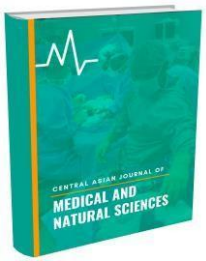

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Article

Evaluation of Immune Response of *Staphylococcus aureus* Isolated from Periodontitis

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Abstract: The present study aims to evaluate the immune response of S. aureus isolated from Periodontitis, which can cross from the oral cavity and lead to systemic inflammation, The isolation and identification of *Staphylococcus aureus* was carried out from twenty patients suffering from Periodontitis with an susceptibility test to estimate the isolated bacteria. The immune response was determined in albino mice serum, specifically for TLR-2, IL-4, IL-10, and IL-17 levels. Susceptibility test results showed that the rate of resistance of isolates to antibiotics varied. The immunological study revealed a difference in cytokine values between the present study groups when stimulated with *S. aureus*. The results showed that TLR-2, IL-4, IL-10, and IL-17 levels estimations were 9.38, 136.56, 98.6, and 288.3 pg/mL, respectively, with significant differences at $p < .05$. The conclusions were that *S. aureus* can affect the immune system of lab mice with Periodontitis and then systemic cytokine progression.

Keywords: Periodontitis, Staphylococcus aureus, Immune response, Susceptibility test,TLR-2,IL-4,IL-10,IL-17serum level.

1. Introduction

Periodontitis is a slow destruction of the alveolar bone that supports the teeth and if untreated, results in teeth becoming mobile and finally falling out. Bacteria that stick to and proliferate on the surfaces of teeth induce periodontitis, as does an overly aggressive immunological response against such microorganisms. In periodontitis patients, *S.aureus* has been shown to have an effect in worsening dental illnesses by producing a biofilm with periodontal infections[1].

*S.aureus*is a key Caused factor of serious human sickness,however it is linked with modest signs in soft tissue or healthy skin, it is the predominant source of infections in particular places, such as hospitals, accounted for over 80 percent of pyogenic disorders. Oral mucosal lesions and dentoalveolar infections in the oral tract have been related to *S. aureus*. Moreover, it has been noted that saliva, the supragingival tooth surfaces, the tongue, mucosal surfaces, and the periodontal pocket are all colonized by staphylococci[2]. Most *S. aureus* virulence factors have a relation with infection and illness; the variety and great variation in the genes associated with these factors may affect the progression of the infection[3]. The acknowledgment of *S. aureus* as an ''adequate'' colonizer of the oral microbiota, as contrary to a simple invader, is still under debate[4]. Other findings also indicate that staphylococci are often found when angular cheilitis, jaw osteomyelitis, mucositis, endodontic infections, and parotitis. Hence, the microbiota that

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is directly linked with oral diseases can act as a source of several clinically relevant pathogens such as multidrug-resistant staphylococci[5].

Simultaneously, *S. aureus* has been connected to bullous facial infections surrounding the lips and nose as well as face cellulitis[6]. Additionally, *S. aureus* has been related to a to numerous of oforo-facial infections,like severe dentoalveolar abscess condition[7], wearers of dentures[8], angular cheilitis[9], and dry mouth and halitosis[10]. Further studies have shown revealed S. aureus in the oral cavity is capable of seeding systemically as well as causing life-threatening incidents like infectious endocarditis[11], rheumatoid arthritis(RA)[12]. The danger of infection increases as the number of colonizations grows, affecting oral and general health conditions[13], whereas Azami et al emphasize the effectiveness of having good mouth hygiene because it has been seen that oral cavity is the primary portal of entry for *S. aureus* in and eventually causing systemic infection. Hence, The purpose of the research was to look into (in vivo) the immunological response of S. aureus isolated from periodontitis in case crossed from the oral cavity environment and reach to the other parts of the body and causes systemic infection[14], [15].

2. Materials and Methods

Sample Collection

Twenty specimens (saliva) were taken from patients suffering from periodontal disease, suspended in 1 milliliter of PBS.

Isolation and identification of bacterial isolate

About 100 microliters of the samples were smeared onto Mannitol salt agar plates after that incubation at 37 C° for 24 hour. The isolates were confirmed morphologically and culturally according to Leboffe*et al* and further by using the Vitek 2 system.

Antimicrobial susceptibility

The method of antimicrobial susceptibility based on the breakpoint is the concentration (μg/mL) of an antibiotic that is selected to determine whether a particular bacterium is susceptible or resistant to it. According to BSAC Resistance Surveillance Project that if the MIC is above this value, the pathogen was categorized into susceptible, intermediately resistant and resistant, which matched the interpretive criteriaestablished by WHO. Amoxicillin, gentamycin , azithromycin ,trimethoprim ,norfloxacin, nalidixic acid, claforan, ciprofloxacin, chloramphenicol, amikacin, nitrofurantoin, coftriaxonewere used.

Animals profiles

Male albino mice (Balb-c), whose ages varied from six to eight weeks, were used for the study. The mice were acquired from the Research and Cancer Center in Baghdad.

The Studied Groups.

Two groups of mice were included in the present study: Group I received daily treatment with normal saline, while Group II received one hundred milliliters of 1.5 x 108 CFU / ml of *S. aureus* intraperitoneally (i.p.). After fourteen days of therapy, blood was obtained from seven mice. The serum was collected and kept at -4 C° for the subsequent experiment.

Immunological Assays

Measurements of TLR-2 IL-4 , IL-10, and IL-17 Level

The standard curves below were used, and all operations were completed in compliance with the manufacturer's instructions provided by Elabscience Figure 1 and Figure 2.

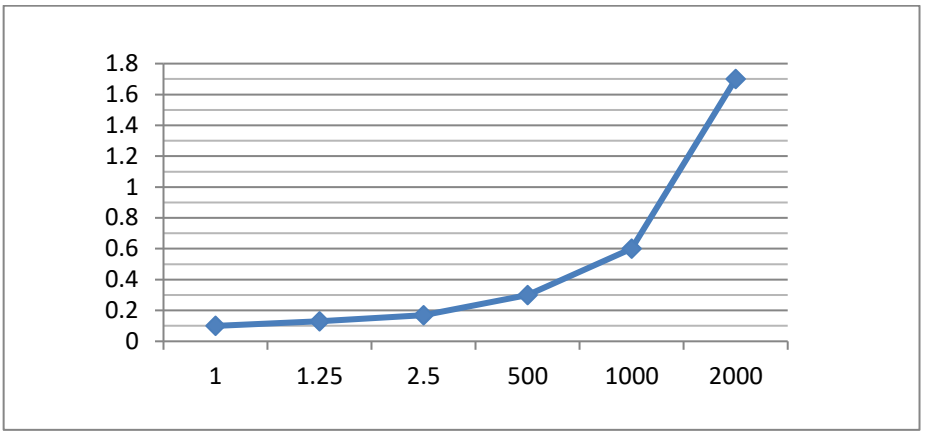

Figure 1. Standard curve of TLR-2 levels.

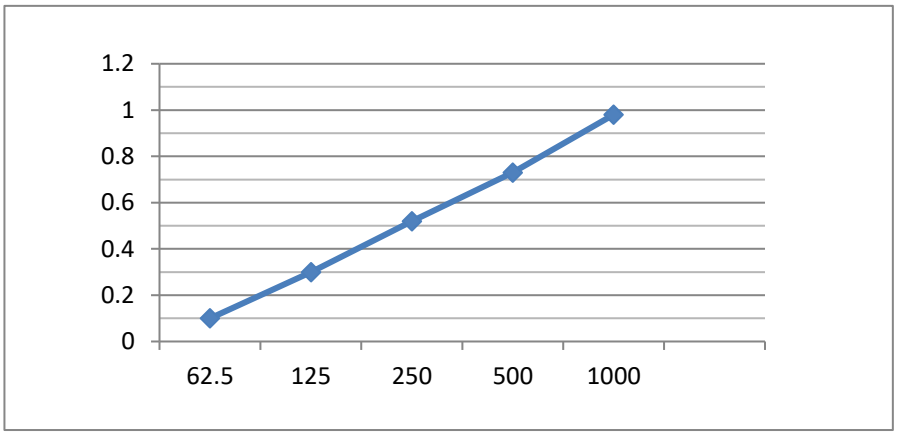

Figure 2. Standard curve for each IL-4,IL-10 and IL-17 levels.

Statistical analysis

Using the computer programs SPSS (version 11) andMicrosoft Excel 2010, were used to analysis the data.Comparative analyses were performed using the t- test. A P value of less than 0.05 was considered significant.

Ethical Clearance

The project was approved by the local ethical committee at University of Al-Muthanna APPLICATION NUMBER: REF-5-Suhair Mahdi Jabbar.

3. Results

Results

Twenty samples from patients with periodontitis were used in this experiment. Moreover, according to morphological characteristics along with the Vitek system, (35%)*S. aureus* isolates were identified, and the other isolates accounted for(65%) as shown in Figure 3.

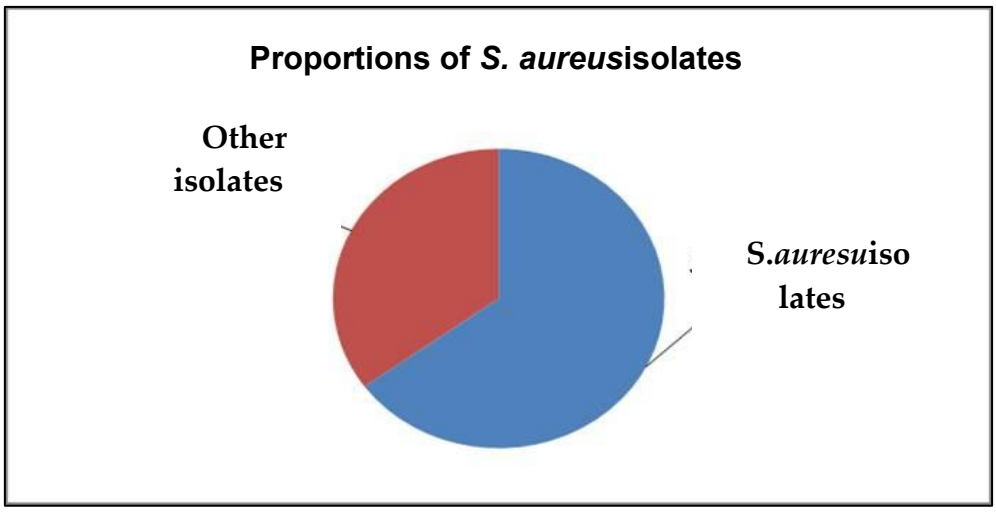

Figure 3. The Percentage occurrence of*S.aureus*in patients with periodontitis.

Antimicrobial Resistance

Twelve antibiotics used to detect the resistance of *S.aureus* , the results showed varied value between antibiotics, amoxicillin (100%) had the highest resistance, followed by gentamycin and azithromycin and (85.3 %),(80.3%). Trimethoprim ,norfloxacin, nalidixic acid , claforan, ciprofloxacin, recorded (70.9 % ,66.8%, 64.5%, 63.6%, 60.2%) respectively, however certain antibiotics exhibited activity against the isolated bacteria, such as chloramphenicol, amikacin, nitrofurantoin, coftriaxone (55.4 %, 44.6 %, 40.7 %, 40.2 %), see Figure 4.

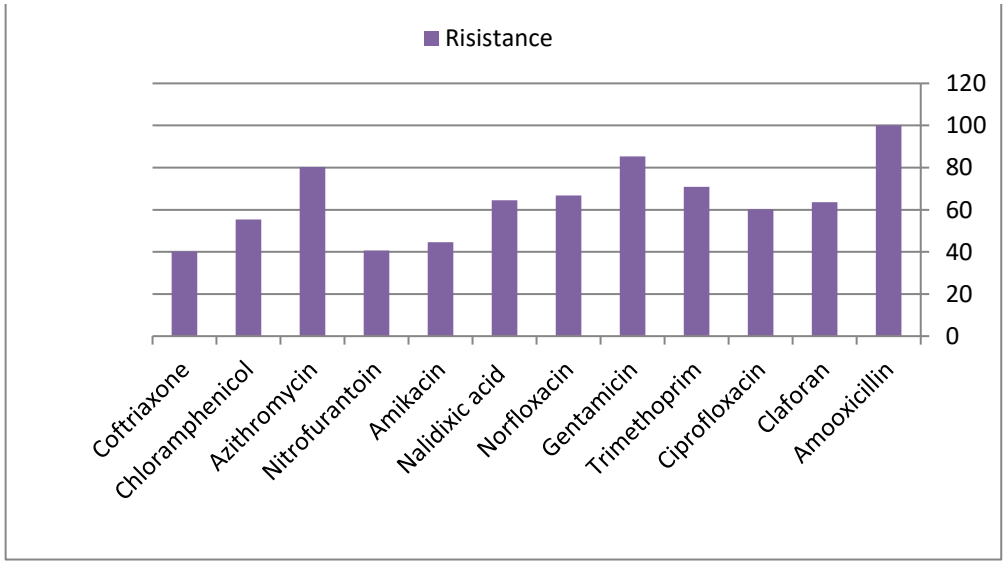

Figure 4. Antibiotic Susceptibility test for *S.aureus*

Immunological Results

The immunological results, which were represented by evaluation TLR-2, IL-4,IL-10,IL17 serum levels was the group that treated with *S.aureus* than the control group, with significant difference at p≤0.05. as in Table 1.

Table 1. Serum levels in study group

Serum Level	Groups	Mean /pg/mL	T-test	*P value*
TLR-2	I	5.85	4.92	0.034*
	II	9.38	1.93	

IL-4	I	58.39	4.92	0.024*
	II	136.56	2.10	
IL-10	I	1.38	0.35	0.002*
	II	98.6	3.23	
IL-17	I	5.85	4.92	0.04*
	II	288.3	1.82	

*The marks show that there is a significant statistical difference.

4. Discussion

According to morphological characteristics along with the Vitek system, (35%) *S. aureus* isolates were identified, and the other isolates accounted for 65%, The findings agreed with[16] who isolated *S. aureus* from 11 (44 percent) of 25 patients who showed symptoms of chronic periodontitis, as well as[17] who isolated 12 *S. aureus* from 50 samples collected from patients with Periodontitis.

Staphylococci bacteria were obtained from both the subgingival of 33 patients (37.50 percent) and from the oral cavity of 54 patients . Loberto et al when studied 88 patients with chronic periodontitis found *S.epidermidis* was in subgingival samples (15.90%) and the oral cavity (27.27%)and found in both locations in 5 individuals (5.68%). *S. aureus* was recovered from samples 25% of the oral cavity and 4.55 % of subgingival samples[18].

Periodontitis is a polymicrobial, complex condition characterized by microbiological dysregulation and immunological imbalance[19]. However, oral cavity itself harbors a large variety of microorganisms apart from *streptococci* and other species like *S. aureus,* Pseudomonas aeruginosa, and the periodontal biofilm can act as a reservoir for spreading these microorganisms[20] . Interestingly, some species, such as the bacteria *S. aureus,* showsto be more prevalent in healthy periodontal conditions[21]; in general, the revelation that the majority of commonly isolated Bacteria in our research were *Staphylococci* concurs with other studies[22, 23].

The results of the rate of resistance of isolates to antibiotics, varied between antibiotics. These findings differed from (Garbacz K) [24], who discovered that isolated *S.aureus* from the oral cavity showed varying resistance degrees to the antibiotics.

The results showed that amikacin ,nitrofurantoin ,coftriaxone, had activity against the isolated bacteria, which agreed with (Ghazi IM) [25]. A concerning factor with staphylococci is the unacceptably high and continuously rising rates of antibiotic resistance; this is one of the major challenges that face the clinicians dealing with staphylococcal infections across the globe. Resistance is especially relevant in the context of multidrug resistance bacteria[26].

The latest research has revealed that the mouth cavity is a important source of bacterium resistant to antibiotics with special reference to MRSA. MRSA can freely exist in many natural niches within the mouth; these include the following :mouth mucosa, tongue, denture, and periodontal pockets[27].

The immunological results, which were represented by evaluation TLR-2, IL-17, IL-4, IL10 serum levels were higher in group II than group I.

In details we found the TLR-2 was greater in the group that handled with *S. aureus* than the control group, the *t*-value is 1.930944, the value of *p* is .034275. The result is significant at $p < .05$. In the study by Bi *et al*., (2020) on mice that's infected with *S. aureus,* where this study investigated the mammary gland fibrosis caused by *S. aureus* infection involves the TLR-NF-B/AP-1 pathways[28], *S. aureus* has over 50 different lipoprotein surface antigens that are equivalent to about 2% of the entire staphylococcal proteome[29]. These lipoproteins play an important role in the bacterial lifestyle and are involved in aspects such as nutrition and iron uptake [30]. Lipoproteins from *S. aureus* have also been found to shield the bacteria after phagocytosis, allowing for greater survival and possibly phagocytic escape[31]. On the other hand, these lipoproteins can be PAMPs that can be sensed by host receptors, including TLR2, resulting in the activation of inflammatory

signaling pathways and therefore informing the hosts' immune system regarding the presence of *S. aureus*[32].

Indeed, it has been observed that efficient host responses against *S. aureus* depend on the recognition of bacterial lipoprotein[33]. TLR2 induces IL 17 production at the same time[34], which agrees with our findings that there was a considerable rise in IL-17 level in treated group more than in control group the *t*-value is 1.821327, the value of *p* is .042171, the result is significant at $p < .05$.

IL-17 is included in the immune response and host defense, regulation of immune, trafficking of cells, and tissue repair. Non-hematopoietic cells are triggered by IL-17A. (e. g. , epithelial cells) before it or in cooperation with other proinflammatory cytokines stimulates chemokine synthesis[35]. In response to extreme pathogen invasion, IL-17A increases the release of AMPs from macrophages and neutrophils (e.g.,-defensins, calgranulin, and lipocalin-2)[36]. Furthermore, IL17 has the potential to stimulate the production of additional AMPs and proteins[37]. Additionally, IL-17A enhances the secretion of IL-2 from T cells, which leads to the advancement of regulatory T cells[38], which subsequently generate IL-10[39] as shown in table (3) which the results noticed increasing in IL-4 level in group injected with bacteria but there was significant difference with the control group the *t*-value is 2.100963, the value of *p* is .02461, the result is significant at $p < .05$.

As well as the results recorded there was significant increasing in IL-10 in group injected with bacteria comparison with control group the *t*-value is 3.231364, the value of *p* is .002197 the result is significant at $p < .05$. Our findings were congruent with those of[40, 41] who investigated the function of IL4 and IL 10 during *S.aureus* infections.

Monocytes/macrophages stimulated by *S. aureus*produce IL-10 depending on TLR2, and because of its capacity to modify TLR2 plasticity and regulate particular downstream signaling pathways, it is feasible to declare with certainty that this bacteria can successfully cut off these cells' generation of pro and anti-inflammatory cytokines[42]. Human monocytes/macrophages have previously been demonstrated to produce a strong the IL-10 responding in response to *S.aureus*, which reduces T-cell stimulation[43] .

The phagocytosis of apoptosis neutrophils at the wound site was brought about by the actions of macrophages [44]. Nevertheless, as a result of this activity, pro-inflammatory macrophages become anti-inflammatory macrophages, or M2, or "alternatively activated" macrophages[45]. Unlike the clear M1 and M2 cell types, these macrophages worked on a scale of activity from inflammatory to anti-inflammatory[46].

In addition to facilitators that promoted this change involve prostaglandins, glucocorticoids, IL-10, the IL-4/IL-13 path, and specific toll-like receptor activity (TLRs) [47].

All macrophages belong to the more diversified cell type known as anti-inflammatory macrophages without the pro-inflammatory phenotype[48]. These cells decreased inflammation and triggered the repair of tissues by generating substances with anti-inflammatory properties, such as growth factors, IL-1 receptor antagonists, and IL-10. such as transformative growth factor and vascular endothelial growth factor[49]. Transformation of a pro-inflammatory to anti-inflammatory macrophage was critical in reducing inflammation and promoting efficient repair[50].

On another side, IL-4 is a crucial distinguishing influence for healing wounds macrophages, where it is required for a tissue regeneration, and it seems to resist Interleukin-17-mediated inflammation such as dermatitis and the experimental autoimmune encephalomyelitis[51]. In addition, IL-4 signaling has been demonstrated in vivo to prevent neutrophil affecting activity, that is relevant to inflammatory disorders with substantial neutrophil infiltrates[52].

Actually, IL-4 which has been observed to promote the formation of the IL-10 in Both T cells and macrophages as well, it's helpful to clarify why IL-4 additionally serves as anti-inflammatory. Considering the generation of cytokines and the role of effectors, Th1 or Th2 responses are categorized based on antigen-specific CD4+ helper T [53]. IL-10, a Th2-type cytokine, has anti-inflammatory properties and protects the host from septic shock,

endotoxin shock[54]. IL-4, on the other hand, is said to be harmful in *S. aureus*-induced infections[55], [56].

5. Conclusion

In present study, *S. aureus*can evaluate the immune system of the lab. Mice with periodontitisthen systemic cytokines progression where it was found that it stimulated the innate immunity represented by TLR-2 and IL-17, an inflammatory cytokine, and anti-inflammatory cytokines IL-10 and IL-4. Antimicrobial-resistant bacteria, in particular, can make treatment challenging, worsen prognoses, induce unforeseen bacterial infections, and promote the emergence of opportunistic pathogens. Determining the patterns of *S. aureus's* multidrug resistance, antibiotic susceptibility, and pathogenic factors is crucial.

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