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HEPATITIS C ANTIVIRAL ACTIVITY OF FAMILY RUTACEAE: A REVIEW

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Abstract
Hepatitis is a health problem in the world that can cause the deaths of millions ofpeople worldwide, but there is no vaccine available for HCV. Currently, pegylated interferon (PegIFN-α) and ribavirin combination therapy are used as standard therapy for chronic HCV infection. Treatment with a combination of standard interferon and Ribavirin has limited benefits because it can lead to resistance during long-term treatment and various side effects. Medicinal plants are one of the potential therapeutic sources for hepatitis drugs. In plants that contain chemical compounds such as flavonoids, terpenoids, lignans, sulfides, polyphenols, coumarin, saponins, furil compounds, alkaloids, proteins and peptides tend to inhibit replication cycles of different types of DNA or RNA. The profile of plant metabolites in one species may be different. This can be due to internal and external factors, these different factors can cause different activities. Family rutaceae is a plant that has been widely reported to have activity as an anti-viral hepatitis C. Objective: explain the activity of family rutaceae as antiviral hepatitis C.

Keyword: Antivirus Hepatitis C, Family Rutaceae, Profil Metabolit

I. INTRODUCTION

Hepatitis virus is one of the health problems in the world because it causes the death of millions. According to WHO it is estimated that the number of deaths due to hepatis C is 333,000 in 1990, 499,000 in 2010 and 704,000 in 2013. Increasing the number of deaths illustrates the high incidence rates of hepatitis C virus for decades. Hepatitis can be caused by various viruses such as hepatitis A, B, C, D, and E virus. In its development of hepatitis virus that is not treated properly it can develop into cirrhosis and liver cancer (1). In general, people suffering from hepatitis C do not cause specific symptoms. Symptoms that are usually felt include fever, fatigue, vomiting, headache, stomach pain or loss of appetite (2). In the world of treatment has not been found any hepatitis C vaccine. Hepatitis C recommended therapy is generally a combination of pegylated interferon alfa (pegIFN-α) and ribavirin given for 12-71 weeks. However, treatment with a combination of pegylated alfa pegifN (pegIFN-α) and ribavirin is only successful in patients infected with hepatitis C with certain genotypes alone and causes side-effects of headache, fatigue, myalgia, depression, neutropenia, thrombocytopenia and costly (3). Medicinal plants are one of the potential therapeutic sources for drug hepatitis. In plants that contain chemical compounds such as flavonoids, terpenoids, lignans, sulfids, polyphenols, coumarins, saponins, furils, alkaloids, proteins and peptides tend to inhibit replication cycles of different types of DNA or RNA (4). The profile of plant metabolites in one species may be different. This can be due to internal and external factors. Internal factors include genetic factors and physiological variations. While external factors such as environmental factors, temperature, humidity, light intensity, water intake, minerals and CO2 content (5). Other environmental factors include climate change, fertilizer use, microorganism damage, radiation induced stress, UV, heavy metals and pesticides (6). Several studies have reported that family rutaceae has activity as an anti-hepatic virus C among others Melicope latifolia, and Ruta angustifolia. In this journal will discuss about antiviral activity hepatitia C from family Rutaceae.

II. HEPATITIS C

Hepatitis is generally defined as inflammation or inflammation of the liver which can be caused by several mechanisms including infectious agents. Hepatitis C virus can be caused by various viruses such as Hepatitis A, B, C, D, and E viruses. Characteristics of this liver disease is the occurrence of jaundice or jaundice and the cause is not just a virus. Appropriate diagnosis can only be established by examination of specific antibodies in the patient (7). Hepatitis C is caused by a hepatitis C virus infection (HCV) which is a single chain RNA virus and beramplop. This virus infects liver cells and causes severe inflammation of the liver resulting in various complications in the long run. Symptoms caused by this disease are not specific that are characterized by anorexia, abdominal discomfort, nausea and vomiting, fever, and jaundice occur in about 25% of patients and are less common than hepatitis B. Of HCV-infected patients about 40% of they recovered completely but 20% of patients progressed to cirrhosis of the liver and more than 20%

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developed into liver cancer (7).

Hepatitis C virus is an RNA virus that has a diameter of 50 nm and has a length of 9.6 kb (WHO, 2014). Hepatitis C virus is classified in the genus Hepacivirus and familia flaviviridae. This virus has a varied genome and various subgenotypes. The genome of HCV has a high mutation ability because HCV is an RNA virus and has less efficient proofreading capabilities. HCV has a rapid mutation in the hypervariable region of the genome that encodes for envelope proteins and causes immune loss from the host. As a result many people infected with HCV develop into chronic infections. Hepatitis C virus (HCV) is mostly transmitted by contact with blood infected by HCV. This can occur through blood transfusions and blood products contaminated by HCV, contaminated injections during medical procedures, and through injecting drug use. HCV is not spread by nursing mothers, sneezing, coughing, and hugging (7).

Symptoms that usually arise from chronic infection are exhaustion on a continuous basis and some other symptoms, namely pain in the quadrant, nausea and decreased appetite. Chronic liver inflammation in patients with chronic HCV infection may result in liver fibrosis. The rate of progression of fibrosis may vary and can not be used as a benchmark for the development of cirrhosis. Approximately 20% of patients with chronic HCV infection will develop liver cirrhosis (8). HCV consists of a viral component (green ball) that is bound to lipoproteins (yellow balls). Viral particles enter the hepatocytes using at least 4 factors including SR-B + cholesterol transporter. The entry of HCV into the cell occurs through the endocytosis endeptor. Upon arriving at the beginning of the endosome, fusion envelopes the virus with the endosome and releases the genome (genetic material) into the cytosol. RNA virus is then translated into viral polyproteins. Non-structural proteins NS3 to NS5B form a replication complex associated with an ER derivative membrane called a web membrane and replicate the genome. After the neosynthesized accumulation of genomic RNA and viral proteins, HCV particles are assembled in an ER-related compartment close to the path of VLDL biogenesis. Then, the HCV particles that bind to the lipoproteins, are sent to the secretory pathway (out of the cell) (9)

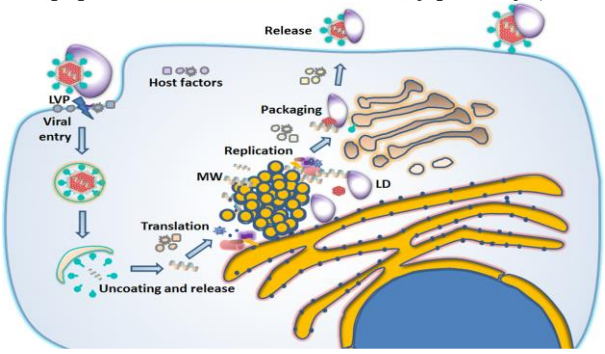

Fig 1. Life Cycle of Hepatitis C
(Carnero elena, 2015)

III. HEPATITIS THERAPY

Standard treatment for hepatitis C virus (HCV) is a combination therapy Pegylated Interferon (PegIFN-α) and Ribavirin (RBV) used for 48 weeks. IFN is a protein made by various cells of the immune system, including white blood cells. IFN is made in response to foreign cells including viruses, bacteria, parasites, and tumor cells. (10). Ribavirin is an intracellular phosphorylated guanosine analogue in host cell enzymes. This drug is used with interferon alfa. Ribavirin treatment should be given according to weight

IV. METABOLITE PROFILING

A plant can have different chemical composition due to internal and external factors. Internal factors include genetic factors and vision and external factors including environmental factors, temperature, humidity, light intensity, water intake and CO2 content (5). Other influential environmental factors include climate change, fertilizer use, radiation induced stress, UV, metals, and pesticides (Canas et al., 2015). The factor that causes the diversity of metabolites in plants, it is estimated that a plant has 5000-10,000 metabolites with a total probability of reaching 200,000 different structures in the plant kingdom (Colquhoun, 2007). C. rosesus plants from different regions with different altitude

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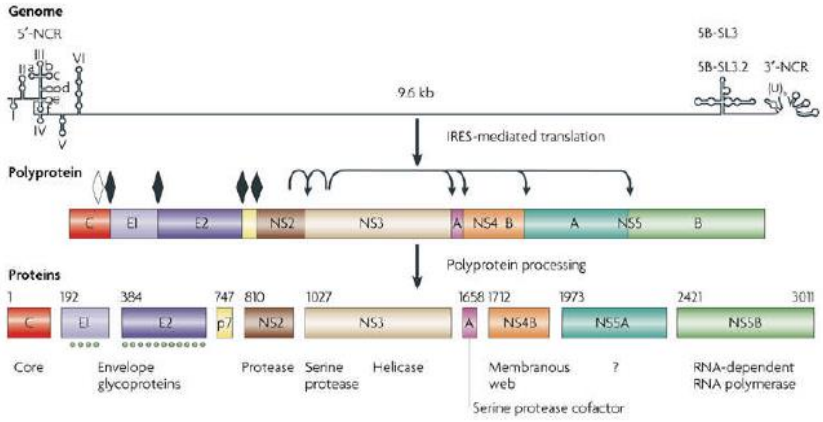
places resulted in differences in the metabolite content of phenolic compounds which resulted in different activities.

V. ANTI HCV ACTIVITY FROM FAMILY RUTACEAE

Several studies have reported that the Rutaceae family of Ruta angustifolia and Melicope latifolia have activity as anti-virus Hepatitis C.Tanaman Melicope latifolia is a plant from family Rutaceae. This plant in Indonesia is better known as Kisampang. This tree typically has a height of about 20 m, commonly found in primary and secondary open forests. Melicope latifolia plants are distributed in peninsular Malaysia, Philippines, Java, Kalimantan and Papua New Guinea. Melicope latifolia grows at an altitude of 600 m above sea level. Melicope latifolia plant has a high economic value, where the wood is used as a building material. In addition, the plant is also used in traditional medicine as a medicine for fever and abdominal cramps (12). Based on Wahyuni et al (4) ethanol extract 80% of Melicope latifolia leaf from Cangar forest, East Java showed potential activity as anti viral hepatitis C with IC50 3.5 ± 1.4 µg / ml against J6 / JFH1 virus and can inhibit hepatitis C virus on entry and post entry. Hepatitis C virus is an RNA virus that has a diameter of 50 nm, classified in the genus Hepacivirus and Flaviviridae family. Hepatitis C virus consists of positive-strand RNA, 9,6-kb, the genome encoding polyprotein precursor of about 3,000 amino acids (13). Viral particles enter the hepatocyte cells using at least 4 factors including cholesterol transporter Scavenger receptor class B member 1 (SRBI). The introduction of VHC into cells occurs through endocytosis receptors. Arriving at the beginning of endosomes, there is a fusion envelope of the virus with the endosome and releasing 12 genomes (genetic material) into the cytosol. Ribonucleic acid virus is then translated into polyproteins that are processed to produce viral proteins. Non-structural proteins form the replication complex associated with the derivative membrane The endoplasmic reticulum (RE) is called the web membrane and replicates the viral genome. After the accumulation of genomic RNA synthesis and viral proteins, VHC particles are assembled in an RE-related compartment close to the path of Very-Low-Density Lipoprotein (VLDL) biogenesis. Then, VHC particles binding to lipoproteins, are sent to secretions or out of cells (14).



Gambar 2. Genom virus hepatitis C

The anti-hepatitis C blocking mechanism is divided into 1). Damage virion of hepatitis C virus (virusidal activity); 2). Inhibits VHC bonding with target cell receptors; 3). Inhibits VHC absorption process into target cells; 4). as well as post entry step inhibiton which includes inhibiting viral RNA genome replication, inhibits the formation of non-structural proteins, the formation of viral progeny, and release of virions (15,16).

Ruta angustifolia is a Rutaceae plant that has been used traditionally as a jaundice remedy. In vitro testing of anti-hepatitis C activity of ethanol extract and Ruta angustifolia on Huh7it hepatocyte cells was performed in previous studies and indicated potential growth in hepatitis C virus. Then continued anti-hepatitis C against the fraction of the ethanol extract. Five of the seven fractions showed potential activity of fractions II, III, IV, VI, and VII with IC50 of 4.3µg / ml, 9.8 µg / ml, 8.62 µg / ml, 4.1µg / ml and 4.4, respectively µg / ml (17).

From the literature study the plant species of the genus melicope contain alkaloids, flavonoids, benzopyran, acetophenon (18,19,20). *Melicope tryphylla* obtained 6 flavonoid, 3,5- dihydroxy -7,8- dimethoxy- 3',4'-methylenedioxyflavone (1), 3,5 –dihydroxy- 7- isopentenyloxy-3',4'-methylenedioxyflavone (2), 3,5- dihydroxy- 7-isopentyloxy- 8- methoxy- 3',4'methylenedioxyflavone (3), 5- hydroxy-3-isopentenyloxy-7-methoxy-3',4' –

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methylenedioxyflavone (4), 5- hydroxyl- 3,7-dimethoxy-3',4'-methylenedioxyflavone (5), 5- hydroxyl- 7-isopenteneloxy- 3,8- methylenedioxyflavone (6) (21)

VI. CONCLUSION

Plants from the Rutaceae family Melicope latifolia and Ruta angustifolia, are reported to have activity as antiviral hepatitis C. In plants that contain chemical compounds such as flavonoids, terpenoids, lignans, sulfids, polyphenols, coumarins, saponins, furils, alkaloids, proteins and peptides can inhibit the replication cycle of different types of DNA or RNA. The plant metabolite profile of one species may be different due to internal and external factors. This difference can lead to different activities.

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