

Diverse roles of microbial indole compounds in eukaryotic systems

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ABSTRACT

Indole and its derivatives are widespread across different life forms, functioning as signalling molecules in prokaryotes and with more diverse roles in eukaryotes. A majority of indoles found in the environment are attributed to bacterial enzymes converting tryptophan into indole and its derivatives. The involvement of indoles among lower organisms as an interspecies and intraspecies signal is well known, with many reports showing that inter-kingdom interactions involving microbial indole compounds are equally important as they influence defence systems and even the behaviour of higher organisms. This review summarizes recent advances in our understanding of the functional properties of indole and indole derivatives in diverse eukaryotes. Furthermore, we discuss current perspectives on the role of microbial indoles in human diseases such as diabetes, obesity, atherosclerosis, and cancers. Deciphering the function of indoles as biomarkers of metabolic state will facilitate the formulation of diet-based treatments and open unique therapeutic opportunities.

Key words: AhR signalling, indoles, inter-kingdom signalling, symbiosis and dysbiosis, tryptophan metabolites, xenobiotic sensor

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I. INTRODUCTION

Indole is an important biomolecule widely distributed in nature. Large quantities of extracellular indole (ranging from 0.3 to 6 mM) have been detected in the fecal samples of healthy individuals indicating the abundance of indole-producing bacteria in the gut (Darkoh *et al.*, 2015; Hubbard, Murray & Perdew, 2015b; Chappell *et al.*, 2016; Dong *et al.*, 2020; Dvořák *et al.*, 2020). It is now well established that human health is profoundly associated with the composition and function of gut microbiota. Qualitative (composition) or quantitative (population) changes in the gut microbiota can greatly influence the physiology of the host, contributing to several chronic diseases such as malnutrition, obesity, neurological disorders, cancers, inflammatory bowel disease (IBD), type 2 diabetes, atherosclerosis, metabolic syndromes, and liver diseases (Hendriks & Schnabl, 2019). Disruption of symbiosis (dysbiosis) can occur due to multiple factors including diet, environmental factors, stress, aging, drug use, etc., which alter systemic levels of indoles (Biscetti *et al.*, 2019; Shi *et al.*, 2020). Although many microbes can synthesize tryptophan through the chorismate-linked biosynthetic pathway, proteolytic activities are the major source of tryptophan for gut bacteria. Only those harbouring the tryptophanase gene can produce indole. There are three possible sources of indoles in eukaryotes: (i) exogenous supply (from the environment); (ii) endogenous supply (self-produced within the tissues); and (iii) microbe derived.

In the gut, the quantity of indole and its derivatives is under the direct or indirect control of the microbiota. Tryptophan metabolism by gut microbiota leads to the synthesis of several catabolites such as tryptamine, indole, indole-3-acetamide, indole-3-acetic acid (IAA), indole acrylic acid, indole-3-aldehyde, indole-3-lactic acid, indole-3-propionic acid, and indole-3-pyruvate (Hendriks & Schnabl, 2019). Moreover, indole can be further metabolized by the host into other biologically active metabolites such as indoxyl-3-sulfate (I3S), oxindole, dioxindole, 3-formylindole, kynurenine, kynurenic acid, isatin, etc. (Wang *et al.*, 2017; Agus, Planchais & Sokol, 2018; Jaglin *et al.*, 2018). In animals, indole is known to affect host intestinal epithelial barrier integrity, to control inflammation in the gut (Bansal *et al.*, 2010), to protect against chemically induced colitis (Shimada *et al.*, 2013), and even to prolong host health span (Sonowal *et al.*, 2017). Indole moiety-containing hormones (e.g. serotonin and melatonin) not only influence the nervous system but also regulate organ development, gastrointestinal functions, and the intestinal immune system as well as bone growth (Beaumont *et al.*, 2018; Roager & Licht, 2018).

To date, microbes have been extensively studied for their influence on gut health, eubiosis, the gut immune system, and the gut–brain and gut–liver axes (Wishart, 2019; McCarville *et al.*, 2020). Among the many microbial metabolites,

indoles have been found to be involved in crosstalk between several organs and to influence host physiology. Most of these molecules exert biological functions through three main receptor-mediated signal transduction pathways, namely the aryl hydrocarbon receptor (AhR), pregnane X receptor (PXR), and toll-like receptor 4 (TLR4) expressed in various cell types within the gut (epithelial cells, fibroblasts, and immune cells) (Zelante *et al.*, 2013; Venkatesh *et al.*, 2014; Rasmussen *et al.*, 2016; Seok *et al.*, 2018; Pulakazhi Venu *et al.*, 2019). Recent advances in metabolomics and metagenomics have enhanced our understanding of the microbiome; however, the mechanistic study of host–microbe interaction in a diseased or healthy person is still an active area of research.

Indole and its derivatives are also known for their roles as inter-species and inter-kingdom signals (Lee, Wood & Lee, 2015b; Tomberlin *et al.*, 2017). The production of indole compounds is largely attributed to microbial metabolism within various ecological niches (Lee & Lee, 2010). For the past two decades, indole and related compounds have been investigated to understand their roles in prokaryotes, particularly in biofilm formation, defence, drug resistance, and virulence. Although microbes share ecological niches with eukaryotes, the effects of microbially produced indole and its derivatives on eukaryotes initially went unnoticed. In eukaryotes, including plants and animals, indole compounds are now known to play major roles as cues, signals, or amplifiers that affect their behaviour. Indoles function differently at different concentrations and govern unique insect behaviours (Liu *et al.*, 2016). This review assesses our current understanding of the roles of microbially derived indole compounds in eukaryotes as signals or effectors influencing a variety of activities. Although indoles as signalling molecules in prokaryotic systems have been widely reported (Lee & Lee, 2010; Lee *et al.*, 2015a, 2015b; Defoirdt, 2018; Zarkan *et al.*, 2020), only a few reviews have considered the effects of indoles as signals in invertebrates (Tomberlin *et al.*, 2017) or indole-based signalling in higher animals (Hubbard *et al.*, 2015b; McCarville *et al.*, 2020; Pernoian, Duarte-Silva & de Barros Cardoso, 2020).

In the light of recent findings, we provide a systematic compilation of indole compounds in different eukaryotes, and their roles in metabolic diseases due to their AhR-dependent and independent activities. We discuss how such information could be exploited for the benefit of humans. The involvement of indoles in human health is also discussed.

II. EFFECTS OF MICROBIAL INDOLE METABOLITES IN EUKARYOTES

Indole is one of the most important volatile bacterial compounds (Audrain *et al.*, 2015). Indole is a valuable

environmental cue that is utilized (emitted or received) by a variety of organisms to provide them with fitness advantages (Mueller *et al.*, 2009; Wang *et al.*, 2017; Gilbert *et al.*, 2018) (Table 1). Indole compounds thus have been exploited for coordinated action within organisms and for influencing their behaviour. Some aspects of the behaviour of indole as a cue or signal have been reviewed previously (Tomberlin *et al.*, 2017). Unique functions of indole and indole-like compounds in diverse eukaryotes (including amoebae, helminths, arthropods, molluscs, mammals, and plants) are presented in Table 1.

(1) Indoles as effector molecules for *Caenorhabditis elegans* (roundworm)

In natural environments, interactions among living organisms are inevitable. These interactions may be either beneficial or harmful to one or both parties. In soil ecosystems, where worms and microbes show consumer–resource dynamics, vertebrate-like olfactory neurons allow nematodes such as *Caenorhabditis elegans* to sense indole and locate their food in the soil (Lee *et al.*, 2017) (Table 1). Indoles produced by soil microbes can modulate this foraging behaviour and pathogen-induced olfactory learning in *C. elegans* (Zhang *et al.*, 2005; Tanaka *et al.*, 2007; Lee *et al.*, 2017; Yang *et al.*, 2020). Microbial food resources can also be altered using chemicals/nanoparticles applied during environmental remediation. For instance, exposure to toxic nanoparticles can affect the indole-producing ability of *Escherichia coli* OP50, reducing its attractiveness as a food for *C. elegans* (Yang *et al.*, 2020).

(2) Indole compounds as biocontrol agents

In the soil, endophytes play an important role in plant growth. Various bioactive compounds have been reported from microbial endophytes with activities including antimicrobial, antiviral, immunomodulatory, nematicidal, etc. (Toghueo, 2019). By contrast, metabolites of nematodes mediate predator–prey interactions and stimulate the activity of IAA-producing bacteria resulting in higher levels in the soil (Li *et al.*, 2020). A tripartite interaction thus can exist between endophytes, nematodes, and plants: the fungal endophyte *Fusarium oxysporum* 162 secretes IAA that both directly repels root-knot nematode (*Meloidogyne incognita*) J2 larvae and acts indirectly *via* stimulation of plant defence mechanisms and vigour (Bogner *et al.*, 2017). Similar effects were shown for the bacterial endophyte *Bacillus cereus* BCM2 that can produce IAA and enhance plant vigour by activating defence-related genes in tomato (*Solanum lycopersicon*) (Hu *et al.*, 2018). Indole also serves as a precursor for deterrent metabolites such as benzoxazinoids produced by some plants as a defence against a variety of pests including aphids, caterpillars, and nematodes (Cna'ani, Seifan & Tzin, 2018; Erb & Reymond, 2019).

Indole-based compounds can lead to high nematode mortality and therefore have the potential to replace toxic

chemicals currently in use for the control of plant-parasitic nematodes. *In vitro* studies with several indole compounds revealed effective nematicidal activity against *C. elegans*, *Bursaphelenchus xylophilus*, and *M. incognita* (Bommarius *et al.*, 2013; Rajasekharan *et al.*, 2017, 2019, 2020). For example, 5-iodoindole led to organ disruption/shrinkage and the formation of multiple vacuoles that rapidly killed juveniles and freshly hatched nematodes (Rajasekharan *et al.*, 2017, 2020). The anthelmintic activity of these compounds was attributed to their antagonistic effect on glutathione *S*-transferase which suppresses the generation of reactive oxygen species (ROS) (Rajasekharan *et al.*, 2020). Root gall formation and egg mass deposition were both reduced by indoles, without impacting the physiological properties of tomato plants (Rajasekharan *et al.*, 2020).

(3) Indoles as a cue in insects

Insects, such as flies and mosquitoes, can recognize indole and 3-methylindole (skatole) (Dekel *et al.*, 2019) (Table 1). For insects, indole and skatole present in carrion and animal wastes are natural cues of food sources, mating, and oviposition sites. Skatole is behaviourally active in several insects; as a sex pheromone in dung beetles and as an attractant for scarab beetles, male euglossine bees, and flies (Urech *et al.*, 2004; Jürgens *et al.*, 2006). Indole receptors present in the antennae of mosquitoes play a key role in identifying olfactory cues – indole, skatole, or a mixture of these – and elicit a strong response (Dekel *et al.*, 2019). Indole, skatole and tryptamine are also known to be electrophysiologically active compounds that can be detected by the highly conserved olfactory receptors OR2 and OR10 (Table 2) in *Aedes aegypti*, *Culex quinquefasciatus*, and *Anopheles gambiae* (Pelletier *et al.*, 2010; Wang *et al.*, 2010; Chen & Luetje, 2014; Ruel *et al.*, 2019). These functionally conserved receptors have important roles in the life cycle of insects (Ruel *et al.*, 2019). Indole and skatole are well-established cues that enable the selection of oviposition sites and hosts (animal or plant) (Lee *et al.*, 2017; Dekel *et al.*, 2019). These cues are indicators of high microbial activity and are present in significant quantities in animal wastes, skin, and sweat. The mammalian skin microbiota plays a role in the production of these indolic kairomones (Meijerink *et al.*, 2000): sweat incubated for 2 days contained 27.9% indole and was more attractive to *A. gambiae* than freshly collected sweat samples. Similarly, indole-3-acetonitrile deters butterfly *Pieris rapae* oviposition, suggesting that insects can detect several indole compounds which influence their behaviour (Tomberlin *et al.*, 2017).

Flies show behavioural variation to different doses of indoles. Both sexes of adult flies are attracted to higher concentrations of indoles, while they are repelled at lower concentrations. However, non-gravid female flies show similar responses to all levels of indoles (Liu *et al.*, 2016). Interestingly, gravid females prefer fresh carrion, which is probably better suited to the development of their offspring compared to decomposing vertebrate carrion (Brodie *et al.*, 2016). Thus, the relative priority given by the female flies to nutrition or

Table 1. Indole and indole derivatives as inter-kingdom signalling molecules

Indole compound	Sources	Target species	Remarks	References
Plants				
Indole	<i>Escherichia coli tnaA</i> mutant (JW3686)	<i>Arabidopsis thaliana</i> Columbia-0 ecotype	Increased plant secondary root network by interfering with auxin signalling	Bailey <i>et al.</i> (2014)
	<i>Proteus vulgaris</i> JBLS202	Chinese cabbage	Promoted seedling growth	Yu & Lee (2013)
	<i>Proteus vulgaris</i> JBLS202	<i>A. thaliana</i> Col-0	Stimulated growth through auxin, cytokinin, and brassinosteroid (hormone-signalling) pathways	Bhattacharyya, Garlandine & Lee (2015)
	<i>Clathrus archeri</i> (stinkhorn fungus) and flowers of fly-pollinated angiosperms	Flies and beetles	Acted as an attractant to pollinators	Johnson & Jürgens (2010); Jürgens, Dötterl & Meve (2006)
Indole and indole-3-lactic acid	Endophytic bacteria	Duckweed	Promoted duckweed growth	Gilbert <i>et al.</i> (2018)
Nematodes				
Indole, indole-3-carboxaldehyde, and indole-3-acetic acid	<i>Escherichia coli</i>	<i>Caenorhabditis elegans</i>	Showed nematocidal activity	Bommarius <i>et al.</i> (2013)
Indole and indole derivatives	<i>E. coli</i>	<i>C. elegans</i>	Modulated chemotaxis, egg-laying behaviour and survival	Lee <i>et al.</i> (2017)
2-oxindole and 3,3'-dimethylene bisindole	<i>E. coli</i>	<i>C. elegans</i>	Showed repellent activity	Lee <i>et al.</i> (2017)
5-iodoindole	Synthetic	<i>Bursaphelenchus xylophilus</i>	Diminished fecundity, embryonic and juvenile lethality and locomotor behaviours	Rajasekharan <i>et al.</i> (2017)
	Synthetic	<i>Meloidogyne incognita</i>	Activated reactive oxygen species (ROS) at high doses, while induced methuosis at low dosage	Rajasekharan <i>et al.</i> (2020)
Melatonin	Natural and synthetic	<i>C. elegans</i>	Influenced locomotory behaviour and pathogen-induced olfactory learning	Tanaka <i>et al.</i> (2007)
Serotonin	Natural and synthetic	<i>C. elegans</i>	Modified olfactory preferences in <i>C. elegans</i> and promoted aversive learning <i>via</i> MOD-1 (modulation of locomotion defective) expressed in sensory interneurons	Zhang, Lu & Bargmann (2005)
Insects				
Indole	<i>Proteus mirabilis</i> and microbes	<i>Lucilia sericata</i> (blowfly)	Acted as an attractant for food and oviposition	Liu <i>et al.</i> (2016)
	Vertebrate host (host-microbe derived)	<i>Anopheles gambiae</i> (mosquito)	Acted as an attractant for blood meal	Meijerink <i>et al.</i> (2000)
	Microbes on human skin	<i>Culex quinquefasciatus</i>	Acted as an attractant for oviposition	Pelletier <i>et al.</i> (2010)
	<i>Zea mays</i> infected with <i>Spodoptera exigua</i> (beet armyworm)	<i>Cotesia marginiventris</i> (female parasitoid wasp)	Acted as an attractant for oviposition	Erb <i>et al.</i> (2015)
	Gram-positive and Gram-negative bacteria	<i>Aedes aegypti</i> (mosquito)	Acted as an attractant for oviposition	Ruel, Yakir & Bohbot (2019)
	<i>Holotrichia reynaudi</i> (female)	<i>Holotrichia reynaudi</i> (male)	Acted as an attractant for mating	Tomberlin <i>et al.</i> (2017)
Indole and 3-methylindole	Natural and synthetic	<i>Toxorhynchites amboinensis</i>	Attractant for oviposition site selection and/or plant-host-seeking	Dekel, Yakir & Bohbot (2019)
Indole derivatives	Natural and synthetic	<i>A. aegypti</i>	Controlled <i>A. aegypti</i> larvae population, without toxicity	Sousa <i>et al.</i> (2019)
Indole mixed with other chemicals	Natural and synthetic	<i>Chrysomya</i> spp. and <i>Lucilia cuprina</i>	Acted as an attractant	Urech <i>et al.</i> (2004)
Oxindole		<i>Spodoptera exigua</i>		

Table 1. (Cont.)

Indole compound	Sources	Target species	Remarks	References
	<i>Xenorhabdus hominickii</i> ANU101 (entomopathogenic bacterium)		Inhibited eicosanoid biosynthesis, haemocyte nodulation and PLA ₂ enzyme activity of the host	Sadekuzzaman <i>et al.</i> (2017)
Mammals				
Indole	Natural and synthetic	<i>Homo sapiens</i> (human enterocyte cell line)	Controlled inflammation and tightened epithelial cell junctions by suppressing nuclear factor kappa B (NF- κ B) and increasing expression of anti-inflammatory genes	Bansal <i>et al.</i> (2010)
		Germ-free mice	Increased expression of molecules associated with tight junction and adherens junction in gut epithelial cells	Shimada <i>et al.</i> (2013)
		Mice	Reduced the expression of proteins of the NF- κ B pathway and prevented the detrimental effects of lipopolysaccharide (LPS) in the liver	Beaumont <i>et al.</i> (2018)
Indoleacrylic acid	<i>Peptostreptococcus</i> sp.	Mice and human immune cells	Promoted anti-inflammatory responses and reduced oxidative stress in intestine	Wlodarska <i>et al.</i> (2017)
Indole-3-aldehyde	Gut microbe (<i>Lactobacillus</i>)	Mice	Protected against candidiasis and colitis through higher interleukin-22 (IL-22) production by aryl hydrocarbon receptor (AhR) activation	Zelante <i>et al.</i> (2013)
Indole 3-lactic acid	Bifidobacteria	Rat adrenal pheochromocytoma (PC12) cells	Worked as AhR agonist and induced neurite growth <i>via</i> extracellular signal-regulated kinase (Ras/ERK) pathway	Wong <i>et al.</i> (2020)
Indole 3-propionic acid	Microbiota-derived	Mice	Regulated endothelium-dependent vasodilation and activated the pregnane X receptor	Pulakazhi Venu <i>et al.</i> (2019)
	Gut microbiota	Human patients with chronic kidney disease (CKD)	Associated with renal function changes and protection against CKD	Sun <i>et al.</i> (2019a)
Indoxyl-3-sulfate	Gut microbiota	Human patients with CKD	Higher levels found in advanced chronic kidney failure	Yeh <i>et al.</i> (2016)
	Natural and synthetic	Human astrocytes	Triggered apoptosis by oxidative stress and inhibiting mitogen-activated protein kinase (MAPK) pathway	Lin <i>et al.</i> (2019b)
Others				
Indole	<i>Vibrio cholerae</i>	<i>Dictyostelium discoideum</i> (soil-dwelling amoeba)	Increased grazing resistance of <i>Vibrio</i> by inducing genes involved in virulence-associated secretion	Mueller <i>et al.</i> (2009)
	<i>Vibrio splendidus</i>	<i>Apostichopus japonicus</i> (sea cucumber)	Altered the expression of immune-related genes (<i>Ajp105</i> and <i>AjLBP/BPTI</i>) in host	Zhang <i>et al.</i> (2017)
	<i>Aquitalea</i> sp. (commensal bacteria)	<i>Dugesia japonica</i> (planarian)	Altered regenerative outcomes in planarians by controlling expression of patterning and Wnt pathway genes	Williams <i>et al.</i> (2020)
Indole and 3-formylindole	<i>Vibrio alginolyticus</i>	Barnacle <i>Balanus albicostatus</i> <i>Perna viridis</i> (green mussel)	Showed antifouling activity without any toxicity to barnacle cyprids Inhibited byssal thread production and showed antifouling activity without toxicity	Wang <i>et al.</i> (2017)

egg-laying is apparently involved in their attraction to indoles. In fresh canine faeces, indole is the most abundant semiochemical that functions as a 'food-indicator' instead of identifying an oviposition resource (Brodie *et al.*, 2016). Recently, it was observed that the presence of indole as a tertiary blend in chemoattractants extracted from rats enhanced

its attractiveness to male Asian tiger mosquito (*Aedes albopictus*) (Díaz-Santiz *et al.*, 2020). Besides acting as a signal, indole compounds can be lethal to insects. The entomopathogenic bacterium *Xenorhabdus hominickii* ANU101 transforms indole to oxindole which suppresses the insect immune response and nodule formation by fifth-instar larvae of *Spodoptera exigua*

Table 2. Microbial indole metabolites that act as ligands to eukaryotic receptors


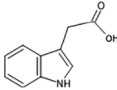
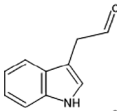
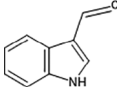
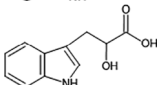
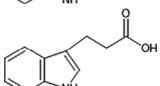
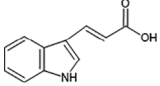
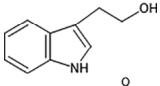
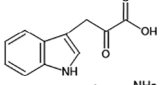
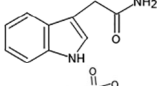
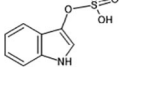

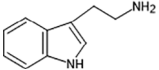
Indole compounds	Structure	Effect on eukaryotic receptor	Assay methods ^a	EC ₅₀ (μM)	References
Mouse and human					
Indole		Weak AhR agonist	Reporter gene assay (AZ-AHR cells)	1485	Vyhldalová <i>et al.</i> (2020)
		Human AhR agonist	AHR responsive luciferase reporter (HepG2 cells)	3	Hubbard <i>et al.</i> (2015a)
		Human AhR agonist	Induction of <i>CYP1A1</i> mRNA (CaCo-2 cells)	>1000	Jin <i>et al.</i> (2014)
		Human AhR antagonist	TCDD competition assay for induction of <i>CYP1A1</i> mRNA (CaCo-2 cells)	>500	Jin <i>et al.</i> (2014)
Indole-3-acetic acid		Weak AhR agonist	Reporter gene assay (AZ-AHR cells)	84.20	Vyhldalová <i>et al.</i> (2020)
		Human AhR agonist	Induction of <i>CYP1A1</i> mRNA (CaCo-2 cells)	37	Jin <i>et al.</i> (2014)
		Weak AhR agonist	Several AhR-dependent bioassay systems (Hepal c1c7 and HIL1.1c2)	500	Heath-Pagliuso <i>et al.</i> (1998)
		Weak AhR agonist	Yeast β-galactosidase assay (<i>S. cerevisiae</i>)	>200	Miller (1997)
Indole-3-acetaldehyde		AhR agonist	Wild-type and Ahr ^{-/-} mouse model	ND ^b	Zelante <i>et al.</i> (2013); Yu <i>et al.</i> (2019)
Indole-3-aldehyde		Weak AhR agonist	Reporter gene assay (AZ-AHR cells)	62.22	Vyhldalová <i>et al.</i> (2020)
Indole-3-lactic acid		Weak AhR agonist	Reporter gene assay (AZ-AHR cells)	82.03	Vyhldalová <i>et al.</i> (2020)
Indole-3-propionic acid		Weak AhR agonist	Reporter gene assay (AZ-AHR cells)	98.33	Vyhldalová <i>et al.</i> (2020)
		Weak agonist to human PXR Agonist to mouse PXR	Human PXR reporter gene (293 T cells) Mouse PXR reporter gene (293 T cells)	120 0.55	Venkatesh <i>et al.</i> (2014) Venkatesh <i>et al.</i> (2014)
Indole-3-acrylate		Weak AhR agonist	Reporter gene assay (AZ-AHR cells)	42.25	Vyhldalová <i>et al.</i> (2020)
Indole-3-ethanol		Weak AhR agonist	Reporter gene assay (AZ-AHR cells)	97.97	Vyhldalová <i>et al.</i> (2020)
Indole-3-pyruvic acid		Weak AhR agonist	Reporter gene assay (AZ-AHR cells)	98.53	Vyhldalová <i>et al.</i> (2020)
Indole-3-acetamide		Weak AhR agonist	Reporter gene assay (AZ-AHR cells)	99.95	Vyhldalová <i>et al.</i> (2020)
Indoxyl-3-sulfate		Active for human and Neanderthal AhR	Induction of <i>Cyp1a1</i> (nAhR and hAhR transfected BP8 cells)	0.0004 and 0.0012	Hubbard <i>et al.</i> (2016)
		Active for human and Neanderthal AhRs	Induction of <i>Cyp1b1</i> (AhR transfected BP8 cells)	0.0007 and 0.0008	Hubbard <i>et al.</i> (2016)
		Human AhR agonist	DRE-coupled luciferase reporter (human hepatoma cells)	ND	Schroeder <i>et al.</i> (2010)
		AhR agonist and partial AhR antagonist	Induction of <i>CYP1A1</i> mRNA (CaCo-2 cells)	ND	Jin <i>et al.</i> (2014)
		Weak AhR agonist	Reporter gene assay (AZ-AHR cells)	103.17	

Table 2. (Cont.)

Indole compounds	Structure	Effect on eukaryotic receptor	Assay methods ^a	EC ₅₀ (μM)	References
Skatole or 3-methylindole		Partial AhR agonist	Reporter gene assay (CaCo-2 cells)	ND	Vyhřídlová <i>et al.</i> (2020)
		AhR antagonist	Reporter gene assay (AZ-AHR cells)	19	Kurata <i>et al.</i> (2019)
		Weak activator and a partial agonist of AhR	Reporter gene assays (HepG2-C3 and human hepatocytes)	ND	Stepankova <i>et al.</i> (2018)
Tryptamine		Weak AhR agonist	Several AhR-dependent bioassay systems (Hep1c1c7 and H1L1.1c2)	200	Rasmussen <i>et al.</i> (2016)
		Weak AhR agonist	Reporter gene assay (AZ-AHR cells)	83.15	Heath-Pagliuso <i>et al.</i> (1998)
		Human AhR agonist	Induction of <i>CYP1A1</i> mRNA (CaCo-2 cells)	48	Vyhřídlová <i>et al.</i> (2020)
Insects, plants, and others					
Indole	AaegOR2	AaegOR2 agonist	Electro-antennogram (EAG) responses from female <i>Anopheles gambiae</i>	1.67×10^{-8}	Wang <i>et al.</i> (2010)
	AaegOR9	AaegOR2 agonist	Two-electrode voltage clamp of <i>Xenopus</i> oocytes expressing olfactory receptors	0.828	
	AaegOR9	Strong AaegOR9 agonist	Two-electrode voltage clamp of <i>Xenopus</i> oocytes expressing olfactory receptors	0.0048	Ruel <i>et al.</i> (2019)
Skatole or, 3-methylindole	AaegOR10	AaegOR10 agonist	Two-electrode voltage clamp of <i>Xenopus</i> oocytes expressing olfactory receptors	0.1	Ruel <i>et al.</i> (2019)
	AaegOR11	Weak AaegOR11 agonist	Electro-antennogram (EAG) responses from female <i>Anopheles gambiae</i>	2.43×10^{-5}	Wang <i>et al.</i> (2010)
	Tryptamine	Insect olfactory receptors (ORs)	ORs antagonist	<i>Xenopus</i> oocytes expressing olfactory receptors	1–48
Indole-3-carbinol	Auxin receptor (<i>A. thaliana</i>)	Auxin antagonist	Seedling germination and root elongation measurement	IC ₅₀ : 125	Katz <i>et al.</i> (2015)
Indole	Auxin receptor (<i>A. thaliana</i>)	Auxin antagonist	Seedling germination and root elongation measurement	IC ₅₀ : 125	Bailly <i>et al.</i> (2014)

AaegOR, *Aedes aegypti* odorant receptor; AhR, Aryl hydrocarbon receptor; EC₅₀, half maximal inhibitory concentration; IC₅₀, half maximal inhibitory concentration; PXR, pregnane X receptor; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin.

^aNote: assay methods to obtain EC₅₀ value vary among studies and may affect the results. Readers are suggested to refer to the original articles.

^bND: not determined.

(Sadekuzzaman *et al.*, 2017) (Table 1). This suppression can be reversed by arachidonic acid, suggesting that the bacterium inhibits phospholipase activity to induce host immunosuppression (Sadekuzzaman *et al.*, 2017). A few indole derivatives have been used to control *A. aegypti* larval populations (Sousa *et al.*, 2019). The intricacy of insect relationships with indoles could be beneficial in exploiting indoles as insecticides, insect repellents, or attractants.

(4) Influence of microbial indoles on marine organisms

In the marine environment, various organisms synthesize indole and related compounds (Table 1). Molluscs are well

known for their ability to produce valuable indole compounds including brominated indoles, which are used as dyes (purple colours) and in traditional medicines for reducing inflammation (Nongmaithem *et al.*, 2017). The hypobranchial glands are the source of halogenated indoles, however increasing evidence suggests that some of the conversion steps are carried out by symbiotic bacteria (Ngangbam *et al.*, 2015b; Baten *et al.*, 2016). It was suggested that the starting point of indole synthesis is tryptophan metabolism by symbionts; this was supported by transcriptomic data (Baten *et al.*, 2016). Brominated indoles produced by molluscs such as *Dicathais orbita* are usually stored as salts of choline esters and display muscle relaxing and analgesic activity (Nongmaithem *et al.*, 2017). The hypobranchial gland of

D. orbita contains *Vibrio* and other symbionts capable of producing indole and other enzymes that may contribute to the synthesis of the Tyrian purple precursor (Ngangbam *et al.*, 2015a).

Some bivalve molluscs produce byssal threads that allow them to attach firmly to ship hulls, piling, concrete, etc. (Wang *et al.*, 2017). Termed 'fouling', this is a serious threat to ships and power plants due to clogging of cooling systems. Controlling fouling using natural compounds is desirable as chemical treatments can have negative effects on non-target organisms. Interestingly, *Vibrio alginolyticus* PE2 associated with sea anemones (*Haliplanella* sp.) secretes antifouling compounds (Wang *et al.*, 2017). Indole and 3-formylindole were found to be the main bioactive compounds in a crude extract of *V. alginolyticus* PE2. Inhibition of byssal thread formation by green mussel (*Perna viridis*) and reduction in barnacle (*Balanus albicostatus*) larval settlement shows the potential for these non-toxic indole compounds to be used as natural antifouling agents (Wang *et al.*, 2017). This study reveals unexplored intricacies of marine ecosystems, but more detailed study will be necessary for a better understanding of the inhibitory mechanisms of indole.

Many indole-based interspecies interactions occur in the marine environment (Wang *et al.*, 2017; Helm, 2018). For example, skin ulceration syndrome in the sea cucumber *Apostichopus japonicus* is caused by pathogens such as *Vibrio splendidus* and *Pseudomonas* spp. (Zhang *et al.*, 2017). In the marine bacterium, *V. splendidus*, indole production is linked to cell density and the presence of glucose inhibits indole production due to cyclic AMP (cAMP)-based catabolite repression of the tryptophanase gene, *tnaA* (Zhang *et al.*, 2017). As an energy-conservation strategy, *V. splendidus* favours the operation of other metabolic pathways and indole-based signalling is used for the suppression of virulence genes such as *vsh*, *vsm*, and *ABC* (Zhang *et al.*, 2017). For *A. japonicus*, the presence of indole upregulated the expression of the immune-related genes for lipopolysaccharide-binding protein (*AjLBP*), bactericidal permeability-increasing protein (*AjBPII*), and a transcription regulator (*Ajp105*) that modulates the ROS response (Zhang *et al.*, 2017). This suggests a similar role of indole as an inter-kingdom signal mediating host–microbe interactions analogous to those discussed above for higher plants or animals. The study of bacterial symbionts associated with marine invertebrates and their biochemical interactions is still in its infancy. Several host–symbiont interactions in marine organisms such as sea anemones, deep-sea tubeworms, sponges, etc., are known to involve unique indole-related genes, and thus metagenomics and a pyrosequencing approach would be helpful to unveil their vast diversity.

(5) Indoles in plants defence

Plants utilize indole compounds for various purposes – as hormones, pollinator attractants, deterrent metabolites against herbivores, and aerial priming agents to alert neighbouring plants (Katz *et al.*, 2015; Cna'ani *et al.*, 2018). Floral

signalling is an important phenomenon in which the plant–pollinator interaction comprises visual (colour and shape) and olfactory (volatile compounds) cues. Floral volatiles contain indole compounds which have pleasant scents at low concentrations (e.g. jasmine) and act as attractants for flies and other insects for pollination (Zito, Dötterl & Sajeve, 2015). Indole elicits a strong antennal response in diverse insect classes such as hummingbird moths, houseflies, and mining bees, which detect the signal while foraging (Cna'ani *et al.*, 2018). Indole present in the floral scent bouquets of *Ipomopsis tenuituba* promotes the visit of nocturnal hawkmoths (Bischoff, Jürgens & Campbell, 2014). Through convergent evolution, some angiosperms have developed the ability to mimic a faecal or carrion scent to attract their pollinators (Johnson & Jürgens, 2010). Consequently, indole and skatole are part of the floral scent in some sapromyophilous plants such as *Orbea variegata* and *O. verrucosa* that rely heavily on olfactory cues for pollination (Table 1) (Johnson & Jürgens, 2010). Similarly, *Desmidorchis flava* flower scent includes a mixture of skatole, carboxylic acid, and isoprenoids. It is thought that sapromyophilous plant species employ a generalist strategy by producing several volatile compounds including indole, phenolics, fatty acids, etc., to attract pollinators from different species and to exploit their behaviour (Jürgens *et al.*, 2006).

Many tritrophic interactions involving bacteria–plant–insect (pollinators or herbivores) exist in nature (Ye *et al.*, 2018; Erb & Reymond, 2019). Negative plant–insect interactions occur in the context of mechanical injury or herbivore attack (Ye *et al.*, 2018). A blend of volatile compounds can be released by insect-infested plants [e.g. maize (*Zea mays*), rice (*Oryza sativa*), tea (*Camellia sinensis*) and cotton (*Gossypium hirsutum*)] which affect herbivores in different ways (Erb *et al.*, 2015; Ye *et al.*, 2021b). These compounds signal the presence of herbivores at the damaged site (and may thus attract herbivore enemies such as wasps) and also the decreased nutritional value of the damaged site, thereby inhibiting further herbivore attacks (Ye *et al.*, 2018). In addition, they also signal to herbivores regarding the synthesis of deterrent compounds. These volatile signals may also work as endogenous aerial priming agents for neighbouring plants (Erb *et al.*, 2015). Indole exposure induces defence mechanisms in nearby plants, providing them with enhanced resistance against likely herbivore attack (Erb *et al.*, 2015). Species-specific priming has been observed in herbivore-infested maize leaves that emit indole. This induced defence mechanisms in other leaves of the plant and in adjacent maize plants involving the enhanced synthesis of terpenes and phytohormones (jasmonic acid, abscisic acid, etc.) (Shen *et al.*, 2018). The exact mechanism by which such priming effects take place remains unclear and indole receptors in plants have yet to be identified. A recent study shows that indole boosts Ca^{2+} signalling and thereby enhances jasmonate-dependent defence and resistance in tea plants (Ye *et al.*, 2020).

Some plants 'outsource' the production of indole compounds through their interaction with endophytic microbes

that are involved in plant growth and defence systems (Gilbert *et al.*, 2018). Thus, conspecific priming by indole or its derivatives may have evolved as a private messaging system to warn close kin and a plant's own tissues. The signal could be received by receptor proteins similar to that found in the bacterium *Stigmatella aurantiaca* (Erb *et al.*, 2015). Signalling would be followed by a chain of events leading to the synthesis of phytohormones or other deterrent indole metabolites (Erb *et al.*, 2015; Erb & Reymond, 2019). Since indole compounds are involved in a variety of plant functions, they are considered key factors in determining plant fitness (Cerboneschi *et al.*, 2016; Cna'ani *et al.*, 2018). Therefore, the exploitation of indole-based signalling for the manipulation of plant–insect interactions has drawn significant attention from agricultural scientists. Indole is also a substrate for IAA, a well-studied plant hormone that can be synthesized by plants as well as rhizobacteria, and influences plant growth (Yu & Lee, 2013; Bhattacharyya *et al.*, 2015). Several reviews have considered bacterial IAA and its role in plant physiology in detail (Cerboneschi *et al.*, 2016; Leyser, 2018; Blázquez, Nelson & Weijers, 2020).

(6) Role of indoles in the healthspan of eukaryotes

Indole-producing microbes have been reported to extend the healthspan (the length of time that organisms are healthy, not just alive) of a wide range of non-chordates (*C. elegans*, *Drosophila melanogaster*) and chordates (e.g. mice) (Sonowal *et al.*, 2017). The conserved AhR ligands seem to play a crucial role, not only in detecting the xenobiotic compounds but also in identifying and relaying signals that induce genes responsible for oogenesis, thereby extending fecundity and reproductive span in worms (Sonowal *et al.*, 2017). Indole-regulated genes showing healthspan augmentation in *C. elegans* were quite different from those involved with longevity (Sonowal *et al.*, 2017). Chronic, low-grade inflammation occurs as part of the aging process and contributes to the pathogenesis of age-related diseases and consequent frailty. Geriatric mice lose goblet cells that protect the gut epithelium by secreting mucin. This may be a consequence of decreased levels of anti-inflammatory cytokines such as interleukin-10 (IL-10), or impairment of the intestinal barrier's ability to reject inflammatory antigens (Powell *et al.*, 2020). Indole-3-carboxaldehyde secreted by the intestinal microbiota was found to increase IL-10 levels via the AhR and restore depleted goblet cells independent of type-I IFN or IL-22 signalling (Powell *et al.*, 2020).

Indoles produced by commensal bacteria show protective effects against stressors in mice. Aged mice colonized with *E. coli* K12 showed better body mass maintenance and improved survival with higher urinary levels of I3S compared to controls (Sonowal *et al.*, 2017). The positive effect of indoles was seen in both geriatric and young mice. While the positive influence of indole compounds on the gut immune system is largely through the AhR, the extension of healthspan cannot be explained solely through the AhR pathway and this requires further research.

These few studies suggest a therapeutic role for indoles in limiting age-associated systemic inflammation and establishing epithelial homeostasis associated with aging (Powell *et al.*, 2020). Indoles could thus be an attractive alternative to faecal transplants, oral probiotic treatments, and other dietary interventions. However, the augmentation of bioactive indole *via* the diet or its exogenous administration and any effects of this on the extension of human healthspan or reduction of frailty in humans remains to be investigated. Variation in gut microbiota according to dietary habits, race, and geographical region are likely to complicate such studies. Metabolomic studies, focused on the identification of compounds linked with longitudinal changes in inflammatory markers, would be helpful in elucidating the underlying mechanisms involved in aging.

III. FUNCTIONAL RELATIONSHIPS BETWEEN GUT INDOLES AND DIFFERENT ORGANS

Indole and indole-containing compounds (both natural and synthetic) are known to influence AhR-mediated signalling activities (Seok *et al.*, 2018; Stepankova *et al.*, 2018; McCarville *et al.*, 2020; Vyhldalová *et al.*, 2020). Due to the absence of the shikimate pathway in animals, the diet and microbiota are the primary sources of indole. Several indole-based AhR ligands are generated in the stomach due to the action of gastric acid on glucobrassicin (Hubbard *et al.*, 2015a). Most of the tryptophan generated through proteolytic activities is absorbed in the small intestine and transported to various organs for conversion to endogenous AhR ligands such as xanthurenic acid, kynurenine, and kynurenic acid (Hubbard *et al.*, 2015b; Roager & Licht, 2018). However, significant quantities of tryptophan do reach the colon, where it is metabolized by gut microbes, which then release indole and indole derivatives such as IAA, indole-3-aldehyde, indole-3-lactic acid, indole-3-propionic acid, skatole, tryptamine, and tryptanthrin (Roager & Licht, 2018).

Human faeces may contain at least 2770 prokaryotic species classified into 11 different phyla, the majority (>90%) of which belong to *Firmicutes*, *Proteobacteria*, *Bacteroidetes*, and *Actinobacteria* (Cryan *et al.*, 2019). More than 85 bacterial species are known to produce indole in large quantities (Lee & Lee, 2010). Their involvement has been established in the body's inflammatory response, blood pressure, neurological functions, multiple sclerosis, neuroprotection in Alzheimer's disease, oxidative stress in the ischemic hippocampus, immune system, and behaviour as well as in the healthspan of higher eukaryotes (Karu *et al.*, 2016; Cheng *et al.*, 2018; Roager & Licht, 2018; Konopelski *et al.*, 2019; Wu *et al.*, 2021). Germ-free mouse models have been used to understand the role of microbes in host physiology. Indole and indole-3-propionic acid are agonists to the receptors AhR and PXR, respectively (Vyhldalová *et al.*, 2020) (Table 2). Activation of these sensors also activates the transcription of drug-metabolizing cytochromes P450 (CYPs)

such as CYP1A1, CYP1A2, and CYP3A4. Some indole compounds, such as indole-3-propionic acid, have been found only after intestinal colonization by *Clostridium sporogenes* (Wikoff *et al.*, 2009). In patients with active colitis, reduced levels of indole-3-propionic acid provide evidence for its protective effect against intestinal inflammation (Alexeev *et al.*, 2018). Recently, indole-3-lactic acid was reported to function as an AhR agonist, increasing nerve growth factor-induced neurite outgrowth plausibly *via* the extracellular signal-regulated kinase (Ras/ERK) pathway (Wong *et al.*, 2020). Skatole can be inhaled in significant quantities during cigarette smoking and can function as a pulmonary toxin. It induces AhR-regulated genes (e.g. *CYP1A1*) in human bronchial cells (Rasmussen *et al.*, 2016).

Tryptophan and its metabolites, usually considered as building-blocks of proteins, thus represent an important group of metabolites that orchestrate host physiology by various mechanisms (Agus *et al.*, 2018; Roager & Licht, 2018). Cross-talk between gut indole metabolites and the host organs *via* the gut–kidney, gut–liver, gut–brain, and gut–immune axes significantly influences the initiation and/or progression of several metabolic disorders, some of which are discussed below.

(1) Gut–immune axis

Microbial activity in the mammalian intestine results in a large repertoire of bioactive metabolites that influence the mucosal immune system. A recent study showed that four *Clostridium* species and *Peptostreptococcus anaerobius* encode phenyllactate dehydratase, an enzyme that catalyses the production of indole-3-propionic acid from tryptophan (Dodd *et al.*, 2017). Subsequently, the tryptophan metabolic pathways of *C. sporogenes* were manipulated to demonstrate that indole-3-propionic acid decreases intestinal permeability and regulates intestinal homeostasis plausibly *via* the PXR and TLR4 pathway (Venkatesh *et al.*, 2014; Dodd *et al.*, 2017). The regulation of PXR, itself an essential regulator of TLR4-mediated intestinal barrier function (innate immunity and its response to xenobiotic injury), is intrinsically linked with gut microbiota-derived indole metabolites such as indole-3-propionic acid (Venkatesh *et al.*, 2014). Besides indole-3-propionic acid, indole-3-aldehyde produced by *Lactobacilli* inhibits the colonization of *Candida albicans* and protects from mucosal inflammation *via* AhR recognition (Zelante *et al.*, 2013). The AhR-dependent increase in IL-22 expression provides mucosal protection from inflammation *via* the host innate immune system. Involvement of IL-18 as a cross-regulator of IL-22 production suggests the regulation of both innate as well as adaptive immunity by microbial indole-3-aldehyde (Borghini *et al.*, 2019). Skin microbiota also produces indole-3-aldehyde that works in an AhR-dependent manner and attenuates skin inflammation by inhibiting the expression of thymic stromal lymphopoietin in keratinocytes (Yu *et al.*, 2019). Another indole derivative produced by *Lactobacillus*, indole-3-lactic acid, activates AhR, downregulates the transcriptional factor

Th inducing POZ-Kruppel factor (Thpok), and reprograms intraepithelial lymphocytes (IELs, CD4⁺ T cells) into double-positive IELs (CD8aa⁺CD4⁺) in mice (Cervantes-Barragan *et al.*, 2017). Thus, a single bacterial species (*Lactobacillus reuteri*) can reprogram intraepithelial CD4⁺ T cells into immunoregulatory T cells, although other microbes, diet, or self-antigens would be required for the expansion of the T cell receptor repertoire among CD4⁺ IELs that convert to double-positive IELs (Cervantes-Barragan *et al.*, 2017).

Other indole derivatives were anticipated to possess similar effects, however, this AhR-mediated T-cell activation is distinct from those where the AhR influences T-cells with regulatory functions, intraepithelial $\gamma\delta$ T cells, and dendritic cells (Cervantes-Barragan *et al.*, 2017). The microbiota–AhR axis thus represents a unique strategy in which coevolving commensals can fine-tune host mucosal reactivity contingent on tryptophan catabolism (Zelante *et al.*, 2013). High salt consumption has been suggested to influence the gut–immune axis *via* T helper 17 (TH17) cells and a reduction in the *Lactobacillus* spp. population (Wilck *et al.*, 2017).

Another metabolite, 5-hydroxytryptamine (5-HT or serotonin), which has immunoregulatory functions, is a key neurotransmitter, a potent secretagogue, and an important regulatory factor that mediates intestinal motility and secretion (Wishart, 2019). 5-HT secreted by enterochromaffin cells (ECs) also plays a role in modulating the immune system by communicating through its cognate receptors present in immune cells (both innate and adaptive) such as dendritic cells, lymphocytes, and macrophages. The significant role of the gut microbiota on serum 5-HT levels was recently established when gnotobiotic germ-free mice exhibited significantly lowered serum 5-HT levels compared to colonized mice (Yano *et al.*, 2015). Endogenous bacteria can enhance the synthesis of 5-HT in colonic ECs, releasing it to the mucosa and lumen (Yano *et al.*, 2015). Indeed *E. coli*, *Streptococcus* spp. and *Corynebacterium* spp. can convert tryptophan to 5-HT *in vivo* while other bacteria (e.g. *Bacteroides fragilis* and *Bacteroides uniformis*) are known to affect 5-HT levels in serum as well as in the colon (Yano *et al.*, 2015). Microbial alteration of 5-HT can regulate the gut microenvironment. For example, disturbance to the enteric flora can result in an imbalance of 5-HT levels while supplementation of probiotics reverses this effect. Therefore, gut–microbial eubiosis is a preferred approach to manage peripheral 5-HT levels and consequently disease symptoms. Another indole-containing compound, melatonin, is also synthesized from tryptophan by gut mucosa ECs. Due to its immunomodulatory effects, particularly the regulation of TH17 cell differentiation, melatonin is considered a potent compound for the treatment of IBD (Esteban-Zubero *et al.*, 2017). Therefore, a deeper understanding of the way indole derivatives regulate the immune system may lead to the identification of novel targets for intervention in diseases such as IBD.

(2) Gut–kidney axis and kidney disease

The gut–kidney axis is associated with chronic kidney disease (CKD) and acute kidney injury. An association of

gut microbes with comorbidities in CKD has been demonstrated: CKD patients showed a higher population of *Enterobacteria* and lower *Bifidobacteria* (correlating with higher faecal indole and serum I3S levels) (Ellis *et al.*, 2016). Colonic indole levels can influence portal and arterial blood pressure, while higher doses (1000 mg/kg body mass) result in toxic tubulopathy and renal hyperemia in rats (Huć *et al.*, 2018a, 2018b). Gut microbial metabolism can generate uremic toxins among which IAA and I3S are notoriously associated with CKD (Yeh *et al.*, 2016; Chen *et al.*, 2019b). IAA and I3S are common effectors influencing the physiology of the kidney and other end-organ toxicity (Dou *et al.*, 2015; Ellis *et al.*, 2016; Shen *et al.*, 2016) (Fig. 1).

These uremic solutes (IAA and I3S) activate inflammation and induce endothelial dysfunction and oxidative stress. I3S is a co-metabolite of indole synthesized by hepatic enzymes in the host liver. Normally I3S is excreted in the urine, but its steady accumulation is linked to the progression of renal dysfunction (Ochi *et al.*, 2015). Due to its affinity for albumin, its removal by haemodialysis is difficult. In acute kidney injury, I3S enhances the expression of IL-1 β -induced E-selectin by the ROS–mitogen-activated protein kinases (MAPKs)–nuclear factor kappa B (NF κ B)–activator protein 1 (AP-1) pathway (Shen *et al.*, 2016). In the human hepatoma HepG2 cell line, the expression of fetuin-A was suppressed by I3S *via* AhR. I3S also induced p38 MAPK phosphorylation and ROS production (Ochi *et al.*, 2015). Therefore, serum levels of IAA and I3S can be used to follow the cardiovascular events and predict mortality in CKD patients (Zgoda-Pols *et al.*, 2011; Dou *et al.*, 2015).

Since I3S is an endogenous AhR ligand (Table 2), it suppresses hepatic fetuin-A expression thereby raising the risk of cardiovascular damage and mortality in dialysis patients (Ochi *et al.*, 2015). I3S is a protein-bound uremic toxin associated with glucose intolerance and promotes vascular calcification through the liver X-receptor (LXR) signalling pathway and glucose transporter 1 (GLUT1) expression (Kappel & Federici, 2019). Based on *in vitro*, *in vivo*, and clinical data, several routes by which I3S can influence the progression of CKD have been identified (Ellis *et al.*, 2016; Wishart, 2019; Chen *et al.*, 2019b). Higher levels of inflammatory biomarkers (IL-6 and glutathione peroxidase) in CKD patients were found to be associated with I3S (Chen *et al.*, 2019b), while low urinary levels of I3S after transplantation were indicative of microbial dysbiosis and a higher risk of graft-versus-host-disease (Weber *et al.*, 2015). Since indoles are largely produced by gut microbes, pre- and probiotics could provide a useful approach to reduce uremic toxins (I3S, *p*-cresyl sulfate and IAA). A trial investigation involving combined prebiotic and probiotic treatments resulted in lower levels of uremic toxins. Similarly, serum levels of I3S were reduced by the oral administration of p-inulin (Chen *et al.*, 2019b).

It is essential to note that a reduction of protein in the diet could be effective in reducing serum levels of uremic toxins but may not prove an efficient preventive measure since bacteria can synthesize tryptophan. The gut microbial

composition controls the level of uremic toxins (I3S and *p*-cresyl sulfate) in plasma. Vancomycin treatment selectively changes the composition of the gut microbiome with a concomitant decline in I3S levels (Nazzal *et al.*, 2017) and indoles influence antibiotic resistance and bacterial persistence (Lee *et al.*, 2010; Lee *et al.*, 2016). Thus, the use of antibiotics could represent an important strategy in reducing uremic toxin levels; however, indiscriminate use of such drugs may lead to dysbiosis with potentially harmful results. In contrast to uremic toxins, another indole metabolite, indole-3-propionic acid suppresses kidney fibrosis induced by I3S (Yisireyili *et al.*, 2017), and protects renal function, possibly due to its antioxidant and hydroxyl radical scavenging activity (Sun *et al.*, 2019a).

(3) Crosstalk between gut indoles and the liver

In recent years, gut microbes have emerged as regulators of liver physiology *via* the gut–liver axis. Apart from the gut, the liver is the organ with most exposure to microbial metabolites. Gut dysbiosis in patients with alcoholic hepatitis is associated with liver inflammation. In fact, the regulation of intestinal barrier function plays a key role in the interaction between gut microbes and the liver (Beaumont *et al.*, 2018). Among the tryptophan-derived indole compounds generated in the gut, levels of indole are higher (millimolar concentrations) than those of other indolics (<10 μ M) (Delzenne *et al.*, 2019). Nevertheless, their ability to control mucosal immunity and intestinal permeability apparently limits the translocation of harmful microbial components [e.g. lipopolysaccharides (LPS)] from the gut to the liver. Oral administration of indole prevents inflammation, alleviates LPS-induced alterations of cholesterol metabolism, and regulates the expression of liver X receptors in mice (Delzenne *et al.*, 2019), suggesting that indole could be used in the treatment of liver inflammatory disorders. *Ex vivo*, indole also reduces hepatic inflammation in LPS-treated livers of genetically obese mice (Delzenne *et al.*, 2019). Although indole and indole co-metabolites can modulate AhR activation (Table 2), only indole has a demonstrated ability to reduce hepatic inflammation (Beaumont *et al.*, 2018). There is a known correlation between a high-fat diet and the caecal and hepatic concentration of indole metabolites, possibly due to gut microbial metabolism. Supplementation of *L. reuteri* can reverse hepatic metabolic alterations in an AhR-dependent manner (Krishnan *et al.*, 2018; Delzenne *et al.*, 2019). Circulating levels of indole can be an indicator of liver fat content in human subjects, and was found to be inversely correlated with body mass index. Administration of indole to animals on a high-fat diet significantly reduced hepatic steatosis and inflammation (Ma *et al.*, 2020). Experiments conducted on different cell cultures further revealed that indole treatment reduces fat deposition and proinflammatory responses (Ma *et al.*, 2020). Human hepatocytes show AhR-dependent increases in *CYP1A1*, *CYP1A2*, and *CYP1B1* expression after treatment with skatole (a partial AhR agonist) demonstrating that liver

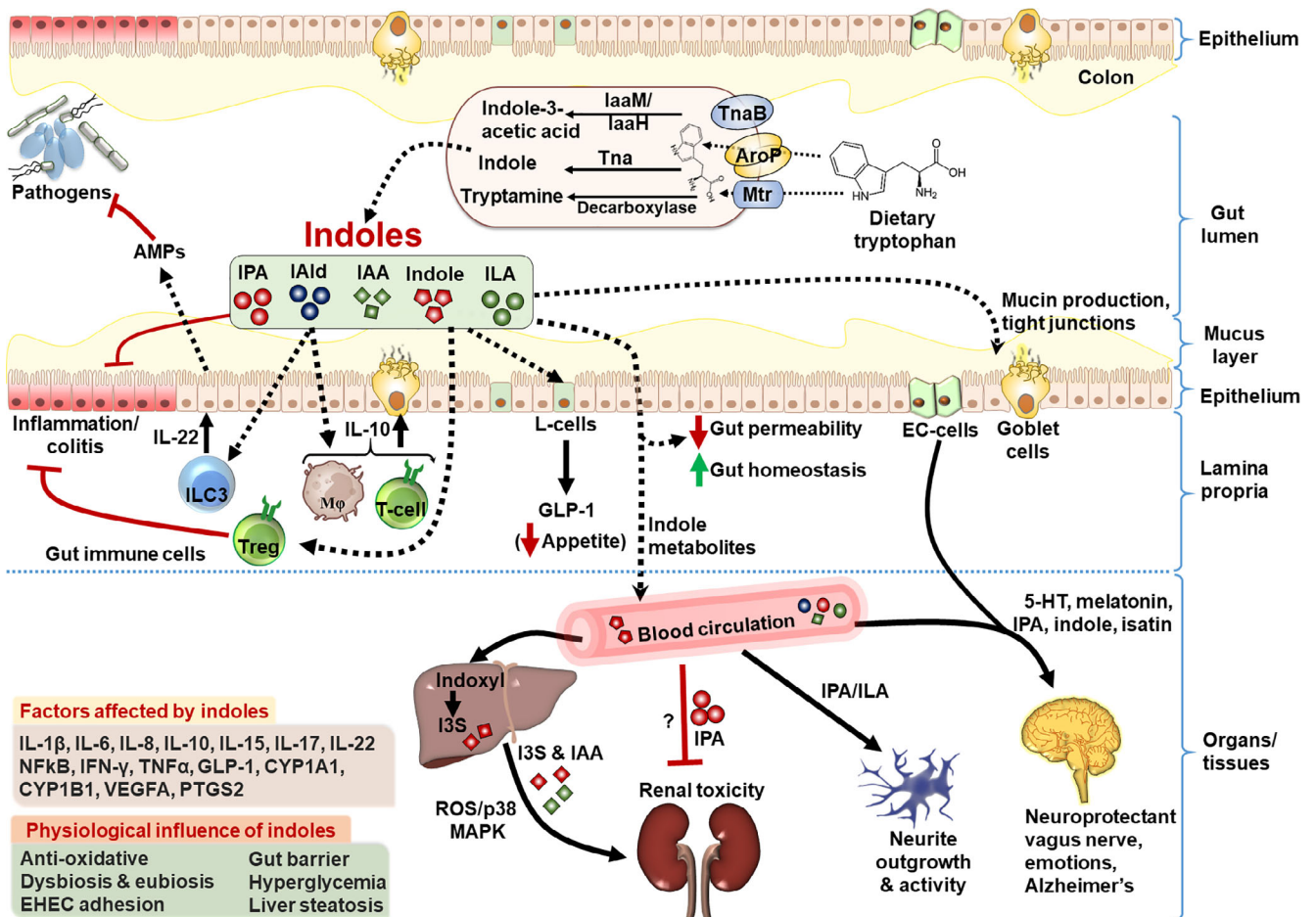


Fig 1. Roles of gut microbe-derived indoles in human physiology. Gut microbes regulate the biosynthesis of a range of indole compounds using dietary tryptophan. The microbial indole metabolites include indole, indole-3-acetic acid, indole-3-lactic acid, indole-3-propionic acid, indole-3-aldehyde, etc. Local effects of these indoles include induction of goblet cells to produce mucin, activation of immune cells in the lamina propria of the gut, and signalling intestinal cells to secrete antimicrobial peptides. Consequently, indoles prevent colonization of pathogens (i.e. dysbiosis), reduce gut permeability through tight junctions, inhibit inflammation *via* the release of anti-inflammatory cytokines, and maintain gut homeostasis. Indole also modulates secretion of incretin hormone (GLP-1) by enteroendocrine L cells hence having a role in microbial indole in host appetite, nutrient absorption and glucose metabolism. Indoles reach systemic organs through the circulatory system where host enzymes (mostly in the liver) may convert them into other bioactive compounds. For example, indoxyl-3-sulphate (I3S) and indole-3-acetic acid are considered uremic toxins that can cause kidney damage. By contrast, indole-3-propionic acid acts as an antioxidant, counteracting the negative effects of uremic toxins. In addition, indole-3-propionic acid helps in neurite outgrowth, and indole compounds function as a neuroprotectant. AMPs, antimicrobial peptides and proteins; 5-HT, 5-hydroxytryptamine; AroP: aromatic amino acid transport protein; CYP, cytochrome; EC, enterochromaffin cell; EHEC enterohemorrhagic *E. coli*; GLP-1, glucagon-like peptide 1; IAA, indole-3-acetic acid; IaaM, tryptophan monooxygenase; IaaH, indole-3-acetamide hydrolase; IAld, indole-3-aldehyde; IL, interleukin; ILA, indole-3-lactic acid; ILC3, type 3 innate lymphoid cells; IFN, interferon; IPA, indole-3-propionic acid; I3S, indoxyl-3-sulfate; MAPK, mitogen-activated protein kinase; M ϕ , macrophage; Mtr, tryptophan-specific permease; NF κ B, nuclear factor-kappa B; PTGS2, prostaglandin-endoperoxide synthase 2; ROS, reactive oxygen species; Tna, tryptophanase; Treg, regulatory T cells; VEGFA, vascular endothelial growth factor.

homeostasis can be regulated by gut metabolites *via* the AhR pathway (Table 2) (Rasmussen *et al.*, 2016). It has been suggested that indole-mimetic activation could be a viable therapeutic approach for the treatment of non-alcoholic fatty liver disease (NAFLD)-associated inflammation.

Microbial indole is transported *via* the portal vein and regulates hepatic physiology. Hepatic enzymes [cytochrome P450 (CYP2E1) and sulfotransferase (SULT1A1)] convert

indole to I3S (Yisireyili *et al.*, 2017; Delzenne *et al.*, 2019). A study carried out with germ-free mice demonstrated the involvement of microbes in the production of I3S and other compounds that accumulate in uremia (Wikoff *et al.*, 2009). Tryptophanase catalyses the formation of indole, which is absorbed and sulfated by the liver (Wong *et al.*, 2014). By contrast, IAA reduces the expression of pro-inflammatory cytokines [tumor necrosis factor- α (TNF- α), IL-1 β , and

monocyte chemoattractant protein-1 (MCP-1)], messenger RNA (mRNA) levels of lipogenesis proteins, and fatty acid deposition in hepatocytes *in vitro* by targeting AhR signalling (Krishnan *et al.*, 2018; Delzenne *et al.*, 2019). Indeed, IAA and tryptamine are key metabolites that facilitate the cross-talk between the host and its microbiome. In the intestinal lamina propria, IL-22-producing innate lymphoid cells are recovered by IAA. Eventually, these cells synthesize antimicrobial proteins (e.g. regenerating family member 3 gamma, REG3G) *via* an AhR-dependent mechanism (Hendrikx & Schnabl, 2019). The exogenous administration of IAA also reduces bacterial translocation to the liver and provides protection against alcoholic steatohepatitis (Hendrikx & Schnabl, 2019). Thus, in addition to the gut-immune axis, microbial indole derivatives also extend protective functions to the liver *via* the gut-liver axis in inflammatory conditions such as alcoholic and non-alcoholic steatohepatitis.

In addition, indole-3-propionic acid is a known free radical scavenger, protecting neurons and hepatic microsomal membranes from oxidative stress (Dodd *et al.*, 2017; Ji *et al.*, 2019). Metagenomic and metabolomic approaches could delineate the bacterial species capable of producing indole metabolites with proven hepatoprotective effects. To dissect the underlying mechanisms (receptors, effector cells, etc.), large-cohort studies with careful monitoring of the dietary intake of the participants will be necessary.

(4) Microbiota-gut-brain axis

The concept of a microbiota-gut-brain axis has emerged recently through extensive research (Cryan *et al.*, 2019). Increased indole levels in the gut are associated with vagus nerve activation and were shown negatively to influence emotional behaviours in rats (Jaglin *et al.*, 2018). Tryptophan-derived microbial metabolites are involved in the microglial control of astrocytes in the central nervous system (Rothhammer *et al.*, 2016). Isatin (1H-indole-2,3-dione), another microbe-derived indole metabolite, affects anxiety-like behaviour in rodents (Jaglin *et al.*, 2018). Although micromolar concentrations of isatin have been observed in the blood and tissues, its exact origin (microbial, or from both host and microbe), and potential impact on the host brain, health, and behaviour remains unclear (Cryan *et al.*, 2019). It has been demonstrated that genes for enzymes involved in indole metabolism by eukaryotes may have arisen from horizontal gene transfer from bacteria, with some such transfers occurring after the divergence of animals from fungi (Cryan *et al.*, 2019). Microbial endocrinology-based media are being established to investigate potential mechanisms by which neuroendocrine signals of microbial origin function in a host-simulated environment. Tryptophan catabolites originating from microbial activity can control intestinal motility and vagal neuronal activation through the receptor transient receptor potential ankyrin A1 (TrpA1) of activated zebrafish (*Danio rerio*), mouse, and human enteroendocrine cells. They also induce 5-HT secretion in mouse and human (Ye *et al.*, 2021a).

IV. ROLES OF INDOLES IN HUMAN HEALTH AND DISEASE

(1) Microbial indoles in inflammatory bowel disease

The consumption of animal protein in large quantities is associated with dysbiosis and raises the risk of IBD for example in ulcerative colitis and Crohn's disease (Kurata *et al.*, 2019; Scott, Fu & Chang, 2020; Jing *et al.*, 2021). In animal models and in patients with IBD, the apoptotic rates of intestinal epithelial cells are elevated. Interestingly, during a psychobiotic study conducted at a specific gut location, a mucin-utilizing *Peptostreptococcus* sp. was found to produce indole-acrylic acid near the gut epithelium and improve barrier function (Wlodarska *et al.*, 2017). The treatment of germ-free mice with indole demonstrated enhanced epithelial tight junction functioning and reduced weight loss in a murine colitis model (Shimada *et al.*, 2013) and similar results were seen in human intestinal epithelial cells (Bansal *et al.*, 2010) (Fig. 1). The nuclear receptor PXR is considered a novel drug target for IBD. In this context, the role of indole-3-propionic acid in regulating intestinal barrier integrity *via* a PXR-dependent mechanism seems intriguing (Alexeev *et al.*, 2018). Indole-3-propionic acid also acts as an AhR (an essential regulator of gut immunity) agonist that activates AhR and shows anti-inflammatory effects in the mouse colitis model (Aoki *et al.*, 2018). The immunomodulatory activity of indole-3-propionic acid in preventing chronic inflammation includes a reduction in T helper (Th1) cytokine levels and enhanced levels of *Il-10* expression in the colon (Aoki *et al.*, 2018). A study conducted on the mouse model of colitis with other microbial indole metabolites (indole-3-aldehyde, indole-3-pyruvate, and indole-3-ethanol) revealed AhR-dependent regulation of intestinal barrier functions. These metabolites maintain the integrity of the apical junctional complex and actin regulatory proteins, including myosin IIA and ezrin (Scott *et al.*, 2020).

Indole metabolites appear to function through AhR and/or PXR-based signalling (Table 2), increase IL-22, IL-10 levels, and enhance mucosal healing by activating innate and adaptive lymphoid cells (Chen *et al.*, 2020). On the contrary, skatole is an inhibitor of CYP1A1, resulting in reduced production of glucocorticoids required for intestinal homeostasis (Gao *et al.*, 2018) (Fig. 1). Skatole is also an agonist to AhR that induces dysfunction and death of intestinal epithelial cells, in addition to activation of p38 (Kurata *et al.*, 2019). Therefore, supplementation of tryptophan or animal protein in IBD patients may not be beneficial (and could be detrimental) if indole or indole-3-propionic acid-producing gut-microbes are not abundant. Further insights towards a better understanding of the effects of microbial indoles on host defence systems may help to identify potential candidates for prophylactic and/or therapeutic treatment for IBD.

(2) Indoles in the progression of diabetes, obesity, and associated ailments

An increasing amount of evidence from studies on murine models and human subjects has suggested that intestinal

dysbiosis is linked to diabetes and obesity. The crosstalk between gut microbe-derived indole and intestinal enteroendocrine L cells modulates the secretion of glucagon-like peptide 1 (GLP-1), an anorectic gut hormone (Chimerel *et al.*, 2014). Incretin secretion, which functions in the regulation of appetite, nutrient absorption, and glucose homeostasis and consequent enhancement of GLP-1, is being considered for the treatment of type 2 diabetes. The intricacy of the crosstalk depends on the concentration of indole, and the time period since indole exposure affects intracellular ATP levels (Chimerel *et al.*, 2014). In addition, gut indole levels are highly dependent on the diet, a sugar-rich diet lowers indole synthesis (possibly *via* catabolic repression of tryptophanase) while a protein-rich diet promotes indole production (Chimerel *et al.*, 2014; Lee *et al.*, 2015b) (Fig. 1).

Higher indole-3-propionic acid levels were associated with reduced risk of development of type 2 diabetes in a Finnish diabetes prevention study (de Mello *et al.*, 2017), while reduced levels were noticed in obese type 2 diabetes subjects (Jennis *et al.*, 2018). Its antioxidant activity was possibly responsible for protecting pancreatic β -cells from damage due to oxidative and metabolic stress (de Mello *et al.*, 2017). Dietary fibre intake directly influences serum indole-3-propionic acid level, negatively affects high sensitivity C-reactive protein levels (de Mello *et al.*, 2017; Tuomainen *et al.*, 2018) and improves insulin secretion, thereby lowering the risk of type 2 diabetes (Tuomainen *et al.*, 2018). In rat models, indole-3-propionic acid improved glucose metabolism and lower fasting glucose level by 0.42 M, showing its potential in the treatment of metabolic diseases linked to insulin resistance (Abildgaard *et al.*, 2018). The fine-tuning of indole secretion, epithelial PXR, and TLR4 at appropriate levels is important for intestinal barrier function, and they have been linked to the pathogenesis of disease states such as IBD, type 1 diabetes, autism, allergies, asthma, etc. (Venkatesh *et al.*, 2014) and the regulation of endothelium-dependent vasodilation (Pulakazhi Venu *et al.*, 2019). Metabolic endotoxemia (intestinal permeability to bacteria or their products) contributes to several disease pathologies, including type 2 diabetes and obesity. Thus indole (or indole-3-propionic acid)-producing bacteria may be a means to maintain intestinal barrier integrity (Jennis *et al.*, 2018) (Fig. 1).

Low faecal levels of indole compounds in obese individuals reveal low AhR agonist activity (Natividad *et al.*, 2018) similar to mice on high-fat diets, which exhibited reduced caecal and hepatic concentrations of indole, IAA, and tryptamine (Krishnan *et al.*, 2018; Natividad *et al.*, 2018). Indole compounds produced by *L. reuteri* reversed the hepatic alterations by improving incretin secretion and the gut barrier function in diet-induced obese mice (Natividad *et al.*, 2018). Interestingly, when *L. reuteri* was introduced in mouse models, IAA and indole-3-lactic acid were found to stimulate T-cell development and thus help develop intestinal immune tolerance to potential antigens present in the diet (Cervantes-Barragan *et al.*, 2017). Obesity in women can have significant consequences on follicular fluid during the pre-conception period.

Due to its antioxidant activity, indole-3-propionic acid levels in the serum and follicular fluid were significantly correlated in obese women. Although because this indole compound can also be produced by microbes within the vagina, further study is necessary to determine the origin of these microbial metabolites (Ruebel *et al.*, 2019). Thus, indole and indole-producing gut microbes are associated with the progression of metabolic diseases such as type 2 diabetes and obesity (Jennis *et al.*, 2018). Further *in vivo* studies are desirable to understand the crosstalk between the gut and microbes and its long-term effects on metabolic diseases.

(3) Role of indoles in non-alcoholic fatty liver disease

NAFLD is the most common chronic liver disease linked to metabolic syndrome and obesity. The involvement of gut microbes in energy metabolism, the immune system, and insulin resistance suggests that they have a role in the development of NAFLD (Zhou & Fan, 2019). In hepatocytes, cytokine-mediated lipogenesis is alleviated *via* the AhR-dependent activity of IAA (Krishnan *et al.*, 2018). Several clinical studies have indicated that a person with obesity and type 2 diabetes is likely to develop hepatic inflammation and steatosis (Ma *et al.*, 2020). On the other hand, manifestations of type 2 diabetes in patients with NAFLD are common (Ma *et al.*, 2020). In addition to the free radical scavenging activity of indole-3-propionic acid, its supplementation reduces body mass and has a positive impact on glucose metabolism and insulin resistance in rats (Abildgaard *et al.*, 2018; Konopelski *et al.*, 2019). Non-alcoholic steatohepatitis is a subtype of NAFLD that may lead to cirrhosis and even hepatocellular carcinoma. Indole-3-propionic acid has been shown to improve the condition in diet-induced steatohepatitis in rats (Zhao *et al.*, 2019). A higher indole-3-propionic acid level in plasma increases the intestinal barrier function and tissue inflammation *via* PXR-based signalling whereas obese subjects show lower plasma levels of indole-3-propionic acid (Venkatesh *et al.*, 2014; Jennis *et al.*, 2018).

In humans, indole levels were lower in obese subjects compared to lean individuals, thus exhibiting an inverse correlation between indole and hepatic fat content (Ma *et al.*, 2020). It has also been demonstrated that indoles not only ameliorate steatosis in high-fat-diet mice but also improve gut microbial composition, insulin resistance, and glucose intolerance (Ma *et al.*, 2020). An *ex vivo* study showed the anti-inflammatory activity of indole in obese mice (Beaumont *et al.*, 2018). Further molecular studies have revealed that indole administration reduces lipogenic gene expression, decreasing fat deposition in hepatocytes (Ma *et al.*, 2020). The anti-NAFLD activity of indole was attributed to its ability to suppress lipogenic events (control lipogenic gene expression and transcription activity of sterol regulatory element binding protein-1c) and decrease the pro-inflammatory response in both macrophages [by stimulating

6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 [PFKFB3] expression] and hepatocytes (Ma *et al.*, 2020).

(4) Influence of indoles in cancer

Early studies have shown that skatole and indole levels may serve as indicators of large bowel polyps or cancer with high skatole levels found in cancer patients (Karlin *et al.*, 1985). In this context, the anticancer roles of diet-derived indoles are well documented (Katz, Nisani & Chamovitz, 2018). Indole-3-carbinol present in cruciferous vegetables is a bioactive compound that influences cancer cells (Katz *et al.*, 2018; Martin-Ruiz *et al.*, 2018). The dimerization of indole-3-carbinol during digestion results in another bioactive compound, 3,3'-diindolylmethane, that has shown potential in the treatment of prostate and breast cancer (Pondugula *et al.*, 2015). Microbial indoles such as indole, tryptamine, IAA, and I3S can modulate AhR activity (Table 2) and have shown AhR-dependent responses in human colon cancer (CaCo2) cells and mouse hepatoma cells (Heath-Pagliuso *et al.*, 1998; Schroeder *et al.*, 2010; Jin *et al.*, 2014). Upregulation of indoleamine 2,3-dioxygenase 1 activity has been linked to escape of malignant cells from the immune system. Tryptamine inhibits indoleamine 2,3-dioxygenase 1 and increases immune surveillance and therefore is a main target in interventions to immune escape of malignant cells (Gao *et al.*, 2018). However, these microbial metabolites showed complex patterns of AhR activity (ligand- and gene-dependent agonist/antagonist) in young adult mouse colonocytes, possibly due to species-specific variations in AhR (Cheng *et al.*, 2015; Hubbard *et al.*, 2016). Selective AhR modulation by indoles will need to be studied further (preferably on human cell lines and patients) to understand the *in vivo* effects of these compounds and predict their anti-cancer effects on the host.

(5) Atherosclerosis progression and its association with indoles

Atherosclerosis is a condition in which fats, cholesterol, calcium, and other substances accumulate in arterial walls, resulting in reduced blood flow to the tissues. Oxidative stress and chronic inflammation are the two main mechanisms in atherosclerosis that lead to cardiovascular disease (Dou *et al.*, 2015). Enhanced production of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) in cultured endothelial cells treated with IAA supports the view that the COX-2/PGE2 axis is involved in atherosclerotic lesion formation (Dou *et al.*, 2015). A targeted metabolomic study of gut microbe-derived metabolites showed that indole, indole-3-propionic acid, and indole-3-aldehyde are associated with advanced atherosclerosis. Indole-3-propionic acid, and indole-3-aldehyde levels were low in atherosclerotic patients, while the ratios of kynurenine/tryptophan were elevated (Cason *et al.*, 2018). The indole metabolites or their transformants may work as potential modulators of atherosclerosis (Cason *et al.*, 2018). Endotoxins are causal mediators that

accelerate atherosclerosis development in rodents, while mice deficient in TLR4 (a receptor for LPS) are more resistant to vascular disease (Kappel & Federici, 2019). Evidence for a reduction in diet-induced atherosclerosis in LDL (low density lipoprotein cholesterol)^{-/-} mice by repression of a bacterial pro-atherogenic metabolite (LPS) through an IL-23–IL-22 axis (Fatkhullina *et al.*, 2018), and indole-based AhR activation through IL-22 to balance mucosal reactivity (Zelante *et al.*, 2013) indicate that indoles have a certain protective role in atherosclerosis *via* AhR activation and IL-22. A correlation with cholesterol has not been reported to date, and the role of indole pathway in the regulation of cholesterolemia needs further investigation (Villette *et al.*, 2020).

In addition to AhR, another xenobiotic sensor, PXR, is associated with atherosclerosis in humans and mice (Kappel *et al.*, 2020). In a mouse colitis model, indole-3-propionic acid activates PXR and regulates gastrointestinal barrier function (Venkatesh *et al.*, 2014), while in a rat steatohepatitis model administration of indole-3-propionic acid reduces endotoxin leakage and gut dysbiosis, a mechanism associated with atherosclerosis (Zhao *et al.*, 2019). By contrast, detrimental effects of PXR or AhR activation were observed in apolipoprotein E (apoE)-deficient mice (representative of accelerated atherosclerosis), whereas deficiency of PXR or loss of AhR reduced atherosclerosis in apoE^{-/-} mice and protected against vascular aging (Kappel *et al.*, 2020). The influence of AhR and PXR activation on the vascular system thus remains obscure as it depends both on the agonist type as well as the species being studied (Zelante *et al.*, 2013; Hubbard *et al.*, 2015a; Kappel *et al.*, 2020). Loss of gut microbial diversity and alterations in their metabolic functions are linked to increased atherosclerosis post-antibiotic treatment (Kappel *et al.*, 2020). Populations of *Akkermansia*, *Collinsella*, *Eubacterium*, *Roseburia*, *Ruminococcus*, and other bacteria are altered in the gut of diseased subjects, leading to dysbiosis (Jennis *et al.*, 2018; Kappel & Federici, 2019). A reduction in *Bacteroidetes* and *Clostridia* by antibiotics was associated with diminished tryptophan and disturbed lipid metabolism. The exact molecular targets of microbial indoles affecting atherosclerosis and its end-stage complications are yet to be elucidated (Kappel *et al.*, 2020).

V. INDOLIC METABOLITES AS BIOMARKERS OF DISEASE

Proteolytic fermentation occurs primarily in the distal part of the colon leading to the production of ammonia, hydrogen sulfide, branched-chain fatty acids, and phenolic and indolic compounds. Studies in animals and humans on these metabolites suggest varied roles in gut integrity and metabolic health (Canfora *et al.*, 2019). The animal data also suggest a valuable role of indole on gut barrier (Shimada *et al.*, 2013; Venkatesh *et al.*, 2014) and liver function (Beaumont *et al.*, 2018; Hendrikx & Schnabl, 2019).

Mounting evidence has revealed that gut microbial metabolism of dietary nutrients significantly influences host physiology. The gut microbial population consists of as many as 2770 microbial taxa, whose composition varies among different individuals (Chappell *et al.*, 2016; Cryan *et al.*, 2019). Of these, beneficial microbes play a key role in eubiosis, maintain the gut microenvironment, and produce 0.3–6.6 mM of indole. A threshold concentration of >2.5 mM faecal indole was found to reduce the risk of *Cryptosporidium* infection (Chappell *et al.*, 2016). A gut lumen rich in microbes contains higher levels of indole than the epithelium, where it is absorbed by colonic epithelia *via* passive diffusion (Hubbard *et al.*, 2015a; Kumar & Sperandio, 2019). This indole concentration gradient was found to be important for pathogenic colonization of the gut (Darkoh *et al.*, 2019). It has been suggested that supplementation of indole-producing bacteria such as *Bacteroides thetaiotaomicron* increases the indole levels and reduces the expression of virulence genes of pathogens (Kumar & Sperandio, 2019).

Therefore, the abundance of indole compounds in the gut is often evaluated as a biomarker in clinical specimens and has various applications in the pharmaceutical industry (Darkoh *et al.*, 2015). A targeted metabolomics study to identify the role of microbial metabolites in advanced atherosclerosis patients showed that the plasma levels of these metabolites (indole and phenyl derivatives) are correlated with postoperative outcomes, thereby suggesting that these compounds may serve as biomarkers in atherosclerosis (Table 3) (Cason *et al.*, 2018; Biscetti *et al.*, 2019).

A similar study conducted on mice to identify biomarkers for acute kidney injury revealed that I3S is a sensitive marker of nicotinic acid receptor agonist-induced renal toxicity in mice (Zgodna-Pols *et al.*, 2011). Indeed, higher levels of I3S in plasma and brain but not in the urine suggest the involvement of I3S in renal- and central nervous system-associated toxicity (Zgodna-Pols *et al.*, 2011). Intestinal conversion of tryptophan to I3S and the host–microbe relationship seems to be important in the development of chemical-induced toxicity in mice (Zgodna-Pols *et al.*, 2011). I3S is a protein-bound uremic toxin found in the serum of individuals with CKD and is difficult to remove by dialysis. This indole metabolite is also associated with glucose intolerance and promotes vascular calcification by the diminished expression of GLUT1 and LXR signalling (Kappel & Federici, 2019). Lower levels of I3S after allogeneic stem cell transplantation were identified as an indirect indicator of microbial dysbiosis in the gut (Table 3) (Weber *et al.*, 2015). Patients with a higher proportion of commensal bacteria showed better survival outcomes post-transplantation, establishing that gut microbe-associated I3S production has an important role in transplant-related mortality (Weber *et al.*, 2015).

The complex interplay of indole compounds also has relevance in cognitive impairment *via* the gut–brain axis. Indole-3-acetic acid and I3S are representative candidate markers of cognitive impairment (Lin *et al.*, 2019a). Serum IAA levels are also associated with cognitive performance and cognitive impairment in patients experiencing chronic haemodialysis

(Lin *et al.*, 2019a). I3S is known to induce oxidative stress and apoptosis in astrocytes by the MAPK pathway, revealing its involvement in the pathophysiology of dementia (Lin *et al.*, 2019b).

Another indole metabolite, indole-3-propionic acid, was considered to serve as a key biomarker and renal protector in the progression of CKD (Sun *et al.*, 2019a) and it was identified as a biosignature to discriminate and predict pre-onset and progression of Alzheimer's disease (Wu *et al.*, 2021). Indole-3-propionic acid is involved in fibrosis and inhibition of genes associated with inflammation in proximal tubular cells, while it also gives protection to hepatic microsomal membranes against iron-induced damage in cancer (Sarode *et al.*, 2019). Indole-3-propionic acid also attenuates arsenic- and copper-mediated cellular and mitochondrial DNA damage. Therefore, lower serum levels of indole-3-propionic acid in Wilson disease were considered indicative of compromised cellular defences (Sarode *et al.*, 2019). Recently, indole-3-propionic acid levels in the serum and follicular fluid of women were referred to as biomarkers that reflect the antioxidant status of the follicular environment and its interaction with gut metabolism (Table 3) (Ruebel *et al.*, 2019). Additionally, microbial metabolites including indoles could be used as a biosignature, alterations of which would be helpful in indicating prenatal alcohol exposure (Virdee *et al.*, 2021). Indole-3-propionic acid was also found to be associated with type 2 diabetes and negatively associated with low-grade inflammation (de Mello *et al.*, 2017). The ability of indole-3-propionic acid to ameliorate chemically induced murine colitis apparently *via* epithelial IL-10 signalling reveals its potential as a novel therapy in mucosal disease (Alexeev *et al.*, 2018). Thus, indole-3-propionic acid functioned as a biomarker of disease remission in human volunteers with active colitis (Alexeev *et al.*, 2018). Serum indole-3-propionic acid levels were found to be linked with dietary fibre intake and showed better maintenance of β -cell function, suggesting a direct role of diet, gut microbes (Firmicutes/Bacteroidetes), and glucose metabolism (de Mello *et al.*, 2017; Kappel & Federici, 2019).

Low serum levels of indole metabolites could indirectly reveal the physiological status of an individual (Table 3) (Sarode *et al.*, 2019). Besides volatile sulfur compounds, indole/skatole can also be detected in human saliva, where they contribute to malodour (Codipilly & Kleinberg, 2008). The microbes generating indole in the oral cavity include anaerobic Gram-negative bacteria such as *Porphyromonas gingivalis*, *P. intermedia*, and *Fusobacterium nucleatum* (Codipilly & Kleinberg, 2008). Compared to the strong odour of volatile sulfur compounds, indole and skatole are less volatile, due to which their contribution to halitosis is considered minimal. However, a few individuals with halitosis have higher levels of indoles in their breath, making this diagnosis inefficient (Mogilnicka, Bogucki & Ufnal, 2020). New methods now make it possible to detect indoles in biological samples in a precise and rapid manner in order to predict or assess the physiological state (particularly with respect to tryptophan metabolism) of an individual (Darkoh *et al.*, 2015). While

Table 3. Indole metabolites as biomarkers in various diseases

Compound	Organism (model)	Disease	Detection source	Mechanism	References
Indole	Human	<i>Cryptosporidium</i> infection <i>Clostridium difficile</i> infection	Faeces	Indole-producing gut microbes influenced <i>Cryptosporidium</i> infection Alters intestinal colonization	Chappell <i>et al.</i> (2016) Darkoh <i>et al.</i> (2019)
Indole-3-acetic acid	Human volunteers with chronic kidney disease	Anxiety and depression Mortality and cardiovascular events	Serum	– Activated AhR/p38MAPK /NF-κB pathway that induces cyclooxygenase-2, a proinflammatory enzyme	Karu <i>et al.</i> (2016) Dou <i>et al.</i> (2015)
Indole-3-lactic acid	Mouse	Salt-sensitive hypertension and cardiovascular diseases	Faeces	Reduced T helper 17 polarization	Wilck <i>et al.</i> (2017)
Indole-3-propionic acid	Human	Chronic kidney disease	Serum	Scavenges hydroxyl radicals without generating pro-oxidant intermediates	Sun <i>et al.</i> (2019a)
		Wilson disease	Serum	Involved in tricarboxylic acid (TCA) cycle, amino acid metabolism, choline metabolism, and oxidative stress	Sarode <i>et al.</i> (2019)
		Obesity	Serum and follicular fluid	Worked as an antioxidant and was negatively correlated with energy intake and obesity	Ruebel <i>et al.</i> (2019)
	Mouse	Type 2 diabetes, low-grade inflammation	Serum	Negatively associated with diabetes and inflammation	Tuomainen <i>et al.</i> (2018); de Mello <i>et al.</i> (2017)
Indoxyl-3-sulfate	Mouse	Anti-inflammatory	Serum	Pregnane X receptor and Toll-like receptor 4 signalling pathway	Venkatesh <i>et al.</i> (2014)
		Colitis	Serum	Indole metabolites worked in anti-inflammatory pathway <i>via</i> epithelial interleukin-10 (IL-10) signalling	Alexeev <i>et al.</i> (2018)
	Human	Chemically induced acute kidney injury	Plasma, urine and brain	Involved in renal- and central nervous system-related toxicity	Zgoda-Pols <i>et al.</i> (2011)
Indole and indole-derivatives	Human	Gastrointestinal (GI) graft-versus-host-disease	Urine	Prognostic indicator of dysbiosis and higher risk of disease	Weber <i>et al.</i> (2015)
		Atherosclerosis	Plasma	Associated with atherosclerosis and postoperative cardiac complications	Cason <i>et al.</i> (2018)

AhR, Aryl hydrocarbon receptor; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B.

several findings suggest that indole metabolites can be used as biomarkers of microbial dysbiosis, atherosclerosis, CKD, type 2 diabetes, and colitis, their exact levels are yet to be medically delineated.

VI. THE EXPLOITATION OF INDOLES FOR THERAPEUTIC PURPOSES

Indoles and indole metabolites have wide implications in human disease diagnosis, progression, and remission. Administration of indole-3-propionic acid is potent in non-

alcoholic steatohepatitis, modulates gut microbial composition, and inhibits dysbiosis (Zhao *et al.*, 2019). Similarly, indoleacrylic acid, produced by commensal bacteria (*Peptostreptococcus* sp.), promotes the functioning of the gut epithelial barrier and mitigates the inflammatory response, suggesting that higher levels of indoleacrylic acid in the gut could offer therapeutic benefits (Wlodarska *et al.*, 2017). Indole metabolites, through type I interferon, help to control gut inflammation, and damage associated with myeloablative chemotherapy, providing a therapeutic option for patients following bone marrow transplant, who are at risk of graft-versus-host disease (Swimm *et al.*, 2018; Qayed *et al.*, 2021). Recently, the therapeutic effects of indole-3-propionic acid

against radiation toxicity were demonstrated at a molecular level using faecal microbiota transplantation in mice exposed to radiation (Xiao *et al.*, 2020). Indole-3-propionic acid alleviated inflammation, catabatic myelosuppression, and improved epithelial integrity in treated mice. *In vitro* and *in vivo* assays indicate the involvement of PXR/acyl-CoA-binding protein signalling in indole-3-propionic acid-dependent radioprotection (Xiao *et al.*, 2020). A conjugate of indole-3-propionic acid (linked with 5-aminonicotinic acid) mitigated colonic damage and inflammation (Lee *et al.*, 2021). These findings open the possibility of microbiome-based therapies for radioactive damage. Microbial metabolites could also be used directly as an effective succedaneum to mitigate acute radiation syndrome.

Similarly, supplementation of indole-3-aldehyde (stimulates AhR-mediated IL-22 production) promotes IL-18 expression and prevents infection in murine vulvovaginal candidiasis (Borghi *et al.*, 2019). Due to the role of indoles in immunomodulation *via* stabilization of regulatory T cells (Treg cells), they can be exploited as microbial-metabolite-derived therapies (Steinmeyer *et al.*, 2017) (Fig. 1). Moreover, skatole can induce some cytochrome P450s (involved in drug metabolism) *via* an AhR-mediated mechanism in the liver suggesting a role in the bioavailability of drugs and their metabolism (Rasmussen *et al.*, 2016). However, further study is required to understand the behaviour of indole as an AhR antagonist or weak agonist/partial antagonist (Steinmeyer *et al.*, 2017). The deeper our understanding of gut metabolite cues and their roles in physiological functions, the better we can design cellular therapeutics and personalized treatments.

The indole moiety itself can be exploited as a versatile molecular scaffold in drug design. Microorganisms have been used as biocatalysts and therefore are considered as a modern tool in chemistry. The capacity of *Aspergillus niger* and *Beauveria bassiana* to modify 3-indolylacetonitrile and tryptamine into 3-methylindole, and 5-hydroxyindole-3-acetamide, respectively indicates that both reduction and oxidation of the indoles are possible using biocatalysts (Boaventura, Lopes & Takahashi, 2004). The use of microbes to carry out reactions in the indole nucleus of serotonin is industrially important. 5-hydroxytryptamine also improves the activity of amphotericin B against *Aspergillus fumigatus in vitro* (Heller *et al.*, 2004). The combination of biogenic amines with existing drugs may be used for novel medical applications. Some natural and synthetic indole derivatives recently have been compiled, revealing diverse therapeutic applications (Chadha & Silakari, 2017) while there are thousands of indoles yet to be investigated.

Metabolite mimics of indole have been used to understand the structure–activity relationships with its target receptors and to develop novel therapeutics. Two potent anti-inflammatory compounds (FKK5 and FKK6) were designed to target intestinal inflammation by interacting with PXR (Dvořák *et al.*, 2020). When FKK6 was further modified using an imidazolopyridyl residue, the agonist activity shifted from PXR to AhR (Li *et al.*, 2021). The indole moiety-containing catabolites of tryptophan were checked for their activity

towards AhR and PXR using a reporter gene assay (Illés *et al.*, 2020; Vyhliďalová *et al.*, 2020). Such information is important to understand the affinity of these metabolites against different receptors so that further metabolite mimics can be designed with higher efficacy. Metabolite mimicry is a new concept but follows a similar philosophy to targeting/blocking the activity of a protein by using known natural compounds as a scaffold. The establishment of a screening method provides us with hope that one or a mixture of such mimics may be used for therapeutic purposes, although more *in vivo* studies and demonstrations will be required.

For the removal of uremic toxins, prebiotics, probiotics, and carbon adsorbents (e.g. AST-120 and Sevelamer (a non-calcium phosphate binder)) were used in a clinical study with CKD patients (Dou *et al.*, 2015; Takkavatakarn *et al.*, 2021). Interestingly, with a large cohort of CKD patients, oral treatment with AST-120 reduced serum I3S levels yet resulted in no improvement in renal outcome and disease progression (Chen *et al.*, 2019a). This contrasts with the common understanding of uremic toxins and indicates that increased I3S levels could indeed be a result of uremia rather than a driver. However, another adsorbent, Sevelamer, has been used successfully in the treatment of CKD for more than a decade (Dou *et al.*, 2015). The absence of a positive treatment outcome using AST-120 highlights the complex pathophysiology of CKD and potentially the ineffectiveness of removing a single uraemic toxin (Massy & Liabeuf, 2018), and warrants further study to identify the exact role of I3S in renal disease.

VII. SIGNIFICANCE AND OUTLOOK

The ubiquitous presence of microbes in all environments make the exchange of metabolites and even of genetic materials inevitable. The potential acquisition of the *tnaA* gene from a bacterial donor (*Entamoeba histolytica*) *via* horizontal gene transfer (Loftus *et al.*, 2005), and the exchange of indole metabolites as growth-promoting hormones (in the diatom *Pseudo-nitzschia multiseriis*) could provide survival advantages to the recipients (Matthews *et al.*, 2020). An interesting role of indole has been reported recently, where secretion of indole by the commensal bacterium (*Aquitalea* sp.) of planarians impacts axial and head patterning of *Dugesia japonica* during regeneration (Williams *et al.*, 2020). RNA-sequencing data has revealed that indole alters the expression of patterning genes, including those involved in the Wnt signalling pathway. Such regulation of the regeneration process and the host's anatomical structure, by a metabolite secreted by its commensal bacteria is an example of the unique role played by indole. Such examples provide support for the holobiont theory that suggests co-evolution with microbes and emphasizes an understanding of the complex multi-partner interactions occurring in the holobiont. In addition to recent evidence about the involvement of microbial indole metabolites in the differentiation of planaria, the egg-laying

behaviour of *C. elegans*, in byssal thread production in molluscs, insect behaviour, plant defences, human gut–organ axes and diseases, it is likely that similarly unique functions of this abundant nitrogenous compound in the life of other eukaryotes remain to be discovered.

The unique behaviour of indole in cell-to-cell communication can lead to hormesis (low-dose stimulation and high-dose inhibition) as observed for algae and human cells (Sun *et al.*, 2019b). Since indole has diverse roles in different eukaryotes (as discussed above) it may be considered an archetypal hormone (Lee *et al.*, 2007). Given that the bio-availability of indole will vary greatly depending on the environment and the associated microbiome, it would be interesting to understand how microbial indoles influence the eukaryotic community, their metabolism, and behaviour. The effective concentration of indole required for its function also varies with the recipient, and in-depth study of the dose-dependent functions of microbial indole metabolites is needed before they can be exploited. In particular, aspects of microbial endocrinology, gut–organ axes, holobiont theory, and inter-kingdom interactions should be studied with respect to microbial indole and indole derivatives.

VIII. CONCLUSIONS

- (1) Indole, the metabolite of tryptophan, and indole moiety-containing compounds influence myriad functions in eukaryotes. They serve as signal molecules, growth promoters, effectors, cues, precursors for bio-active compounds, immunomodulators, and activators of defence systems. These nitrogenous compounds are not only important in the nitrogen cycle but are also essential for the whole ecosystem. It is clear that the functionality of indole compounds can differ among different organisms (Table 1).
- (2) The hormetic function of indoles in eukaryotic cells may reflect a primitive communication system between prokaryotes and eukaryotes. In particular, the effects of microbial metabolites on different aspects of the host *via* the gut–organ axes provide support for the holobiont theory suggesting the co-evolution of holobionts.
- (3) Systemic levels of indole metabolites have the potential to serve as diagnostic markers of metabolic disorders and to be indirect indicators of gut health. From the perspective of disease, *in vivo* levels of systemic indoles are related to the dietary supply of tryptophan and the composition of the gut microbiota. The preparation of unique formulations to control systemic levels of these metabolites will be helpful in understanding metabolic disorders. Several synthetic compounds containing an indole moiety or targeting indole metabolites are already being tested for various pharmacological purposes (e.g. AST and Sevelamer). However, complex physiological conditions must be assessed by

'omics studies to identify the exact causative agent(s) before exploiting or targeting indoles. Since other uremic toxins may be of equal importance, the use of AST-120 or other adsorbents may only be appropriate as preventive measures. Detailed understanding of indole compounds is of utmost importance as some are beneficial to health while others may be harmful. Such knowledge may offer a novel dietary-based strategy for the prevention and/or treatment of metabolic diseases.

- (4) Unique indole and indole-based compounds from the marine environment are yet to be explored for biotechnological applications.
- (5) Much remains to be understood regarding the extent of microbial indole production within the gut as well as in the environment. Relatively few research studies are available on ecological and metabolic interactions potentially occurring within multi-partner symbioses. It will be interesting to investigate mutual exchanges involving indole compounds and their influences on the participants of such exchanges.

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