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Review article

Microbiota metabolites in the female reproductive system: Focused on the short-chain fatty acids

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ABSTRACT

Several disorders have been linked to modifications in the gut microbial imbalance, intestinal epithelium, and host immune system. In this regard, microbiota derived short-chain fatty acids (SCFAs) play a key function in the regulation of histone deacetylases (HDACs), which affect modulation of immunity and regulation of inflammatory responses in the intestine and other organs. Studies examining the metabolites produced by polymicrobial bacterial vaginosis (BV) states and *Lactobacillus*-dominated microbiota have noted a dramatic reduction of lactic acid and a shift toward SCFA synthesis. Along with higher levels of SCFAs, acetate is typically the main metabolite in the cervicovaginal fluid of women with symptomatic bacterial vaginosis. The fact that SCFAs made by the vaginal microbiota have been shown to exhibit antibacterial and immune-modulating properties suggests that they may have promise as indicators of disease and/or disease susceptibility. In this review, we overview and summarize the current findings on the detrimental or protective roles of microbiota metabolites especially SCFAs in the health and disease of the female reproductive system.

1. Introduction

The gut and genital tract microbiota as an essential and complex biological ecosystem has numerous functions [1,2]. Of note, the gut microbiota consists of approximately 10^{13} to10^{14} different microbes [3]. The uterine cavity (upper reproductive tract) is free of bacteria [4], whereas the cervicovaginal region (lower reproductive tract) contains trillions of microbes which play a significant role in the prevention of genital tract infections [1]. Colonization resistance is mainly mediated by *Lactobacillus*, which inhibit the overgrowth of pathogenic bacteria through the lactate formation [5,6]. The most common species of *Lactobacillus* identified in the vagina of most asymptomatic cases are as follows: *Lactobacillus crispatus*, *Lactobacillus iners*, *Lactobacillus jensenii*, and *Lactobacillus gasseri* [7].

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Furthermore, strictly anaerobic microorganisms are also found in asymptomatic cases, which include *Gardnerella*, *Prevotella*, *Atopobium*, *Peptoniphilus*, and *Megasphaera* [8]. It has been found that the origin of the female reproductive system microbiota is the rectum, which functions as a reservoir for the colonization of the normal vaginal flora [5,9]. The female vaginal microbiota prevents some urogenital disorders like bacterial vaginosis (BV), urinary tract infections (UTIs), yeast infections, human immunodeficiency virus (HIV) infection, as well as sexually transmitted infections (STIs) [8,10]. Several host factors influence the composition of the female reproductive microbiota, including, age, pregnancy, sexual activity, menarche, individual habits such as douching, as well as the use of spermicides or contraceptives [11].

Microbial metabolites in the female reproductive system are endproducts of metabolic reactions induced by the interaction of nutrition and microbiota, and they represent some downstream gene expression events [12]. As significant contributors to female genital tract inflammation, malignancies, and pregnancy, metabolites in the female reproductive tract can serve as indicators for illness severity, diagnosis, and prognosis [13,14]. In this regard, short-chain fatty acids (SCFAs) produced in the female reproductive system are the carbohydrates fermentation products and amino acid catabolism that are produced by BV-associated anaerobes [15]. Lactate produced by the asymptomatic women microbiota acidifies the cervicovaginal region, while SCFAs produced by BV-associated bacteria (BVAB) lead to creating a dysbiotic vaginal environment [10]. Among the most widely studied bacterial metabolites, SCFAs are fatty acids with one to six carbon in their backbone. The SCFAs typically have anti-inflammatory functions on the mucosa [16].

Despite the composition of the vaginal microbiota varies in asymptomatic reproductive-age cases, it seems that acidifying the vaginal environment by lactate-forming bacteria, mainly the *Lactobacillus*, is a conserved function [8]. In general, lactobacilli prevent the colonization and overgrowth of opportunistic pathogens by producing lactic acid, leading to maintaining low concentrations of SCFAs in asymptomatic women [10,17]. A reduction in lactate and an increase in vaginal SCFAs simultaneously indicate infection and dysbiosis because it increases vaginal pH above 4.5 [10]. The gut and vaginal microbiota affect the host health and disease as well as interact with other organs and systems. In addition, both microbiotas can modulate host immune responses and affect the homeostasis of other organs [1,18]. Therefore, in this review, we aimed to discuss and summarize the function and mechanism of microbiota-derived metabolites especially SCFAs in the health and disease of the female reproductive system.

2. Overview of microbiota metabolites

The human microbiota contains approximately 100 trillion microbial cells and 22 million unique microbial genes, which is more than the sum of total human cells and genes [19]. The human microbiota can synthesize various metabolites by these genes, which have a variety of bioactivities in the host [20]. The human microbiota has a high metabolic capacity and acts as a bioreactor that can cooperate with the host cells in many biological activities [21]. Microbial-derived metabolites can derive changes in the host and coordinate physiology and responses in numerous ways. In this regard, some gut microbiota members synthesize metabolites with direct effects at both systemic and local levels [22]. Systemically, the microbial metabolites can displace past the intestinal epithelium via active or passive transport and directly affect the extra-intestinal tissues and cells [23]. Locally, metabolites produced by bacteria are sensed directly by the intestinal epithelial cells and affect the function of the gut epithelial barrier [24,25]. The lamina propria is a layer of loose connective tissue beneath the epithelial layer that its immune cells contribute to forming the mucosal immune system. The metabolites could directly impact the role of immune cells in the lamina propria and cause an immune response in the host [22,26]. In addition, the local effects caused by metabolites can lead to downstream systemic effects [22]. Moreover, some bacteria synthesize metabolites that can alter the function or composition of other members of the microbiota. The metabolites generated by this group of bacteria have indirect effects on the host at both systemic and local levels. Microbially derived metabolites can maintain the composition of the microbial community and lead to competition with other species in the community. For instance, microbially derived antibacterials as one of the secondary metabolites can target other bacteria in the community and influence microbiota composition [22,27,28]. Based on the origination, microbially derived metabolites can broadly be divided into 3 classes: (1) metabolites that are synthesized by the host cells and biochemically modified by gut microbiota, such as secondary bile acids; (2) metabolites that are synthesized by gut microbiota directly from dietary components like SCFAs and indole derivatives; (3) metabolites that are synthesized *de novo* by gut microbiota, such as polysaccharide A [16,20]. Most gut microbiota metabolites have similar functions and chemical structures. Typical gut microbiota metabolites include SCFAs, bile acids, gases (hydrogen sulfide, hydrogen, carbon dioxide, methane, and nitric oxide), tryptophan and indole derivatives, choline metabolites, vitamins, neurotransmitters, and lipids, which play an crucial function in health and diseases of the host [20]. These metabolites have numerous functions, such as regulation of the function and gut microbiota composition, host metabolism modulation, gut motility, improve intestinal barrier, impacting the systemic immune response, influencing the nervous system, circadian rhythm modulation, affecting drug toxicity and efficacy, as well as, serving as nutrition and influencing nutrition absorption [20]. Microbiota produces high rate of SCFAs such as butyrate, propionate, and acetate, which are endproducts of fermentation of dietary fibres [29]. Saccharolytic bacteria (*Firmicutes*, *Bacteroidetes*, and *Actinobacteria*) which are exist in the colon and distal small intestine produce SCFAs through fermentation of dietary fibres such as inulin, resistant starch, and other low-digestible polysaccharides. These bacteria are also able to degrade some peptides and proteins through the parallel Pentose-phosphate and/or Embden–Meyerhof–Parnas (glycolytic) pathways, resulting in the formation of SCFAs [18,30,31]. SCFAs can decrease the pH of the colon and affect the competition of gut microbial community for survival and growth. *Bifidobacteria* and *lactobacilli*, for example, thrive in this low pH, while organisms such as yeasts and opportunistic bacteria *Escherichia coli* and *Clostridium* are unable to tolerate low pH conditions [31–33]. Intestinal epithelial cells absorb SCFAs according to their charges by passive diffusion, electrogenic, or electroneutral absorption (carrier-mediated uptake) mechanism. The transporters include monocarboxylate transporter 1 (MCT1) and MCT4, which are electroneutral transporters; and sodium-coupled MCT1 (SMCT1) and SMCT2, which are electrogenic and electroneutral transporters, respectively [3,34]. The immunity and

metabolic-related effects of SCFAs in the intestine are derived from their interaction with 3 free fatty acid receptors (FFARs) or G-protein coupled receptors (GPRs), i.e., FFAR3 (GPR41), FFAR2 (GPR43), and HCAR2 (GPR109A). Also, histone deacetylases (HDACs) inhibition which is mainly mediated by propionate and butyrate is another factor of such effects [34–37]. The FFARs are produced on the gut epithelium, adipose tissue, and immune cells such as macrophages, B/T lymphocytes, peripheral blood monocytes (PBMC), polymorphonuclear neutrophils (PMN), dendritic cells, and peripheral blood mononuclear cells [34,35,38,39]. Based on several studies' claims, immunomodulatory roles of microbiota-generated SCFAs are different in the gut and vaginal [36,37,40]. SCFAs produced in the gut promote eubiosis (including the raise in *Lactobacillus* and low pH), homeostasis, and tolerance by inhibiting the translocation of bacteria (metabolic bacteremia) and lipopolysaccharide (LPS) (metabolic endotoxemia) into the systemic circulation, suppressing the production of pro-inflammatory chemocytokines such as tumor necrosis factor-α (TNF- α), Interferon gamma (IFN-γ), Interleukin (IL) 1 beta (IL-1 β), IL-8, IL-6, etc., as well as increasing IL-10 (anti-inflammatory cytokine), Foxp3C CD4C T cells and prostaglandin E2 (PGE2) [18,41]. By contrast, an increase SCFAs in the female reproductive system leads to a decrease in the *Lactobacilli* population and lactic acid concentration, which increases vaginal pH. Overall, it leads to mixed anaerobic populations and induces inflammation [10,18]. These mixed anaerobic populations include *Streptococcus*, *Bacteroides, Gardnerella*, *Prevotella*, *Mycoplasma*, *Ureaplasma*, *Finegoldia*, *Mobiluncus*, *Leptotrichia*, *Eggerthella*, *Veillonella*, *Dialister*, *Atopobium*, *Megasphaera*, *Sneathia*, *Clostridiales* BVAB 1–3, etc., that are seen in female genital tract diseases such as BV and vulvovaginal candidiasis (VVC) [10,17,42]. It is worth noting that a species of *Lactobacillus* known as *L. iners* is also mediated to BV and dysbiotic vaginal microflora [42]. Anaerobes associated with BV can produce SCFAs in the women reproductive system through the fermentation of carbohydrates and amino acid catabolism. The most common SCFAs in the female genital tract include propionate, acetate, isovalerate, isobutyrate, and n-butyrate [43]. Collectively, SCFAs can lead to proinflammatory and dysbiotic effects in the female reproductive system.

3. Microbiota short-chain fatty acids, and roles in health and diseases

One of the main benefits of SCFAs in the digestive system is their ability to acidify the digestive tract and increase the absorption of some nutrients, and they can also directly affect the microbial composition of the normal intestinal flora using different mechanisms [44]. SCFAs, if they are in low concentration, exert their beneficial effect by providing a carbon source for the intestinal microbiota, and if their concentration is high, they can be toxic to the normal intestinal flora and destroy them [45]. Some gastrointestinal SCFAs can cross bacterial membranes and cause effects such as altering osmotic balance, affecting gene expression, amino acid uptake, and oxidative metabolism to chemotactic responses, among others [46]. For example, at high concentrations, SCFAs can strongly inhibit the growth of *Salmonella*, a common food pathogen that causes many gastrointestinal disorders, by acidifying environmental conditions, and by reducing the expression of virulence genes responsible for the invasion [47,48]. Most of the produced SCFAs are absorbed by intestinal colonocytes and only about 5% of them are secreted in the feces. Most SCFAs are in ionized form and their entry into the host usually requires specialized transporters, but a small part of SCFAs present in non-ionized form and can directly cross the epithelial barrier through non-ionic diffusion [49–51].

Acetate, butyrate, and propionate are the main SCFAs produced by fermentation by bacteria, butyrate being the preferred substance for gut colonocytes as an crucial energy source and largely metabolized in the epithelial mucosa to maintain colon health [52]. On the other hand, propionate and acetate can move from different parts of gut to the liver, where most propionate is metabolized but not acetate [53]. Hence, acetate is the most abundant SCFA in the circulatory system of human. The SCFAs can have many health benefits for the host body [54]. In this sense, the SCFAs maintain the integrity of the epithelial barrier by regulating tight junction proteins such as occludin, claudin-1,as well as zonula occludens-1 [55]. The reduction of these proteins weakens the strength of the epithelial barrier, and in this case, the transfer of bacteria and their LPS from the epithelial membrane barrier becomes easier and facilitates the stimulation of the inflammatory reaction [56]. The SCFAs can also protect the colonic epithelium by increasing mucin expression and modulating oxidative stress and immune reactions. This function of SCFAs is especially crucial for the human body in fighting intestinal abnormalities such as Crohn's disease (CD), Ulcerative colitis (UC), and colorectal cancer [39]. After SCFAs are absorbed into the body, these substances can be transported to various organs. For example, propionate is involved in gluconeogenesis while butyrate and acetate are involved in lipid biosynthesis. In addition to acting as important energy sources, these molecules can modulate various biological responses of the host including inflammation and oxidative stress [57,58].

The health and integrity of the colon are strongly supported by SCFAs, especially butyrate. The primary and preferred metabolic substrate for colonocytes is butyrate, which meets at least 60–70% of their energy needs for growth and differentiation [59]. Due to this lack of SCFAs, colonocytes from germ-free animals suffer from severe energy deprivation, as shown by the decreased expression of important enzymes involved in fatty acid metabolism in mitochondria [59]. In addition to providing colonocytes with a significant amount of energy, SCFAs in the gut also regulate gastrointestinal pH, colonic motility, and colonic blood flow, all of which can affect how well nutrients and electrolytes are taken in and absorbed [59]. Finally, SCFAs play important immunological roles both systemically and locally in the female reproductive system, extending beyond their local effects on enterocytes and digestion function in the gut.

4. Female reproductive tract microbiota in health and disease

The mucous of the female genital tract contains microflora that play an crucial role in the health [60]. The vaginal microbiota includes various species of *Lactobacilli* including L. *crispatus, L. gasseri, L. iners, L. jensenii,* etc [61]. These vaginal microbiota is considered desirable because of the protective properties, which include the production of lactate to lower vaginal pH and the production of bacteriocin and hydrogen peroxide, which provide an antimicrobial environment for pathogenic microorganisms and limit

their growth [62]. Despite this issue, different species of *Lactobacillus* are significantly capable of producing different antimicrobial agents [63]. New molecular methods have provided detailed information on vaginal bacterial diversity, which reveals that the *Lactobacillus* often is not the dominant microorganism of the female genital tract, and some cases have a higher diversity of non--*Lactobacillus* bacterial community with an overgrowth of e anaerobes like *Gardnerella*, *Provetella*, *Mobiluncus,* and *Atopobium*,which cause various infections including vaginosis [64,65]. Vaginal bacterial dysbiosis is mediated to changes in the mucosal microenvironment i.e. enhanced inflammatory mediators, numbers of cells like activated $CD4^+$ T cells, altered pathways, and disruption of the epithelial barrier and formation of immunomodulatory metabolites [66]. Vaginal bacterial dysbiosis has harm to the reproductive health of people, including an increase in the incidence of STIs, an increase in the risk of premature birth, and an increase in the risk of human papillomavirus (HPV) infection and subsequent cervical cancer [67–69]. BV is the common vaginal disease for adult cases, which affects women worldwide and has devastating influence on the quality of life of women in terms of physical, emotional, sexual, and social aspects [70].

The study of the upper female genital tract and, in particular, the intrauterine and endometrial microbiota is hampered by the difficult sterile access without cervicovaginal contamination and the lower biomass of the upper compared to the lower female genital tract [71]. Studies have shown that some bacterial species share an upper female genital tract with a lower female genital tract [72]. Whilst the vaginal microbiota is dominated by *Lactobacillus*, it is not known whether this feature is shared in healthy or un healthy of

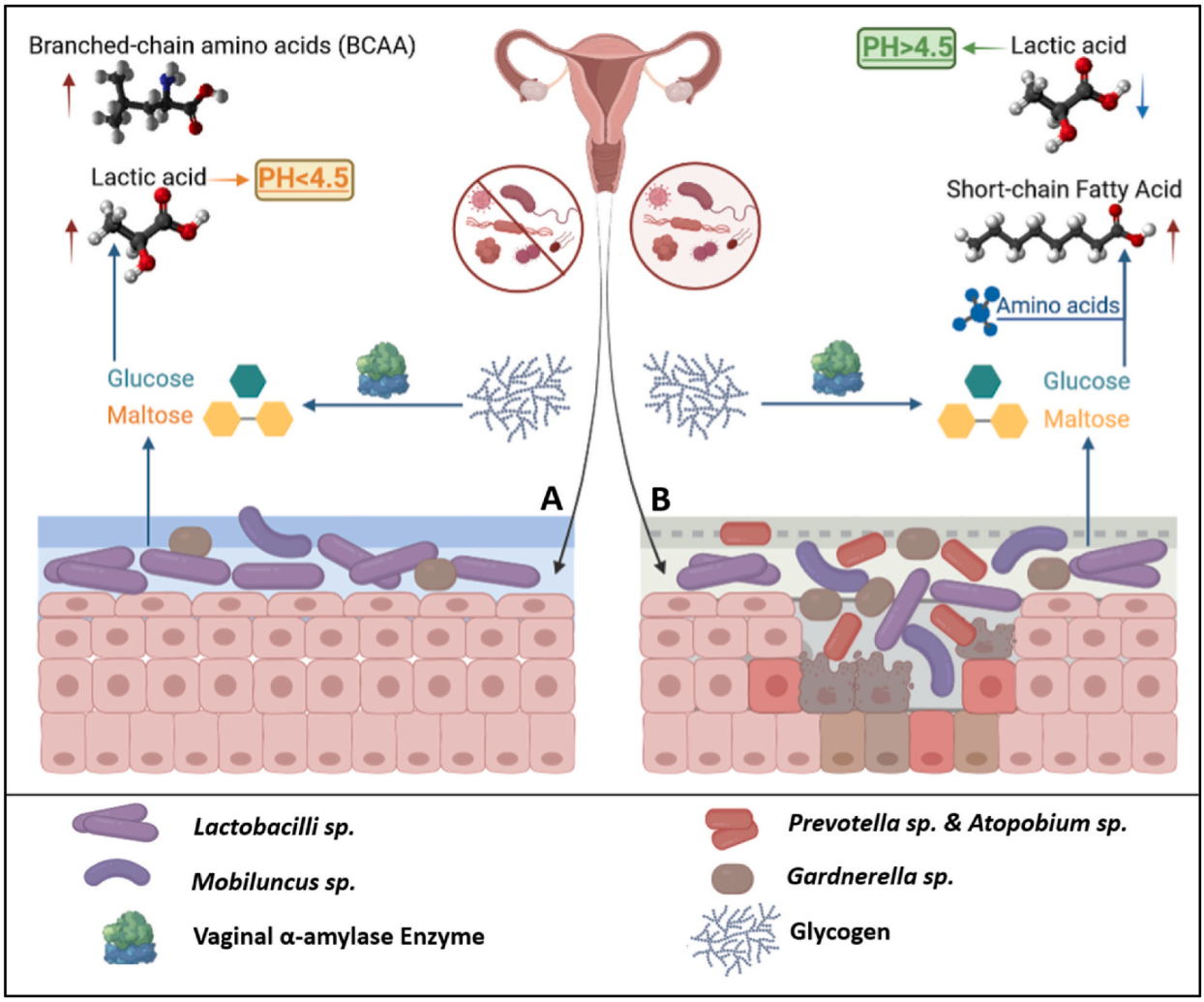

Fig. 1. Female genital tract microbiota in healthy (A) and disease (B) conditions. A) In a healthy vagina, during eubiosis, the lactobacilli group of bacteria produces lactic acid which regulates the vaginal PH < 4.5, in this situation acid-tolerant bacteria can be alive and pathogenic bacteria inhibited. Also, lactic acid has anti-inflammatory effects that protect epithelial cells. Further, the viscoelasticity of mucus is maintained. **B)** During dysbiosis and BV, lactic acid-producing bacteria are limited then lactic acid decreases, and other pathogenic bacteria like *Prevotella* sp, *Gardnerella* sp, *Atopobium* sp, and *Mobiluncus* sp grow over. These pathogens produce short-chain fatty acids (SCFAs) from glucose, maltose, and some amino acids, at a high level. In this condition, epithelial integrity is compromised by bacterial virulence factors, viscoelasticity of mucus damage, and a pro-inflammatory environment with malodor is generated. Created using www.biorender.com.

the upper female genital tract such asthe endocervical canal and uterine cavity [73]. Whilst some studies of intrauterine specimens obtained from the transcervical approach show a predominance of *Lactobacillus*, the existence and relative number of *Lactobacillus* in uterine specimens when obtained from sterile open hysterectomy specimens was more variable [74,75].

Several studies have shown a decrease in *Lactobacillus* abundance from the lower to upper female genital tract microbiome [76]. They show high diversity in the uterine cavity and the number of non-*Lactobacillus* spp. in healthy and malignant states [77]. Despite similarity in structural compositional between the lower and upper female genital tract, functional analyzes of the upper female genital tract microbiota have not yet been seen, and it is unclear whether the same species can have particular interplays with the endometrial mucosa compared with the vagina or cervix [78]. The immunological states of the endometrium and their ability to respond against pathogens and immune modulation have been found in the context of embryo implantation, infertility treatments, as well as female reproductive health [79]. The role of immune reactions within the endometrium for immune tolerance to fetal antigens and the possibility of trophoblast invasion and vascular remodeling during implantation is well defined [80]. Furthermore, there is a growing body of documents that host immune responses in the endometrium can be modulated by the presence of the upper female genital tract and the uterine microbiota [81].

The vaginal tract includes a dynamic bacterial community. This microbiota is composed of diverse bacterial species that can vary in different conditions such as changes in estrogen hormone levels, menstrual cycle, menopause, sexual activity, pregnancy, lactation, diabetes mellitus, stress, and antibiotic therapy [82]. In healthy women, during the eubiotic state, lactic-acid producer bacteria (*Lactobacilli*) are the dominant species. The concentration of lactic acid may reach as high as 120 mM in the lower genital tract and the concentration of acetic acid is 0–4 mM [83,84]. This mutualistic vaginal microbiota is located in the lower reproductive tract (vagina and ectocervix) covered with a cervicovaginal fluid containing many anti-microbial compounds. *Lactobacilli* can utilize the glycogens indirectly according to the following steps; first, high estrogen levels released glycogens from vaginal epithelial cells cleaved by the vaginal α-amylase enzyme into pyruvate. Next, pyruvate changes into maltose, maltotriose, maltopentaose, and maltodextrins. Then, *Lactobacilli* break maltose into lactic acid in the glycolysis pathway in anaerobic conditions which regulate the vaginal pH lower than 4.5 and are responsible for vaginal acidity in healthy women [10,85,86]. Therefore, free glycogen levels and α-amylase to cleave the glycogen and *Lactobacilli* in the vaginal tract correlate with low vaginal pH in healthy women. In addition, the availability of maltose in the healthy vagina is a basic reason for the overgrowth of lactobacilli [87]. Lactic acid and hydrogen peroxide (H_2O_2) production by *Lactobacilli* and low pH are anti-microbial factors that protect the host from the colonization of pathogens [10]. Although, lactic acid bacteria species can produce branched-chain amino acids (BCAA) such as valine, leucine, and isoleucine, which is another hallmark of *Lactobacilli* in a healthy vagina (Fig. 1, A), [17].

In dysbiotic, BVAB, *Prevotella, Gardnerella*, *Bacteroides*, *Mobiluncus*, *Atopobium*, *Mycoplasma*, *Ureaplasma*, *Sneathia*, *Streptococcus*, *Eggerthella*, *Dialister*, *Leptotrichia*, *Finegoldia*, *Megasphaera*, *Veillonella*, and *Clostridiales* are the dominant species [83]. These BV-associated anaerobes species cannot produce lactic acid (<20 mM) and thus break glycogens into glucose and SCFAs metabolites such as butyrate, propionate, succinate, and especially acetate (the acetate concentration is < 120 mM) [86] as well as, SCFA produced by the degradation of amino acids. Although SCFAs are predominant metabolites in dysbiosis of the vaginal tract, the causality of the relationship between dysbiosis and SCFAs production is still under debate [83]. Lactic acid and SCFA metabolites known as anti-microbial and immune modulators can represent their potential as biomarkers of disease. In the human gut, SCFAs have an

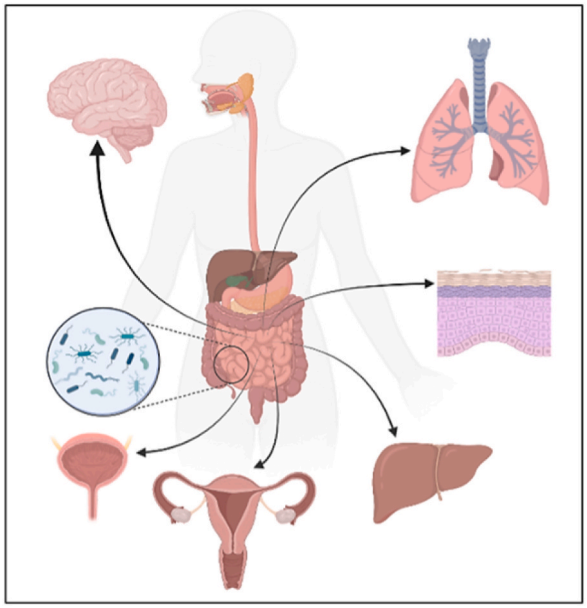

Fig. 2. Different microbiota crosstalk networks; gut-brain axis, gut-liver axis, gut-bladder axis, gut-lung axis, gut-skin axis, and gut-vagina axis. Created using www.biorender.com.

anti-inflammatory role by inhibiting proinflammatory cytokines (IL-8, IL-1β, and TNF-α) from peripheral blood mononuclear cells. Peritoneal macrophages may be a potentially important regulator in the communication between endometriosis and gut microbiota, in contrast, in the vagina, SCFAs failed to induce a pro-inflammatory response [18].

Also, BV-associated anaerobes species make changes in amines (including cadaverine, tyramine, and trimethylamine) which are responsible for the fishy odor of vaginal discharge, which make changes in amino acids and BCAA [88]. As well as, they can generate virulence factors including proteases, LPS, lipoteichoic acids (LTA), flagella, and peptidoglycans (PGN) which stimulate immune responses [89]. In this situation, the vaginal pH elevates more than 4.5, epithelial barrier integrity is compromised, mucin degrades, and therefore BV and other female genital tract disorders like gynecological cancers increase (Fig. 1, B) [10].

5. Gut-vagina microbiota axis

Different microbiota-host interactions are understood in the human body by metagenomic and culturomic analysis [1]. Human microbiota can form a network including human cells and microorganisms that can cross-talk through microbial-derived metabolites such as SCFAs [90]. Among different microbiota, the gut microbiota is very important, and it can play the main role in many crosstalk networks, including the gut-brain axis [91], gut-liver axis [92], gut-bladder axis [93], gut-lung axis [94], gut-skin axis [95], and gut-vagina axis (Fig. 2) [18,96].

The metabolic role of the gut microbiota are significant for maintaining homeostasis and the health of other organs by exerting mechanisms of regulation on extra-intestinal bacteria, circulating hormone, and immunity [1,90]. Thus, the composition of gut microbiota, including *Bifidobacterium*, *Lactobacillus*, *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, and *Proteobacteria* [34], these bacteria that are common in the vaginal tract too [1], are associated with human health homeostasis and the dysbiosis has been associated with both

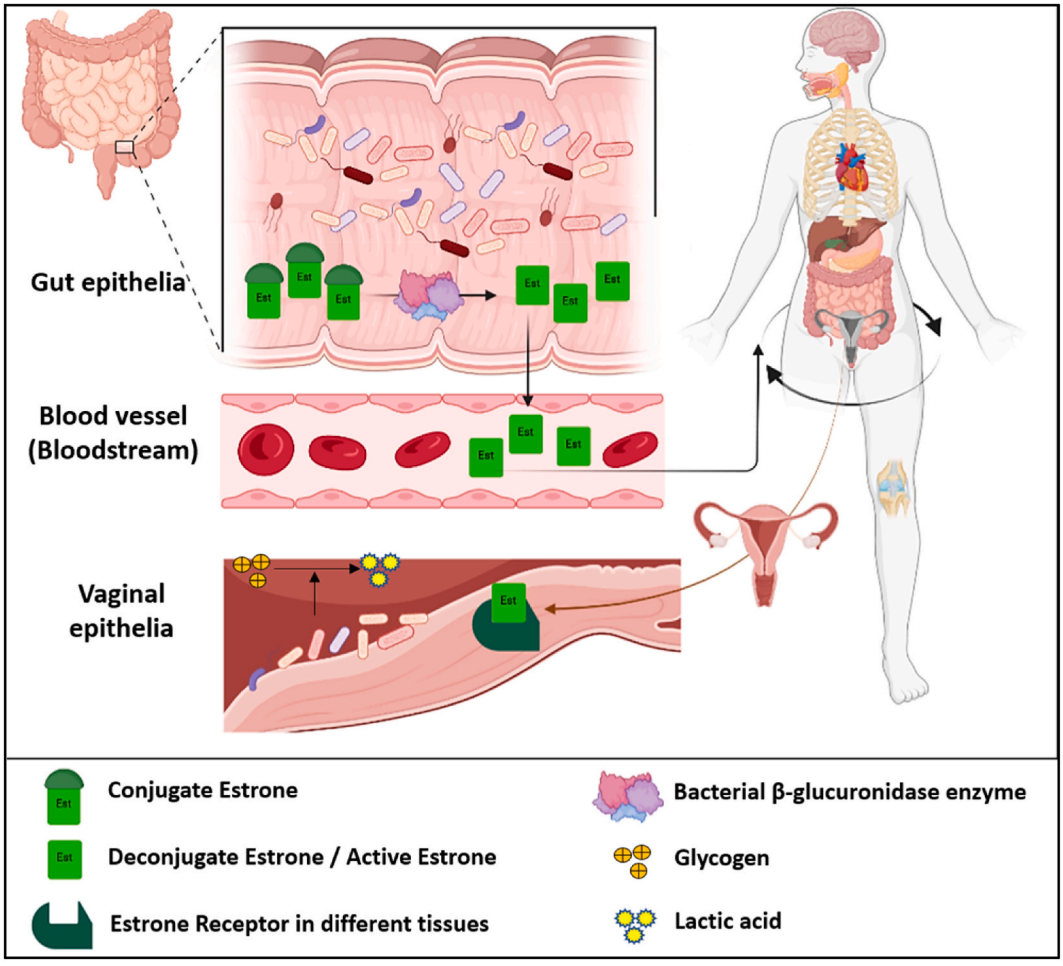

Fig. 3. Effect of gut microbiota on estrogens metabolized. At first, conjugated estrogens are metabolized by bacterial β-glucuronidase enzymes and into deconjugated or active estrogens. Then, deconjugated estrogens translocate into the bloodstream and circulate in the body at distal sites. Finally, active estrogens interact with their receptors in different tissues like vaginal epithelium which leads to physiological changes. Through a lack of circulating estrogen and SCFAs, hypo estrogen-related disorders were observed. Created using www.biorender.com.

intestinal and extra-intestinal disorders directly and indirectly.

The metabolic profile of gut microbiota shows important critical compounds in the gut microenvironment, such as butyrate, acetate, and propionate, the SCFAs, with anti-inflammatory effects that maintain intestinal homeostasis, immunological homeostasis, and provide an energy source for colon cells lead to epithelial barrier integrity [34,89]. In gut microbiota, dysbiosis and changes in SCFA production lead to a deficiency in epithelial barrier function and tight junction thus translocation of the gut microbiome into the bloodstream (especially their LPS) increases, causing systemic inflammation [89]. Consequently, TLR-4 is triggered by LPS, cytokines, and chemokines such as IL-1β, IL-8, IL-6, and TNF-α being released. Also, macrophages, Natural killer (NK) cells, T helper (Th), cytotoxic T cells (CTLs), and B-lymphocytes subsequently promote appropriate immune reactions. These inflammatory reactions control pathogen infections but, in some cases, affect the integrity of the mucosal surface and therefore facilitate the transmission of other pathogens [83]. Consequently, dysbiosis changes physiological responses and contributes to disease states directly.

The gut microbiota could impact the distal mucosal sites like genital microbiota homeostasis through estrogen-mediated mechanisms, indirectly (Fig. 3) [97]. Estrogens play an crucial function in stimulating the women's reproductive system, such as increasing epithelial cell thickness, glycogen levels, mucus secretion, and decreased vaginal pH by promoting the population of lactobacilli and lactic acid formation [89]. Due to estrogen receptors located in various tissues like bone, brain, liver, adipose tissue, skin, salivary gland, prostate, and colon, they are critical to many other physiological functions [98]. In normal conditions, a beta-glucuronidase enzyme produced by microbiota metabolizes the body's circulating estrogens (estrobolome; a collection of gut microbiota's genome needed for metabolizing estrogen) and converts them from conjugated to deconjugated form. The deconjugated form, the active form, enters the bloodstream and attaches to its specific estrogen receptors in various tissues, such as the brain, affecting tissues' physiological responses. However, dysbiosis disrupts estrogen metabolism. Through a lack of circulating estrogen and SCFAs, physiological responses change and occur in hypo estrogen-related disease [99]. Gut-vagina axis remains less investigated than the gut-brain axis and hormonal changes and dysbiosis in microbiota lead to inflammation in the gut and vaginal tract [1].

6. Female reproductive tract microbiota metabolites with a focus on short-chain fatty acids in health and disease

Along with host factors, vaginal fluid also contains bacteria metabolites [100]. Compared to L. *iners*, which solely generates L-lactic acid (L-LA), L. *gasseri*, *L. crispatus*, and *L. jensenii* generate more D-lactic acid (D-LA) than L-LA [101,102]. According to certain theories, the variety and health of the vaginal microbiome can be significantly influenced by the levels of D- and L-LA in the vagina. Contrary to mucus with low rate of D-LA typical of *L. iners* dominating microbiomes, vaginal mucus with high rate of D-LA exhibit improved entrapment of HIV-1 [102]. D-LA and L-LA could lower the pH of the vagina, inhibit yeast and bacteria from growing there, and lessen the formation of pro-inflammatory mediators by the epithelial cells [103]. Hearps et al. [103] demonstrated that the anti-inflammatory cytokine IL-1RA was produced when LA (pH 3.9) was applied *in vitro* to human cervical and vaginal epithelial cell lines. Additionally, LA reduced the generation of IL-6 and IL-8 produced by exposure to seminal plasma and suppressed pro-inflammatory mediators IL-8, IL-6, TNF, Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted (RANTES), and Macrophage Inflammatory Protein-3 (MIP3) from epithelial cells when administered concurrently with or before stimulation [103].

Additionally, all *Lactobacillus* spp., except *L. iners*, create bacteriocins and hydrogen peroxide as byproducts, both of which prevent the development of dangerous non-indigenous bacteria [104,105]. As an alternative, *L. iners* and *G. vaginalis* both release vaginolysin and cholesterol-dependent cytolysin, which are cauterized to their cytotoxic effects against cervical and vaginal epithelial cells [106, 107]. In an *in vitro* experiment, compared to *L. crispatus* supernatant *Gardenella*, and *L. inners'* culture supernatant enhanced the permeability of endocervical and ectocervical cell culture by weakening the E-cadherin and enhanced formation of soluble cadherin [108]. As opposed to *Gardenella, L. crispatus* produced byproducts in the culture supernatant that served to repair the integrity of the ectocervical and endocervical barriers [108]. Unfortunately, the profiling of byproducts of supernatants were not investigated in this work. However, substantially larger quantities of SCFAs have been discovered in BV patients [109]. The upregulation of the butyrate metabolizing enzymes i.e. butyryl-CoA-dehydrogenase as well as butyrate kinase during BV, together with an increase in *Megasphaera,* and *P. amnii* was also demonstrated by a *meta*-transcriptomic research [106].

New research has identified SCFAs as essential metabolic and immunological mediators [110,111]. In this aspect, SCFAs function as an energy source, a regulator of gene expression and cell differentiation, and an anti-inflammatory agent, all of which are critical to sustaining colonic health [112]. The cervicovaginal area is made acidic by the lactic acid generated by the microbiota of asymptomatic women, whereas the dysbiotic vaginal environment is made by the SCFAs produced by BVAB. The makeup of vaginal bacterial communities affects the mucosal barrier's vaginal defense by preventing the growth of harmful bacteria that cause illness, either by creating microbicidal chemicals or by improving the host's barrier function [113]. Mucus is one of the essential elements of the barrier function at the mucosa of the female reproductive system. *L. crispatus*-dominated vaginal microbiota capture microorganisms, such as HIV more effectively compared to mucus associated with vaginal microbiota dominated by *Gardenella* and L. *iners* [102]. There is still little information available on how vaginal microorganisms alter the function of mucus in defense. Mucus can become impaired if BV-associated bacteria degrade it. A vital component of the mucus in the female reproductive system, sialic acid, is aggressively degraded by BVAB like *Prevotella, Gardnerella,* and *Bacteroides* [114,115]. The integrity of the female reproductive system's barrier is harmed by other mucus-degrading enzymes such as sulfatases, mucinases, galactosidases, and prolidases, which also contribute to the watery vaginal discharge that is a BV symptom [114,115]. Along with mucus, host derived proteins in vagina are essential for the vaginal epithelial barrier's proper function. It has been discovered that the intestinal epithelial barrier function and the toll-like receptor 4 (TLR4)-Nuclear factor kappa B (NF-κB) pathway are both maintained by SCFA propionate host cell function [115]. The SCFAs might control mucus production, microbial homeostasis, and intestinal epithelial tight junction to stop intestinal endotoxin from spreading to the liver and lowering oxidative stress and inflammatory levels [115]. The innate immune cells' ability to participate in

the immune system like dendritic cells, might be regulated by the SCFAs [3]. The SCFAs can also control T and B cell development and operation, which would therefore facilitate antigen-specific adaptive immunity. For instance, GPR41 interaction and HDAC inhibition by SCFAs caused $CD4^+$ T cells to produce IL-22 [116]. In summary, SCFAs influence the immune system's operation by boosting T and B cell differentiation to control antigen-specific adaptive immunity and inhibiting dendritic cell migration and activation to reduce allergies [117]. SCFAs' immunoregulatory effects are mostly brought about by their direct binding to SCFA-specific GPCRs (such as GPR41) on the cell surface and entry inside cells, where they control cell metabolism and inhibit HDAC [117]. The majority of the time, SCFAs have a positive effect on the gut mucosa by enhancing epithelial integrity, differentiation, and proliferation as well as decreasing the release of pro-inflammatory chemicals from mucosal epithelial and immune cells [118,119]. There is still little understood about the function of SCFAs in the female genital tract mucosa. Contrary findings from an *in vitro* investigation indicate that vaginal and cervical epithelial cells can secrete pro-inflammatory molecules in response to high amounts of SCFAs [119]. There is still much to learn about how greater SCFA levels affect the female genital tract mucosal barrier function and how it relates to BV problems.

Few studies have investigated the role of SCFAs in female reproductive tract health and diseases. In a study, Guo et al. [120] showed that the administration of sodium butyrate alleviates LPS-induced endometritis in mice by inhibiting inflammatory response. In another study, Chadchan et al. [121] reported that the progression of endometriosis can be inhibited by gut microbiota–derived SCFAs. Zhang et al. [122] reported that following the administration of *Bifidobacterium lactis* V9 the secretion of sex hormones in polycystic ovary syndrome (PCOS) patients regulated through the gut-brain axis. The authors declared that the regulatory mechanism can be described as follows. Consumption of *B. lactis* V9 enhances the growth of SCFA-forming bacteria which in turn affects the secretion of ghrelin and PYY (gut-brain mediators). Finally, ghrelin and PYY changes lead to alteration in the sex hormones levels through the gut-brain axis [122]. Haidari et al. [123] showed the positive effects of flaxseed supplementation on metabolic status in women with PCOS. They suggested that because flaxseed contains a high amount of soluble fiber which can be fermented to SCFAs, downregulating inflammatory pathways in the body and reducing the levels of inflammatory mediators like TNF-α, CRP, and IL-6 [123]. He et al. [124] showed that *Lactiplantibacillus plantarum* CCFM1019 improved PCOS symptoms in rats through a butyrate-dependent gut–brain axis. In this study, *L. plantarum* CCFM1019 reduced the pathological changes in the ovaries and restored testosterone and luteinizing hormone levels. Results demonstrated that treatment with *L. plantarum* CCFM1019 showed higher butyrate and polypeptide YY rates compared to the letrozole-treated rats [124]. Also, another study showed that acetate can restore ovarian function in experimentally induced PCOS rats [125]. In this study, it has been observed that treatment of PCOS rat model with acetate reduced body weight and ovarian weight, plasma and ovarian triglyceride, total cholesterol, 1-hr post-load glucose and plasma insulin, TNF-α and HDAC, ovarian malondialdehyde, testosterone, and Luteinizing hormone (LH)/follicle stimulating hormone (FSH) ratio as well as increased insulin sensitivity and plasma 17-β estradiol and sex hormone binding globulin [125].

7. Multi-omics studies in female reproductive tract microbiome

In recent years, the large amount of information and data about the microbiome has revolutionized the field of microbiology. The new methods of DNA sequencing and bioinformatics and analysis have caused an abundance of data and, on the other hand, difficulty in interpreting them [126,127]. Omics technologies aim to characterize and measure the pools of biological molecules of organisms. Genomics, proteomics, metabolomics, metagenomics, and transcriptomics are many known branches of omics sciences. Each branch provides information on only one part of biological systems. Integration of multiple omics (multi-omics) can give a better interpretation of the performance and interactions of the whole system [128]. Microbiome multi-omics findings integrate multiple types of omics such as metagenomics, metabolomics, metatranscriptomics, etc, collecting data from a microbiome sample and its environment or host [129].

Studies show that host-microbe interaction in the cervicovaginal microenvironment participates in the health and disease of this area. Since analyzing is challenging, recently, a few multi-omics studies have been conducted to help interpret these complex interactions. In a study, Bokulich et al. [130] performed a multi-omics analysis to develop predictive models of the cervicovaginal microenvironment as well as explore important features of the microbiome, inflammation, and disease state of the female reproductive system and their interactions. They collected cervicovaginal samples of 72 women (with or without cervical neoplasm) and evaluated microbiomes, vaginal pH, immunoproteomes, and metabolomes. They used multi-omics techniques including neural networks (mmvec) and Random Forest supervised learning. Their study suggested a close correlation between cervical carcinogenesis and genital microbiome, metabolome, and inflammation. The microbiome, metabolome, and immunoproteome were predictive of genital inflammation status. They reported that lipids are strong predictors of genital inflammation, whilst changes in amino acid metabolism are considered predictors of the vaginal microbiota and vaginal pH. Also, they introduced IL-6, IL-10, and MIP-1α as key immune biomarkers of genital inflammation and MIF as a key immune biomarker of the vaginal microbiota composition and vaginal pH [130]. In another multi-omic study, Jean et al., in 2019 explored microbiome profiles in the female reproductive tract using vaginal specimens of 58 women during early pregnancy. They declared that there are significant correlations between microbial taxa, cytokines, and specific eicosanoids and sphingomyelins [131]. Yeoman et al., in 2013 employed a multi-omic study, to assess metabolic markers of BV and insight into the disease. Lavage samples were obtained from 36 women, which were varied in terms of demographic, behavior, and health status. Based on metabolomic profiles, there were two different symptomatic BV types (SBVI and SBVII) with similar features (disruption of epithelial integrity), and different features (different microbial taxa and metabolites, as well as different host behaviors). The authors found that the increase of putrescine and cadaverine, which were correlated to *Dialister* spp., was linked to the featured odor of BV. Also, they observed links between the presence of discharge and 2-methyl-2-hydroxybutanoic acid and *Mobiluncus* spp., as well as between the pain and diethylene glycol and *Gardnerella* spp [132].

8. Conclusion and future directions

It has been discovered that metabolic by-products of bacteria, such as SCFAs in the vagina, elicit immune responses. This has serious implications for the host's gynecological, reproductive, and overall health, as well as her offspring. In this regard, the gut microbiota SCFAs' homeostatic and immunomodulatory roles are better defined than those in the vagina. High SCFA levels during pregnancy can lower the risk of infection-inflammation-mediated preterm birth. SCFAs are typically found in the gut mucosa, but they have also been found in low concentrations in the human vaginal mucosa. Nonetheless, in the presence of BV, higher concentrations of microbiota SCFAs were produced. Furthermore, some studies have found that high concentrations of SCFAs cause vaginal epithelial cells to produce pro-inflammatory mediators. However, additional research is needed to determine the precise effects of SCFA concentrations on changing the mucosal barrier function in the female genital tract and their relationship to conditions such as BV. Higher concentrations of SCFAs in the human vaginal along with a decrease in lactate in BV can be explained by microbiota dysbiosis, which results in pathogen growth. As a result, bacterial pathogens can colonize in a dysbiotic environment and cause infection, leading to adverse reproductive outcomes such as miscarriage and preterm birth. These findings may support the use of microbiota testing in the assessment of infertility in couples to better plan appropriate therapies. In fact, the microbiota provides a unique opportunity to develop specific therapies aimed at their modification; however, some issues must still be identified. Although there is no conclusive evidence on humans, the findings of some clinical studies indicate that SCFAs can be used as a promising medicinal combination to prevent and/or treat some diseases; however, standard administration cannot be recommended until larger studies confirm SCFAs efficacy. In this regard, for example, because the dose of SCFAs delivered to the target is unstable, a new SCFA administration targeting technique should be developed to provide a more stable and accurate dose. Because the total intake of butyrate, acetate, and propionate varies and might result in varying local concentrations of these SCFA, the environment adjacent to the epithelium is more complicated. To evaluate the local amount of SCFAs, as well as to ascertain their impact on the host's vaginal epithelium while also changing the intensity and quantity of female reproductive pathogens, *in vitro* and *in vivo* methodologies must be improved. Further studies on the interactions between the vaginal microbiota and its metabolites are also required because they may affect the likelihood of developing certain gynecological and reproductive problems. Future research should examine the potential functions of the female reproductive tract microbiome using multi-omics techniques, such as metagenomics, metaproteomics, and metabolomics, to gain a more precise and thorough understanding of the function of SCFA for personalized medicine.

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