CHAPTER 1: INTRODUCTION

Influenza is the most common infectious disease that's caused by the influenza virus. Influenza causes 4 to 5 million cases annually and causes an economic burden of around 11 billion per year in the US alone(Grohskopf et al., 2019)Influenza itself is caused by different forms of the virus, such as influenza A B C. Influenza A virus is the most common cause of influenza with seasonal patterns, thus also known as seasonal influenza. Symptoms of seasonal influenza vary greatly and do not have to be present to indicate influenza infection, with fever, cough, sore throat, runny nose, body aches, headaches and malaise as the common symptoms of influenza(Moghadami, 2017). A high-risk group such as children under six month, pregnant women, adults above 65 and immunocompromised individuals are prone to Influenza complications(Moghadami, 2017). The complications of influenza, such as bacterial pneumonia, myocarditis, and multiple organ failure can be fatal; thus, high-risk groups are often treated compared while the non-high-risk group did not receive direct treatment against influenza.

Influenza A is an enveloped virus that encodes its genetic information in 8 segmented negative-sense RNA. The genes on IAV is divided into two categories according to its function. Structural genes encode for structural protein such as M1 matrix protein, M2 ion channel, neuraminidase and hemagglutinin while Non-structural genes that encode protein for influenza replication inside host cells such as PB1, PB2, and PA that encodes viral polymerase complex, nuclear export protein, viral nucleoprotein(Ferhadian et al., 2018). Influenza A virus infects epithelial cells in the upper airways of the respiratory system by cleaving through N-acetylneuraminic or sialic acid, a glycoprotein that is commonly found in the surface of epithelial cells. Influenza A virus that affects human prim arily enters the cell through a variation of a sialic acid called **α** 2,6, commonly found in upper epithelial cells on the airway. IAV is

endocytosed to cells by cleaving through **α** 2,6 sialic acid through hemagglutinin on the surface of the virus envelope(Bouvier & Palese, 2008). Once inside the host cell, the pH of the host cell allows for the fusion protein inside of IAV with the envelope, creating holes for the IAV RNAs to escape the matrix. M2 ion channel of the IAV pumps ions from the endosome into the viral structure, pushing the genetic material through the hole initially made. IAV viral nuclear localization signal uses host localization protein to move segmented RNAs into the nucleus of the host cell to be transcribed. In the nucleus, the negative strand RNAs of IAV are used as a template to generate mRNAs for viral proteins and complementary RNA, which will be further processed by RNA polymerase to generate vRNA that are the genome of the IAV. The messenger RNA is then capped by PB1 and PB2 protein from mRNA precursor of the host cell through a process called cap snatching(Bouvier & Palese, 2008). mRNAs of the IAV are then transported into the endoplasmic reticulum of the host cell to translate mRNAs into structural proteins such as hemagglutinin, neuraminidase, and matrix protein. The proteins undergo post-translational modifications to signal the protein to near the surface of the cell where new viruses are being assembled, and IAV genetic materials are packed. Once assembled, Neuraminidase of IAV cleaves through the residues of sialic acid receptor inside the cell, enabling the virus to be endocytosed outside(Ferhadian et al., 2018).

Seasonal influenza can be mitigated by a seasonal vaccine that gives immunity against predicted IAV strain in the area(Grohskopf et al., 2019), while treatment against IAV is usually performed on high-risk patients. Current approved antiviral for influenza are oseltamivir and zanamivir that belong in a class of drugs called neuraminidase inhibitors, which blocks neuraminidase of IAV to inhibit virus release(Wolkewitz & Schumacher, 2016). Prolonged use

of both drugs may lead to antiviral resistance which places the need to discover a new antiviral against influenza(Samson, Pizzorno, Abed, & Boivin, 2013)

Brown algae contain many classes of bioactive compounds such as carrageenans, lectins, polyphenols and fucoidan(Pádua, Rocha, Gargiulo, & Ramos, 2015). Fucoidans are a group of sulfated polysaccharides first isolated in 1913 from several brown algae species. The structure of fucoidan, in general, is polymerized L fucose with sulfated ester groups, with variation in sugar such as D galactose, D glucose, D mannose, D xylose and glucuronic acid It is mainly found in the cell walls of Phaeophyceae with molecular sizes ranging from 3000 Da to 32000 Da(Li, Lu, Wei, & Zhao, 2008). Different extraction process and harvest conditions can yield different fucoidan, which may have different bioactivity(Ale & Meyer, 2013). Fucoidan has been shown to contain many bioactivities and has shown antiviral properties against avian influenza A (H5N1) by inhibiting the release of influenza virus(Makarenkova, Deriabin, L'vov, Zviagintseva, & Besednova, n.d.).As avian influenza uses a similar mechanism with seasonal influenza, it is possible that fucoidan also exhibits an inhibiting effect against seasonal influenza.