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Trichomonas Vaginalis Parasite and its Relationship with Some Inflammatory Cytokines

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Abstarct: The parasite Trichomonas vaginalis is a flagellated, anaerobic, single-celled primary parasite that infects the genitourinary tract in humans. It invades the vagina, cervix, and urinary system in women, and the bladder, seminal vesicle, and prostate in men. The symptoms caused by the parasite in women are more pronounced, The Trichomonas vaginalis parasite infects males and females, and the symptoms of the disease in females are more common than in males, and the parasite inhabits the external cavities and halls of humans. The Trichomonas vaginalis parasite is an external parasite that usually lives in the female reproductive system and may be found in the urethra and prostate glands in males.

Cytokines are defined as a large group of proteins, including sharks, peptides, glycoproteins, and glycoproteins, which are secreted by certain cells in the immune system. They are produced throughout the body by various indigenous cells. The high levels of chemotactic protein for monocytes in the group of people infected with the symptomatic Trichomonas vaginalis parasite is due to the host's response to parasite antigens and the activation of chemotactic protein-generating cells, which are mast cells. It is known that mast cells quickly secrete powerful inflammatory mediators such as chemokines and histamine in response to infection with the Trichomonas parasite Vaginal. Whoconfirmed that Trichomonas vaginaliscauses significant increase in IL-6concentration of patients' serum comparison to the control group. Another study showed that human neutrophils or macrophages stimulated with live T.vaginalis produce the chemokine interleukin (IL-8) and the proinflammatory cytokines tumor necrosis factor-x, IL-6 and IL-1β.

Key points: Trichomonas vaginalis parasite, inflammatory cytokines, Interlukine.

Introduction

The parasite *Trichomonas vaginalis* is a flagellated, anaerobic, single-celled primary parasite that infects the genitourinary tract in humans. It invades the vagina, cervix, and urinary system in women, and the bladder, seminal vesicle, and prostate in men. The symptoms caused by the parasite in women are more pronounced [(1).] *Trichomoniasis* is the most common type of infection transmitted through sexual contact and is caused by the parasite *Trichomonas vaginalis*. There are no estimates of the severity of the infection among females of reproductive age, and symptoms do not appear in half of infected females. It is diagnosed by microscopic examination of a sample of vaginal fluid. Infection may occur through sexual intercourse or oral-genital contact [(2)].

The *Trichomonas vaginalis* parasite is characterized by its shape, which ranges from fusiform to pear-shaped, and its length ranges from 7 to 30 micrometres. The parasite takes an amoeboid form when it attaches to epithelial cells. The parasite ferments glucose, which is not completely oxidized, to produce acetate, lactate, malate, glycerol, and CO_2. Under anaerobic conditions, it produces hydrogen. *Trichomonas vaginalis* infection is characterized by a number of clinical signs, which are characterized by greenish-yellow vaginal discharge with a foul odor, peeling of epithelial cells, and

a change in the pH of the vagina. These symptoms are divided depending on the stage of severity of the infection:

- The acute stage: It is characterized by abundant vulvar inflammation, yellowish green secretions and blood spots in the mucous membrane.
- The chronic stage: It is characterized by moderate symptoms and is accompanied by a mixture of secretions with mucous materials. This stage is the stage of the spread of the infection [3].

The parasite *Trichomonas vaginalis* belongs to the unicellular eukaryotes, and it is considered an obligate parasite because it cannot synthesize many of the large macromolecules important for life, such as purines, pyrimidin, and many lipids. It obtains these substances from vaginal secretions or from phagocytizing host cells or existing bacteria, and to a degree Preferred acidity

It has a pH range of 6.0-6.3 but tolerates a wide spectrum of acidity changes [4]. The parasite most likely obtains iron from lactoferrin found in the vaginal mucosa or from red blood cells (erythrocytes) [5].

Trichomonas vaginalis constitutes half of the sexually transmitted diseases (STD). These diseases affect public health. Their danger lies in their ability to transform from an acute infection into a chronic infection with several complications. This is attributed to poor accuracy of diagnosis and appropriate treatment [6]. Recently, all modern studies have confirmed that the parasite Trichomonas vaginalis is a contributing factor for the transmission of the Human Immuno Deficiency Virus (HIV) or AIDS. It also increases the chance of cancers occurring in the cervix in women and the prostate in men [7].

The *Trichomonas vaginalis parasite* infects males and females, and the symptoms of the disease in females are more common than in males, and the parasite inhabits the external cavities and halls of humans [8]. The parasite infects the female vagina, urethra, bladder, and Skenes glands, Bartholine glands [9]. Affected women experience many infections, including vaginal burning and itching, accompanied by greenish-yellow or white vaginal discharge with a foul odor, pain after intercourse, and urinary retention [10].

In males, the parasite infects the urethra, prostate, seminal vesicles, and epididymis [11]. The parasite is transmitted through sexual intercourse and the use of contaminated tools [12]. Infected women develop a cellular immune response that is often insufficient to prevent recurrence or recurrence of the infection [13]. The succession or recurrence of infection is not accompanied by the presence of acquired immunity. Despite this, repeated infection causes less severe symptoms than the first infection in women, and therefore it is believed that some resistance may develop during the infection [14].and On a cellular level, dietary may influence various leukocytic effector functions, including adherence, migration, phagocytosis, and cytokine secretion. Several members of the selenoprotein family regulate or are regulated by cellular redox tone, a crucial modulator of immune cell signaling and function20 [15]

Historical Background

The *Trichomonas vaginalis parasite* was first seen by the scientist Doone in 1836, and he considered it a cause of vaginal infections after noticing the parasite in vaginal secretions. He called it Trichomonas vaginale, while the scientist Ehrenberg changed the name to Trichomonas in 1838. This parasite was re-described by many vaginalis researchers, especially Powell in 1936 and Wenrich during the years 1944-1947 The parasite is found in the vagina and cervix in females, but the Bartholine tract and the urinary bladder are places where the parasite can be found, and the parasite can ascend to the level of the fallopian tubes [16]. The scientist Lynch was considered the first to culture the parasite in 1915 outside the living body. In vitro, the scientist Hochen also noted in 1916 that the symptoms of vaginal infections disappear by eliminating the parasite, which confirmed its role in the occurrence of vaginal infections. He diagnosed the disease caused by this parasite, called Trichomonad vaginitis, as being It is a sexually transmitted disease. It was possible to obtain a culture of the parasite B, free of bacteria and fungi, for the first time in 1945 [17].

Diamond's medium is one of the most widely used media for cultivating this parasite. The *Trichomonas vaginalis parasite* consumes the glycogen present in the epithelial cells lining the vagina, which facilitates the attack of the bacteria present in it, causing vaginal infections. This was shown by Asami and Nakamur (1955) when they incubated the isolated parasite. From volunteers in Japan and conducting their studies on it [18]. Infection with the parasite results in infectious vaginal infections, which is one of the most important problems in clinical medicine, and Trichomonas vaginalis is one of the most widespread non-viral diseases transmitted through sexual contact [19].

The parasite infects both sexes, and infection with this disease results in serious consequences, including infertility [20] and cervical cancer [21], as the parasite infects women more than men. Estimates indicate that 50-200% of cases of trichomoniasis appear Symptoms in women and men: Trichomonas vaginalis infection is usually asymptomatic [22]. If symptoms are present, they include urethritis, accompanied by slight itching in the urethra, as well as the presence of simple secretions with urine, and inflammation of the urethra and prostate [23]. This is due to the nature of the male reproductive tract and its containment of zinc, so the male duct is toxic to the parasite [24]. In addition to dysuria, urethral pain, testicular pain, and lower abdominal pain [25] Women infected with this disease appear to have foamy, foul-smelling vaginal secretions that are green or yellow in color, along with vaginal itching and irritation. One of the consequences of contracting this disease in pregnant women is miscarriage or rupture of the placental membranes before the time of birth, leading to premature birth as well as low birth weight [27].

Taxonamy of Parasite

Parasite: During the rapid development in science and the careful study of the parasite in terms of its composition and genetic and structural features, the parasite was placed in the following classification [28].

Kingdom: Protista

phylum: Sarcomastigophora

Sup phylum: Mastigophora

Class: Zoomastigophora

Order: Trichomonadida

Family: Trichomonadidae

Genus: Trichomonas

Species: vaginalis

Parasite Morphology

The *Trichomonas vaginalis parasite* is an external parasite that usually lives in the female reproductive system and may be found in the urethra and prostate glands in males [29]. It is an anaerobic, pear-shaped parasite that possesses one nucleus, four anterior flagella, and a fifth lateral flagellum linked to a wavy membrane that extends to two-thirds of the body length [30]. The five flagella arise from kinetosomes located in front of them, and with the help of these flagella, the parasite is able to move actively [31]. The parasite possesses a basal chromatid rod called the costa that originates from the motor body and is darkly pigmented. It runs in the body superficially under and parallel to the wavy membrane. It has a distinctive transverse plan and acts as a flexible support in the region of the wavy membrane [32].

The length of the parasite ranges from 7-23 µm and its width is 5-10 µm [33]. The light-pigmented parabasal body is located near the nucleus, and the nucleus, like other eukaryotic organisms, is surrounded by a nuclear envelope [34]. There is also a protein substance called Chromatin Protien around the nucleus, which are granules found in the cytoplasm and are more numerous around the costa and the axial pen [35]. The axial pen (Axostyle) is a rod-shaped structure that starts from the front end near the motor body in the form of a thick rod resembling a crescent and ends outside the

body at the back end of the parasite. The parasite does not contain mitochondria, but it contains particles called hydrogenosomes that are used to produce energy [36]. These particles are considered one of the best criteria for distinguishing between the *Trichomonas vaginalis parasite* and other types of *Trichomonas* [37]. The parasite also possesses the oral groove, which represents the cellular mouth (cytostome), where it obtains food with the help of flagella [38].

The movement of the flagella is distinctive and is called the rocking or oscillatory movement [39]. The parasite is characterized by having only a vegetative stage and lacks a cystic stage that is resistant to environmental conditions. This explains the parasite's need to adhere to mucous surfaces in order for the disease to be transmitted from one person to another [40]. The parasite is highly sensitive to both oxygen in the atmosphere and lack of humidity, and therefore does not survive for Long outside the body [41]. The parasite is an anaerobic organism due to its anaerobic metabolism, but it may tolerate low concentrations of oxygen [42].

Also, the *Trichomonas vaginalis parasite* belongs to the order Trichomonadida, and this order lacks mitochondria. Instead, there are minute granules that are associated with the axial stylus. There are two groups of these granules: the Paracostal side and the Paraxostylar side. This last group is arranged in three rows along the axial stylus. It is an important characteristic of the *Trichomonas vaginalis parasite* [43]

Studies have shown that these granules serve the same purpose as mitochondria, and they are called hydrogen bodies because the final product of the metabolism process is partial hydrogen. As in Figure (1), which shows the structure of *Trichomonas vaginalis parasite.*

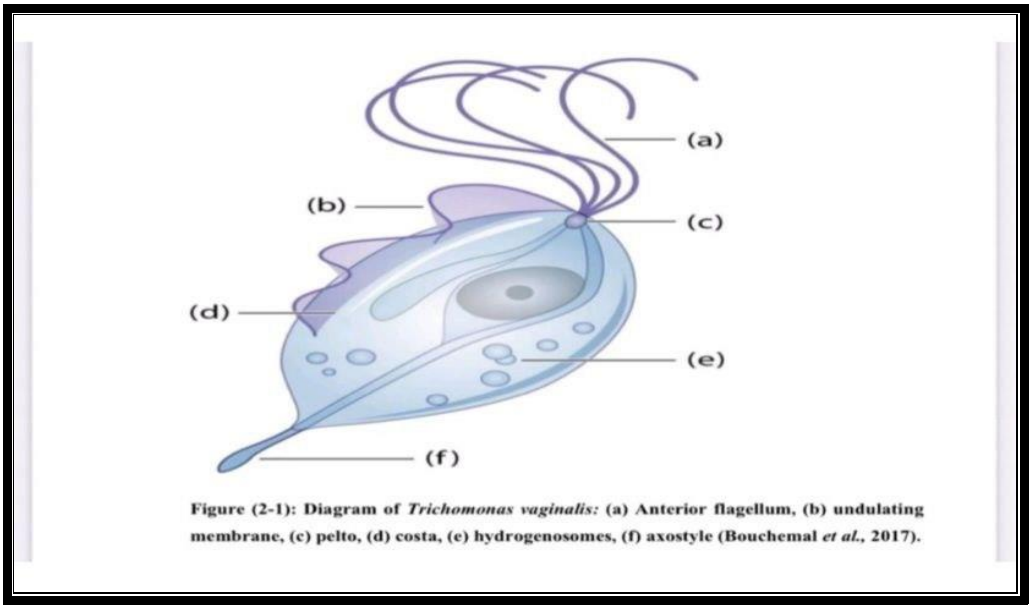

Figure (2-1): Diagram of *Trichomonas vaginalis:* (a) Anterior flagellum, (b) undulating membrane, (c) pelto, (d) costa, (e) hydrogenosomes, (f) axostyle (Bouchemal *et al.*, 2017).

Figure (1): shows a schematic diagram of the *Trichomonas vaginalis parasite* [44]

Life cycle of *Trichomonas vaginalis parasite*

The *Trichomonas vaginalis parasite* has a simple life cycle, as the parasite (infectious vegetative phase) is transmitted from an infected person to an uninfected person through sexual intercourse [45]. This parasite spreads in adults and is rarely found in children, and it may be transmitted using the infected person's tools [46]. Reproduction in the parasite occurs through longitudinal binary fission, and it does not reproduce sexually [47]. The parasite thrives in anaerobic conditions and at high pH values, and the incubation period ranges between 4-28 days [48].

The parasite cannot survive for a long time outside the human body, and the urogenital tract is the appropriate place for it [49]. Parasite reproduction begins with the multiplication of movement organelles, which is followed by the growth of two Attractophores on the sides of the nucleus, which later become poles. From these Attractophores, chromosomal micronuclei grow that elongate towards the nucleus, holding the central bodies of the chromosomes. Also extending between the

Attractophores is a spindle outside the nucleus called Paradesmose, which elongates. The spindle and the two daughter cells separate, and each daughter cell produces the missing organelles [50].

Pathogenesis and clinical signs of the disease

The *Trichomonas vaginalis parasite* resides in the genitourinary tract. The parasite has been isolated from all parts of the genitourinary tract [51,52]. The parasite infects the epithelial cells of the reproductive tract, and infection is accompanied by clinical signs ranging from asymptomatic to clear symptoms, and even asymptomatic cases become evident within 6 months of infection [53]. The incubation period of the disease ranges from 3-28 days [54]. Trichomonas vaginalis is classified according to the severity of the infection into:

- Acute case Acut.
- Chronic condition
- Asymptomatic state [55].

In the event of an acute infection, women suffer from vaginal itching (Atchi), accompanied by vaginal secretions of a greasy greenish-yellow color (greenish forthy vagina). The discharge has a foul odor at a pH higher than 4.5 [56]. The acute infection is accompanied by many symptoms, including scarlet cervicitis. Inflammation of the lining of the uterus, erosion, and redness of the cervix [57]. The symptoms of chronic infection are moderate and include dysuria, intercourse, lower abdominal pain, and few secretions. As for asymptomatic infection, it is observed in about 50% of women, and this percentage may increase during pregnancy because menstruation triggers symptoms in infected women [58]. Because during this period, the vaginal environment undergoes significant changes with an increase in the flow of red blood cells and serum contents, as well as changes that occur in the degree of acidity. Such changes do not enable the parasite to survive, but rather increase the chance of recurrence of the infection [59]. As menstrual blood flow provides nutrients to the parasite as well as the preparation of iron, which is the main factor in the genetic regulation of the parasite, infection during pregnancy may be accompanied by premature rupture of the membrane, premature birth, and the birth of low-weight children [60].

As for the infection in males, it is classified into three cases:

- The condition is asymptomatic.
- The acute condition is characterized by profuse purulent urethritis.
- As for the third case, the symptoms are moderate and include itching and burning after intercourse, dysuria, and purulent mucous secretions [61].

Some experiments have proven that the symptoms of infection with *Trichomonas vaginalis* affect the concentration of estrogen in the vagina, such that the higher the concentration of this hormone, the fewer the symptoms associated with the disease [62]. The finding results in the present study demonstrate the association between blood group system example toxoplasmosis infection, where the highest infection was among O blood group (42.10% and 57.10%), followed by B blood group (31.60% and 28.60%) for each chronic and acute Toxoplasma, respectively[63].

Mode of infection

Only humans are considered a natural host for the *Trichomonas vaginalis parasite*. This parasite exists in the eutrophic stage and is transmitted from one person to another through sexual intercourse [64]. Sexual intercourse is not the only method of transmission of the parasite, but there are other cases of transmission, including dilated vaginal speculum and medical materials. Other contaminated and unsterile ones [65] as well as the use of contaminated underwear and bathtubs [66]. It can also be transmitted through Western sanitary facilities and towels contaminated with the parasite [67]. In addition, there are conditions that are suitable for the growth of the parasite and are a source of infection, including lack of attention to personal hygiene [68]. Newborn infants acquire the parasite from their infected mothers [69]. In 1990, Rein & Mullar recorded the infection of 2-17% of newly born females born to infected mothers, as sexual intercourse is the most effective method of

transmitting the *Trichomonas vaginalis parasite* compared to other methods, which are rare, because the parasite dies outside the human body unless it is protected from infection Drought [70].

Laboratory diagnostic methods

Microscopic examination method

The microscopic examination method is one of the traditional laboratory methods used to diagnose the parasite and relies on the distinctive vibrating movement of the parasite resulting from the flagella and the undulating membrane [71]. However, sometimes the flagella may be lost during the process of preparing the slides, so they become similar to pus cells and are difficult to diagnose. However, the importance of this examination lies in its speed, as it enables the patient to receive the appropriate treatment from the first visit to the doctor [72]. Studies indicate that the sensitivity of this method is 50-72%, so this method cannot be relied upon alone [73].

Dyeing method

There are several types of dyes used to stain the parasite as a method of diagnosis, such as acridine orange stain, papanicolaou stain, Camza stain, and Hematoxylin stain. However, the efficiency of these dyes varies among them, in addition to the lack of accuracy in diagnosing the parasite, as fixation operations lead to the parasite losing its distinctive movement and becoming similar to cells. Purulent and epithelial cells accompanying it. There are studies that compared types of dyes to diagnose the parasite in terms of their efficiency. Hematoxylin stain recorded 3.5% of the rate of infection with the parasite, and Papanicola stain recorded 4% compared to microscopic examination, which recorded 2.4%, and the culture method in the medium, which recorded 5.45% of the rate of infection [74].

Implantation method

The method of cultivation in culture media specific to the parasite, such as Diamond medium, Kupferberg medium, and Trichomonas modified culture (CPLM), under conditions of little ventilation, is a standard method for diagnosing the parasite, as its efficiency ranges from 85-95% and requires 300-500 Parasite [75]. The incubation period is 2-7 days, the temperature is 35-37°C, and the pH is 6.5-6. These media need a number of nutrients and antibiotics to protect against contamination by other organisms [76]. The sensitivity of this method may reach 100%, but it is not used in the daily work of laboratories because it requires a long period of incubation and is high in cost [77].

Immunological methods

Various immunological methods are used, including the agglutination test, the complement fixation test, the immunofluorescence test, and the enzyme-linked immunosorbent test to obtain the best results and the lowest percentage of errors to diagnose the parasite [78]. However, these immunological methods have a number of disadvantages, as sometimes these methods cannot detect antibodies to the parasite if their concentration is low [79]. Also, these antibodies can remain in the body after treatment for a long period, so it is not possible to differentiate between a recent infection or old infections, and the sensitivity of these methods varies and ranges between 80-90%, depending on the method used [80].

Treatment

Metronidazole (Alpha-hydroxyethyl-2methyl-5-nitroimidazole) is a common treatment and has a trade name called Flagel. This treatment was discovered in 1959 and was used in 1960 in the United States and has high effectiveness against the Trichomonas vaginalis parasite [81]. As it is known that the parasite infects both sexes, therefore both partners must be treated. When treatment is taken, absorption occurs and reaches the vaginal membrane and enters by diffusion into the hydrogen bodies of the parasite, where the nitro group of the drug is reduced in anaerobic conditions by the Pyruvate oxidoreductase ferredoxin system [82]. The result is the formation of free radical intermediates that are cytotoxic and break down the parasite's DNA strands [83].

Cytokines inflammation

Cytokines are defined as a large group of proteins, including sharks, peptides, glycoproteins, and glycoproteins, which are secreted by certain cells in the immune system. They are produced throughout the body by various indigenous cells. Cytokine is a general name. Other names are determined based on: Specialized in this, or secretory cell, or target of action that can be cooled to cytokines made by lymphocytes as lymphokines, many lymphokines are also known as interleukins -IL, and are not secreted by honeycomb blood cells, but they are also effective in influencing. On cellular responses to leukocytes, there are five types of cytokines:

- Interferon
- Interleukin.
- Tumor necrosis factor.
- Chemokines [84].

The action of cytokines in general is diverse, as they have the ability to stimulate cell growth and differentiation, inflammation, apoptosis, reforming, and chemical attraction [85].

Cytokines can also be classified according to their effect on the inflammatory response to pro-inflammatory cytokines, which mediate the action of multiple white cells, which in turn act as chemoattractants [86]. Anti-inflammatory cytokines, which work against inflammation and have a clear effect in inhibiting the production of cellular kinetics before inflammation or counteracting their effect by reducing the gene expression of tumor necrosis factor, interleukin I, and chemokines [87].

Interleukins

Interleukins are proteins that stimulate the body's immune system to do its job of resisting infections. The body's interleukins are formed in white blood cell cells, which are the cells that work to destroy harmful bacteria and other harmful bodies that enter the body. The term interleukin is derived from two words (Inter-) meaning a connection. Internally, “Leukin” means white proteins that are secreted from white blood cells and act on them. Interleukins regulate cell growth, differentiation, and movement, and are particularly important in stimulating immune responses such as inflammation [88].

Interleukins (IL), which are a type of cytokines, were initially thought to be produced by white blood cells alone, but it was later discovered that they are also produced by many other cells in the body. These interleukins work together and cause a series of reactions that will arm the white cells in the body against disease, wounds, and the entry of bacteria. The white cells detect the presence of bacteria at the site of infection, and then these cells release interleukin-2, which in turn gives a signal to blood cells. Other white cells are called T-cells, which in turn release interleukin-2 and similar chemicals such as interleukin-7, which stimulate various cells of the immune system to defend the body [89] Interleukin 6 is a pro-inflammatory cytokine that is produced by various types of cells, including B lymphocytes, T-lymphocytes, macrophages, monocytes, mast cells, and other non-lymphocytes such as lymphocytes. Fibroblasts, endothelial cells, keratinocytes, and cancer cells [90].

IL6 targets cells whose surfaces contain special receptors, as the alpha chain is attached to the transmembrane interleukin receptor (IL-6Rα), which leads to the release of compounds. These compounds work to stimulate the receptor signal, carbohydrate protein 130 (gp130) [91]. IL-6 directly activates white blood cells, which leads to directing the immune response. It also works to stimulate the production of acute phase protein by hepatocytes. This leads to enhancing the proliferation of T cells and the differentiation of B cells and keeping them alive. It also works to produce IgG immune proteins. IgA, IgM, by stimulating plasma cells. In addition, it works to enhance the production of other interleukins such as IL-2 and IL-17 [92] and enhance allergic stimuli. The figure represents a summary of the most important functions performed by IL-6.

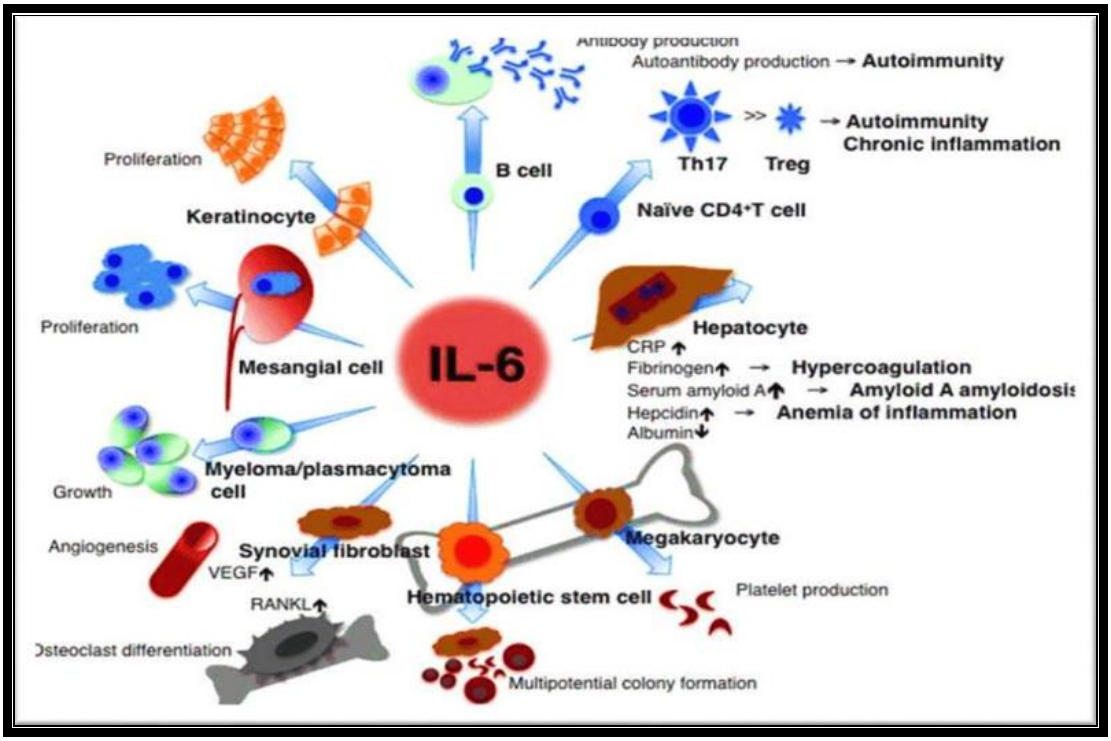

Figure 2:- Functions of Interleukin-6 [93]

Interleukin-7

It is a heterodimeric complex consisting of the α chain (CD127) and γ chain of common cytokine receptors, colocalized with the IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptors, and is expressed In a variety of cells [94] and as in Figure (3).

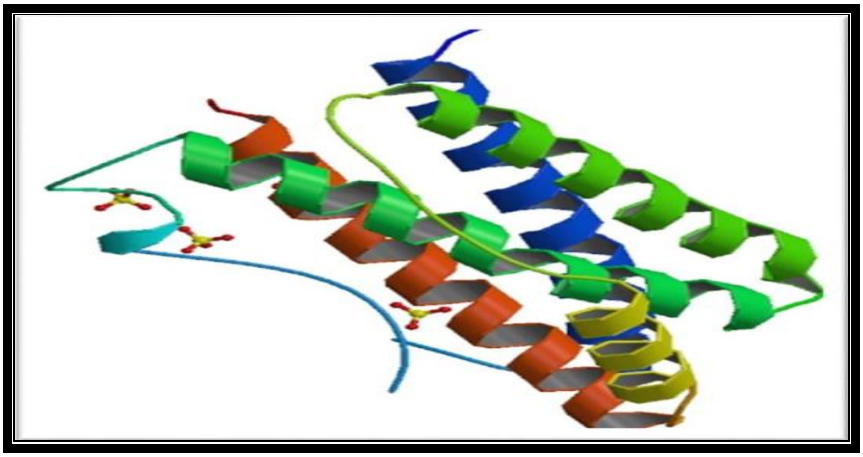

Figure (3): shows the structure of interleukin-7 [95].

IL-7 is an essential cytokine for regulating lymphatic homeostasis. These cytokines stimulate similar responses from lymphocytes, but play markedly divergent roles in lymphatic biology in vivo [96]. IL-7 is produced by stromal cells in lymphoid tissue and is essential for T cell development and persistence in the periphery, unlike many other cytokines that act on lymphocytes [97]. The function of IL-7 promotes the growth of lymphocytes in the bone marrow and thymus as well as T-cell homeostasis [98].

Tumor necrosis factor alpha is a cytokine that is secreted by macrophages, killer cells, and T cells. This cytokine works to enhance inflammation and activate the lining of blood vessels [99], as it is an angiogenic factor that stimulates them by promoting endothelial cells to divide and influencing elements. Pro-angiogenic [100]. It is considered one of the cytokines that have an important role in stimulating reactions in the advanced stages of inflammation [101]. It is produced by many cells,

including CD4 lymphocytes, killer cells, and Nervous Cells in acute infections. It is responsible for causing signals within cells that lead to necrosis or. Cell death [102] .The high levels of chemotactic protein for monocytes in the group of people infected with the symptomatic *Trichomonas vaginalis parasite* is due to the host's response to parasite antigens and the activation of chemotactic protein-generating cells, which are mast cells. It is known that mast cells quickly secrete powerful inflammatory mediators such as chemokines and histamine in response to infection with the *Trichomonas parasite Vaginal* [103]. A study indicated a significant increase in the concentration of cytokines such as of IL-6, IL-7,TNF-α in women infected with the parasite trichimonas vaginalis. [104] . groupmaybe due to increase in number of monocyte as response to inflammation caused by Trichomonas vaginalis . This result also corresponding to the result of [105] Whoconfirmed that Trichomonas vaginaliscauses significant increase in IL-6concentration of patients' serum comparison to the control group. Another study showed that human neutrophils or macrophages stimulated with live T.vaginalis produce the chemokine interleukin (IL-8) and the proinflammatory cytokines tumor necrosis factor-x, IL-6 and IL-1β [105,106].

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