L-Carnitine may extinguish the COVID19 fire:

A review on molecular aspects

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Abbreviations:

LC: L.Carnitine

RAS: renin-angiotensin system

PARP: Poly-ADP ribose polymerase-1

COVID19: Coronavirus 2019 infection

CoV: Coronavirus, Ang: Angiotensin

PARG: poly (ADP-ribose) glycohydrolase

BER: base excision repair

Abstract

Currently, COVID19 has been converted to a catastrophic pandemic worldwide. SARS-CoV-2 virus targets the ACE2 receptor in the human cells and triggers a chain of deleterious events. Despite the high morbidity, there is not yet an efficient treatment for this infection. In this review, some protective aspects of L.Carnitine (LC) have been addressed. In COVID19, renin-angiotensin system (RAS) is upregulated, and the NF-κB pathway is overexpressed. Moreover, a progressive cytokine storm is established. In all of these pathogenic processes, LC could play a modifier role to improve the condition. LC could be beneficial against the antioxidant effects of Angiotensin II by inhibition of NF-κB and down-regulation of NOX1 and NOX2. An anti-apoptotic and genome-stabilizer function has been determined for LC through inhibition of pro-apoptotic caspases and activation of PARP-1. LC is an immunomodulator that downregulates the pro-inflammatory cytokines including TNF-α, IL-6, and IL-1 which could quench the cytokine storm. LC also can act as a protective agent against the cardiotoxicity caused in COVID19 because of the disturbance in the ACE2-mediated signaling pathway, cytokine storm, pulmonary dysfunction, and drug side-effects. Given the potential protective effects of LC, it is suggested as a supportive and therapeutic option in the patients with coronavirus infection.

Introduction

The novel Coronavirus 2019 infection (COVID19) was officially confirmed as pandemic by WHO on 11 March 2020 as total number of the deaths passed 4000 globally [1]. SARS-CoV-2 virus, the pathogen of COVID19, is a member of Beta-CoV genera from the positive single-stranded RNA viruses called the Coronavirus (CoV) family which are known as the major causes of respiratory disease outbreaks. Two well-known members of this family, SARS-CoV and MERS-CoV, had been registered as the cause of serious epidemics at the time of their outbursts [2]. The envelope spike glycoproteins of Coronaviruses create the shape of a crown and are essential for the attachment and entrance of the virus as they provide receptor-binding domains [3]. Based on the accurate molecular analysis, these domains in SARS-CoV-2 share 76.5% homology to the spike proteins in SARS-CoV [4] but the flexible glycyl residues within the distinct loop of SARS-CoV-2 receptor-binding domains elevate their affinity for Angiotensin Converting Enzyme 2 (ACE2) which is their mutual receptor [5]. Therefore, COVID19 is more communicable [6] and its death toll has exceeded the SARS and MERS epidemics combined [7].

Despite the global restless efforts to investigate treatment options and control the concerning pandemic, the therapeutic strategies have been only preventive and supportive by the present time. Current management strategies are mainly based on reducing transmission by travel restrictions and aggressive isolation [8].

Given the urge to find the therapeutic options for the novel COVID19, medications like Hydroxychloroquine [9], AT1R blockers such as Losartan and Olmesartan [10,11], and the nonsteroidal anti-inflammatory drug indomethacin [12] are being investigated and have shown to relieve symptoms in some patients. Meanwhile, the search for a more definitive treatment still continues as the virus is spreading rapidly around the world. In this review, some potential protective aspects of L.Carnitine (LC) have been discussed.

Pathophysiology of COVID19

As mentioned, SARS-CoV-2 similar to the original SARS-CoV, binds to human body cells through the transmembrane enzyme ACE2. The attachment of the virus to its receptor facilitates its entrance and replication and is also responsible for several serious complications of the disease through protein interactions. The virus- ACE2 interaction has been established to result in the down-regulation of the enzyme [13,14]. The enzyme ACE2 reverses the functional pathway of Angiotensin (Ang)II by the production of Ang (1-7) in the RAS system [15]. Disturbance in the balance of the RAS system and the increase in Ang II/Ang(1-7) ratio is one of the leading causes of severe lung, heart and kidneycomplications in Coronavirus patients [14]. AngII is known to be a pro-inflammatory factor. The over-expression of AngII not only as a vasoconstrictive agent but also as an activator of the enzyme NADPH oxidase and a stimulus for the expression of NF-κB is established to play a pivotal role in the pathogenesis of chronic hypertension, chronic kidney diseases, heart failure and other systemic inflammatory diseases [16,17].

NADPH oxidase is a reactive oxygen species (ROS) producing enzyme which has five homologous subgroups in human body. NOX1 is expressed in epithelial cells, endothelial cells, interstitial fibroblasts and smooth muscle cells, while NOX2 is expressed in phagocytes, vascular cells, heart, kidneys, neurons and hepatocytes. These two enzymes could be stimulated by AngII, produce ROS and decrease the available cellular NADPH in pathological conditions [18]. It could lead to the oxidative damage in DNA which is primarily repaired through the base excision repair (BER) pathway [19]. Poly-ADP ribose polymerase-1 (PARP-1), is a DNA base repair enzyme contributing to BER and has an essential role in the genomic stability maintenance [20]. PARP-1 has an antiviral function using ADP-ribosylation of virus genome (RNA or DNA) and inhibiting the translation of viral trnscripts. There are several viral families, including Togaviridae, Hepeviridae and Coronaviridae with encoding

ability of a macrodomain protein with poly (ADP-ribose) glycohydrolase (PARG) activity. This macrodomain can hydrolyze ADP-ribose from proteins and nucleic acids to accelerate the viral replication and virulence [21]. (Figure 1)

L-Carnitine Potencies Against COVID19 Pathology

L-Carnitine (LC) is a crucial and natural component of body cells participating in the metabolism of fatty acids. LC naturally exists in dietary sources including dairy and red meat and can also be produced in the body from the amino acids Lysine and Methionine. L-isomer of Carnitine is biologically active and D-isomer is inactive in the body [22]. In fact, LC naturally acts as an obligatory cofactor for the oxidation of fatty acids in the mitochondria. Some new studies, however, have demonstrated its antioxidant and anti-inflammatory potency to be of great importance [23]. (Figure 1)

I) L-Carnitine and Antioxidant properties

Some experimental studies presented a potentially significant synergistic role for α-lipoic acid and acetyl-L-carnitine in normal mitochondrial function, so insufficiency of these compounds could lead to raising mitochondrial oxidant production. Moreover, LC is able to decrease production of oxygen free radicals [24,25]. The reductive effect of acetyl-L-carnitine on oxidative stress that has been confirmed in some experimental researches, could lead to promote the overall antioxidant status of cells [26–28]. A protective event which can reduce the stress and infection-induced tissue damages like COVID19. LC could be also beneficial against the antioxidant effects of Angiotensin II by the inhibition of the expression of NF-κB and the down-regulation of the enzymes NOX1 and NOX2 [28], a pathway which is overactivated during COVID19 pathogenesis [29]. According to some experimental studies,

LC could Improve the early haemodynamic parameters and also mortality rate in the patients with septic shock [30–32], a critical condition in which NF-κB overactivation and oxidative stress have been already introduced as culprits [33,34].

II) L-Carnitine as an Anti-apoptotic and genome-stabilizer agent

Moreover, LC has a potency to suppress the proteolytic activation of caspase9 mediated by cytochrome C and ATP [27,35]. Apoptosis is mediated by caspases, a group of highly specific cysteine proteases. Pro-apoptotic caspases can be activated by Palmitoyl-L-carnitine [36]. It has been also determined that LC can inhibit apoptosis by reducing caspase activation [37]. Meanwhile, LC leads to a reduction in DNA-single strand breaks in human peripheral blood lymphocytes treated to hypoxanthine likely through modulating the PARP-1 activation and other related repair mechanisms [38]. The anti-apoptotic effect of LC and its biotypes has been determined in different pathological conditions. For example, for human lymphoma cells treated with apoptotic agents, LC presented a significant anti-apoptotic effect [39]. The therapeutic effects of LC have been also established in AIDS and Alzheimer's disease and ischemic injury [40,41]. Apoptosis and cell death in infected organ tissues has been identified as a common histopathological finding in the patients with coronavirus infection [42]. Accordingly, LC may ameliorate the deleterious complications of COVID19 by improving the mitochondrial dysfunction in hypoxic conditions and also by decreasing apoptosis [23]. It seems, LC anti-apoptotic potency could be considered as a therapeutic effect in the patients with COVID19.

III) L-Carnitine and its Immunomodulatory effects

Moreover, a new study has statistically reported that number of T cells, including CD4+ and CD8+ T cells, falls below the critical threshold in severe, critical and perished groups of COVID19 patients. The expression of ACE2, the predicted receptor of the SARS-CoV-2 virus, is absent on T cells suggesting that the depressed numbers of T cells is not directly caused by infection of these lymphocytes. Consistently, the amount of secreted cytokines including TNF-α, IL-6 and IL-10 was increased in COVID19 patients which negatively correlates with levels of CD4+ and CD8+ T cells [43]. Previous studies have also demonstrated the interfering role of LC with the apoptotic process through down-modulation of the proapoptotic Fas signals transduction and suppressing the generation of ceramide. The events which have been shown to trigger signaling pathways to lymphocyte apoptosis [23,44,45]. Generally, LC appears to downregulate the pro-inflammatory cytokines including TNF-α, IL-6 and IL-1 which can prevent patients from cytokine storm. A pilot study demonstrates that LC supplementation for HIV patients leads to an increase in the number of CD4+ and CD8+ T cells due to LC interference with ceramide production and Fas-induced apoptotic signal [46]. The anti-viral and anti-inflammatory effects of LC have also been evaluated in the treatment of HCV and it has been established that the supplement could improve the injury of hepatic cells by decreasing oxidative stress [47].

In a study on lymphocytes of aged rats it was reported that in addition to reducing apoptosis and decreasing TNF-α levels, LC can increase the levels of antioxidant enzymes (SOD, Cat, GSH-Px and GSH-Red) and reduce DNA damage [48]. The carnitine palmitoyltransferase (CPT) system is responsible for transporting the long-chain fatty acids from the cytoplasm into the mitochondria where the fatty acids undergo β-oxidation. This CPT system contains two separate proteins localized in the outer (CPT1) and the inner (CPT2) mitochondrial membrane. While CPT2 is ubiquitously expressed, there are three tissue-specific CPT1 isoforms: CPT1a, CPT1b, and CPT1c. CPT1a is the primary isoform in lymphocytes, liver,

kidney, spleen, lung, intestine, pancreas, and ovary [49]. It was reported that the administration of carnitine could increase the expression of CPT1 in a study on HCV-infected hepatocytes [50]. The higher CPT1 expression accounted for increased spare respiratory capacity that improves the memory T cells resistance to stress. Furthermore, CPT1a overexpressing into the antigen-specific T cells improved their recovery after infection [51].

 (Table 1)

The Cardioprotective effects of L-Carnitine in COVID19

L-Carnitine is a known nutritional supplement suitable for the control and even prevention of metabolic and cardiovascular diseases[52]. It may be beneficial against the detrimental effects of COVID19 on the cardiovascular system due to the following statements: (Figure 2,3)

1.   The disturbance of ACE2-mediated signaling pathway could result in the cardiovascular complications. This enzyme is abundantly expressed not only in the lung tissue but also in the cardiovascular system. CoV-ACE2 binding can interfere with the signaling pathway of the enzyme. As mentioned, the disturbance of the functional pathway of ACE2 leads to an increase in AngII and a decrease in $Ang_{(1-7)}$, resulting in the cardiovascular complications including: the endothelial dysfunction [53–55], the intoxication of myocytes due to the AngII-induced inflammation [56–58], and a raised incidence of arrhythmia[59]. As explained earlier, LC could counteract with destructive effects and the inflammation caused by the RAS imbalance through inhibiting the enzymes NOX1 and NOX2 and decreasing the expression of NF-κB factor[60]. This supplement which acts as a free radical scavenger, can decrease the peroxidation of fatty acids, reduce the amount of toxic Acyl-Coa in human cells, prevent or moderate the intoxication and damage of myocytes caused by the virus replication or the following inflammation [61].

In addition to the harmful effects on myocytes, the RAS disturbance and the suppression of ACE2 function could lead to the endothelial dysfunction. AngII affects the vascular endothelium by increasing the expression of monocyte chemoattractant protein-1 (MCP-1) molecules, IL1B, IL-6, and the activation of NADPH oxidase. These changes eventually disturb the cycle of NO and could result in endothelial dysfunction [53,58,62–64]. Additionally, AngII increases the expression of Profilin-1 which could induce the peroxynitrite damage on the vascular endothelial surface. LC through downregulating the NOX enzyme, acts as a free radical scavenger, and by upregulating the eNOS enzyme could exert a protective role against the endothelial dysfunction in COVID19 patients [52,60,61,65].

2.   The cytokine storm resulted from the imbalance of lymphocytes could affect cardiac function [66,67]. According to studies, cytokine storm is one of the main pathologic reasons for cardiac toxicity in the patients with COVID19. As mentioned, LC could be a preventive agent against the cardiac complications of COVID19 through its immunomodulatory effects, particularly the modulation of T-cell ratio.

3.   The pulmonary dysfunction due to severe alveolar damage in COVID19 and the following hypoxemia could cause myocardial injury [68]. Some studies have demonstrated that the level of myocardial carnitine is critically declined during the ischemic and hypoxemic conditions. In the patients with COVID19, the hypoxic conditions could be induced in the myocytes through severe involvement of the lungs and the following insufficiency to provide the required oxygen for the body [68]. The carnitine supplementation in ischemic heart disease could lead to downregulation of ROS and decrease the fatty acid concentration in the cytoplasm. The accumulation of fatty acids in the cytoplasm of myocytes in hypoxic

conditions can induce the peroxidation of fatty acids, resulting in the elevation of oxidative stress in the myocardium [69].

4. Despite the fact that there is still no definitive treatment strategy for Coronavirus infection, several medications are prescribed corresponding to regional health policies. These medications include: Hydroxychloroquine, potent empiric antibiotics to prevent bacterial super-infections and antiviral drugs like Lopinavir, Ritonavir or the combination of both (KALETRA®). A number of these medications including Hydroxychloroquine and KALETRA® are known as the causes of adverse cardiovascular effects in the patients [70–72]. Particularly, given the fact that the simultaneous consumption of these drugs could exacerbate the adverse effects, the patients with COVID19 are susceptible to cardiac complications and specially cardiac arrhythmia [66,68]. Several studies have established the protective effects of LC against the cardiotoxicity caused by different medications [73–77]. These drugs primarily contribute to cardiotoxicity through inducing inflammation and elevating the level of ROS in the myocytes [74]. Furthermore, it has been demonstrated that carnitine supplementation in cardiovascular patients, particularly susceptible ones, could successfully reduce the occurrence of cardiac arrhythmia [52]. Accordingly, LC could prevent the toxicity caused by drug-induced inflammation, cardiac arrhythmia and myocardial inflammation through decreasing the cellular oxidative stress and modulating the aerobic metabolism system in the cardiac conducting cells and myocytes. Meanwhile, it has been determined that LC has anti-inflammatory and antiarrhythmic effects in ischemic and cardiomyopathy conditions [52,61].

Conclusion

Given the fact that currently, there is no definitive medication for the treatment of Coronavirus patients, and considering the progressive course of the disease which starts with a limited involvement of the lungs, leading to progressive Acute Respiratory Distress Syndrome in the advanced cases, it is expected that the supplementation of patients with L-Carnitine in primary stages of the disease could prevent the deterioration of overall health and the fatal complications of the virus.

Author contributions

MF contributed in proposal preparing, searching and writing the paper; MJK and SGSh contributed also in the searching and writing the paper; AASh designed the infographic figures and diagrams and also contributed in the writing; HKh contributed in supervision and technical writing; MZ contributed also in proposal preparing and was the supervisor of the project.

Conflict of interest statement

The authors declare that they have no conflict of interest toward the content of this article.

References

[1]   "WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020," available at https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020, **n.d.**

[2]   M. Cascella, M. Rajnik, A. Cuomo, S. C. Dulebohn, R. Di Napoli, in *StatPearls*, StatPearls Publishing, Treasure Island (FL) **2020**.

[3]   S. Baron, Ed. , *Medical Microbiology*, University Of Texas Medical Branch At Galveston, Galveston (TX) **1996**.

[4]   X. Xu, P. Chen, J. Wang, J. Feng, H. Zhou, X. Li, W. Zhong, P. Hao, *Sci. China Life Sci.* **2020**, *63*, 457–460.

[5]   Y. Chen, Y. Guo, Y. Pan, Z. J. Zhao, *Biochem. Biophys. Res. Commun.* **2020**, DOI 10.1016/j.bbrc.2020.02.071.

[6]   Y. Wan, J. Shang, R. Graham, R. S. Baric, F. Li, *J. Virol.* **2020**, DOI 10.1128/JVI.00127-20.

[7]   E. Mahase, *BMJ* **2020**, *368*, m641.

[8]   M. Cascella, M. Rajnik, A. Cuomo, S. C. Dulebohn, R. Di Napoli, in *StatPearls*, StatPearls Publishing, Treasure Island (FL) **2020**.

[9]   X. Yao, F. Ye, M. Zhang, C. Cui, B. Huang, P. Niu, X. Liu, L. Zhao, E. Dong, C. Song, S. Zhan, R. Lu, H. Li, W. Tan, D. Liu, *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2020**, DOI 10.1093/cid/ciaa237.

[10]   D. Gurwitz, *Drug Dev. Res.* **2020**, DOI 10.1002/ddr.21656.

[11]   "A potential protective role of Losartan against coronavirus induced lung damage | Infection Control & Hospital Epidemiology | Cambridge Core," available at https://www.cambridge.org/core/journals/infection-control-and-hospital-epidemiology/article/potential-protective-role-of-losartan-against-coronavirus-induced-lung-damage/196AA8922246C70F26BC8F0B72C6533A, **n.d.**

[12]   C. Amici, A. Di Caro, A. Ciucci, L. Chiappa, C. Castilletti, V. Martella, N. Decaro, C. Buonavoglia, M. R. Capobianchi, M. G. Santoro, *Antivir. Ther.* **2006**, *11*, 1021–1030.

[13] K. Kuba, Y. Imai, S. Rao, H. Gao, F. Guo, B. Guan, Y. Huan, P. Yang, Y. Zhang, W. Deng, L. Bao, B. Zhang, G. Liu, Z. Wang, M. Chappell, Y. Liu, D. Zheng, A. Leibbrandt, T. Wada, A. S. Slutsky, D. Liu, C. Qin, C. Jiang, J. M. Penninger, *Nat. Med.* **2005**, *11*, 875–879.

[14] Y. Imai, K. Kuba, S. Rao, Y. Huan, F. Guo, B. Guan, P. Yang, R. Sarao, T. Wada, H. Leong-Poi, M. A. Crackower, A. Fukamizu, C.-C. Hui, L. Hein, S. Uhlig, A. S. Slutsky, C. Jiang, J. M. Penninger, *Nature* **2005**, *436*, 112–116.

[15] R. A. S. Santos, A. C. Simoes e Silva, C. Maric, D. M. R. Silva, R. P. Machado, I. de Buhr, S. Heringer-Walther, S. V. B. Pinheiro, M. T. Lopes, M. Bader, E. P. Mendes, V. S. Lemos, M. J. Campagnole-Santos, H.-P. Schultheiss, R. Speth, T. Walther, *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*, 8258–8263.

[16] M. I. Phillips, S. Kagiyama, *Curr. Opin. Investig. Drugs Lond. Engl. 2000* **2002**, *3*, 569–577.

[17] C. M. Ferrario, W. B. Strawn, *Am. J. Cardiol.* **2006**, *98*, 121–128.

[18] T. Ago, J. Kuroda, M. Kamouchi, J. Sadoshima, T. Kitazono, *Circ. J. Off. J. Jpn. Circ. Soc.* **2011**, *75*, 1791–1800.

[19] T. B. Kryston, A. B. Georgiev, P. Pissis, A. G. Georgakilas, *Mutat. Res.* **2011**, *711*, 193–201.

[20] M. T. Mathews, B. C. Berk, *Arterioscler. Thromb. Vasc. Biol.* **2008**, *28*, 711–717.

[21] Kouhpayeh, S.; Shariati, L.; Boshtam, M.; Rahimmanesh, I.; Mirian, M.; Zeinalian, M.; Salari-jazi, A.; Khanahmad, N.; Damavandi, M.S.; Sadeghi, P.; Khanahmad, H. The Molecular Story of COVID-19; NAD^+ Depletion Addresses All Questions in this Infection. *Preprints* **2020**, 2020030346 (doi: 10.20944/preprints202003.0346.v1).

[22] C. J. Rebouche, D. J. Paulson, *Annu. Rev. Nutr.* **1986**, *6*, 41–66.

[23] M. Modanloo, M. Shokrzadeh, *Iran. J. Kidney Dis.* **2019**, *13*, 74–86.

[24] D. A. Ford, X. Han, C. C. Horner, R. W. Gross, *Biochemistry* **1996**, *35*, 7903–7909.

[25] E. Esposito, D. Rotilio, V. Di Matteo, C. Di Giulio, M. Cacchio, S. Algeri, *Neurobiol. Aging* **2002**, *23*, 719–735.

[26] M. Modanloo, M. Shokrzadeh, *Iran. J. Kidney Dis.* **2019**, *13*, 74–86.

[27] R. W. Orrell, R. J. M. Lane, M. Ross, *Amyotroph. Lateral Scler. Off. Publ. World Fed. Neurol. Res. Group Mot. Neuron Dis.* **2008**, *9*, 195–211.

[28] A. J. Blanca, M. V. Ruiz-Armenta, S. Zambrano, J. L. Miguel-Carrasco, F. M. González-Roncero, A. Fortuño, E. Revilla, A. Mate, C. M. Vázquez, *Food Chem.* **2017**, *228*, 356–366.

[29] "The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status | Military Medical Research | Full Text," available at https://mmrjournal.biomedcentral.com/articles/10.1186/s40779-020-00240-0, **n.d.**

[30] A. Gasparetto, G. G. Corbucci, R. A. De Blasi, M. Antonelli, E. Bagiella, S. D'Iddio, C. Trevisani, *Int. J. Clin. Pharmacol. Res.* **1991**, *11*, 83–92.

[31] M. A. Puskarich, J. A. Kline, V. Krabill, H. Claremont, A. E. Jones, *JPEN J. Parenter. Enteral Nutr.* **2014**, *38*, 736–743.

[32] J. B. Belsky, C. R. Wira, V. Jacob, J. E. Sather, P. J. Lee, *Nutr. Res. Rev.* **2018**, *31*, 281–290.

[33] J. Macdonald, H. F. Galley, N. R. Webster, *Br. J. Anaesth.* **2003**, *90*, 221–232.

[34] X. Li, J. Su, X. Cui, Y. Li, A. Barochia, P. Q. Eichacker, *Expert Opin. Investig. Drugs* **2009**, *18*, 1047–1060.

[35] A. V. Plioplys, S. Bagherpour, I. Kasnicka, *Brain Dev.* **1994**, *16*, 146–149.

[36] M. C. Mutomba, H. Yuan, M. Konyavko, S. Adachi, C. B. Yokoyama, V. Esser, J. D. McGarry, B. M. Babior, R. A. Gottlieb, *FEBS Lett.* **2000**, *478*, 19–25.

[37] S. Moretti, E. Alesse, L. Di Marzio, F. Zazzeroni, B. Ruggeri, S. Marcellini, G. Famularo, S. M. Steinberg, A. Boschini, M. G. Cifone, C. De Simone, *Blood* **1998**, *91*, 3817–3824.

[38] D. J. Paulson, J. Traxler, M. Schmidt, J. Noonan, A. L. Shug, *Cardiovasc. Res.* **1986**, *20*, 536–541.

[39] S.-N. Qi, Z.-F. Zhang, Z.-Y. Wang, A. Yoshida, T. Ueda, *Oncol. Rep.* **2006**, *15*, 119–122.

[40] T. M. Hagen, R. Moreau, J. H. Suh, F. Visioli, *Ann. N. Y. Acad. Sci.* **2002**, *959*, 491–507.

[41] J. Haorah, N. A. Floreani, B. Knipe, Y. Persidsky, *Free Radic. Biol. Med.* **2011**, *51*, 1601–1609.

[42] T.-N. Chau, K.-C. Lee, H. Yao, T.-Y. Tsang, T.-C. Chow, Y.-C. Yeung, K.-W. Choi, Y.-K. Tso, T. Lau, S.-T. Lai, C.-L. Lai, *Hepatol. Baltim. Md* **2004**, *39*, 302–310.

[43] "Reduction and Functional Exhaustion of T Cells in Patients with Coronavirus Disease 2019 (COVID-19) | medRxiv," available at https://www.medrxiv.org/content/10.1101/2020.02.18.20024364v1, **n.d.**

[44] L. Di Marzio, E. Alesse, P. Roncaioli, P. Muzi, S. Moretti, S. Marcellini, G. Amicosante, C. De Simone, M. G. Cifone, *Proc. Assoc. Am. Physicians* **1997**, *109*, 154–163.

[45] G. Delogu, G. Famularo, F. Amati, L. Signore, A. Antonucci, V. Trinchieri, L. Di Marzio, M. G. Cifone, *Crit. Care Med.* **1999**, *27*, 2413–2417.

[46] "Effect of L-carnitine on human immunodeficiency virus-1 infection-associated apoptosis: a pilot study. - PubMed - NCBI," available at https://www.ncbi.nlm.nih.gov/pubmed/?term=Effect+of+L-Carnitine+on+Human+Immunodeficiency+Virus-1+Infection-Associated+Apoptosis%3A+A+Pilot+Study, **n.d.**

[47] Y. Tsukuda, G. Suda, S. Tsunematsu, J. Ito, F. Sato, K. Terashita, M. Nakai, T. Sho, O. Maehara, T. Shimazaki, M. Kimura, K. Morikawa, M. Natsuizaka, K. Ogawa, S. Ohnishi, M. Chuma, N. Sakamoto, *J. Med. Virol.* **2017**, *89*, 857–866.

[48] T. Thangasamy, P. Jeyakumar, S. Sittadjody, A. G. Joyee, P. Chinnakannu, *Biogerontology* **2009**, *10*, 163–172.

[49] J.-P. Bonnefont, F. Djouadi, C. Prip-Buus, S. Gobin, A. Munnich, J. Bastin, *Mol. Aspects Med.* **2004**, *25*, 495–520.

[50] Y. Tsukuda, G. Suda, S. Tsunematsu, J. Ito, F. Sato, K. Terashita, M. Nakai, T. Sho, O. Maehara, T. Shimazaki, M. Kimura, K. Morikawa, M. Natsuizaka, K. Ogawa, S. Ohnishi, M. Chuma, N. Sakamoto, *J. Med. Virol.* **2017**, *89*, 857–866.

[51] G. J. W. van der Windt, B. Everts, C.-H. Chang, J. D. Curtis, T. C. Freitas, E. Amiel, E. J. Pearce, E. L. Pearce, *Immunity* **2012**, *36*, 68–78.

[52] Z.-Y. Wang, Y.-Y. Liu, G.-H. Liu, H.-B. Lu, C.-Y. Mao, *Life Sci.* **2018**, *194*, 88–97.

[53] L. Wang, X. Hu, W. Zhang, F. Tian, *Inflamm. Res.* **2013**, *62*, 219–228.

[54] A. Daugherty, L. Cassis, *Trends Cardiovasc. Med.* **2004**, *14*, 117–120.

[55] H.-Y. Jin, B. Song, G. Y. Oudit, S. T. Davidge, H.-M. Yu, Y.-Y. Jiang, P.-J. Gao, D.-L. Zhu, G. Ning, Z. Kassiri, J. M. Penninger, J.-C. Zhong, *PLOS ONE* **2012**, *7*, e38502.

[56] A. C. Simões e Silva, M. M. Teixeira, *Pharmacol. Res.* **2016**, *107*, 154–162.

[57] P. Kong, P. Christia, N. G. Frangogiannis, *Cell. Mol. Life Sci.* **2014**, *71*, 549–574.

[58] A. Daugherty, L. Cassis, *Trends Cardiovasc. Med.* **2004**, *14*, 117–120.

[59] H. J. Jansen, M. Mackasey, M. Moghtadaei, D. D. Belke, E. E. Egom, J. M. Tuomi, S. A. Rafferty, A. W. Kirkby, R. A. Rose, *J. Mol. Cell. Cardiol.* **2018**, *124*, 12–25.

[60] A. J. Blanca, M. V. Ruiz-Armenta, S. Zambrano, J. L. Miguel-Carrasco, F. M. González-Roncero, A. Fortuño, E. Revilla, A. Mate, C. M. Vázquez, *Food Chem.* **2017**, *228*, 356–366.

[61] M. Modanloo, M. Shokrzadeh, *Iran. J. Kidney Dis.* **2019**, *13*, 74.

[62] S. J. Forrester, G. W. Booz, C. D. Sigmund, T. M. Coffman, T. Kawai, V. Rizzo, R. Scalia, S. Eguchi, *Physiol. Rev.* **2018**, *98*, 1627–1738.

[63] H. Zhang, J. M. Penninger, Y. Li, N. Zhong, A. S. Slutsky, *Intensive Care Med.* **2020**, DOI 10.1007/s00134-020-05985-9.

[64] H.-Y. Jin, B. Song, G. Y. Oudit, S. T. Davidge, H.-M. Yu, Y.-Y. Jiang, P.-J. Gao, D.-L. Zhu, G. Ning, Z. Kassiri, J. M. Penninger, J.-C. Zhong, *PLOS ONE* **2012**, *7*, e38502.

[65] M. Mohammadi, A. Hajhossein Talasaz, M. Alidoosti, *Clin. Nutr. ESPEN* **2016**, *15*, 1–10.

[66] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, *The Lancet* **2020**, *395*, 497–506.

[67] M. Bartekova, J. Radosinska, M. Jelemensky, N. S. Dhalla, *Heart Fail. Rev.* **2018**, *23*, 733–758.

[68] Y.-Y. Zheng, Y.-T. Ma, J.-Y. Zhang, X. Xie, *Nat. Rev. Cardiol.* **2020**, DOI 10.1038/s41569-020-0360-5.

[69] J. J. DiNicolantonio, C. J. Lavie, H. Fares, A. R. Menezes, J. H. O'Keefe, *Mayo Clin. Proc.* **2013**, *88*, 544–551.

[70] C. Chatre, F. Roubille, H. Vernhet, C. Jorgensen, Y.-M. Pers, *Drug Saf.* **2018**, *41*, 919–931.

[71] "FDA Issues Safety Labeling Changes for Kaletra," available at http://www.medscape.com/viewarticle/590940, **n.d.**

[72] P. Mladěnka, L. Applová, J. Patočka, V. M. Costa, F. Remiao, J. Pourová, A. Mladěnka, J. Karlíčková, L. Jahodář, M. Vopršalová, K. J. Varner, M. Štěrba, TOX-OER and CARDIOTOX Hradec Králové Researchers and Collaborators, *Med. Res. Rev.* **2018**, *38*, 1332–1403.

[73] G. K. Wong, C. Pehora, M. W. Crawford, *Can. J. Anesth. Can. Anesth.* **2017**, *64*, 270–279.

[74] M. M. Aziz, M. A. Abd El Fattah, K. A. Ahmed, H. M. Sayed, *Can. J. Physiol. Pharmacol.* **2019**, 183–193.

[75] M. Zhao, Q. Jiang, W. Wang, M. Geng, M. Wang, Y. Han, C. Wang, *Int. J. Mol. Sci.* **2017**, *18*, DOI 10.3390/ijms18061229.

[76] M. M. Sayed-Ahmed, A. Q. Darweesh, A. J. Fatani, *Oxid. Med. Cell. Longev.* **1900**, *3*, 160182.

[77] S. H. Armenian, *Ann. Nutr. Metab.* **2016**, *68(suppl 3)*, 10–14.

Figures and Table

L-Carnitine may extinguish the COVID19 fire:

A review on molecular aspects
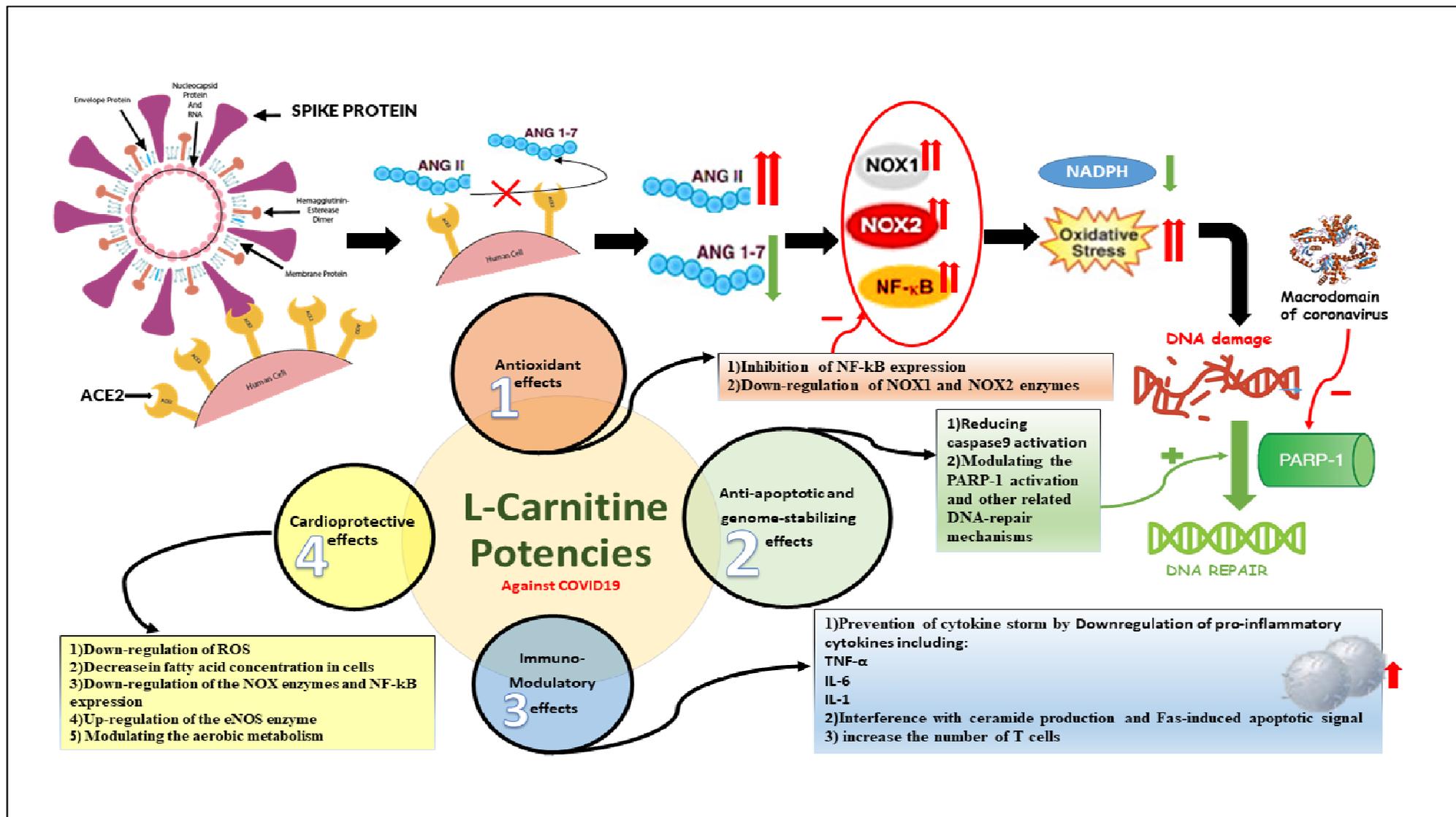
Figure 1: An infographic picture illustrating the molecular mechanisms of SARS-Cov-2 pathogenicity (Upper) and the molecular effects of L-Carnitine against the virus pathologic damages.
ACE: Angiotensin Converting Enzyme, ANG: Angiotensin, PARP-1: Poly-ADP ribose polymerase-1
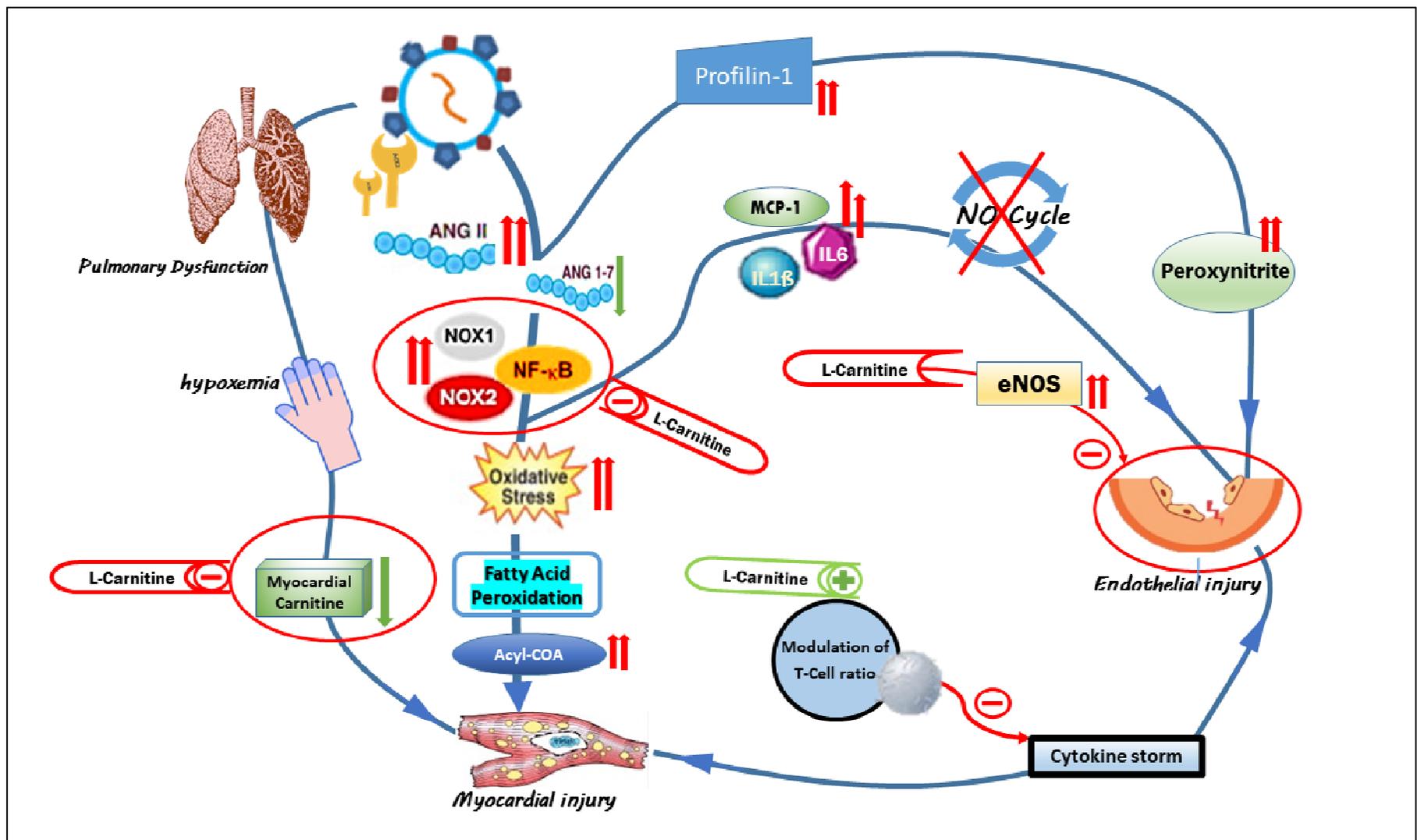
Figure 2: An infographic picture illustrating the molecular mechanisms of cardio-toxicity effects of SARS-Cov-2 in COVID-19 and the molecular effects of L-Carnitine against the induced cardiovascular damages.

ANG: Angiotensin, MCP-1: monocyte chemoattractant protein-1
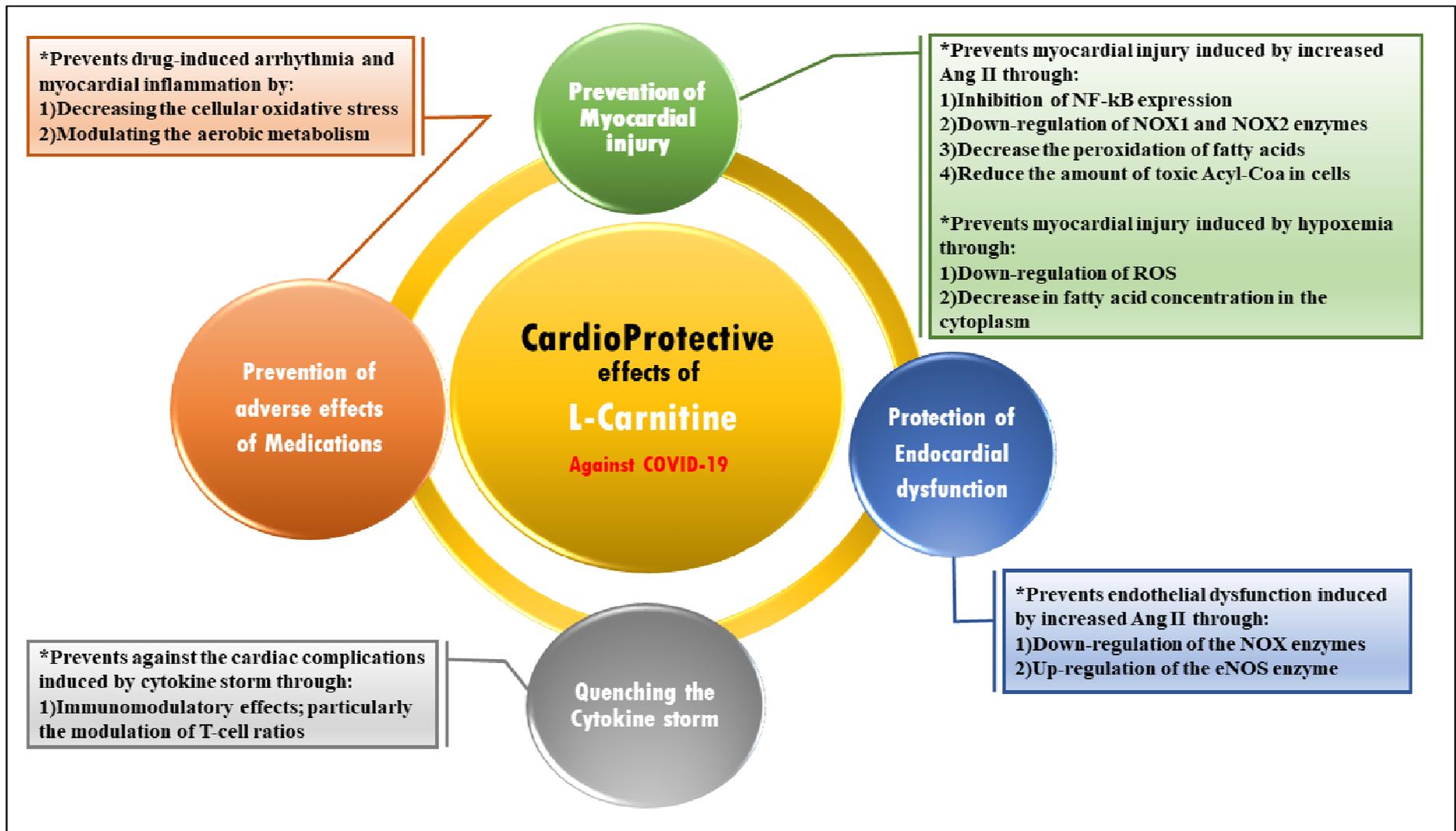
Figure 3: An infographic diagram illustrating the cardio-protective effects of L-Carnitine and the molecular pathways involved

Table 1. A Summary of L-Carnitine molecular effects against COVID-19		
Area of effect	Affected molecules	outcome
1) Antioxidant effect	NOX1 ↓ NOX2 ↓ NF-kB ↓	Oxidative stress ↓
2) Anti-apoptotic and Genome-stabilizing effect	PARP-1 ↑ Caspase9 ↓	Apoptosis and Cell injury ↓ DNA repair and Cell healing ↑
3) Immunomodulatory effect	TNFα ↓ IL6 ↓ IL1 ↓ Ceramide ↓ FAS-induced signal ↓	CD4+ & CD8+ T-cells ↑ Reducing the Cytokine storm ↓
4) Cardio-protective effects	AngII ↑ NOX1 ↓ NOX2 ↓ NF-kB ↓ ROS ↓	Myocardial injury ↓ Endothelial dysfunction ↓