ejpmr, 2018,5(6), 232-238

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

DEFENSE MECHANISM OF GINGIVA

***[1]Dr. Vivek Bhalla, [2]Dr. Gurpreet Kaur, [3]Dr. Deepak Grover and [4]Dr. Sumeet Kaushal**

[1]MDS, Post-graduate Student, Dept. of Periodontology and Oral Implantology, National Dental College, Dera Bassi, Punjab.

[2]MDS, Professor and Head of the Department of Periodontology and Oral Implantology National Dental College, Dera Bassi, Punjab.

[3,4]MDS, Reader, Dept. of Periodontology and Oral Implantology, National Dental College, Dera Bassi, Punjab.

***Corresponding Author: Dr. Vivek Bhalla**

MDS, Post-graduate Student, Dept. of Periodontology and Oral Implantology, National Dental College, Dera Bassi, Punjab.

Article Received on 31/03/2018 **Article Revised on 21/04/2018** **Article Accepted on 11/05/2018**

ABSTRACT

Gingiva is a part of oral mucous membrane that covers the alveolar processes of jaws and surrounds the neck of the teeth in a collar like fashion. Gingiva is exposed to variety of thermal and chemical stimuli but its specific structure of gingiva reflects its effectivenss as a barrier to the penetration by microbes and noxious agents into deeper tissues. This paper will discuss the defense mechanism that enables the gingiva to protect the underlying structures.

KEYWORDS: gingiva, saliva, gingival crevicular fluid, epithelium, innate immunity, adaptive immunity.

INTRODUCTION

The gingiva tissue is constantly subjected to mechanical and bacterial noxious products. If gingiva is not able to protect the underlying structure, the condition will clinically manifest as gingivitis and periodontitis. The defense mechanism of gingival can be categorized into innate and adaptive immune responses (Figure 1).[1,2]

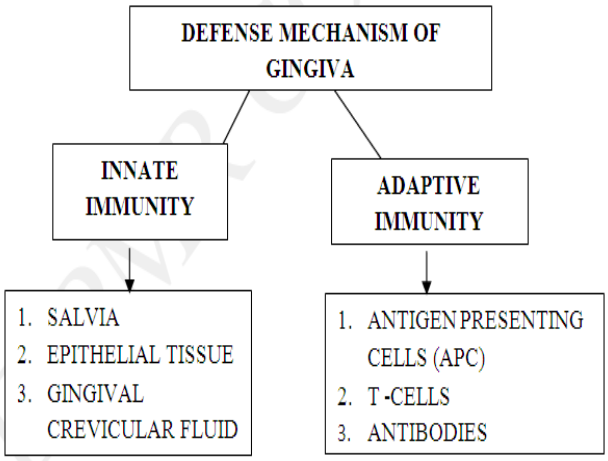


Figure 1: Defense mechanism of gingiva

SALVIA

Saliva (oral fluid) is a mirror of the body. It could be used to monitor the general health and the onset of specific diseases and helps to maintain the oral tissues in their physiological state[3]. The components of salvia that play a role in innate immunity are depicted below (Figure 2). The functions are depicted in Table 1.

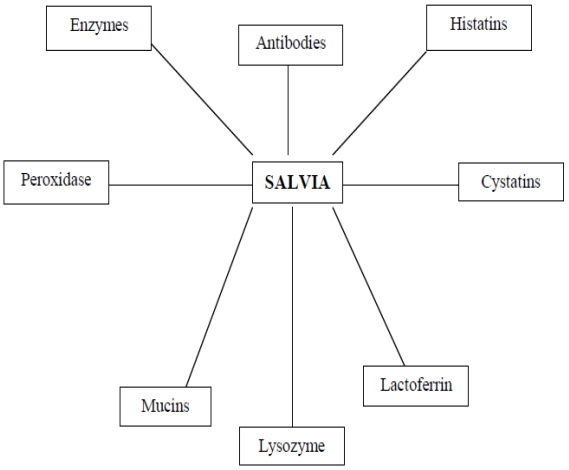


Figure 2: Components of salvia that contribute to innate defense.

Table 1: Functions of various components of saliva.[5,6,7,8]

Salivary components	General information	Function
MUCINS- **MG1- >1000KDa** **MG2- 25KDa**	1- High molecular weight glycoprotein produced by submandibular, sublingual and minor salivary glands 2- Highly viscous and insoluble that helps to maintain the membrane integrity under harsh condition	1- Selective adhesion of fungal and bacterial agent and helps to prevent biofilm formation 2- Protect both hard and soft tissue by forming lubricating coating on tissue 3- MG1-involved in tissue coating 4- MG2- affect aggregation and adherence of streptococci
LYSOZYME	1. Small cationic protein present in all major body fluids 2. Secreted by intercalated duct cells	1. Lyses the bacterial species by hydrolyzing the glycosidic linkages in cell wall of peptidoglycan 2. Leads to destabilization of cell membrane by activation and degranulation of endogenous bacterial autolysin
LACTOFERRIN	1. Iron binding glycoprotein 2. Produced by intercalated duct cells	1. Inhibits bacterial growth by sequestering iron in the environment
SALIVARY PEROXIDASE	1. Secreted by gland acinar cells	1. Removes hydrogen peroxide produced by oral microorganism 2. Reduces acid production in dental plaque
SECRETORY IgA	1. Secreted by plasma cells 2. Predominant type found in salvia 3. First line of defense against pathogens	1. Inhibition of bacterial adherence
HISTATINS	1. Family of 12 histatins and 8 derived peptides(3-5KDa) 2. Contain histidine rich residues 3. Secreted by parotid and submandibular salivary gland 4. Histatin 1, 3, 5 are major ones found in salvia	1. Inhibits hydroxyapaptite formation maintaining surface integrity of enamel 2. Role in primary innate defense mechansim
CYSTATINS	1. Family of cysteine containing phosphoproteins 2. Secreted by acinar cells	1. Act as thiol protease inhibitors and inhibit the proetases produced by periodontopathogens
ENZYMES	1. Major ones are parotid amylase, others being hyaluronidase, chondrotin sulphate, peroxidises and collagenases. 2. They contribute to intiation and progession of periodontal disease	1. To combat these enzymes, saliva has antiprotease- TIMP – Inhibits the activity of collagen degrading enzyme 2. Lactoperoxidase thiocynate system- bactericidal to strains of lactobacillus and streptococci by preventing accumulation of lysine and glutamic acid essential for bacterial growth
MYLEOPEROXIDASE	1. Released by leukocytes	1. Bactericidal for actinobacillus and inhibits the attachment of actinomyces strains to hydroxyapatite

EPITHELIAL TISSUE

Gingiva is composed of epithelial layer consisting of stratified squamous epithelium and provides a physical barrier to infection and has an active role to play in innate host defense.

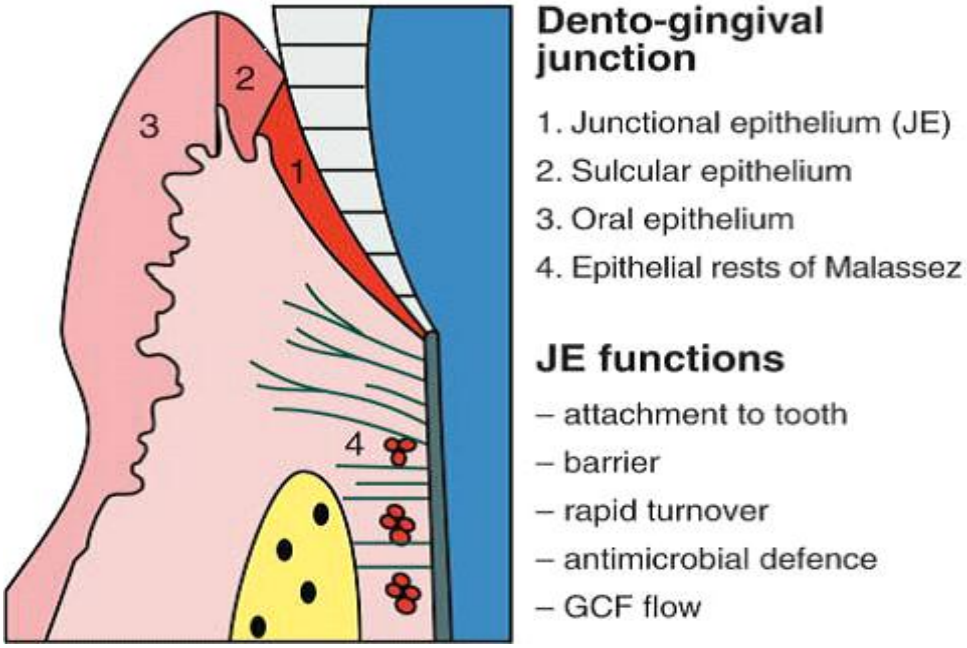
HOW EPITHELIUM RESIST THE PATHOGEN ENTRY?

It resists the entry by acting as a barrier-

- Mechanical barrier
- Chemical barrier
- Biological barrier

MECHANICAL BARRIER- Based upon the functional and morphological characteristics, gingival epithelium is divided into[9,13] – (diagram depicting the three epithelium)

1. Oral epithelium
2. Sulcular epithelium
3. Junctional epithelium



ORAL EPITHELIUM[9,13]

A. Faces the oral cavity.
B. Parakeratinized and cells are tightly packed
C. Function- it is to protect the deeper structures while allowing a selective interchange with the oral environment.

SULCULAR EPITHELIUM[9,13]

A. Faces the tooth without being in contact with the tooth surface
B. Non –keratinized and presence of intercellular spaces
C. Function- high turn over rate and proliferative potential helps to clear the pathogens.

JUNCTIONAL EPITHELIUM

A. It is a a layer of epithelial cells united to the surface of the crown or root by hemidesmosomes and a basal lamina and has its sloughing surface at the base of the gingival sulcus.[10]
B. Non- keratinized stratified squamous epithelium.[11]
C. **Functions**[12]- 1) It is firmly attached to the tooth surface and forms an epithelial barrier against the plaque bacteria

2) It allows the access of gingival fluid, inflammatory cells and components of immunological host defense to gingival margin
3) It exhibits rapid turnover rate of host parasite equilibrium and rapid repair of damaged tissues
4) Cells of junctional epithelium has an endocytic capacity equal to that of macrophages and neutrophils.

ROLE OF KERATINOCYTES

These are the principal cell type of the gingival epithelium as well as of other stratified squamous epithelia. The main function of the gingival epithelium (Protection and barrier against the oral environment) is achieved by the proliferation and differentiation of the keratinocytes.

Proliferation[13]

The proliferation of keratinocytes takes place by mitosis in the basal layer and less frequently in the suprabasal layer, where a small proportion of the cells remain as a proliferative compartment while a larger number begin to migrate to the surface.

Differentiation[13]

It involves following biochemical and morphologic events

- Progressive flattening of the cell with its long axis parallel to the epithelial surface and increasing prevalence of tonofilaments

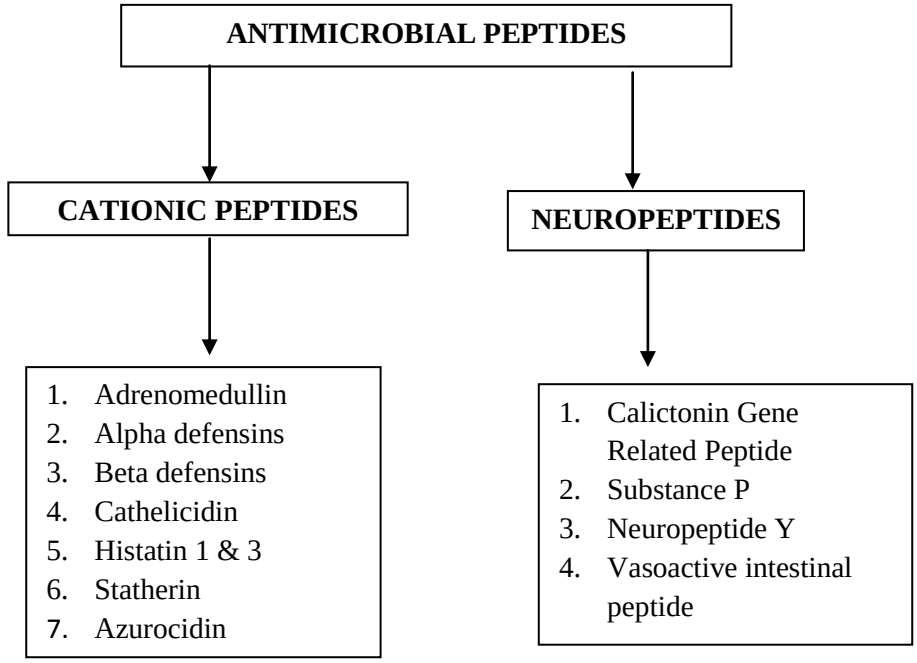
- Intercellular junctions coupled together to the production of kertohyaline granules
- Disappearance of nucleus
- Cells lose the ability to multiply by mitotic divison
- Cells lose the cytoplasmic oragnelles responsible for preotein synthesis and energy production
- Cells eventually degenerate into a cornified layer due to the process of intracellular keratinisation
- Cells are ultimately sloughed away from the epithelial surface and into the oral cavity as the cell-cell attachment mechanisms i.e. desmosomes and gap junctions finally disintegrate

CHEMICAL BARRIER- Here, ANTIMICROBIAL PEPTIDES play a major role.

ANTIMICROBIAL PEPTIDES[14]

A. Peptides with anti microbial activity – first described by Zeya and Spitznagel (1966).
B. Weight ranging from 3500-6500kDa.
C. Wide range of activity against Gram-positive and Gram-negative microorganism.
D. Small, polcationic peptides that disrupt the bacterial cell membranes.

CLASSIFICATION[15]



DEFENSINS[16,32]

A. These are the first anti microbial peptides to be identified
B. Small, cystein rich cationic AMP's containing three pairs of intramolecular disulfide bonds having following categories.

TYPE	FUNCTION
Alpha- defensin	It attracts CD4+ T cells and immature dendritic cells by using chemokine receptors to stimulate mast cell degranulation and regulate complement activation
Beta- defensin	There occurs electrostatic interaction between positively charged defensin and negatively charged bacterial cell membrane Pore formation in bacterial membrane leads to the leakage of small molecules and leads to bacterial cell death

CATHELICIDIN LL37[17]- It is a family of endogenous antimicrobial peptides and has been detected in the gingival epithelium, junctional epithelium and connective tissue (Lehre and Ganz 2002).

Functions of ANTIMICROBIAL PEPTIDES

A. Pore formation is the basic mechanism of action
B. Regulates innate and adaptive immune responses
C. Helps in wound healing through effect on kertainocyte differentiation
D. Stimulates mast cell degranulation and cytokine production
E. Helps in chemotaxis through chemokine like activity

BIOLOGICAL BARRIERS- These includes

1. PAMPs, PRR and TOLL LIKE RECEPTORS
2. LANGERHANS Cells of gingival epithelium
3. Neutrophils associated with junctional epithelium

PAMPs(Pathogen Associated Molecular Patterns)[18]

A. These are the conserved epitopes expressed by the pathogens
B. Molecular signatures of microbial metabolism
C. Examples-Flagella, LPS, Lipotechoic acid etc

PRRs (Pattern Recognition Receptors)[19]

A. They serve as encoded receptors for conserved molecular patterns
B. They are present on- Myelomonocytic cells, endothelial cells, epithelial cells and hepatocytes
C. Types- Receptors that signal the presence of infection

Secreted PRRs

Phagocytic or endocytic receptors

TOLL LIKE RECEPTORS(TLR)[20]

A. These cells are responsible for the recoginition of pathogen associated molecular patterns (PAMPs) expressed by pathogens.
B. Function- synthesis and secretiob of pro-inflammatory cytokines and lipid mediators leading to intiating the inflammatory response that recruits both soluble immune components and immune cells from the blood.

LANGHERAN CELLS[21]

A. Described by Paul Langerhan (1868)- dendrtically shaped cells.
B. They are responsible for communications with the immune reactions.
C. They act as antigen presenting cells for lymphocytes.
D. They detect, capture foreign antigens and present them to T cells.
E. They are found five times more in inflamed gingival in comparsion to healthy gingiva.[22]

NEUTROPHILS[23]

A. They also act as biological barrier.
B. They stem from the bone marrow- neutrophil precursors- neutrophils- systemic circulation- gingival vasculature and then they enter junctional epithelium.
C. They are called neutrophils because their granules stain poorly with the mixture of dyes used in staining leukocytes. Because of the granules, they are considered as one of the granulocytes.
D. There are two types of granules, the specific granules and azurophilic granules. Specific granules are present in abundance and contain proteolytic enzymes such as lysozyme, collagenase and elastase. They stain neither with acidic nor basic dyes. The azurophilic granules are actually lysosomes.

GINGIVAL CREVICULAR FLUID (GCF)

Gingival crevice fluid (GCF) is a complex mixture of substances derived from serum, leukocytes, structural cells of the periodontium and oral bacteria.[1]

There are two different school of thoughts regarding the nature of GCF.

Brill (1959)[24]- He confirmed the presence of GCF in humans and consider it to be a transudate.

Loe H et al (1965)[25]- He demonstrated that GCF is inflammatory exudate and not a common transudate.

But the latest thought regarding the nature of GCF which is being followed till date is model by PASHLEY.[27] He predicted that GCF production is governed by the passage of fluid from capillaries into the tissues (capillary filtrate) and the removal of this fluid by the lymphatic system (lymphatic uptake).When the rate of capillary filtrate exceeds that of lymphatic uptake, fluid will accumulate as edema and/or leave the area as GCF.

It exerts its defense mechanism by following ways[26]

1) Cleanse the non adherent bacteria and their toxic products and metabolites from the sulcus.
2) Contain plasma proteins that may improve the adhesion of the epithelium to the tooth.
3) Possess antimicrobial properties.
4) Exert antibody activity to defend the gingiva.
5) Contains a wide array of biochemical factors offering potential use as a diagnostic or a prognostic biomarker of the biologic state of the periodontium in health and disease.

If above described components of innate immunity are not able to overcome the pathogens and if they enter the connective tissue then following things happens.

I. The alternate pathway of complement system gets activated
II. Release of complement components such as C3a, C3b
III. Degranulation of mast cells and release of vasoactive amines trigerring the inflammatory response
IV. Neutrophils comes out of the connective tissue
V. Bacterial killing by neutrophils

ANTIGEN PRESENTING CELLS[28]

A. These are the sentinel cells that detect, take up the microorganism and their antigens, then migrating to the lymph nodes and interacts with the T cells and present the antigen
B. These cells includes- B cells, macrophages, Langerhan cells and dermal dendritic cells
C. They express MHC class II molecules that are necessary for uptake of specific antigens, their transport and then presentation to T cells.

T CELLS[29,30,31]

A. The response of T lymphocytes to the challenges by antigen is called as cell mediated immune responses.
B. Types – CD4+ (T helper lymphocytes)
   CD8+(cytotoxic T lymphocytes)
C. T helper cell are divided into- T helper 1 cells
   T helper 2 cells
D. Th1 cells- secrete IFNγ-activates cell mediated immunity against pathogens
E. Th2 cells- regulate humoral immunity through release of cytokines like IL-4, IL-5

CONCLUSION

Periodontal disease has multifactorial etiology and severity of the disease depends upon the host microbial interaction. So we need to understand the mechanism that increases the susceptibility of the host to the periodontal disease. One of the host mechanism that controls the pathogens in the gingival sulcus is via the elaboration of GCF. The outflow of the gingival crevicular fluid cleanse the dentogingival space of non-adherent microbes and reduces the concentrations of their toxins and their metabolic byproducts. It also contains antimicrobial compounds and enzymes that acts on the site of bacterial colonization. The epithelium is constantly renewing and high turnover rate aids in the clearance of bacteria adhering to the oral mucosa. It also plays an important role in the initial defense of the dentogingival space and display morphologic characteristics that aids in removing the periodontal pathogens. Neutrophils also play a critical role in the protection of the dentogingival space Thus, the permeability of the junctional and sulcular epithelia, leukocytes, and the protective role of sulcular fluid and saliva; form the defence mechanisms of the gingiva.

REFRENCES

1. Carranza's Clinical Periodontology: Newman, Takei, Klokkevold, Carranza: 10th Edition.
2. Shalu Bathla Periodontics Revisited, 1st edition.
3. Grinnobile WV, Beikler T, Kinney JS, Ramseier CA, Morelli T, Wong DT. Saliva as a diagnostic tool for periodontal disease: Current state and future directions. Periodontol, 2000. 2009; 50: 52–64,
4. Schenkels LC, Veerman EC, Nieuw Amerongen AV. Biochemical composition ofhuman saliva in relation to other mucosal fluids. Crit Rev Oral Biol Med, 1995; 6(2): 161-75.
5. Schenkels LC, Veerman EC, Nieuw Amerongen AV. Biochemical composition ofhuman saliva in relation to other mucosal fluids. Crit Rev Oral Biol Med, 1995; 6(2): 161-75.
6. Kaufman E, Lamster IB. The diagnosticapplications of saliva: a review. Crit Rev OralBiol Med, 2002; 13: 197-212.
7. The American Academy of Periodontology. The pathogenesis of periodontal disease (position paper). Journal of Periodontology, 1999; 70: 457- 70.
8. Balwant R, Sammi K, Rajnish J, Suresh CA.Biomarkers of periodontitis in oral fluid. J Oral Sci, 2008; 50(1): 53-56.
9. Beverly A. Dale. Periodontal epithelium: a newly recognized role in health and disease. Periodontol, 2000. 2002; 30(1): 70-78.
10. Irving B. Stern. Current concepts of the Dentogingival Junction. J.Periodontol, 1981; 52: 9.
11. Schroder, Listgarten. Junctional Epithelium; from strength to defense. Journal of Dental Research, 2003; 31: 12-31.
12. Bosshardt, N.P.Lang. The Junctional Epithelium, from health to disease. JDR, 2005; 84: 9-20.
13. Clinical Periodontology and Implant Dentistry: Jan Lindhe, 5th edn.
14. F.S. Mariano et al. Antimicrobial peptides and nitric oxide production by neutrophils from periodontitis subjects. Braz J Med Biol Res, November 2012; 45(11): 1017-1024.
15. Gorr S-U, Abdolhosseini M. Antimicrobial peptides and periodontal disease. J Clin Periodontol, 2011; 38(Suppl. 11): 126-141. doi: 10.1111/j.1600-051X.2010.01664.x.
16. Bedi T, Mahendra J. Defensins in periodontal health. Indian J Dent Res, 2015; 26: 340-344.
17. Lehre R,Ganz T. Cathelicidins- family of endogenous antimicrobial peptides. Curr Opin Hematol, January 2002; 4(1): 18-22.
18. Akira S, Takeda K, Kaisho T. Toll like receptors, critical proteins linking innate and acquired immunity. Nat Immunol, 2: 675-686.
19. Song B, Zahang YL, Chen LJ. The role of Toll like receptors in periodontitis. Oral diseases, March 2017; 23: 168-78.
20. Takeda k, Akira S. Toll like receptors in innate immunity. Int Immunology, 2005; 17: 1-14.
21. Shewta Jaitley, Saraswathi TR. Pathphysiology of Langerhan cells. J Oral Maxillofac Pathol. 2012 May-Aug; 16(2): 239–244.
22. Ingeberg R.Bos, Arne Burkhardt. Interepithelial cells of the oral mucosa Light and electron microscopic observations in germfree, specific pathogen-free and conventionalized mice. Journal of Oral Pathology and Medicine, March 1980; 9(2): 65-81.
23. Elena A. Nicu,Bruno G. Loos. Polymorphonuclear neutrophils in periodontitis and their possible modulation as a therapeutic approach. Periodontology, 2000; June 2016, 71(1): 140-163.
24. Brill N. The gingival pocket fluid. Studies of its occurrence, composition and effect. Acta Odontol Scand, 1962: 20(Suppl. 32): 1–115.
25. Löe H, Holm-Pedersen P. Absence and presence of fluid from normal and inflamed gingivae. Periodontics, 1965; 3: 171–177.
26. Cimasoni G. The crevicular fluid. Monogr Oral Sci, 1974; 3: 1–122.
27. Pashley H. A mechanistic analysis of gingival fluid production. Journal of Periodontal Research, April 1976; 11(2): 121-134.

28. Neeraj Deshpande. Antigen presenting cells in periodontal disease. Indian Journal of Oral Sciences, May 2013; 3(2): 69.
29. Roy C. Page & Kenneth S. Kornman. The Pathogenesis Of Human Periodontitis: An Introduction. *Periodontology*, 2004 *Vol. 14*, 1997, 9-11.
30. Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. Nature, 1996 Oct 31; 383(6603): 787-93.
31. Janeway CA. The road less travelled by role of innate immunity in adaptive immune response. J Immunol, 161: 539-544.
32. Bhagwati S B, Bhagwati B T, Mittal S.Role of defensins in oral diseases:An Overview.J Indian Acad Oral Med Radiol, 2012; 24(2): 142-145.