REVIEW ARTICLE

Potential of Flavonoids in Fruit Peel from Agricultural Waste on Cancer Cell Growth Through Expression of Ki 67: A Review

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ABSTRACT

Cancer is characterized by uncontrolled cell growth and division, cancer cells that are in the proliferative phase express several specific proteins and can be detected with certain monoclonal antibodies such as Ki-67, which can be used as a marker of cell proliferation. The fruit peel contains bioactive compounds. The aim of this review was to describe the potential of flavonoid fruit peels, which are agricultural wastes on cancer cell proliferation, by using search articles through the electronic database google scholar, pubmed, scopus, and sciencedirect. A review of the literature has been found that *Punica granatum, Citrus iyo, Citrus sinensis, Myrciaria jaboticaba,* and *Garcinia mangostana* fruit peels are sources of flavonoids, which can inhibit the proliferation of cancer, and it needs to be investigated further.

Keywords: Cancer, Fruit peel, Flavonoids, Ki 67

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INTRODUCTION

Cancer treatment with chemotherapy is the most basic approach, chemotherapy drugs exert their effects by interfering the cell cycle and the process of mitosis (1), despite the high success in stopping or controlling cancer progression, have the side effects that can be observed directly on the skin and hair, bone marrow, blood, gastrointestinal tract and kidneys. All organs of the body can be affected, including important organs, such as the heart, lungs and brain. As well as neurotoxicity can cause paresthesias, paralysis, ataxia, and coma. In addition, can occur drug resistance, carcinogenicity and infertility (2).

Agricultural production and food supply chains are major sources of biomass waste and pose unprecedented risks to soil, water pollution, and human health (3). Combating food waste is an important global challenge of the 21st century that is compatible with green and sustainable chemistry. Prevention by reducing the amount of food is not possible, so the right way is to reprocess waste into a product(4). Orange fruit waste is about 50-60% w/w (wet weight) of processed fruit of which 60-65% w/w consists of peel, 30-35% w/w internal tissue and seed residue (5). Research by Alacynet et al. the discarded parts of mango such as peel, husk seed, and seed have bioactive compounds (6), in line with that previous research on the measurement of total flavonoids in extract of several peel fruit such as mango peel (57.1 ± 2.4 mg/g), pomegranate peel (35.7 ± 4 mg/g), appel peel (26.6 ± 1.9 mg/g)(7), and citrus peel (1.90 to 5.51 mg CE/g) (8), which total flavonoids were found to be different in various maturation stages such as the mature *Garcinia mangostana* fruit peel (4.08 g quercetin equivalents/100 g) than the young fruit peel (2.91 g quercetin equivalents/100 g) (9), and total of flavonoid anthocyanins in *Myrciaria jaboticaba* peel (802.89 ± 22.88 (mg/100 g) (10), also other phytochemical compounds such as saponins, tannins, and alkaloids were found in the peel fruit (11).

Polyphenols are secondary metabolites of plants that can accumulate in leaves, fruits, roots, and stems. Polyphenolic compounds found in many plants are flavonoids (12), one source of flavonoid is fruit peel and the content varies in each species(13), flavonoids are secondary metabolites widely distributed in the plant kingdom(14) and has the effect of inhibiting the proliferation of cancer cells at various phases of the cell cycle(15).

Flavonoid bioactive compounds are interesting to study because of their antitumor effect and there are more than 5000 flavonoids with various pharmacological properties (16), and the one of the most important classes of natural compounds with successful preclinical outcomes in the management of cancer are flavonoids (17). Flavonoid compounds give color to fruit (18), although each color in the peel fruit has different levels of flavonoids (19), and flavonoid metabolites are more diverse in fruit peels because flavonoid compounds are more differentiated in the peel (20). The aim of this study was to describe the potential of flavonoid fruit peels, which are agricultural wastes on cancer cell proliferation through the examination of Ki-67.

METHODS

The method used in this study is literature review, the electronic data base used is google scholar, pubmed, scopus, and sciencedirect, with the keywords "Fruit peel, Cancer, Ki-67" obtained 10 journals google scholar, sciencedirect 5 journals, scopus 3 journals, and pubmed 3 journals, then categorized based on inclusion and exclusion criteria, such as IC1 = type of quantitative research, IC2 = English journal, IC3 = articles published between 2017 and 2022, and IC4 = no duplicates from google scholar, sciencedirect, pubmed, or elsevier then IC5 = selected articles based on the suitability of titles and abstracts, whereas studies were excluded if there was no data on fruit peel flavonoids on cancer proliferation through the examination of Ki-67.

RESULT

The results obtained 5 articles that are suitable for further study where the effects of flavonoids in fruit peels on cancer cell proliferation through the Ki-67 examination can be seen in table.

Table I : The effect of fruit peel flavonoids on the expression of Ki-67

Plant	Title	Results
Punica granatum	Standardized Punica granatum pericarp extract, suppresses tumor proliferation and angiogenesis in a mouse model of melanoma: possible involvement of PPARα and PPARγ pathways (27)	Expression of Ki-67, VEGF and CD31 decreased dose dependently in Melanoma animal models
Citrus sinensis	Protective and curative role of *Citrus sinensis* peel on cadmium-induced testicular and spermatic damage: a morphometric and immunohistochemical evaluation using monoclonal antibodies against Ki-67 and proliferating cell nuclear antigen (32)	Expression of Ki-67 and PCNA decreased in Cadmiu -induced testicular tumor model animals
Myrciaria jaboticaba	Beneficial effects of anthocyanin-rich peels of myrtaceae fruits on chemically-induced liver fibrosis and carcinogenesis in mice (10)	Reducing ki-67 expression on hepatocarcinogenesis in mice
Citrus iyo	Supercritical fluid extraction of *Citrus iyo* hort. ex tanaka pericarp inhibits growth and induces apoptosis through abrogation of STAT3 regulated gene products in human prostate cancer xenograft mouse model (41)	Decreases KI-67 expression in prostate cancer cells
Garcinia mangostana	α-Mangostin suppresses the de novo lipogenesis and enhances the chemotherapeutic response to gemcitabine in gallbladder carcinoma cells via targeting the AMPK/SREBP1 cascades (48)	Decreased levels of proliferation with reduced Ki-67 expression

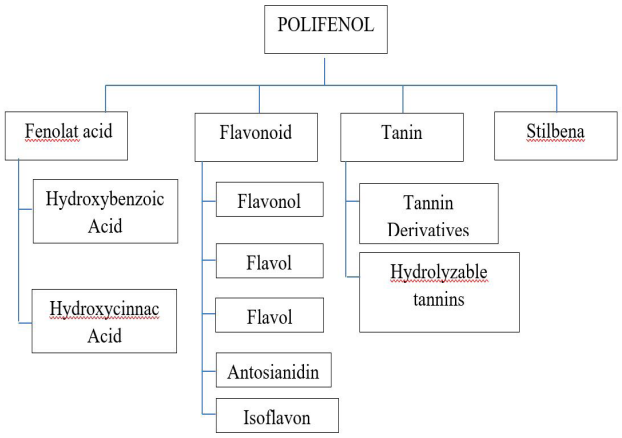

Fig. 1: Classification of flavonoids. Flavonoids are a group of polyphenols and are classified based on their chemical structure and biosynthesis.

DISCUSSION

Peel Fruit Bioactive Compound

Processing of fruits produces substantial waste of 25–30% of the total product (21), and mostly fruit peels and seeds (22). Fruits peel is the outer skin (cover) of the fruit (23), or also called the pericarp (24), usually treated as industrial waste, but contain valuable phytochemicals that can be extracted and utilized (Figure). Fruit peel representing 30% of the total weight can be a natural source of flavonoid extraction which is known to be beneficial for human health, the environment, and the economy of society (25).

Punica granatum, Citrus, Myrciaria jaboticaba, and *Garcinia mangostana* are the most common tropical fruits. It is mainly cultivated in Thailand, Indonesia, Malaysia, Sri Lanka, Myanmar, India, and Cina (26)(27). Pomegranate or *Punica granatum*, commonly known as grenade / punica apple belongs to the punicaceae family (28), the bioactive phytochemicals in *Punica granatum* peel consist of flavonoids (anthocyanins such as pelargonidin, delphinidin, cyanidin along with their derivatives and anthoxanthins such as catechins, epicatechin and quercetin), tannins (ellagitannins and ellagic acid derivatives such as punicalagin, punicalin and chlorpedunculagin and phenolic acids (such as caffeic, syringic, sinapic, p-coumaric, ferulic, ellagic, gallic and cinnamic acids (29). The fruit of *Garcinia mangostana* is about 2.5-7.5 cm long and has a purple skin with a thickness of about 0.6-1.0 cm, the peel is

rich in antioxidants such as flavonoids, anthocyanins, proanthocyanidins, xanthones, and epicatechins (30).

Myrciaria jaboticaba belongs to the myrtaceae family, has small fruit and has dark purple skin and white flesh. Analysis using chromatography found that *Myrciaria jaboticaba* peel extract consisted of flavonols quercetin and myricetin, ellagic acid (EA) derivatives, and 3-O-methylellagic acid derivatives (MEA) (31) and anthocyanins (10). Citrus sinensis fruit, also known as sweet orange belongs to the family rutaceae. Citrus sinensis peel have higher amounts of total phenolics such as limonene, hesperidin, narirutin, naringin and eriocitrin (32), and *Citrus iyo* which is one of a variety of citrus fruits, where the main flavonoids abundant in citrus fruit peels are neohesperidin, naringin, hesperidin and nobiletin, sinensetin, and tangeretin (33).

Classification of flavonoid

Flavonoids are secondary metabolites that are commonly found in plants, The basic structure consists of C6-C3-C6 with different substitution patterns resulting in a series of flavonoid subclass compounds(34). Flavonoids are classified into different subgroups depending on the carbon of the C ring on which the B ring is attached and the degree of unsaturation and oxidation of the C namely flavones (apigenin, chrysin, luteolin, and tangeritin), flavanones (narigenin, hesperitin), flavanols (epicatechin gallate, epigallocatechin, and epigallocatechin gallate), isoflavones (genistein and daidzen), flavonols (quercetin and kaempehrol) and anthocyanins (cyanidin, delphinidin, pelargonidin, peonidin, petunidin and malvidin) (35)(36).

Extraction, Isolation and purification flavonoid

The problem in extracting flavonoids in plants is the low concentration, which is around micrograms to milligrams/kilograms (37). The first step of extracting peel fruit was washed to remove impurities with distilled water and dried at room temperature to constant weight(38), crushed, then carried out the maceration process using a solvent. The extract was filtered after that each filtrate was concentrated to dryness under pressure using a rotary evaporator. The total phenolic content and the total flavonoid content of the fruit peel extract could be measured using several method such as the Folin-Ciocalteau method or aluminum chloride colorimetric method. The phenolic acid and organic acid composition of the bark extract can be determined by high performance liquid chromatography (HPLC) while the flavonoid content was identified through ultraperformance liquid chromatography (UPLC)(39).

The Mechanism of Flavonoids inhibit Cancer proliferation

Cell proliferation is an important process, the dysregulation of cell proliferation causes cancer. Cell proliferation consists of four main periods defined as G1, S, G2, and M phases (40). *Citrus iyo* peel extract significantly suppressed the growth of prostate carcinoma in animal models and downregulated Ki-67 expression(41), tangeretin also know as 4,5,6,7,8-pentamethoxyflavone is a type of flavonoid found in citrus peels (42), STAT3 plays a role in human oncogenesis, Once activated STAT3 undergoes phosphorylation induced homodimerization, leading to nuclear translocation, DNA binding, and subsequent gene transcription. The phosphorylation is mediated through the activation of nonreceptor protein tyrosine kinases called janus kinase (JAK) : JAK1, JAK2, JAK3, and TYK2 have been implicated in the activation of STAT (41), tangeretin reduced the total level and phosphorylated nuclear level of STAT3, inhibits STAT3 signaling pathway and cancer cell proliferation (43), suppresses STAT3 activity parallel to inhibition of JAK1, JAK2, c-Src activity, then induces cancer cell apoptosis (41). Citrus sinensis peel extract also decreased proliferation in animal models of testicular tumors, where there was a decrease in Ki-67 expression, this was due to the presence of active compounds such as hesperidin, a citrus flavonone, protecting the testes from cadmium-induced oxidative dysfunction in mice by providing protection involving the stimulation antioxidant mechanism (32).

Pericarp *Punica granatum* polyphenol extract inhibits melanoma development via PPAR receptors, Peroxisome proliferator-activated receptors (PPARs) including α, β, δ, and γ isoforms are ligand activated transcription factors and members of the nuclear hormone receptor superfamily (27), punicalagin induces cell cycle arrest by targeting the PPAR pathway in melanoma. Peroxisome proliferator-activated receptors (PPARs) are nuclear receptor proteins that, when activated, act as transcription factors and play an important role in the regulation of several diseases, including cancer (44).

Myrciaria jaboticaba fruit has the highest levels of total anthocyanins in the myrtaceae family, as well as higher levels of anthocyanins in the peel fruit when compared to seeds and pulp (10). Anthocyanins are known to inhibit the proinflammatory cytokine tumor necrosis factor-alpha (TNF-a), inflammation plays a role in promoting various types of cancer (45), and inhibits the activation of mitogen-activated protein kinase (MAPK). MAPK is an enzyme belonging to the serine/threonine protein kinase family, which is responsible for directing proliferative activity from the cell cytoplasm to the nucleus (46). De novo lipogenesis (DNL) is a metabolic pathway that converts excess carbohydrates into fatty acids which are then esterified into storage triacylglycerols (TGs). Deregulation in lipogenic pathways is associated with a variety of pathological conditions (47), Abnormalities of fat metabolism participate in gallbladder cancer. Xantones present in the pericarp of Garcinia mangostana can induce cell cycle arrest by suppressing de novo lipogenesis in gallbladder cancer (48).

KI 67 as a Biomarker Of Cancer Cell Proliferation

Ki-67 protein expression is strongly associated, during interphase Ki-67 can be detected exclusively in the nucleus, whereas in mitosis most of the protein is transferred to the surface of the chromosomes. Ki-67 protein is present during all active phases of the cell cycle (G1, S, G2, and mitosis), but is absent in resting cells (G0), making it an excellent marker for cell proliferation biomarkers (49).

Ki-67 protein is a nuclear protein which is closely related to somatic cell proliferation. The raised antibody against the human Ki-67 protein paves the way for immunohistologic assessment of cell proliferation, especially useful in many studies of the prognostic value of cell growth in clinical samples of human neoplasms(50), can be identified quickly through immunohistochemistry(51). Ki-67 is associated with cell proliferation, differentiation, metastasis and apoptosis. Ki-67 is a protein expressed in proliferating nuclei. closely related to the cell cycle and is mainly expressed in the S and G2 phases of the cell cycle (52), Ki-67 index is stated as the percentage of positive stained cells among the total number of invasive cancer cells in the scored area, scoring involves counting at least 500 malignant invasive cells with a 40Ч object lens (53).

CONCLUSION

Punica granatum, Citrus iyo, Citrus sinensis, Myrciaria jaboticaba, and *Garcinia mangostana* fruit peels are sources of flavonoids, which can inhibit the proliferation of cancer, and it needs to be investigated further.

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