Infertility: Plant Derived Bitter Tasting Compounds to Slack off the Bitterness of Genital Infections. Real or Just a Hype?

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LETTER TO EDITOR

Infertility refers to the inability of a reproductive-aged woman (from 15 to 49 years old) to conceive after 12 months of sexually active life [1]. Globally, infertility affects about 80 million couples and is associated with a huge psychosocial burden [2]. Both male and female factors comprising about 20–50% and 26-50% respectively contribute to development of infertility. Though multiple causes of infertility have been reported [3–5], genital infections continue to constitute the greatest risk for infertility, accounting for about 15–35% of infertility cases in males [5] and 50–75% of infertility cases in females [4]. Despite substantial improvement in medical treatment, incidence of genital infections has continued to increase over the past years in addition to ever increasing microbial resistance experienced in clinical practice [1,5]. This evidently substantiates the need to search for alternative areas that may lead to discovery of novel therapy for genital infections.

Bitter taste receptors (T2Rs) were initially discovered in the gastrointestinal tract, and are now believed to be expressed in many regions of the body where they detect toxins to mobilize protective mechanisms that ensure elimination of the toxins, and also, serve as sentinels of the immune system [6]. Relatively recently, T2Rs were found in cell and tissues of the cervix, vagina, endometrium, myometrium, placenta, ovary, prostate, testis, and spermatozoa [7–9]. T2Rs are transmembrane G protein-coupled receptors (GPCR) that sense bitter compounds by stimulating the α-gustducin, which signals downstream the cell, activating cytoplasmic acceptors that mediate responses that subsequently culminate in activation of defense mechanisms aimed at abating pathogenic aggression [7, 8]. To date, twenty-five human T2Rs have been discovered and are activated by bitter molecules including caffeine, amarogentin, denatonium, among others. There are more than 1000 currently identified bitter compounds [10] and numerous naturally occurring bitter compounds mainly derived from plant sources [11]. The following plant derived bitter tasting compounds are potential activators of T2Rs: (−)-epicatechin, (−)-epigallocatechin gallate, 6-n-propyl-2-thiouracil, 8,8’-bieckol, amarogentin, andrographolide, anthocyanin, apigenin, apocynin, arctigenin, berberine, caffeic acid, catechin, chlorogenic acid, clovamide, crebanine, cryptolepine, cryptopleurine, cyanidin, dicentrine, dieckol, diphenitol, eckol, ellagic acid, ferulic acid, fisetin, gallic acid, isoliquiritigenin, isoorientin, isorhynchophylline, kaempferol, kolaviron, leonurine, neoechinulin A, nobiletin, O-methylbulbocapnine, oxymatrine, paonol, procyanidin A2, protoatechuic acid, pseudocoptisin, punicalagin, quercetin, quinine, resveratrol, rynchophylline, sinomenine, skimmianine, tangeretin, tetrandrine, theaflavins, tournefoliacid B, tryptanthrin, umbelliferone, xanthoxin, and yohimbine [11]. Though is lack of studies, these polyphenols, tannins, anthocyanins, alkaloids, and quinolones are natural chemicals that can be harnessed as...
T2R agonists for possible future therapeutics of genital infections.

Binding of the bitter compounds to T2Rs causes stimulation of the α-gustducin, which signals downstream intracellular proteins that ultimately culminates in activation of inflammatory signaling cascades that appear to serve as defensive mechanisms against the pathogens [12]. Though the molecular pathways are not exactly known, available evidences [12–14] suggest that defensive mechanisms against the pathogens due to activation of T2Rs by their agonists (i.e. bitter compounds) is associated with inflammatory signaling cascades that appear to be associated with the master regulators of inflammation –NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and NLRP3 (nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing 3) inflamasomes. NF-κB is transcription factor that control gene expression of NLRP3 and proinflammatory cytokines/chemokines. The NLRP3 inflamasome is a key inflammatory molecule in priming and maturation of inflammatory cytokines. Under normal conditions, the NF-κB and NLRP3 are controlled at low level and inactive in cells through specific molecular interactions that prevent their activation. However, in cases of T2R dysfunctions, activation of NF-κB and NLRP3 inflamasome cascades and the resultant upstream signaling may stimulate the matrix metallopeptidases or other proteolytic enzymes to mediate characteristic inflammatory and destructive processes in cells and tissues of the genital tract.

Indeed, dysfunctional T2R signaling in spermatozoa was demonstrated to cause multiple damages by microbial pathogens, suggesting that disorders in genital tract T2R signaling may predispose or even cause genital infections, which in turn may lead to infertility [15]. Similar findings were reported by Deckmann et al. who demonstrated T2Rs of the urogenital tract effectively detected bitter substances and uropathogenic Escherichia coli to initiate cellular signaling that ultimately resulted in prevention of pathogenic colonization of the tract [16]. Zheng et al. also reported that chloroquine, a T2R agonist, prevented uterine infection induced by bacterial lipopolysaccharide in experimental animals through activation of the α-gustducin [8]. Interestingly, this protective effect of chloroquie was abolished in α-gustducin knock out animals [8].

It is therefore important for future studies to investigate the role of T2R signaling and bitter tasting compounds derived from different plant sources in genital tract infections, and possibly on animal models of infection-induced fertility. It is not also known how these T2Rs may affect endocrine functions of the gonads. Thus, goal driven research aimed at unraveling the relationship between T2R signaling and endocrine functions of the gonads may provide further insights into potential molecular culprits of infertility.

REFERENCES


