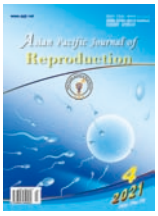

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# Etiopathogenesis of reproductive tract infections and the emerging role of bitter taste receptors: A scoping review

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## ABSTRACT

Reproductive tract infections pose an immense public health concern worldwide as over 600 million new cases are recorded annually along with several complications, including infertility, ectopic pregnancy, preterm delivery, and neonatal death. Despite improved understanding of the mechanisms of pathogenic invasion, the etiopathogenesis of reproductive tract infections is yet to be completely understood. Recent data has suggested a critical role of bitter taste receptors of the reproductive tract in etiopathogenesis of reproductive tract infections. Here, we review the literature on current etiopathogenesis of reproductive tract infections and the role of bitter taste receptors of the reproductive tract in etiopathogenesis of reproductive tract infections. Emerging evidence suggests a critical role of microbiota disorder of the reproductive tract in reproductive tract infections. Several bacterial, protozoan parasitic, helminthic parasitic and viral pathogens have been identified as causative agents of reproductive tract infections. These pathogens subvert host defenses and activate specific architectural units of the uroepithelium such as Toll-like receptors, which recognize conserved motifs on the pathogens. The activated Toll-like receptors mediate downstream signaling, stimulating nuclear factor-κB, which in turn activates the production of proinflammatory cytokines. This pathway is also associated with recruitment of immunocytes to the site of aggression and release of proteinases, which drive tissue damage in the reproductive tract. Defects in detection of pathogenic components by the bitter taste receptors of the reproductive tract may play a critical role in the etiopathogenesis of reproductive tract infections. This review provides important information for identification of novel frontiers for the treatment of reproductive tract infections.

**KEYWORDS:** Infection; Genital inflammation; Reproduction; Reproductive tract infections; Bitter taste receptor; Etiopathogenesis; Cytokines

## 1. Introduction

Reproductive tract infections pose a significant public health concern worldwide, with an estimated 600 million new cases recorded annually among people aged 15-49 years[1]. Reproductive tract infections are some of the most frequent infectious diseases in clinical practice[2], substantially surpassing respiratory tract, gastrointestinal tract, and surgical site infections put together[3]. Though the incidence rate among young people is higher, reproductive tract infections can affect all ages, including neonates, children, and pregnant women[4-6]. It is widely accepted that reproductive tract infections such as epididymitis, urethritis, orchitis, and prostatitis constitute critical cause of infertility[7]. Indeed, reproductive tract infections due to *Chlamydia* have been reportedly associated with approximately 40% incidence of prostatitis[7]. Multiple lines of evidence have consistently shown a key role of reproductive tract infections in development of infertility in both males and females[8,9] of the reproductive age. For instance, Ricci *et al* demonstrated that *Enterococcus faecalis*, *Mycoplasma hominis* or *Ureaplasma urealyticum* in genital samples of infertile couples were associated with reduced sperm quality, bacterial vaginosis, and failure of *in vitro* fertilization[8].

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Reproductive tract infections are associated with severe complications including ectopic pregnancy, end stage renal disease in adults, premature delivery, neonatal death, chronic pelvic pain and neurological and cardiovascular diseases[1,10], cervical neoplasia in women[11] and penile cancer in men[12]. Furthermore, some types of reproductive tract infections are associated with stigma, stereotyping, shame, vulnerability and can lead to gender related violence[1], thereby increasing the psychosocial impact on the individual[2,4]. The efforts made to characterize the molecular mechanisms of virulence and resistance to antibiotics appear to have had no impact on the incidence rate, diagnosis and effectiveness of treatment of reproductive tract infections[13]. Thus, it is essential to investigate the etiopathogenesis of reproductive tract infections and search for new frontiers that could translate to the development of novel therapeutics.

Emerging data suggest a critical role of bitter taste receptors of the reproductive tract in etiopathogenesis of reproductive tract infections. Bitter taste receptors are 7-transmembrane G protein-coupled receptors that sense bitter substances to trigger signaling downstream several acceptors, mediating responses that ultimately culminate in protection of the cell against pathogenic aggression or toxigenic substances[14]. In humans, 25 bitter taste receptors (T2Rs) have been identified[15,16], whereas murine bitter taste receptors, designated "T2r", have 35 subtypes[16]. Bitter taste receptors are activated by bitter compounds such as amarogentin, denatonium, caffeine, 6-propyl-2 thiouracil, picrotin, salicin, and cycloheximide[17-19]. These receptors were first discovered in the oral cavity in taste bud cells[20,21] where they were thought to act only as detectors of poisonous bitter-tasting compounds to prevent their ingestion[17]. Further research led to the discovery of these receptors in other regions of the gastrointestinal tract, in particular, the stomach and intestines[22], which suggested that these receptors may perform roles other than just sensing poisonous bitter substances[17]. Bitter taste receptors are now believed to be ubiquitously expressed in several cells and tissues of the body[23,24].

More recently, researchers have reported the expression of bitter taste receptors in multiple tissues and organs of the reproductive tract[17,25,26], where they are believed to sense bitter compounds or metabolites produced by pathogenic microbes, in particular, microbial quorum-sensing signal molecules[25,27,28]. Under normal condition, stimulation of T2R by microbial quorum-sensing signal molecules activates downstream targets that lead to the mobilization of protective mechanisms against the microbial aggression. However, disorders in T2R signaling activate proinflammatory and destructive processes, consequently resulting in the development of diseases[26]. Here, we review the literature on current etiopathogenesis of reproductive tract infections and highlight the role of bitter taste receptors of the reproductive tract in etiopathogenesis of reproductive tract infections. This review provides important data for identification of novel frontiers for the treatment of reproductive tract infections.

## 2. Current perspectives on etiology and pathogenesis of reproductive tract infections

The etiological factors of reproductive tract infections can be grouped as primary and infections resulting from disorders of the microbiome. Our discussion will be based on the former as it is the most widely studied, but emerging data about the latter will also be summarized.

### *2.1. Role of genital microbiome in etiopathogenesis of reproductive tract infections*

The reproductive tract contains several millions of normal microflora[29-31], which produce a variety of molecules such as lactic acid, hydrogen peroxide, bacteriocins that protect against pathogenic invasion or bacterial overgrowth[29]. Disorders of the microflora of the reproductive tract can predispose to reproductive tract infections[29].

Though the mechanism of dysfunction of the genital tract microbiome and its role in etiopathogenesis of reproductive tract infections are not exactly understood, available data indicate that disorders arising from the normal microbiome are mainly due to antibiotic use or immunosuppression that causes substantial decrease in beneficial bacterial population and increase in harmful species[32]. Tabatabaei *et al* recently reported decreased quantity of vaginal *Lactobacilli* and *Bifidobacteria* spp. in pregnancy complications due to uterine and vaginal inflammation[33]. Furthermore, the authors showed that vaginal pathogens such as *Atopobium vaginae*, *Gardnerella vaginalis* and *Veillonellaceae bacterium* were associated with reproductive tract inflammation and pregnancy complications[33]. Similar findings were reported by Hočevar *et al*[34].

Therefore, disorders of the genital tract microflora can readily predispose to the development of inflammatory diseases of the reproductive tract[30,31,35].

### *2.2. Role of genital pathogens in etiopathogenesis of reproductive tract infections*

Though specific etiological agent has peculiar pathogenetic mechanism, here we will give an overview of pathogenesis of reproductive tract infections. The primary etiological factors of reproductive tract infections are pathogenic bacteria, protozoan parasites, helminthic parasites, and virus, and are usually transmitted sexually. These pathogenic microbes can affect different structures of the reproductive[36-38].

Ascension of infection through the urethra, vagina and cervix is a key mechanism of colonization of the reproductive tract by pathogens[32,39]. In addition, certain pathogens including the human immunodeficiency virus and *Treponema pallidum* that affect the reproductive tract may disseminate through the bloodstream[40,41].

Despite activation of defense mechanisms of the host, genital pathogens still adhere to the mucous surface where they begin their destructive actions, in part, due to the presence of adhesive

appendages on their surface[42–44]. The reproductive tract epithelial cells recognize the presence of pathogens by specific cellular signatures on the invading microbes or danger signal molecules released upon pathogenic invasion (*vide infra*).

### *2.3. Cellular signaling mechanisms initiated by genital pathogens in pathogenesis of reproductive tract infections*

Cellular signatures of the invading microbes [such as lipopolysaccharide (LPS), peptidoglycan, lipoteichoic acid, teichoic acid, lipoarabinomannan, arabinogalactan, lipopeptides, flagellin, pathogenic bacterial DNA and viral RNA] or damage-related signals activate several architectural units of the epithelial cells [*e.g*. Toll-like receptor (TLR) 2 and TLR4, which belong to the broad class of pattern recognition receptors that enable cells to recognize conserved motifs on the surface of bacteria, protozoa, virus, known as pathogen-associated molecular patterns][45–49]. The pattern recognition receptors can also respond to molecules released from cellular damage [(damage-associated molecular patterns (DAMPs)]. Examples of DAMPs include laminin, elastin and collagen-derived peptides, fibronectin, heat shock proteins, RNA, nuclear DNA, mitochondrial DNA, interleukin (IL)-1, high mobility group box 1 protein, histones, adenosine triphosphate, antimicrobial peptides, versican, biglycan, matrix metalloproteinase-3 and -13[45–47,49].

#### *2.3.1. TLR activation by the components of genital pathogens triggers proinflammatory cascades, immune cell chemotaxis and tissue damage*

The activation of TLR2 or TLR4 by components of genital pathogens triggers cellular signaling downstream several intracellular acceptors, activating protein kinases and other signaling molecules, including the nuclear factor κ-B (NF-κB) with resultant production of proinflammatory cytokines such as IL-1β, IL-2, IL-6, IL-8, IL-12, IL-15, IL-21, INF-γ, and TNF-α[40,46,47].

The pathogenic components and proinflammatory cytokines recruit and activate the cells of the immune system, which initially is meant to resolve the microbial aggression, but also leads to collateral tissue damage. The secreted cytokines and other factors increase the expression of endothelial adhesion molecules, which in turn promotes chemotaxis of immunocytes to the site of aggression. Recruitment of neutrophils, natural killer cells, monocytes, and plasma cells, as well as homing T and B cells further increases the production of cytokines, in addition to the activities of resident macrophages, which also stimulate cytokine/chemokine synthesis, thereby amplifying the inflammatory response[29,50]. Furthermore, the inflammatory response is accompanied by mucosal infiltration[50]. The infected reproductive tract epithelial cells, neutrophils and monocytes secrete matrix metalloproteinase (MMP)-2, MMP-9, and elastase. MMPs participate in resynthesis and remodeling of the extracellular matrix, whereas elastase drives proteolytic cleavage that contributes to tissue damage[50,51]. These processes are usually associated with pyuria[32].

#### *2.3.2. Cellular mechanisms underlying complications associated with reproductive tract infections*

Over the past few decades, there has been substantial increase in research interest on the complications of reproductive tract infections. Notwithstanding, however, the cellular and molecular mechanisms fundamental to the development of these complications are not completely understood. Here, we will discuss the cellular mechanisms underlying ectopic pregnancy, preterm labor, female and male infertility as complications of reproductive tract infections.

The action of pathogens in the intrauterine and fallopian microenvironment favors implantation of the blastocyst in regions of the reproductive system other than the endometrium, resulting in ectopic pregnancy[52–55]. Though the molecular signaling cascades are not exactly clear, it is believed that genital pathogens cause disorders in expression of hormones, cytokines, chemokines and cell adhesion molecules that participate or direct the implantation of the blastocyst to the extra-uterine epithelium[52,53]. Indeed, the movement of the fertilized egg to the endometrium for implantation is primarily dictated by environmental cues controlled by hormones, endogenous small molecules (including cytokines) and cell adhesion receptors[53]. For instance, Ashshi reported that up-regulation of the expression of IL-6 predisposes to ectopic pregnancy in cytomegalovirus infection[54]. Again, the high nitric oxide (NO) output mediated by inducible NO synthase can cause substantial loss of structural and functional integrity of the reproductive tract epithelium, thereby resulting in implantation of the blastocyst in unusual locations other than the endometrium[55]. Thus, pathogen-induced changes in the milieu of the uterine tube send stronger signal to the blastocyst, dictating the site of implantation at the fallopian tube, rather than the endometrium, consequently resulting in ectopic pregnancy[53].

Research data have consistently shown that infection or inflammation induces preterm delivery[56], which is the commonest cause of neonatal death[57]. Statistical estimate indicates that over 40% of preterm deliveries are associated with intrauterine infections[58]. The mucosal reactions resulting from pathogenic invasion or microbial aggression in the reproductive tract are also accompanied by production of prostaglandins (PG), such as $PGE_{2a}$ and $PGF_{2a}$. These eicosanoids are strong stimulators of uterine contraction[39,59] that results in preterm labor. Indeed, microbial invasion of the amniotic cavity and funisitis have been shown to induce a significant increase in $PGE_2$ and $PGF_{2\alpha}$ in preterm labor[60]. Therefore, intrauterine infections in pregnancy can predispose to preterm labor through the action of proinflammatory prostaglandins[39]. However, reproductive tract infection can induce preterm labor by alteration of vaginal, uterine and placental microbiome (*vide supra*)[33,34,61]. For example, Tabatabaei *et al* investigated vaginal microbiome between preterm (< 34-36 weeks) and term births and found association between vaginal *Lactobacilli* and *Bifidobacteria* spp. with uterine inflammation and preterm delivery[33]. In addition, proinflammatory bacterial species such as *Atopobium vaginae*, *Gardnerella vaginalis*, and *Veillonellaceae* were associated with increased risk of preterm birth[33]. Research has

shown that specific pattern of chemokine expression in gestational tissues is associated with preterm labor. Using a model of LPS-induced preterm labor in mice, Mizoguchi *et al* observed the harmful role of CX3CL1-CX3CR1 in the uterine milieu before and during preterm labor[57]. LPS-treated mice with intact CX3CR1 experienced preterm delivery through a mechanism related to increased recruitment of macrophages by CX3CL1 and its cognate receptor CX3CR1. In contrast, CX3CR1-deficient mice did not experience preterm labor despite LPS treatment[57]. Interestingly, evidence indicates that anti-inflammatory prostaglandin or drug therapy using FP receptor antagonist (*e.g.* AS604872 and OBE022), cyclooxygenase-2 inhibitors, and non-steroidal anti-inflammatory drug may be helpful in preventing preterm labor[62-64].

Available data indicate that about 15% of all cases of infertility are due to reproductive tract infections[65]. Ascending infection resulting in pelvic inflammatory diseases can cause infertility in both males and females[66]. Reproductive tract infections involving *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Escherichia coli* and *Herpes simplex* are mostly associated with infertility in both sexes. In females, these pathogenic microbes are involved in cervical, tubal, and peritoneal damage (lacerations and/or obstruction), as well as pelvic inflammatory disease, and adhesions that lead to infertility[66,67]. In males, genital pathogens (*e.g. Chlamydia trachomatis*) can produce antisperm antibodies, and increase the rate of generation of reactive oxygen species that affect not only the structure and functions of the testis and epididymis, but also spermatozoa functions and the process of spermatogenesis, thereby interfering with their development, maturation, and motility, consequently, resulting in infertility[68-70].

#### *2.3.3. Predisposing factors for reproductive tract infections*

The occurrence and severity of complications associated with reproductive tract infections depend on several factors, which include structural and functional abnormalities of the reproductive tract[29,44,71,72], promiscuous sexual behavior[29], antibiotic use, comorbidities, *etc*[29,72].

Genetic predisposing factors include ABH blood group non-secretor phenotype, TLR2, TLR4, Heat Shock Protein Family A, Hsp70 Member 1B (HspA1B), C-X-C motif chemokine receptor (CXCR)-1, CXCR-2, transforming growth factor beta-1 (TGF β 1), and *IFN-λ* genes among others[32,42,73,74]. Notably, Caine *et al* established greater reproductive tract infection following intravaginal Zika virus inoculation in female mice lacking IFN-λ signaling[75]. Additionally, polymorphisms in G protein-coupled estrogen receptor (*GPER) 1* gene[76] and NO synthase 2 gene[77] respectively have been associated with recurrent spontaneous abortion and benign prostatic hyperplasia. Furthermore, Liassides *et al* demonstrated in a sample of 145 pregnant women that minor alleles of single nucleotide polymorphisms of *TLR4* gene and autophagy-related gene 16-like-1 (*ATG16L1*) rs2241880 GG genotype constitute critical predisposing factors to early preterm delivery[78]. Similarly, previous findings by Taylor *et al* revealed that certain polymorphisms in *TLR1* and *TLR4* genes increase pathogenic signaling that is associated with increased *Chlamydia trachomatis* infection in women[79]. Consequently, deletion of *TLR4* gene has been found to confer protection against reproductive tract infections[42]. Likewise, deletion of myeloid differentiation factor 88 (*MyD88*), Toll/interleukin-1 receptor-domain-containing adaptor-inducing interferon- β (*TRIF*), and TRIF-related adaptor molecule (*TRAM*) genes (encode MyD88, TRIF, and TRAM signaling proteins, respectively, as cytoplasmic targets of the TLR-NF-κB pathway) reportedly abrogated inflammatory reactions of epithelial cells in response to pathogenic challenge, and protected the host from tissue damage and reproductive tract infections[42].

Virulence factors[72] also substantially modulate the pathogenesis and outcome of reproductive tract infections[29,72]. The role of microbial virulence in the pathogenesis of reproductive tract infections has been extensively discussed elsewhere[80-84].

## 3. Emerging concepts in etiopathogenesis of reproductive tract infections: The role of bitter taste receptors of the reproductive tract

### *3.1. Bitter taste receptors as novel immune sentinels of the reproductive tract milieu*

Over the past few years, accumulating research evidence has shown that bitter taste receptors serve as immune sensors owing to their participation in effectively recognizing not only toxins, but also components of pathogenic microbes and mobilize protective mechanisms against the aggression[85]. For this reason, bitter taste receptors have been regarded as a key part of the sensory[86] and immune system[87]. Taste receptors are expressed in different structures and regions of the reproductive tract (Table 1) and are believed to serve as immune sentinels[89].

Zheng *et al* demonstrated that chloroquine, a bitter taste receptor agonist, prevented LPS- or mifepristone (progesterone receptor

**Table 1.** Bitter taste receptor expression in the murine and human reproductive tract.

| Cell, tissue or region | Bitter taste receptor | Organism | References |
|---|---|---|---|
| Testes | T2r, T2R38, T2r105 and T2r131 | Human and murine | [17,23,25-27] |
| Spermatozoa, seminiferous tubules | T2R and 35 T2r | Human and murine | [17,25] |
| Prostate | T2R38 | Human and murine | [27] |
| Vagina | T2r126, T2r135 and T2r143 | Murine | [26] |
| Cervix | T2R38, T2r126, T2r135 and T2r143 | Human and murine | [26,27] |
| Ovaries | T2R38, T2r105 and T2r131 | Human and murine | [27,88] |
| Endometrium | T2R38 | Human only | [27] |
| Myometrium | T2R10, T2R14 and T2R38 | Human only | [27,28] |
| Placenta | T2R38 | Human and murine | [27] |

Note: T2R designates human bitter taste receptor; T2r designates murine bitter taste receptor.

**Table 2.** Quorum sensing signal molecules produced by Gram-negative bacteria, Gram-negative bacteria, and parasites.

| Signal molecule | Microbe | Genera | References |
|---|---|---|---|
| Farnesol and tyrosol (alkanols) | Parasites | *Candida albicans* | [91,99] |
| Oligopeptides, thiolactone and PapR (autoinducing peptides) | Gram-positive bacteria | *Bacillus* sp., *Clostridium* sp., *Listeria* sp., *Enterococcus* sp., *Streptomyces griseus*, *Streptococcus pordonii*, and *Staphylococcus* sp. (*e.g. Staphylococcus aureus*) | [99–101] |
| Autoinducer (AI)-3 | Gram-negative bacteria | *Escherichia coli* and *Xanthomonas campestris* | [101] |
| N-acyl-L-homoserine lactone, N-(3-oxoacyl)-L-homoserine lactone, N-(3-hydroxyacyl)-L-homoserine lactone; AI-1 | Gram-positive bacteria | *Acinetobacter* sp., *Aeromonas hydrophyla*, *Burkholderia* sp., *Erwinia* sp., *Pseudomonas* sp., *Serratia marcescens*, and *Yersinia* sp. | [99,101] |
| Butyryl-homoserine lactone; AI-1 | Gram-positive bacteria | *Pseudomonas aeruginosa* | [99,101] |
| Furanosyl borate diester (AI-2) | Gram-positive bacteria | *Escherichia coli* | [101,102] |
| 2-methy-2,3,3,4-tetrahydroxytetrahydrofuran (AI-2) | Gram-positive bacteria | *Escherichia coli*, *Salmonella enterica*, and *Shigella flexneri* | [101,102] |
| 2-heptyl-3-hydroxy-4 quinolone, 3-oxododecanoyl-l-homoserine lactone | Gram-positive bacteria | *Pseudomonas aeruginosa* | [91] |
| NgAI-2 (AI) | Gram-positive bacteria | *Neisseria gonorrhoeae* | [103,104] |
| TpAI-2 (AI) | Gram-positive bacteria | *Treponema pallidum* | [105–107] |
| CtAI, certain fatty acids (AI) | Gram-positive bacteria | *Chlamydia trachomatis* | [108,109] |

antagonist)-induced preterm delivery in murine models. The researchers also reported that chloroquine was more effective in preventing preterm delivery, compared to currently used tocolytics[28]. However, this effect of chloroquine was lost in α -gustducin-knockout mice, suggesting that bitter taste receptors are critical players in preterm delivery induced by intrauterine infections[28]. *In vitro* model also showed that T2R14 knockdown abated the effect of chloroquine in human myometrial cells[28].

Disorders in placental bitter taste receptor signaling may play a role in neonatal death. The bitter taste receptors of the placenta may be involved in detection of toxigenic and pathogenic substances. Under normal condition, these receptors mobilize protective mechanisms that prevent toxigenic and pathogenic substances from getting to the embryo or fetus, thereby preventing inflammatory responses in the placenta. Though there is a severe scarcity of data, it can be suggested that placental bitter taste receptors may be integral to the pathophysiology of villitis, chorioamnionitis and stillbirth. Apart from the inflammatory responses associated with bitter taste receptors, evidence also indicates that myometrial bitter taste receptors are involved in contractile activities in the uterine microenvironment, suggesting that these receptors may be involved in preterm delivery and may serve as potential target for novel tocolytics for more effective management of preterm labor[28,90].

The expression of bitter taste receptors in spermatozoa strongly indicates a possible link between inflammatory/infectious diseases and infertility[17]. Indeed, the uropathogenic microbe *Pseudomonas aeruginosa* was shown to cause disorders in bitter taste receptor signaling in spermatozoa with resultant multiple damages to these gamete cells[91]. Thus, bitter taste receptors of spermatozoa are involved in detection of toxigenic compounds and uropathogenic microbes and initiate responses that culminate in their elimination or prevention of microbial aggression[90].

Interactions between the bitter taste receptors and microbiota of the reproductive tract under normal conditions may be required to maintain the integrity of the reproductive tract epithelium *via* bitter taste receptor-dependent sensing of bitter metabolites (*e.g.* short chain fatty acids) and other signaling molecules (*vide infra*) of the microbiota[92,93]. Indeed, abundance of the beneficial microflora has been shown to positively correlate with bitter taste receptor expression, suggesting that downregulation of these receptors may predispose to reproductive tract infections[93,94]. Thus, disorders of the reproductive tract microbiota can drive pathological signaling by the bitter taste receptors[92].

### *3.2. Bitter taste receptors of the reproductive tract mobilize defense mechanisms against pathogens by sensing the "quorum"*

Bitter taste receptors of the reproductive tract regulate the activities of pathogens by detecting microbial quorum-sensing signal molecules. Quorum sensing can be defined as a process that allows microbes to communicate amongst themselves and share information about cell density and adjust gene expression through the release of molecules known as microbial quorum-sensing signal molecules[91,95]. The virulence of pathogens to a large extent depends on production of quorum-sensing signal molecules[91,96–98]. Thus, quorum sensing of signal molecules is an important mechanism used by pathogens to invade the host, in part, by delaying the secretion of virulence factors until adequate number of pathogens is available to counter the host defense[95,99]. There are different types of quorum-sensing signal molecules (Table 2)[100,110]. The quorum-sensing molecules produced by Gram-negative bacteria are called autoinducers[91,100,111], whereas Gram-positive bacteria produce autoinducing peptides as their quorum-sensing signal molecules[111].

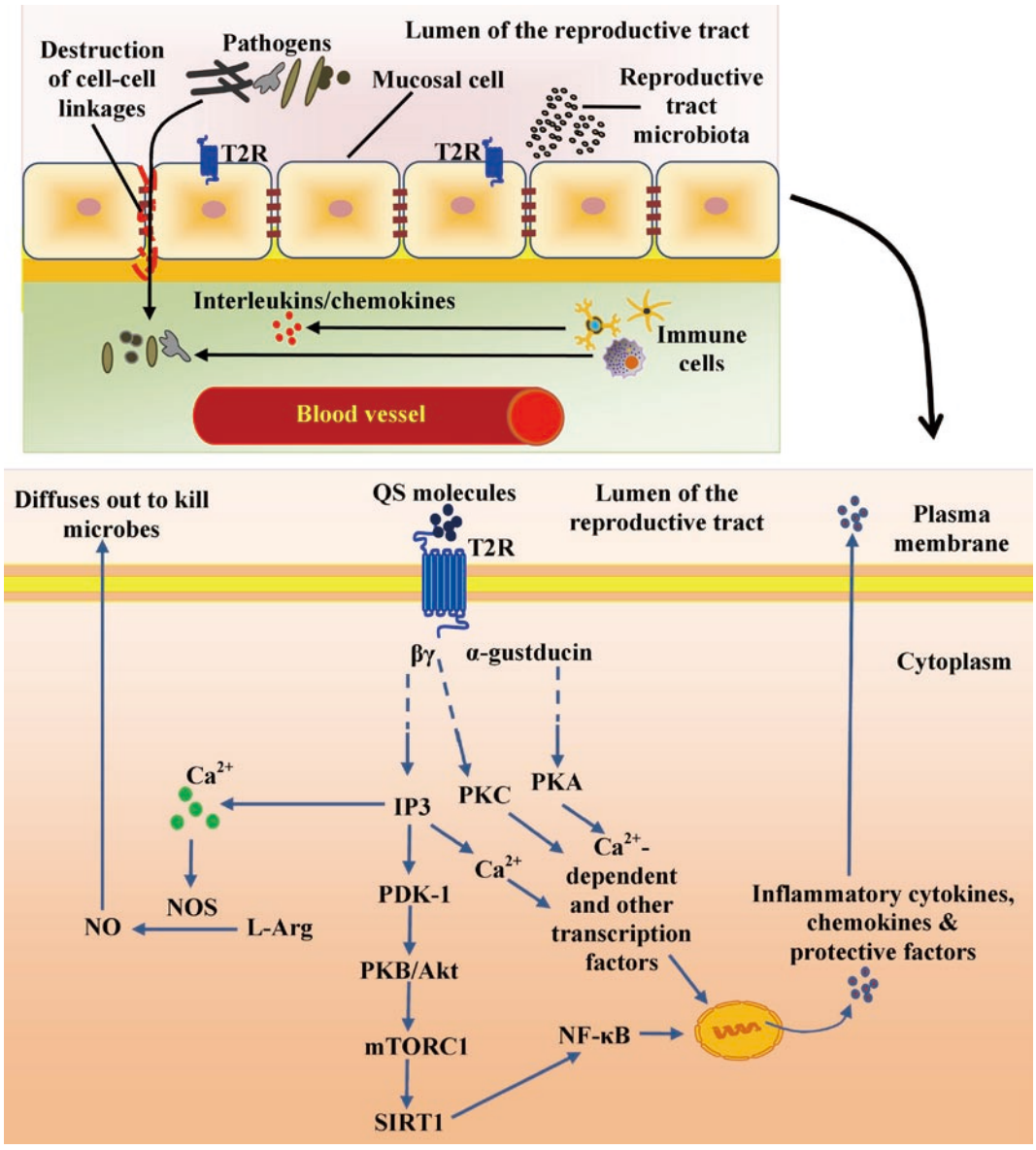


**Figure 1.** Role of bitter taste receptor (T2R) in reproductive tract inflammation. βγ and α-gustducin are subunits of T2R. Functional T2R detects physiological concentration of bitter microbial substances [*e.g.* quorum sensing (QS)] leading to dissociation of the α-subunit gustducin from the βγ subunits with exchange of guanine diphosphate for guanine triphosphate. The dissociated α-gustducin activates adenylate cyclase, which converts adenosine triphosphate to cyclic adenosine monophosphate (cAMP). Increase in cAMP level can activate protein kinase A (PKA). The βγ subunits activate phospholipase Cβ, which breaks down phosphatidylinositol 4,5-bisphosphate to form diacylglycerol and 1,4,5-inositol trisphosphate (IP3). IP3 is responsible for the release of $Ca^{2+}$ from intracellular stores. Increased cytosolic $Ca^{2+}$ activates $Ca^{2+}$-dependent kinases and transcription factors. IP3 can mediate increase in the activity of SIRT1 (consecutively *via* PDK-1, Akt and mTORC1), the sensor that can activate NF-κB to regulate the expression of inflammatory mediators and protective factors. diacylglycerol can stimulate protein kinase C (PKC). PKA and PKC can regulate gene expression *via* interaction with $Ca^{2+}$-dependent and other transcription factors involved in inflammatory responses. However, $Ca^{2+}$ can activate calmodulin to form $Ca^{2+}$-calmodulin complex, which in turn activates nitric oxide synthase (NOS). This enzyme catalyzes the oxidation of L-arginine (L-Arg) to L-citrulline and nitric oxide (NO). The latter has microbicidal effects in living cells. SIRT1: Sirtuin 1 or NAD (nicotinamide-adenine dinucleotide)-dependent deacetylase sirtuin-1. PDK-1: phosphoinositide-dependent protein kinase-1; PKB/Akt: protein kinase B; mTORC1: complex 1 of mammalian target of rapamycin; NF-κB: nuclear factor kappaB.

Quorum-sensing signal molecules serve as targets for bitter taste receptors. Stimulation of these receptors by the quorum-sensing molecules can initiate signaling cascades that activate defense mechanisms against pathogenic aggression[85]. For example, under normal circumstance, spermatozoa is believed to actively sense the signal molecules produced by *Pseudomonas aeruginosa* and pathogenic fungi *Candida albicans* to avert potential aggression[91]. However, dysfunctional bitter taste receptor signaling predisposes to impairment in spermatozoa functions. Similarly, bitter taste receptors in multiple regions of the reproductive tract detect the quorum-sensing signal molecules to control colonization of the tract by pathogens through initiation of microbicidal effects and other

responses that lead to elimination or control of pathogenic invasion. Thus, investigating the signaling mechanisms of quorum-sensing signal molecules and bitter taste receptors of the reproductive tract may lead to identification of novel frontiers in the treatment of reproductive tract infections. Indeed, current research interest includes the investigation of effectiveness of novel antimicrobial therapy on pathogenic quorum-sensing signal molecules to control multi-resistant species[95,99]. Thus, the mechanisms of bitter taste receptor detection of quorum sensing molecules and the molecular basis of downstream signaling that ultimately lead to elimination of pathogenic aggression can provide important data for possible medical application in the treatment of reproductive tract infections (Figure 1).

## 4. Conclusions

Reproductive tract infections are caused by genital microbiome disorders and/or invasion of the reproductive tract by bacterial, protozoan parasitic, helminthic parasitic or viral pathogens that subvert the host defense mechanisms, activating specific architectural units, including TLR-2 and TLR-4, to stimulate downstream intracellular targets such as NF-κB, which mediates expression of proinflammatory cytokines/chemokines. These processes are associated with recruitment of immunocytes to the site of aggression and secretion of proteinases that drive tissue damage in the reproductive tract. Bitter taste receptors of the reproductive tract also play a critical role in etiopathogenesis of reproductive tract infections by detecting microbial quorum-sensing signal molecules to mediate inflammatory signaling cascades and mobilize defense measures against pathogenic invasion. This paper provides a background on potential therapeutic significance of pharmacological targeting of bitter taste receptors of the reproductive tract for the treatment of reproductive tract infections.

## Conflict of interest statement

The authors declare that there is no conflict of interest.

## Authors' contributions

Menizibeya O. Welcome developed the idea and concept, conducted literature search, analyzed the relevant literatures, prepared the draft, edited and revised the text; Abraham Jeremiah participated in conducting the literature search, analyzed the relevant literatures, and edited the text; Dennis O. Allagoa participated in analysis of the literatures, edited and revised the text; Senol Dane participated in analysis of the literatures, edited and revised the text; Vladimir A. Pereverzev participated in analysis of the literatures, edited and revised the text.

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