POTENTIAL THERAPEUTIC EFFECT OF CITRUS PEEL COMPONENTS AGAINST CANCER

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Abstract: Cancer is a globally significant death cause. However, drug development for cancer treatment has always been associated with side effects and several limitations in applications. Citrus fruit belonging to the family *Rutaceae* has many health-promoting activities such as anticancer, antitumor, anticarcinogenic, anti-inflammatory and antiproliferative which have been linked with many active compounds while at the same time is highly consumed worldwide. Citrus peels that are generally discarded as waste to the environment can act as potential therapeutic resources in addition to their low-cost and easy availability. Flavonoids are bioactive components in the citrus peel that are largely related to anticancer potential. Among the flavonoid derivatives, particularly flavone glycosides and polymethoxy flavones have shown potent anticancer properties as found in many scientific studies. Action mechanism of flavonoids modulated including apoptosis, metastasis, angiogenesis, cell proliferation and cell cycle regulation. These bioactive rich citrus extracts also have been utilized as a chemotherapeutic agent against the growth of different cancer cells such as breast cancer, colon cancer, prostate cancer, and others. This review highlights new research in the field, especially the nanoparticles from citrus peel used to treat cancer and the signal pathways or action mechanisms modulated by potent compounds in citrus peel on the cancer cell line. Besides, this study also showed the great potential of citrus peel as a plant-based substance to be developed as the source of a chemopreventive agent in suppressing and inhibiting the cancer cells growth. Therefore, further study about the citrus peel potential needs to be conducted.

Keywords: Citrus peel, anticancer, flavonoids, cytotoxic activity, chemopreventive

1. Introduction

Regardless of advancements in illness detection, prevention and treatment strategies, cancer is a severe metabolic syndrome and one of globally significant death causes (Iqbal et al., 2017). The unregulated multiplication of aberrant cells, which causes genetic instabilities and mutations, builds up within cells and tissues, transforming a healthy cell into a cancerous one (Iqbal et al., 2017). The spreading pattern of proliferative cancerous cells can be characterised or developed by several mechanisms such as transformation, proliferation, angiogenesis, apoptosis malfunction, invasion and metastasis (Shirisha et al., 2019).

This deadly disease is associated with several adverse effects that are usually treated with synthetic drugs and treatments (Shafique et al., 2019). However, conventional chemotherapy treatment has the potential to have negative and toxic side effects on normal cells during treatment, and it fails to achieve the goal of curing cancer (Shirisha et al., 2019). Thus, plant-derived natural

compounds, which give an excellent addition to current treatments due to their cytotoxic and cancer-preventive activities, have been chosen as an alternative to synthetic drugs' adverse effects in combating cancer (Diab, 2016).

2. Discussion

2.1. Anticancer activity of citrus peel

According to recent scientific investigations, fruits high in phenolics and flavonoids have substantial antioxidant and anticancer properties (Shirisha et al., 2019). In addition, the mechanism of interaction between several phytochemicals and cancer cells also has been thoroughly investigated (Selim et al., 2019). In vitro cytotoxic assay study, it was found that all the tested citrus peel extracts significantly reduced cell viability in human leukaemia HL-60 cells in a concentration-dependent manner (Diab, 2016).

Besides, it is also able to suppress the lymphocyte proliferation response where interestingly, at low doses of 100 and 50 µg/mL, grapefruit and mandarin peels respectively had no significant increase in the stimulation index on proliferation of mouse splenocytes. Furthermore, the protective activity of citrus peel extracts was also examined with chemotherapeutic agent cisplatin (CDDP) which the result showed the reduction rate for the lemon peel ranged from 32.4 % to 69.1 %, for the grapefruit peel from 42.6 % to 73.5 %, and for the mandarin peel from 52.9 % to 79.4 % (Diab, 2016).

2.2. Citrus peel flavonoid as chemopreventive agent

Chemopreventive agents are substances that can prevent, delay, or stop the cancer progression and citrus fruits are a type of chemopreventive agent that contains flavonoids, which have been linked to cancer treatment (Arafa et al., 2021). This is consistent with an in vivo study in which *Citrus reticulata* peels ethanolic extract at a dose of 500 mg/kgBW reduced the number of cells expressing N-Ras in dimethylbenz[a]anthracene (DMBA)-induced rats' hepatic carcinogenesis and suppressed c-Myc expression (Meiyanto et al., 2012). Besides, nobiletin, a flavonoid derived from *Citrus reticulata* peels, inhibited carcinogenesis on the skin of DMBA-induced mice.

Another citrus species, *Citrus aurantifolia* peels that can be found containing flavonoids such as naringin, hesperidin, naringenin, rutin, nobiletin and tangeretin inhibited DMBA-induced breast carcinogenesis in female sprague sawley rats by inducing apoptosis and inhibiting cell proliferation (Meiyanto et al., 2012). In an in vivo study, Tajaldini et al. (2020) reported that the combination of doxorubicin (Dox) with orange peel extract and naringin reduced the volume of the oesophagal cancer cell (YM1) tumour in naked mice by increasing the cell cycle arrest in S phase as well retained the body weight of nude mice compared to Dox alone treatment. As stated by Goh et al. (2019) body weight is frequently employed as a proxy indicator for toxicity, with the expectation that if toxicity develops, the weight will drop significantly.

2.3. Effectiveness of nanoparticle from citrus peel in preventing cancer

Synthetization of zirconium nanoparticles (NPs) with combining its ion and lemon peel was stated to be more stable and may be stored for a long time compared with lemon peels (Salih et al., 2021). The NPs and the citrus extracts were studied for their activity against MCF-7 (human breast

cancer) cell line where it was reported that there was a synergism effect between the NPs and the extract, with NPs + Peel having the highest inhibitory percentage impact (95.16) at a concentration of 300 µg/ml and 25 µg/ml of NPs having the lowest impact (18.42) (Salih et al., 2021). Therefore, it can be concluded that zirconium lemon peel nanoparticles have shown good anticancer activity potential against breast cancer based on a cytotoxic test conducted. This is in accordance with the statement of Meiyanto et al. (2012) who stated that citrus flavonoids also have a promising anti-cancer impact when combined with various chemotherapeutic drugs.

3. Conclusion

Many proven evidence exhibited that flavonoids are bioactive components abundantly found in the citrus peel are largely related to strong anticancer potential and this is evidenced by the ability of citrus peel flavonoid to be used as an effective chemopreventive agent for cancer in chemotherapy treatment. Therefore, further studies on the significant anticancer properties of citrus peel flavonoid for cancer prevention are very meaningful to be carried out in the future.

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