



## Invited Review

## Targeting the aryl hydrocarbon receptor by gut phenolic metabolites: A strategy towards gut inflammation

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## ABSTRACT

The Aryl Hydrocarbon Receptor (AHR) is a ligand-dependent transcription factor able to control complex transcriptional processes in several cell types, which has been correlated with various diseases, including inflammatory bowel diseases (IBD). Numerous studies have described different compounds as ligands of this receptor, like xenobiotics, natural compounds, and several host-derived metabolites.

Dietary (poly)phenols have been studied regarding their pleiotropic activities (e.g., neuroprotective and anti-inflammatory), but their AHR modulatory capabilities have also been considered. However, dietary (poly)phenols are submitted to extensive metabolism in the gut (e.g., gut microbiota). Thus, the resulting gut phenolic metabolites could be key players modulating AHR since they are the ones that reach the cells and may exert effects on the AHR throughout the gut and other organs. This review aims at a comprehensive search for the most abundant gut phenolic metabolites detected and quantified in humans to understand how many have been described as AHR modulators and what could be their impact on inflammatory gut processes. Even though several phenolic compounds have been studied regarding their anti-inflammatory capacities, only 1 gut phenolic metabolite, described as AHR modulator, has been evaluated on intestinal inflammatory models. Searching for AHR ligands could be a novel strategy against IBD.

### 1. The AHR

The Aryl Hydrocarbon Receptor (AHR) is a widely conserved ligand-activated transcription factor that can sense a wide range of molecules, including those from environmental, dietary, and microbial sources. Upon ligand sensing, the AHR integrates information from the different signals and translates it into cellular responses, tailored to a specific ligand, cell type, and tissue context, albeit by not fully understood mechanisms. Notably, the AHR has been reported to crosstalk and be a convergence point with several signalling pathways inside the cell, including those regulating inflammation, immunity, cell proliferation and differentiation, among others. Altogether, the AHR is known to modulate processes highly relevant to cellular, tissue and organism development, maintenance and homeostasis. Furthermore, modulation

of the AHR pathway(s) (both canonical and non-canonical) in response to a perturbation of cellular and tissue homeostasis profoundly impacts therapy in diseases such as inflammatory diseases, cancer and microbial infections [1–5].

The AHR was initially discovered as the target receptor for dioxin (e.g., 2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD), being involved in its toxicity [6,7]. Further studies uncovered a variety of AHR ligands [8], including synthetic and naturally occurring molecules. Synthetic ligands, polychlorinated biphenyls, halogenated-dioxins and related compounds are often harmful environmental pollutants [9] (e.g., the potent ligand, TCDD), and are generated from modern industrial and manufacturing processes and have been associated with toxicity. Natural AHR modulators consist of food-derived compounds, microbiome-derived metabolites (including those arising from pathogenic and opportunistic pathogenic microbes), plant-derived, and

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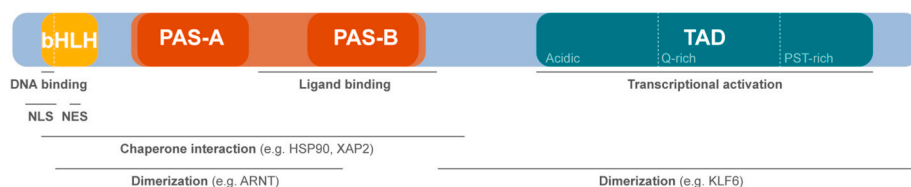
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Abbreviations	
3MI	Skatole
5-HT	Serotonin
AHR	Aryl Hydrocarbon Receptor
AHRR	AHR Repressor
ARNT	AHR Nuclear Translocator
BCL-2	B-cell lymphoma 2
BMDCs	Primary bone marrow-derived dendritic cells
BMDMs	Mouse bone marrow derived macrophages
Caco-2	Human colorectal adenocarcinoma cell line
CD	Crohn's disease
Cldn4	Claudin 4
COX-2	Cyclooxygenase-2 c-SRC Proto-oncogene tyrosine-protein kinase Src
CUL4B	Cullin 4 B
CXCL1	Chemokine (C-X-C motif) ligand 1
CYP	Cytochrome P450
CYP1A1	Cytochrome P450 Family 1 Subfamily A Member 1
CYP1A2	Cytochrome P450 Family 1 Subfamily A Member 2
DC	Dendritic cells
DHNA	1,4-dihydroxy-2-naphthoic acid
DOPAC	3',4'-dihydroxyphenylacetic acid
HO-1	Heme oxygenase-1
HSP90	Heat shock protein 90
IA	Indole-3-aldehyde
IAA	Indole-3-acetate
IAC	Indole-3-acrylate
IAD	Indole-3-acetamide
IBD	Inflammatory bowel disease
IECs	Intestinal epithelial cells
IET	Indole-3-ethanol
IL-1 $\beta$	Interleukin 1 beta
IL-6	Interleukin 6
ILA	Indole-3-lactate
ILCs	Innate lymphoid cells
IND	Indole
IPA	Indole-3-propionate
IPY	Indole-3-pyruvate
KLF6	Kruppel-like factor 6
Lgr5+	Leucine-rich repeat-containing G-protein coupled receptor 5
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
miR-212/132	microRNA cluster 212/132
miR-335	microRNA 335
MPO	Myeloperoxidase
NES	Nuclear Export signal
bHLH	Basic-helix-loop-helix
NF $\kappa$ B	Nuclear factor kappa-light-chain-enhancer of activated B cells
NLS	Nuclear Localization signal
Notch 1	Neurogenic locus notch homolog protein 1
NQO1	NAD(P)H dehydrogenase [quinone] 1
NRF2	Nuclear factor erythroid 2-related factor 2
Ocln1	Occludin 1
p53	Tumour protein 53
PD-1	Programmed cell death protein 1
PER	Period circadian protein
PRR	Pattern Recognition Receptor
RE	Responsive element
RNF43	Ring finger protein 43
ROR $\gamma$ t+	Positive t isoform of the retinoic-acid-receptor-related orphan nuclear receptor gamma
ROS	Reactive oxygen species
SCFAs	Short-chain fatty acids
SIM	Single-minded Protein
SOCS3	Suppressor of cytokine signalling 3
SOX4	SRY-related HMG-box4
SPF	Specific pathogen-free
TA	Tryptamine
TAD	Transactivation Domain
TC	Total cholesterol
TCDD	2,3,7,8-Tetrachlorodibenzo-p-dioxin
TGF- $\beta$	Transforming growth factor beta
TiPARP	TCDD Inducible Poly(ADP-Ribose) Polymerase
TJs	Tight junctions
TNBS	2,4,6-Trinitrobenzenesulfonic acid
TNF- $\alpha$	Tumour necroses factor alpha
UC	Ulcerative colitis
XAP2	Hepatitis B virus X protein associated protein
XRE	Xenobiotic responsive element
ZNRF3	Zinc/ring finger protein 3
ZO-1	Zonula occludens-1

endogenous tryptophan metabolites [10]. Of note, in this review, whenever ligand binding studies have been performed, confirming direct interaction between the molecule and the AHR, molecules are listed as ligands, otherwise, described as modulators (either agonist or antagonist). Food-derived compounds include flavonoids like quercetin and apigenin [11], microbiome-derived metabolites include indole,

indole-3-acetate, and tryptamine [12] and endogenous ligands include tryptophan metabolites such as 6-Formylindolo[3,2-*b*]carbazole (FICZ) [13], kynurenine [14] and kynurenic acid [15]. The capacity of the AHR to detect diverse molecules from pathogenic and opportunistic pathogens, including pigments (e.g., naphthoquinones and phenazines) and quorum sensing molecules (e.g., homoserine lactones), unveiled its role



**Fig. 1. The AHR protein domains.** The AHR contains three major domains, the bHLH domain, the PAS domains and the TAD. The bHLH domain located at the N-terminus is involved in interaction with chaperones, HSP90 and XAP2, dimerization with ARNT and binding to DNA. This is followed by the PAS domain which consists of two repeats, A and B. PAS A is involved in dimerization with ARNT and interaction with HSP90 and XAP2, the PAS B domain

is the ligand binding domain. At the C-terminus is the transactivation domain. This domain consists of three subdomains, an acidic residue (glutamate/aspartate) rich subdomain, a glutamate-rich subdomain and a proline/serine/threonine-rich domain. The transactivation domain is involved in nucleocytoplasmic shuttling and interaction with other transcription factors. HSP90- heat shock protein 90; XAP2- Hepatitis B virus X protein associated protein 2; ARNT- AHR Nuclear Translocator; KLF6- Kruppel-like factor 6; NLS- Nuclear Localization signal; NES- Nuclear Export signal; bHLH- basic-helix-loop-helix; TAD- Transactivation Domain; PAS- Period circadian protein (PER) | Aryl Hydrocarbon Receptor Nuclear Translocator (ARNT) | Single-minded Protein (SIM).

as a Pattern Recognition Receptor (PRR) [16,17].

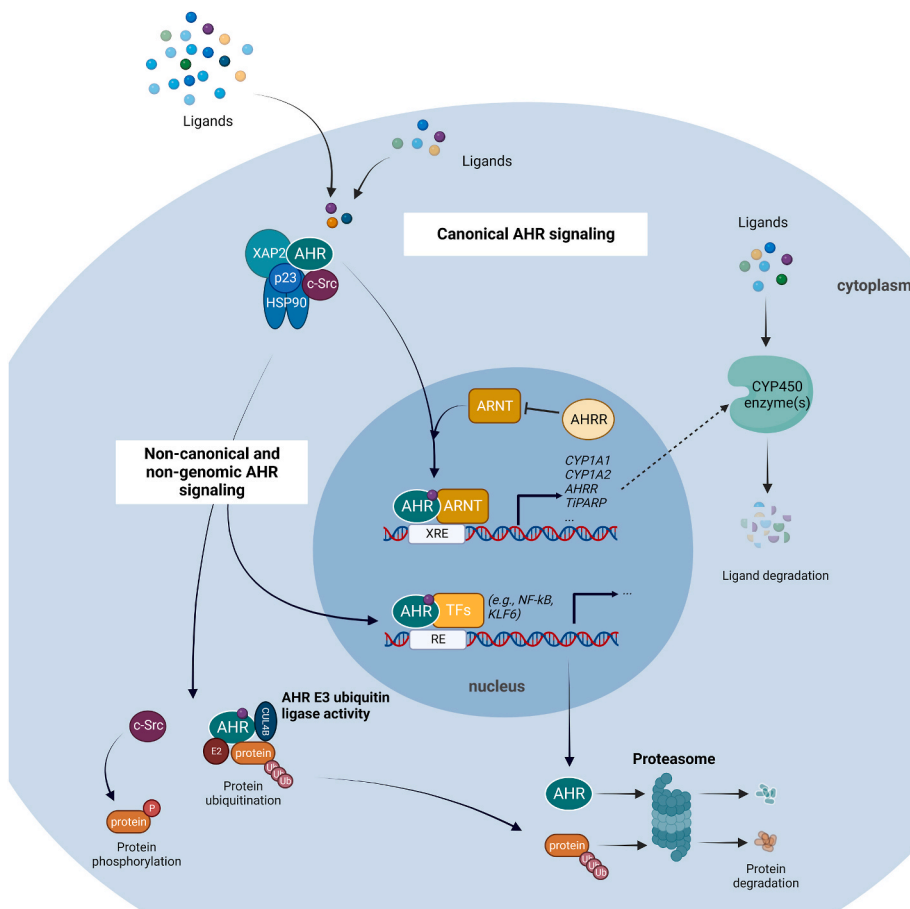
The AHR is a member of the family of basic helix-loop-helix/(Period circadian protein (PER) | Aryl Hydrocarbon Receptor Nuclear Translocator (ARNT) | Single-minded Protein (SIM); PER-ARNT-SIM) (bHLH/PAS) transcription factors and consists of an N-terminal bHLH, followed by two PAS domains (PAS A and PAS B) and a C-terminal transactivation domain (TAD) (Fig. 1) [18]. The bHLH domain mediates the binding of AHR to ARNT and DNA, whereas the PAS A domain is required for the interaction between AHR and ARNT [19] and for enhancing DNA binding [20]. The PAS B is the ligand-binding domain [18]. Of note, in this review, we focus on the canonical AHR pathway, its modulators and AHR functions (Fig. 2). In the absence of a ligand, the AHR is localized to the cytoplasm, bound to a chaperone complex, composed of heat shock protein 90 (HSP90) [21], the Hepatitis B virus X protein associated protein 2 (XAP2) [22] and p23 proteins [23]. Upon ligand binding, the AHR undergoes a conformation change, resulting in the dissociation from HSP90 and translocation into the nucleus. In the nucleus, the AHR forms a heterodimer with the ARNT [24] and binds to xenobiotic response elements (XRE, 5'-TA/TGCGTG-3') [25] on the promoter of its downstream target genes to induce gene expression. Activation of the AHR by different ligands (e.g., TCDD) leads to the expression of different genes, among those are the well-studied members of the xenobiotic-metabolizing cytochrome P450 (CYP) enzymes such as CYP1A1 and CYP1A2 [26]. AHR activation also leads to the expression of aryl-hydrocarbon receptor repressor (AHRR), and TCDD-inducible poly(ADP-ribose) polymerase (TiPARP) [27], resulting in a negative

feedback loop. The AHRR negatively regulates AHR signalling by interacting with ARNT, displacing AHR from the AHR:ARNT complex. The displaced AHR is then exported into the cytosol where it is targeted to the 26S proteasome for degradation [15]. TiPARP also promotes the degradation of the AHR [28] via the 26S proteasome (Fig. 2).

In the last couple of years, there have been more insights into AHR biology and crosstalk with other signalling pathways. These include the interaction of AHR with RelB to modulate immune responses [29,30], with the Wnt signalling [31] to influence tissue regeneration, with retinoblastoma protein to mediate cell cycle arrest [32] and with KLF6 to modulate cell cycle control and tissue regeneration [33]. Furthermore, the AHR regulates protein phosphorylation and ubiquitination, via its interaction with c-SRC and via its E3 ubiquitin ligase activity, respectively [4,5,34,35]. The details and impacts of the crosstalk of AHR signalling with other signalling pathways have been reviewed by others [4,5,36]. In this review, we will be focusing on the involvement of AHR in inflammation and immunity.

## 2. AHR in immunity

For many years, the AHR has been mostly the focus of toxicologists due to its role as a receptor for dioxins [37]. The AHR was subsequently found to be important in the regulation of other processes, including immune/inflammatory responses in the skin [38] and gut [39,40], expression of many cytokines [41–44], lipopolysaccharide (LPS)-induced septic shock [42] and disease tolerance [45]. However,



**Fig. 2. The AHR signalling pathways.** The AHR is found in a complex containing HSP90, p23, XAP2 and c-SRC. Upon ligand binding, AHR dissociates from the complex leading to either canonical or non-canonical downstream signalling. Canonical AHR signalling involves the translocation of AHR into the nucleus where it dimerises with ARNT and binds to specific DNA sequences known as xenobiotic-response elements (XRE). This leads to the expression of canonical AHR target genes, *Tiparp*, *Ahrr* and P450 cytochromes such as *Cyp1a1* and *Cyp1a2*. Expression of P450 cytochromes and AHRR act as a negative feedback loop to attenuate AHR signalling. P450 cytochromes degrade AHR ligands and AHRR forms a heterodimer with ARNT, displacing AHR from the AHR-ARNT complex. The displaced AHR is then targeted for proteasomal degradation. The AHR can also carry out non-canonical signalling through both genomic and non-genomic signalling. During non-canonical genomic signalling, the AHR can bind to transcription factors such as KLF6, and nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) to induce specific downstream gene expression. Regarding non-canonical and non-genomic signalling functions of the AHR, it can act as an E3 ubiquitin ligase in a complex with CUL4B. The AHR/CUL4B ubiquitin ligase ubiquitinates and targets proteins such as steroid receptors for proteasomal degradation, or lead to protein phosphorylation events in a c-SRC-dependent mechanism. AHR- Aryl Hydrocarbon Receptor; c-SRC- Proto-oncogene tyrosine-protein kinase Src; XRE- Xenobiotic responsive element; CYP1A1- Cytochrome P450 Family 1 Subfamily A Member 1; CYP1A2- Cytochrome P450 Family 1 Subfamily A Member 2; AHRR- AHR Receptor; TiPARP- TCDD Inducible Poly(ADP-Ribose) Polymerase; ARNT- AHR Nuclear Translocator; HSP90-Heat Shock Protein 90; XAP2- Hepatitis B virus X protein associated protein 2; KLF6- Krueppel-like factor 6; CUL4B- Cullin 4 B; NFkB- Nuclear factor kappa-light-chain-enhancer of activated B cells; RE-

observations that activation of the AHR by TCDD inhibited T-cell responses [46], the loss of AHR decreased lymphocyte accumulation in lymph nodes and spleen [47] and increased expression of different cytokines (e.g., IL-12 and IFN- $\gamma$ ) in spleen cells of ovalbumin immunised mice [43], pointed to the involvement of the AHR in immune cell development and regulation. These observations led to further investigations into the role of AHR in immunity (reviewed in detail in Refs. [4,5]). In 2008, two seminal studies demonstrated a role for the AHR in T helper 17 (Th17) and regulatory T (Treg) cell polarization [37,48]. The AHR is highly expressed in Th17 cells and activation of the AHR by FICZ induces Th17 differentiation, expression of IL-17 $\alpha$  and IL-22, and worsens experimental autoimmune encephalomyelitis [37,48]. However, when activated by TCDD, the AHR induced Treg differentiation and suppresses experimental autoimmune encephalomyelitis [37]. In line with this, the AHR was found to suppress immune activation, with AHR deficiency leading to autoimmunity in mice [49,50], further evidencing the direct role of the AHR in immune regulation. The involvement of the AHR in T-cell differentiation, maintenance and function also extend to other T-cell types, including T regulatory type 1 (Tr1) cells, gamma-delta ( $\gamma\delta$ ) T-cells and T-cell receptor (TCR)  $\alpha\beta$  cluster of differentiation (CD) 8 $\alpha\alpha$  (TCR $\alpha\beta$ +CD8 $\alpha\alpha$ ) T-cells [51,52].

The AHR also plays a role in the development and function of B-cells. The AHR promotes the maturation and maintenance of B-cells [53] and drives B-cell proliferation via cyclin O [54]. Typical of the context-specific functions of the AHR, and the opposing effects reported to occur upon AHR activation, AHR activation can also inhibit B-cell development [55,56], inhibit B-cells class switching [56] and suppress the IgM secretion in B cells [57].

In addition to the regulation of adaptive immune cell development and function, the AHR is also involved in the function and maturation of different innate immune cells. In macrophages, the AHR suppresses the transcriptional activities and expression of different cytokines, including IL-6, TNF- $\alpha$  [41] and IL-1 $\beta$  secretion, preventing excessive inflammation [42]. The AHR can also affect the recruitment of neutrophils during infection [16,17], wound healing [58], and modulate the antigen uptake of inflammatory bone marrow-derived dendritic cells (BMDCs) [1,44]. The mechanism may be linked to an AHR regulation of neutrophil chemoattractants, including diverse chemokines and cytokines, (e.g., cxcl5, IL-8) [16,17,59]. However, loss of the AHR can also result in increased neutrophil infiltration in an imiquimod-induced skin inflammation model [38]. Recently, Diny et al. demonstrated that the activation of the AHR signalling in the intestinal eosinophils results in a transcriptional adaptation of eosinophils, as they migrated from the bone marrow to the intestinal tissue [60]. The AHR can also modulate dendritic cell (DC) activities and influence DC differentiation, in a ligand and context-dependent manner [49,61–63]. Moreover, the AHR plays an important role in the maturation of Langerhans cells via both cell-autonomous and non-cell-autonomous mechanisms [64]. The involvement of the AHR has also been shown to affect the immune function of natural killer (NK) cells, by promoting IL-10 expression [65].

Altogether, and linked to the different roles of AHR in the differentiation and function of various immune cells, several studies demonstrated an important role in host-pathogen interactions. Indeed, infection studies provided direct evidence for the role of the AHR in influencing host-pathogen interaction and infection outcomes. The AHR protects against infections, such as to *Citrobacter rodentium* [66], *Listeria monocytogenes* [67], *Candida albicans* [68], *Staphylococcus epidermidis* [69], *Streptococcus pneumoniae* [70], *Aspergillus fumigatus* [71], *Mycobacterium tuberculosis* [1,16,17,72], and *Pseudomonas aeruginosa* [16,17]. On the other hand, activation of the AHR showed detrimental effects on the immune response towards infections by *Trypanosoma cruzi* [73], *Leishmania major* [74], Zika virus [75], dengue virus, influenza virus [63], Herpes simplex virus [76], and HIV [77]. One explanation for the opposing effects of the AHR and its elicited functions is the context and the ligand-specific activation of the AHR, and its involvement in the maintenance and differentiation of different immune cells [37]. In the

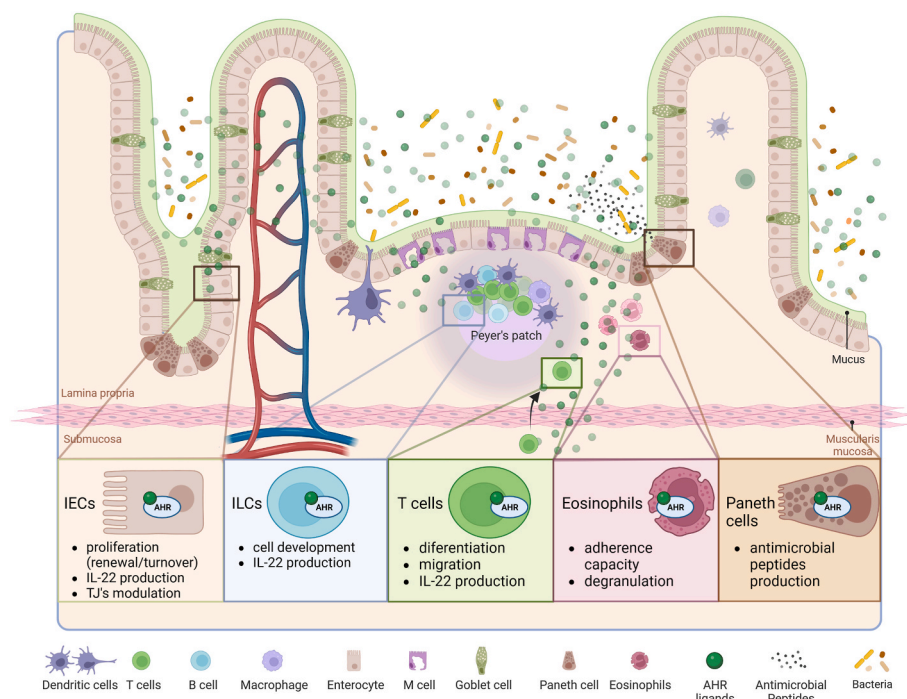
human body, the gut can accommodate an abundance of AHR ligands which can be produced by the metabolism of the microbial community present in the gut, the microbiota. As such, there is much interest in the involvement of AHR in the homeostatic control of gut and intestinal pathologies.

### 3. AHR and intestinal inflammation

The human gastrointestinal tract has a large area (250–400 m<sup>2</sup>), continuously exposed to xenobiotics, food and microorganisms, such as bacteria, fungi and parasites. Over thousands of years, the co-evolution of these microbes with the host led to a mutualistic relationship between the host and its gut microbes. In this regard, the microbiome is the dynamic ecosystem composed of the microbiota, their genetic pool, metabolites, viruses and other mobile genetic elements [78], which plays an important role in the development and homeostasis of the gut. Studies using mouse and zebrafish models have demonstrated that the microbiome helps to educate the gut immune system [79], for example, stimulating the proliferation and differentiation of intestinal cells [80–83], influencing the level of neuroendocrine peptides [84], or modulating gut motility [81,85], amongst other functions.

The expression of the AHR has been shown to maintain specific ratios of the various bacterial populations in the caecum [86]. Diets rich in AHR ligands can also influence the gut microbiota in mice. Wild type (WT) mice fed with a diet depleted of natural AHR ligands (e.g., phenols and tryptophan derivatives) have more Actinobacteria, Bacteroidetes and Tenericutes in their intestine compared to AHR<sup>-/-</sup> mice, whereas the presence of AHR ligands in the diet of mice led to an expansion of Firmicutes and reduction in Bacteroidetes population [87]. The AHR can also modulate the microbiota population by changing the level of mucus production in the gut. This is due to the inhibition of Neurogenic locus notch homolog protein 1 (Notch 1) signalling by AHR which leads to induced differentiation of secretory cells to produce more mucus [88].

In addition to the regulation of the gut microbiome, the AHR is involved in various intestinal immune cell development and associated inflammatory responses in the gut [89], as depicted in Fig. 3. The AHR is thought to influence the immune response in inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC). Expression of the AHR is lowered in inflamed tissues of CD patients compared to uninflamed tissues or healthy individuals [90], while AHR ligands have been shown to reduce colitis in mice [91,92]. The single layer of intestinal epithelial cells (IECs) forms a physical and biochemical barrier that acts as the first line of defence against pathogens. The renewal of this epithelial layer is maintained by the proliferation of the leucine-rich repeat-containing G-protein coupled receptor 5 (Lgr5+) stem cell population [93], and the WNT- $\beta$ -catenin pathway is essential for the proliferation of these Lgr5+ stem cells [94]. The AHR modulates the expression of negative regulators of WNT signalling, E3 ubiquitin ligases ring finger protein 43 (RNF43) and zinc/ring finger protein 3 (ZNRF3) to ensure a coordinated IECs regeneration [95]. The coordinated regeneration of IECs by AHR is important to maintain gut homeostasis and prevent intestinal pathologies. AHR deficiency has also been shown to reduce the levels of TCR $\gamma\delta$  cells in the small intestine, leading to a reduced turnover of the intestinal epithelial and an increased bacterial load [96]. The AHR deficiency in CD11c+ cells leads to a perturbation of the epithelium development [97]. The AHR also inhibits the negative regulation of IL-22 signalling by suppressor of cytokine signalling 3 (SOCS3) [98]. IL-22 stimulation of colonic stem cells is shown to induce cell proliferation [98], and activation of the AHR ensures the production of IL-22, which in turn increases cell proliferation of the IECs to maintain an intact intestinal barrier. Another way that AHR can maintain the intestinal barrier is through the modulation of tight junctions (TJs) proteins. Administration of FICZ, an endogenous AHR ligand [99], attenuates the loss of TJs proteins in a DSS-induced colitis mouse model [100]. Singh et al. also showed that 3, 8-Dihydroxy-urolithin (urolithin A), a metabolite of ellagic acid which is



**Fig. 3. Schematic representation of key intestinal immunity players and the impact of the AHR.** Compounds present in the intestinal lumen can be metabolized either by microbiota or in the enterocytes generating several metabolites. The parent compounds and their metabolites can serve as ligands for the AHR, modulating several cell functions and immune system responses. These include the modulation of IECs proliferation, as well as TJs expression and IL-22 production in this and other immune cells; innate lymphocytes' development; T cells differentiation and migration, and eosinophils adherence capacity and degranulation. The expression of the AHR has also been shown to maintain specific ratios of the various bacterial populations in the caecum by modulating the production of antimicrobial peptides and by modulating mucus production and intestinal motility. Abbreviations: AHR – Aryl Hydrocarbon Receptor; IECs – Intestinal epithelial cells; ILCs – Innate lymphoid cells; IL-22 – Interleukin 22; TJs – Tight junctions. Figure created with [BioRender.com](https://www.biorender.com).

found in high levels in pomegranate, acts on the AHR and nuclear factor erythroid 2–related factor 2 (NRF2) signalling pathways to upregulate the expression of TJs proteins and ameliorate colitis [101]. Indoles from bacteria are also known to activate the AHR, reduce inflammation and improve TJs' permeability [102]. Together, these results point to the important role of AHR in the maintenance of gut barriers and function.

In addition to the IECs, gut health and homeostasis are regulated by a plethora of immune cells in the *lamina propria* and specialised immune tissues such as the mesenteric lymph nodes and gut-associated lymphoid tissues. These lymphoid tissues are dedicated sites of immune cell priming and include Peyer's patches in the small intestines and isolated lymphoid follicles, found in both small and large intestines [103]. The AHR is required for the proper development of the lymphoid follicles. The AHR is highly expressed in the positive t isoform of the retinoic-acid-receptor-related orphan nuclear receptor gamma ( $ROR\gamma^t$ ) innate lymphoid cells (ILCs) and drives the postnatal expansion of these cells [66,104,105]. In  $CD4^+ROR\gamma^t$  T cells, AHR-mediated tyrosine-protein kinase KIT expression leads to its maintenance and expansion, leading to the development of intestinal lymphoid follicles [104]. The maintenance of  $ROR\gamma^t$  + ILCs by AHR was later found to be related to reduced apoptosis of  $ROR\gamma^t$  + ILCs [105], as AHR deficient  $ROR\gamma^t$  + ILCs showed increased Annexin V staining and decreased expression of anti-apoptotic genes, *Bcl2* and *Bcl2l1* [105]. As such, AHR-deficient mice have a reduced number of IL-22-producing  $ROR\gamma^t$  + ILCs and are unable to produce IL-22 to mount a protective immune response to *Citrobacter rodentium* infection [66,104]. The susceptibility to *C. rodentium* infection was also observed in  $R26^{Cyp1a1}$  mice that constitutively express the enzyme CYP1A1 leading to the depletion of endogenous AHR ligands and generating a *quasi*-AHR-deficient state [106]. The AHR also regulates the expression of the transcription factor Aiolos, suppressing the expression of Programme cell death protein 1 (PD-1) in intestinal type 2 innate lymphoid cells (ILC2s). The absence of AHR resulted in reduced Aiolos and IL-5 expression, and decreased cell proliferation in ILC2s, leading to what the authors described as an "exhaust-like" phenotype [107]. Together, it shows that the AHR plays an important role in the development of ILCs in the gut to maintain homeostasis and prevent microbial-induced pathogenesis. The AHR also modulates the function of T cells in the gut. AHR activation by

microbial-converted tryptophan metabolites induces a rare population of  $CD4^+CD8\alpha\alpha^+$  T cells that promotes tolerance to dietary antigens [92]. In a model of DSS-induced colitis,  $AHR^{-/-}$  mice show altered frequencies of the T cell subsets, Th17, Th1, and Tc1 (type1  $CD8 \pm$  T cells) in the gut, when compared to those of WT mice [108]. It is suggested that the AHR induces Th17 differentiation and migration into the *lamina propria* during colitis by modulating the expression of miR-212/132 [109]. The AHR was also recently shown to be important for driving the transcriptional adaptation of eosinophils to the intestine. The intestinal gene expression program of  $AHR^{-/-}$  eosinophils is impaired, including the expression of extracellular matrix and cell junction-related genes, impairing their capacity to adhere to and degrade extracellular matrix and rendering them more prone to degranulation [60].

Due to the involvement of the AHR in various aspects of gut homeostasis and immunity, many have attempted to modulate the outcome of gut pathology by modulating its activity using AHR ligands. For example, consumption of indole-3-aldehyde (IA) enhances resistance to *Candida albicans* infection by an AHR-dependent induction of IL-22 [68], while indole-3 carbinol can restore immunity towards *C. rodentium* infection in mice [106]. Altogether, these results confirm the important role of the AHR, and its direct and indirect modulation by different molecules, in maintaining gut health. Consequently, through the homeostasis regulation of IECs and the control of immune responses to prevent overt inflammation and damage to the gut, and while ensuring sufficient immune response to prevent infections, the ability of AHR ligands to modulate gut inflammation and TJs expression provides an avenue to target the AHR as a therapeutic intervention against intestinal inflammatory diseases.

#### 4. AHR ligands present in the gut

Since the AHR was first described, the number of xenobiotics and other compounds that were depicted to be able to modulate the AHR has greatly increased. As a recognized key regulator of homeostatic processes in the skin, lungs and gut, the search for physiological AHR ligands [4,110] led to the identification of several dietary and microbiota-derived metabolites as AHR modulators, including short-chain fatty acids (SCFAs), tryptophan metabolites, phenolic

microbial metabolites, among others [10]. Regarding the compounds that act as AHR modulators, Table 1 highlights endogenous and microbiota-derived metabolites, compounds related to (poly)phenol's metabolism will be detailed below (Table 2). Table 1 comprises compounds identified as agonists and/or antagonists of the AHR canonical pathway, being the metabolites from the tryptophan metabolism and related pathways the most studied so far.

Vyhlídalová et al. recently performed a comprehensive *in vitro* study on the effect of eleven gut microbiota tryptophan metabolites (indole (IND), tryptamine (TA), skatole (3MI), indole-3-pyruvate (IPY), indole-3-lactate (ILA), indole-3-acrylate (IAC), indole-3-propionate (IPA), indole-3-acetamide (IAD), indole-3-acetate (IAA), indole-3-ethanol (IET), and IA) as AHR agonist/antagonist modulators [111]. Their agonist/antagonist capabilities were assessed taking into account: (i) their ability to activate the nuclear translocation of the AHR; (ii) the formation of the AHR:ARNT heterodimer; (iii) the binding of the AHR:ARNT heterodimer to the target gene promoter; (iv) the expression of the AHR target gene *Cyp1a1*. Furthermore, AHR ligand binding studies were performed using the well-established [<sup>3</sup>H]-TCDD competitive radio-ligand binding assay using mouse hepatocyte cell extracts. All eleven tryptophan metabolites were classified as low-potency agonists of the human AHR, indicating that are able to activate the nuclear translocation of the AHR and the formation of the AHR:ARNT heterodimer.

Moreover, these authors identified six-strong inducers of *Cyp1a1* (IND, TA, 3MI, IAD, IAC, and IPY), and described IAD, IPY, IAC, and IET as AHR ligands [111]. The authors also concluded that the AHR activation is dependent on ligand concentration and that it is cell type-specific, as observed by others [12,129].

In another study, Dong et al. showed that both endogenous and microbiota-derived tryptophan metabolites present in caecal and faecal samples of mice and humans, respectively, can induce AHR activation [112]. Among the thirteen tryptophan metabolites identified from the samples of mice and humans, only five of them were identified as AHR modulators (IAA, 2,8-dihydroxyquinoline, kynurenic acid, 2-oxindole, and IND) at the concentrations found in intestinal contents [112]. Importantly, the fact that Dong et al. did not identify some of the tryptophan metabolites identified by Vyhlídalová et al. as AHR ligands, may reside in the range of concentrations tested. For instance, Vyhlídalová et al. used TA in a wide range of concentrations ( $EC_{50} = 83.15 \mu\text{M}$ ) while the study of Dong et al. used a maximum concentration of  $5.2 \mu\text{M}$ . Importantly, in the work of Dong et al. they showed that in germ-free mice, alterations in the production of AHR ligands occur, highlighting the essential role of microbiota in the production of AHR ligands. The authors were able to identify twelve tryptophan metabolites (IAA, IND, IAC, TA, serotonin (5-HT), indole-3-carboxaldehyde, 2,8-dihydroxyquinoline, kynurenic acid, xanthurenic acid, 2-oxindole, indole-3-carboxylic acid and 5-hydroxyindole-3-acetic acid) in specific pathogen-free (SPF) C57Bl/6J mice, while only five (IAA, indole-3-carboxaldehyde, kynurenic acid, indole-3-carboxylic acid, and 5-hydroxyindole-3-acetic acid) were identified in germ-free animals. Out of those five, only two metabolites (indole-3-carboxylic acid and 5-hydroxyindole-3-acetic acid) were present at similar concentrations as those of the conventionally raised mice.

Recently, it has been shown that 5-HT can indirectly modulate the AHR activity by competing for CYP1A1 action with the AHR ligands that are substrates of CYP1A1, preventing ligand metabolism, resulting in the maintenance of the levels of the AHR ligands in the cells [149]. A similar indirect modulation of the AHR has been previously proposed to different dietary (poly)phenols (e.g., quercetin, resveratrol and curcumin), through the inhibition of *Cyp1a1* and resulting in a lack of metabolism of AHR ligands [150]. Schiering et al. showed a similar result with *Cyp1a1* chemical inhibitors [151].

Dietary tryptophan is also metabolized by mammalian cells through the kynurenine pathway, resulting in several kynurenine derivatives. Among those, kynurenic acid has been described as an AHR ligand

capable of mediating immune responses by activation of the AHR signalling pathways, both canonical and non-canonical [15,112,113]. Kynurenic acid has also been previously described to exert the maintenance of the immunosuppressive microenvironment in some cancer types through AHR modulation [152,153].

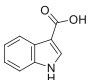
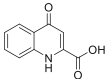
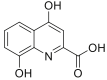
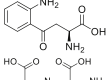
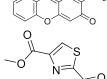
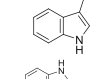
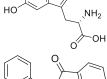
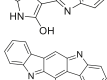
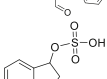
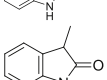
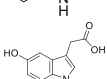
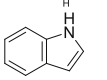
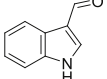
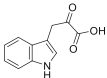
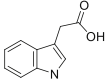
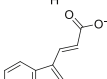
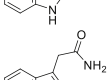
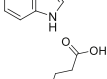
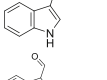
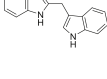

The AHR is described as capable of assessing the relative abundance of the bacterial communities and modulating the type and strength of the immune response, from induction of inflammatory cytokines and anti-microbial factors to the differentiation of Th17 and Treg cells and promoting bacterial clearance [16,17,37,104,154]. Phenazines, such as pyocyanin and 1-hydroxyphenazine, have been described as AHR ligands, and several negative effects on host cells are associated with the presence of these compounds, such as cytokine production, inhibition of ciliary motion and mucus production [17,155]. An *in vitro* study identified the *Mycobacterium tuberculosis* naphthoquinone phthiocol as ligand of the AHR, thus the reported toxic effects due to the reactive oxygen intermediates generated by its degradation it is most likely due to the activation of the transcription of canonical detoxifying genes regulated by the AHR [17].

The precursor of vitamin K2, 1,4-dihydroxy-2-naphthoic acid (DHNA), can exert an inhibitory action on DSS-induced colitis in mice through the modulation of the AHR. It has been shown that DHNA is an agonist of the AHR, promoting the induction of both *Cyp1a1* and *Cyp1b1* expression, in an AHR dependent manner, and can also act as an antagonist by inhibiting TCDD-induced *Cyp1a1* expression in a Caco-2 (human colorectal adenocarcinoma cell line) cells [145]. In a mice model of colitis, feeding the animals with DHNA resulted in an increased expression of *Cyp1a1* in the intestine of the animals, improved survival, reduced inflammation score and pro-inflammatory cytokine production (e.g., IL-6 in macrophages). Therefore DHNA is an interesting candidate molecule for the treatment of IBD, considered to be safe as it can be produced by the probiotic bacterium strain *Propionibacterium freudenreichii* ET-3 [146].

Other microbial metabolites, such as SCFAs, have been initially studied as modulators of the AHR, although it was further demonstrated that the modulation of the AHR occurs via an indirect action of the SCFAs [156]. These small metabolites are the main metabolic products of indigestible fibres from anaerobic bacterial fermentation in the intestine and are involved in several pathways through the modulation of G-protein-coupled receptors, histone deacetylase inhibition, mammalian target of rapamycin (mTOR) activation and hormone secretion, as such affecting epithelial integrity, differentiation, proliferation, and immune responses, as reviewed recently by Visekruna and Luu [156]. In the case of butyrate, there is evidence that it is capable to increase the expression of AHR target genes, such as *Cyp1a1*, both in mouse colonocytes and on the human Caco-2 cells, in an AHR-dependent manner [157]. Interestingly, butyrate enhanced *Cyp1a1* in these cells to a similar extent as other well-known microbiota-derived ligands, such as tryptamine, indole and DHNA. These outcomes appear to be cell-context dependent and did not ascertain a direct interaction of the SCFAs with the AHR, as SCFAs inhibit histone deacetylases, which causes an increase in the AHR ligand-induced responses [157].

A large number of gut metabolites can affect a wide variety of cells and tissues, from intestinal epithelium to neuronal cells. The modulation of the AHR activity by gut metabolites is an area of intense research since AHR activity is involved in several inflammatory outcomes, such as immune cell proliferation and differentiation, among other processes. Nonetheless, the unveiling of the mechanism(s) involved in the interaction of these gut metabolites and the AHR activity is still lacking. Some of these metabolites generate a significant interest towards IBD treatments, due to their capacity to maintain the integrity of the intestinal barrier in animal models of colitis, through the modulation of apical junctional complex and associated actin regulatory proteins in an AHR-dependent manner [158]. Importantly, it is already clear that the gut metabolites' AHR modulatory properties and the AHR elicited functions, either agonist or antagonist of the AHR canonical pathway, or an AHR

**Table 1**  
AHR described ligands of host and microbial origin<sup>a</sup>.

Metabolite Structure	Metabolite Name	Origin	Pathway	Modulatory capacity	References
	Indole-3-carboxylic acid	Host	Tryptophan metabolism	Agonist	[112]
	Kynurenic acid	Host	Tryptophan metabolism	Agonist	[15]
	Xanthurenic acid	Host	Tryptophan metabolism	Agonist	[15,112]
	1-Kynurenine	Host	Tryptophan metabolism	Agonist	[14,45,113,114]
	Cinnabarinic acid	Host	Tryptophan metabolism	Agonist	[115,116]
	methyl 2-(1H-indole-3-carbonyl)-1,3-thiazole-4-carboxylate (ITE)	Host	Tryptophan metabolism	Agonist	[117]
	5-Hydroxytryptophan	Host	Tryptophan metabolism	Agonist	[118]
	Indirubin	Host Microbial	Hepatic metabolism Tryptophan metabolism	Agonist	[119–121]
	6-formylindolo[3,2-b]carbazole (FICZ)	Host Microbial	Tryptophan metabolism Tryptophan metabolism	Agonist	[122–125]
	Indoxyl sulfate	Microbial + Host	Tryptophan metabolism	Agonist	[126]
	3-Methoxyindole	Microbial	Tryptophan metabolism	Agonist	[112]
	5-Hydroxyindole-3-acetic acid	Microbial	Tryptophan metabolism	Agonist	[112]
	Indole (IND)	Microbial	Tryptophan metabolism	Agonist	[111,127–129]
	Indole-3-aldehyde (IA)	Microbial	Tryptophan metabolism	Agonist (concentration dependent antagonist)	[68,130]
	Indole-3-pyruvate	Microbial	Tryptophan metabolism	Agonist (concentration dependent antagonist)	[91,111]
	Indole-3-acetic acid (IAA)	Microbial	Tryptophan metabolism	Agonist	[12,111,127,131]
	Indole-3-acrylate (IAC)	Microbial	Tryptophan metabolism	Agonist	[111,112]
	Indole-3-acetamide (IAD)	Microbial	Tryptophan metabolism	Agonist (concentration dependent antagonist)	[111]
	Indole-3-propionic acid (IPA)	Microbial	Tryptophan metabolism	Agonist	[111,132]
	Malassezin	Microbial	Tryptophan metabolism	Agonist	[133–135]
	Tryptanthrin	Microbial	Tryptophan metabolism	Agonist	[136]

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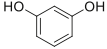
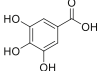
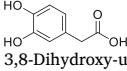
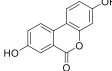
Table 1 (continued)

Metabolite Structure	Metabolite Name	Origin	Pathway	Modulatory capacity	References
	Indole-3-ethanol (IET)	Microbial	Tryptophan metabolism	Agonist (concentration dependent antagonist)	[111]
	Indole-3-lactate (ILA)	Microbial	Tryptophan metabolism	Agonist	[111]
	Skatole (3-methylindole) (3MI)	Microbial	Tryptophan metabolism	Agonist (concentration dependent antagonist)	[111,128,129,137]
	Tryptamine (TA)	Microbial	Tryptophan metabolism	Agonist (concentration dependent antagonist)	[12,111,127,136,138]
	2,8-Dihydroxyquinoline	Microbial	Tryptophan metabolism	Agonist	[139]
	Indole-3-carboxaldehyde	Microbial	Tryptophan metabolism	Agonist	[112,140]
	2-Oxindole	Microbial	Tryptophan metabolism	Agonist	[112]
	Bilirubin	Host	Heme metabolism	Agonist	[141,142]
	Biliverdin	Host	Heme metabolism	Agonist	[142]
	Lipoxin A <sub>4</sub>	Host	Arachidonic acid metabolite	Agonist	[143]
	Prostaglandin G <sub>2</sub>	Host	Arachidonic acid metabolite	Agonist	[144]
	1,4-Dihydroxy-2-naphthoic acid	Microbial	Intermediate in the biosynthesis of menaquinone (vitamin K <sub>2</sub> )	Agonist	[145,146]
	Phenazine 1-carboxamide	Microbial	Shikimic acid pathway	Agonist	[17]
	Phenazine 1-carboxylic acid	Microbial	Shikimic acid pathway	Agonist	[17]
	N-(3-oxodecanoyl)-l-homoserine Lactone (3-oxo-C <sub>12</sub> -L-HSL)	Microbial	Acyl-homoserine lactones synthase	Antagonist	[16]
	4-hydroxy-2-heptylquinoline (HHQ)	Microbial	4-hydroxy-2-alkylquinolines pathway	Antagonist	[16]
	2-heptyl-3,4-dihydroxyquinoline (PQS)	Microbial	4-hydroxy-2-alkylquinolines pathway	Antagonist	[16]
	Pyocyanin	Microbial	Chorismate metabolization by <i>phz</i> operons	Agonist	[17]
	1-Hydroxyphenazine	Microbial	Chorismate metabolization by <i>phz</i> operons	Agonist	[16,17,147]
	Phthiocol	Microbial	Chorismate metabolization	Agonist	[1,17]
	Tapinarof	Microbial	Ketosynthase-directed stilbenoids biosynthesis pathway	Agonist	[148]

<sup>a</sup> Ligands originated exclusively from the consumption of (poly)phenols or the (poly)phenols metabolism were excluded from this table and described in Table 2.

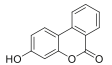
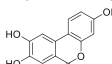
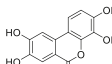


**Table 2**  
List of gut phenolic metabolites described as AHR agonists/antagonists.

Metabolite	Model	Approach	Concentration	AHR modulation	Outcomes	Reference	
Benzene-1,3-diol (resorcinol) 	<i>In vitro</i>	HaCaT - human keratinocyte cell line	500, 1000, 3000 µM	Antagonist	↑NRF2, ↑NQO1, ↑HO-1	[244]	
		Hepa1.12 cR –murine hepatoma cell line	0.01–1000 µM	–	↓B[a]P-induced nuclear translocation of the AHR, ↓ROS, ↓Pro-inflammatory cytokines	[250]	
3,4,5-Trihydroxybenzoic acid (gallic acid) 	<i>In silico</i>	Computational approach	–	–	No agonist activity on its own, Enhance TCDD-induced activation of the AHR	[251]	
		Computational approach	–	–	Identification as a human AHR ligand by molecular docking simulation	[252]	
	<i>In vitro</i>	Ligand binding	15, 30, 45 µM	–	Displacement of [ <sup>3</sup> H]-TCDD from AHR: ARNT heterodimer	[251]	
		MDA-MB-231–human breast cancer cell lines	15, 30, 45, 60, 90 µM	Agonist	↑ <i>Cyp1a1</i> , ↑p53, ↑miR-335, ↓proliferation, migration and invasion, ↓BCL-2, ↓COX-2, ↓SOX4	[252]	
		ER-positive T47D – human breast cancer cell lines	15, 30, 45, 60, 90 µM	Agonist	↑ <i>Cyp1a1</i> , ↑miR-335, ↓proliferation, migration and invasion, ↓BCL-2, ↓COX-2, ↓SOX4	[252]	
	<i>In vivo</i>	Th17 derived cells	40, 80, 120 µM	Agonist	↑ <i>Cyp1a1</i> , ↑CYP1A1, ↑miR-212/132	[252]	
		Derived macrophage cells	40, 80, 120 µM	Agonist	↑ <i>Cyp1a1</i> , ↑CYP1A1, ↑miR-212/132	[252]	
		Ah-I receptor-binding assay in a free cell system	0.5–50 µM	–	No inhibitory effect on 0.025 nM of TCDD-induced AHR	[235]	
		H1L1 – Murine hepatoma cell line	0.01 nM–100 µM	–	No induction of AHR dependent luciferase activity	[234]	
		MDA-MB-231 and ER-positive T47D cell lines injected into athymic nude BALB/c female mice	3 mg/day, for 2 days, orally <sup>a</sup>	Agonist	↑ <i>Cyp1a1</i> in tumour cells ↓growth of breast cancer cells	[251]	
Experimental Autoimmune Encephalomyelitis, C57BL/6 female mice	2 mg/day for 10 days, i. p. <sup>b</sup>	Agonist	↑ <i>Cyp1a1</i> , ↑TGF-β, ↓IL-6, ↓IL-1β, ↓TNF-α, ↓IL-10, ↓infiltration of CD4 <sup>+</sup> CD45 <sup>+</sup> T cells, ↓infiltration of monocytes into central nervous system	[252]			
3,4-dihydroxyphenylacetic acid (DOPAC) 	<i>In vitro</i>	Hepa1c1c7 - murine hepatoma cell line	10, 20, 50 µM	Agonist	↑AHR nuclear translocation, ↑NRF2 nuclear translocation, ↑ALDH activity, ↑ <i>Aldh1a1</i> , ↑ <i>Aldh2</i> , ↑ <i>Aldh3a1</i>	[253]	
3,8-Dihydroxy-urolithin (urolithin A) 	<i>In silico</i>	Computational approach	–	–	Identification as a AHR ligand by molecular docking simulation	[254]	
		HepG2 40/6 – human hepatoma cell line	1–20 µM	Antagonist	↓ <i>Cyp1a1</i> , ↓AHR dependent luciferase activity	[208]	
	<i>In vitro</i>	Caco-2 – human colorectal adenocarcinoma cell line	10 µM	Antagonist	↓ <i>Cyp1a1</i> , ↓IL-6, ↓COX-2		
		Hepa1.1 – murine hepatoma cell line	10 µM	Agonist	↑AHR dependent luciferase activity		
		HT-29 – human colorectal adenocarcinoma cell line	50 µM	Agonist	↑CYP1A1, ↑ <i>Cyp1a1</i> , ↑NRF2, ↑AHR nuclear translocation, ↑HO-1, ↑ <i>Cldn4</i> , ↑ <i>ZO-1</i> , ↑ <i>Ocn1</i> , ↑NQO1	[101]	
		Bone marrow-derived dendritic murine cells	5 µM	Agonist	↑ <i>Cyp1a1</i> ↓BMDCs activation, ↓Th17 differentiation in T cell and DC-CD4 <sup>+</sup> T cell	[254]	
		<i>In vivo</i>	LPS-induced peritonitis C57BL/6J male mice	20 mg/kg, orally	Agonist	↓IL-6, ↓TNF-α	[101]
			C57BL/6 mice	20 mg/kg/d for 7 days, orally	Agonist	↑CYP1A1	
			TNBS-induced colitis model C57BL/6J male mice	20 mg/kg at 12 h intervals, orally, from t = 12h to t = 60h after TNBS	Agonist	↑ <i>Cldn4</i> ↓TNBS-induced body weight loss, ↓disease activity index, ↓intestinal permeability, ↓colonic inflammation, ↓neutrophil infiltration, ↓MPO activity, ↓IL-6, ↓TNF-α, ↓CXCL1, ↓IL-1β	
				4 or 20 mg/kg, orally post 12 h of TNBS instillation	Agonist	↓intestinal permeability ↓TNBS-induced body weight loss, ↓IL-6, ↓TNF-α, ↓CXCL1, ↓IL-1β	
	20 mg/kg/d for 3 days, orally, after TNBS	Agonist	↑barrier function ↓intestinal permeability ↓TNBS-induced body weight loss, ↓IL-6, ↓TNF-α				
	20 mg/kg/d for 7 days, orally, before TNBS treatment	Agonist	↑barrier function ↓intestinal permeability ↓TNBS-induced body weight loss, ↓IL-6, ↓TNF-α				
TNBS-induced colitis model C57BL/6J AHR <sup>-/-</sup> male mice	20 mg/kg at 12 h intervals, orally, from t = 12h to t = 60h after TNBS	–	No effect on colon length No effect on intestinal permeability No effect on IL-6 levels				
DSS-induced colitis C57BL/6J male mice		Agonist					

(continued on next page)

Table 2 (continued)

Metabolite	Model	Approach	Concentration	AHR modulation	Outcomes	Reference
			20 mg/kg/d, 4th and 6th day after DSS treatment		↑Cldn4, ↑colon length ↓disease activity index, ↓intestinal permeability, ↓IL-6, ↓IL-1β, ↓TNF-α,	
		Experimental Autoimmune Encephalomyelitis, C57BL/6 female mice	25 mg/kg/d, for 30 days orally	Agonist	↓disease progression, ↓inflammatory cells, ↓demyelination, ↓M1-type microglia, ↓DC, ↓Th1/Th17	[254]
3-Hydroxy-urolithin (urolithin B)	<i>In vitro</i>	HepG2 40/6 – human hepatoma cell line	1–20 μM	Antagonist	↓Cyp1a1, ↓AHR dependent luciferase activity	[208]
 3,8,9-Trihydroxy-urolithin (urolithin C)	<i>In vitro</i>	HepG2 40/6 – human hepatoma cell line	10 μM	Antagonist	↓ AHR dependent luciferase activity	[208]
 3,4,8,9-Tetrahydroxy-urolithin (urolithin D)	<i>In vitro</i>	HepG2 40/6 – human hepatoma cell line	10 μM	Agonist	↑ AHR dependent luciferase activity	[208]
 3,8,9,10-Tetrahydroxy-urolithin (urolithin M6)	<i>In vitro</i>	HepG2 40/6 – human hepatoma cell line	10 μM	Agonist	↑ AHR dependent luciferase activity	[208]
		Hepa1.1 – murine hepatoma cell line	10 μM	Agonist	↑ AHR dependent luciferase activity	

Abbreviations: AHR – Aryl Hydrocarbon Receptor; ALDH – Aldehyde dehydrogenase; BCL-2 – B-cell lymphoma 2; BMDCs – Primary bone marrow-derived dendritic cells; BMDMs – Mouse bone marrow derived macrophages; Cldn4 – Claudin 4; COX-2 – Cyclooxygenase-2; CXCL1 – Chemokine (C-X-C motif) ligand 1; CYP1A1 – Cytochrome P450 Family 1 Subfamily A Member 1; DC – Dendritic cells; HO-1 – Heme oxygenase-1; I3A – Indole-3-acetic acid; IL-1β – Interleukin 1 beta; IL-6 – Interleukin 6; LPS – Lipopolysaccharide; miR-212/132 – microRNA cluster 212/132; miR-335 – microRNA 335; MPO – Myeloperoxidase; NFκB – Nuclear factor kappa-light-chain-enhancer of activated B cells; NQO1 – NAD(P)H dehydrogenase [quinone] 1; NRF2 – Nuclear factor erythroid 2-related factor 2; Occludin – occludin 1; p53 – Tumour protein 53; ROS – Reactive oxygen species; SOX4 – SRY-related HMG-box4; TC – Total cholesterol; TCDD – 2,3,7,8-Tetrachlorodibenzo-p-dioxin; TGF-β – Transforming growth factor beta; TNBS – 2,4,6-Trinitrobenzenesulfonic acid; TNF-α – Tumour necroses factor alpha; ZO-1 – Zonula occludens-1.

<sup>a</sup> Estimated circulating concentration 12.16 mM.

<sup>b</sup> Estimated circulating concentration 8.11 mM.

direct-ligand, is organism, cell, tissue and context-dependent. This indicates that the conclusions about modulation of the AHR by gut metabolites should be carefully drawn for every single molecule and experimental/disease model.

## 5. Diet and gut inflammation

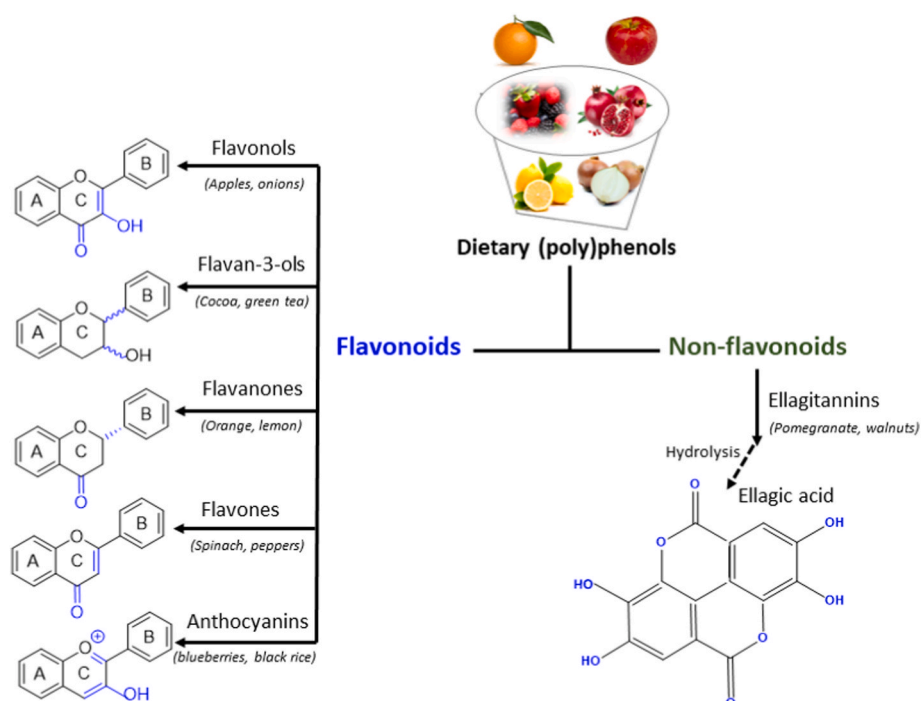
The Western diet, characterized by the low consumption of fibre and high levels of refined sugar, animal fats and animal protein, is considered a potentially reversible risk factor in gut inflammation. This pattern of diet is known to increase intestinal permeability, contribute to the overexpression of pro-inflammatory cytokines and induce alterations in the gut microbiota, which altogether can promote low-grade chronic intestinal inflammation [159]. In contrast to Western diets, the consumption of specific diets rich in plant-based foods contributes to a high intake of phytochemicals, including (poly)phenols. In particular, the Mediterranean diet is a good source of plant-based foods, and its key components, such as fruits and vegetables, olive oil or red wine, are (poly)phenols-rich foods. Many studies have shown a direct modulatory effect of these compounds on the gut microbiota and inflammatory diseases [160–162]. Particularly, IBD is considered a chronic intestinal inflammation and an abnormal immune response caused by alterations in gut microbiota, with several repercussions on the host's immune system [163]. In this regard, interventional studies have shown that the intake of bioactive compounds like (poly)phenols provides a potential approach to influence the microbiota–immunity dialogue, alleviating the symptoms in these patients [164,165].

Several clinical trials support that the specific CD exclusion diet and the UC exclusion diet are well-established procedures to achieve remission in those patients [166]. Besides, carbohydrate diet patterns

have been shown to help clinical remission in paediatric patients with CD [167,168]. However, these diets are very restrictive diets depriving people of a large number of foods. The Mediterranean diet has gained popularity to prevent and/or treat IBD due to its potential in decreasing inflammatory markers and mortality in IBD patients [169,170]. Regular consumption of a Mediterranean diet in healthy people decreases the risk of developing IBD associated with specific gut microbiome regulation as well as a reduction in gut inflammatory markers (e.g., calprotectin) [171]. The beneficial effects of long-lasting adherence to the Mediterranean diet have been attributed to specific components like (poly)phenols [172], which are very abundant in this diet and are associated with immunomodulatory properties and a reduced incidence of inflammation.

### 5.1. Dietary (poly)phenols and gut inflammation

Dietary (poly)phenols are phytochemicals extensively studied due to their health-promoting properties. (Poly)phenols have been studied regarding their pleiotropic activities, such as cardio-vascular activity, antioxidant capabilities, neuroprotective, anti-cancer and anti-inflammatory action, as reviewed elsewhere [173–177]. (Poly)phenols are present in a great variety of vegetables and fruits, and in beverages like coffee, tea and wine, making them the most abundant phytochemicals in the human diet (Fig. 4) [178]. Due to their plethora of bioactivities, (poly)phenol-containing products may be appropriate nutraceuticals and supplementary treatments with wide-ranging health benefits [179]. However, most (poly)phenols have very low bioavailability, and to exert a positive effect on health, they need to be absorbed in the human gut and become bioavailable in circulation. These compounds are submitted to extensive metabolism and when they reach the



**Fig. 4. Main flavonoid and non-flavonoids (ellagitannins) classes with nutritional relevance.** The bonds and atoms in blue indicate the major characteristics of the classes. Ellagic acid is the product obtained from the hydrolysis of ellagitannins, which are a diverse class of non-flavonoids. In brackets are representative food examples from each class of (poly)phenols. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

colon, gut microbiota catabolizes them, producing metabolites that are better absorbed. Lastly, they can undergo phase I and phase II metabolism in enterocytes and hepatocytes, and the resulting phenolic metabolites (i.e., glucuronide or sulfate conjugates) can enter the blood circulation or be excreted into the bile, intestinal lumen, or urine.

Thus, the metabolism of (poly)phenols by both the host and the gut microbiota into small molecules creates a wide range of gut phenolic metabolites that can have different biological effects, which may be responsible for health-promoting effects attributed to the consumption of dietary (poly)phenols [173,180,181]. In particular, in the digestive tract where they are mainly produced, the pool and concentration of those resulting metabolites locally will impact the intestinal integrity and could interfere with intestine homeostasis and consequently cause or prevent the disease onset, the inflammatory response and recovery. The health impact associated with the (poly)phenol metabolites can happen through different pathways, either directly or indirectly. Therefore, the study of the impact of these metabolites in the intestine is key to understanding their effect on gut inflammation or related illness.

Several studies aiming to evaluate the effect of (poly)phenols have been performed using *in vivo* models of colitis, mostly in rodents, by either supplementing their diets with berries or with berry extracts, as berries are a rich source of dietary (poly)phenols, such as phenolic acids, flavonols and anthocyanins [182]. In these studies, reduction in neutrophil infiltration in the colonic mucosa was described, reducing the formation of oxidants linked to inflammation, the restoration of IL-10 levels, the inhibition of NFκB and a decreased expression of genes relevant to the inflammatory response, such as TNF-α, COX-2, IL-1β and IFN-γ [183–186]. The results also showed that not all food sources render the same outcome. For example, supplementation of the diets with blueberry products leads to a reduction of neutrophil infiltration and suppression of oxidative stress markers, which is not mirrored when supplementing a DSS-colitis animal model's diet with black raspberry [183,184]. Bilberries and their anthocyanin extracts also reduce disease severity and the expression of pro-inflammatory cytokines in a model of acute-induced colitis in mice and reduced epithelial cell apoptosis [187]. A reduction in mucosal inflammation, histologic score and faecal

calprotectin were observed in a human intervention study with UC patients consuming bilberries. Despite these results, the improvement in these patients was reverted once they stop the consumption of the berries [188], indicating that the chronic consumption of (poly)phenols is needed for the amelioration of the disease symptoms.

Curcumin, a (poly)phenol present in the turmeric plant, has been reported to have anti-inflammatory, anti-cancer and antioxidant activities in a DSS-induced colitis mice model. Curcumin can improve induced-colitis markers, such as weight loss and mucosal inflammation [189,190], most likely due to its capability of inhibiting NFκB activation, as has been observed with a lower secretion of pro-inflammatory cytokine by macrophages and epithelial cells [191,192]. Additionally, the gut microbiota-derived metabolite of curcumin, tetrahydrocurcumin, has been observed to prevent colitis-associated colon cancer in animal models [190,193]. Chlorogenic acid, a (poly)phenol present in a wide variety of foods and beverages, reduced the expression of macrophage inflammatory protein-2, a homolog of human IL-8, in a mouse model of UC [194,195].

In addition, innumerable *in vitro* studies have been carried out on the role of dietary bioactive compounds pointing them to anti-inflammatory activity. For example, bilberry extracts and single anthocyanins showed, in human monocytic THP-1 cells, inhibition of the secretion of different pro-inflammatory cytokines (e.g., TNF-α) [188,196]. Maqui berry extracts decreased the growth of HT-29 (human colorectal adenocarcinoma) and Caco-2 cell lines, correlating with the inhibition of COX-2 and NFκB [197]. TNF-α/IL-1β activation followed by VEGF stimulation was observed as an anti-angiogenic effect of black raspberry extracts, mediated by protein kinase B (Akt), mitogen-activated protein kinase (MAPK), and JNK phosphorylation inhibitions [198]. Chlorogenic acid promotes a decrease in the expression of TNF-α and IL-8 in Caco-2 cells supporting this compound's *in vivo* effects [194,195]. However, these studies do not have a nutritional relevance, i.e., regardless of bioavailability, metabolism, and distribution of dietary (poly)phenols, since whatever reach these cells, are mainly gut phenolic metabolites and not the parent compounds present in the plants or their extracts.

Overall, the *in vitro* and *in vivo* studies indicate that the ability of dietary (poly)phenols to prevent and ameliorate disease markers of IBD is related to their capability of inhibiting oxidative stress by acting as free radical scavengers and, mainly, by the reduction of the expression of pro-inflammatory proteins through modulation of the NF $\kappa$ B signalling pathway [199]. However, the specific potential of their metabolites that could be directly linked to the observed effects remains to be determined. Therefore, in the next sections of this review, we focus on the potential physiologically relevant gut phenolic metabolites that could be the main players in the protective effects of gut inflammation and concerning the AHR.

## 5.2. (Poly)phenol-derived metabolites produced by gut microbiota

As mentioned, the bioavailability and metabolism of (poly)phenols are key factors to consider since they may increase or limit their beneficial effects. The dietary (poly)phenols, as they are present in fruits and vegetables are mainly conjugated with glycosides and organic acids (e.g., quinic acid), or can occur as oligomers (e.g., condensed tannins). Nonetheless, each of these forms is poorly or not absorbed at all, and is extensively submitted to metabolic reactions in the gut.

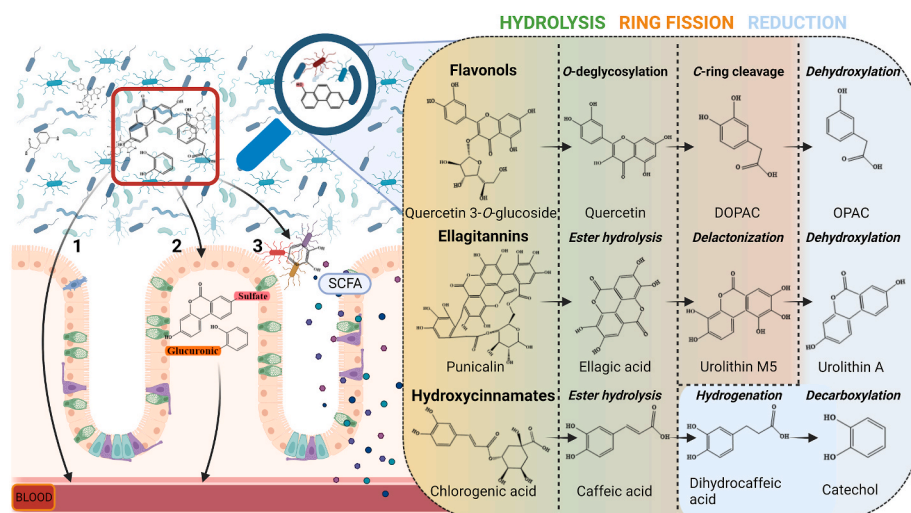
In the gut, the microbiota is the main responsible to transform dietary (poly)phenols mainly through three different reactions: (i) hydrolysis; (ii) ring fission, and (iii) reduction (Fig. 5). Flavonoids represent the most abundant family of phenolic compounds in the diet, with more than 8000 flavonoids described so far [200]. Most flavonoids are present as O- or C-glycosides. Although these flavonoids can be absorbed in the small intestine due to the action of glycosidases, such as lactase phloridzin hydrolase or cytosolic  $\beta$ -glucosidase [201,202], these compounds can be hydrolyzed into smaller metabolites prior to absorption by gut microbiota [203]. As an example of this dual metabolism, quercetin glycosides (e.g., quercetin 3-O-glucoside and quercetin 4'-O-glucoside) can be hydrolyzed by phloridzin hydrolase [201], and further catabolized by intestinal bacteria into ring-fission products producing 3',4'-dihydroxyphenylacetic acid (DOPAC) and 3'-hydroxyphenylacetic acid (OPAC), with a small production of 3,4-dihydroxybenzoic acid (protocatechuic acid) [204]. Another example of a metabolic reaction is the ester hydrolysis by some bacterial species (Fig. 5). For instance, the release of 3',4'-dihydroxycinnamic acid (caffeic acid) by microbial esterases after incubation of chlorogenic acid [205] or acteoside [206] with human faecal samples has been described. In general terms, ring fission reactions are site-dependent on the structure of the phenolic compound. For instance, ring fission of flavan-3-ols (e.g., catechin) produces 5-(hydroxyphenyl)valeric acid and 5-(hydroxyphenyl)- $\gamma$ -valerolactones, which are not produced by any

other flavonoid classes [207]. The ring fission of flavan-3-ols also produces other phenolic metabolites, such as hydroxycinnamic acids, which are non-specific biomarkers of the dietary (poly)phenols intake. On the other hand, some of the (poly)phenol-derived metabolites are unique metabolites derived from a specific family of (poly)phenols. In this regard, the 6H-dibenzo[b,d]pyran-6-one derivatives (known as urolithins) are unique metabolites from ellagic acid, produced by gut microbiota [208]. The first step to producing urolithins from ellagic acid is the ring cleavage, and then the sequential decarboxylation leads to the formation of different urolithins (Fig. 5). This exclusive class of phenolic metabolites are not further metabolized into smaller compounds, remaining just as they are produced in the gut, although they are conjugated in the liver and/or enterocytes to be excreted in urine as phase II conjugates [209].

Nonetheless, it should be pointed out that the smaller metabolites derived from flavonoids can also appear in the gut or circulate in the bloodstream after (poly)phenol-rich foods intake, as they can be absorbed from the food matrix without further metabolism (e.g., caffeic acid). Another important mechanism to note is the metabolic convergence resulting from progressive cleavage into common phenolic metabolites as it has been suggested for different (poly)phenol classes (e.g., benzenes, benzoic acids, and hippuric acids) [181] which leads to high and sustained concentrations in the circulation of these metabolites. In addition, these phenolic metabolites are not exclusively derived from dietary (poly)phenols, as they can be produced in the host by endogenous pathways, such as the phenylalanine metabolic pathway, which generates hippuric acids.

An increasing number of studies are looking for protective benefits against IBD with gut phenolic metabolites, which could have fewer undesirable effects in conditions of acute or chronic intestinal inflammation through the improvement of colonic oxidative and pro-inflammatory status. The production of specific isoflavone-gut microbiota metabolites (e.g., equol) has been associated with differences in the gut microbial ecologies, proposing that specific gut microbes may explain the differences observed and their causal role in health effects related to (poly)phenol consumption. Nevertheless, the core of this review is focused on those originating from ellagitannins, and the main dietary flavonoids—namely anthocyanins, flavones, flavonols, flavanones, and flavan-3-ols because they are well represented in diverse foods and therefore could be ingested daily (e.g., wine, walnuts, berries, oil, apples, etc) [210].

The metabolism by the gut microbiota gives rise to other relevant compounds, like branched-chain amino acids or SCFAs [173,176,211,212]. Moreover, it has been shown that the SCFAs contribute to the maintenance of gut homeostasis, by modulating the equilibrium of interactions between the intestinal epithelium and the host immune



**Fig. 5.** Main transformation reactions by gut microbiota of dietary (poly)phenols. Hydrolysis (O-glycosylation, ester hydrolysis), ring fission (C-ring cleavage, delactonization) and reduction (dehydroxylation, hydrogenation and decarboxylation) reactions. Examples of dietary (poly)phenols as found in food: flavonols (onions, apples), ellagitannins (berries, nuts), and hydroxycinnamates (coffee, whole grains) are converted into lower molecular weight metabolites by gut microbiota. These gut phenolic metabolites can: 1) be absorbed by intestinal epithelium entering entero-hepatic circulation and being redirected to the gut, 2) undergo direct phase II metabolism reactions into the enterocyte (e.g., glucuronidation, sulfation); 3) be further metabolized into short-chain fatty acids (SCFAs) by gut microbiota. Finally, all these microbiota metabolites and their conjugates can be absorbed and reach systemic circulation. The non-metabolized or non-absorbed dietary (poly)phenols are then excreted in faeces [175,213]. Figure created with BioRender.com.

system [156].

Taking into account the transformations of dietary (poly)phenols by the gut microbiota, understanding their impact on the health benefits attributed to dietary (poly)phenols should be redirected towards their absorbable gut-derived metabolites. Some specific products of bacterial transformation, such as ring-fission products and reduced metabolites, could exhibit enhanced properties.

These smaller phenolic metabolites derived from the dietary (poly)phenols can also have their origins within the human body from other exogenous sources. Some of the gut microbes, and host enzymes involved in the described biotransformations, are responsible for the general metabolism of any chemical substance not naturally produced by or expected to be present within the human organism (xenobiotic metabolism). Therefore, it is not surprising that some phenolic metabolites could be obtained in humans not only through regular ingestion of dietary (poly)phenols but also by metabolizing other ingested compounds, like residues of industrial chemicals and pharmaceuticals [214]. Some of these compounds are intermediates of xenobiotics biodegradation and metabolism pathways like the bacterial aminobenzoate degradation pathway. Of notice, aminobenzoate metabolites are also derived from tryptophan and other indole ring-containing compounds metabolism [176]. On the other hand, it is also known that some of these metabolites could appear in human circulation from endogenous origin, due to the overlap with endogenous pathways such as the tyrosine or dopamine pathways [176].

## 6. Role of (poly)phenols and derived metabolites in the AHR modulation

### 6.1. Dietary (poly)phenols and AHR modulation

Several dietary (poly)phenols have been identified as AHR ligands, either agonists and/or antagonists. Their effect in the AHR modulation can result in several outcomes, as highlighted in Fig. 6, impacting cell fate, proliferation and differentiation, xenobiotic metabolism and inflammatory processes, among others; and is host, cell, tissue type, and context-dependent, as described for other AHR ligands. Although many studies revealed the potential of the dietary (poly)phenols to modulate the AHR, these are not relevant at the organ level due to their extensive metabolism and rapid elimination in the gut as described before. Still, these studies are a good indication of the (poly)phenols' potential to be explored as lead compounds for AHR modulation. However, not only (poly)phenols and their metabolites affect the AHR in the gut, but other

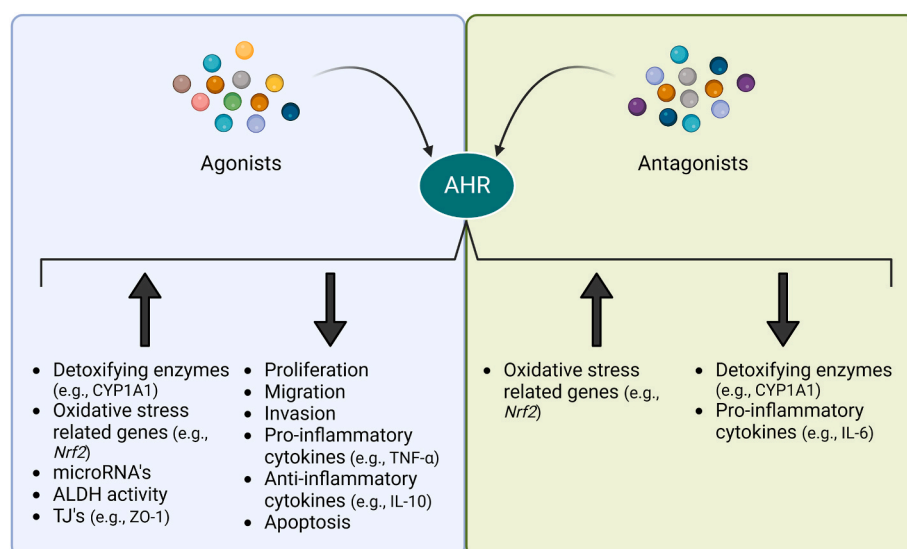
compounds like xenobiotics (food contaminants, pollutants or drugs) are also described to affect this pathway. Some examples of xenobiotics that can modulate the AHR include dioxins, polychlorinated biphenyls (PCBs), and certain pesticides [7,53,57]. Concerning xenobiotics, some have been studied regarding their ability to impact gut health and how they affect drug metabolism, efficacy and toxicity, taking a special relevance to the role of the microbiota, as reviewed elsewhere [215, 216].

Some anthocyanidins and anthocyanins have been studied regarding their role in the AHR-CYP1A signalling pathway. The anthocyanidin pelargonidin was found to be an AHR agonist and induce the expression of the *Cyp1a1* in human hepatocellular carcinoma cells and human colon adenocarcinoma cells [217]. Among twenty-one different anthocyanins studied for their ability to modulate AHR, only two, pelargonidin-3-*O*-rutinoside and cyanidin-3,5-*O*-diglucoside, could activate AHR in a dose-dependent manner in hepatic and intestinal cancer cells. Those two anthocyanins induced *Cyp1a1* mRNA expression in these cells but not protein expression, and no *Cyp1a1* mRNA or protein was induced in primary human hepatocytes cultures [218].

Initially, some flavonoids, like epigallocatechin gallate and epigallocatechin, were identified as strong antagonists of the mouse AHR [219], but later research on epigallocatechin gallate established that the previous result was associated with its interaction with the HSP90 protein, demonstrating that this effect occurs by indirect inhibition of the AHR [220,221]. Other subclasses of flavonoids, like flavones, flavonols, and flavanones, inhibit the binding between agonists and the AHR, indicating that they are competitive antagonists of the AHR [222].

Likewise, quercetin was first described as a ligand of both human and mouse AHR [223] with protective effects against inflammation [224, 225] and hepatotoxicity [226]. Shortly after, Mohammadi-Bardbori et al. showed that quercetin, resveratrol, and curcumin indirectly activate the AHR [150]. Other authors demonstrate that quercetin is capable of inducing *Cyp1a1* in an AHR dependent manner [227] and inhibiting EGFR phosphorylation and UV-associated AHR-mediated signalling [225].

Luteolin, previously described as having anti-inflammatory activity *in vitro* [228,229], was studied for its ability to induce AHR activation. A dose-dependent activation of the AHR with an optimal concentration of 80  $\mu$ M was defined for luteolin [230]. Since AHR is considered a sensor that connects the outside environment with cellular processes regulating the immune system, one can speculate that the anti-inflammatory role of luteolin in LPS-induced macrophages may occur due to the AHR activation by this (poly)phenol. Notwithstanding, the biological relevance



**Fig. 6. Outcomes of AHR modulation by (poly)phenol metabolites.** Schematic representation of selected outcomes regulated by the AHR upon modulation by (poly)phenol metabolites. Of note, the classification of ligands/modulators as agonists and antagonists herein adopted is based on their listed effects on the AHR canonical pathway. Complementary information related to the ligand/modulator, host, cell, tissue and context-dependent effects can be seen in Table 2. Abbreviations: ALDH – Aldehyde dehydrogenase; CYP1A1 – Cytochrome P450 Family 1 Subfamily A Member 1; IL-6 – Interleukin 6; Nrf2 – Nuclear factor erythroid 2-related factor 2; TJs – Tight junctions; TNF- $\alpha$  – Tumour necroses factor alpha; ZO-1 – Zonula occludens-1. Figure created with BioRender.com.

of luteolin in the gut is arguable due to its rapid metabolization in the colon [230]. Baicalein and 4-O-caffeoylquinic acid showed a dose-dependent AHR activation with an optimal concentration of 320, and 40  $\mu\text{M}$ , respectively [230]. Recently it has been shown that baicalein is capable of protecting the colon from inflammatory damage in the DSS-induced colitis mice model by improving the intestinal epithelial barrier through decreasing intestinal permeability and restoring TJs via AHR/IL-22 pathway, regulating Treg cell differentiation and maintaining immune homeostasis and suppresses NF $\kappa$ B activation [231–233].

A screening on the ability to activate AHR by natural compounds, that include (poly)phenols, was made on hepatoma cells (H1L1). Ninety-five (poly)phenols from five different classes were screened using an *in vitro* reporter gene assay. In this screening, sixteen dietary compounds were able to activate AHR in this cell line displaying agonist activity [234]. In another study carried out by the same authors, they tested the antagonist effect of thirty-four (poly)phenols from eight different classes [235], using an AHR-Immunoassay. Among these compounds, flavones, flavonols, anthraquinones, piperine, coumestrol, brevifolincarboxylic acid, and resveratrol showed marked inhibitory effects on AHR-based bioassay activation by TCDD, and their effects were dose-dependent [235]. Some of the studied (poly)phenols were revealed to have both agonist and antagonist abilities to modulate AHR [235]. Denison and Nagy reviewed both natural and synthetic compounds that can directly activate and/or inhibit the AHR signalling pathway. They reported that curcumin, diosmin, tangeritin, and tamarixetin have been described as AHR ligands and substrates for CYP1A1 [150,236].

Resveratrol, another minor (poly)phenol in the human diet, was first described as an AHR antagonist by Ciolino et al. and can inhibit directly [237] or indirectly [150] the induction of the CYP1 family members by inhibiting the recruitment of the transcription factors AHR and ARNT to XREs of the enhancer regions of *Cyp1a1* and *Cyp1b1* genes [238]. Resveratrol has also been described as a partial agonist in human hepatocytes since is capable of inducing CYP1 family members in an AHR dependent manner [239,240].

Throughout the years, the effect of dietary (poly)phenols in the modulation of the AHR has been extensively studied, both *in vivo* and *in vitro*, revealing its potential to modulate the AHR. However, since they are submitted to extensive metabolism in the gut and rapid elimination, gut phenolic metabolites are the ones able to exert locally the effects in AHR modulation. Therefore, the trend of the research should be redirected towards evaluating the role of these gut phenolic metabolites, thus increasing the real knowledge of their possible effects in the AHR throughout the gut.

## 6.2. Gut phenolic metabolites and AHR modulation

Due to the importance to consider the final phenolic metabolites produced after multiple steps involving the gut microbiota, and not the parent compounds, a comprehensive search in *Pubmed* resorting to a list with 108 (using in the search terms also their respective synonyms + “AHR” or “aryl hydrocarbon receptor”) of the most abundant gut phenolic metabolites identified and/or quantified in human circulation (Supplementary Table S1 [181,241]) was performed. In this list, we have excluded phase II metabolites (i.e., glucuronides and sulphates), and comprise a total of thirteen different compound classes and other (poly)phenol compounds, aiming to understand how many of these metabolites have been described as AHR modulators and having an impact in inflammatory processes.

Among the 108 metabolites, we could only find a link between eight of these metabolites and crosstalk with the AHR (Table 2). The metabolites described as AHR agonists/antagonists have been studied on resourcing *in silico*, *in vitro* and *in vivo* models. Most studies have been done in tissues such as skin, lung and liver, unrelated to the gut, but reveal the potential for these compounds to modulate the AHR. Other gut phenolic metabolites have been evaluated *in vitro* for their ability to be potential ligands but with no clear AHR modulatory capabilities (see

Supplementary Table S2). These results could be related to either the range of concentrations tested, the cell type used, or even can be in fact no AHR ligands. However, due to the limited studies, we decided to exclude them from our discussion and just list the evidence collected in Supplementary Table S2.

Benzene-1,3-diol (resorcinol) has been reported as an anti-melanogenic, anti-cancer, and antibacterial metabolite [242,243], but only recently was published the first report describing its biological activity in the skin [244]. High concentrations of resorcinol (0.5–3 mM) were described to suppress AHR activation by the environmental pollutant B[a]P in human keratinocytes resulting in a lower AHR nuclear translocation and inhibition of *Cyp1a1* expression; decrease in B[a]P-induced damaged in human keratinocytes [245]; decrease of ROS production and IL-8 excretion [150]; an increase in the NRF2 nuclear translocation and upregulation of its target genes, although the data indicate that NRF2 activation is AHR-independent [244]. Nevertheless, a crosstalk between the NRF2 and AHR pathways has been previously described [246–249]. In another cell model study by Kruger et al. in Hepa 1.12 cR cells, resorcinol, in a wide range of concentrations, acts as a competitive ligand of AHR in the presence of TCDD, although no agonist activity was observed in this study [250]. In conclusion, resorcinol reveals the potential to modulate AHR activity although, due to the limited number of studies, it is not clear if its antagonist/agonist effects are cell specific or dependent on the concentration tested.

3,4,5-trihydroxybenzoic acid (gallic acid), a gut metabolite, but also a parent compound present in some fruits (i.e., berries), is one of the most studied metabolites as an AHR modulator [234,235,251,252]. *In silico* analysis pointed out gallic acid as a ligand of the AHR [251,252]. *In vitro* tests in different cell types (breast cancer cells, T cells, macrophages) indicate that gallic acid is an agonist of the AHR, capable of inducing AHR nuclear translocation and expression of AHR target genes, such as *Cyp1a1* [251,252]. In an *in vitro* breast cancer model, gallic acid promoted apoptosis of the cancer cells and decreased proliferation, migration and invasion capacities in an AHR dependent manner [251]. It was also observed that gallic acid can modulate, in an AHR-dependent and -independent manner, the expression of B-cell lymphoma 2, COX-2, SOX4, and tumour protein 53 [251]. Although some *in vitro* studies point out gallic acid as an AHR agonist, the concentrations tested are far from relevant to reach that type of cell in a nutritional scenario. Moreover, near physiological circulating concentrations tested in liver cells reveal no induction of AHR [234]. *In vivo* analysis in an autoimmune encephalomyelitis mice model has shown that the animals treated with gallic acid display increased CYP1A1 activity (EROD assay), increased resistance to the disease and TGF- $\beta$  (transforming growth factor-beta), have lower levels of pro-inflammatory cytokines and reduce infiltration of T cells and monocytes into the central nervous system [252]. In an *in vivo* orthotopic model, where human breast cancer cells are injected into mice, it was shown that gallic acid is capable of activating the AHR pathway (e.g., inducing *Cyp1a1* expression) and reducing the growth of breast cancer cells [251]. In summary, these works show from *in silico*, *in vitro* and *in vivo* data that gallic acid has therapeutical potential as an AHR ligand and is a compound able to reduce inflammatory responses and cancer spread through the activation of the AHR signalling pathway.

DOPAC has previously been identified as an inducer of drug-metabolizing enzymes, an inhibitor of the secretion of pro-inflammatory cytokines and P-selectin in platelets [205,255–257]. In liver cells was shown that pre-treatment with DOPAC can increase total aldehyde dehydrogenases activity and stimulate nuclear translocation of the NRF2 and AHR, both responsible for the expression of phase I and phase II drug-metabolizing enzymes [253].

Several studies pointed to the beneficial effects of urolithins, microbiota metabolites of ellagitannins and ellagic acid, namely due to their anti-inflammatory, anti-cancer, and anti-estrogenic properties [258,259]. A recent work from Bobowska et al. describes urolithin A, as the most potent urolithin to inhibit an inflammatory response, whereas urolithin A phase II conjugates are inactive, hence losing the beneficial

effects in macrophages and neutrophils [260]. In a model of experimental autoimmune encephalomyelitis has been shown that urolithin A is an agonist of AHR, and able to reduce the expression of inflammatory genes in DC, resulting in less active cells, and regulating the IL-17 family signalling pathway through the activation of the AHR, blocking Th17 differentiation [254]. In a related study, using both *in vitro* and *in vivo* approaches, Singh et al. demonstrated that urolithin A activates and acts via the AHR-NF $\kappa$ B, improving gut barrier function and preventing unnecessary inflammation by the upregulation of epithelial TJs [101]. The authors also confirmed the role of this compound in preventing experimental colitis through AHR *in vitro* using HT-29 cells, and *in vivo* using a TNBS-induced colitis model. Moreover, the authors reported that urolithin A is capable of improving intestinal permeability; reducing colonic inflammation (e.g., IL-6, TNF- $\alpha$ , CXCL1, IL-1 $\beta$ ); reducing body weight loss and overall disease activity index [101]. In addition, Muku et al. identified in HepG2 and Caco-2 human cells, urolithin A as an AHR antagonist while in Hepa1.1 mouse cells showed agonist potential [208].

Furthermore, Muku et al. also tested several other urolithins using an AHR luciferase reporter assay, namely 3-hydroxy-urolithin (urolithin B), 3,8,9-trihydroxy-urolithin (urolithin C), 3,4,8,9-tetrahydroxy-urolithin (urolithin D) and 3,8,9,10-tetrahydroxy-urolithin (urolithin M6), all were found to be AHR modulators. Urolithin B and urolithin C showed antagonist activity of the AHR in HepG2 cells, whereas urolithin D and urolithin M6 were described as agonists of the AHR, in both HepG2 and Hepa1.1 cells [208]. To the best of our current knowledge, no further studies were performed to ascertain the response of urolithins in the modulation of the inflammatory response in an AHR dependent manner.

Overall, only gallic acid and urolithin A were evaluated for their ability to modulate the AHR in intestinal and immune cells. The lack of studies with other relevant gut phenolic metabolites in the gut reveals the large gap that exists regarding the effect that those metabolites may exert on AHR in the intestine.

## 7. Gaps in the field of AHR, inflammation and (poly)phenols

The AHR modulation in the gut can be affected by a myriad of compounds. To date, we are only at the beginning of unravelling which physiological metabolites can affect inflammation-related gut diseases acting through this receptor. Although we are starting to understand the complex role(s) of the AHR in gut inflammation, it has become unequivocally clear that the AHR is an important regulator of metabolic and immunological processes. One remarkable role of the AHR in intestinal health is its capacity to “spy” on quorum sensing molecules to monitor the luminal environment, access the bacterial composition and the presence of virulence factors, and promote either tolerogenic or defence responses according to the context [16,17]. The AHR’s ability to sense the luminal environment and to activate or inhibit inflammatory responses using microbial metabolites could become an extremely important tool, opening new possibilities for different therapeutic/nutritional approaches aiming at the prevention and control of inflammatory diseases [261].

Several pending aspects should be addressed in future studies. For example, there is a need to explore the effect that the gut phenolic metabolites can exert on the AHR expressed in the intestinal cells, especially considering the quantity and diversity of these metabolites that can occur in the gut. The majority of research has been performed taking into account the availability and concentration of parent dietary (poly)phenol compounds in human circulation. Regarding the availability/concentration of (poly)phenol metabolites in the gut, it is expected to be at higher concentrations than those found in circulation, in the majority of the cases [262,263], due to the convergent metabolism of (poly)phenols, as discussed. Most of the articles resorting to ileostomy volunteers upon ingestion of fruit juices or extracts with high levels of (poly)phenols only resolve the concentration of the most abundant

parent dietary (poly)phenol compounds, not giving information on the gut phenolic metabolites generated in the small intestine. Similarly, studies on the colonic availability of (poly)phenols focus on dietary (poly)phenols and not on (poly)phenol metabolites. A research paper studying the presence of ellagitannin and ellagic acid metabolites in colorectal cancer patients and healthy subjects showed that the concentration of their metabolites ranges from nanomolar to micromolar, depending on the metabolite [262].

One characteristic that has been observed among several known AHR ligands is their planar structure, which could indicate that this is an important feature for the ability of the ligands to interact with the AHR [230]. Thus, the planar conformation, and also hydroxyl groups present in the B and C rings of flavonoids (Fig. 4) could be related to these compounds being AHR ligands [264]. Nevertheless, other structurally different molecules as potential AHR modulators should not be disregarded and be evaluated and studied in detail in the future. As mentioned above, the AHR is endorsed with a remarkable capacity to bind to a broad range of structurally different molecules.

Until now, the most studied microbial-derived metabolites involved in AHR modulation have been the tryptophan metabolites. The literature has shown that a significant number of microbial-derived tryptophan metabolites are able to bind to and modulate AHR activity, although only a small subset has been shown to modulate the inflammatory response in an AHR dependent manner. This connection between microbial tryptophan metabolites and human health is promising, albeit further studies are still needed. Considering the gut phenolic metabolites explored in this review (Supplementary Table S1), only a few of them have been studied regarding their AHR modulatory capabilities in different cell types (Table 2), spanning from *in vitro* breast cancer models to induced-colitis *in vivo* models. Both *in vitro* and *in vivo* results indicate that gut phenolic metabolites have the capacity to modulate inflammatory players by targeting the AHR [101,208,254], and also these metabolites maintain barrier integrity [101]. However, out of the eight gut phenolic compounds referred on Table 2, only one was tested regarding the modulatory action on intestinal inflammatory models.

The gut phenolic metabolites are derived from the metabolism of the dietary (poly)phenols present in vegetables and fruits, among others. As so, a healthy diet rich in fruits and vegetables, with a high concentration of essential substrates for the synthesis of these microbial metabolites, could contribute to the prevention and treatment of the most prevalent inflammatory diseases [173]. The fact that these phenolic metabolites are present in the gut and may have the ability to modulate the AHR and improve gut microbiota ecology opens the avenue to be studied with great therapeutic and nutritional potential.

An important aspect that is frequently overlooked is that several different types of metabolites, besides phenolics, are simultaneously present in the gut and can produce a mixture of effects in the AHR pathway. Another potential pitfall that animal studies can face while trying to establish this connection and be translated to humans is linked to the fact that humans and rodents have different microbiomes and consequently slightly different phenolic metabolism pathways. It would be important to resort to more suitable models that could allow us to take more generalized conclusions, such as the utilization of humanized mice models or human organoid models, where human phenolic metabolites should be evaluated. There is also a need to perform more diet intervention studies on both healthy volunteers and patients. Another issue that can be identified is that some metabolites can act both as agonists or antagonists of the AHR, depending on the concentration of the metabolite and/or the cell type/host, this is also important to consider for extrapolating the results from animal models to human context. Besides, depending on a nutritional approach, careful selection of the physiologically relevant concentrations for the metabolites should be considered for mechanistic studies concerning the biological impact on AHR modulation. For a pharmacological approach, a controlled delivery of a specific concentration can be envisaged to achieve the desired

effect on AHR.

There is much potential in gut phenolic metabolites concerning the prevention and/or treatment of intestinal inflammation. Whether intestinal phenolic metabolites can modulate the AHR and its specific effects throughout the gut, is an area that answers to an unmet need to address serious clinical problems such as IBD. Therefore, it is a topic in which knowledge is in its infancy and should arouse great interest in the scientific community due to its great impact on managing these pathologies.

### Declaration of competing interest

I declare that there is no competing interests and that funding source was disclosed as requested.

### Data availability

Data will be made available on request.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.redox.2023.102622>.

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