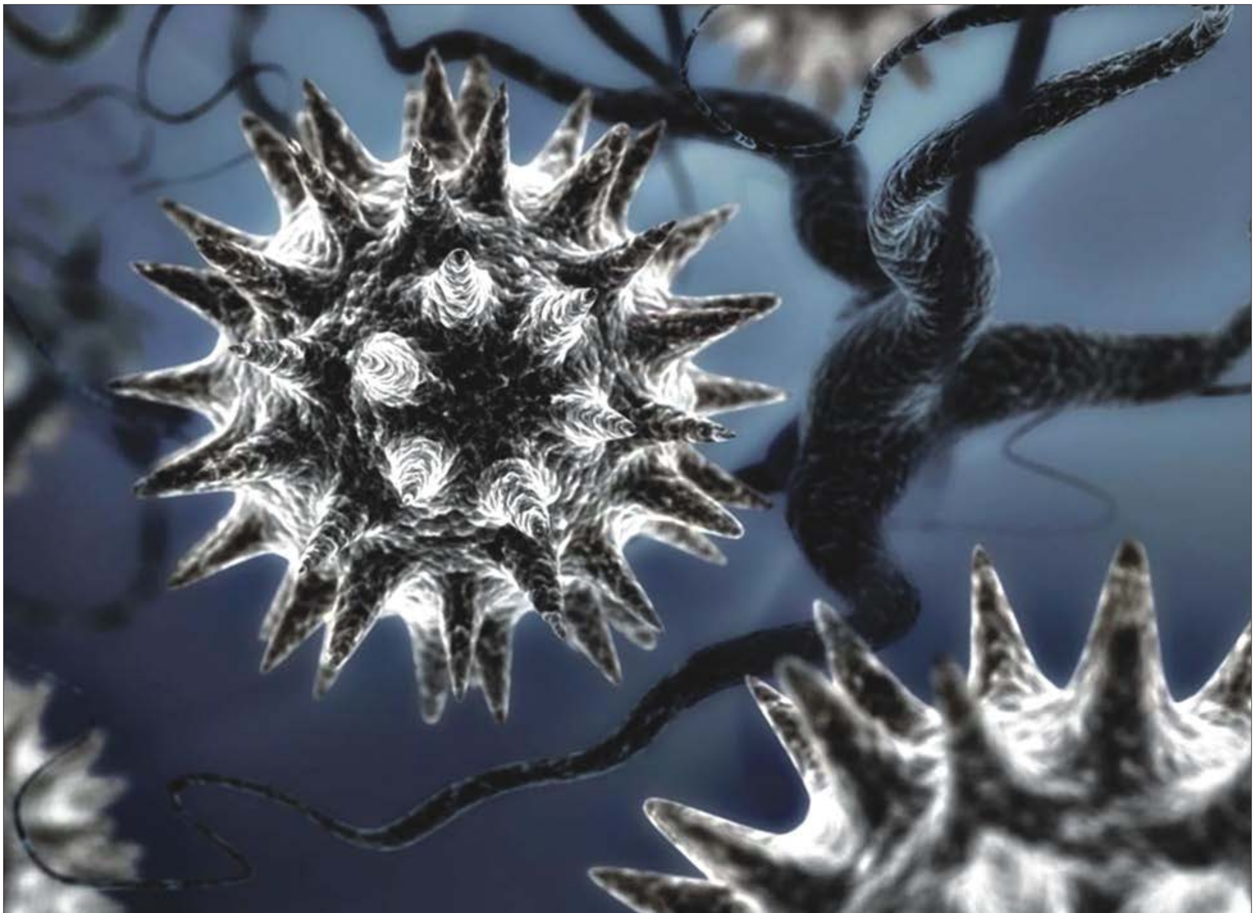

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Squalamine: May Be an Effective Viral Control

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It's long ago that viruses are causing lethal diseases in humans and their control has always been an important issue (Berrocal *et al.*, 2000; Busse, 1995; Davis, 1990; Riddell *et al.*, 1992). Viruses have a large burden on human population, as nearly 50 million peoples are annually infected with dengue and almost 40% world population is at the risk of dengue infection (WHO, 2007). Another important death causing virus, Hepatitis B Virus (HBV) caused 1507 deaths in 2001 in France (Marcellin *et al.*, 2008). Some human viruses have their origin in animals e.g., influenza virus, West Nile virus, rabies etc., some of which are transmitted by vector (Griffin, 2010). Thus viruses are one of major threats to human health and should be eliminated. Virus survival depends on host metabolic machinery and it involves many processes to penetrate into the host cell (Mercer *et al.*, 2010; Smith and Helenius, 2004). To control the viruses the understanding of mechanism involved in viral entry into the cell is proved to be helpful. Some viruses take entry into the host cell through glycosylated and non-glycosylated proteins (Burlone and Budkowska, 2009). Once the virus has entered in host cell, its genome cause several disorders in host genome responses to benefit the viral life cycle (Clementz *et al.*, 2008; Egger *et al.*, 2002; Netherton *et al.*, 2007; Weitzman *et al.*, 2010). Thus, the infection of virus can be controlled if its cell entry is inhibited and squalamine may stop the viral entry. Nature has provided many sources of antiviral compounds and squalamine is one of them (Sohail *et al.*, 2011). Squalamine is a cationic aminosteroid obtained from the dogfish shark, its natural presence in shark explains its defensive property (Moore *et al.*, 1993; Thornthwaite and Henderson, 2010). It has provided many benefits to human health via its role in signaling pathway (Djouhri-Bouktab *et al.*, 2011; Ciulla *et al.*, 2007). It affects the cell membrane integrity by depolarizing it and its function depends upon the phospholipids on cell membrane (Salmi *et al.*, 2008). Thus it may be able to interact with the viral signaling pathway and stops its proliferation too.

Zasloff *et al.* (2011) studied both *in vitro* and *in vivo* antiviral activity of squalamine against some RNA and DNA viruses. According to their results this aminosteroid caused some changes in the mammalian membrane integrity which stopped the movement of virus particles. Its positively charged functional groups joined with the anionic phospholipids of membrane and neutralized them. Moreover, it replaced some positively charged membrane proteins and showed double potential to combine with anionic phospholipids than Rac1 protein. It was easily sandwiched between the polarized bilayers of membrane which enhances its efficiency of neutralization. Due to this, it could easily interrupt membrane including cell processes. During *in vitro* studies it was observed that squalmine could efficiently stop the movement of dengue, hepatitis B and Hepatitis δ-Virus (HDV). It inhibited 100% of dengue virus in human microvascular endothelial cells and did not cause any toxicity. Its effective anti-hepatitis B virus concentration was also nontoxic to hepatocyte cells but the anti-HDV effective concentration (60 $\mu g\ mL^{-1}$) was significantly cytotoxic. Thus its application against HDV needed more care to avoid its harmful aspects. Its ability to inhibit Yellow Fever Virus (YFV), Eastern Equine Encephalitis Virus (EEEV) and Murine

Cytomegalovirus (MCMV) was studied in mice and golden Syrian hamster. Squalamine treatment of these animals was started one day before the virus infection and was supplemented through s.c. or i.p. pathways. Its application in animals resulted in excellent inhibition of virus which was dependant on the subsequent s.c. or i.p. pathway used. As in mouse, its supplementation through i.p. pathway showed the better antiviral activity against MCMV than s.c. and by day 14 there was undetectable amount of virus. Squalamine activity against YFV was also reliable as its application saves the 100% population of hamster; otherwise a significant population was at the great risk of death. As due to YFV caused hepatitis 85% animals were died only after 9 days of virus infection. This protective activity of squalamine was due to lower levels of liver enzyme; it reduced the detrimental levels of the enzymes and stabilized their normal concentration. Moreover, it's very small (10 mg kg^{-1} only) concentration was enough to stop the entry of EEEV in hamster. Thus, squalamine showed antiviral activity against number of viruses and induced cytotoxicity only in HDV infected hepatocytes. That's why its membrane binding and sandwiching property could be used to stop the invasion of many human viruses.

Today's world is facing many health problems caused by different viruses. The virus commands the host metabolic machinery, after getting entry into the cell through its membrane. Thus cell membrane can play an important role in controlling the virus infection. Zasloff *et al.* (2011) studied a compound, squalamine which has the potential to control the cell membrane permeability and to inhibit the virus entry. Their results confirm its reliabe antiviral activity against dengue, HBV, EEEV, YFV and MCMV in concentration dependent manner. As a result, it can be conclude that squalamine is a potent antiviral agent and its application will bring great success in medicinal sciences.

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