Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 662 - 675
Received 16 February 2021; Accepted 08 March 2021.

Latency in Viral Infections

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ABSTRACT

In latent infections , overt disease is not produced but the virus is not completely eradicated. Latency can be defined as a persistent infection with reservoirs that fail to produce infectious virus but are capable of reactivating to repeat the infection cycle. The main feature of this persistence is the failure of host immune response in the elimination of such viruses.Viral latent infections have numerous pathogenesis associated with birth defects, cancers, chronic inflammation, and immunological dysfunctions. Several external factors such as stress,environmental triggers play an important role in the reactivation of viruses .The mechanisms controlling the latency are complex and diversified among virus families, species, and strains. Vaccines are most effective in controlling the viral infections but are

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active only on the reactivation of the lytic phase.In this review properties of latency, latency viral infections, reactivation can be defined. Eradicating latent virus has become an important but elusive challenge and will require a more complete understanding of the mechanisms controlling these processes and it is essential in developing future therapeutic drugs against viral infection and subsequent disease.

Keywords: Latency , Infections , Reactivation , Genes.

INTRODUCTION

A number of viruses can cause persistent infections in the host .The main feature of such persistence is the failure of host immune response in the elimination of such viruses. In latent infections ,overt disease is not produced ,but the virus is not eradicated.The latent period is known as the interval between the infection of a bacterial cell and the first release of infectious phage particles .A latent viral infections usually does not cause any noticeable symptoms . Latency can be defined as a persistent infection with reservoirs that fail to produce infectious virus but are capable of reactivating to repeat the infection cycle.(Speck and Ganem, 2010). During latency, the viral genome can either exist as a provirus that is integrated into the DNA of a host cell (proviral latency) or the use of genetic episomes (episomal latency) (Jane Flint *et al.*, 2015)**,**(Klein, 1976). Viral latent infections are neither innocuous nor inert. The escape of cell mediated immune response is the main cause of chronic persistent infections in viral latency (Pooggin, 2018). Viral latency can also be seen in the development of chronic disease depending on immunological response. Latency and reactivation is common among the virus family of herpes simplex viruses,cytomegalovirus, human immunodeficiency viruses,adenovirus ,Epstein Barr virus,varicella zoster virus ,paramyxovirus, hepatitis viruses.Eradicating latent reservoirs in HIV, SSPE, hepatitis B ,HSV, adenovirus infections has become more challenge in the treatment such diseases.Our team has rich experience in research and we have collaborated with numerous authors over various topics in the past decade (Ariga *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, 2019; Hema Shree *et al.*, 2019; Rajakeerthi and Ms, 2019; Rajendran *et al.*, 2019; Sekar *et al.*, 2019; Sharma *et al.*, 2019;

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

LATENCY VIRUSES

The capacity for latency is a defining feature of all herpesviruses .The herpesviral infections display latency in every infected individual. The important feature of the clinical manifestations of infections are the anatomic site of latency and the frequency of latency is reversed to lytic infections (Vaishali and Geetha, 2018). The other important virus family in which exhibit latency are the retroviruses. These small, enveloped RNA viruses replicate via reverse transcription of their RNA genomes and the resulting DNA establishes persistence by integrating into the host genome (M, Geetha and Thangavelu, 2019). In the intact host, the retroviral latency occurs in HIV infection of humans, in which a small subpopulation of long-lived memory T cells can undergo this form of latent infection(Girija As and Priyadharsini J, 2019).

HERPES SIMPLEX VIRUSES

The herpesviruses resulting in human diseases include HSV, VZV, CMV, HHV-6,-7, EBV, and HHV-8. The clinical manifestations of Herpesvirus infections are usually asymptomatic or subclinical in immunocompromised populations. During the latent phase of herpes simplex virus infection the viral genomes proteins can be detected in sensory and autonomic neurons. T and B lymphocytes are important while recovering from viral infections and are not responsible for the maintenance of latency in neurons. When the immune system is disordered or deficient, latent viruses may reactivate and cause asymptomatic infections, even fatal complications. HSV-1 infection is more common than HSV-2(Minarovits, Gonczol and Valyi-Nagy, 2006).

CYTOMEGALO VIRUSES

Cytomegalovirus infects 70-80% of healthy individuals .The peripheral blood monocytes are the major site of carriage of human cytomegalovirus DNA in healthy carriers. Human cytomegalovirus occurs particularly in immunocompromised people and there is a evidence that human immune response likewise plays an important role in limiting the dissemination of that virus .During organ transplant patients ,the dominant cause of this infection is the reactivation of transplant recipient's own CMV rather than virus transfer from

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donor(Bakhareva *et al.*, 2012).CMV-associated with end-organ diseases include colitis, pneumonitis, enteritis, hepatitis, retinitis and encephalitis, and so on. Ganciclovir is the first-line drug for the treatment of CMV diseases.

MORBIDITY AND MORTALITY

The reactivation of latent viral infections are important causes of morbidity and mortality in transplantation patients who are immunocompromised . Viruses acquired from the community, such as the respiratory and gastrointestinal viruses, are also important pathogens of post-transplant viral diseases(Rubin, 2013). Most of the viral infections present with asymptomatic conditions that result in complications in severe immunocompromised people. Currently, molecular diagnostic methods such as PCR and viral culture are used in the diagnosis of viral infections. Rapid and early diagnosis of infection in patients can reduce infection-related morbidity and mortality.Adoptive cellular therapy is a promising method in the treatment of viral diseases.

ROLE OF MACROPHAGES AND MONOCYTES

Latency viruses group will establish the latency in the macrophage and monocyte lineage and CD4+ T cells.The cells of monocyte and macrophage lineage are unique, resistant to the cytopathic effects and spread virus for longer periods of time. In HIV-1 infection, activated peripheral blood monocytes cross the blood brain barrier and cause HIV infections in brain .Increased and expansion of monocyte activation, as well as the level of HIV-1 DNA positive monocytes (CD14+/CD16+) have been associated with HIV-1 associated neuroinflammation(Granai *et al.*, 2020). The persistent HIV-1 replication in microglial cells and macrophages of the brain causes neuronal damage and neuroinflammation . Several efforts have been made in the analysis of reactivating latent reservoirs, enhancing cytotoxic response ,apoptosis of infected cells. In addition, circulating monocytes isolated from HIV-1 infected individuals exhibit different program cell death genes .Therefore, the determination of program cell death genes can help in targeting cells of monocytes and macrophage lineage infected with HIV-1.

LATENCY RESERVOIRS

The site and size of latent reservoirs in viruses determine the stability of latency and frequency of reactivation(Ashwin and Muralidharan, 2015). The latently infected CD4+ cells

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can rekindle productive viral infection when the HAART is withdrawn The latent reservoirs of HIV estimated between 1 and 6 *10^6 CD4+ T cells based on rates of virus detected after disruption of antiviral therapy(Pinkevych *et al.*, 2015)).Therefore , latent reservoir has been considered as a major obstacle to viral eradication.

Herpes simplex virus 1:

The latency reservoir of HSV1 is the trigeminal ganglion .The active occlusal disease,lacrimal gland and other tissues plays an important role in virus production which reinfects the eyes and continuously causes infections in ganglion (Johnston and Corey, 2015).

Epstein Barr virus :

The normal nasopharyngeal lymphocytes can act as a reservoir for EBV in normal individuals.It establishes an asymptomatic long-term latent infection and the reservoirs are detected chronically in saliva and blood at variable levels. Mathematical modeling predicts stable latent(Thorley-Lawson, 2015). The latently EBV-infected host cells can be destroyed by graft-versus-host reactivity, irradiation, or cytotoxic drugs ((Girija *et al.*, 2019).

GENOME MAINTENANCE MECHANISMS

Latent viruses involved in several mechanisms to maintain viral genome integrity. For herpes viruses ,viral genome is present in the latent cells .This is expected because viruses can be reactivated from these cells (Camarena *et al.*, 2010). In latency ,the terminal fragments of HSV1 DNA have lower mortality than in viral DNA virion . herpes viruses integrate into the host chromosome during latency, resembling HIV and retrovirus integration, but achieved through homologous recombination rather than with viral-encoded integrase(Selvakumar and Np, 2017)

EPISOMAL MAINTENANCE FACTORS

Episomal maintenance requires an epigenetic program for the control of DNA replication,viral gene expression .The metaphase chromosome is essential for episome maintenance and genome persistence in rapidly dividing cells.However, non integrating episomal genomes like EBV, KSHV, and HPV recruit the host cell replication machinery to the episome and maintain a stable episomal copy number by segregating newly replicated genomes equally to daughter cells after each cell division(Frappier, 2013),(Marickar, Geetha

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and Neelakantan, 2014).Recently, a potential episome maintenance factor has been identified for HCMV latency. (Tarrant-Elorza, Rossetto and Pari, 2014).

VIRAL IMPACT ON IMMUNE SURVEILLANCE

Herpesviruses are known for their ability to establish lifelong .In the strategy of immune evasion ,viruses have evolved a variety of ways to manipulate the immune system of the host. Most of the viruses encode homologs of cellular interleukins (IL), chemokines, or chemokine receptors(Nicholas, 2005). In HSV1 ,CD8+T cells restrict gene expression in infected neurons and preventing the production of infectious neurons .The IL-10 impairs NK cell-mediated killing of infected B-cells, interferes with CD4+ T-cell activity, and modulates cellular cytokine response(Girija, Jayaseelan and Arumugam, 2018)(Shahzan *et al.*, 2019). Another strategy for immune evasion is to reduce the viral antigens via the major histocompatibility complex (MHC) of infected cells(Mocarski, 2004),(Smiline, Vijayashree and Paramasivam, 2018). The manipulation of the immune system offers the reactivated virus at least partial relief from immune surveillance (Fishman, 2013).

EXTERNAL FACTORS INVOLVED IN REACTIVATION

Humans experience reactivation of herpesviruses through local trauma (e.g. in the form of surgery) systemic stress or immunocompromised .However corticosteroids treatments also influence reactivation in mice (Worrall, 1996).

Stress :

Both mental and physical stressors inhibit the activity of CD8+ T-cells through the release of neuroendocrine factors and the mechanism may link the control of HSV latency to activity in the sympathetic nervous system(Freeman *et al.*, 2007). In the case of EBV, the latent virus harbored in B-cells can be reactivated in vitro by stimulating B-cell receptors .The changes in EBV VCA IgG were associated with stress and the EBV proteins get reactivated as a result of stress (Leger, St. Leger and Hendricks, 2011). In fact, the stress associated with space flight is sufficient to cause reactivation of latent herpesviruses, presumably by downregulating cellular immunity(Stowe *et al.*, 2001),(Pawelec *et al.*, 2005).

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Environmental triggers :

The environmental triggers such as fever, sunlight, drugs ,UV exposure, hormonal changes, dental surgery, and cranial trauma can cause activation; but it is not known whether these stimuli act directly on the infected neuron, or indirectly by means of bodily functions(Shahana and Muralidharan, 2016). A skin trauma affecting the nerve endings of infected neurons may cause a similar reactivation. In order to maintain latency, the neuron must be functional, active, and healthy(Wilson and Mohr, 2012).

ROLE OF VACCINES DURING LATENCY

Vaccines are the most efficient and cost effective in controlling the viral infections.But viral vaccines are completely ineffective during latency ,but active only on the reactivation of lytic phase (Pratha, Ashwatha Pratha and Geetha, 2017) vaccines must target the viral proteins during latency ,it might be more effective in preventing the recurrent infections .The successful α-herpesvirus antivirals available is targeted towards the viral proteins .During latency, the virus does not express genes coding for virus proteins, including both DNA-polymerase and thymidine kinase(Paramasivam, Vijayashree Priyadharsini and Raghunandhakumar, 2020).Particularly the vaccine targeting CD8+ T cells are more effective in HSV1 infections (Priyadharsini *et al.*, 2018a). Although vaccination against herpes viruses has been difficult, advancements have been made .HSV was the very first infections to be treated successfully using antiviral compounds, proving that a viral disease could be successfully treated in this way(Priyadharsini *et al.*, 2018b). Vaccines will prevent the establishment of latency to an extent, preventing the virus from gaining entry into the host cell by the circulating antibodies. 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; Vijayashree Priyadharsini, Smiline Girija and Paramasivam, 2018; Ezhilarasan, Apoorva and Ashok Vardhan, 2019; Ramadurai *et al.*, 2019; Sridharan *et al.*, 2019; Vijayashree Priyadharsini, 2019; Chandrasekar *et al.*, 2020; Mathew *et al.*, 2020; R *et al.*, 2020; Samuel, 2021)

POTENTIAL FOR NEW THERAPIES IN VIRAL INFECTIONS

The use of the CRISPR/Cas9 genome editing to selectively delete or mutate latent virus DNA(Williamson *et al.*, 2018). CRISPR/Cas9 is potentially used in antiviral therapy by targeting the viral genome of the herpes viruses (Wang and Quake, 2014) . Lytic reactivated

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viruses can be selectively targeted by existing antiviral drugs and as adjuvants for immunological therapies(Shirakawa *et al.*, 2013). Additionally,current therapies are used to limit the latent infections efficacy and cannot eradicate the viruses . Consequently, latently infected cells with cytomegalovirus are more sensitive to chemotoxic agents.(Weekes *et al.*, 2013). These therapies are target to viral-specific noncoding RNAs associated with latent infection(Saayman *et al.*, 2015). These play key roles in regulating virus latency, this approach could have high therapeutic potential.

CONCLUSION :

This review is far from comprehensive or complete and yet hopefully shows the enormous complexity of viral latency and its regulation at the genetic and epigenetic levels. This information provides a great opportunity for the development of innovative and highly selective therapeutic intervention. As viral latency is responsible for life-long pathogenesis and mortality risk, the tasks ahead are in sight, but challenges remain.

REFERENCES :

1. 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.

2. Ashwin, K. S. and Muralidharan, N. P. (2015) 'Vancomycin-resistant enterococcus (VRE) vs Methicillin-resistant Staphylococcus Aureus (MRSA)', *Indian Journal of Medical Microbiology*, p. 166. doi: 10.4103/0255-0857.150976.

3. Bakhareva, N. V. *et al.* (2012) 'POST-EXPOSURE PROPHYLAXIS OF VARICELLA IN ORDER TO STOP INFECTION OUTBREAKS IN KRASNOYARSK CHILDREN ORGANIZED GROUPS', *Current pediatrics*, p. 109. doi: 10.15690/vsp.v11i2.221.

4. 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.

5. Camarena, V. *et al.* (2010) 'Nature and Duration of Growth Factor Signaling through Receptor Tyrosine Kinases Regulates HSV-1 Latency in Neurons', *Cell Host & Microbe*, pp. 320–330. doi: 10.1016/j.chom.2010.09.007.

6. 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.

7. 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.

8. Ezhilarasan, D., Apoorva, V. S. and Ashok Vardhan, N. (2019) 'Syzygium cumini 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.

9. Fishman, J. A. (2013) 'Overview: Cytomegalovirus and the Herpesviruses in Transplantation', *American Journal of Transplantation*, pp. 1–8. doi: 10.1111/ajt.12002.

10. Frappier, L. (2013) 'EBNA1-DNA Interactions', *EBNA1 and Epstein-Barr Virus Associated Tumours*, pp. 19–25. doi: 10.1007/978-1-4614-6886-8_3.

11. Freeman, M. L. *et al.* (2007) 'Psychological Stress Compromises CD8 T Cell Control of Latent Herpes Simplex Virus Type 1 Infections', *The Journal of Immunology*, pp. 322–328. doi: 10.4049/jimmunol.179.1.322.

12. Gheena, S. and Ezhilarasan, D. (2019) 'Syringic acid triggers reactive oxygen species-mediated cytotoxicity in HepG2 cells', *Human & experimental toxicology*, 38(6), pp. 694–702.

13. Girija, A. S. S. *et al.* (2019) 'Plasmid-encoded resistance to trimethoprim/sulfamethoxazole mediated by dfrA1, dfrA5, sul1 and sul2 among Acinetobacter baumannii isolated from urine samples of patients with severe urinary tract infection', *Journal of Global Antimicrobial Resistance*, pp. 145–146. doi: 10.1016/j.jgar.2019.04.001.

14. Girija As, S. and Priyadharsini J, V. (2019) 'CLSI based antibiogram profile and the detection of MDR and XDR strains of isolated from urine samples', *Medical journal of the Islamic Republic of Iran*, 33, p. 3.

15. Girija, S. A. S., Jayaseelan, V. P. and Arumugam, P. (2018) 'Prevalence of VIM- and GIM-producing Acinetobacter baumannii from patients with severe urinary tract infection', *Acta Microbiologica et Immunologica Hungarica*, pp. 539–550. doi: 10.1556/030.65.2018.038.

16. Granai, M. *et al.* (2020) 'Immune landscape in Burkitt lymphoma reveals M2-macrophage polarization and correlation between PD-L1 expression and non-canonical EBV latency program', *Infectious agents and cancer*, 15, p. 28.

17. 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.

18. 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.

19. 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.

20. 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.

21. Jane Flint, S. *et al.* (2015) *Principles of Virology, Volume 2: Pathogenesis and Control*. ASM Press.

22. 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.

23. 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.

24. Johnston, C. and Corey, L. (2015) 'Current Concepts for Genital Herpes Simplex Virus Infection: Diagnostics and Pathogenesis of Genital Tract Shedding', *Clinical Microbiology Reviews*, pp. 149–161. doi: 10.1128/cmr.00043-15.

25. 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.

26. 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.

27. Klein, R. J. (1976) 'Pathogenetic mechanisms of recurrent herpes simplex virus infections', *Archives of Virology*, pp. 1–13. doi: 10.1007/bf01317829.

28. Kumar, D. and Antony, S. D. P. (2018) 'Calcified canal and negotiation-A review', *Journal of advanced pharmaceutical technology & research*, 11(8), p. 3727.

29. Leger, A. J. S., St. Leger, A. J. and Hendricks, R. L. (2011) 'CD8 T cells patrol HSV-1-infected trigeminal ganglia and prevent viral reactivation', *Journal of NeuroVirology*, pp. 528–534. doi: 10.1007/s13365-011-0062-1.

30. 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.

31. Marickar, R. F., Geetha, R. V. and Neelakantan, P. (2014) 'Efficacy of contemporary and novel Intracanal medicaments against enterococcus faecalis', *The Journal of clinical pediatric dentistry*, 39(1), pp. 47–50.

32. 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.

33. 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.

34. Minarovits, J., Gonczol, E. and Valyi-Nagy, T. (2006) *Latency Strategies of Herpesviruses*. Springer Science & Business Media.

35. M, M. A., Geetha, R. V. and Thangavelu, L. (2019) 'Evaluation oEvaluation of anti-inflammatory action of Laurus nobilis-an in vitro studyf anti-inflammatory action of Laurus nobilis-an in vitro study', *International Journal of Research in Pharmaceutical Sciences*, pp. 1209–1213. doi: 10.26452/ijrps.v10i2.408.

36. Mocarski, E. S. (2004) 'Immune escape and exploitation strategies of cytomegaloviruses: impact on and imitation of the major histocompatibility system', *Cellular Microbiology*, pp. 707–717. doi: 10.1111/j.1462-5822.2004.00425.x.

37. 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.

38. 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.

39. Nicholas, J. (2005) 'Review:Human Gammaherpesvirus Cytokines and Chemokine Receptors', *Journal of Interferon & Cytokine Research*, pp. 373–383. doi: 10.1089/jir.2005.25.373.

40. Paramasivam, A., Vijayashree Priyadharsini, J. and Raghunandhakumar, S. (2020) 'N6-adenosine methylation (m6A): a promising new molecular target in hypertension and cardiovascular diseases', *Hypertension research: official journal of the Japanese Society of Hypertension*, 43(2), pp. 153–154.

41. Pawelec, G. *et al.* (2005) 'Human immunosenescence: is it infectious?', *Immunological Reviews*, pp. 257–268. doi: 10.1111/j.0105-2896.2005.00271.x.

42. 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.

43. Pinkevych, M. *et al.* (2015) 'HIV Reactivation from Latency after Treatment Interruption Occurs on Average Every 5-8 Days—Implications for HIV Remission', *PLOS Pathogens*, p. e1005000. doi: 10.1371/journal.ppat.1005000.

44. Pooggin, M. M. (2018) 'Small RNA-Omics for Plant Virus Identification, Virome Reconstruction, and Antiviral Defense Characterization', *Frontiers in microbiology*,

9, p. 2779.

45. Pratha, A. A., Ashwatha Pratha, A. and Geetha, R. V. (2017) 'Awareness on Hepatitis-B vaccination among dental students-A Questionnaire Survey', *Research Journal of Pharmacy and Technology*, p. 1360. doi: 10.5958/0974-360x.2017.00240.2.

46. Priyadharsini, J. V. *et al.* (2018a) 'An insight into the emergence of Acinetobacter baumannii as an oro-dental pathogen and its drug resistance gene profile – An in silico approach', *Heliyon*, p. e01051. doi: 10.1016/j.heliyon.2018.e01051.

47. Priyadharsini, J. V. *et al.* (2018b) 'In silico analysis of virulence genes in an emerging dental pathogen A. baumannii and related species', *Archives of Oral Biology*, pp. 93–98. doi: 10.1016/j.archoralbio.2018.07.001.

48. Rajakeerthi and Ms, N. (2019) 'Natural Product as the Storage medium for an avulsed tooth – A Systematic Review', *Cumhuriyet Üniversitesi Diş Hekimliği Fakültesi dergisi*, 22(2), pp. 249–256.

49. 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', *Pesquisa brasileira em odontopediatria e clinica integrada*, 19(1), pp. 1–10.

50. 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.

51. 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.

52. Ravinthar, K. and Jayalakshmi (2018) 'Recent advancements in laminates and veneers in dentistry', *Journal of advanced pharmaceutical technology & research*, 11(2), p. 785.

53. 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.

54. Rubin, R. (2013) *Clinical Approach to Infection in the Compromised Host*. Springer Science & Business Media.

55. Saayman, S. *et al.* (2015) 'HIV Latency and the Noncoding RNA Therapeutic Landscape', *Advances in Experimental Medicine and Biology*, pp. 169–189. doi: 10.1007/978-1-4939-2432-5_9.

56. 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.

57. 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.

58. Selvakumar, R. and Np, M. (2017) 'COMPARISON IN BENEFITS OF HERBAL MOUTHWASHES WITH CHLORHEXIDINE MOUTHWASH: A REVIEW', *Asian Journal of Pharmaceutical and Clinical Research*, p. 3. doi: 10.22159/ajpcr.2017.v10i2.13304.

59. 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.

60. Shahana, R. Y. and Muralidharan, N. P. (2016) 'Efficacy of mouth rinse in maintaining oral health of patients attending orthodontic clinics', *Research Journal of Pharmacy and Technology*, p. 1991. doi: 10.5958/0974-360x.2016.00406.6.

61. Shahzan, M. S. *et al.* (2019) 'A computational study targeting the mutated L321F of ERG11 gene in C. albicans, associated with fluconazole resistance with bioactive compounds from Acacia nilotica', *Journal de Mycologie Médicale*, pp. 303–309. doi: 10.1016/j.mycmed.2019.100899.

62. Sharma, P. *et al.* (2019) 'Emerging trends in the novel drug delivery approaches for the treatment of lung cancer', *Chemico-biological interactions*, 309, p. 108720.

63. Shirakawa, K. *et al.* (2013) 'Reactivation of latent HIV by histone deacetylase inhibitors', *Trends in Microbiology*, pp. 277–285. doi: 10.1016/j.tim.2013.02.005.

64. 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.

65. Smiline, A. S. G., Vijayashree, J. P. and Paramasivam, A. (2018) 'Molecular characterization of plasmid-encoded blaTEM, blaSHV and blaCTX-M among extended spectrum β-lactamases [ESBLs] producing Acinetobacter baumannii', *British Journal of Biomedical Science*, pp. 200–202. doi: 10.1080/09674845.2018.1492207.

66. Speck, S. H. and Ganem, D. (2010) 'Viral Latency and Its Regulation: Lessons from the γ-Herpesviruses', *Cell Host & Microbe*, pp. 100–115. doi: 10.1016/j.chom.2010.06.014.

67. 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.

68. Stowe, R. P. *et al.* (2001) 'Immune responses and latent herpesvirus reactivation in spaceflight', *Aviation, space, and environmental medicine*, 72(10), pp. 884–891.

69. Tarrant-Elorza, M., Rossetto, C. C. and Pari, G. S. (2014) 'Maintenance and

Replication of the Human Cytomegalovirus Genome during Latency', *Cell Host & Microbe*, pp. 43–54. doi: 10.1016/j.chom.2014.06.006.

70. 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.

71. Thorley-Lawson, D. A. (2015) 'EBV Persistence—Introducing the Virus', *Current Topics in Microbiology and Immunology*, pp. 151–209. doi: 10.1007/978-3-319-22822-8_8.

72. Vaishali, M. and Geetha, R. V. (2018) 'Antibacterial activity of Orange peel oil on Streptococcus mutans and Enterococcus-An In-vitro study', *Research Journal of Pharmacy and Technology*, p. 513. doi: 10.5958/0974-360x.2018.00094.x.

73. Vijayashree Priyadharsini, 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.

74. Vijayashree Priyadharsini, J., Smiline Girija, 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.

75. Wang, J. and Quake, S. R. (2014) 'RNA-guided endonuclease provides a therapeutic strategy to cure latent herpesviridae infection', *Proceedings of the National Academy of Sciences*, pp. 13157–13162. doi: 10.1073/pnas.1410785111.

76. Weekes, M. P. *et al.* (2013) 'Latency-Associated Degradation of the MRP1 Drug Transporter During Latent Human Cytomegalovirus Infection', *Science*, pp. 199–202. doi: 10.1126/science.1235047.

77. Williamson, R. C. *et al.* (2018) *The Future of Precision Medicine in Australia*.

78. Wilson, A. C. and Mohr, I. (2012) 'A cultured affair: HSV latency and reactivation in neurons', *Trends in Microbiology*, pp. 604–611. doi: 10.1016/j.tim.2012.08.005.

79. Worrall, G. (1996) 'Evidence for efficacy of topical acyclovir in recurrent herpes labialis is weak', *BMJ*, pp. 46–46. doi: 10.1136/bmj.313.7048.46a.