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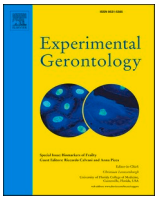

Microbiota-derived tryptophan metabolism: Impacts on health, aging, and disease

Sonu Kumar Gupta [a], Sagar Vyavahare [a], Ian L. Duchesne Blanes [a], Ford Berger [a], Carlos Isales [a,b], Sadanand Fulzele [a,b,c,d,*]

[a] Department of Medicine, Medical College of Georgia, Augusta University, Augusta, GA, USA
[b] Centre for Healthy Aging, Medical College of Georgia, Augusta University, Augusta, GA, USA
[c] Department of Cell Biology and Anatomy, Medical College of Georgia, Augusta University, Augusta, GA, USA
[d] Department of Orthopedic Surgery, Medical College of Georgia, Augusta University, Augusta, GA, USA

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ABSTRACT

The intricate interplay between gut microbiota and the host is pivotal in maintaining homeostasis and health. Dietary tryptophan (TRP) metabolism initiates a cascade of essential endogenous metabolites, including kynurenine, kynurenic acid, serotonin, and melatonin, as well as microbiota-derived Trp metabolites like tryptamine, indole propionic acid (IPA), and other indole derivatives. Notably, tryptamine and IPA, among the indole metabolites, exert crucial roles in modulating immune, metabolic, and neuronal responses at both local and distant sites. Additionally, these metabolites demonstrate potent antioxidant and anti-inflammatory activities. The levels of microbiota-derived TRP metabolites are intricately linked to the gut microbiota's health, which, in turn, can be influenced by age-related changes. This review aims to comprehensively summarize the cellular and molecular impacts of tryptamine and IPA on health and aging-related complications. Furthermore, we explore the levels of tryptamine and IPA and their corresponding bacteria in select diseased conditions, shedding light on their potential significance as biomarkers and therapeutic targets.

1. Introduction

The microbial community that is metabolically active and coevolves inside the host is called the gut microbiota. The symbiotic gut microbiota plays a vital role in host-microbe interactions. It maintains homeostasis in host health and nutrient metabolism (Das and Nair, 2019). It seems that host and gut microbiota both benefit from a symbiotic relationship. Several factors have an impact on host-microbe symbiotic relationships. The gut microbiota is supposed to work as an organ that affects human health and metabolism-related diseases (Amar et al., 2011; Chassaing et al., 2015; D.M. Lee et al., 2020; C.J. Lee et al., 2020; O'Hara and Shanahan, 2006). The irregularity produced in the composition of microbiome leads to dysbiosis that involves gastrointestinal diseases (Chassaing and Darfeuille-Michaud, 2011), infectious diseases (Khan et al., 2019), metabolic disorders (Ley et al., 2006; Qin et al., 2012), neurological disorders (Sampson and Mazmanian, 2015) and altered immune response of the host (Blacher et al., 2017). These effects are facilitated by cellular interactions and by some metabolites either being produced by the microbes or conversion of host molecules. The gut microbiota is recognized as a virtual endocrine organ, synthesizing vital compounds essential for host physiology and eliciting intrinsic responses (Zhang and Davies, 2016).

There are three well-known categories of metabolites produced by the specific gut microbiota includes short-chain fatty acids (SCFAs) from food fibers, bile acids made in the liver, and tryptophan (TRP) derivatives (Blacher et al., 2017). SCFAs, also known as volatile fatty acids, are linear carboxylic acids comprising less than six carbon members, including acetate, propionate, and butyrate (Cook and Sellin, 1998). SCFAs have a significant effect on human health which show anti-inflammatory (Al-Lahham and Rezaee, 2019), hypotensive (Kondo et al., 2001; Natarajan et al., 2016; Onyszkiewicz et al., 2019), hypolipidemic (Demigne et al., 1995), and vasodilatory (Hulsmann, 1976; Knock et al., 2002; Mortensen et al., 1990; Nutting et al., 1991) responses along with improved endothelial dysfunction induced by angiotensin II (Robles-Vera et al., 2020). Bile acids were considered to be involved in lipid breakdown in the intestinal lumen for decades, but

* Corresponding author at: Department of Medicine, Division of Endocrinology, Department of Orthopedic Surgery, Cell Biology and Anatomy, Augusta University, Augusta, GA 30912-2000, USA.
E-mail address: sfulzele@augusta.edu (S. Fulzele).

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now it has been seen to have multiple physiological effects, such as homeostasis of lipids, glucose, and some metabolic substrates (Li and Chiang, 2014; Qi et al., 2015) that affect the immune responses (Sipka and Bruckner, 2014) as well as microbiota composition (Ridlon et al., 2014). Moreover, bile acids act as hormones as they bind to various cytoplasmic domains and nuclear receptors in different tissues and organs (Houten et al., 2006). On the other hand, TRP is metabolized by gut microbiota to produce various derivatives involved in diverse biological functions. In this review, we explore TRP metabolism and focus particularly on the roles of tryptamine and IPA in age-related secondary complications.

2. Tryptophan metabolism

TRP is an essential amino acid that cannot be synthesized de novo by human cells (Paeslack et al., 2022). It is the largest amino acid by molecular weight out of 20 common amino acids. It is a precursor for several metabolic compounds necessary for the body's growth and development and is supplied through the diet (Le Floc'h et al., 2011). The common dietary sources of TRP are bread, oats, bananas, cheese, milk, peanuts, chocolates, dried prunes, tuna fish, and poultry products. The recommended dose by the World Health Organization is 4 mg/kg/day, declared safe for a normal human being, and no adverse effect of excess intake has yet been reported (Agus et al., 2018). It is an important constituent of protein (Fernstrom, 2012), which is absorbed from the gut and made available in circulation as a free or albumin-bound segment (Fernstrom and Fernstrom, 2006). Metabolism of TRP progresses in the gastrointestinal tract through three distinct pathways: (1) the Kynurenine pathway in both host immune cells and intestinal cells (Clarke et al., 2013); (2) the Serotonin pathway performed by enteroendocrine cells (Yano et al., 2015); and (3) Bacterial transformation of TRP into its derivatives (Zelante et al., 2013) (Fig. 1). While 95 % of ingested TRP is catabolized to N-formyl kynurenine (NFK) by the enzyme indoleamine 2,3-dioxygenase (IDO) 1 (Melhem and Taleb, 2021; Kanova and Kohout, 2021) which further metabolized to kynurenine by an enzyme arylformamidase that ultimately transforms into its derivatives such as anthranilic acid, picolinic acid, and quinolinic acid through the kynurenine pathway. Only 1–2 % of TRP is catabolized to 5-Hydroxytryptophan by the enzyme TRP hydroxylase 1 (TpH1), which further metabolizes to serotonin by an enzyme aromatic amino acid decarboxylase which ultimately transforms to melatonin by the enzyme *N*-acetyltransferase through serotonin pathway (Kanova and Kohout, 2021). The larger portion of digested TRP is absorbed in the intestine to metabolize by the host's cells. A smaller fraction of this metabolite remains in the intestinal lumen, which is absorbed by the symbiotic bacteria. Gut microbiota uses this amino acid for their growth and development and simultaneously produce biologically active metabolites which also play an important role in host's physiological processes (Agus et al., 2018; Alexeev et al., 2018; Konopelski and Ufnal, 2018; Melhem and Taleb, 2021).

3. Gut-specific microbiota involved in TRP metabolism

Many symbiotic microbes are listed in the literature that metabolize TRP into indole, tryptamine, IPA, and other derivatives. TRP is converted to tryptamine by the action of the TRPD enzyme, including bacteria such as *Clostridium sporogenes* and *Ruminococcus gnavus* (Williams et al., 2014). IPA also produce from TRP by the activity of the enzyme TNA (tryptophanase) comprised of symbiotic bacterial species *Lactobacillus reuteri* (Rothhammer et al., 2016) and some members of the genus Clostridium (Dodd et al., 2017) and Peptostreptococci (Roager and Licht, 2018; Wlodarska et al., 2017). However, some particular species of Clostridium, Bacteroides, and *Escherichia coli* are involved in synthesizing indole using tryptophanase enzyme (Roager and Licht, 2018). In addition, indole acetic acid is synthesized particularly by

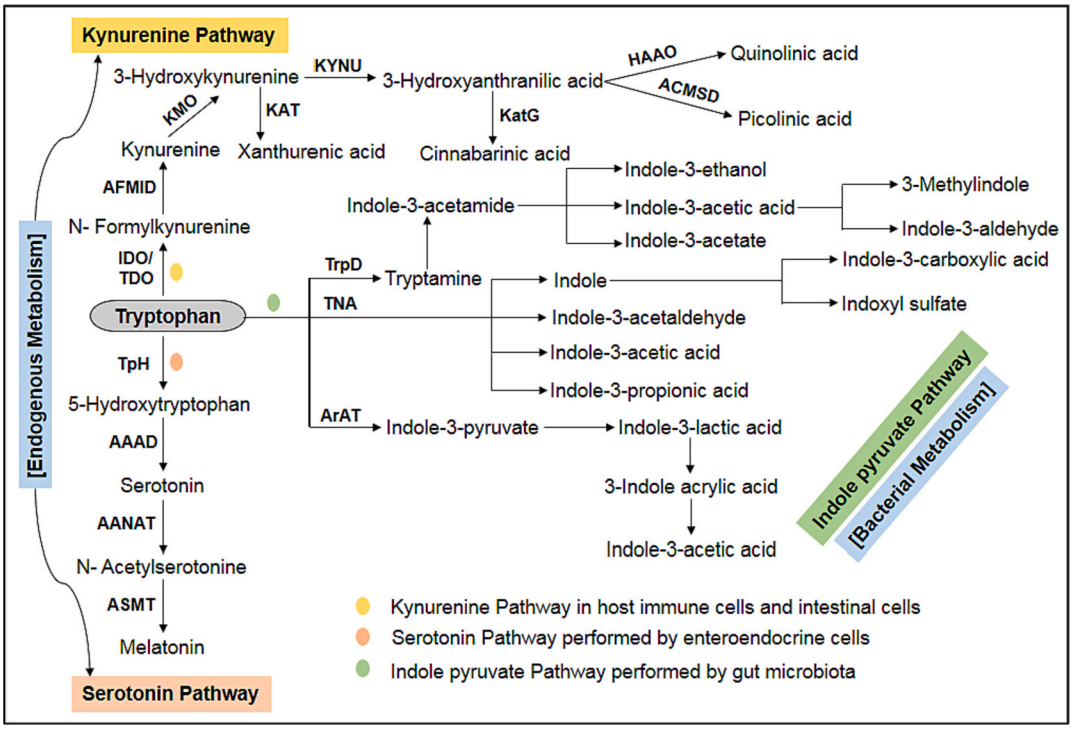

Fig. 1. A schematic diagram of TRP metabolic pathways in animals. TRP can be metabolized through the kynurenine and serotonin pathways endogenously and through the indole pyruvate pathway by gut microbiota. Abbreviations: IDO: indoleamine 2,3-dioxygenase; TDO: tryptophan 2,3-dioxygenase; AFMID: arylformamidase; KMO: kynurenine 3-monooxygenase; KAT: kynurenine aminotransferase; KatG: catalase-peroxidase; KYNU: kynureninase; HAAO: 3-hydroxyanthranilate 3,4-dioxygenase; ACMSD: aminocarboxymuconate-semialdehyde decarboxylase; TpH: tryptophan hydroxylase; AAAD: aromatic amino acid decarboxylase; AANAT: aralkylamine *N*-acetyltransferase; ASMT: acetylserotonin *O*-methyltransferase; TRPD: tryptophan dehydrogenase; TNA: tryptophanase; ArAT: aromatic amino acid transaminase.

members of the genus Bacteroides, Bifidobacteria and Eubacteria. Indole-3-aldehyde is synthesized by the symbiotic bacteria Lactobacilli using the enzyme aminotransferase (Parthasarathy et al., 2018; Pappolla et al., 2021) (Table 1). Furthermore, indole-3-pyruvate is directly synthesized from TRP by the action of the enzyme aromatic amino acid transaminase (Fig. 1). The details of the bacteria involved in the metabolism of the TRP are given in Table 1.

4. Level of TRP metabolites modulated by the gut microbiota content

Generally, the microbiota composition is more highly diverse in younger people than in older ones (Mangiola et al., 2018; Xu et al., 2021). For example, the members of *Firmicutes*, *Clostridium*, and *Faecalibacterium* were found to decrease in the aged population (Biagi et al., 2010). However, the level of corresponding bacteria with TRP metabolites in diseased conditions has not been discussed yet. Zuo et al. recently reported that patients suffering from COVID-19 have a higher abundance of bacterial species *Morganella morganii* (Zuo et al., 2021). Simultaneously, it was confirmed in non-human species tuna that the tryptamine level was higher when injected with *Morganella morganii* or *Proteus mirabilis* (Ahmed, 2019). Additionally, a change in microbiota composition and increased levels of tryptamine and other indoles was observed in a primate model called macaque while showing mild symptoms of COVID-19 (Sokol et al., 2021).

The human gut microbacteria also get infected by viruses (phages) and cause cascading effects on other bacterial species. The phage infection reduces *Clostridium sporogenes* and tryptamine levels in the gut of mammalian host (Hsu et al., 2019). *Clostridium sporogenes* is one of the bacteria which metabolize TRP into tryptamine (Williams et al., 2014). Like tryptamine, IPA levels also get affected during disease progression with alteration in corresponding bacteria that metabolize them. In an experimental model, the germ-free mice, when injected with IPA intraperitoneal, showed higher levels of serum IPA, but it cleared rapidly, which indicates serum IPA levels in animals are associated with gut microbiota (Jiang et al., 2022). In another study, the IPA level in germ-free mice was detected after 5 days of colonization of enteric bacteria (Wikoff et al., 2009). However, the metagenome sequencing studies of patients with coronary artery disease (CAD) showed reduced serum IPA content with significant depletion of corresponding bacteria such as *Clostridium* and *Peptostreptococcus* genus (Dodd et al., 2017). These studies suggested that tryptamine and IPA with their corresponding bacteria, which metabolize them, may be involved in disease pathogenesis. Additionally, the response of TRP metabolites in various pathophysiological and immunological functions has been summarized and depicted in Fig. 2.

Table 1
List of TRP metabolites produced by different microbacteria.

Tryptophan metabolite	Bacteria	References
Indole	*Bacteroides thetaiotaomicron*	Devlin et al., 2016; Elsden et al., 1976
	Bacteroides ovatus	Lee and Lee, 2010
	Clostridium bifermentas	Smith and Macfarlane, 1996
	Clostridium ghoni	Smith and Macfarlane, 1996
	Clostridium tetani	Smith and Macfarlane, 1996
Indole-3-acetic acid (IAA)	*Bacteroides thetaiotaomicron*	Elsden et al., 1976; Russell et al., 2013
	Bacteroides eggerthii	Smith and Macfarlane, 1996
	Bacteroides ovatus	Smith and Macfarlane, 1996
	Bifidobacterum pseudolongum	Smith and Macfarlane, 1996
	Clostridium bartlettii	Smith and Macfarlane, 1996
3-Indole acrylic acid (IA)	*Clostridium sporogenes*	Dodd et al., 2017
	Peptostreptococcus russellii	Wlodarska et al., 2017
Indole-3-aldehyde (IAld)	*Lactobacillus acidophilus*	Cervantes-Barragan et al., 2017
	Lactobacillus murinus	Wilck et al., 2017
	Lactobacillus reuteri	Zelante et al., 2013
Indole-3-lactic acid (ILA)	*Anaerostipes hardus*	Aragozzini et al., 1979
	Anaerostipes caccae	Dodd et al., 2017
	Bifidobacterum adolescelentis	Williams et al., 2014; Wlodarska et al., 2017
	Bifidobacterum bifidum	
Indole-3-propionic acid (IPA)	*Clostridium botulinum*	Dodd et al., 2017
	Clostridium caloritolerans	Elsden et al., 1976
	Clostridium cadvareris	Wlodarska et al., 2017
	Clostridium paraputrificum	Wikoff et al., 2009
	Clostridium sporogenes	Williams et al., 2014
Tryptamine	*Clostridium sporogenes*	Williams et al., 2014
	Ruminococcus gnavus	Williams et al., 2014

5. Microbiota-derived TRP metabolites in health and disease

Several reports demonstrated that microbiota-derived TRP metabolites are important in physiological functions. 3-methyl indole (Skatole) stimulates the growth and reproduction of some intestinal bacteria and causes bacteriostatic effects on gram-negative enterobacteria such as salmonella and shigella. It also prevents the growth and fermentation of *Lactobacillus acidophilus* (Gao et al., 2018; Yokoyama and Carlson, 1979). The presence of excessive saturated fatty acids causes lipotoxicity, which enhances hepatic damage in hyperlipidemia conditions. In contrast, skatole inhibits the negative effect of lipotoxicity by reducing fat accumulation, ER stress, and reactive oxygen species (ROS) production in hepatocytes (Hong et al., 2023). In addition, skatole also regulates caspase activity and thus reduces lipoapoptosis (Hong et al., 2023). Several studies suggested that skatole level can be used as a biomarker to detect pathological conditions (Zgarbova and Vrzal, 2022), such as colorectal cancer (Karlin et al., 1985), irritable bowel syndrome (Prospero et al., 2021), and schizophrenia (Nakao, 1960).

Previously, Kim et al. (2008) reported an increased level of the enzyme glutamic pyruvic transaminase (GPT)/alanine aminotransferase (ALT) in the blood, which is a well-known marker for liver damage (Kim et al., 2008), whereas IAA treatment protects from the liver damage by reducing GPT secretion in high-fat diet fed mice (Ji et al., 2019). Moreover, IAA relieves hepatic steatosis and protects C57BL/6 male mice against Non-alcoholic fatty liver disease (NAFLD). The mice also showed reduced hepatic triglyceride accumulation by downregulating lipogenesis genes such as Srebf1, Scd1, PPARγ, Acaca, and Gpam (Ji et al., 2019). In the case of rheumatoid arthritis, an increased level of IAA reduces disease severity in collagen-induced arthritis (CIA) rats (X. Li et al., 2020; J. Li et al., 2020). Wong et al. (2020) reported that ILA significantly enhanced NGF-induced neurite outgrowth of PC12 cells in a dose-dependent manner (up to 100 mM) through the Ras/ERK pathway (Wong et al., 2020). Hwang et al. (2009) reported oral supplementation of IPA for 15 days before ischemic surgery protected neurons from ischemic forebrain damage in the rodent model. They also reported the activation of glial fibrillary acidic protein (GFAP), S-100, and ionized calcium-binding adapter molecule 1 (Iba-1) and isolectin B4 (IB4)-immunoreactive microglia after ischemia/reperfusion, whereas IPA-treated ischemic group, prevent these effects (Hwang et al., 2009). However, IAld binds to IL-10R1 to increase mucosal barrier function and regulate epithelial homeostasis through the AhR-dependent pathway (Alexeev et al., 2018). Importantly, the combination of indole, IAA, and ICA showed nematicidal activity, which kills *Caenorhabditis elegans* (Bommarius et al., 2013). These findings collectively highlight the significant roles of these metabolites in various pathophysiological conditions. Recent studies primarily focused on how these metabolites regulate oxidative stress and inflammation, summarized below.

6. Microbiota-derived TRP metabolites regulate the immune response

Tryptophan metabolites can cross the physiological barriers and be

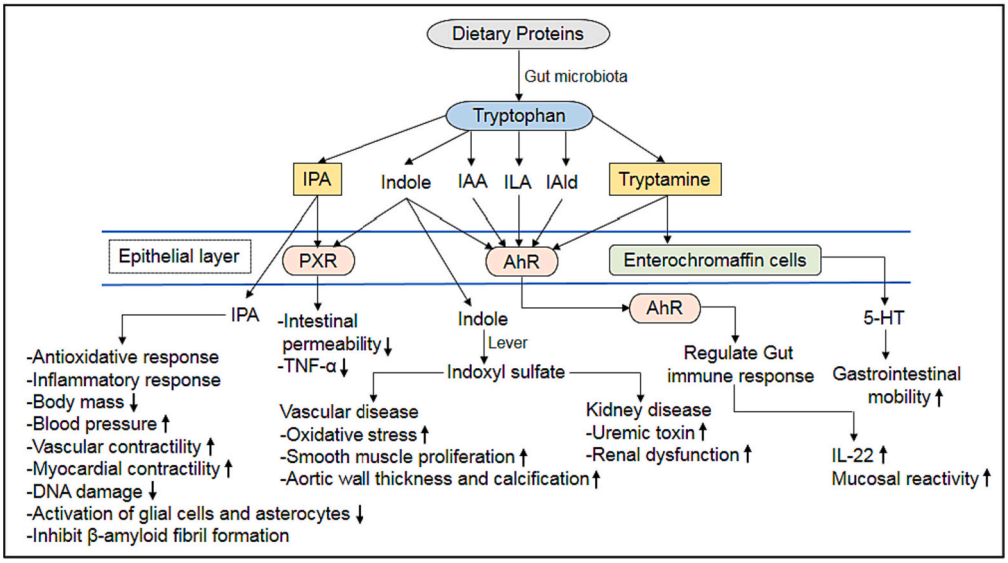

Fig. 2. The schematic diagram represents mechanism of action of microbial TRP metabolites in health and diseases in animals. Abbreviations: IPA: indole-3-propionic acid; IAA: indole acetic acid; ILA: indole-3-lactic acid; IAld: indole-3-aldehyde; PXR: pregnane-X-receptor; AhR: aryl hydrocarbon receptor; 5-HT: 5-hydroxytryptamine; IL-22: interleukin-22; TNF-α: tumor necrosis factor- α.

involved in the regulation of the host immune system (Bhattarai et al., 2018; Galligan, 2018; Jennis et al., 2018; Konopelski et al., 2019; Kurata et al., 2019; Lamas et al., 2016; Wlodarska et al., 2017). The endogenous TRP metabolites (e.g., kynurenine) and xenobiotics (e.g., phenolic compounds, alkaloids, drugs, and environmental pollutants) act as a ligand for the activation of aryl hydrocarbon receptor (AhR) transcription factor and regulate the immune response (Hubbard et al., 2015a, 2015b; Lamas et al., 2016; Sadik et al., 2020; Zelante et al., 2013). AhR is expressed on the surface of innate lymphoid cells, Th17 cells, dendritic cells (DCs), neutrophils, and macrophages (Cella et al., 2009; Kiss et al., 2011) and mediates vital metabolic pathways and immune response (Lamas et al., 2018).

Interestingly, microbiota-derived tryptophan metabolites, such as indole and several indole derivatives [e.g., indole-3-aldehyde (IAld), indole-3-acetic acid (IAA), indole-3-lactic acid (ILA), indole-3-propionic acid (IPA), indole acrylic acid (IA), indole-3-acetaldehyde (IAAld)], also regulates AhR and induces physiological responses (Zelante et al., 2013). For example, IAld, the metabolite produced by lactobacilli from TRP, regulates IL-22 transcription through AhR signaling (Zelante et al., 2013). In addition, IAld induces IL-22 secretory responses in lamina propria lymphocytes and restores intestinal mucosa barrier function (Hou et al., 2018). Walter and co-workers recently reported that microbiota-derived TRP metabolites IAA and IAld inhibit LPS-induced IL-6 expression through AhR signaling. Notably, they reported that these metabolites regulate fatty acid metabolism and maintain the gut barrier function (Walter et al., 2021). Fang et al. (2022) reported that indole-3-carbaldehyde (I3C) produced by *Bifidobacterium longum* suppresses abnormal T helper type 2 immune response to improve atopic dermatitis symptoms in animal and clinical experiments through the AhR signaling pathway (Fang et al., 2022).

Garcez et al. (2020) reported the anti-inflammatory effect of IPA in human astrocytes. They reported pretreating primary cultures of human astrocytes with IPA effectively prevented the LPS-induced elevation of MCP-1, IL-12, IL-13, and TNF-α levels (Garcez et al., 2020). IPA decreases the IL-1β-induced expression of inflammatory factors (IL-6 and TNF-α) in the liver, astrocytes, and muscles (Du et al., 2021; Rothhammer et al., 2016; Zhao et al., 2019). In osteoarthritis patients, IPA can decrease chondrocyte premature senescence and inflammation through the AhR/NF-κB pathway (Zhuang et al., 2023). Additionally, IPA decreased synovitis, cartilage degeneration, and serum inflammatory cytokine expression in vivo, illuminating its preventive role in the development of osteoarthritis (Zhuang et al., 2023). In addition, IPA increases the expression of anabolic markers (aggrecan and collagen-II) that work together in the articular cartilaginous tissue to resist and provide resistance to the forces of compression (Jariwala et al., 2022). Zhao and his colleagues reported the inhibitory impact of IPA on NF-κB signaling, leading to decreased levels of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6 in macrophages (Zhao et al., 2019). Krishnan et al. (2018) reported activation of TLR4 and nuclear factor-kB (NF-kB) signaling pathway and elevated levels of cytokines in the presence of palmitate and LPS and the addition of I3A or tryptamine to the culture medium significantly decreased cytokine levels in a dose-dependent manner (Krishnan et al., 2018).

Indole acetic acid (IAA) also regulates the immune response by activating AhR (Agus et al., 2018; D.M. Lee et al., 2020; C.J. Lee et al., 2020). It shows anti-inflammatory activity by reducing the LPS-induced expression of pro-inflammatory cytokines such as IL-1β, IL-6, and MCP-1 in RAW264.7 macrophages. In addition, it reduces the LPS-induced translocation of NF-κB p65 from the cytoplasm to the nucleus, thereby relieving the inflammatory response (Ji et al., 2020). Moreover, IAA could decrease the levels of pro-inflammatory cytokines (IL-6, TNF-a, IL-17A, IL-23) and increase anti-inflammatory cytokines in an autoimmune disease, ankylosing spondylitis (AS) mice. IAA can slow down the AS progression and relieve disease severity by suppressing inflammatory cytokines (Shen et al., 2022).

Aoki-Yoshida et al. (2013) recently reported that microbiota-derived TRP metabolites Indole-3-lactic acid (ILA) inhibit the ultraviolet B-induced production of IL-6 (Aoki-Yoshida et al., 2013). It also reduced TH17 polarization dose-dependently in the experimental autoimmune encephalomyelitis mice model (Wilck et al., 2017). ILA engages in a contest with human hydroxycarboxylic acid receptor 3 and induces a decline in cyclic AMP (cAMP) in human monocytes (Peters et al., 2019). Ehrlich et al. (2018) reported that ILA reduces LPS-induced activation of NF-kB in macrophages and intestinal epithelial cell lines at concentrations ranging 1–10 mM. In addition, it also weakens LPS-induced growth in the pro-inflammatory cytokine IL-8 (Ehrlich et al., 2018). Zhang et al. (2023) reported that a probiotic strain, *Lactobacillus plantarum* L168, and its metabolite ILA improve intestinal inflammation, tumorigenesis, and gut dysbiosis in numerous mice models. ILA encouraged IL12a production of DCs by ameliorating H3K27ac binding at the enhancer regions of IL12a, which contributed to priming $CD8^+$ T cell immunity against tumor growth. Furthermore, ILA improves the function of

tumor-infiltrating $CD8^+$ T cells by reducing the cholesterol level of $CD8^+$ T cells via lowering the expression of Saa3, an important gene for regulating cholesterol metabolism (Zhang et al., 2023). In addition, an experiment performed by De Giovanni et al. (2022) confirmed loss in neutrophil recruitment to the site of inflammation in a mice model deficient in 5-hydroxyindoleacetic acid (5-HIAA), which is a ligand for G-protein coupled receptor (GPR35) pathway (De Giovanni et al., 2022). However, microbiota-derived TRP metabolism is also known to protect from oxidative stress besides regulating immune response.

7. Microbiota-derived TRP metabolites regulate oxidative stress

In living cells, reactive oxygen species (ROS) are continuously generated by extrinsic factors that induce oxidative damage to cellular macromolecules (Rothhammer and Quintana, 2019). But, microbiota-derived TRP metabolism prevents cells from inflammatory insult, oxidative stress, and free-radical scavengers. IAA inhibits the generation of free radicals (ROS and NO) in RAW264.7 macrophages (Ji et al., 2020) as well as overcomes the hydrogen peroxide-induced oxidative damage to human dental pulp stem cells (hDPSCs) (Kim et al., 2017). IPA is considered a potent hydroxyl radical scavenger that inhibits the generation of ROS and lipid peroxidation (Iwan et al., 2021; Karbownik et al., 2001, 2006; Ortial et al., 2006; Qi et al., 2000; Rynkowska et al., 2021; Stasiak et al., 2010). Karbownik and colleagues reported that the male Wistar rats when concomitantly injected with potassium bromate (110 mg/kg) and melatonin or IPA (0.0645 mmol/kg) intraperitoneal for ten days, the oxidative damage to lipid peroxidation products such as malondialdehyde and 4-Hydroxyalkenals in rat kidneys and blood serum was decreased (Karbownik et al., 2006). Moreover, when rat hepatic microsomal membranes were treated with different concentrations of IPA and ferric chloride (0.2 mM), a reduction in lipid peroxidation was reported (Karbownik et al., 2001). Similarly, Iwan and the group demonstrated porcine thyroid cells, when treated concomitantly with melatonin (5 mM) and, IPA (10 mM), and potassium, oxidative damage was inhibited by the melatonin and IPA (Iwan et al., 2021). Furthermore, IPA significantly decreased the level of 4-hydroxy-2-nonenal, a marker of lipid peroxidation, in ischemic hippocampal (Hwang et al., 2009).

Owumi et al. (2023) recently reported that IPA prevents epirubicin (EPI)'s cytotoxic effect in rat models through an anti-oxidative and anti-inflammatory mechanism. They reported that co-treatment with EPI (2.5 mg/kg) and 3-IPA (20 mg/kg) encounters EPI-mediated reduction in antioxidant enzymes, reduced glutathione level, and total sulfhydryl groups in the hypothalamus, ovary, and uterus (Owumi et al., 2023). Microbiota-derived Tryptophan metabolites have anti-oxidant properties and cytostatic properties (Sari et al., 2020). Cytostatic metabolites inhibit cancer cells' proliferation, movement, and metastasis formation. Sari and the group reported that IPA selectively targeted breast cancer cells but did not affect non-transformed, primary fibroblasts. The cytostatic effect was induced through oxidative and nitrosative stress and boosting antitumor immune response. Moreover, they further reported that these effects were mediated through downregulation of nuclear factor erythroid 2-related factor 2 (NRF2), upregulation of inducible nitric oxide synthase (iNOS), and enhanced mitochondrial reactive species production (Sari et al., 2020). On the whole, the contemporary literature abundantly supports the notion that the metabolism of tryptophan by microbiota plays a pivotal role in governing oxidative stress and yielding advantageous outcomes in disease-afflicted states.

8. Role of tryptamine in aging-related diseases

The change in nutritional patterns plays a crucial role in influencing the aging process and the associated risks (Chiuve et al., 2006; King et al., 2013). As individuals age, their nutritional needs may change due to various factors, such as declining metabolism, changes in body composition, and alterations in nutrient absorption or failure to convert into active forms (Araujo et al., 2015; Bauer et al., 2013; Breen et al., 2013; Kaur et al., 2019; Kjeldby et al., 2013). Proper nutrition becomes increasingly important to maintain overall health and prevent age-related health issues. However, TRP metabolites, particularly those derived from the gut (Tryptamine, IPA, and Indol derivatives), hold promising potential in preventing aging-related diseases. These metabolites, generated through the gut microbiota's activity, have emerged as significant players in influencing various physiological processes and immune responses, impacting age-related health outcomes. Understanding and harnessing the role of these gut-derived TRP metabolites may open new avenues for interventions aimed at promoting healthy aging and mitigating age-associated diseases.

Tryptamine is a secondary aromatic amine that acts as a neurotransmitter and modulates intestinal homeostasis by altering gastrointestinal motility (Wlodarska et al., 2015). It decreases gastric pathogens' migration and invasion abilities (*Salmonella Typhimurium*) to distant places (Davis, 2013). Furthermore, its relevance extends to diagnosing inflammatory bowel disease (IBD) (Bischoff et al., 2009). Tryptamine exerts a strong cytotoxic effect on prostate cancer (PC-3) cell lines and other cell lines through the caspase-3-dependent pathway. It provides a novel strategy for prostate cancer therapy (Li et al., 2022). Moreover, tryptamine induces immune response by altering action against IDO1 inhibition, which is considered a possible anticancer therapy strategy (Tourino et al., 2013). Interestingly, *Lactobacillus* and *Clostridium* produce tryptamine through the indole pathway, which induces the release of serotonin from enterochromaffin cells in the gut and enhances the inhibitory effect of serotonin on neuronal cells (Takaki et al., 1985; Zucchi et al., 2006). N-salicyloyl tryptamine is a derivative of tryptamine which acts as a free radical scavenger and COX inhibitor and reduce neuronal injury as well as an anticonvulsant and anti-inflammatory agent in RAW264.7 cells (Gasparotto et al., 2013; Oliveira et al., 2001; Quintans-Junior et al., 2009, 2010; Sousa-Neto et al., 2018). The higher concentrations of tryptamine induce autophagy in brain cells by increasing dopamine secretion and preventing consumption (Herrera et al., 2006). Furthermore, tryptamine and other indoles lower the inflammatory capabilities of cytokines in cultured macrophages and TNF-α in hepatocytes (Krishnan et al., 2018). *N*-acetyl-5-methoxytryptamine, also known as melatonin, controls the circadian rhythm and is synthesized by the serotonin pathway (Leja-Szpak et al., 2004; Moreno et al., 2013). Cardiovascular disease is one of the important aging-related problems caused by the deposition of cholesterol and cellular waste products at the inner wall of arteries. But, the mechanism by which these metabolites regulate disease development is yet to be established. However, recent study discussed that tryptamine derivatives such as 5-fluorotryptamine/5-chlorotryptamine/5-hydroxytryptamine inhibit LDL oxidation via myeloperoxidase (MPO). MPO is an immune enzyme found in neutrophils and macrophages in the body responsible for the oxidative damage of biomolecules if leaking outside the cells that leads to atherosclerosis and other chronic inflammatory diseases (Jantschko et al., 2005; Soubhye et al., 2020). Furthermore, tryptamine derivatives showed activity against the hepatitis B virus and cytotoxicity in the hepatoblastoma cell line HepG2.2.15 (Qu et al., 2011). Based on recent studies, it seems that tryptamine is one of the important microbiota-derived metabolites involved in maintaining cellular homeostasis.

9. Role of IPA in aging-related diseases

The role of TRP metabolites has been implicated in many diseases. Western lifestyles impact the levels of TRP metabolites, which in turn play a role in various diseases including inflammatory bowel disease (IBD), ulcerative colitis (UC), irritable bowel syndrome (IBS), as well as metabolic conditions like diabetes, obesity, non-alcoholic fatty liver disease (NAFLD). Additionally, these metabolites are implicated in chronic diseases such as atherosclerosis and neuropsychiatric disorders. Recently, several groups confirmed the decreased production of IPA in

the serum of patients suffering from UC compared to average healthy persons (Alexeev et al., 2018). Furthermore, IPA shows anti-inflammatory properties on immune cells via decreased production of cytokines such as IL-1β (Du et al., 2021; Zhao et al., 2019), IL-6 (Zhao et al., 2019), IL-12, IL-13, TNF-α and MCP-1 (Du et al., 2021). It also inhibits bacterial growth, such as *Legionella pneumophila* (Grossowicz, 1990) and *Salmonella typhimurium* (Chelala and Margolin, 1983). Interestingly, IPA protects the cells from ROS and inhibits oxidative damage of lipids by inorganic salts (Iwan et al., 2021; Rynkowska et al., 2021). The activated ROS induces amyloid β-protein folding abnormally, leading to the deposition of amyloid plaques and causing neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease (Konopelski and Mogilnicka, 2022). In addition, IPA has some other physiological effects, such as protecting mice from harmful cardiometabolic effects on their lever and blood vessels (D.M. Lee et al., 2020; C.J. Lee et al., 2020) and reducing inflammation (Du et al., 2021; Zhao et al., 2019). Moreover, IPA activates the expression of pregnane-X-receptor (PXR) in mice aorta and reduces blood vessel response (Venu et al., 2019). The PXR is a ligand-operated nuclear receptor superfamily that monitors the expression of metabolic enzymes and drug transporters (Pavek, 2016). IPA was identified as a ligand that induces blood pressure through the cardiovascular mechanism and negatively regulates the advanced stage of atherosclerosis (Cason et al., 2018; Konopelski et al., 2021). Interestingly, IPA is involved in the mitochondrial respiration mechanism, and its prolonged exposure will cause loss of mitochondrial functions in the myocardium, hepatic, and endothelial cells (Gesper et al., 2021). IPA enhances the intestinal barrier function by decreasing intracellular permeability with increased tight junction proteins such as claudin-1, occludin, and ZO-1. In addition, it makes the mucus barrier stronger by increasing mucin (MUC2 and MUC4) proteins and goblet cell secretion proteins (TFF3 and RELMβ). Hence, IPA has an essential role in conserving and renewing gastrointestinal mucosa through mucins (X. Li et al., 2020; J. Li et al., 2020). Recently, it is reported that IPA inhibits endotoxin leakage from the gut to the bloodstream (Zhao et al., 2019). Apart from this, IPA is negatively associated with high-sensitivity C-reactive protein (hsCRP) in diabetes mellitus type II patients (Tuomainen et al., 2018). Moreover, the synthesis of IPA drastically reduced in patients with HIV infection (Nystrom et al., 2021). Interestingly, a group of researchers found that the bone mineralization and osteoblasts process dramatically increased in mice while fed a high IPA-supplied diet (Behera et al., 2021). Several other TRP-derived metabolites other than IPA and tryptamine also have protective roles against age-related complications.

10. Conclusion

We provide an in-depth exploration of Microbiota-derived TRP metabolism and their pivotal role in both physiological processes and the onset of aging-related diseases (Fig. 3). The TRP metabolism proceeds mainly through the kynurenine, serotonin, and indole pyruvate pathways. While the kynurenine and serotonin pathways are categorized as endogenous metabolism, the indole pyruvate pathway is categorized as bacterial metabolism controlled by gut microbiota (Fig. 1). The interactions between TRP metabolism, gut microbiota, and host immunity have been significantly studied over the past decades. The previous studies confirmed that endogenous and microbial metabolites such as indoles, tryptamine, and IPA profoundly affect microbiota composition and their functions. It has been observed that some indole derivatives such as IAA, ILA and IPA, and tryptamine have direct positive impact on human health by having anti-inflammatory, ROS-scavenging, and synergistic properties (Fig. 2). The decreased level of TRP metabolites indicates many pathological conditions associated with an increased risk of developing diseases such as autoimmune, inflammatory, cardiovascular, and oncological diseases. Furthermore, a decrease in tryptamine and serum IPA levels during disease progression is related

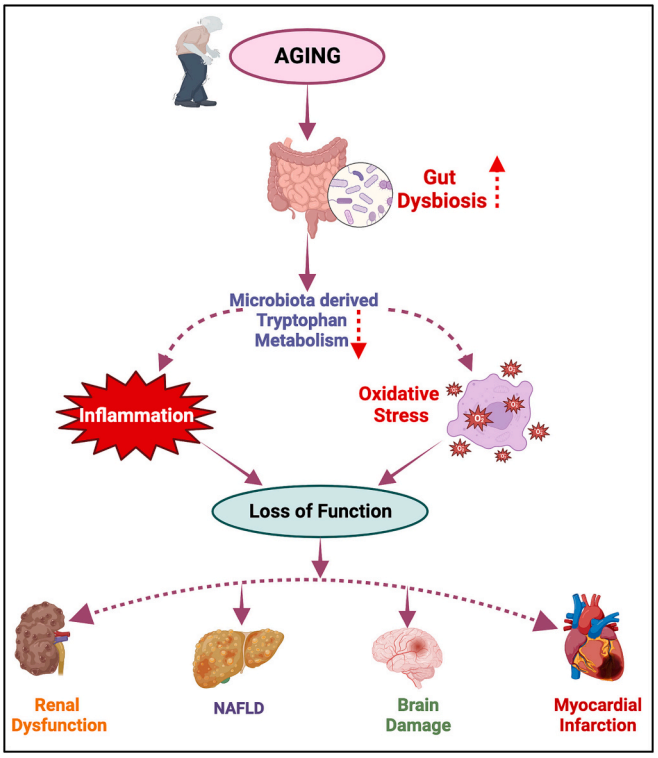

Fig. 3. The schematic diagram represents the summary of tryptophan metabolism irregularity arises due to gut dysbiosis and their cascading effects on inflammatory and oxidative stress resulting into loss of function with age.

to a reduction in corresponding microbes. However, future studies will be needed at the molecular and cellular level using well-defined animal models to find their possible therapeutic involvement to cure aging-related diseases. Such endeavors promise to shed light on potential interventions for addressing aging-related ailments.

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Ethics approval and consent to participate

Not applicable.

CRediT authorship contribution statement

SKG, SV, IDB, FB, CS and SF each made substantive intellectual contributions to the work described in this manuscript. SF and SKG conceived the idea for the manuscript and drafted it. SKG, SV, IDB, FB, CS and SF made the final edits to the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors state that they do not possess any conflicting interests. The funders played no part in designing study, conducting analyses, interpreting data, composing the manuscript, or determining the release of the findings.

Availability of data and materials

All the data and material presented and discussed in this manuscript are available in the previously published articles listed below in the reference section.

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