Introduction
Tobacco smoke consists of more than 7000 chemical compounds, 250 of which are toxic or carcinogenic, such as nicotine, carbon monoxide, aldehydes, hydrogen cyanide, and nickel, which irritate the respiratory system and mucous membrane (1,2). These compounds can damage various organs of the body, especially the lungs and digestive systems, and provide the conditions for the growth of microbial and parasitic pathogens, including *Trichomonas vaginalis* (1,3). *T. vaginalis* infection is one of the non-viral sexually transmitted diseases and the most common curable sexually transmitted infection in the world, which can increase the risk of pelvic inflammatory disease and HIV transmission. This infection is still relatively common, especially in women who smoke and in groups with lower socioeconomic status. We aimed to present a comprehensive review of the probability of being infected with *T. vaginalis* in smokers compared to non-smokers.

Materials and Methods: PubMed and Google databases were searched for research articles related to smoking and its association with *T. vaginalis* infection.

Results: The smoking status of the person is an independent risk factor for *T. vaginalis* infection and leads to an increased likelihood of developing this infection.

Conclusion: Finally, the results of various studies showed that the prevalence of *T. vaginalis* infection is higher in smokers than in non-smokers.

Keywords: *Trichomonas vaginalis*, Smoking, Risk factor, Infection

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sexual partners increases the rate of recovery and reduces the rate of its recurrence. *T. vaginalis* can be isolated from vaginal secretions, prostate, urethra, semen, and urine of patients (5). The usual method for the diagnosis of *T. vaginalis* infection is wet mount microscopic examination. The prevalence of trichomoniasis depends on access to health services, age, sexual behavior, health-related habits, presence of other sexually transmitted diseases, and various social and economic factors (11). In terms of the pathogenicity of the parasite in humans, the stage of attachment of the parasite to the vaginal epithelial cells, and its multiplication are very important. *T. vaginalis* can damage the cell through mechanisms such as adhesion, colony formation, secretion of cell separation factors, expression of membrane-piercing proteins, and secretion of proteinases (11). The first line of defense in the host is the activation of complement through alternative pathways, the increase of zinc ions, and the accumulation of phagocytic cells, especially cells such as neutrophils and macrophages in the vagina (12,13). Although this immunity is not enough and the disease remains in the person for a long time in two forms with or without symptoms (14). It seems that smoking is also a major risk factor for the respiratory system. Exposure to cigarette smoke increases the risk of infections, complications, and mortality of infectious diseases caused by smoking. Smoking and any factor that affects the immune system and weakens it, including some diseases or the use of some medications, can increase the risk of parasitic infection. For example, in people undergoing chemotherapy, the incidence of this infection is high, which can indicate the role of the immune system in the occurrence of this infection (1,15,16). Vaccines are the best tools for preventing parasitic diseases (17). Trichomoniasis is often asymptomatic and therefore untreated, creating reservoirs of *T. vaginalis* that allow the disease to spread in the community. This protozoan leads to cell cytolysis through attachment to the epithelial cells of the cervix and prostate (7). One of the most important proteins that play a role in the adherence of *T. vaginalis* to host epithelial cells is AP65 protein (18). During the attachment process, *T. vaginalis* turns into an amoeba form and by stimulating the immune system and increasing the expression of genes related to inflammatory cytokines, including interleukin 8, it causes an increase in inflammation in the attachment area and ultimately cell destruction. The spread of *T. vaginalis*, in addition to threatening women’s health, can lead to other diseases that can be transmitted through sexual contact (19,20). In most cases, *T. vaginalis* infection is associated with the bacterium *Mycoplasma hominis*, which is involved in the metabolism of this protozoan and local inflammation. Because of this, there has been little success in controlling the incidence of trichomoniasis, especially among disadvantaged people. Developing a vaccine against *T. vaginalis* can reduce human costs (pregnancy complications, infertility, etc.), medical costs, and social costs (21,22). Various demographic and behavioral factors such as education level and smoking are related to the prevalence of *T. vaginalis* (23). Few studies have investigated the incidence of *T. vaginalis* infection. Factors associated with this infection in women include older age, black race, chlamydia infection, multiple sexual partners, new sexual partners, previous *T. vaginalis* infection, smoking, and alcohol consumption (23,24). There is a lack of information on risk factors for *T. vaginalis*, especially smoking. Various factors, including the use of tobacco, cause changes in the normal flora of the vagina and can cause various infections in the lower genital tract, including trichomoniasis (23). Therefore, the aim of this study was to identify the relationship between the prevalence of *T. vaginalis* infection and smoking. Given the limited diagnostic technology, lack of screening guidelines, the high proportion of asymptomatic infections, and concerns about treatment failures, the identification of factors associated with infection may be important for the prevention of *T. vaginalis* infection and other sexually transmitted diseases (23).

**Pathogenicity of Trichomonas vaginalis in Humans**

In terms of the pathogenicity of the parasite in humans, the stage of attachment of the parasite to the vaginal epithelial cells, its multiplication, and differentiation are very important. This parasite multiplies in the urinary and genital tracts through a simple binary fission in the longitudinal axis and attacks the mucosa of these organs (25,26). *Trichomonas vaginalis* can damage the host through mechanisms such as adhesion, colony formation, secretion of cell separation factors, expression of membrane-piercing proteins, and secretion of hemolysin and proteinases (27,28). The adhesion of this parasite to vaginal epithelial cells is done by adhesion proteins including AP65, AP51, AP33, and AP23. Among these proteins, AP65 is a dominant functional protein that is not only a part of hydrogenosomes but mediates its binding to cells (29-33). Red blood cells are the main source of lipids and iron for the metabolism of *T. vaginalis*. The acquisition of iron from hemoglobin in this process is achieved by the activity of AP51 and AP65. In addition, many previous studies have shown that the amount of AP65 secreted by *T. vaginalis* increases in contact with host cells and that this protein is expressed and transcribed by iron (18,34). Anti-AP65 serum IgG antibodies can inhibit the adhesion of live *T. vaginalis* to the epithelium of the host. Further studies have shown that the adhesion of TVAP65 to the host cell surface is determined by the polypeptide formed by N-terminal 1-25-amino acids, which may constitute the epitope binding to the surface receptor on host cells. The analysis of AP65 protein sequence revealed that AP65 contains...
malic enzyme and oxidized coenzyme I binding sites. AP65 proteins can be secreted from trophozoites of *T. vaginalis* and bind to the surface of trophozoites and host cells (34). The next protein is AP33; however, its location in trophozoites is not clear. The results obtained using both antisense inhibition of gene expression and AP33 synthesis and heterologous expression of AP33 in *Trichomonas* fetus confirmed the role of it as an adhesion protein in *T. vaginalis* (6). Further studies showed that there are two binding regions in AP33 protein, located in the N-terminal and C-terminal of the protein, respectively. An indirect immunofluorescence antibody test showed that monoclonal antibody against AP33 can significantly inhibit the adhesion of *T. vaginalis* to HeLa cells (6,35). In addition, among different genotypes of *T. vaginalis*, there is a great similarity (98.2%–100%) in the AP33 gene sequence. The results of database retrieval showed that AP33 has a significant similarity to succinyl-CoA synthetase as a subunit and almost 100% identical to *T. vaginalis* subunit. All of these studies suggested that AP33 could be used as an excellent vaccine candidate antigen against *T. vaginalis* infection (35). In the researchers’ efforts to determine what factors play a key role in adhesion, a protein called TVAG-393390 was identified, which was found to be significantly increased in the 2 strains that were more adherent (36). TVAG-393390 was also identified as a possible rhomboid substrate of *T. vaginalis* (Rhomboid). Protease 1 (TVROM 1) is a membrane serine protease that plays a role in parasite attachment. These findings have determined the potential role of TVAG-393390 protein in interactions between *T. vaginalis* and host cells. Bioinformatic analysis showed that TVAG-393390 is structurally and functionally similar to cadherin-like protein (CLP) (36,37). Homologous CLPs also play a role in the binding and lysis of host cells and parasite penetration. This protein is more abundant on the surface of parasites that are better at binding host cells. CLPs are conserved metazoan proteins with central roles in cell-cell adhesion, growth, and maintenance of tissue structure. The functional description of these proteins from the single-celled parasite *T. vaginalis* showed that the protein mediates both parasite-parasite, and parasite-host adhesion, which leads to increased killing of host cells by *T. vaginalis*. The findings of the present study show the presence of CLPs in single-celled pathogens and the identification of a new host cell binding protein family in a human-infective parasite. The activation of these proteins depends on time, temperature, and pH (37,38). The pathogenicity of *T. vaginalis* is such that the parasite starts multiplying and growing in an acidic environment with a pH of 5.5. Therefore, the parasite does not multiply in the vagina of women who are in a normal state and the pH of the environment is 4–4.5 because the environment is more acidic. However, in case of a change in the pH of the environment, the environment becomes suitable for the proliferation of the parasite (26,39). Another reason for the growth of the parasite, especially in adult women, is that glycogen is formed in the walls of the vaginal mucosa cells, which is one of the important nutrients needed by the parasite. This parasite does not occur in immature girls and postmenopausal women because the pH is neutral in them. Second, the cells of the vaginal mucosa lack glycogen, which is a suitable food for the parasite. If the mother is infected, the baby may be infected when leaving the birth canal. Immature girls can also be infected due to direct contact with infected women (26,39,40).

**Lactobacilli and the Pathogenesis of *Trichomonas vaginalis***

The most common and abundant component of the vaginal microbiota is *Lactobacillus*, which contributes to the health of the genitourinary system. Therefore, it is not unexpected that strong competition exists between lactobacilli and other genital microorganisms including *T. vaginalis* (10,41). Lactobacilli create an acidic and oxidative environment. Additionally, they produce molecules that inhibit the growth of parasites and other microorganisms and reduce the virulence of many microbial pathogens. *Lactobacillus* is the most common microbial inhabitant of the human vagina. This bacterium can affect the severity of infection with *T. vaginalis* and other genital pathogens through adhesion (42,43). The number of vaginal lactobacilli is greatly reduced in *T. vaginalis* infection. *Lactobacillus* suppositories have been used for thirty years in the treatment of trichomoniasis. *Lactobacillus* is a lactic acid bacterium. *Lactobacillus* is found in the vaginal fluid of a healthy premenopausal woman at a concentration of $10^7$–$10^8$ CFU/mL. Disruption of lactobacilli as a natural protector is clearly associated with many genital tract infections, including trichomoniasis (10). It is clearly associated with many infections of the genitourinary tract, including trichomoniasis. Lactobacilli can inhibit the growth of parasites and other microorganisms and negatively affect the virulence of various pathogens. Although it is said that *T. vaginalis* and *Lactobacillus* are competitors, the investigation of this microbial interaction still needs further investigation. *Lactobacillus* significantly affects the labeling of host ectocervical cells by *T. vaginalis*. Lactobacilli inhibit the adhesion of *T. vaginalis* (10,44). The effects of lactobacilli on *T. vaginalis* adhesion are highly contact-dependent. Lactobacilli can interfere with parasite attachment by competing for receptors, blocking or killing the parasite and host cells, and promoting aggregation (41,45). As the number of lactobacilli increases, it may act as a physical bridge between cell receptors and The parasite can act and the parasite can’t identify any of them and connect. At this stage, lactobacilli...
Smoking and Infection

Smoking is common worldwide, affecting approximately one-third of the adult population. Smoke from the combustion of tobacco contains many harmful chemicals, including carbon monoxide, nicotine, and nitrogen oxides. Exposure to tobacco smoke is considered one of the most important preventable causes of death. The main component of cigarettes, tobacco, is a natural product with a complex molecular composition. When exposed to high temperatures and varying oxygen concentrations, it produces more than 7000 toxic compounds (16). Chronic inhalation of cigarette smoke changes cell proliferation, endothelial function, mucus, and immune response.

To date, more than 60 carcinogenic and mutagenic compounds have been identified in cigarette smoke. In addition, cigarette smoke has high levels of reactive oxygen, peroxynitrite, peroxynitrite, and free reactive radicals (1). The mechanism of the increased susceptibility of smokers to infections is multifactorial and includes changes in the host’s structural and immunological defenses. Cigarette smoke and many of its components cause structural changes in the respiratory and mucosal systems. These changes include peribronchial inflammation, destruction of Lactobacillus, fibrosis, increased mucus permeability, impaired mucus clearance, changes in pathogens, and respiratory epithelial disorders. Smoking affects both cellular and humoral immune responses (2,15).

The Effect of Smoking on Lactobacilli

Smoking has been identified as a risk factor for bacterial vaginosis, a condition defined by the destruction of Lactobacillus species. Smoking is closely related to the increased risk of vaginosis and other infections with parasites. In smokers, the protective lactic acid-producing bacteria, mainly Lactobacillus species, are replaced with a diverse array of anaerobic bacteria (41,46). Patients with bacterial and parasitic vaginosis often experience complications such as vaginal odor and emotional, sexual, and social problems and are at greater risk for sexually transmitted infections. Cigarette smoke is mainly formed by low molecular weight components such as nicotine, nitrosamines, polycyclic aromatic compounds, and heavy metals. These particles can be absorbed by the epithelial cells of body surfaces, such as mucous membranes, skin, and alveoli, and the digestive and reproductive systems (47). In fact, high levels of nicotine, probably the most frequently studied particle found in cigarettes, have been found in gastric fluids. Therefore, the effects of smoking may be directly related to the number of particulate compounds that reach the epithelial cells and can cause tissue damage. Tobacco affects vaginal infections caused by parasites and bacteria through the following mechanisms: physiological and structural changes and impairment in immune function. In the studies done before, nicotine and its metabolite, cotinine, have been detected in the cervical mucus of smokers. Moreover, smoking can lead to the accumulation of vaginal amines, which combine with antiestrogens. Female smokers have significantly lower mid-cycle and luteal phase estradiol levels compared to non-smokers. In addition, small amounts of benzo(a)pyrene diol-epoxide are found in the vaginal secretions of female smokers, which can significantly increase bacteriophage induction of lactobacilli. Smoking reduces the abundance of lactobacilli to some extent by promoting the induction of vaginal protective phage (41,48,49).

Role of Lactobacilli in the Mucosal Cervicovaginal Defense

The vaginal canal is colonized by microorganisms known as vaginal microbiota. These microorganisms play an essential role in defending the female reproductive system against infectious and inflammatory processes (41,50). In a healthy mucosal state, various components are in balance, but a change in one of the various factors often leads to an increase in the susceptibility of the host to infection. The dominant component of vaginal microbiota is Lactobacillus species, but other microorganisms can be present in a lesser number such as Gardnerella, Proteus, Streptococcus, Ureaplasma, Staphylococcus, and Lactobacillus. Lactobacilli play an important role in maintaining the health of the vaginal environment by combating the overgrowth of other microorganisms (50,51). Lactobacilli exert their protective effect by several mechanisms: 1) microbial competition for nutrients and adhesion to the vaginal epithelium, 2) reducing the pH of the vagina by producing organic acids, especially lactic acid, through the destruction of glycogen released by the cells of the vagina and exerting selective antimicrobial activity against non-resident microbiota, 3) production of antimicrobial by-products such as bacteriocins and hydrogen peroxide (H2O2), which are able to suppress the growth of several microorganisms, and 4) variation of the local immune system (41,52). Lactobacillus is found in the vaginal fluid of a healthy premenopausal woman at a concentration of 10^8 CFU/mL. The vaginal microbiota consists of four species including Lactobacillus...
inners, Lactobacillus crispatus, Lactobacillus gasseri, and Lactobacillus jenseni. The important point is that in women with T. vaginalis, the vaginal microbiota consists of a low proportion of lactobacilli and a high proportion of anaerobic microorganisms. Disruption of this natural protective mucosal barrier is clearly seen in many genital tract infections that are related to trichomoniasis. Lactobacilli can inhibit the growth of the parasite and negatively affect its severity. There is a lot of evidence that T. vaginalis and lactobacilli are competitors. Lactobacilli have significant importance in the adhesion of T. vaginalis to the host cells; in other words, they have an inhibitory effect on parasite adhesion. Lactobacilli can completely change the natural adhesion of different strains of T. vaginalis, which is necessarily contact-dependent, and change the abundant surface lipoglycans of T. vaginalis. In addition, the natural microbiota of the vagina plays a role in the virulence of T. vaginalis (41,42,47).

Discussion
Smoking is one of the most important public health issues. According to the World Health Organization report on the prevalence of tobacco use, smoking is responsible for 9% of all deaths from 2000 to 2025 worldwide. More than half of smokers die from smoking and related diseases. In addition to smoking, including cigarettes, exposure to second-hand smoke is harmful to those around smokers and increases the risk of infectious diseases (1,53). It not only threatens women’s lives but also affects their reproductive status and the development of genital diseases. Smoking poses many risks to human health as it can cause various cancers. However, female smokers face unique challenges. The fact is that far too many women around the world smoke. Smoking is the most common cause of death from infectious diseases. Smoking can damage almost all organs of the human body and is one of the main risk factors for the destruction of epithelial cells throughout the body. Smoking increases infection by affecting different body systems, including the respiratory, digestive, and reproductive systems. T. vaginalis infection remains relatively common worldwide, especially in women (2,16). According to various studies, it has been shown that smoking can cause inflammation and change the microbial flora of vaginal environment, including lactobacilli, which play a protective role. Additionally, the chemicals in tobacco can change cervical secretions (2,4). The chemicals in cigarettes weaken the ability of cervical cells to fight infections such as parasitic and bacterial infections, including T. vaginalis. As a result, the ground is provided for the proliferation of abnormal cervical cells. Cervical cancer patients who quit smoking have a better chance of survival compared to patients who continue to smoke (4). Smoking is associated with infectious diseases and leads to an increase in their prevalence and mortality (15). We searched PubMed and other relevant databases for scientific studies on the relationship between smoking and T. vaginalis infection. The mechanisms of susceptibility to infection in smokers may include changes in the host’s structural, functional, and immunological defenses. Smoking is one of the main risk factors for infections in the respiratory, digestive, reproductive, and other systems in humans and increases their prevalence. Quitting smoking can reduce the risk of infection. Smoking increases the incidence of infection and worsens the progress and prognosis of infectious diseases, including Trichomonas vaginalis infection (43). Álvarez-Lobos et al conducted a study in 2019 and investigated the effects of smoking on mucosal inflammation in mice. They concluded that smoking can be one of the main risk factors for the destruction of epithelial cells, inflammation, and chronic diseases (54). It can be inferred that smoking can cause an increase in the prevalence of infection among female smokers by changing the natural microbiota of the mucosa, including the vagina. The natural microbiota (e.g., Lactobacillus) plays the role of a protective barrier in the entry of various infectious agents, including the parasite T. vaginalis (47). According to a study conducted by Tompkins et al in 2013-2014 on the prevalence of T. vaginalis infection and its associated risk factors, the serum cotinine levels were significantly higher in smokers with T. vaginalis infection than in non-smokers. The measurement of serum cotinine concentration showed almost a ten-fold increase in T. vaginalis infection rate. Therefore, the smoking status of the individual is an important independent risk factor for T. vaginalis infection (23). Even exposure to nicotine increases the chance of getting trichomoniasis. This indicates a biological effect of smoking on the immune or local tissue level, which affects the propensity for infection (23). The parasite T. vaginalis uses its surface proteins to attach to the epithelial cells, enter the mucosa, and cause trichomoniasis. The various substances and compounds in cigarettes increase the number of lactobacilli that prevent the binding of these proteins and increase infection (41). The promotion of smoking cessation and education are the most practical and economic preventive measures to reduce the infectious diseases caused by smoking. The vaginal epithelium is the most important site for the initial contact of the parasite T. vaginalis. In human infection, parasite adhesion, invasion, and survival are of particular importance (47). Among other effects of smoking, we can mention the decrease in the secretion of the female hormone estrogen, which decreases the pH of the vagina and provides an environment for T. vaginalis to attach and cause disease. Habits such as smoking can interfere with the immune system and cause the onset of sexually transmitted diseases, including trichomoniasis (55). In a study conducted in 2013, smoking was investigated as one of the risk factors for trichomoniasis. In the end, the results of the present study showed that the prevalence...
of trichomoniases was higher in 25-45-year-old female smokers than non-smokers; in other words, trichomoniases was more common in this age group. Due to the fact that this is a sexually active and reproductive age group, there may be predisposing factors for infection (56).

Conclusion
Finally, according to the studies, smoking reduces the number of lactobacilli and changes the pH of the vaginal environment towards alkalinity, creating suitable conditions for the growth of *T. vaginalis* parasites. Additionally, it damages the vaginal mucosal system, creating suitable conditions for adhesion. In addition, the adhesive proteins of *T. vaginalis*, such as AP65, increase the incidence of *T. vaginalis* infection in female smokers. Our study shows that smoking causes differences in important vaginal metabolites in female smokers, resulting in greater susceptibility to genital tract infections.

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