SCRIPTA SCORE Scientific Medical Journal, Vol. 3, No. 2
https://doi.org/10.32734/scripta.v3i2.5522
pISSN: 2088-8686
eISSN: 2686-0864

SCRIPTA SCORE
Scientific Medical Journal
Literature Review

Role of Tomato (*Solanum lycopersicum*) in Management and Prevention of Four Most Common Cancer in Indonesia

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ABSTRACT

Introduction: The rate of new cancer cases in Indonesia is very high. With various risk factors, cancer becomes easier to attack individuals, but that does not mean these factors cannot be changed. One of the modifiable risk factors of cancer is diet from food. **Objective:** This review aims to investigate the role of chemical compound in tomato (*S. lycopersicum*) in management and prevention of breast, cervix uteri, lung, and liver cancer. **Method:** Method for writing this review is by searching for literature published in 2012 - 2020 was carried out to prove the effect of tomatoes on cancer incidence through in vitro, in vivo, and clinical studies. **Results:** Lycopene in tomatoes has been shown to withstand the cell cycle, inhibit NF-κB, and affect enzymes that produce toxic metabolites, thus preventing the development of various types of cancer. Other active compound such as carotenoid lutein can act as cytotoxic agents by increasing p53 phosphorylation and suppressing the expression of anti-apoptotic genes in breast cancer cells. Interaction between tomatine or tomatidine (another compound in tomatoes) with EGFR will prevent the development or metastasis of non-small cell lung carcinoma. **Conclusion:** These facts can be concluded that tomato (with various active compound in it) consumption potentially strong in preventing breast, cervix uteri, lung, and liver cancer. Further research should clarify the recommended tomato active compound level for daily consumption and its long-term side effect.

Keywords: cancer, diet, *Solanum lycopersicum*

ABSTRAK

Pendahuluan: *Tingkat kasus baru kanker di Indonesia sangatlah tinggi. Terdapat 65.858 kasus baru kanker payudara pada 2020. Dengan berbagai macam faktor risiko, kanker menjadi lebih mudah menyerang individu, namun bukan berarti faktor tersebut tidak dapat diubah. Salah satu faktor risiko yang dapat dimodifikasi adalah diet.* ***Tujuan:*** *Ulasan ini bertujuan untuk membahas bagaimana konsumsi tomat dapat mengurangi risiko terkena kanker maupun memperbaiki prognosis penderita kanker.* ***Metode:*** *Metode penulisan ulasan ini adalah mencari literatur yang dipublikasi selama 2016 – 2021 secara daring dilakukan untuk membuktikan pengaruh tomat terhadap kejadian kanker baik secara in vivo, in vitro, serta penelitian klinis.* ***Hasil:*** *Lycopene yang terkandung pada tomat terbukti menahan siklus sel, menginhibisi NF-κB, dan menekan efek enzim yang memproduksi metabolit beracun sehingga bermanfaat dalam mencegah perkembangan berbagai jenis kanker. Bahan aktif lain seperti karotenoid lutein mampu bertindak sebagai agen sitotoksik yang meningkatkan fosforilasi p53 dan menekan ekspresi gen anti – apoptotic pada sel kanker payudara. Interaksi tomatine dan tomatidine (kandungan lain pada tomat) dengan EGFR akan mencegah perkembangan maupun metastasis non-small cell lung carcinoma.* ***Kesimpulan:*** *Beberapa fakta tersebut dapat disimpulkan bahwa konsumsi tomat berpotensi mencegah kanker payudara, serviks uteri, paru – paru, dan hepar. Penelitian selanjutnya perlu membuktikan berapa rekomendasi banyaknya konsumsi tomat harian.*

Kata Kunci: diet, kanker, tomat
Received [29 Jan 2021] | Revised [21 Jun 2021] | Accepted [27 Feb 2022]

INTRODUCTION

The latest cancer epidemiology data (December 2020) from WHO states that breast, cervix uteri, lung, and liver cancer being in the highest new cases and death number sequentially.[1] Cancer has many risk factors (variables that increase a disease's occurrence) that can even be unknown. Changes in risk factors such as diet can prevent the cancer occurance.[2] Anticancer drugs have many classification based on their mechanism of action including: alkylating agent and antimetabolite agents prevent cell division and proliferation at all cell cycle by inhibiting DNA replication and translation inside the cell, cytotoxic agent induce cell apoptosis, monoclonal antibodies that targets EGFR, and antioxidant which not only act in cancer prevention, but also in cancer patient by protecting cell damage induced by other cancer theraphy for example chemotheraphy and radiation that increases Reactive Oxygen Species (ROS) production. [3,4,5]

High antioxidant diet has been proved to reduce carcinogenic agents *in vivo*, *in vitro*, and clinically. This review discusses how lycopene, carotenoid lutein, α-tomatine, and tomatidine act as antioxidant and support tomato intake, reducing the cancer risk by showing epidemiology findings of each cancer mentioned on first sentence.

METHOD

This review was made by searching and compiling 31 literature from search engines including PubMed and Google Scholar that published between 2012 - 2020. Keywords such as "tomato active compound", "tomato role in cell", and "tomato and breast cancer" and three other cancer were searched were used without any exclusion.

DISCUSSION

Breast

Based on Globocan from WHO, breast cancer is the most common cancer in Indonesia on 2020 with 65.858 cases and second leading cause of death in cancer with 22.430 deaths.[1] There are many treatment options in breast cancer such as surgery, radiation, chemotherapy, endocrine therapy, and also nowadays there are many researchs for anticancer activity in carotenoid that includes lycopene, carotenoid lutein, and flavonoid.[6]

Lycopene is one of the compound found in tomato, which is a phytochemical compound that has many functions such as removal of free radicals, alleviation of bio-oxidative stress, modulation of body immune functions, prevention of cardiovascular disease, and anti-cancer effect. Based on *In vitro* experiment conducted by Peng et al, lycopene triggers MC-7 cancer cells shrinkage or damage and inhibits MC-7 cell proliferation by regulating the expression of p53 and Bax thus inducing apoptosis.[7,8,9] Other anti-cancer effects are via regulation of cell growth factor signaling pathways, initiation of cell cycle arrest, and induction of cell apoptosis. Apoptosis occurred by inhibit cell growth from G phase into S phase. Lycopene also potentially inhibited cell proliferation by blocking the phosphorylation of Akt.[10]

Carotenoid lutein is lipophilic pigments that also found in tomatoes. Lutein is inhibiting cell cycle progression in MCF-7 and MDA-MB-468 cancer cells by inhibits S phase in cell proliferation just like the lycopene. it also increased ROS production inside MDA-MB-468 cancer cells that induces p53 phosphorylation so that apoptosis can occurred. Lutein enhances the cytotoxic effects of chemotherapeutic agents to the cancer cells.[11] It also can decrease the

expression of anti-apoptotic Bcl-2 gene.[9] Another study with other active compound with high antioxidant activity, flavonoid, found that MC-7 cancer cells viability can be reduced by induction of apoptotic pathway.[9]

Cervix uteri

Cervical cancer is the 2nd for most new cases per year and the 3rd rank cause of death with cancer in 2020.[1] Cervical cancer caused by Human Papilloma Virus (HPV) infection, and in most cervical cancer cases are from the type 16 and 18 HPV.[13] As an antioxidant, lycopene reacting with free radical to prevent Reactive oxygen species (ROS) which lead to DNA damage and promote cell mutation.[14,15] In previous studies, the abilty of lycopene to induced arrest cell cycle at early cell division stages (G1 and S) believed as antiproliferative mechanism of lycopene.[16]

Recent in vitro study, conducted by Aktepe, HeLa human cervical cancer line was used to prove the antiproliferative effect from lycopene. From this study, shows that lycopene with cis – plastine decrease the viability of the cervical cell line, moreover lycopene and cis – plastine also inhibit the activation of NF-κB which act as proinflammatory pathway.[17,18,19]

Lung

30.843 deaths by the end of 2020 makes lung cancer become the top of death causes by cancer in Indonesia.[1] A tyrosine kinase receptor, epidermal growth factor receptor (EGFR) found increased in non-small cell lung carcinoma (NSCLC).[20] Its ligands such as Epidermal growth factor (EGF) and Tumor growth factor-alpha (TGF-α) result in the cell's growth, proliferation, and differentiation.[21] α-tomatine from tomato can interact with EGFR at 5-amino acid residue, outside EGFR active binding site so several signaling pathway namely focal adhesion kinase pathway (FAK), Phosphatidylinositol 3-kinase (PI3K)/Protein kinase B (AKT) signaling pathway, and Extracellular signal-regulated kinase (ERK) pathway inactivated.[22] Those signaling pathways play a role in various cell functions, including cell physiology and various pathological effect: facilitate cancer development, progression, metastasis, and invasion.[23,24,25,26] Another active compound, tomatidine, interacts with EGFR at 6-amino acids residue, making hydrogen bonds at the binding site, indicating strong potential in inhibiting EGFR activation by changing the active site form. [22,27]

Liver

The fourth cause of cancer – related death is hepatocellular carcinoma (HCC).[1] Surgical resection, liver transplantation, or multi-kinase inhibitor sorafenib and vascular growth factor – 2 (VEGFR – 2) antagonist ramucirumab for the advanced stage are curative treatment options for HCC.[28,29,30] Here, the authors give more attention to alternative methods to support the curative treatment. A meta–analysis shows a significant reduction of tumor incidence, depression in tumor number, and HCC growth inhibition in animal model (in vivo).[31] Orally administered lycopene enervates liver-specific carcinogen diethylnitrosamine induced hepatocarcinogenesis.[2]

While hepatocytes inflamed, CYP2E1 expressed more so that ROS and aldehyde production be higher. Furthermore, aldehyde, toxic metabolites, plays a role in ethanol metabolism and contributes to ethanol-induced liver injury, worsening the inflammation.[32] Suppressing effect on the expression of cytochrome p450 2E1 (CYP2E1) enzymes, Stimulating ability for Nrf2 (transcription factor for antioxidant expression), Upregulating capacity on CDK p21 and p27 inhibitor, and inhibiting G1 to S progression propensities are the reasons why tomato are potential.[29,31,33,34,35] Accumulation of lycopene from 200ml tomato juice in 1

month-long intake gives better cell cycle and apoptosis regulation by transcriptomic analysis of HepG2 cells from obese patients.[34]

CONCLUSION

Based on the discussion, different bioactive compounds found in tomato has different effect on each cancer; lycopene in breast cancer, cervix uteri cancer, and liver cancer; carotenoid lutein in breast cancer; α-tomatine and tomatidine in lung cancer. These compounds have many potential roles in managing various type of cancer and expected to be usefull as cancer cell development inhibitor, interrupt cell progression, prevent cell proliferation and differentiation through various mechanisms and pathways in the future to give the alternative of cancer prevention and management.

RECOMMENDATIONS

Further research in preclinical and clinical trials need to be done to ensure the potentiality of lycopene as anti-cancer agent in human, the amount and long term side effect of tomatoes daily consumption.

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