ABSTRACT
Cardiovascular disease (CVD) has taken up to average 30% of death diagnoses in the world. Prevalent attempts of physicians to treat this disease came down to focus on using drugs with their specific mechanism of action. Since the method only cures the symptoms and need to be pharmacologically monitored, physicians and scientists have been struggling to find other treatment strategies. This problem led us to search for another substance dealing with CVD via preventive therapy, which does not require such close monitoring by physicians in its use. The answer relies on using L-citrulline as potential therapeutics in treating and preventing CVDs. This compound, found mostly in Citrus sp., contains chemical traits that could affect other bodily substances with its metabolic pathways. It has several functions, but boosting NO production is the dominant one in the cardiovascular system. By enhancing NO bioavailability, it suppresses the risk of having myocardial oxidative stress due to ischemia, cardiac pressure-overload, and post-infarct reperfusion. Thus, understanding of L-citrulline effects on endothelial NOS pathway in the generation of NO and its uncoupling mechanisms could be used as a foundation in developing alternative treatment and prevention of oxidative stress-induced CVD.

Keywords: cardiovascular; l-citrulline; nitric oxide; oxidative; treatment

INTRODUCTION
Cardiovascular disease (CVD) has been the most common nationwide cause of death. It accounts for average 30% ultimate cause of death in both developed and developing countries. The era of rapid industrialization and urbanization has promoted higher emergent of the diseases, with some examples such as pathological cardiac hypertrophy, myocardial infarction, and cardiac valve lesions. Risk factors increasing probability of suffering CVDs include the molecular scope of genetics into wide exposure of environmental factors (Loscalzo & Harrison, 2013).

Physicians’ attempts to relieve CVDs have come down into usage of specific pharmacological strategies, such as antihypertensive agents or diuretics. Although they are often deployed to treat CVDs with such low therapeutic index, their amounts in blood plasma must be controlled very carefully to minimize any adverse effects (Katzung et al., 2015). Since the method only cured symptoms and needed to be pharmacologically monitored, physicians and scientists have been struggling to find other treatment strategies. This problem led us to search for another substance dealing with CVD via preventive therapy, which does not require such a close monitoring by physicians in its use. The proximate and ultimate answer for these problems is yes. It is L-citrulline. L-citrulline is known to have potential therapeutics in relieving CVDs. Following discussions of L-citrulline are explained further into its molecular structure, biochemistry, pharmacology, physiology, as well as its utilization in treating cardiovascular system.

L-citrulline is a non-essential amino acid classified specifically as a non-protein monomer (Kaore & Kaore, 2014). It means that L-citrulline cannot be used as raw material in cellular protein synthesis, except that it emerges as post-translational modification or Golgi’s products. L-citrulline does not charge with tRNA normally as it does not correspond within the known 20 types of amino acids. Moreover, it is discovered in muskmelons, squashes, gourds, cucumbers, and pumpkins, as well as watermelons. Watermelons or Citrus vulgaris are the ones contain lots of L-citrulline, which constitutes approximately 2.1 mg per gram of fresh weight (Frank et al., 2017). Schematic representation of watermelon functions can be seen in Figure 1.

L-citrulline may serve as antioxidant that prevents DNA damage-induced oxidative stress and reticuloendothelial system over activity. L-citrulline could also enhance muscle protein synthesis, reduce gastrointestinal tract injury during exercise, and improve blood-tissue perfusion. In this review, focus of L-citrulline activities would be in the cardiovascular system. Any supplementation of L-citrulline for human could be obtained through chemical industries, genetically modified microorganisms, or enzymatic reaction (Jiang et al., 2017).
Biochemistry of L-citrulline

Chemical Characteristics of L-citrulline

L-citrulline is a non-protein amino acid with C$_6$H$_{13}$N$_3$O$_3$ alpha-structured configuration with molecular mass 175.19 Dalton. Its high solubility in water makes it perfect for oral administration via aqueous solution. Available in white powder form and alkalized-smell, its natural structure is often discovered in levorotatory stereoisomerization. Considering its hydrophilic custom, high intake of L-citrulline orally might cause osmotic diarrhea (Kaore & Kaore, 2014).

Figure 2. Molecular structure of L-citrulline (Kaore S et al., 2014)

Metabolism and Biosynthesis of L-citrulline

L-citrulline is biosynthesized through nitric oxide and urea cycles. Urea cycle covers up to 90% production of L-citrulline in hepatocytes (Frank et al., 2017). Arginine is first transformed into ornithine by arginase, releasing urea into blood plasma to be further cleared via kidneys (Kaore & Kaore, 2014). Ornithine then combined with carbamoyl phosphate as constituents of ammonia to form citrulline by the enzymatic activity of ornithine carbamoyltransferase (Frank et al., 2017). Besides, citrulline could be metabolized back into arginine using argininosuccinate as intermediates by argininosuccinate synthase and lyase (Mori et al., 2015).

Another process involved in the generation of L-citrulline is the nitric oxide cycle in blood vessels which covers up 10% production of plasma L-citrulline (Frank et al., 2017). Direct transformation of arginine into citrulline using nitric oxide synthase gives out NO into plasma. Reverse metabolism from citrulline into arginine is associated with the same pathway using argininosuccinate as biosynthetic intermediate (Jiang et al., 2017). In double-blind randomized research crossover design, supplementation of L-citrulline could remove any excess ammonia accumulation in blood, alleviating any central fatigue in athletes (Chen et al., 2016). Detail schematic metabolism of L-citrulline can be seen in Figure 3 and 4.

Although nitric oxide cycle only constitutes tiny part of L-citrulline production, it gives the biggest point of information regarding mechanisms of L-citrulline towards cardiovascular system. Studies conducted to prove this hypothesis explained that consumption of Citrus vulgaris regularly would resist cellular damage due to its antioxidative activity. As Citrus sp. elevates plasma concentration of L-citrulline, it encourages the bioavailability of NO gas throughout systemic and pulmonary blood vessels. This condition provide basis for applying L-citrulline in promoting cardiovascular health (Hong et al., 2015).

Physiological Mechanisms of L-citrulline in Cardiovascular System

L-citrulline: Nitric Oxide Production Booster

NO is a rapidly diffusing gaseous molecule that is released at several locations, such as vascular endothelial cells, neurons, and glial cells. It acts as vasodilator by relaxing vessels’ smooth muscle. Production of NO gas is done by nitric oxide synthase using L-arginine as primary substrate in the NO cycle. L-citrulline, in this NO cycle, could be in paradoxical functions: precursor of L-arginine or byproducts of L-arginine metabolism while making NO as well (Lorin et al., 2014). Supplementation
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of L-citrulline orally increases plasma concentration of L-arginine. Additionally, arginine is then metabolized back into citrulline via either urea or nitric oxide cycle (Kurauchi et al., 2017). Beside the use of L-citrulline as single agent, the combination of L-arginine and L-citrulline supplementation would further increase the amount of plasma citrulline (Suzuki et al., 2017). Metabolic balance manages the whole concentration of arginine and citrulline itself in blood plasma. Graphical presentation between L-citrulline administration and amount of plasma citrulline is explained in Figure 5.

In vascular endothelium, NO is released by endothelial nitric oxide synthase (eNOS) involving L-arginine and L-citrulline as substrate and product respectively (Incalza et al., 2017). Adequate L-citrulline supplementation gradually activates NO production due to recycling of L-citrulline into L-arginine. As a result, L-citrulline would indirectly increase NO levels in plasma (Mori et al., 2015). Furthermore, NO does not exist long enough in plasma soon after its release. Its maximum distance of diffusion is 300 µm with half-life of 0.05-1.8 milliseconds (Mori et al., 2015).

Relationship between L-citrulline and plasma NO is explained in Figure 6.

Effects of L-citrulline on Plasma Amino Acids and other Substances

Not only L-citrulline increase nitric oxide levels in blood, but also it reduces plasma GSH which then dramatically decrease the degradation of NO by oxidation. As a matter of fact, serum nitrite (NO$_2^-$) concentration elevate significantly (Frank et al., 2017). NO$_2^-$ ion would be reduced to become NO under ischemic condition (Kaore & Kaore, 2014). Furthermore, L-citrulline affects certain substances in plasma; for example, glutamine, ornithine, and arginine. Arginine is transformed into L-citrulline

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**Figure 3.** L-citrulline in metabolic pathways: urea and nitric oxide cycle (Frank et al., 2017).

**Figure 4.** L-citrulline metabolism in liver, enterocytes, and kidneys. Note that L-citrulline could be used as biomarker (Kaore et al., 2014).
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to generate ATP by enzymatic reaction of arginine deiminase, ornithine transcarbamoylase, and carbamate kinase. Because of sufficient L-citrulline is found in blood plasma, the backward mechanisms occur, which is the transformation of L-citrulline into arginine via argininosuccinate synthase (ASS) and argininosuccinate lyase (ASL) (Jiang et al., 2017).

Other amino acids are not significantly affected. L-citrulline provides serum buffering effect through the retention of plasma bicarbonate, for it is absorbed as equally as the urea is excreted (Frank et al., 2017). Since the urea is formed through urea cycle involving L-citrulline, it is therefore needed to be cleared along urine.

Other Functions of L-citrulline

L-citrulline is one of the potent hydroxyl radical scavengers that prevents excessive release of superoxide anion (O$_2^-$) as oxidative stress may happen in any ischemic tissues. L-citrulline could also become biomarker for certain inflammation, such as that citrullinated joint protein prone to autoantibodies attack in rheumatoid arthritis. (Kaore & Kaore, 2014) L-citrulline is also considered to be a powerful anabolic amino acid because it increases the rate of muscle protein synthesis. Therefore, weight gain is observed with massive reconstruction in muscular system (Jiang et al., 2017).

Pharmacological Mechanisms of L-citrulline

Pharmacodynamics of L-citrulline

No direct pharmacological effect of L-citrulline towards
Table 1. Risk of pulmonary hypertension with plasma citrulline. Its relative risk of suffering pulmonary hypertension is significantly lower with more than 37 µM plasma citrulline treatment.14

| Plasma Citrulline 12 h Postoperatively | Pulmonary Hypertension Absent | Pulmonary Hypertension Present | P value |
|---------------------------------------|--------------------------------|--------------------------------|---------|
| < 37 µmol/L                           | 18                             | 9                              | .036    |
| 37 µmol/L                             | 12                             | *0                             |         |

Figure 8. Pharmacokinetic modeling of IV administered bolus of citrulline, followed by 4 hours later by infusion. Bolus dose of 150 mg/kg was determined most likely to yield 4-hour trough of 80-100 µM, and infusion of 9 mg/kg/h was predicted to achieve steady state. Note that the plasma half time is 60 minutes with dose-dependent increase along with the added bolus dosage (Barr F et al., 2007).

Pharmacokinetics of L-citrulline
L-citrulline is well absorbed in enteral route. Its bioavailability in this route would be reduced to certain concentration, since it faces first-pass effect in the liver. Despite its conversion to other substances, constant supplementation of oral L-citrulline marked a linear and dose-dependent increase of plasma citrulline (Schwedhelm et al., 2008). The optimal dosage of L-citrulline is controlled by liver and kidneys. As a result, latter restriction of plasma citrulline elevation occurs after excessive supplementation of oral L-citrulline. In addition, 83% of ingested citrulline will be taken up by kidneys to be transformed into L-arginine (Kaore & Kaore, 2014).

Enteral absorption of L-citrulline requires sodium-dependent cotransporter. Comparing to arginine, L-citrulline enters bloodstream much easier from intestinal lumen. It also provides buffering effect to other metabolic substances, especially arginine, involving urea cycle, NO cycle, and arginine biosynthesis. That is why it is safer and efficient to replenish plasma arginine using L-citrulline than directly using arginine (Kurauchi et al., 2017).

Effective dosage of L-citrulline in human is estimated to be 40 mg/kg body weight with maximum 15 g of L-citrulline per oral administration (Frank et al., 2017). Clearance of plasma citrulline in kidneys is estimated to be 0.6 L/kg/h with volume of distribution 0.9 L/kg for 60-minute plasma half-time (Barr et al., 2007). Maintenance of certain plasma citrulline levels needs calculation involving citrulline infusion intravenously (Barr et al., 2007). Graphical presentations of L-citrulline pharmacokinetics in one study can be seen in Figure 8.

Protection of L-citrulline Against Cardiovascular Disease
Some CVDs has been recognized along to be related with oxidative stress; for example, hypertrophic cardiomyopathy, cardiac remodeling, and myocardial infarction. They manifest in the apoptosis or necrosis of normal cardiac myocytes. Some of these disorders are even maintained in certain body conditions or drug-induced states. Furthermore, molecular pathophysiology...
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Figure 9. a) Generation of NO and L-citrulline via electron transfer in NOS pathway. Note that the electron is taken up from NADPH domain in order to reduce heme domain for both L-citrulline and NO synthesis. b) Uncoupling mechanisms compensating for low BH4 cofactor and substrate L-arginine. Note that superoxide anion replaces nitric oxide as byproducts of this pathway (Incalza M et al., 2017).

Involving the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) of these diseases is the ultimate ‘culprit’. Hence, comprehension in the ROS/RNS generation mechanisms would give beneficial effect of using L-citrulline to counteract their pathological activities.

Pathophysiology of Oxidative Stress-induced Cardiovascular Diseases

Reactive oxygen species are hyperreactive intermediates of oxygen-related molecules, which are generated physiologically in mitochondria as byproducts of oxidative phosphorylation. RNS have similar chemical characteristics with ROS but with different element participated, that is nitrogen. Several examples of ROS/RNS are hydrogen peroxide (H\textsubscript{2}O\textsubscript{2}), superoxide anion (O\textsubscript{2}\textsuperscript{-}), oxygen nascent (O\textsuperscript{.}), and peroxynitrite (ONOO\textsuperscript{-}). They are generated as a result of incomplete amounts of electrons in their atomic valence shell. Destructive activities of these species, to fulfill their outer electron shell, are highly related to their oxidative reaction. Oxidation of nuclear materials, membrane fragmentation, cellular autolysis, and protein digestion are the devastating ones. Oxidative stress happens when ROS/RNS levels exceeds the capability of antioxidant defense system to suppress them. Cellular ischemia or hypoxia would be the most dominant factor in triggering oxidative stress. In this case, myocardial ischemia or hypoxia may happen to cause oxidative stress. Post-infarct angiogenesis and fibrosis may lead to ischemic-reperfusion injuries that cause more oxidative damages within nearby cells. In this way, myocardial infarction develops other complications as main effects of cellular oxidative stress (Incalza et al., 2017). Besides myocardial infarction, cardiac remodeling also induces oxidative attacks. Excessive cardiac hypertrophy due to remodeling increased contractility, but with much lower end-diastolic blood volume. This means that it is designed to compensate reduced cardiac output due to aortic stenosis, high cardiac afterload, et cetera. Lower amount of blood stroked with powerful ventricular contraction would dramatically decrease the perfusion of blood into myocardium via coronary arteries. Greater and greater impact of oxidative stress could gradually deteriorate cardiac physiology into vicious cycle of heart failure.

In the situation where cells are experiencing oxidative stress, formation of peroxynitrite occurs most. Peroxynitrite is a radical molecule resulted from the combination of NO and O\textsubscript{2} via a pathway called eNOS uncoupling (Moens et al., 2011). The ‘uncoupling’ mechanism involves decreased amount of tetrahydrobiopterin (BH\textsubscript{4}) which normally stabilize the dimerization of NOS enzyme (Moens et al., 2011). This structure optimally facilitates the transfer of electron from NADPH in its reductase domain to heme group in its oxidase domain to convert arginine into citrulline by generating NO gas (Tang et al., 2014). Relative subtraction of BH\textsubscript{4} cofactor in NOS is primarily caused by oxidation of BH\textsubscript{4} into dihydrobiopterin (BH\textsubscript{2}) via oxidative stress (Moens et al., 2011). As a result, partial transfer of electrons in non-dimer NOS might lead to generation of superoxide anion, instead of nitric oxide (Tang et al., 2014). Further destruction of cells due to
peroxynitrite slowly damage heart pump ability to fulfill metabolic demands (Tang et al., 2014) eNOS uncoupled mechanisms can be seen in Figure 9.

**Protective Effects of L-citrulline Towards Oxidative Stress**

Because L-citrulline is seen to maintain vascular NO level, L-citrulline potentially reverses the damaging effects of oxidative stress in cardiovascular system. L-citrulline is known to upregulate the expression rate of normal eNOS enzyme, subsequently compensating for the uncoupled activity eNOS (Xuan et al., 2015). NO is the key modulator of cardiac function through regulation of myocytes contraction and growth (Tang et al., 2014). NO activates cGMP signaling cascades that eventually modifies NOS protein post-translationally by adding nitrosyl group in free thiol of its cysteine residue (Tang et al., 2014). Thiol-nitrosylation of cysteine residue firmly hold the dimer structure of NOS, subsequently reducing O$_3^-$ production (Tang et al., 2014). In this condition, NO could prevent formation of atherosclerotic plaques, excessive ventricular hypertrophy, as well as pulmonary arterial hypertension (Van Deel et al., 2015). It also counteracts complication of hypercholesterolemia and diabetes mellitus (Moens et al., 2011). Disturbances in nitroso-redox balance, that tightly controls NO and O$_3^-$ level, would finally cause oxidative stress. eNOS expression levels has been known to linked with aggravation of left ventricular hypertrophy and dysfunction in aortic stenosis-induced pressure overload. Knockout of eNOS gene would increase capillary density, fibrosis, and natriuretic peptide expression in heart, rising the risk of cardiac oxidative stress (Van Deel et al., 2015). L-citrulline is known to reduce systemic arterial stiffness at rest and aortic pressure responses to coldpressor test. Randomized controlled study of L-citrulline supplementation could attenuate any exaggerated arterial stiffness regarding either combined metaboreflex or cold exposure; thus, this piece of evidence might provide insight on potential protection against increased cardiac afterload during physical stress (Figueroa et al., 2016).

Chronic and long-term administration of NO as prophylaxis would affect vascular demand, or further induce formation of radical molecules (Xuan et al., 2015). That is why it would be best to increase NO bioavailability and balancing nitroso-redox system via NO cycle, using L-citrulline as substrate. Thus, L-citrulline serves to protect against cardiovascular disease in the sense of preventing cellular oxidative stress.

**Clinical trials: L-citrulline Towards Cardiovascular Diseases**

Advanced application of L-citrulline has come to major clinical trials in hospitals. Improvement of six-minute walking test and quality of life of patients has been seen in patients with arterial pulmonary hypertension comorbid with Eisenmenger syndrome (Sharif et al., 2014). Additionally, pre-exercise L-citrulline administration could enhance splanchnic perfusion, attenuating intestinal ischemia during strenuous exercise. It prevents occurrence of oxidative stress in the enterocytes due to increased number of adequately perfused small vessels compared to placebo (7.8 ± 6.0 vs. -2.0 ± 2.4, p = 0.06) (Van Wijck et al., 2014). Further studies include that assessment of L-citrulline in randomized cross over clinical trials of thirty patients diagnosed with coronary artery disease have shown significant improvement in endothelial function. Ratio flow mediated dilation (FMD) to nitroglycerin dependent vasodilation (NMD) in assessing endothelial function increases significantly conformed with statistical analysis (p < 0.001) after L-citrulline administration (Safi et al., 2017). Ultimately, utilization of L-citrulline in experimental clinical group consisting of 35 patients with systolic heart failure has successfully improved left ventricular ejection fraction (LVEF) up to 35% via evaluation though radioisotopic, ventriculography, and photoplethysmography (Balderas et al., 2012).

**CONCLUSION**

Physicians and scientists’ approaches in managing CVDs regarding strategies’ simplicity, curability, and preventability had led to using L-citrulline as alternative pharmacological substance. Chemical characteristics of L-citrulline are closely related with its biosynthesis and metabolic processes. It provides wide range of plasma active dosage with minimal side-effect and is best administered orally or intravenously to reach its maximum bioavailability. Furthermore, its antioxidant capacity would be effective to prevent oxidative stress-induced cardiovascular diseases. eNOS uncoupling, which produces more radical molecule, could be reversed by L-citrulline existence. Generating NO gas through transformation of L-citrulline into arginine in NO cycle would stabilizes the dimer structure of NOS; on the other hand, monomer NOS would produce O$_3^-$ as byproducts, instead of NO. Indirectly promoting vasodilation, reducing pulmonary hypertension, and regulating of ventricular ejection fraction are all functions of L-citrulline. Lastly, diverse advantages of L-citrulline in cardiovascular system is further comprehended to encourage its utilization in protecting against CVDs.

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