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ABSTRACT

Numerous experiments demonstrated that pyruvate is more beneficial than anions in current medical fluids because of its beneficial biological and pharmacological properties via increasing hypoxia/anoxia tolerance, correcting hypoxic lactic acidosis, and exerting anti- oxidative stress, -inflammation, and -apoptosis. These target against major features of pathological defects in Covid-19 viral infection: hypoxia and cytokine storm that induce clinical dyspnoea and lymphopenia. The spontaneous pyruvate reduction with lactate dehydrogenase (LDH) may play a pivotal role in enhancing nicotinamide adenine dinucleotide oxidized/ reduced form (NAD^+/NADH) ratio, preserving canonical glycolytic pathways. Also, the core of exogenous pyruvate actions may be the reversal of Warburg effect in aberrant glucometabolic pathways in hypoxia with viral infections by reactivating pyruvate dehydrogenase (PDH) activity due to its direct inhibition of the PDH kinase (PDK), eliminating intracellular acidosis and energy crisis.

Keywords: covid-19; hypoxia; cytokine storm; oral rehydration solution; prevention; pyruvate; viral infection.

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SUMMARY

Numerous experiments demonstrated that pyruvate is more beneficial than anions in current medical fluids because of its beneficial biological and pharmacological properties via increasing hypoxia/anoxia tolerance, correcting hypoxic lactic acidosis, and exerting anti-oxidative stress, -inflammation, and -apoptosis. These target against major features of pathological defects in Covid-19 viral infection: hypoxia and cytokine storm that induce clinical dyspnoea and lymphopenia. The spontaneous pyruvate reduction with lactate dehydrogenase (LDH) may play a pivotal role in enhancing nicotinamide adenine dinucleotide oxidized/ reduced form (NAD^+/NADH) ratio, preserving canonical glycolytic pathways. Also, the core of exogenous pyruvate actions may be the reversal of Warburg effect in aberrant glucometabolic pathways in hypoxia with viral infections by reactivating pyruvate dehydrogenase (PDH) activity due to its direct inhibition of the PDH kinase (PDK), eliminating intracellular acidosis and energy crisis. The characteristics indicate that pyruvate is robustly systemic metabolism and multiorgan function protective in critical care patients with or without Covid-19 viral infection, particularly in Covid-19 patients suffered from diabetes, parenchymatous comor-bidities, or aging. Albeit it is not an anti-virus agent, studies suggest that pyruvate potentially facilitates anti-virus drugs, interferons, cytokine IL-6 blockers, and Na^+-glucose cotransporter-2 (SGLT2) inhibitor (Dapagliflozin) against Covid-19 and even may inhibit virus replication, like Chloroquine treats Covid-19. Pyruvate may also diminish Coivid-19 virus-cellular receptor binding by inhibiting the glycosylation of viral receptor, the virus endocytosis by enhancing intracellular pH in endosomes, and the virus replication and release in the endoplasmic reticulum (ER) by protecting ER function. Despite not FDA-approved, clinical studies in several hundred patients subjected to various diseases strongly support pyruvate effectiveness and safety. Currently, pyruvate is a nutritional supplement, like melatonin and NAD^+ supposed in treating Covid-19, in markets, and would be superior to them. This review proposes that compassionate uses of pyruvate-enriched intravenous or oral rehydration solutions are encouraged in fluid intervention and prophylaxis of Covid-19 viral infection.

Keywords: covid-19; hypoxia; cytokine storm; oral rehydration solution; prevention; pyruvate; viral infection.

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I. INTRODUCTION

A specific medicine or proven treatment for severe Covid-19 has been a lack in clinical scenarios, though Remdesivir is attractive [1]. As to the prophylactic agents of Covid-19, to date, only Chloroquine and vaccine are most popular, but both potential efficacies are facing challenges regarding the safety and effectiveness [2,3]. Therefore, we propose that pyruvate-based fluids (intravenous (IV) pyruvate solutions and pyruvate-enriched oral rehydration salts (Pyr-ORS) modified by equimolar pyruvate replacement of bicarbonate or citrate in WHO-ORS) would be not only a volume

expander, but also a therapeutic agent to preserve multiorgan function and acid-base balance in the resuscitation of severe patients with or without Covid-19 [4,5]. Pyruvate, *per se*, in novel fluids may be additionally beneficial in combating Covid-19 virus infection by modulation of immunoreaction and attenuation of the virus replication, particularly in combination with relevant agents, including Remdesivir and Chloroquine. Oral Pyr-ORS, hence, may also be feasible and helpful for prophylaxis of Covid-19.

II. PYRUVATE IN A FLUID INTERVENTION

2.1 Pyruvate in the reversal of Warburg effect

The fluid therapy certainly plays a pivotal role in critical care patients with or without Covid-19. Still current oral and IV fluids are unsatisfied because anion compositions are not optimal according to clinical needs. Numerous experimental studies demonstrate that pyruvate has beneficial biomedical attributes with the increase of hypoxia/anoxia tolerance, correction of hypoxic lactic acidosis, exertion of anti-oxidative stress/inflammation, and protection of mitochondrial function and against cellular apoptosis under various pathogenic insults [4,5]. These superior clinical pharmacological characteristics are unique relative to anions in current fluids. Of those, the key activity of pyruvate is that under anoxia, including hypoxia/ischemia, trauma, inflammation, and high glucose, etc., it can preserve canonical glycolytic pathways through the spontaneous pyruvate reduction with lactate dehydrogenase (LDH) and rejuvenation of key glycolytic enzymes (like pyruvate kinase), resultantly improving NAD^+/NADH (nicotinamide adenine dinucleotide oxidized/ reduced form) and GSH/GSSG (glutathione reduced/oxidized form) ratios; predominantly, it can also reactivate pyruvate dehydrogenase (PDH) activity, which is always declined by diverse pathogenic insults, by direct inhibition of PDH kinase (PDK) [5,6]. Consequently, pyruvate promotes oxidative phosphorylation in the tricarbonyl acid (TCA) cycle in hypoxia and other pathogenic attacks. Therefore, it is of paramount importance that pyruvate can restore glucose metabolic disorders (Warburg effect) in various diseases [5,6]. Also, pyruvate is a potent inherent anti-oxidative and anti-inflammatory agent and exogenous pyruvate is an inhibitor of interleukins, like IL-2 and IL-6 [7]. Accordingly, pyruvate precisely targets the major pathological features of Covid-19 patients: hypoxemia and inflammatory cytokine storm (dyspnoea and lymphopenia), which were already shown in early clinical reports [8].

2.2 Pyruvate in the correction of hypoxic lactic acidosis

It has been notable since the early reports that hyperlactatemia is recurrently with a rise of serum lactate dehydrogenase (LDH) activity due to infection and hypoxia [9,10], despite data absence of metabolic acidosis (lactic acidosis) and reduced PDH activity in patients subjected to severe Covid-19 [10,11]. It is not controversial that the PDH activity and energy metabolism are depressed in severe and critical Covid-19 patients, as shown in patients subjected to severe influenza with mitochondrial energy crisis [12]. Hypoxic lactic acidosis is one of the lethal complications in patients with various critical diseases, including severe Covid-19 [13,14]. Specifically, diabetes is a risk cause for developing severe and critical Covid-19 and death; while Metformin and sodium-glucose linked transporter-2 (SGLT2) inhibitors in diabetes treatment may contribute to lactic acidosis and ketoacidosis [14,15].

However, pyruvate can reduce the LDH activity and eliminate blood lactate levels [6,7,16]; it also promotes lactate oxidation through the restored PDH activity in the TCA cycle, contributing to lactic acidosis correction by various proton ($[H^+]$)-consumed pathways [4,5]. Accordingly, pyruvate would enable to prevent and correct hyperlactatemia and energy crisis in Covid-19 patients. It is reasonably envisioned that pyruvate-enriched fluids, which contain low concentrations of pyruvate in IV pyruvate solutions and Pyr-ORS (see below), would be specifically suitable for clinical resuscitation of severe and critical Covid-19 patients, improving survival and attenuating acute and chronic organ dysfunction including respiratory failure as shown in novel coronavirus pneumonia. Intriguingly,

animal studies demonstrated that pyruvate promisingly protected lung energy metabolism and function [17,18]. Additionally, pyruvate preservation of glucose metabolism in multiple organs with various insults is also resulted from its stimulation of the hypoxia-inducible factor-1α-erythropoietin (HIF-1α-EPO) pathway to improve glucose metabolic disorders [19]. Dichloroacetate (DCA) displayed suppression of pulmonary fibrosis through the HIF-1α/PDK axis [20], while pyruvate is the HIF-1α stimulator [19]. Thus, pyruvate may be similarly favorable in the decline of pulmonary fibrosis in Covid-19-induced novel coronavirus pneumonia.

Therefore, innovative experimental pyruvate-enriched fluids are advantageous over current fluids in resuscitation from severe and critical patients with or without Covid-19 viral infection. The biological functions of anions in regular fluids are inferior in organ protection and lactate acidosis correction. The post-exogenous pyruvate metabolic profile was explicitly illustrated previously [4-6].

III. PYRUVATE AND ANTI-VIRUS RELEVANT AGENTS IN COVID-19

3.1 Pyruvate with anti-virus agents in Covid-19

As to its effects on viral infection, pyruvate has the dearth of direct evidence at present; however, studies indicate pyruvate inhibition of viral infection. It is not an antiviral drug, but pyruvate may facilitate interferons (IFNs)' efficiency in viral infections. Type I IFNs, broad-spectrum anti-RNA viral agents, have been approved in clinical settings, including the treatment of hepatitis viral infections. A study recently found that IFN-α/β exhibited potent anti-SARS-CoV-2 activities in cell cultures, suggesting the therapeutic potency of type I IFNs for Covid-19 [21]. Preliminary clinical trials demonstrated that INF-β-1b, combined with anti-virus drugs, showed more efficiency in treating Covid-19 patients [22]. Interestingly, it was shown that 10 mmol/L pyruvate, opposite to lactate, could elicit a redox imbalance to increase the apoptosis of colon cancer cells induced by the type II IFNγ [23]. The above clues imply a possibility that pyruvate may enhance IFNs effects on Covid-19 viral infection.

It was recently found in clinical studies that Tocilizumab, an IL-6 blocker, efficiently treated severe and critical Covid-19 patients [24]. As a potent endogenous IL-6 (in addition to IL-2, TNF-1α, NF-kB, and HMGB-1) inhibitor with anti-inflammatory nature [7], pyruvate had been demonstrated to be IL-6 inhibitive in influenza A virus infection [25]. Thus, pyruvate may promote IL-6 blockers' inhibition of the specific cytokine storm in Covid-19.

On the other hand, as to anti-inflammation, some animal researches have indicated that pyruvate as supportive care may facilitate control of bacterial infection and improve survival in clinical settings. As to antiviral effect, DCA as a PDK inhibitor has been demonstrated to decline hepatitis C virus (HCV) replication, and anti-HCV agents may repurpose against Covid-19 [26]. Also, there was cell experimental evidence that ethyl pyruvate (EP, a derivative of sodium pyruvate), one of histone deacetylase inhibitors (HDACi) also, prevented hepatitis B virus-induced autophagy in hepatocytes [27]. As both a PDK inhibitor like DCA and an HDACi like EP, therefore, sodium pyruvate would be probably favorable in inhibition of Covid-19 virus replication, particularly with co-administration of Ribavirin or interferon-α, improving organ function and survival of critical Covid-19 patients [26].

Also, Dapagliflozin (SGLT2 inhibitor) that raises intracellular pH and reduces lactate level was proposed in the protective effect against Covid-19 [28]. Pyruvate, as a superior alkalizer to rapidly improve intracellular pH, thereby significantly preserve organ function and metabolism [4-6], may resemble the Dapagliflozin effect on Covid-19 and additionally reduce viral entry into susceptible target cells by prevention of endosomal acidification as Chloroquine and ammonium chloride (NH_4Cl) shown in cell experiments with SARS coronavirus as well as influenza and Ebola viruses. Both Remdesivir and Chloroquine are highly effective in inhibiting the Covid-19 virus in cell experiments, *in vitro* [29], and several clinical trials preliminarily

demonstrated that Chloroquine is favorable in the prophylaxis and treatment of Covid-19 patients. However, a high-quality clinical trial is needed [30,31]. Although the underlying mechanism of its effectiveness in treating Coivid-19 remains explored, it is well known that Chloroquine first blocks the viral infection by interfering with the glycosylation of human angiotensin-converting enzyme 2 (ACE2) receptor [32]. The terminal glycosylation of the ACE2 receptor could also be resisted by pyruvate because of its inhibitory property of glycation as advanced glycosylation end products (AGEs) inhibitor [6,33,34], therefore, probably preventing Coivid-19 virus-cellular receptor binding. Chloroquine further obstructs virus infection by enhancing intracellular pH in endosomes, while endosomal acidification is required for virus/cell fusion (endocytosis) [30-33]. Accordingly, pyruvate as a potential inhibitor of endosomal acidification may inhibit the virus endocytosis by the pH-dependent endocytic pathway in Covid-19. Furthermore, in the infected cells, Covid-19 virus membrane proteins require targeting and assembling in the endoplasmic reticulum (ER) for further virus replication and release [30]. The functional ER might block this process, while pyruvate has shown protection against ER stress and apoptosis [35].

3.2 Pyruvate in viral infection

Although there has been neither experimental nor clinical research report on pyruvate effects on Covid-19 viral infection, a preliminary investigation showed that pyruvate attenuated the immune response of macrophages in mice infected with influenza A virus [25]. The data indicated that pyruvate significantly reduced cytokine (IL-6, IL-1β, and TNF-α) levels via its effect as an antioxidant and products of reactive oxygen species via its protection against mitochondrial damage. Pyruvate might also modulate the metabolism and function of immune cells synergistically to suppress virus replication, *in vivo,* as Chloroquine showed, *in vitro* [25]. EP (an anti-inflammatory agent, a high mobility group box 1 (HMGB1) protein inhibitor, too) also inhibited macrophage pyroptosis in experimental endotoxemia and inflammation induced by a viral infection with hepatitis, Dengue, and porcine circovirus type 2 viruses [27,36,37]. These facts that EP inhibits viral infections support potential pyruvate effects on Covid-19 treatments, however, EP is not helpful in humans [5]. Prospectively, pyruvate replacement in fluid resuscitation plus antiviral drugs (such as Remdesivir or Chloroquine), INFs, and IL-6 blockers, etc. would significantly improve clinical outcomes of severe Covid-19 patients. Novel pyruvate fluids, including inhalation of nebulized pyruvate alone, would be applicable in prophylaxis and cure of asymptomatic and moderate Covid-19 patients to promote recovery, but mainly in severe or critical Covid-19 patients with or without comorbidities, such as cardiovascular, hepatorenal parenchymatous diseases, obesity, diabetes, and aging, to enhance survival. Pyruvate fluids may also be beneficial in other severe viral infections, like Ebola, SARS, and MERS, relative to current fluids. Enteral Pyr-ORS is also adding a functional drink to rehydrate and supply energy as one of the nutrition remedies in patients subjected to Covid-19, like patients with WHO-ORS used in Ebola viral infection.

IV. PYRUVATE IN CLINICAL INVESTIGATIONS OF VARIOUS DISEASES

4.1 Clinical studies with intravenous, oral or inhalable pyruvate

Despite not FDA-approval, many clinical studies have illustrated pyruvate treatments of various diseases in the brain, heart, liver, and diabetes in various etiologies with the products at the time since the 1940s. The promising outcomes were achieved by intra-coronary artery or IV pyruvate injection with a large dosage from several grams to over 80 grams each infusion for 1-10 days [5,38], while a small pyruvate dose in cardioplegia for open-heart surgery was also demonstrated with robust cardioprotection [39]. Notably, there were several reports on IV pyruvate loading tests with 0.5 g/kg in 10 min in young adults, even diabetic subjects with 10 g in 4 min without clinical cytotoxic effects during past decades [5,40].

Alternatively, although oral pyruvate is limited effective in a dose less than 25 g in humans [5,41], a large dose (30-60g/d) of oral pyruvate ingestion for days showed effectiveness in treating diabetic patients with a reduction of daily insulin injection because it stimulates insulin secretion and hypoglycemia [5,42]. Oral pyruvate (0.75-1.5g/kg/d for months) also showed clinical improvement in patients with lactic acidosis-accompanied mitochondriopathy [5,43]. Also, inhalation of a small dosage of pyruvate showed clinical effectiveness in chronic obstructive pulmonary diseases [44].

4.2 Safety of clinical pyruvate application

All adverse effects were merely symptoms of gastrointestinal irritation, such as nausea, flatulence, and diarrhea, in patients reported following oral ingestion instead of IV infusion of pyruvate because of ingestion of dosages over 15 g at once. This can classify pyruvate as a nontoxic substance in humans [5]. Clinical studies on pyruvate treatments and IV loading tests with early products of pyruvate without adverse effects strongly suggest its safety in several hundred patients, which resembled a clinical phase II trial, demonstrating its clinical value with the absence of significant clinical toxicity. The early data concerning pyruvate acute toxicology indicated that oral pyruvate LD_{50} was over 10.0 g/kg in rats and IV pyruvate LD_{50} was over 1.25 g/kg in mice [38]. Recently, pyruvate was strongly encouraged with its clinical use [45]. It is worth noting that despite pyruvate not being cytotoxic in humans, a large amount of oral pyruvate is not clinically tolerant due to its GI irritation. However, a small dose of pyruvate combined with an appropriate amount of glucose in Pyr-ORS formulas would overcome this difficulty owing to the easy absorption of pyruvate via Na^+-glucose cotransporters in the intestinal epithelium as demonstrated with cell/organ protection in various pathogen insults in animal studies [6,46]. Accordingly, clinical trials with pyruvate-enriched fluids compared with current fluids are urgently warranted under protocols of compassionate use in combating severe patients with Covid-19.

V. RELEVANT ISSUES

A hypothesis was recently proposed that melatonin, an antioxidative and anti-inflammatory agent, like pyruvate in supplemental food markets, may be beneficial in the prevention and treatment of Covid-19 [47,48]. The experimental data reported are consistent with pyruvate applications [49], as recommended here. Intriguingly, as pyruvate, oral melatonin also showed protective effects on the diabetic retina [50]. There are many similar biomedical properties in organ protection between pyruvate and melatonin. However, pyruvate should be superior to melatonin at least in protecting against intracellular acidosis and energy crisis in severe viral infection like Covid-19 virus.

Because aqueous pyruvate solutions are not stable at room temperature and pyruvate dimers (para-pyruvate) generated in pyruvate solutions are toxic in cell experiments due to the inhibition of ketoglutarate dehydrogenase activity [51], pyruvate products should be stored in solid forms like powder [52]. However, there has been no cytotoxic evidence of para-pyruvate, *in vivo*, in humans to date, as demonstrated in many human studies previously. Albeit a long-term stable pyruvate solution is not available at present, IV pyruvate: pyruvate saline ($[Na^+]$ 154 mM, $[Pyr^-]$ 50 mM, $[Cl^-]$ 104 mM) and pyruvate Ringer's solution ($[Pyr^-]$ 28 mM) or oral Pyr-ORS (pyruvate 3.5g/L and glucose 13.5-20.0g/L and other chemicals) fluids can be simply prepared just prior to clinical uses [39,46,53,54]. Long-term stable pyruvate solutions at room temperature were issued by an US invention patent [55].

Pyr-ORS, modified if needed, may be therefore pertinent as an effective adjuvant for prophylaxis against Covi-19 viral infection in a higher risk population even though the efficacious vaccine has developed. Alternatively, Pyr-ORS may be favorable in strenuous exercises/sports, prehospital rescue, and perioperative fluid supplement; it may also be valuable as a daily functional drink in weight loss, anti-diabetes, and anti-aging in a large population [5,6]. Finally, pyruvate inhalation may be also useful in

prophylaxis and intervention of Covid-19 viral infection [44].

Addendum:

Recently, a hypothesis was proposed that NAD^+, a molecule of youth, may influence on Covid-19 infection as an aging-related immunomodulator [56]. Also, NAD^+ upregulation may attenuate aspects of immunosenesescence and inflammaging with aging. A clinical trial of nicotinamide riboside (NR, a precursor of NAD^+) in the elderly with Covid-19 infection is recruiting [57]. Pyruvate as a NAD^+ provider spontaneously via the LDH reductive reaction on the equal molecular basis in the whole body's cells, thus, could favor patients infected with Covid-19, specifically in elderly patients with or without severe comorbidities. Additionally, pyruvate could be advantageous over NAD^+, at least in avoiding energy crisis and severe acidosis, in the protection of cell function and intervention of Covid-19 infection [5,58,59].

Note:

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Declarations:

The Author declares that there is no conflict of interest.

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REFERENCES

1. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - Final report. N Engl J Med. 2020: NEJMoa2007764. doi: 10.1056/NEJMoa 2007764.
2. Shah S, Das S, Jain A, Misra DP, Negi VS. A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in coronavirus disease-19 (COVID-19). Int J Rheum Dis. 2020; 23:613-619. doi: 10.1111/ 1756-185X.13842.
3. Kaur SP, Gupta V. COVID-19 Vaccine: A comprehensive status report. Virus Res. 2020; 288:198114. doi: 10.1016/j.virusres. 2020.198114.
4. Wang Y, Huang Y, Yang J, Zhou FQ, Zhao L, Zhou H. Pyruvate is a prospective alkalizer to correct hypoxic lactic acidosis. Mil Med Res. 2018; 5:13. doi: 10.1186/s40779-018-0160-y.
5. Zhou FQ. Pyruvate research and clinical application outlooks a revolutionary medical advance. Int J Nutr. 2020; 5:1-8. doi: 10.14302/issn.2379-7835.ijn-20-3159.
6. Zhang XM, Deng H, Tong JD, et al. Pyruvate-enriched oral rehydration solution improves glucometabolic disorders in kidneys of diabetic *db/db* mice. J Diabetes Res. 2020; Article ID 2817972:1-13.
7. Xia S, Chen G, Wang B, et al. Addition of sodium pyruvate to stored red blood cells attenuates liver injury in a murine transfusion model. Mediators Inflamm. 2016; 2016:3549207. doi:10.1155/2016/3549207.
8. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395:497-506. doi: 10.1016/S0140-6736(20) 30183-5.
9. Shi J, Li Y, Zhou X, et al. Lactate dehydrogenase and susceptibility to deterioration of mild COVID-19 patients: a multicenter nested case-control study. BMC Med. 2020; 18:168. doi:10.1186/s12916- 020-01633-7.
10. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020; 146:110-118. doi:10.1016/j.jaci. 2020. 04.006.
11. Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clin Infect Dis. 2020:ciaa270. doi: 10.1093/cid/ciaa270.
12. Kido H, Indalao IL, Kim H, Kimoto T, Sakai S, Takahashi E. Energy metabolic disorder is a major risk factor in severe influenza virus infection: Proposals for new therapeutic options based on animal model experiments. Respir Investig. 2016; 54:312-319. doi:10. 1016/j.resinv.2016.02.007.

13. Gunnerson KJ, Saul M, He S, Kellum JA. Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. Crit Care. 2006; 10:R22. doi: 10.1186/cc3987.
14. Orioli L, Hermans MP, Thissen JP, Maiter D, Vandeleene B, Yombi JC. COVID-19 in diabetic patients: Related risks and specifics of management. Ann Endocrinol (Paris). 2020; 81:101-109. doi: 10.1016/j.ando.2020.05.001.
15. Erener S. Diabetes, infection risk and COVID-19. Mol Metab. 2020; 39:101044. doi:10.1016/j.molmet.2020.101044.
16. Eggert MW, Byrne ME, Chambers RP. Impact of high pyruvate concentration on kinetics of rabbit muscle lactate dehydrogenase. Appl Biochem Biotechnol. 2011; 165: 676-686. doi:10.1007/s12010-011-9287-y.
17. Peltz M, Hamilton TT, He TT, et al. Lung preservation solution substrate composition affects rat lung oxidative metabolism during hypothermic storage. Respir Physiol Neurobiol. 2005; 148:275-283. doi: 10.1016/j.resp.2005.02. 010.
18. Koustova E, Rhee P, Hancock T, et al. Ketone and pyruvate Ringer's solutions decrease pulmonary apoptosis in a rat model of severe hemorrhagic shock and resuscitation. Surgery. 2003; 134:267-274. doi: 10.1067/msy.2003.245.
19. Goodwin J, Choi H, Hsieh MH, et al. Targeting hypoxia-inducible factor-1α/pyruvate dehydrogenase kinase 1 axis by dichloroacetate suppresses bleomycin-induced pulmonary fibrosis. Am J Respir Cell Mol Biol. 2018; 58:216-231. doi: 10.1165/rcmb.2016-0186OC.
20. Hu S, Lin ZL, Zhao ZK, et al. Pyruvate is superior to citrate in oral rehydration solution in the protection of intestine via hypoxia-inducible factor-1 activation in rats with burn injury. JPEN J Parenter Enteral Nutr. 2016; 40:924-933. doi: 10.1177/0148607115577817.
21. Mantlo E, Bukreyeva N, Maruyama J, Paessler S, Huang C. Antiviral activities of type I interferons to SARS-CoV-2 infection. Antiviral Res. 2020; 179:104811. doi: 10.1016/j.antiviral.2020.104811.
22. Shalhoub S. Interferon beta-1b for COVID-19. Lancet. 2020; 395:1670-1671. doi: 10.1016/S0140-6736(20)31101-6.
23. Tai Y, Cao F, Li M, et al. Enhanced mitochondrial pyruvate transport elicits a robust ROS production to sensitize the antitumor efficacy of interferon-γ in colon cancer. Redox Biol. 2019; 20:451-457. doi: 10.1016/j.redox.2018.10.024.
24. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci USA. 2020; 117:10970-10975.doi:10.1073/pnas.2005615117.
25. Abysalamah H. Sodium pyruvate alters the immune response to influenza A virus infection in macrophages. PhD Thesis, Missouri State University, USA 2018.
26. Jung GS, Jeon JH, Choi YK, et al. Pyruvate dehydrogenase kinase regulates hepatitis C virus replication. Sci Rep. 2016; 6:30846. doi: 10.1038/srep30846.
27. Fu S, Wang J, Hu X, et al. Crosstalk between hepatitis B virus X and high-mobility group box 1 facilitates autophagy in hepatocytes. Mol Oncol. 2018; 12:322-338. doi: 10.1002/1878-0261.12165.
28. Cure E, Cumhur Cure M. Can dapagliflozin have a protective effect against COVID-19 infection? A hypothesis. Diabetes Metab Syndr. 2020; 14:405-406. doi:10.1016/j.dsx.2020.04.024.
29. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020; 30:269-271. doi: 10.1038/s41422-020- 0282-0.
30. Hong W. Combating COVID-19 with chloroquine. J Mol Cell Biol. 2020; 12:249-250. doi: 10.1093/jmcb/mjaa015.
31. Cortegiani A, Ippolito M, Ingoglia G, Einav S. Chloroquine for COVID-19: rationale, facts, hopes. Crit Care. 2020; 24:210. doi: 10.1186/s13054-020-02932-4.
32. Dos Santos WG. Natural history of COVID-19 and current knowledge on treatment therapeutic options. Biomed Pharmacother.

2020; 129:110493. doi: 10.1016/j. biopha. 2020.110493.
33. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020; 181:281-292.e6. doi: 10.1016/j.cell.2020.02.058.
34. Scott GF, Nguyen AQ, Cherry BH, et al. Featured Article: Pyruvate preserves antiglycation defenses in porcine brain after cardiac arrest. Exp Biol Med (Maywood). 2017; 242:1095-1103. doi: 10.1177/ 1535370217703353.
35. Zhang XM, Wang YZ, Tong JD, et al. Pyruvate alleviates high glucose-induced endoplasmic reticulum stress and apoptosis in HK-2 cells. FEBS Open Bio. 2020; 10:827-834. doi: 10.1002/2211-5463.12834.
36. Ong SP, Lee LM, Leong YFI, Ng ML, Chu JJH. Dengue virus infection mediates HMGB1 release from monocytes involving PCAF acetylase complex and induces vascular leakage in endothelial cells. PLoS ONE. 2012; 7:e41932. doi:10.1371/journal.pone.0041932.
37. Sun R, Sun S, Zhang Y, et al. PCV2 induces reactive oxygen species to promote nucleocytoplasmic translocation of the viral DNA binding protein HMGB1 to enhance its replication. J Virol. 2020; 94:e00238-20. doi: 10.1128/JVI.00238-20.
38. Mateva L, Petkova I, Petrov K, Beniozef D, Bojilova M, Vankova L, Thown W. Ten-Day course of sodium pyruvate infusions in patients with chronic liver diseases (CLD). Jpn Pharmacol Ther. 1996; 24:2629-2639. www.researchgate.net>scientific-contributio ns > 2032284700.
39. Olivencia-Yurvati AH, Blair JL, Baig M, Mallet RT. Pyruvate-enhanced cardioprotection during surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth. 2003; 17:715-720. doi: 10.1053/j.jvca.2003.09.007.
40. Moorhouse JA. Pyruvate-tolerance tests in healthy and diabetic subjects. Lancet. 1964; 1:689-693. doi: 10.1016/s0140-6736(64) 91519-3.
41. Olek RA, Kujach S, Wnuk D, Laskowski R. Single sodium pyruvate ingestion modifies blood acid-base status and post-exercise lactate concentration in humans. Nutrients. 2014; 6:1981-92. doi: 10.3390/nu6051981.
42. Petkova I, Hristov V, Petrov K, Thorn W. Oral application of sodium pyruvate in healthy persons and patients with diabetes mellitus type 1. Comptes rendus de l'Acad´emie bulgare des Sciences. 2007; 60:579-584. www.researchgate.net>scientific-contributio ns > 2029590614.
43. Koga Y, Povalko N, Inoue E, Nashiki K, Tanaka M. Biomarkers and clinical rating scales for sodium pyruvate therapy in patients with mitochondrial disease. Mitochondrion. 2019; 48:11-15. doi: 10.1016/ j.mito.2019.02.001.
44. Votto JJ, Bowen JB, Barton RW, Thrall RS. Inhaled sodium pyruvate improved FEV1 and decreased expired breath levels of nitric oxide in patients with chronic obstructive pulmonary disease. J Aerosol Med Pulm Drug Deliv. 2008; 21:329-334. doi: 10.1089/ jamp.2007.0678.
45. Mallet RT, Olivencia-Yurvati AH, Bünger R. Pyruvate-enriched resuscitation for shock. Exp Biol Med (Maywood). 2018; 243:663-664. doi: 10.1177/ 1535370218773717.
46. Liu R, Wang SM, Li ZY, Yu W, Zhang HP, Zhou FQ. Pyruvate in reduced osmolarity oral rehydration salt corrected lactic acidosis in severe scald rats. J Surg Res. 2018; 226:173-180. doi: 10.1016/j.jss.2018.01.018.
47. Anderson G, Reiter RJ. Melatonin: Roles in influenza, Covid-19, and other viral infections. Rev Med Virol. 2020; 30:e2109. doi:10.1002/rmv.2109.
48. Zhang R, Wang X, Ni L, et al. COVID-19: Melatonin as a potential adjuvant treatment. Life Sci. 2020; 250:117583. doi: 10.1016/j. lfs.2020.117583.
49. Bahrampour Juybari K, Pourhanifeh MH, Hosseinzadeh A, Hemati K, Mehrzadi S. Melatonin potentials against viral infections including COVID-19: Current evidence and new findings. Virus Res. 2020; 287:198108. doi:10.1016/j.virusres.2020.198108.
50. Mehrzadi S, Motevalian M, Rezaei Kanavi M, Fatemi I, Ghaznavi H, Shahriari M. Protective effect of melatonin in the diabetic

rat retina. Fundam Clin Pharmacol. 2018; 32:414-421. doi: 10.1111/fcp.12361.
51. Chang SC, Lee I, Ting H, Chang YJ, Yang NC. Parapyruvate, an impurity in pyruvate supplements, induces senescence in human fibroblastic Hs68 cells via inhibition of the α-ketoglutarate dehydrogenase complex. J Agric Food Chem. 2018; 66:7504-7513. doi:10.1021/acs.jafc.8b01138.
52. Margolis SA, Coxon B. Identification and quantitation of the impurities in sodium pyruvate. Anal Chem. 1986; 58:2504-2510. doi.org/10.1021/ac00125a033.
53. Hu S, Bai XD, Liu XQ, et al. Pyruvate Ringer's solution corrects lactic acidosis and prolongs survival during hemorrhagic shock in rats. J Emerg Med. 2013; 45:885-893. doi: 10.1016/j. jemermed. 2013.04.062.
54. Gou DM, Tan HJ, Cai HJ, Zhou FQ. Pyruvate effects on red blood cells during in vitro cardiopulmonary bypass with dogs' blood. Artif Organs. 2012; 36:988-991. doi: 10.1111/j.1525-1594.2012.01482.x.
55. Zhou FQ. Stable aqueous solution containing sodium pyruvate, and the preparation and use thereof. US Patent No.: US 8,835,508 B2. 2014.
56. Omran HM, Almaliki MS. Influence of NAD^+ as an aging-related immunomodulator on Covid-19 infection: A hypothesis. J Infect Public Health. 2020;13:1196-1201. doi:10. 1016/j.jiph.2020.06.004.
57. Radenkovic D, Reason, Verdin E. Clinical evidence for targeting NAD therapeutically. Pharmaceuticals (Basel). 2020;13:247. doi: 10.3390/ph13090247.
58. Kim JY, Lee SH, Bae IH, et al. Pyruvate protects against cellular senescence through the control of mitochondrial and lysosomal function in dermal fibroblasts. J Invest Dermatol. 2018;138:2522-2530. doi:10. 1016/j.jid.2018.05.033.
59. Iannetti EF, Smeitink JAM, Willems PHGM, Beyrath L, Koopman WJH. Rescue from galactose-induced death of Leigh Syndrome patient cells by pyruvate and NAD^+. Cell Death Dis. 2018;9:1135. doi: 10.1038/ s41419-018-1179-4.

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