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The Etiological Role of Human Papillomavirus in Oral Cancer

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ABSTRACT

The etiological role of Human Papilloma Virus is firmly established in the cases of anogenital cancers. However, it is also proved to be a vital cocarcinogen along with tobacco in oral carcinogenesis. Henceforth , the review of literature aims to evaluate awareness among people about Human Papillomavirus , it's virulence and its potential role in oral carcinogenesis. Further, the review shall focus to differentiate the role of Human Papilloma Virus in both mucosal and cutaneous carcinogenesis. Search engines like Pubmed database were used for compilation of significant concepts related to HPV and its role in oral cancer. The review fulfills the need to

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establish connection between molecular transformation of HPV which triggers malignancies. The study also aims to display suggestive treatment protocol, screening techniques for earlier diagnosis and cure.

KEYWORDS: Oral Cancer, HPV, Etiology, Carcinogenesis , Virulence, Pathogenesis of HPV

INTRODUCTION

The Human Papilloma Virus (HPV) is considered to be one among the virulent strains which are responsible for kinds of malignancies like those of anogenital origin.(Chaudhary *et al.*, 2009) The primary types of Human Papilloma Virus include mucosal tropic and cutaneous variety. The cutaneous strain is responsible for skin lesions whereas the mucosal strain is mostly found to be associated with oral cancer(Kansy, Thiele and Freier, 2014) . One among the previous study done by Herrero et al revealed HPV prevalence among Indian population with a notable average of 75%.(Herrero *et al.*, 2003; Rajeshkumar, 2018)Among numerous etiological factors of cervical malignancies, infection caused due to certain strains of HPV is considered to be the critical cervical cancer risk factor.

Over 150 subtypes of HPV have been identified and proven ; more than 40 types of HPVs are generally transmitted either through sexual contact or skin to skin and thereby infect the oral cavity and the anogenital region.(Herrero *et al.*, 2003)(Lassen, 2010). The virus is known to cause multiple diseases which include genital warts and throat warts typically known as respiratory recurrent papillomatous(Silverberg and Silverberg, 2014; Anitha and Ashwini, 2017). Further , infections caused due to HPV are predominantly asymptomatic in both males and females. Hence, women are recommended to undergo PAP smear diagnostic screening at the age of twenty one upwards, for earlier detection of HPV infections. On the other hand there are no FDV - approved screening tests available for men.(World Health Organization, 2009)Risk factors for the onset of HIV related infections include damaged skin.The recent vaccine against the HPV infection is effective against certain subtypes of HPV that are associated with genital warts, cervical cancers and some less common cancers, including the oropharyngeal cancer.(Liang *et al.*, 2008)(Pannone*et al.*, 2011) Two HPV vaccines, bivalent and quadrivalent types that use virus-like particles (VLPs), are used at present in the medical commercial market.(Pringle, 2014)(Ashwini, Ezhilarasan and Anitha, 2017; Raj *et al.*, 2019)

Oral mucosa in every individual is constantly subjected to exposure among various stimuli which may range from mild microbial infection to severe trauma.(Combes and Franceschi, 2014; Rajeshkumar, Agarwal, *et al.*, 2018)Similar previous studies(Gillison and Shah, 2001; Lakshmi *et al.*, 2015)believe that oral cavity is highly susceptible to chronic diseases which may progress towards fatality if not treated during early onset of the same.

While the value of HPV vaccination for oral cancer prevention is yet under controversy, evidence supports the possibility that HPV vaccination may be effective in reduction of oral cancer incidence.(Syrjänen, 2010)Hence,the study considers this fact to be vital for determination of incidence of Oral cancer in near future.

Our team has rich experience in research and we have collaborated with numerous authors over various topics in the past decade (Arigа*et al.*, 2018; Basha, Ganapathy and Venugopalan, 2018; Hannah *et al.*, 2018; Hussainy*et al.*, 2018; Jeevanandan and Govindaraju, 2018; Kannan and Venugopalan, 2018; Kumar and Antony, 2018; Manohar and Sharma, 2018; Menon *et al.*, 2018; Nandakumar and Nasim, 2018; Nandhini, Babu and Mohanraj, 2018; Ravinthar and Jayalakshmi, 2018; Seppan*et al.*, 2018; Teja, Ramesh and Priya, 2018; Duraisamy*et al.*, 2019; Gheena and Ezhilarasan, 2019a; Hema Shree *et al.*, 2019; Rajakeerthi and Ms, 2019; Rajendran *et al.*, 2019; Sekar*et al.*, 2019; Sharma *et al.*, 2019; Siddique

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et al., 2019; Janani, Palanivelu and Sandhya, 2020; Johnson *et al.*, 2020; Jose, Ajitha and Subbaiyan, 2020).

GENOMIC STRUCTURE OF HUMAN PAPILLOMA VIRUS

The Human Papilloma Virus is structurally small and non enveloped. It consists of non enveloped double stranded circular DNA.(Tran, Rose and O'Brien, 2007)While its precisional diameter is known to be about 52- 55 nm (Zandberg*et al.*, 2013) It consists of a genome with eight thousand base pairs.The life cycle of the virus strictly follows the differentiation pattern of the host keratinocyte.(Liu *et al.*, 2005; Rajeshkumar, Venkat Kumar, *et al.*, 2018). The phylogeny of the various strains of the Human Papillomavirus(HPV) generally reflects the migration patterns of humans and is evidential that HPV might have diversified along with the human population.(Mazul, 2018)Studies report that HPV evolved along five various branches that reflect the ethnicity of human hosts, and have diversified along with the developing human race. Researchers have identified two major variants of HPV16, European (HPV16-E), and Non-European (HPV16-NE).(Lefeuvre*et al.*, 2020). The two primary oncoproteins of high risk HPV types are E6 and E7. The "E" denotes that these two proteins are expressed early in the HPV life cycle, while the "L" denotes that late expression.(Bodelon*et al.*, 2015; Sharma *et al.*, 2019)The E6/E7 proteins participate and thereby inactivate the two tumor suppressor proteins, p53 (inactivated by E6) and (inactivated by E7). The viral oncogenes namely,E6 and E7 are detected to modify the cell cycle so as to retain the differentiating host keratinocyte in a state which is favourable for the amplification of viral genome replication and the subsequent late gene expression.(Monsonégo, 2006)

HPV AND ITS ROLE IN ORAL SQUAMOUS CELL CARCINOMA - ORAL POTENTIALLY MALIGNANT DISORDERS

Our institution is passionate about high quality evidence based research and has excelled in various fields ((Pc, Marimuthu and Devadoss, 2018; Ramesh *et al.*, 2018; VijayashreePriyadharsini, SmilineGirija and Paramasivam, 2018; Ezhilarasan, Apoorva and Ashok Vardhan, 2019; Ramadurai*et al.*, 2019; Sridharan *et al.*, 2019; VijayashreePriyadharsini, 2019; Chandrasekar *et al.*, 2020; Mathew *et al.*, 2020; R *et al.*, 2020; Samuel, 2021)

The subsequent low risk HPV mainly HPV - 6 and HPV - 11 appears to be closely associated with a range of oral benign papillomatous lesions including oral squamous papilloma, oral verruca vulgaris, oral condyloma accuminatum and epithelial hyperplasia(Agrawal, Joshi and Agrawal, 2013) Moreover, on the other hand, the High risk HPV strains which are HPV-16, HPV-18 are in turn associated with Oral Potential Malignant Disorders (OPMDS) and Oral Squamous Cell Carcinoma (OSCC)(Andrews, Seaman and Webster-Cyriaque, 2009), (Angiero*et al.*, 2010). The strains of HPV - 16 and HPV- 18 have been found to be associated with OPMDS and OSCC ranging from 0% to 100% (Attner*et al.*, 2010; Lakshmi *et al.*, 2017). This extreme variation is the contributing factor to the difference in ethnicity, geographic locations to variations in methods used for detection of HPV. (Chaturvedi and Chocolatewala, 2009; Perumalsamy*et al.*, 2018)Hence, a thorough search was done for detection of prevalence of the Human Papilloma Virus in oral lesions including Oral Lichen Planus, Lichen Planus , OSCC, Oral Papilloma , Verrucous Carcinoma (VC) and PVL. A wide range of human papillomavirus (HPV) genotypes have been detected in oral mucosa(D'Souza and Dempsey, 2011)Clinical infections with high risk genotypes have been associated along with numerous malignant lesions(Lassen, 2010; Karthiga, Rajeshkumar and Annadurai, 2018)According to recent studies,

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the most common genotype isolated from subclinical infection is HPV - 16(Liang *et al.*, 2008; Mehta *et al.*, 2019)

DETECTION AND PATHOLOGICAL VIRULENCE OF HUMAN PAPILLOMA VIRUS

Studies reveal that D - HPV DNA has been detected approximately in 2.5% in numerous cases of Human Squamous Cell Carcinomas.(Feller *et al.*, 2010; Menon *et al.*, 2018) In specific , about 45 -100 % of the Oral Squamous Cell Carcinoma Cases were reported to be HPV positive(Attner*et al.*, 2010; Ezhilarasan*et al.*, 2017). It is predicted or assumed that the latter variation may depend on the location of the specific Oral Squamous Cell Carcinoma , the different types of specimens available , the various techniques used for testing , time period and the country from which the sample material was obtained(Chaturvedi and Chocolatewala, 2009). The primary analysis of HPV DNA is mentioned to be done using formalin fixed , paraffin embedded tissue which includes partial degradation of DNA(D'Souza and Dempsey, 2011). Studies also emphasise that this method is the most widely accepted for easier detection of longer HPV DNA fragments in fresh or fresh - frozen material , although newer techniques are much more sensitive(Feller *et al.*, 2010). However, many studies during the early 1980's also reflected on the use of Southern blot techniques or in situ hybridisation for detection of HPV(Anitha and Ashwini, 2017; Ezhilarasan, 2018). Since the 1990's , Virology laboratories have used PCR techniques for detection of HPV DNA(Angiero*et al.*, 2010)(Anitha and Ashwini, 2017). Screening for the Human Papilloma Virus was initially performed by using general PCR primers for HPV , which enabled detection of several HPV types. Polymerization Cell Reaction (PCR) of a control cellular gene was used to assess the DNA quality of samples.(Zandberg*et al.*, 2013)(Andrews, Seaman and Webster-Cyriaque, 2009)These techniques are robust, yet are still used. They do require additional methods for HPV typing. Recent advances offer various other methods available to directly determine the presence of several types of Human Papilloma Virus.(Kansy, Thiele and Freier, 2014; Ezhilarasan, Sokal and Najimi, 2018)

The food and drug administration has approved hybrid capture II (Digene Corporation , Guthersburg,MD,USA) reports to detect 5 low risk and 13 high risk HPV types and uses the fact that HPV DNA hybridises with synthetic RNA probes complementary DNA sequences from specific HPV types.(Kaul and Wadhwa, 2017)(Ashwini, Ezhilarasan and Anitha, 2017)It is also found that an assay used in several studies, the Roche (Basel, Switzerland) - Linear assay HPV genotyping tests detects 37 HPV types and is based on a method developed by Gravitt et al. Schmitt et al, produced a sensitive bead based multiplex method for 22 different HPV types which later included HPV PCR products which are coupled to type specific probes on beads and analysed by using Luminex.(Lakshmi *et al.*, 2015)(Sharma *et al.*, 2019)

CONCLUSION

Consolidated concepts based on the role of Human Papilloma Virus in Oral Carcinogenesis reveal that, risk factors mainly responsible for oral squamous cell carcinoma includes Tobacco, Alcohol, Ultraviolet rays but it is also noted that many cases are asymptomatic to the latter mentioned factors.(Gheena and Ezhilarasan, 2019b)(Sujatha, Asokan and Rajeshkumar, 2018) On the basis of high frequency of HPV in some types of OSCC and OPMDs, an oral malignant potential of HPV infection in oropharyngeal carcinoma is very likely to occur.(Menon *et al.*, 2018)Further, the association of high frequency of HPV in oral cancers is of particular significance , owing to the involvement of base of tongue in younger patients without the prior history of exposure to the usual risk factors.(Rajeshkumar, Venkat Kumar, *et al.*, 2018; Gheena

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and Ezhilarasan, 2019b), (Karthiga, Rajeshkumar and Annadurai, 2018) But further search is required in order to standardise a particular protocol for screening of patients with OSCC and OMPDs for HPV as well as to determine a specific and universal method for analysis.

REFERENCES

1. Agrawal, G. P., Joshi, P. S. and Agrawal, A. (2013) 'Role of HPV-16 in Pathogenesis of Oral Epithelial Dysplasia and Oral Squamous Cell Carcinoma and Correlation of p16INK4A Expression in HPV-16 Positive Cases: An Immunohistochemical Study', *ISRN Pathology*, pp. 1–7. doi: 10.1155/2013/807095.
2. Andrews, E., Seaman, W. T. and Webster-Cyriaque, J. (2009) 'Oropharyngeal carcinoma in non-smokers and non-drinkers: A role for HPV', *Oral oncology*, 45(6), pp. 486–491. doi: 10.1016/j.oraloncology.2008.07.008.
3. Angiero, F. *et al.* (2010) 'Frequency and Role of HPV in the Progression of Epithelial Dysplasia to Oral Cancer', *Anticancer research*, 30(9), pp. 3435–3440. Available at: http://ar.iiarjournals.org/content/30/9/3435.abstract.
4. Anitha, R. and Ashwini, S. (2017) 'Antihyperglycemic activity of Caralluma fimbriata: An In vitro approach', *Pharmacognosy Magazine*, p. 499. doi: 10.4103/pm.pm_59_17.
5. Ariga, P. *et al.* (2018) 'Determination of correlation of width of Maxillary Anterior Teeth using Extraoral and Intraoral Factors in Indian Population: A systematic review', *World journal of dentistry*, 9(1), pp. 68–75. doi: 10.5005/jp-journals-10015-1509.
6. Ashwini, S., Ezhilarasan, D. and Anitha, R. (2017) 'Cytotoxic effect of Caralluma fimbriata against human colon cancer cells', *Pharmacognosy Journal*, 9(2). Available at: https://www.phcogj.com/article/252.
7. Attner, P. *et al.* (2010) 'The role of human papillomavirus in the increased incidence of base of tongue cancer', *International journal of cancer. Journal international du cancer*, 126(12), pp. 2879–2884. doi: 10.1002/ijc.24994.
8. Basha, F. Y. S., Ganapathy, D. and Venugopalan, S. (2018) 'Oral hygiene status among pregnant women', *Journal of advanced pharmaceutical technology & research*, 11(7), p. 3099. doi: 10.5958/0974-360x.2018.00569.3.
9. Bodelon, C. *et al.* (2015) 'Abstract 5580: Characterization of HPV integration sites in the human genome', *Epidemiology*. doi: 10.1158/1538-7445.am2015-5580.
10. Chandrasekar, R. *et al.* (2020) 'Development and validation of a formula for objective assessment of cervical vertebral bone age', *Progress in orthodontics*, 21(1), p. 38. doi: 10.1186/s40510-020-00338-0.
11. Chaturvedi, P. and Chocolatewala, N. (2009) 'Role of human papilloma virus in the oral carcinogenesis: An Indian perspective', *Journal of Cancer Research and Therapeutics*, p. 71. doi: 10.4103/0973-1482.52788.
12. Chaudhary, A. K. *et al.* (2009) 'Role of human papillomavirus and its detection in potentially malignant and malignant head and neck lesions: updated review', *Head & neck oncology*, 1(1), p. 22. doi: 10.1186/1758-3284-1-22.
13. Combes, J.-D. and Franceschi, S. (2014) 'Role of human papillomavirus in non-oropharyngeal head and neck cancers', *Oral oncology*, 50(5), pp. 370–379. doi: 10.1016/j.oraloncology.2013.11.004.
14. D'Souza, G. and Dempsey, A. (2011) 'The role of HPV in head and neck cancer and review of the HPV vaccine', *Preventive medicine*, 53 Suppl 1, pp. S5–S11. doi: 10.1016/j.ypmed.2011.08.001.

15. Duraisamy, R. *et al.* (2019) 'Compatibility of Nonoriginal Abutments With Implants: Evaluation of Microgap at the Implant-Abutment Interface, With Original and Nonoriginal Abutments', *Implant dentistry*, 28(3), pp. 289–295. doi: 10.1097/ID.0000000000000885.
16. Ezhilarasan, D. *et al.* (2017) 'Acacia catechu ethanolic seed extract triggers apoptosis of SCC-25 cells', *Pharmacognosy Magazine*, p. 405. doi: 10.4103/pm.pm_458_16.
17. Ezhilarasan, D. (2018) 'Oxidative stress is bane in chronic liver diseases: Clinical and experimental perspective', *Arab Journal of Gastroenterology*, pp. 56–64. doi: 10.1016/j.ajg.2018.03.002.
18. Ezhilarasan, D., Apoorva, V. S. and Ashok Vardhan, N. (2019) 'Syzygiumcumini extract induced reactive oxygen species-mediated apoptosis in human oral squamous carcinoma cells', *Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology*, 48(2), pp. 115–121. doi: 10.1111/jop.12806.
19. Ezhilarasan, D., Sokal, E. and Najimi, M. (2018) 'Hepatic fibrosis: It is time to go with hepatic stellate cell-specific therapeutic targets', *Hepatobiliary & pancreatic diseases international: HBPD INT*, 17(3), pp. 192–197. doi: 10.1016/j.hbpd.2018.04.003.
20. Feller, L. *et al.* (2010) 'Human papillomavirus-mediated carcinogenesis and HPV-associated oral and oropharyngeal squamous cell carcinoma. Part 2: Human papillomavirus associated oral and oropharyngeal squamous cell carcinoma', *Head & Face Medicine*. doi: 10.1186/1746-160x-6-15.
21. Gheena, S. and Ezhilarasan, D. (2019a) 'Syringic acid triggers reactive oxygen species-mediated cytotoxicity in HepG2 cells', *Human & experimental toxicology*, 38(6), pp. 694–702. doi: 10.1177/0960327119839173.
22. Gheena, S. and Ezhilarasan, D. (2019b) 'Syringic acid triggers reactive oxygen species–mediated cytotoxicity in HepG2 cells', *Human & Experimental Toxicology*, pp. 694–702. doi: 10.1177/0960327119839173.
23. Gillison, M. L. and Shah, K. V. (2001) 'Human papillomavirus–associated head and neck squamous cell carcinoma: mounting evidence for an etiologic role for human papillomavirus in a subset of head and neck cancers', *Current Opinion in Oncology*, pp. 183–188. doi: 10.1097/00001622-200105000-00009.
24. Hannah, R. *et al.* (2018) 'Awareness about the use, ethics and scope of dental photography among undergraduate dental students dentist behind the lens', *Journal of advanced pharmaceutical technology & research*, 11(3), p. 1012. doi: 10.5958/0974-360x.2018.00189.0.
25. Hema Shree, K. *et al.* (2019) 'Saliva as a Diagnostic Tool in Oral Squamous Cell Carcinoma - a Systematic Review with Meta Analysis', *Pathology oncology research: POR*, 25(2), pp. 447–453. doi: 10.1007/s12253-019-00588-2.
26. Herrero, R. *et al.* (2003) 'Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study', *Journal of the National Cancer Institute*, 95(23), pp. 1772–1783. doi: 10.1093/jnci/djg107.
27. Hussainy, S. N. *et al.* (2018) 'Clinical performance of resin-modified glass ionomer cement, flowable composite, and polyacid-modified resin composite in noncarious cervical lesions: One-year follow-up', *Journal of conservative dentistry: JCD*, 21(5), pp. 510–515. doi: 10.4103/JCD.JCD_51_18.
28. Janani, K., Palanivelu, A. and Sandhya, R. (2020) 'Diagnostic accuracy of dental pulse

oximeter with customized sensor holder, thermal test and electric pulp test for the evaluation of pulp vitality: an in vivo study', *Brazilian dental science*, 23(1). doi: 10.14295/bds.2020.v23i1.1805.

29. Jeevanandan, G. and Govindaraju, L. (2018) 'Clinical comparison of Kedo-S paediatric rotary files vs manual instrumentation for root canal preparation in primary molars: a double blinded randomised clinical trial', *European archives of paediatric dentistry: official journal of the European Academy of Paediatric Dentistry*, 19(4), pp. 273–278. doi: 10.1007/s40368-018-0356-6.
30. Johnson, J. *et al.* (2020) 'Computational identification of MiRNA-7110 from pulmonary arterial hypertension (PAH) ESTs: a new microRNA that links diabetes and PAH', *Hypertension research: official journal of the Japanese Society of Hypertension*, 43(4), pp. 360–362. doi: 10.1038/s41440-019-0369-5.
31. Jose, J., Ajitha and Subbaiyan, H. (2020) 'Different treatment modalities followed by dental practitioners for Ellis class 2 fracture – A questionnaire-based survey', *The open dentistry journal*, 14(1), pp. 59–65. doi: 10.2174/1874210602014010059.
32. Kannan, A. and Venugopalan, S. (2018) 'A systematic review on the effect of use of impregnated retraction cords on gingiva', *Journal of advanced pharmaceutical technology & research*, 11(5), p. 2121. doi: 10.5958/0974-360x.2018.00393.1.
33. Kansy, K., Thiele, O. and Freier, K. (2014) 'The role of human papillomavirus in oral squamous cell carcinoma: myth and reality', *Oral and maxillofacial surgery*, 18(2), pp. 165–172. doi: 10.1007/s10006-012-0383-0.
34. Karthiga, P., Rajeshkumar, S. and Annadurai, G. (2018) 'Mechanism of Larvicidal Activity of Antimicrobial Silver Nanoparticles Synthesized Using Garcinia mangostana Bark Extract', *Journal of Cluster Science*, pp. 1233–1241. doi: 10.1007/s10876-018-1441-z.
35. Kaul, S. C. and Wadhwa, R. (2017) *Science of Ashwagandha: Preventive and Therapeutic Potentials*. Springer. Available at: https://play.google.com/store/books/details?id=c7I1DwAAQBAJ.
36. Kumar, D. and Antony, S. D. P. (2018) 'Calcified canal and negotiation-A review', *Journal of advanced pharmaceutical technology & research*, 11(8), p. 3727. doi: 10.5958/0974-360x.2018.00683.2.
37. Lakshmi, T. *et al.* (2015) 'Azadirachta indica : A herbal panacea in dentistry - An update', *Pharmacognosy Reviews*, p. 41. doi: 10.4103/0973-7847.156337.
38. Lakshmi, T. *et al.* (2017) 'Acacia catechu ethanolic bark extract induces apoptosis in human oral squamous carcinoma cells', *Journal of advanced pharmaceutical technology & research*, 8(4), pp. 143–149. doi: 10.4103/japtr.JAPTR_73_17.
39. Lassen, P. (2010) 'The role of Human papillomavirus in head and neck cancer and the impact on radiotherapy outcome', *Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology*, 95(3), pp. 371–380. doi: 10.1016/j.radonc.2010.04.022.
40. Lefeuvre, C. *et al.* (2020) 'Urinary HPV DNA testing as a tool for cervical cancer screening in women who are reluctant to have a Pap smear in France', *The Journal of infection*. doi: 10.1016/j.jinf.2020.05.006.
41. Liang, X.-H. *et al.* (2008) 'Prevalence and Significance of Human Papillomavirus in Oral Tongue Cancer: The Mayo Clinic Experience', *Journal of Oral and Maxillofacial Surgery*, pp. 1875–1880. doi: 10.1016/j.joms.2008.04.009.

42. Liu, X. *et al.* (2005) 'Crystal Structure of HPV E7 CR3 domain'. doi: 10.2210/pdb2b9d/pdb.
43. Manohar, M. P. and Sharma, S. (2018) 'A survey of the knowledge, attitude, and awareness about the principal choice of intracanal medicaments among the general dental practitioners and nonendodontic specialists', *Indian journal of dental research: official publication of Indian Society for Dental Research*, 29(6), pp. 716–720. doi: 10.4103/ijdr.IJDR_716_16.
44. Mathew, M. G. *et al.* (2020) 'Evaluation of adhesion of Streptococcus mutans, plaque accumulation on zirconia and stainless steel crowns, and surrounding gingival inflammation in primary molars: Randomized controlled trial', *Clinical oral investigations*, pp. 1–6. Available at: https://link.springer.com/article/10.1007/s00784-020-03204-9.
45. Mazul, A. (2018) 'HPV Structure and Integration Impact the Genomic Profile of HPV-Positive Oropharyngeal Squamous Cell Carcinoma', *International Journal of Radiation Oncology*Biology*Physics*, p. 1313. doi: 10.1016/j.ijrobp.2017.12.033.
46. Mehta, M. *et al.* (2019) 'Oligonucleotide therapy: An emerging focus area for drug delivery in chronic inflammatory respiratory diseases', *Chemico-Biological Interactions*, pp. 206–215. doi:10.1016/j.cbi.2019.05.028.
47. Menon, S. *et al.* (2018) 'Selenium nanoparticles: A potent chemotherapeutic agent and an elucidation of its mechanism', *Colloids and surfaces. B, Biointerfaces*, 170, pp. 280–292. doi: 10.1016/j.colsurfb.2018.06.006.
48. Jahan, I., Begum, M., Akhter, S., Islam, M.Z., Jahan, N., Haque, M.Effects of alternate nostril breathing exercise on respiratory functions in healthy young adults leading stressful lifestyle(2020) Journal of Population Therapeutics and Clinical Pharmacology, 27 (1), pp. e104-e114.
49. Nandakumar, M. and Nasim, I. (2018) 'Comparative evaluation of grape seed and cranberry extracts in preventing enamel erosion: An optical emission spectrometric analysis', *Journal of conservative dentistry: JCD*, 21(5), pp. 516–520. doi: 10.4103/JCD.JCD_110_18.
50. Nandhini, J. S. T., Babu, K. Y. and Mohanraj, K. G. (2018) 'Size, shape, prominence and localization of gerdy's tubercle in dry human tibial bones', *Journal of advanced pharmaceutical technology & research*, 11(8), p. 3604. doi: 10.5958/0974-360x.2018.00663.7.
51. Pannone, G. *et al.* (2011) 'The role of human papillomavirus in the pathogenesis of head & neck squamous cell carcinoma: an overview', *Infectious agents and cancer*, 6, p. 4. doi: 10.1186/1750-9378-6-4.
52. Pc, J., Marimuthu, T. and Devadoss, P. (2018) 'Prevalence and measurement of anterior loop of the mandibular canal using CBCT: A cross sectional study', *Clinical implant dentistry and related research*. Available at: https://europepmc.org/article/med/29624863.
53. Perumalsamy, H. *et al.* (2018) 'In silico and in vitro analysis of coumarin derivative induced anticancer effects by undergoing intrinsic pathway mediated apoptosis in human stomach cancer', *Phytomedicine: international journal of phytotherapy and phytopharmacology*, 46, pp. 119–130. doi: 10.1016/j.phymed.2018.04.021.
54. Pringle, G. A. (2014) 'The role of human papillomavirus in oral disease', *Dental clinics of North America*, 58(2), pp. 385–399. doi: 10.1016/j.cden.2013.12.008.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 762 - 771
Received 16 February 2021; Accepted 08 March 2021.

55. Rajakeerthi and Ms, N. (2019) 'Natural Product as the Storage medium for an avulsed tooth – A Systematic Review', *CumhuriyetÜniversitesiDişHekimliğiFakültesidergisi*, 22(2), pp. 249–256. doi: 10.7126/cumudj.525182.
56. Raj, A. T. *et al.* (2019) 'Reviewing the role of human papillomavirus in oral cancer using the Bradford Hill criteria of causation', *Disease-a-month: DM*, 65(6), pp. 155–163. doi: 10.1016/j.disamonth.2018.09.007.
57. Rajendran, R. *et al.* (2019) 'Comparative evaluation of remineralizing potential of a paste containing bioactive glass and a topical cream containing casein phosphopeptide-amorphous calcium phosphate: An in vitro study', *Pesquisabrasileiraemodontopediatria e clinicaintegrada*, 19(1), pp. 1–10. doi: 10.4034/pboci.2019.191.61.
58. Rajeshkumar, S., Venkat Kumar, S., *et al.* (2018) 'Biosynthesis of zinc oxide nanoparticles usingMangifera indica leaves and evaluation of their antioxidant and cytotoxic properties in lung cancer (A549) cells', *Enzyme and Microbial Technology*, pp. 91–95. doi: 10.1016/j.enzmictec.2018.06.009.
59. Rajeshkumar, S., Agarwal, H., *et al.* (2018) 'Brassica oleracea mediated synthesis of zinc oxide nanoparticles and its antibacterial activity against pathogenic bacteria', *Asian Journal of Chemistry*, 30(12), pp. 2711–2715.
60. Rajeshkumar, S. (2018) 'Synthesis of Zinc oxide nanoparticles using algal formulation (Padina tetrastromatica and Turbinariaconoides) and their antibacterial activity against fish pathogens', *Research journal of biotechnology*, 13(9), pp. 15–19.
61. Ramadurai, N. *et al.* (2019) 'Effectiveness of 2% Articaine as an anesthetic agent in children: randomized controlled trial', *Clinical oral investigations*, 23(9), pp. 3543–3550. doi: 10.1007/s00784-018-2775-5.
62. Ramesh, A. *et al.* (2018) 'Comparative estimation of sulfiredoxin levels between chronic periodontitis and healthy patients - A case-control study', *Journal of periodontology*, 89(10), pp. 1241–1248. doi: 10.1002/JPER.17-0445.
63. Ravinthar, K. and Jayalakshmi (2018) 'Recent advancements in laminates and veneers in dentistry', *Journal of advanced pharmaceutical technology & research*, 11(2), p. 785. doi: 10.5958/0974-360x.2018.00148.8.
64. R, H. *et al.* (2020) 'CYP2 C9 polymorphism among patients with oral squamous cell carcinoma and its role in altering the metabolism of benzo[a]pyrene', *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, pp. 306–312. doi: 10.1016/j.oooo.2020.06.021.
65. Samuel, S. R. (2021) 'Can 5-year-olds sensibly self-report the impact of developmental enamel defects on their quality of life?', *International journal of paediatric dentistry / the British Paedodontic Society [and] the International Association of Dentistry for Children*, 31(2), pp. 285–286. doi: 10.1111/ipd.12662.
66. Sekar, D. *et al.* (2019) 'Methylation-dependent circulating microRNA 510 in preeclampsia patients', *Hypertension research: official journal of the Japanese Society of Hypertension*, 42(10), pp. 1647–1648. doi: 10.1038/s41440-019-0269-8.
67. Seppan, P. *et al.* (2018) 'Therapeutic potential of Mucuna pruriens (Linn.) on ageing induced damage in dorsal nerve of the penis and its implication on erectile function: an experimental study using albino rats', *The aging male: the official journal of the International Society for the Study of the Aging Male*, pp. 1–14. doi: 10.1080/13685538.2018.1439005.
68. Sharma, P. *et al.* (2019) 'Emerging trends in the novel drug delivery approaches for the

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 762 - 771
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treatment of lung cancer', *Chemico-biological interactions*, 309, p. 108720. doi: 10.1016/j.cbi.2019.06.033.
69. Siddique, R. *et al.* (2019) 'Qualitative and quantitative analysis of precipitate formation following interaction of chlorhexidine with sodium hypochlorite, neem, and tulsi', *Journal of conservative dentistry: JCD*, 22(1), pp. 40–47. doi: 10.4103/JCD.JCD_284_18.
70. Silverberg, J. I. and Silverberg, N. B. (2014) 'Childhood atopic dermatitis and warts are associated with increased risk of infection: a US population-based study', *The Journal of allergy and clinical immunology*, 133(4), pp. 1041–1047. doi: 10.1016/j.jaci.2013.08.012.
71. Sridharan, G. *et al.* (2019) 'Evaluation of salivary metabolomics in oral leukoplakia and oral squamous cell carcinoma', *Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology*, 48(4), pp. 299–306. doi: 10.1111/jop.12835.
72. Sujatha, J., Asokan, S. and Rajeshkumar, S. (2018) 'ANTIDERMATOPHYTIC ACTIVITY OF GREEN SYNTHESISED ZINC OXIDE NANOPARTICLES USING CASSIA ALATA LEAVES', *Journal of Microbiology, Biotechnology and Food Sciences*, pp. 348–352. doi: 10.15414/jmbfs.2018.7.4.348-352.
73. Syrjänen, S. (2010) 'The role of human papillomavirus infection in head and neck cancers', *Annals of Oncology*, pp. vii243–vii245. doi: 10.1093/annonc/mdq454.
74. Teja, K. V., Ramesh, S. and Priya, V. (2018) 'Regulation of matrix metalloproteinase-3 gene expression in inflammation: A molecular study', *Journal of conservative dentistry: JCD*, 21(6), pp. 592–596. doi: 10.4103/JCD.JCD_154_18.
75. Tran, N., Rose, B. R. and O'Brien, C. J. (2007) 'Role of human papillomavirus in the etiology of head and neck cancer', *Head & neck*, 29(1), pp. 64–70. doi: 10.1002/hed.20460.
76. VijayashreePriyadharsini, J. (2019) 'In silico validation of the non-antibiotic drugs acetaminophen and ibuprofen as antibacterial agents against red complex pathogens', *Journal of periodontology*, 90(12), pp. 1441–1448. doi: 10.1002/JPER.18-0673.
77. VijayashreePriyadharsini, J., SmilineGirija, A. S. and Paramasivam, A. (2018) 'In silico analysis of virulence genes in an emerging dental pathogen A. baumannii and related species', *Archives of oral biology*, 94, pp. 93–98. doi: 10.1016/j.archoralbio.2018.07.001.
78. World Health Organization (2009) 'WHO position on HPV vaccines', *Vaccine*, 27(52), pp. 7236–7237. doi: 10.1016/j.vaccine.2009.05.019.
79. Zandberg, D. P. *et al.* (2013) 'The role of human papillomavirus in nongenital cancers', *CA: a cancer journal for clinicians*, 63(1), pp. 57–81. doi: 10.3322/caac.21167.