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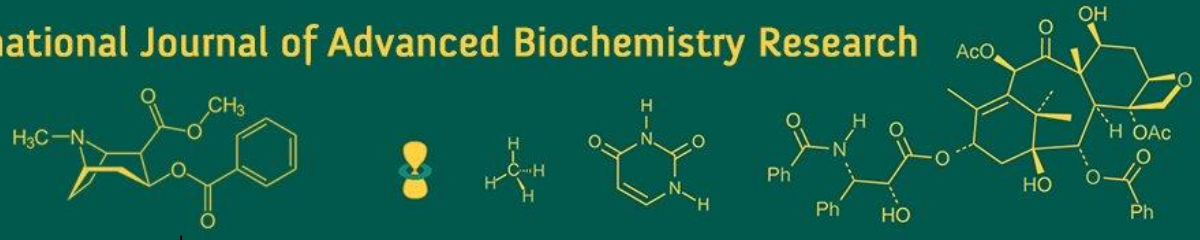

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Recent trends in the study of Roseoloviruses causing diseases, complications and cancer in human

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Abstract
Roseoloviruses are ubiquitous worldwide. Its infection in children is very common causing a disease named as *Roseola infantum.* It appears that most of the children are still being suffered by the same disease without any proper treatment all over the world. And, the situation becomes worst when these latent viruses reactivated in future to develop disease complications and cancer in human. The Present review is an attempt to describe Roseoloviruses causing diseases including cancer in human in the light of recent researches done so far in the past.

Keywords: Roseoloviruses, diseases, reactivation, cancer

Introduction
Roseoloviruses is a linear, double stranded DNA virus belonging to the order Herpesvirales, family Herpesviridae and the subfamily Betaherpesvirinae. These are of two types named HHV-6 & HHV-7. HHV-6 has further been categorized as HHV-6A & HHV-6B. These viruses were first isolated either from patients suffering from lymphoproliferative diseases and AIDS (HHV-6) or from CD4+ T cells taken from peripheral blood lymphocytes (HHV-7) [Salahuddin *et al.* 1986 and Frenkel *et al.* 1990] [29, 10]. Roseoloviruses cause a rash developing disease in human known as *Roseola infantum* whose entire disease cycle is completed within 3 to 6 days. Once after an infection, the Roseoloviruses remain latent for lifelong. Virus may cause cancer (Masroor *et al.*, 2020) [23] and tumor suppressor genes may be reactivated (Saha *et al.*, 2020) [28]. Studies have shown that some of these hidden viruses if reactivated in future develop severe complications in human [Anni *et al.* 2015, Henri *et al.* 2015 and Vanessa and Louis 2017] [4, 11, 33]. The present study discusses the Roseoloviruses causing diseases, complications and cancer in human.

Clinical presentation
Roseola infantum is a mild viral infection of children most commonly involving 6 months to 3 years. Almost all children have been infected with the virus during their childhood. The disease is also known as the *Exanthema subitum* or "sixth disease" because this is sixth in series of rash developing disease which also lasted in about six days [Taspinar *et al.* 2013] [32].

The disease is characterized by a sudden onset of rise in temperature followed by the rose coloured rashes that dissipitates after a few days. Usually, these rose coloured rashes are formed on neck, trunk and thighs first and then spread on legs and face. The infections are contagious during the fever phase especially by saliva but not spread via rashes. The salivary glands are the natural reservoir of these Roseoloviruses [Agut 2011 and Jessica *et al.* 2020] [3, 14]. No treatment is generally required except to keep the fever down and drink plenty of fluids. Although, rare, febrile seizures may occur due to high fever. Similar, symptoms are associated with HHV-7 virus too. If these viruses reactivated later in life due to some unavoidable circumstances such as immunocompromisation or with the use of immunosuppressants they may cause several ailments, diseases and even cancer in future [Stone *et al.* 2014 and Henri *et al.* 2015] [31, 11].

Oncology of the virus

Roseoloviruses have got their own distinguishing ability to be integrated in human chromosomes. They are covalently integrated into subtelomeric region of human chromosomes in about 1% of the general population [Henri *et al.* 2015] [11]. Further, the process of gametogenesis and the fusion of gametes transfer the same integration to the next generation increasing the risk of developing three times angina in humans [Anni *et al.* 2015 and Vanessa and Louis 2017] [4, 33]. Some of other ailments and diseases including cancer caused by these viruses are briefly summarized as under:

1. HHV-6 has been found to be associated with the patients suffering from multiple sclerosis, a neuroinflammatory disease, causing demyelination in brain [Ablashi *et al*. 2000, Hernan *et al*. 2001, Delbue *et al*. 2012 and Pietilainen and Virtanen 2014] [1, 12, 7, 25]. Further, it has been detected in some kind of brain tumors [Kofman *et al*. 2011] [17]. The human p53 protein functions as a tumor suppressor. The persons not having this protein experience a higher incidence of cancer, a phenomenon known as "Li-Fraumeni syndrome". Deregulation of p53 protein factor is associated with cancer. For example, two of the HHV-6 viral gene products named U14 and ORF-1 proteins bind with p53 protein and inactivating it to cause cancer [Kofman *et al*. 2011] [17].
2. HHV-6 has also been implicated as a cofactor in chronic fatigue syndrome (CFS). CFS is a debilitating disease of unknown etiology showing neurological, immunological and metabolic findings. Scientists have shown an association between CFS and HHV-6. But, largely, it remains found to be unproven [Buchwald *et al*. 1992, Wagner *et al*. 1996, Ablashi *et al*. 2000, Nicolson *et al*. 2003 and Komaroff 2006] [5, 34, 1, 24, 18].
3. Similarly, the cells infected with the roseoloviruses are comprehensively being engaged in complete replication cycle to cause disturbed apoptosis and necrosis developing cancer and death of cells respectively [Henri *et al*. 2015] [11].
4. In addition, HHV-6 develops fibromyalgia in AIDS patient [Pietilainen and Virtanen 2014] [25].
5. Researchers have shown that T-cells are highly infectable by HHV-6 virus. [Lusso *et al*. 1995 and Laurie and Philip 2014] [20, 19].
6. Further, Roseoloviruses has been found to be associated with the pathogenesis of a common neurological disorder as epilepsy. HHV-6 has some connection with temporal lobe epilepsy [Fotheringham *et al*. 2007] [9]. Further, it has also been reported that the virus enters the brain via olefactory pathways. But, it still requires more researches to prove the link [Santa *et al*. 2020] [30]. These viruses have also been found to be linked with Alzheimers [Readhead *et al*. 2018 and Denner *et al*. 2019] [26, 8].
7. Roseoloviruses can also cause encephalitis and brain dysfunction in both immunocompetent and immunocompromised individuals [Joseph *et al*. 2017] [15].
8. HHV-6 has also been found as an important factor for female infertility [Roberto *et al*. 2016] [27].
9. Hoshimoto thyroiditis disease has been found to be linked with HHV-6. This is a kind of thyroid ailment where increased lymphocytes are found [Caselli *et al*. 2012] [6].
10. Finally, there are reports that Roseoloviruses have frequently been reactivated in transplant recipients [Joshua and Danielle 2014 and Denner *et al*. 2019] [8].

Prevention of infections

To date, no any specific prevention measure is available for Roseoloviruses. We can only hope a good hygiene can only keep us away from the virus. The disease and the disease complications are still being treated symptomatically. Similarly, there is no vaccine available for the prevention of infection. Further studies are still required to establish various casualties of same viral infections to explore the prevention and treatment options [Joshua and Danielle 2014].

Treatment of the disease

Roseola infantum is a common paediatric disease caused by the Roseoloviruses. Though, the primary infections of the Roseoloviruses do not require any treatment, other complications arising after reactivation of the viruses are being treated with the help of an antiviral ganciclovir [Imataki and Uemura 2015] [13]. It can also reduce the risk of reactivation in high risk transplant patients [Joshua and Danielle 2014]. Currently, an effective vaccine is utmost needed for the prevention and treatment of Roseoloviruses and *Roseola infantum* respectively.

Conclusion

Roseoloviruses cause a disease in children known as *Roseola infantum*. Almost, all children of the world have been infected with the same virus at least once in their lifetime with lifelong latencies in the same individuals. Further, the extra quality being acquired by this virus to be integrated with the human chromosomes enlarges the risk of reactivation causing complications developing several diseases including cancer in future course of time.

Unfortunately, no vaccines have so far been discovered for the prevention and treatment of Roseoloviruses. However, some antivirals have been tried to control the disease complications. Last but not the least, as cancer often takes years, even decades to develop after a person gets an infection, there is nothing more to worry about it except to be alert. Similarly, since there is no way to know which people who have cancer causing pathogens will develop cancer, it arises from his bad luck. [Masroor *et al.* 2018, 2019 and 2020] [21, 22, 23].

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Conflict of interest

There are no conflicts of interest. The authors have approved the final version of the manuscript contributing equally.

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