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Literature Review

Piperin and piplartin as natural oral anticancer drug

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ABSTRACT

Background*: Since the last few decades, oral cancer as pathology has become an attention in medicine and dentistry. The majority cases of oral cancer are affecting people with smoking habit and alcohol consumption. Many herbs contain substances which can stop cancer cells proliferation, such as Piper retrofractum/Retrofracti fructus, an herb plant from Piperaceae family which contains piperin and piplartin.* ***Purpose****: The purpose of this study was to examine the mechanism of piperin and pilplartin as natural oral anticancer drug.* ***Reviews****: Piperin and piplartin has function as antioxidant that can protect body cell from damage caused by free radicals. Piperin works synergistically with another bioactive substance like capsaicin and curcumin. Piperin increase the number of serum and life time of serum from a few nutrition substance like co-enzyme Q10 and beta-carotene. Beta-carotene can catch reactive O_2 and peroxil radicals. The activity of anticancer piplartin related with obstruction of proliferation cell rate, observe form Ki67 reduction as antigen in nucleus that associated with G1, S, G2, and M phase in cell cycle. Comparing with piplartin, piperin is more potential to inhibit proliferation rate of Ki67, but piplartin's antiproliferation mechanism will increase if supported by piperin.* ***Conclusion****: Piperin and piplartin contained in Javanese chili are potential for natural oral anticancer, by directly or indirectly suppress tumor cell development by increasing the number of immunity cells (immunomodulator), and by inhibiting cell proliferation with reduction of Ki67, nucleus antigen that associated with G1,S,G2, dan M phase of cell cycle.*

Key words*: Oral cancer, piperin, piplartin*

ABSTRAK

Latar belakang*: Sejak beberapa dekade terakhir, patologi kanker rongga mulut telah banyak menjadi perhatian di bidang kedokteran dan kedokteran gigi. Risiko paling tinggi ditemukan pada penderita perokok dan peminum alkohol. Banyak tanaman herbal yang memiliki kandungan untuk menghambat pertumbuhan sel kanker atau antiproliferasi sel, seperti tanaman herbal yang berasal dari suku Piperaceae, salah satunya adalah cabe jawa (Piper retrofractum) yang mengandung piperin dan piplartin.* ***Tujuan****: artikel ini bertujuan untuk mengetahui mekanisme kerja piperin dan pilplartin sebagai antikanker alami rongga mulut.* ***Tinjauan pustaka****: Piperin dan piplartin berfungsi sebagai antioksidan yang dapat melindungi sel tubuh dari kerusakan akibat radikal bebas. Piperin bekerja secara sinergis dengan zat-zat bioaktif lainnya seperti capsaicin dan curcumin. Piperin meningkatkan jumlah serum dan umur serum dari beberapa substansi nutrisi seperti koenzim Q10 dan betakaroten. Betakaroten mampu menangkap oksigen reaktif dan radikal peroksil. Aktivitas antitumor piplartin berhubungan dengan penghambatan laju proliferasi sel, ditinjau dari reduksi Ki67 yaitu antigen pada inti sel yang berasosiasi dengan G1, S, G2, dan M pada siklus sintesa sel. Dalam mekanisme kerjanya piplartin akan lebih meningkat aktivitas antiproliferasinya jika disinergiskan dengan piperin.* ***Kesimpulan****: Piperin dan piplartin yang terkandung dalam cabe jawa berpotensi sebagai antikanker rongga mulut alami, dengan menekan perkembangan sel tumor baik secara langsung*

maupun tidak langsung melalui peningkatan sel imun (immunomodulator), dengan penghambatan laju proliferasi sel, ditinjau dari reduksi Ki67, yaitu antigen pada inti sel yang berasosiasi dengan G1, S, G2, dan M pada siklus sintesis sel.

***Kata kunci**: Kanker rongga mulut, piperin, piplartin*

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INTRODUCTION

Since the last few decades, oral cancer as pathology has become an attention in medicine and dentistry among health professionals and the public because there is increased death rate and number of cancer patients. According to World Health Organization (WHO), each year the number of cancer patients in the world increased to 6.25 million people. In the next 10 years an estimated of 9 million people will die each year by cancer. Two-thirds of cancer patients in the world will be in developing countries.[1] Highest risk was found in tobacco smokers and alcoholic dringkers. Expenses incurred for treatment of cancers in developed countries is still quite high. It is also felt by the developing countries. The spread of cancer cases is due to the low level of public awareness on the danger of cancer, the high cost of treatment and care, leads to only certain people who can cover medical cost, even though cancer treatment can only slow down the spread of cancer cells.[2]

Many curative measures has been taken to cope the oral cancer include radiation therapy, chemotherapy, surgery, and combination therapy. Radiation therapy is a treatment that uses an ion light that can destroy the DNA cell in cancer cells, so cancer cells can not grow. Radiation therapy has side effects depend on the area treated, dose, and distance to the cancerous tissue lesions that rapidly divide. Long-term effects of this radiation therapy include infertility, fibrosis, permanent hair loss, osteoradionecrosis, and others. Chemotherapy is one form of palliative therapy, used when the cancer recurs or metastasis occurred. Chemotherapy uses chemicals that destroy cancer cells. The side effects of this therapy are fatigue, nausea and vomiting, digestive disorder, hair loss, weakness in the muscles and nerves, disorders of blood formation, and others. Surgery is often performed when the lesion involves throat, but can also be done in the oral cavity. Surgery is performed to remove the entire lesion to prevent the spread of cancer cells in the lymph nodes, blood vessels, and nerves. Combination therapy is a combination of several therapies. [3] On the whole oral cancer therapies that exist today still have an adverse effect on patients. To cope with an increasing number of patients with oral cancer cases, especially in developing countries, need effective and efficient efforts. One of the efforts is the prevention of oral cancer. In addition, prevention efforts should be affordable by all levels of society to reduce the number of cancer patients.

Empirically herbs are believed to have optimal efficacy in curing various diseases. Many herbal plants that contain substances to inhibit cancer cell growth or antiproliferrative cell, such as herbal plants from the family of Piperaceae. Javanese chili (*Piper retrofractum*) with the content of piperine and piplartin can act as anti-proliferative cells, where both substances are also found in black pepper. Piperine and piplartin also serves as an antioxidant that may protect body cells from free radical damage. These herbs can be used as an alternative to oral cancer prevention (chemo-prevention).[4–6] Piperine pharmacological effects are antioxidant, antipyretic, analgesic, anti-inflammatory, and central nervous system suppressor. Pharmacological effects as anti-proliferative piplartin is a substance that can inhibit cell growth and reduce cells number.[7]

Javanese chili is a plant easily found in Indonesia compared to black pepper, cayenne and the market price is relatively cheaper to black pepper. Javanese chili contains about 2.03 to 3.65% piperine, while the level of black pepper piperine is around the 3–5%. [8,9] Although the levels of piperine in black pepper is higher, it is still possible to continue using Javanese chili as a natural oral anticancer.

This review describe the mechanism of piperin and piplartin as active ingredients in Javanese chili (*Fructus retrofracti*) as an alternative natural oral anticancer drug (oral cancer chemo-prevention).

Oral cancer

Cancer is a disease caused by abnormal and uncontrolled cells mutations. If cell growth is not stopped then the growth will continue slowly. If the cancer has invaded a cell or group of cells, the progress will be faster, doubled on an ongoing basis. Growth of benign (non-cancerous, benign) and malignant growth (cancer, malignant) can be derived from various tissues in and around the mouth, including the bones, muscles and nerves.[10]

Oral cavity cancer has a multifactorial cause and a process that consists of several stages, namely initiation, promotion and development of progressive oral cancer etiology.[8] Etiology of cancer can be grouped on local factors, environmental factors and host factors. Local factors include poor oral hygiene, chronic irritation of the restorations, dental caries, denture. Environmental factors, including chemical carcinogens and their use of cigarettes, tobacco, ionizing radiation, viruses, sunlight. Host factors, including age, gender, nutrition, immune response and

genetic. Etiologic factors are combination of three factors. In the last decades, the molecular pathogenesis of neoplasm suggests that the neoplasm is a genetic disease. Tumor formation as a result of genetic drift is caused by etiologic factors resulting in excessive and uncontrolled cell division. Genes that were target genetic changes are oncogenes (genes that promote growth), antioncogenes (genes that inhibit growth) and genes that regulate apoptosis.[11]

Signs to consider on the possibility of early oral cancer in advanced stages are the white patches, scaly, persistent, pigment spots which suddenly increase in size, this non-healing ulcer, swelling and bleeding gums, which eventually forming progressive facial asymmetry.[12] Early stages of oral cancer does not cause pain and are usually found on routine dental examination. Cancer on the floor of mouth is usually a squamous cell carcinoma, which looks like an open wound and tend to grow into the underlying structures. [13]

Javanese chili (*Piper retrofractum*)

Javanese chili plant height is between 10–12 meters long, with round trunk and woody, branching with soft consistency. The fruit is oval with light green color when young and red when matured. Small fruit size arranged into one shaped like a chili and a length of 2–7 cm. Spicy fruit flavors and smells fresh. Javanese chili fruit contains piperine, palmitic acids, tetrahydropiperic acids, 1-undercyclnyl-3, 4-methylenedioxy benzene, piperidine, essential oils, n-isobutildecatrans-2-trans-4-dienamide and sesamin. Meanwhile, the root contains piperine, piplartin and piperlongumin. Substances in its fruit essential oil contains in an amount of about 1% of dry weight. Essential oil contains 6% piperine. Researches in several countries stated that the average amount of Javanese chili essential oil almost the same as black pepper, about 0.9% consisting of 0.19% piperine alkaloids. Javanese chili fruit is used to cleanse the mouth, reducing mouth odor, reduce tooth pain, and treat gingivitis. Safety of Javanese chili fruit as a raw material have been studied in medicine and obtained the conclusion that use empirical form of Javanese pepper fruit infusion which is safe and classified as relatively harmless materials. Javanese chili fruit has androgenic, anabolic and anti-proliferative effect.[14]

Piperine and piplartin

Piperine is an alkaloid contained in the Piperaceae plant family. Piperine is potential as antioxidant, sedative, anti-inflammatory, antiproliferative and analgesic. Piperine also serves as an antioxidant that may protect body cells from free radicals.[15,16] Piperine is the solid substance and not soluble in water. The molecular structure of piperine is $C_{17}H_{19}NO_3$, molecule weight 285.34 Daltons. Piperine is a trans-trans stereoisomer of 1-piperoylpiperidine or known as (E, E)-1-[5-(1,3-benzodioxol-5-y1)-1-oxo-2,4-pentdienyl] piperidine.[17] Piperine may increase the activity of some nutritional substances and drug.[18] This drug have anti-inflammatory activity, analgesic, and support the metabolic process of digestion.[19,20] Piperine was found to be non-specific inhibitors on the metabolism of drugs and xenobiotics. Piperine inhibits the cytochrome P450 as well as hepatic UDP-glucuronyltransferase and arylhydrocarbon hydroxylase and other enzymes contained in the drug and xenobiotic.[21,22] Many studies have shown that piperine can inhibit lipid peroxidation. Piperine has been shown to stimulate the secretion of digestive enzymes in pancreas such as amylase, trypsin, chymotrypsin and lipase in rats. Piperine work synergistically with other bioactive substances such as capsaicin and curcumin.[23,24] Piperine may increase the number and age of coenzyme Q10 and beta carotene. Beta carotene is able to capture reactive oxygen and peroxyl radicals that play a role in the process of cancer. Analgesic and antiinflammatory effects of beta-carotene-related activities as antioxidant.[25-27] There is evidence that piperine-containing antioxidant, anticonvulsant, anti-carcinogenic and anti-inflammatory.[28] Piplartin is an alkaloid contained in Piperaceae plant family. Piplartin is potential as anti-proliverative agents. The chemical structure: {5,6-dihydro-1-[l-oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl]-2(1H) pyridinone}. Piplartin have antidepressant, cytotoxic, and anti-proliferrative effects.[30]

DISCUSSION

Oral cancers in developing countries require effective prevention efforts. Curative attempts to cope with cancer of the oral cavity still cause adverse side effects and high cost. Use of medicinal herbs is increasingly popular among modern medicine and dentistry, including the use of herbs as natural anti-cancer drugs. One herb that potential as a natural anticancer is Javanese chili in Piperaceae plant family. Javanese chili containing active substance of piperine and piplartin possess anti-proliferative cells. Piperine and piplartin also serves as an antioxidant that may protect body cells from free radical damage. Piperine and piplartin can suppress tumor cell growth both directly and indirectly through increased activity of the immune system in advance (immunomodulators).[28] Circumstances that indicate the role of immune system in cancer is that a tumor can be cured. In patients with immune deficiency and received immunosuppression therapy, malignancy can be doubled to 200 times. Malignant transformation causes a change in the phenotype of normal cells, the loss component of the surface antigen, a neo-antigen, and other changes in the cell membrane. This will affect the immune response of antigen that stimulates the body to produce antibodies. Distribution of tumor antigens found is divided into 3 classes. Class 1 antigen is found only in certain tumors, are not found in normal cells as well as other malignancies. Class 2 antigens are found in tumors, and class 3 antigen is found in normal cells and malignant cells.[31]

Piplartin work synergistic with piperine. Khajuria et al., noted that piperine and piplartin showed positive activity in inhibiting some tumor cells. In research conducted in-

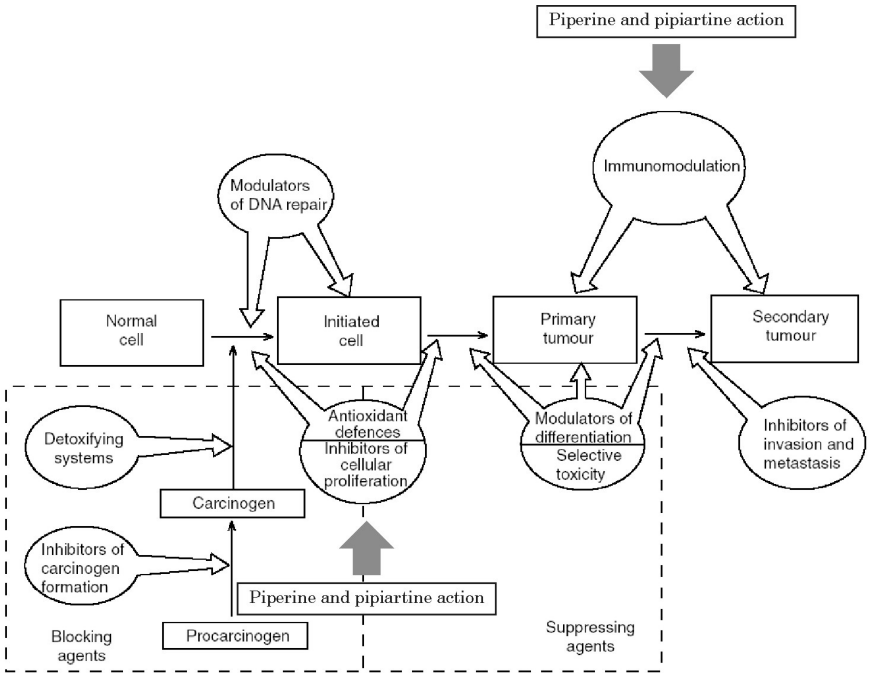

Figure 1. The role and mechanism of piperine and piplartin as anticancer drug.

vivo testing of antitumor activity of piperine and piplartin. In-vivo test involved 60 female mice in which each of 10 groups of mice transplanted with Sarcoma 180.[28] Analysis of histopathology and morphology of tumor cells with multiple organs such as liver, kidney, and lung, demonstrated piperine and piplartin as a treatment against the tumor cells. Piperine and piplartin with a dose of 50 or 100 mg/day continuously in 7 days can inhibit tumor cell growth in mice that had been transplanted with Sarcoma 180. The average resistance was 28.7–52.3% for piperine and 55.1-56.8% for piplartin. Piplartin antitumor activity associated with inhibition of cell proliferation rate, in terms of reduction of Ki67, an antigen on the cell nucleus that is associated with the G1, S, G2, and M on the synthesis of the cell cycle. Piplartin as an anticancer role in the initiation phase of the cell by inhibiting the rate of cell proliferation. Compared with piplartin, piperine is still not enough potential in inhibiting the proliferation rate of Ki67 antigen. However, the mechanism of action, will increase anti-proliferative activity of piplartin if synergized with piperin.[28]

Piperine and piplartin also serves as an antioxidant that may protect body cells from free radicals damage. This herb can be used as an alternative to oral cancer prevention (oral cavity cancer chemo-prevention).[4-6] The pharmacological effects of piperine as an antioxidant, antipyretic, analgesic, anti-inflammatory, and suppress the central nervous system. The pharmacological effects of piplartin as anti-proliferative agent, a substance that can inhibit cell growth and reduce the number of cells.[7]

Anti-cancer mechanism can be explained as follows (Figure 1): The first mechanism is an inhibition of carcinogens. Carcinogen inhibitor works as a barrier to the formation of procarcinogenic to be carcinogenic. The second mechanism is inhibition on the formation of cells initiation from normal cell. Cells initiation can lead to tumor cell if the cell promoter happens continuously. This mechanism plays a role in the formation of DNA repair or repair of the mutated DNA structure. The last mechanism is by inhibiting the formation of primary tumor cells into secondary tumor cells that more malignant or cancerous. Inhibiting agents that play a role in this mechanism is an immunomodulator. Immunomodulator will increase or decrease the body's immune cells in accordance with necessary needs.[32]

Piplartin as an anticancer role in the initiation phase of the cell by inhibiting the rate of cell proliferation. Piperine and piplartin also play a role in the stage of inhibition of primary tumor cells into secondary tumor cells by enhancing immune cell first (immunomodulator).[28] The content of active piperine and piplartin ingredient have shown that Javanese chili can be used as a natural alternative to oral anticancer drug. However, its use has not been optimal. A breakthrough is needed to process Javanese chili fruit as a natural oral anticancer drug that is easy to consume and apply in everyday use. Alternative processing of Javanese chili fruit as a natural oral anticancer may include food products such as candy, and product of dental care such as toothpaste and moutwash. Javanese chili fruit extracts can be added as instant

beverage to be consumed every day with the right dose. It can be concluded that piperine and piplartin contained in Javanese chili are potential as natural oral anticancer drug, by suppressing tumor cell growth either directly or indirectly through increasing immune cells (immunomodulator).

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