [PMID] [PMCID]

Yang, S. Y., Ahmed, S., Satheesh, S. V, & Matthews, J. (2018). Genome-wide mapping and analysis of aryl hydrocarbon receptor (AHR)-and aryl hydrocarbon receptor repressor (AHRR)-binding sites in human breast cancer cells. *Archives of Toxicology, 92*, 225-240. [DOI:10.1007/s00204-017-2022-x] [PMID] [PMCID]

Yu, Y. Y., Jin, H., & Lu, Q. (2022). Effect of polycyclic aromatic hydrocarbons on immunity. *Journal of Translational Autoimmunity, 5*, 100177. [DOI:10.1016/j.jtauto.2022.100177] [PMID] [PMCID]

Zedan, Z. K., & Al-Ameri, S. H. A. (2023). In vitro study of primary isolation and culture of adipose-derived stem cells and induction of Chondrogenic differentiation. *Archives of Razi Institute, 78*(1), 125. [DOI:10.22092/ARI.2022.358603.2255] [PMID]

Zelante, T., Iannitti, R. G., Cunha, C., De Luca, A., Giovannini, G., & Pieraccini, G., et al. (2013). Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. *Immunity, 39*(2), 372-385. [DOI:10.1016/j.immuni.2013.08.003] [PMID] [PMCID]

Zhang, M., Hu, Y., Yang, F., Zhang, J., Zhang, J., & Yu, W., et al. (2022). Interaction between AhR and HIF-1 signaling pathways mediated by ARNT/HIF-1β. *BMC Pharmacology and Toxicology, 23*(1), 26. [DOI:10.1186/s40360-022-00564-8] [PMID] [PMCID]

Zhang, P., Li, Y., Du, Y., Li, G., Wang, L., & Zhou, F. (2016). Resveratrol ameliorated vascular calcification by regulating Sirt-1 and Nrf2. *Transplantation Proceedings, 48*(10), 3378-3386. [DOI:10.1016/j.transproceed.2016.10.023] [PMID]

Zhang, Y., Pan, Y., Zhang, P., Wang, F., Han, Y., & Li, K., et al. (2023). AhR agonist tapinarof ameliorates lupus autoimmunity by suppressing Tfh cell differentiation via regulation of the JAK2-STAT3 signaling pathway. *Immunity, Inflammation and Disease, 11*(6), e903. [DOI:10.1002/iid3.903] [PMID] [PMCID]

This Page Intentionally Left Blank