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TOMATO ROLE ON SEVEN DEADLIEST NON-COMMUNICABLE DISEASE

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Abstract:
Non-communicable diseases such as ischemic heart disease, stroke, chronic obstructive pulmonary disease, lung cancer, Alzheimer, diabetes melitus, and kidney disease are leading causes of death in the world. There are many risk factors which can contribute to non-communicable diseases such as dietary. Vegetable consumption such as tomato may lower risk factors to non-communicable diseases because of its active ingredient, lycopene, retinol, alpha tomatine, and tomatidine. In this review, authors aim to explain the mechanism of tomato's active compound in lowering risk factors of non-communicable disease based on biomarker found on each disease collected from articles and journals. Lycopene and retinol have proven in reducing ischemic heart disease and stroke because of its anti-atherogenic properties and anti-inflammatory effect. Anti-oxidative and anti-inflammatory effect of lycopene also proven in lowering risk factors of chronic obstructive pulmonary diseases by modulate reverse cholesterol transport, so cholesterol homeostasis is created. In lung cancer, lycopene and other bioactive compound such as α-tomatine and tomatidine also have an anti-proliferative effect by interacting with Epidermal growth factor receptor (EGFR). Its ability to reduce the final product of lipid peroxidation level makes lycopene lower Alzheimer risk factor. There is much more function of tomato's active coumpound although pure tomato has contradictive effect on some disease.

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Introduction

The latest epidemiology data for 10 highest death cause in world is taken from WHO 2019 top 10 death cause. There are three infectious disease and seven non – communicable diseases based on that data. Based on these data, ischemic heart disease, stroke, chronic obstructive pulmonary disease, lung cancer, and Alzheimer's become the five non-communicable diseases as the leading causes of death worldwide (WHO, 2020).

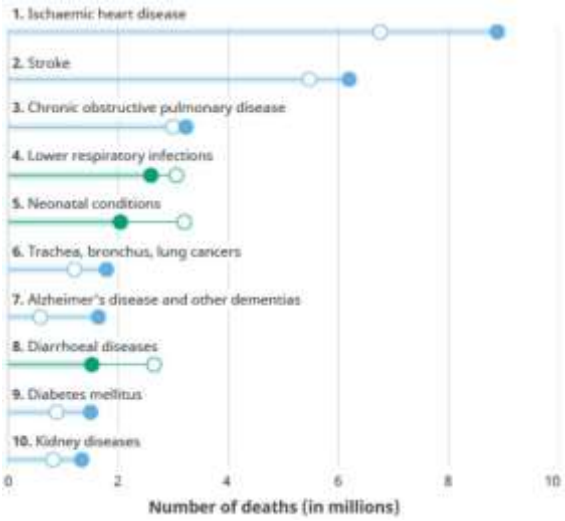

Figure 1 Top 10 world death causes (WHO, 2020)

Non-communicable diseases have many risk factors that can even be unknown. Risk factors are variables that increase the occurrence of a disease in an individual. There are several risk factors in one disease and sometimes together to create disease (National Cancer Institute, 2020). Because one risk factor can also lead to several diseases, with only one risk factor, a person can develop several diseases at once. Not all risk factors can be avoided so that risk factors are categorized into two, namely modifiable and non-modifiable risk factors. One risk factor that can be changed is dietary. Changes in risk factors can prevent the occurrence of non-communicable diseases and aid in healing or improving prognosis in individuals with non-communicable diseases (Joshi et al., 2020).

Vegetables are healthy foods that can reduce risk factors for non-communicable diseases, one of which is tomatoes, which have various active ingredients (Chaudhary et al., 2018). The phytochemicals in tomato have various functions such as anti-atherogenic properties, anti-oxidative, anti-inflammatory, anti-proliferative, anti-carcinogenic, anti-tumorigenic, and anti-mutagenic so that their consumption can reduce the chance of contracting non-communicable diseases. We conducted a review based on peer-reviewed published articles and journals to discuss how tomatoes' active ingredients can affect the course of non-communicable diseases and is supported by the measurement of existing biomarkers according to each disease from existing epidemiological studies. Authors hope that this review can explain the importance of tomatoes in reducing risk factors of non-communicable diseases.

Research Methods

The authors look for a list of deadliest non-communicable diseases first and then considers which natural ingredients can be used for several non-communicable diseases at once. We search through PUBMED and Google Scholar with keywords Herbs for non-communicable diseases, Vegetables for lowering risk factor of non-communicable diseases, Dietary changing for patients with non-communicable disease yielded results that tomatoes with their ability as anti-oxidant and anti-inflammation can play a role in five deadliest non-communicable diseases. Based with this information, we search peer-reviewed articles and journals with keywords from each of non-communicable disease name and added with the word tomato or tomato active ingredients such as lycopene, tomatine, and retinol to be the last keyword for searching before writing this review. Each authors reviewed articles and journals independently and brainstorming is carried out to connect the pathogenesis and pathophysiology of diseases to be discussed with the properties of the ingredients in tomatoes. The authors also look for epidemiological research so that there is direct evidence in humans about these tomatoes' efficacy.

Result and Discussion

Ischaemic Hearth Disease and Stroke

The low level of free radicals and the low incidence of ischemic heart disease in Italy are related to tomatoes' consumption in Italian society (Joshi et al., 2020). Active ingredients such as lycopene in tomatoes are associated with ischemic heart disease incidence where low serum lycopene concentrations increase the intima-media thickness of the common carotid artery (CCA-IMT) as evidenced in a 4-year study with 2682 subjects as well as in other studies (Joshi et al., 2020). The decrease in intracellular cholesterol levels is due to modulation of LDL receptors, modulation of acyl-coenzyme A, and inhibition of the enzyme 3-hydroxy-3- methylglutaryl coenzyme A (HMG-CoA) reductase by lycopene so that the course of CVD is slow and reduces risk factors for ischemic heart disease. It was found that the mean number of LDL, systolic blood pressure, and triglycerides were higher in the group with low serum lycopene levels, although not significantly. Oxidized LDL in the walls of blood vessels will also inhibit nitric oxide, so that blood pressure regulation through vasodilation is also disrupted and results in high blood pressure. A week-long tomato intervention on healthy youth in America resulted in serum lipid peroxidation and LDL oxidation decreased significantly (Joshi et al., 2020).

Table 1. Patient profile with different serum lycopene level (Joshi et al., 2020)

	Patients with 0.00μmol/L serum lycopene	Patients with 0.34 ± 0.12 μmol/L serum lycopene
Serum LDL cholesterol (mmol/L)	3.1 – 4.88	3.16 – 4.84
Serum triacylglycerols cholesterols (mmol/L)	1.7 ± 1.18	1.51 ± 1
Systolic blood pressure (mmHg)	138.1 ± 16.7	132 ± 15

The efficacy of tomatoes to lower risk factor for these diseases is still limited in vivo but has been widely demonstrated in vitro and epidemiology. Research proves a correlation between the incidence of myocardial infarction with serum lycopene levels in 11 countries by EURAMIC (Joshi et al., 2020). Another risk factor for ischemic heart disease is the level of IGF-1 which appears to be modulated in action by lycopene from tomatoes and other properties of inhibiting platelet aggregation (Xie & Yang, 2020). Other ingredients such as retinol in tomatoes, which are fat-soluble, make LDL more resistant to oxidation (McKay et al., 2020).

Several types of stroke with similar manifestations have different pathophysiology. The type that often occurs is an ischemic stroke in which the occurrence of blockage of blood vessels so that the brain is not properly perfused. The course of this disease is more or less the same as ischemic heart disease, so the mechanism of action of tomatoes' active ingredients is the same. This is supported by a meta-analysis of several studies where there was an inverse correlation between serum lycopene levels and stroke risk (Bahonar et al., 2017). As a modifiable factor, the dietary aspect becomes excellent education given to healthy individuals or patients with both diseases so that the disease can be prevented or the treatment being carried out is also supported or adjuvanted by changes in nutritional intake (Joshi et al., 2020).

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD), a chronic inflammatory lung disease from various mechanisms such as alveolar epithelial injury, oxidative stress, et cetera (figure 4), is the third cause of death in the world by 2019 (WHO, 2020) and (Biswas et al., 2013). This disease usually consists of emphysema and bronchitis. Oxidative resistance of whole blood on COPD patients lower than the healthy subjects and it associated with lower total plasma alpha-carotene (or has been mentioned before as lycopene) in COPD group (Lin et al., 2010).

Cholesterol homeostasis is closely related to lung disease incidence because intracellular cholesterol buildup will lead to dysregulated inflammatory response and amplify inflammation in macrophages. Lycopene can modulate Reverse cholesterol transport (RCT) which plays a role in transporting excess cholesterol by inducing LXRa and PPARa. Experiments on Ferret who had COPD with the most similar symptoms to humans compared to rodents reported an increase in mRNA expressions of LXRa, PPARa and even the expression of these mRNAs could be at the same level as healthy controls. The study also reported a decrease in bronchitis grade and decreased alveolar diameter, which means an improvement in emphysema in the high and low dose intervention groups (Rakic et al., 2019).

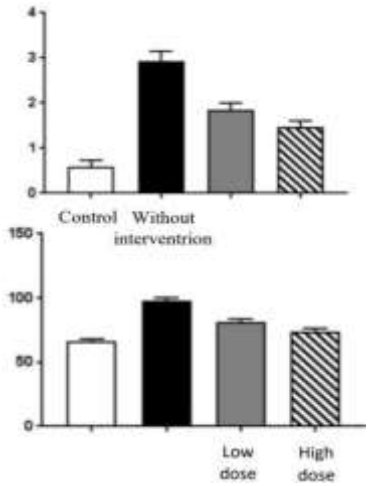

Figure 2 Bronchitis grade and alveolar diameter (Rakic et al., 2019)

Lung Cancer

Lung cancer known for the 1st cause of death by cancer and 3rd rank in the most new cases per year in Indonesia with 5 years prevalence at 37.663 cases until December 2020 (IARC, 2020). Non-small cell lung cancer (NSCLC) includes different types of cancer cell such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (Clark & Alsubait, 2020). Epidermal growth factor receptor (EGFR) is a tyrosin kinase receptor that can be found and increase in several types of cancer including NSCLC (Wee & Wang, 2017). Native ligand of EGFR are Epidermal growth factor (EGF) and Tumor growth factor alpha (TGF-α), and result in the growth, proliferation, and differentiation of the cell (Merphey et al, 2020). *In silico* study was done by Amalia et al to inhibit native ligand binding for EGFR with bioactive compound of tomato; α-tomatine and tomatidine. In this study, α-tomatine interacts with EGFR at 5 amino acid residue at outside EGFR active binding site. Even though it's not at the active binding site, the interaction between α-tomatine and these amino acid residue inactivated several signaling pathways such as Focal Adhesion Kinase pathway (FAK), Phosphatidylinositol 3-kinase (PI3K)/Protein kinase B (AKT) signaling pathway, and Extracelullar signal-regulated kinase (ERK) pathway (Amalia et al., 2020). These pathways play role in various cell function including cell growth, proliferation, differentiation, apoptosis, cell stress response and various pathological effect: facilitate cancer development and progression, metastasis, and invasion (Guo et al., 2020); (Jiang et al., 2020); (Shi et al., 2019) ; (Tai et al., 2015). Tomatidine interacts with EGFR at 6 amino acids

residue, 2 of them forms hydrogen bond at the binding site which indicate tomatidine has strong potential role to inhibit EGFR activation by its native ligand (Amalia et al., 2020).

Alzheimer

Dementia is one of the global health problem, the reported cases for dementia is 24 million cases. Alzheimer is a type of dementia, and it's commonly occur at elderly community (Mayeux & Stern, 2012). Alzheimer is a progressive neurodegenerative disease, and one of the pathogenesis of this disease is buildup of toxic plaques: β-amyloid (Aβ). Aβ deposition in central nervous system initiated by oxidative stress which is an increase amount out free radical (oxidant) compared to antioxidant, therefore the increase of antioxidant activity and antibody development against Aβ can be used to prevent or minimize the risk of Alzheimer disease (Huang et al., 2016); Kumar et al, 2020; (Tiwari et al., 2019). Lycopene can be found in several types of fruits, including tomato. Lycopene in *In vivo* study using mice shows reduced in the final product of lipid peroxidation Malondialdehyde (MDA), and reduce glutathione peroxidase in mice serum after 8 weeks of lycopene treatment, indicating that lycopene has antioxidant activities (Chen et al., 2019). The study on mice (in vivo) to develop antibody against Aβ was conducted by Youm et al by using transgenic tomato, with Aβ DNA inserted to the tomato genome, and it's proven with PCR analysis before the tomato extract being fed to the mice as an oral vaccine. In this study, mice from control group (immunized with non-transformed tomato extract) develop no reactive antibodies to Aβ, on the other hand, mice from treatment group (immunized with transgenic tomato extract) develop significant amount of serum 3Aβ specific antibody, especially after being given with booster (Youm et al., 2008).

Diabetes Melitus

Diabetes is a multi-factorial disease in which the blood levels of the glucose transporting hormone insulin are lower or absent. It can also occur even if there is sufficient insulin present, from reduced Glucose Transporter Type (GLUT)-4 or reduced insulin binding to its receptor. Obesity plays a major role in the development of diabetes and insulin resistance (Mohabbulla Mohib et al., 2016). Tomato appears to regulate insulin mechanisms and control HbA1c levels in diabetics and healthy adults (Alam et al., 2019). Beneficial effect of lycopene in insulin tolerance and resistance proved on *in vivo* study in mice fed a high-saturated-fat and cholesterol-rich diet that received different doses of dry tomato peel (DTP) for 12 weeks. Result from oral glucose tolerance tests (OGTT) at 4 and 12 weeks showed significantly higher plasma glucose in the high-fat control diet (HF Ctrl) and HSF/HC high-saturated-fat/high-cholesterol mice (HSF-HC) than in high-saturated-fat/high-cholesterol diet supplemented with 9% DTP mice (HSF/HC TP1) and high-saturated-fat/high-cholesterol diet supplemented with 17% DTP (HSF/HC TP2). At 4 weeks, the time course of glucose clearance was significantly longest in HSF/HC mice, followed by HF Ctrl, and then DTP-supplemented mice ($P<0.05$). At 12 weeks, the areas under the curve showed significant differences between the HSF/HC group, the HF Ctrl and the DTP-supplemented groups (Figure 3B) (Zidani et al., 2017).

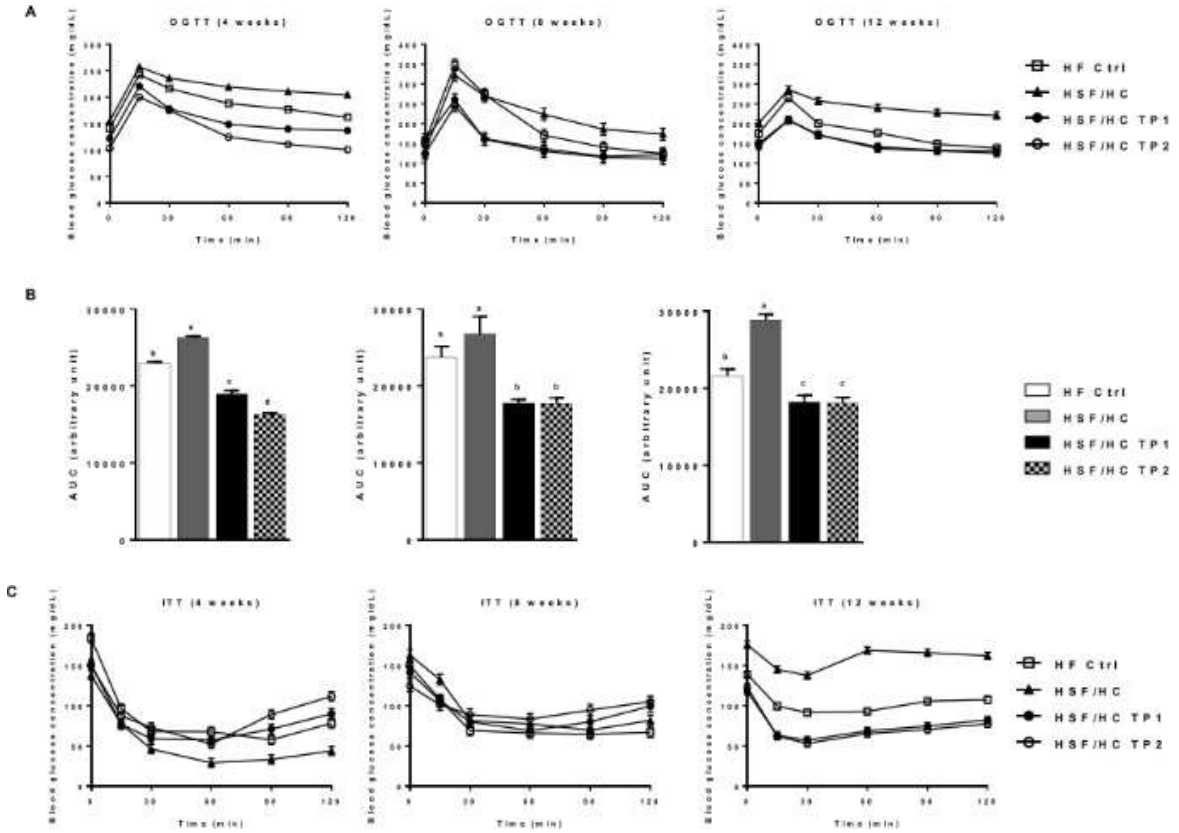

Figure 3 Dry tomato peel effect on glucose, insulin, and hepatic markers (Zidani et al., 2017)

The Insulin Tolerance Test (ITT) declined quickly 15 min after insulin injection for all groups at 4 weeks (Fig. 3C). At 12 weeks, plasma glucose was the lowest at all time points from 0 to 120 min in HSF/HC TP1 and HSF/HC TP2, without significant differences between these two groups (Zidani et al., 2017). Study of antihyperglycemic effect of tomato by Al-Numair KS *et al.* was reported by administration of kaempferol, an antioxidant flavonoid found in tomato, to STZ-diabetic rats was found to normalize the plasma glucose. Figure 4 shows the effects of kaempferol at three different doses (50, 100, and 200 mg/kg BW) on plasma glucose (initial day, 7th days, 15th days, and 45th days) and insulin (45th days) levels in normal and STZ-diabetic rats. Diabetic rats showed a gradually elevated level of plasma glucose on initial, 7th, 15th, and 45th days, respectively, and a decreased level of insulin on 45th days when compared to these levels in normal rats. Oral administration of kaempferol or glibenclamide in diabetic rats showed a decrease level of plasma glucose and increase level of insulin when compared to these levels in the diabetic control rats. The dose of 100 mg/kg BW showed maximum glucose lowering effect in comparison to the lowering effects of the 50 and 200 mg/kg BW doses. So the 100 mg/kg BW dose was fixed as the optimum dose and used for further study (Al-Numair et al., 2015).

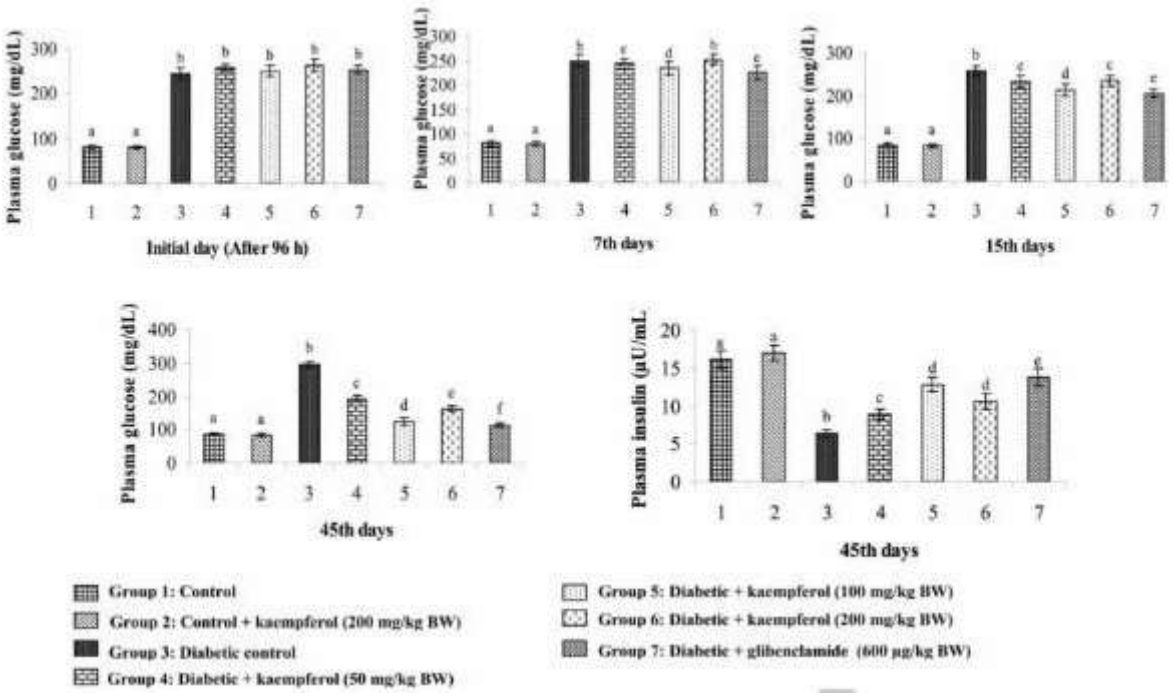

Figure 4 Effect of kaempferol on plasma glucose and insulin (Al-Numair et al., 2015)

Furthermore, long-term tomato intake by patients with type 2 diabetes resulted in decreased glycosylated hemoglobin levels (Bose & Agrawal, 2006). In these patients, an antioxidative stress effect (i.e., higher antioxidant enzyme activity and lower lipid peroxidation rates was observed after tomato consumption (Banihani, 2017); (Bose & Agrawal, 2006). Maintenance of cholesterol homeostasis is important especially in diabetic patients whereas imbalance of cholesterol level leads to hypercholesterolemia, a pre-dominant risk factor for atherosclerosis and associated coronary and cerebrovascular diseases (Ballantyne et al., 2005); (Edwards & Ericsson, 1999); (Meagher, 2004). The reduction of intracellular cholesterol by lycopene and tomato derivatives has been associated with a decrease in cholesterol synthesis through an inhibition of HMG-CoA reductase activity and expression, a modula- tion of LDL receptor, and acetyl-coenzyme A acetyltrans- ferase (ACAT) activity. The committed step in the biosynthesis of cholesterol and isoprenoids is catalyzed by HMG-CoA reductase, which promotes the deacylation of HMG-CoA to mevalonate (Bilheimer et al., 1983); (Istvan & Deisenhofer, 2001). Lastly, table 2 presents a summary of the studies performed on tomato and its derived compounds and their reported effects in preventing diabetes-induced oxidation. The data indicate that tomato (fresh or cooked) or its derived compounds, such as lycopene, kaempferol, and naringenin, show potent antioxidant effects against diabetes-induced oxidative stress. This antioxidant effect mainly occurs by enhancing the activities of antioxidant enzymes, increasing the level of nonenzymatic antioxidants, and decreasing the formation of reactive oxygen species (i.e., H_2O_2) (Banihani, 2017).

Table 2. Antioxidant effect on diabetic condition from tomato (Banihani, 2017)

Affecter (Tomato or tomato-derived compound)	Dose	Duration	Population	Antioxidant effect	Reference
Tomato-extract lycopene	90 mg/kg of body weight	Single dose	Streptozotocin-induced diabetic rats	(–) H_2O_2 formation (+) Catalase, superoxide dismutase, and glutathione peroxidase	[16,45]
Natural tomato extract	0.2% of the diet	5 weeks	Diabetic sand rats	(+) Glutathione	[15]
Ripe cooked tomato	200 g of ripe tomatoes (cooked)/day	60 days	Patients with type 2 diabetes	(+) Superoxide dismutase, glutathione peroxidase, glutathione reductase. (–) Lipid peroxidation	[21]
Cooked tomato	200 g/day	30 days	Patients with type 2 diabetes	(+) Superoxide dismutase, glutathione peroxidase, and glutathione reductase (–) Lipid peroxidation	[46]
Tomato-derived lycopene	30 mg/day	4 weeks	Obese patients	(+) Plasma carotenoids	[47]
Kaempferol	100 mg/kg of body weight	45 days	Streptozotocin-induced diabetic rats	(+) Glutathione peroxidase, catalase, and glutathione-*S*-transferase. (+) Antioxidant status	[18,32]
Naringenin	(5–10 mg/kg)	10 weeks	Diabetic Wistar rats	(+) Superoxide dismutase, catalase, and glutathione enzyme. (–) Tissue malondialdehyde	[34]
Dry tomato peels	9% or 17% of the diet	12 weeks	BALB/c male mice	(+) Plasma lycopene concentration	[23]

(–) decrease; (+) increase.

Kidney Disease

Kidney disease has numerous complex causes like diabetes, cardiovascular disease, and many more (Levin et al., 2017). Chronic kidney disease is non-communicable, irreversible, progressive, and clinical syndrome secondary to the definitive change in function or structure of the kidney (Ammirati, 2020); (Levin et al., 2017). Based on data GBD 2017, in 2017 chronic kidney disease resulted in 1,23 million deaths. Total deaths from 2007 to 2017 increased by 33,7% (Roth et al., 2018). Additionally, around 1,7 million people each year are thought to die from acute kidney injury (Mehta et al., 2015). Oxidative stress is likely a potential factor in the progression of AKI, as OS causing renal epithelial and tubular cell dysfunctions by depletion of proximal renal tubular antioxidant capacity and induction of free radicals (Mahgoub et al., 2017). Oxidative stress is a result of the imbalance between formed oxidants and body antioxidants and related to the overproduction of reactive oxygen species (ROS) (Gwozdzinski et al., 2021). The study by Rasheed et al lycopene has an effect to prevent AKI through modulation of OS and lipid peroxidation (Rasheed et al., 2020). Lycopene has indeed received special attention because it is a highly efficient antioxidant as well as having the function of singlet-oxygen and free radical scavenging. So, lycopene, as a bioactive compound may help prevention of chronic disease, but it needs some research on humans (Taheri et al., 2015). In tomatoes there are many nutrients, like lycopene, potassium, calcium, and many more. But the nutrients in tomatoes can be different depends on the types of tomatoes, raw, color, and ripe. In tomatoes which is ripe, red, and raw the content of lycopene is 2573 µg and the potassium is 237 mg, but in tomatoes which is ripe, red, and cooked the content of potassium is decreased by 19 mg, and the lycopene is increased by 463 µg, In tomatoes which is green, raw do not have lycopene and have potassium is 204 mg (Chaudhary et al., 2018). Lycopene have a good efficient antioxidant, but inpatient with chronic kidney disease there is a limitation on intake of dietary potassium because patient

CKD did not have normal kidney function to excrete the waste of the body, so if the intake of potassium is high, residual potassium accumulates in the body and may cause hyperkalemia and lead to arrhythmias, muscle weakness, disturbed consciousness, heart failure, and even leading to sudden death (Talukder et al., 2016). Low potassium vegetable and fruit now is produced with hydroponic culture and multi-Russ training and it is effective in producing tomato with low potassium and could decrease potassium at least 50%, but to know there is a decrease in other nutrients in tomatoes, so it needs some research (Tsukagoshi et al., 2016). If tomatoes with low potassium and high lycopene can be produced, it is good for patients with chronic kidney disease, because tomatoes have many benefit like antioxidants and anti-inflammatory, so future research can be conducted to know the effect of tomatoes on the kidney.

Conclusion

Lycopene, retinol, alpha tomatine, and tomatidine that found abundantly in tomatoes, proves in reducing risk factors of non-communicable diseases based on in vivo, in vitro, or in silico experiments such as decrease in intracellular cholesterol levels in ischemic heart disease, modulate reverse cholesterol transport in chronic obstructive pulmonary disease, interacting with Epidermal growth factor receptor (EGFR) as an anti-proliferative effect in lung cancer, reduce lipid peroxidation Malondialdehyde (MDA), and reduce glutathione peroxidase in Alzheimer, regulate insulin and plasma glucose in diabetes mellitus, and modulate OS and lipid peroxidase to prevent acute kidney injury. Even though it has not reach clinical trials, it is imperative to educate patients in non-communicable diseases to improve their dietary habits, including more consumptions of fruits and vegetables such as tomatoes. Authors hope that in future, further researches need to be done in order to increase understanding the role of tomato's active compound in non-communicable diseases. Authors also hope that randomized controlled clinical trials can also be done in near future for clinical use in among non-communicable diseases patients.

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