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NEURAMINIDASE INHIBITOR ACTIVITY OF GARCINIA PLANT : A REVIEW

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A B S T R A C T

Influenza is a respiratory infectious disease caused by influenza viruses. Indonesia is a country with the highest percentage of cases of death in the world in 2002. Management of influenza generally uses neuraminidase inhibitor agents, but the emergence of resistance in these agents decreases its effectiveness. Herbal plants and natural products are rich resources for the development of new anti-influenza drugs. The Garcinia genus is the most investigated plant species regarding pharmacological activity including as hypolipidemic, anti-ulcer, antioxidant, anti-inflammatory, anticancer, antimicrobial, antiviral and anti-influenza agents. Based on the literature study, there were 5 plants of the Garcinia genus that had been studied on anti-influenza activity, namely G. Mangostana, G. atroviridis, G. multiflora, G. Afzelli, and G. cola. Among the 5 plants, Garcinia mangostana showed the highest activity with inhibition of IC50 0.27 and 2.2 µM by smeaxanthone A and ɣ-mangostin respectively. Garcinia mangostana has the potential as a natural source for the development of anti-influenza drugs.

INTRODUCTION

Influenza (flu) is an acute respiratory infection that is caused by influenza viruses. Influenza is a pandemic that is responsible for the deaths of 20 to 40 million people worldwide. One of the worst cases of this disease occurred in 1918 known as "The Spanish Flu" (C. F. Basler, 2007). Influenza is referred to as Highly Pathogenic Avian Influenza (HPAI) because it produces 50% more presentation of mortality (Skeik and Jabr, 2008). According to WHO, Indonesia is the country with the highest percentage of deaths in the world where 161 deaths from 193 cases in 2002 (WHO, 2013).

Influenza viruses belong to the Orthomyxoviridae family with a single RNA strand. Influenza is divided into four types, namely A, B, C and Thogotovirus where types A and B are relevant to cause disease in humans (Wright and Webster, 2001). Influenza has two glycoprotein antigens namely neuraminidase (NA) and hemagglutinin (HA) on the surface of the virion which functions to bind to host cells (King, Hippe and Weiser, 2006). Neuraminidase is the main target for inhibiting influenza virus activity. Some drugs have been found and used intensively in inhibiting neuraminidase activity, namely neuraminidase inhibitor agents (Memoli, Morens, and Taubenberger, 2008).

There are 3 neuraminidase inhibitor agents that have been launched on the market, one of which is oseltamivir, which is the first oral neuraminidase inhibitor available as a prodrug and is the agent of choice in overcoming flu pandemics in many countries. Zanamivir is approved by the FDA as an inhaled neuraminidase inhibitor and intravenous Peramivir form approved in 2009-2010 (Kim *et al.*, 1997; Li *et al.*, 1998; Gubareva *et al.*, 2000) But with the emergence of cases of resistance caused by mutations in viral genes can reduce the effectiveness of treatment of this agents (Nguyen H. T. *et al*, 2012). So from that, another source is needed as an alternative to the development of anti-influenza drugs.

Herbal medicines and purified natural products are rich resources for the development of new anti-influenza drugs, one of which is a group of plants originating from the genus Garcinia. Garcinia is the largest genus in the family Guttiferae (Clusiaceae) which consists of nearly 450 species of tropical trees and shrubs with yellow resin. In Indonesia, there are 64 types of Garcinia found based

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on examination of herbarium collections and literature studies. Overall, 6 species including cultivated plants (G. atroviridis, G. beccari, G. dulcis, G. mangostana, G. nigrolineata and G. parviflora), 58 species as wild plants, 22 species as edible fruit, and 21 species as wood plants (Nguyen, 2015; Hemshekhar *et al.*, 2011; Sobir *et al.*, 2011).

There are approximately 107 plant species of the genus Garcinia that has been investigated, including the content of each part of the plant. A variety of secondary metabolites are known to have pharmacological activity as hypolipidemic agents, anti-ulcers, antioxidants, anti-inflammatory, anticancer, anti-oxidative stress, antihepatotoxic, antimicrobial, antifungal, antibacterial, antiprotozoal, antiviral and anti-influenza (Nguyen, 2015; Hemshekhar *et al.*, 2011; Grienke *et al.*, 2011). Based on the description above, the plant genus Garcinia has the potential as a source of development of new anti-influenza drugs. Therefore this review aims to provide information about the potential for anti-influenza activity from the genus Garcinia.

Primary data search is done online through a web browser by typing the source address that has trusted scientific journal publications such as Pubmed, Google Scholar, and Science Direct. Search is continued based on sources from the library. The inclusion criterion is a collection of scientific articles that contain data on the potential for anti-influenza in the genus Garcinia with the average publication time of the last 15 years. The literature which has a publication time of more than 15 years is used as supporting data.

RESULT

Based on the search for scientific articles, the authors obtained 5 genes of Garcinia genus that have been studied regarding anti-influenza activity, namely G. Mangostana, G. atroviridis, G. multiflora, G. Afzelli, and G. cola.

Garcinia Mangostana

Testing of anti-influenza activity has been carried out both in silico, in vitro and in vivo. Screening of in silico influenza neuraminidase inhibitory activity was carried out by Lee et al (2003), where phenolic active compounds from Reynoutriaelliptica plant extracts had the highest inhibitory activity against neuraminidase C.perfringens. The subsequent application of in silico testing by Grienke et al (2009) has found 4 diarylheptanoid group compounds which have inhibitory activity against bacterial neuraminidase. Virtual screening of 3000 natural compounds using the Pharmacophore-based screening method has also been conducted. The screening results succeeded in obtaining 167 active compounds which were then docked to the active site of neuraminidase. Chlorogenic acid compounds (MSC927) are defined as compounds with the best belay value compared to DANA (2-deoxy-2,3-didehydro-N-acetylneuraminic acid), which is an endogenous analog which is used as a lead compound that can inhibit neuraminidase activity. Validation from the results of the Pharmacophore-based screening and docking method has been proven both statistically and experimentally (Muchtaridi et al, 2014).

Virtual screening methods for the Garcinia mangostana plant have also been carried out. Ikram et al (2015) succeeded in identifying 5 types of plants (G. mangostana, E. longifolia, T. divaricata, M. charantica, and B. javanica) with compounds that were predicted to optimally have neuraminidase inhibitory activity against the H5N1 sub-type virus. The results showed that the fractions and extracts of the 5 plants provided good to moderate inhibitory activity on neuraminidase H5N1. The methanol extract of G. mangostana has the highest inhibitory activity of 82.95% at a concentration of 250 µg/ml based on the MUNANA assay. Predicted IC50 values or inhibition constant (Ki) from G. mangostana compounds were 89.71, 91.95, 95.49 and 126.64 µM for rubraxanthone, α-mangostin, garcinone C and Gartanin respectively. Gartanin is a compound of G. mangostana with the smallest free bond energy value that is equal to -11.07 kcal/mol.

In vitro research conducted by Ryu *et al.* (2010) showed that 12 isolates of xanthone compounds from mangosteen seeds (G. mangostana) had neuraminidase inhibitory activity. The isolate compounds are (1) β-mangostin, (2) 9-hydroxycalabaxanthone, (3) mangostanol, (4) α-mangostin, (5) garcinone D, (6) ɣ-mangostin, (7) cudraxanthone, (8) 8-deoxygartanin, (9) gartanin, (10) smeaxanthone A and two new isolates namely (11) mangostenone F and (12) mangostenone G. Neuraminidase inhibitory activity was measured using MUNANA (2 '- (4-methyllumbelliferyl) -aDN-acetylneuraminic acid) as a substrate and neuraminidase C. perfringens as an enzyme. The results showed that all xanthone isolates had a competitive inhibitory effect on neuraminidase activity with IC_{50} values ranging from 0.27-65.7 µM. The highest neuraminidase inhibition activity was shown by compounds (10) smeaxanthone A and (6) ɣ-mangostin with IC_{50} values of 0.27 and 2.2 µM respectively.

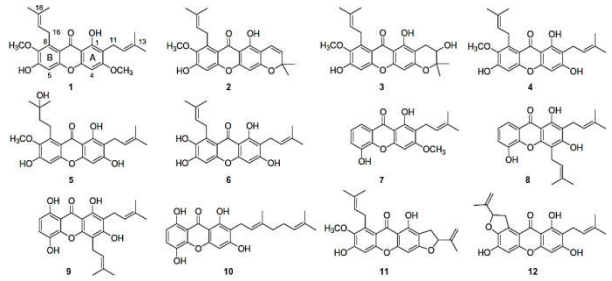

Figure 1 Chemical structure of compound isolates Garcinia mangostana (Ryu *et al.*, 2010)

Xanthone compounds are secondary metabolites with unique structures that have an aromatic tricyclic system (C6-C3-C6). Xanthone compounds have been found in several high-level plant families, at least 68 types of xanthone compounds found in various parts of the plant Garcinia mangostana. The most xanthone compounds found in mangosteen peel are α- and γ-mangostin compounds (Obolskiy *et al*, 2009).

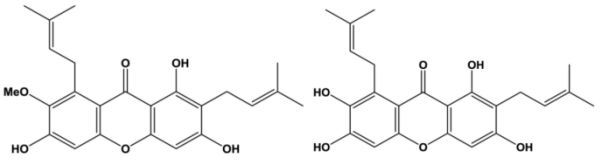

Figure 2 The chemical structure of compounds (a) α-mangostin and (b) γ-mangostin (Gutierrez-Orozco and Failla, 2013)

Garcinia Atroviridis

Research conducted by Muchtaridi *et al* (2015) showed that methanol extract of Garcinia atroviridis fruit had neuraminidase inhibition activity of C. perfringens and H5N1 neuraminidase bacteria with IC_{50} values of 9.43 µg/mL and 5.15 µg/mL respectively. Other studies regarding extracts and fractions of dried fruit at G. atroviridis have investigated neuraminidase activity of H5N1 influenza virus in vitro using the MUNANA (2 '-(4-methyllumbelliferyl) -a-D-N-acetylneuraminic acid) method as a substrate. The results showed ethanol extract, ethyl acetate fraction, n-hexane fraction and G. atroviridis water fraction had inhibitory activity of neuraminidase with IC_{50} values of 207.2 µg / mL, 50.92 µg / mL, 1227.10 µg / mL, and 159.1 µg/mL respectively -accordingly The highest neuraminidase H5N1 inhibition activity was shown by ethyl acetate fraction (Nurwada, 2017).

Garcinia Cola

Kolaviron compound is a biflavonoid group from Garcinia cola plant extract which has been investigated in vivo to have antioxidant activity and immunomodulators which are effective in inhibiting the development of clinical symptoms due to influenza virus infection. Research conducted by Awogbindin *et al* (2015) aimed to examine the protective effects of Kolaviron compounds on BALB / c strain rats that were induced by influenza A / Perth / H3N2 / 16/09 (Pr / H3N2) viruses. The Kolaviron dosage given is 400 mg/kg orally to the test group with 3 days, 3 hours and 1 hour before induction of the influenza virus. Measurements of Pr / H3N2 in the lungs are detected through the amount of hemagglutination, whereas oxidative stress biomarkers and inflammation are measured through two organs, namely the lungs and liver (Awogbidnin *et al.*, 2015).

The results showed that giving a single dose of Kolaviron at 1 hour, 3 hours and 3 days before induction of influenza viruses could improve aeration and consolidation of the lungs. Kolaviron immunomodulatory activity can increase inflammatory cell infiltration against viral clearance while its antioxidant activity can affect the activity of myeloperoxidase and the production of nitric oxide thereby increasing the preservation of lung and liver organ function. Indirectly, the mechanism of antioxidant activity and immunomodulators of Kolaviron compounds can improve morbidity and can reduce mortality due to influenza virus infection (Awogbidnin *et al.*, 2015).

Garcinia Afzelii

Lannang *et al.* (2010) conducted a study of anti-influenza, anti-HIV and cytotoxic activity of 13 compounds of hexane extract isolates of Garcinia afzelii Engl seeds. Two new isolates were found, namely (1) guttiferone O and (2) 3-methoxycheffouxanthone and 11 other polyphenol isolates which had been previously isolated (3) 2-hydroxy-1,7-dimethoxyxanthone, (4) smeathxanthone A, (5) 1,5-dihydroxyxanthone, (6) 1,6-dihydroxy-5-methoxyxanthone, (7) cheffouxanthone, (8) 1,3,5-trihydroxyxanthone, (9) smeathxanthone B, (10) isoxanthochymol and (11) guttiferone E.

The method of testing anti-influenza activity was carried out in vitro using MDCK cells induced by influenza subtype A/H1N1, A/H3N2, and sub-type B. Activity measurements were assessed by microscopy based on CPE (Cytopathic Effect). Positive controls used in anti-influenza testing were oseltamivir carboxylic and ribavirin, while cytotoxic testing was measured using normal MDCK cells based on the value of MCC (Minimal Cytotoxic Concentration) (Neasens *et al.*, 2009). Anti-HIV activity was carried out using colorimetry with azithromycin as a positive control. The results showed 11 polyphenol isolates were not able to inhibit the cytopathic effect of influenza subtype A/H1N1, A/H3N2 and sub-type B infections at sub-toxic concentrations. Some isolates showed toxicity to MDCK cell measurements with MCC values ≤4 µg / mL. Anti-HIV testing also shows that none of the isolates can inhibit HIV-1 or HIV-2 virus replication in sub-toxic concentrations (Lannang *et al.*, 2010).

Gacinia Multiflora

Volkensilflavone compounds are biflavonoid isolates from the Garcinia multiflora plant. Research conducted by Lin et. al (1999) showed the inhibitory activity of influenza virus infection by volkensilflavone and ether derivatives, volkensilflavon hexamethyl ether. Test methods carried out on influenza A / Texas / 36/91 (H1N1), A / Beijing / 2/92 (H3N2) and B / Panama / 45/90 influenza viruses in vitro using MDCK and ribavirin cells as positive controls.

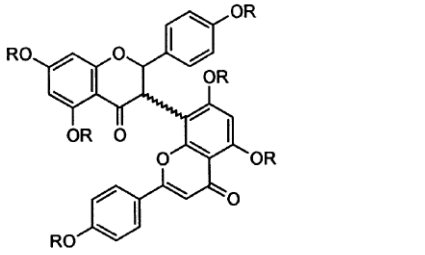

Figure 3 Structure of volcensylflavone and volcensylflavone hexamethyl ether compounds

The results showed inhibition of CPE (Cytopathic Effect) by volkensilflavone isolates had an EC_{50} of > 32 µg/mL (IC_{50} = 13 µg / mL), 56 µg/mL (IC_{50} = 42 µg / mL) and 1.1 µg/mL (IC_{50} = 38 µg / mL) for influenza A / Texas / 36/91 (H1N1), A / Beijing / 2/92 (H3N2) and B / Panama / 45/90 viruses, respectively. The inhibiting activity of ether derivatives, volkensilflavon hexamethyl ether decreased compared to volensensilflavone. Compared with positive control of ribavirin which had activities of EC_{50} 1.9 µg / mL (IC_{50} = 562 µg / mL), 4.1 µg/mL (IC_{50} = 562 µg / mL) and 1.5 µg/mL (IC_{50} ≥ 1000 µg / mL) respectively -one for influenza A / Texas / 36/91 (H1N1), A / Beijing / 2/92

(H3N2) and B / Panama / 45/90. influenza viruses, volkensilflavone has a small inhibitory activity against influenza viruses (Lin *et al.*, 1999).

CONCLUSION

Based on the description above it can be seen that the genus Garcinia has an influenza neuraminidase inhibitory activity. There are 5 genes of Garcinia genus that have been studied regarding anti-influenza activity, namely G. Mangostana, G. atroviridis, G. multiflora, G. Afzelli, and G. cola. Among the 5 plants, G. mangostana is the genus Garcinia which has the most potent anti-influenza activity compared to other plants so that it can be a reference for the next development process. Garcinia mangostana (mangosteen) showed inhibitory influenza activity with IC_{50} values of 0.27 and 2.2 μM for smeaxanthone A and mang-mangostin respectively. The journal study is expected to provide information on the development of alternative anti-influenza drugs from natural ingredients.

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