International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Review Article

Pathogenic Mechanisms of *Candida Albicans* in Oral Mucosa - A Review

Supriya H[1], Harishchandra Rai[2], Suhasini PD[1], Rajalekshmi V[1]

[1]PG Student, [2]Professor and Head,
Department of Oral Pathology and Microbiology, KVG Dental College and Hospital, Sullia - 574 237, D.K, Karnataka, India.

Corresponding Author: Supriya H.

Received: 16/12/2015 *Revised: 28/12/2015* *Accepted: 30/12/2015*

ABSTRACT

The predominant fungi isolated from human mouth belong to the genus *Candida,* and while there are more than 150 *Candida* species, approximately only 10 of these colonize the oral cavity. *Candida albicans (C. albicans)* is the most prevalent species recognized (70 to 75% of isolates), followed by *C. glabrata* and *C. tropicalis* (7% of isolates). Array of factors including host, systemic and iatrogenic has been associated with an increase in the incidence of opportunistic infections involving *Candida* and thus regarded as pathogenic species. The transition of this innocuous commensal into disease-causing 'parasite' may be associated with the virulence attributes of the microorganism and an array of host factors. Factors contributing to the pathogenicity include surface molecules which mediate adhesion to and invasion into host cells, secretion of hydrolases, yeast-to-hypha transition, contact sensing and thigmotropism, biofilm formation, phenotypic switching and a range of fitness attributes. Here we overview the various modalities as how this normal commensal turns pathogenic, it's possible interactions with host epithelial cells and role in malignant transformation of oral mucosa.

Key words: *C. albicans*, candidiasis, colonization, pathogenesis, squamous cell carcinoma.

INTRODUCTION

Oral cavity plays host to wide array of microorganisms inclusive of variety of bacteria, viruses and fungi. [1] Candidiasis is the most common significant fungal infection in the oral cavity, and is usually associated with local and systemic predisposing factors. [2] In most individuals; *C. albicans* resides as part of harmless natural microflora and appears as a transient flora in immunocompromised individuals. It is the causative in majority of cases of mucosal disease and hence the most widely studied species of *Candida.* Under varying circumstances, it can cause infections ranging from superficial infections of the skin to life-threatening systemic infections. [3]

Host factors: Diverse arrays of local and systemic factors have been implicated in the pathogenesis of oral candidiasis. These factors act in concert and the eventual outcome of these disease processes is frequently related to the superimposition of the local factors upon systemic factors or vice versa. [4] Host immune status is of critical importance in the development of the disease state and *Candida* species are strictly opportunistic pathogens that cause disease when the host defences are inadequate. [5]

Local host factors include mucosal barrier, salivary flow, host defence and morphogenesis of organism. Changes in the epithelium of the oral mucosa like atrophy, hyperplasia or dysplasia may affect the efficiency of the mucosal barrier.

[6] The superficial mucosa protects the host against *Candida* because constant desquamation of the mucosa takes place at a rate greater than *Candidal* growth. Saliva flow rate, quantity and the quality of the saliva affect microbial clearance in the oral cavity. In addition it also contains antifungal factors such as lysozyme, lactoperoxidase, lactoferrin and histidine-rich polypeptides, which may help to keep the oral *Candida* populations under control. [7] Morphological forms of *Candida* ranges from yeast to hyphal to pseudohyphal forms. *C. albicans* strains can exhibit switching of colony morphology when nutritionally stressed accompanied by chromosomal translocation. This phenotypic switching may be a genetic mechanism that allows asexual *C. albicans* to adapt to environmental change. [8]

Systemic factors affecting the pathogenesis include the immune status and nutrition factors of the host. In the immunocompromised patient, alterations in phagocytic or lymphocytic cell numbers or function are often the most critical factors predisposing to fungal infection. [2] In conditions like diabetes the cell surface receptors modulate yeast adhesion. [9] Also nutritional factors like iron and vitamin deficiency act in concert with a number of co-factors in the pathogenesis of oral candidiasis. [10] HIV infection is another major risk factor for developing oral candidiasis. The high frequency of oral *Candida* carriage and candidiasis among HIV-seropositive and AIDS patients emphasises that a fully-functional immune system is needed to prevent candidiasis. [2]

Iatrogenic factors include antibiotic, corticosteroid therapy and irradiation. [2] Broad-spectrum antibiotic therapy and corticosteroids with potent anti-inflammatory and immunosuppressive properties lower host resistance and predispose individuals to systemic and superficial candidiasis. Irradiation affects T and B cell function, resulting in profound suppression of cell-mediated and humoral immunological reactions. [7] In addition wearing of dentures and extremes of age provide a ideal surface for *Candida* colonisation. [11] Rather than a single factor, combinations of different factors appear to be responsible for the pathogenicity of *C. albicans* and its colonisation.

Colonization: Oral colonization with yeast entails acquisition from the environment, attachment to surfaces, and growth/replication. While the micro-organisms are trying to grow, host defence systems try to eradicate them. The balance among acquisition, growth and removal determines whether it is colonized and will lead to candidiasis. [12] Thus microbial adherence mechanisms play significant role in determining where this balance lies. Several candidal adherence mechanisms have been proposed which include electrostatic attraction, cell hydrophobic interaction, and specific adhesins. In addition morphological transition between yeast and hyphal forms, expression of adhesins and invasins on the cell surface, thigmotropism, formation of biofilms, phenotypic switching and the secretion of hydrolytic enzymes are considered as virulence factors. [13]

Adherence mechanisms exhibited by *C. albicans* enables it to colonize many oral niches. Innate primary defence mechanisms of the host play key roles in preventing yeast colonization of the oral cavity. The balance among clearance, colonization, or candidiasis therefore depends on the ability of *Candida* strains to modulate expression of virulence factors in response to environmental change, combined with the competence of the host immune system. [6]

Mechanism of Pathogenicity of *C. albicans*: The ability of *Candida* to adhere to oral surfaces which are exposed to the flushing action of saliva is considered as a prerequisite for successful colonisation of the mouth to initiate infection. [14] It is generally accepted that candidal adherence is a multifactorial phenomena, also related

to the site of attachment in the oral cavity. [15] The genus *Candida* comprises more than 150 species which are widespread in the environment. The fact that the majority of the species cannot survive at the human body temperature explains why the oral cavity is colonized with limited number of opportunistic pathogenic *Candida* species. [16]

As a normal commensal of oral cavity, the carriage rate for *Candida* is high, with nearly one half of the healthy population harbouring the organism. [17] Depending on the type of infection the clinical presentation could vary as multiple types such as acute, chronic and mucocutaneous patterns. Other than the oral cavity it can also cause infections of the oesophagus, skin, gastro-intestinal tract, vagina and vascular system. [18] Although rarely fatal in the absence of other serious underlying disease, oral candidiasis may serve as a useful clinical marker for the presence of significant predisposing conditions. [17]

The development of candidiasis depends on a delicate balance between the fungi and the host's immune status which determines the commensal or parasitic relationship. [19] The spores of *Candida* are a commensal, harmless form of a dimorphic fungus that becomes invasive and pathogenic pseudohyphae when there is imbalance of flora or debilitation of the host. [15]

Adherence mechanisms:

- *Polymorphism: Candida albicans* is a polymorphic fungus that can grow either as ovoid-shaped budding yeast, as elongated ellipsoid cells with constrictions at the septa (pseudohyphae) or as parallel walled true hyphae. While yeast and true hyphae are regularly observed during infection pseudohyphae and chlamydospore have not been observed in patient samples. Polymorphism has been proposed to be important for pathogenicity, with the hyphal form shown to be more invasive than the yeast form. [20]
- *Adhesins and invasions: Candida albicans* has a specialized set of proteins (adhesins) which mediate adherence to other *C. albicans* cells, to other microorganisms, to abiotic surfaces and to host cells. Invasion into host cells by *C. albicans* relies on two likely complementary mechanisms: induced endocytosis mediated by Als3 (agglutinin-like sequence) and Ssa1 (cell-surface expressed member of the heat shock protein 70) and active penetration mediated by yet undefined molecular mechanisms. [21]
- *Biofilm formation:* Catheters, dentures (abiotic) and mucosal cell surfaces (biotic) are the most common substrates which could help in *Candida* biofilm formation. It is a sequential process of adherence of yeast cells to the substrate, proliferation of yeast cells, and formation of hyphal cells in the biofilm, accumulation of extracellular matrix material and finally dispersion of yeast cells from the biofilm complex. [22] Mature biofilms are more resistant to antimicrobial agents and host immune factors. Dispersed yeast cells from this biofilm were found to be more virulent in comparison to the blastospores. [4]
- *Contact sensing and thigmotropism:* An important environmental cue that triggers hypha and biofilm formation in *C. albicans* is contact sensing. Upon contact with a surface, yeast cells switch to hyphal growth (thigmotropism). [23] Contacts with solid surfaces can also induce the formation of biofilms thus increasing virulence of the organism. Thus contact sensing and directional growth is important for pathogenicity.
- *Secreted hydrolases:* Upon adhesion to host cell surfaces and hyphal growth, *C. albicans* hyphae secretes hydrolases, which have been proposed to facilitate active penetration into host

niche. In addition, secreted hydrolases are thought to enhance the efficiency of extracellular nutrient acquisition. Secreted hydrolases expressed by *C. albicans* are proteases, phospholipases and lipases. Sap (secreted aspartic proteases) proteins are the key virulence determinants of *C. albicans because of the large size of the family.* [24] They are involved in both active penetration and induced endocytosis.

- *pH-sensing and regulation: C. albicans* senses, adapts to and actively modulate extracellular pH. All these features contribute to its remarkable capacity to co-exist as a commensal and to prevail as a fungal pathogen in humans. [5] Its ability to modulate extracellular pH contributes to the capacity to exist both as a commensal and pathogen.
- *Metabolic adaptation:* Metabolic adaptability enables the effective assimilation of alternative nutrients for survival and growth in dynamic environments. Depending on the anatomical niche, nutrient sources could vary from glucose, lipids, proteins and amino acids. Nutrient availability strongly varies in respect to the infected host niche and pathogens may possess different strategies to acquire nutrients, promote survival and growth. This metabolic flexibility is particularly important for pathogenic fungi during infection of varying host niches. [25]
- *Environmental stress response:* A robust stress response contributes to the survival and virulence of *C. albicans* by facilitating the adaptation of the fungus to changing conditions and protecting it against host-derived stresses. Stress-responsive regulatory pathways, as well as downstream targets, were shown to be essential not only for efficient stress adaptation, but also for full virulence of the fungus. [5]

Thus the interplay between host nutritional immunity and fungal nutrient acquisition systems is responsible for pathogenicity of *C. albicans.* [5]

Oral epithelium and *C. albicans*: The oral epithelium provides a barrier that physically protects the underlying tissues from invasion by microorganisms and blocks the penetration of some exogenous proteins. As a first step in establishing infection in the mouth, *C. albicans* must adhere to oral keratinocytes, because adhesion enables it to exercise its virulence. Adherence is mediated by several surface adhesins expressed by *C. albicans,* which bind to the surface of the keratinocytes. [14] It must also be able to compete with commensal oral flora and to tolerate hostile environmental circumstances, including variations in temperature, moisture and pH, and to resist the effects of biological antifungal agents secreted by keratinocytes and innate immune cells. [26]

Once adhesion has been established, in order to invade the epithelium, the fungal hyphae must penetrate the epithelium at a rate faster than the rate of multiplication, maturation and desquamation of the epithelial cells; otherwise the fungus will be shed together with the shedding keratinocytes. In response to invading *Candida* hyphae, oral keratinocytes secrete antifungal agents, and biological mediators that activate myeloid dendritic cells and macrophages. On the other hand, commensal *Candida* blastoconidia induce regulatory immune responses thus maintaining tissue tolerance to the commensal fungi. [27]

Invasion of keratinocytes: The ability of *C. albicans* to colonize, penetrate, and damage host tissues depends on an imbalance between *C. albicans* virulence factors and host defences, often due to specific defects in the immune system. Two different mechanisms by which *C. albicans* can invade keratinocyte have been proposed:

- The secretion of degradative enzymes by the fungus, particularly aspartic proteases that can digest epithelial cell

surface components and, thereby, allow the physical movement of hyphae into, or between, host cells.

- The second proposed mechanism is the induction of epithelial cell endocytosis. *C. albicans* stimulates keratinocyte to produce pseudopod-like structures that surround the fungus and draw it into the cell in the process. [28]

Adhesion, invasion, and damage by C. albicans depends not only on fungal morphology and activity, but also on the keratinocyte type and stage of differentiation, indicating that epithelial cells differ in their susceptibility to the fungus. [29]

Invasion of epithelia: Penetration into the epithelial surfaces is the limit of the infectious process in most cases, leading to the establishment of a superficial candidiasis. Normally the fungi are incapable of further invasion into the immunologically intact host. When fungi reach the bloodstream, they must face the blood-borne cellular defense system. Finally to cause invasive infections *Candida* cells should be able to penetrate the endothelial surfaces and invade the tissues. Various factors of host and fungal cells have a major role at each step of the infectious pathway, although no component has yet been found to be absolutely essential. From clinical data, it appears that both antibody- and the cell-mediated immune response contribute to host protection against candidiasis. [29] In severely immunocompromised patients, infections can be systemic and are significant because of their associated high mortality. [28]

Influence of procarcinogens on *C. albicans*: Tobacco products were known to cause epithelial changes through nitrosation potential. [1] An alternative hypothesis was that cigarette smoke contains nutritional factors that *C. albicans* uses readily. [2] Tobacco smoke exposure has been shown to promote microbial biofilm formation. [30] Aromatic hydrocarbons in cigarette smoke may be converted by inducible enzyme systems in *Candida* species to carcinogen end products. This, together with the observation that *C. albicans* can catalyse the formation of N-nitrosobenzyl-methylamine, may partly explain why *Candida*-associated leukoplakia has a higher potential for malignant change than other leukoplakias. [31]

In addition certain enzymes metabolize the hydrocarbons of tobacco and transform them into carcinogens that are more powerful such as aryl hydrocarbon hydroxylase, which was effective in increasing the carcinogenic potential of benzopyrene. The heat released by tobacco combustion worsens the aggressive action on the oral mucosa.[32] *Candida* colonization in the mouth may be enhanced by the depressed activity of oral leukocytes and reduced gingival exudate. A study by Ritz *et al* has shown that tobacco smoke increases adrenaline levels in blood and blood glucose levels. Accumulation of these glycosylation products on buccal epithelial cells may increase the number of available receptors for *Candida.* [33]

Another major virulent attribute of *Candida* is its ability to invade superficial layers of the epithelium, aided in particular by their hyphal appendages. This activity is more at acidic pH of saliva which was seen in diseased states. *Candida* overgrowth reported in tobacco smoking individuals could be due to induction of increased epithelial keratinization, reduction in salivary IgA levels and possible depression of polymorphonuclear leukocyte function. [1] It has been suggested that cigarette smoking might lead to localized epithelial alteration in the form of increased keratinization that allows *Candida* colonization. *Candida* adherence to the oral mucosa is interplay of several complex factors related to the yeast cells, host cells and various environmental factors (e.g. saliva, sugars & pH). Smoking increases the keratinization of the oral mucosa which

further enhances the adherence of *C. albicans* to the oral cavity thereby influencing the pathogenicity of the organism in development of cancer and pre-cancer. [34]

***Candida* and carcinogenesis:** *Candida* in general is more prevalent on carcinoma lesions than on healthy mucosa. Yeasts invade oral epithelium and may be causally involved in dysplastic changes. [35] Leukoplakia with candidal infection has been shown to have a higher rate of malignant transformation than in those not infected with *Candida.* [36]

Malignant transformation however, is often also associated with other risk factors such as smoking and alcohol. Hence a synergistic effect with candidiasis and life-style factors may exist in oral carcinogenesis. *Candida* also efficiently converts ethanol into carcinogenic acetaldehyde. Further contributing factors include the integrity of the oral mucosa and tobacco smoking habits which might enhance the virulence of the organism. [1] *C. albicans* has also been demonstrated to degrade E-cadherin, a transmembrane glycoprotein important in adhesion of adjacent keratinocytes. These findings have implications not only on the potential for tissue invasion by the organism, but on the potential to enhance the invasion of genetically altered epithelial cells, first by reducing keratinocyte cohesion and then by assisting their passage through the basement membrane. [37] Though the direct role of *C. albicans* in development and progression of oral squamous cell carcinoma is debatable, various authors suggest that *C. albicans* in conjunction with host and etiological agents enhance the progression of carcinogenesis.

Another hypothesis is that *Candida* might induce oral squamous cell carcinoma by directly producing carcinogenic compounds like nitrosamines. These nitrosamines produced by *Candida* may activate specific proto-oncogenes. Such a carcinogen binds with DNA to form adducts with bases, phosphate residues, and/or hydrogen bonding sites that could cause miscoding or irregularities with DNA replication. Point mutations thus induced may activate specific oncogenes and initiate the development of oral cancer. [13] It was also suggested that the tubular hyphal structure of *C. albicans* might be important, as this structure allows ingress of precursors from saliva and release of the nitrosamine product to keratinocyte, potentially initiating OSCC. [37]

Ramirez-Garcia *et al* in his review has summarized evidence of this opportunistic fungus in increasing the risk of carcinogenesis and metastasis. Chronic inflammation enhancing microbial infections is an established fact. *C. albicans* might promote cancer and metastasis through a pro-inflammatory response, mediated by an increase in cytokine production and adhesion-molecule expression. Stimulation by *C. albicans* causes increase in tumor cell adhesion and metastasis by an inflammatory response of endothelial cells. The yeast adheres to endothelial cells and activates the production of cytokines and adhesion molecules. In healthy individuals, these molecules attract and recruit leukocytes to destroy the microorganisms. In immunosuppressed cancer patients, however, the tumor cells may adhere instead of leukocytes to endothelial cells and give rise to a secondary tumor. Further, molecular mimicry of the complement receptor 3-related protein (CR3-RP) of *C. albicans*, could also favour cancer progression. [38]

Thus the presence of *C. albicans* in carcinoma patients should be considered with caution and controlled during cancer treatment to prevent taking advantage of immunocompromised state of the patient.

Ability to modify the microenvironment and induce chronic inflammation:

The role of epithelial connective tissue interactions and the activity of chronic inflammatory cells, mediators in the tumor

microenvironment have been gaining attention recently. Multiple interactions between tumor cells and stromal cells are responsible for tumor growth and invasion. The different stromal events that contribute to carcinogenesis induction include activation of specific proteolytic enzymes, ability to degrade components of the basement membrane and/or fibrous stroma.

Candida albicans has been shown to secrete specific proteinases, capable of degrading basement membrane and extracellular matrix. Degradation of laminin-332, a laminin present in the basement membrane associated with oral epithelium, by *C. albicans* has been described. [39] Further degradation of E-cadherin, a protein associated with epithelial cell junctions have implications not only on the potential for tissue invasion by the organism, but also on the potential to enhance the invasion of genetically altered epithelial cells, first by reducing keratinocyte cohesion and then by assisting their passage through the basement membrane. [5]

Mucosal infection can induce chronic inflammation in the adjacent connective tissue leading to up regulation of cytokines and growth factors, which in turn may influence carcinogenesis. Toll-like receptors may be activated that communicates with the tumor promoter NF-kB involved in carcinogenesis. Thus cancer-related inflammation is also involved in the metastasis of malignant cells. [40] The mere presence of *C. albicans* may not be an etiological factor but nevertheless can be a promoter of carcinogenesis.

CONCLUSION

The interaction between *C. albicans* and its host is dynamic and complex as this pathogen exhibits multifaceted strategies for growth, proliferation, and survival within the host accompanied by mechanisms to evade host defense. As stressed by researchers in literature identification of *C. albicans* should be monitored closely. A better understanding of *C. albicans* host interactions provides important insights into other fungal pathogens. It expands the scope of developing diagnostic strategies to prevent dissemination through epithelial barriers, reaching the bloodstream and prevent life-threatening systemic infections.

REFERENCES

1. Sanjaya PR, Gokul S, Gururaj Patil B, Raju R. Candida in oral pre- cancer and oral cancer. Med Hypotheses. 2011; 77(6):1125-8.
2. Van Wyk C, Steenkamp C. Host factors affecting oral Candidiasis. South Afr J Epidemiol Infect 2011; 26(1):18-21.
3. Williams DW, Walker R, Lewis MA, Allison RT, Potts AJ. Adherence of Candida albicans to oral epithelial cells differentiated by Papanicolaou staining. J Clin Pathol. 1999; 52(7):529-31.
4. Naglik JR, Moyes DL, Wachtler B, Hube B. Candida albicans interactions with epithelial cells and mucosal immunity. Microbes Infect 2011; 13: 963–76.
5. Mayer FL, Wilson D, Hube B. Candida albicans pathogenicity mechanisms. Virulence. 2013; 4(2): 119-28.
6. Cannon RD, Holmes AR, Mason AB, Monk BC. Oral Candida: clearance, colonization, or candidiasis? J Dent Res 1995; 74: 1152-1161.
7. Samaranayake LP. Host factors and oral candidosis. *In:* Samaranayake LP, MacFarlane TW, (eds) Oral Candidosis. London: Wright, 1990; 66-103.
8. Soll DR. High-frequency switching in *Candida albicans*. Clin Microbiol Rev 1992; 5: 183-203.
9. Darwazeh A, Lamey PJ, Samaranayake LP, MacFarlane TW. The relationship between colonisation, secretor status and in vitro adhesion of *Candida* to buccal epithelial cells from diabetics. *J Med Microbiol* 1990; 33: 43-49.

10. Samaranayake LP. Nutritional factors and oral candidosis. *J Oral Pathol* 1986; 15: 61-65.
11. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr.,Calandra TF, Edwards JE Jr., et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009; 48(5): 503-35.
12. Cannon RD, Chaffin WL. Colonization is a crucial factor in oral candidiasis. J Dent Educ. 2001; 65(8):785-7.
13. Molero G, Díez-Orejas R, Navarro-García F, Monteoliva L, Pla J, Gil C, et al. Candida albicans: genetics, dimorphism and pathogenicity. Int Microbiol. 1998;1(2):95-106.
14. Zhu W, Filler SG. Interactions of Candida albicans with epithelial cells. Cell Microbiol 2010; 12: 273–82.
15. Williams DW, Jordan RPC, Wei X-Q, et al. Interactions of *Candida albicans* with host epithelial surfaces. J Oral Microbiol. 2013;5:10.3402
16. Darwazeh AMG, Darwazeh TA. What Makes Oral Candidiasis Recurrent Infection? A Clinical View. Hindawi Publishing Corporation. J Mycology. 2014, Article ID 758394 5 pages.
17. Abah AA, Agbelusi GA, Odukoya OA, Ayanbadejo PO, Adefule-Ositelu AO, Adebiyi K.E. Garcinia Kola Extracts As Antifungal Therapy for Oral Candida Infections'- A Comparative Study. IOSR-JDMS 2014; 13(2):20-24.
18. Lynch DP. Oral candidiasis: History, classification, and clinical presentation. Oral Surg Oral Med Oral Pathol. 1994;78(2):189-93.
19. Mishra NN, Prasad T, Sharma N, Payasi A, Prasad R, Gupta DK, Singh R. Pathogenicity and drugresistance in Candidaalbicans and other yeast species. A review. Acta Microbiol Immunol Hung. 2007; 54(3):201-35.
20. Berman J, Sudbery PE. *Candida Albicans*: a molecular revolution built on lessons from budding yeast. Nat Rev Genet. 2002; 3(12):918-30.
21. Verstrepen KJ, Klis FM. Flocculation, adhesion and biofilm formation in yeasts. Mol Microbiol 2006; 60:5-15.
22. Finkel JS, Mitchell AP. Genetic control of *Candida albicans* biofilm development. Nat Rev Microbiol 2011; 9:109-18.
23. Kumamoto CA. Molecular mechanisms of mechanosensing and their roles in fungal contact sensing. Nat Rev Microbiol 2008; 6:667-73.
24. Wächtler B, Citiulo F, Jablonowski N, Förster S, Dalle F, Schaller M, et al. *C.albicans*-epithelial interactions: dissecting the roles of active penetration, induced endocytosis and hostfactors on the infection process. PLoS One. 2012;7(5):e36952.
25. Fleck CB, Schöbel F, Brock M. Nutrient acquisition by pathogenic fungi: nutrient availability, pathway regulation, and differences in substrate utilization. Int J Med Microbiol 2011; 301:400-7.
26. Conti HR, Gaffen SL. Host responses to Candida albicans. Th17 cells and mucosal candidiasis. Microbes Infect 2010; 12:518–27.
27. Feller L, Khammissa RA, Chandran R, Altini M, Lemmer J. Oral candidosis in relation to oral immunity. J Oral Pathol Med. 2014 Sep; 43(8):563-9.
28. Mohd Bakri M, Mohd Hussaini H, Rachel Holmes A, David Cannon R, Mary Rich A. Revisiting the association between candidal infection and carcinoma, particularly oral squamous cell carcinoma. J Oral Microbiol. 2010; 21(2):1-6.
29. Williams D, Lewis M. Pathogenesis and treatment of oral candidosis. J Oral Microbiol. 2011; 3:10.3402.
30. Semlali A, Killer K, Alanazi H, Chmielewski W, Rouabhia M. Cigarette smoke condensate increases *C. albicans* adhesion, growth, biofilm formation, and EAP1, HWP1 and SAP2 gene expression. BMC Microbiol. 2014; 14(61):1-9.
31. Soysa NS, Ellepola ANB. The impact of cigarette/tobacco smoking on oral candidosis: an overview. Oral Diseases 2005;11,:268–273.

32. DeMarini DM. Genotoxicity of tobacco smoke and tobacco smoke condensate: a review. Mutat Res. 2004; 567(2-3):447-74.
33. Ritz E, Benck U, Franek E et al. Effects of smoking on renal hemodynamics in healthy volunteers and in patients with glomerular disease. J Am Soc Nephrol 1998: 1798–1804.
34. Sitheeque MAM, Samranayake LP. Chronic hyperplastic candidosis/ candidiasis (Candidal Leukoplakia). Crit Rev Oral Biol Med 2003; 14:253–67.
35. Scully C. Oral cancer aetiopathogenesis; past, present and future aspects .Med Oral Patol Oral Cir Bucal. 2011; 16 (3):e306-11.
36. Hebbar PB, Pai A, Sujatha D. Mycological and histological associations of *Candida* in oral mucosal lesions. J Oral Sci, 2013:55(2): 157-160.
37. Cutler JE. Putative virulence factors of *Candida albicans*. Annu Rev Microbiol 1991,45:187–218.
38. Ramirez-Garcia A, Rementeria A, Aguirre-Urizar JM, Moragues, Antoran AM, Pellon A, Diaz-de-Cerio AA, Hernando FL. *Candida albicans* and cancer: Can this yeast induce cancer development or progression? Crit Rev Microbiol 2014; 1–13.
39. Pa¨rna¨nen P, Kari K, Virtanen I, Sorsa T, Meurman JH. Human laminin-332 degradation by Candida proteinases. J Oral Pathol Med 2008; 37: 329-35.
40. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008; 454: 436-44.

How to cite this article: Supriya H, Rai H, Suhasini PD et al. Pathogenic mechanisms of *candida albicans* in oral mucosa -A review. Int J Health Sci Res. 2016; 6(1):489-497.

****