JOURNAL OF AEROSOL MEDICINE AND PULMONARY DRUG DELIVERY
Volume 35, Number 0, 2022
Mary Ann Liebert, Inc.
Pp. 1–5
DOI: 10.1089/jamp.2022.0025

Research Article

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Sodium Pyruvate Nasal Spray Reduces the Severity of Nasal Inflammation and Congestion in Patients with Allergic Rhinitis

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Abstract

Background: As an anti-inflammatory and antioxidant, sodium pyruvate significantly reduces inflammatory cytokines and oxygen radicals such as interleukin (IL) IL-6, IL-8, Monocyte Chemoattractant Protein-1, and hydrogen peroxide. Thus, sodium pyruvate holds promise as a treatment for many respiratory diseases, including allergic rhinitis (AR). Novel treatments for AR are needed as current medications, including steroids, often fail to treat severe symptoms.
Methods: The data from five human clinical studies were analyzed to determine the effect of 20 mM sodium pyruvate nasal spray (N115) in patients with AR. Nasal inflammation scores were compared to a placebo control or a no-treatment baseline control. Three studies were open-labeled and two were appropriately blinded to both patients and clinicians using computer randomization of subjects.
Results: The intranasal administration of sodium pyruvate significantly improved nasal inflammation scores in all five clinical trials of patients with AR ($p < 0.0001$ in all trials).
Conclusions: These results give credence to the overall ability of sodium pyruvate, administered by nasal spray, to treat inflammation of the nasal airways.

Keywords: allergic rhinitis, anti-inflammatory, inhaled pyruvate

Introduction

Elevated levels of reactive oxygen species (ROS) induce a variety of pathological changes that are highly relevant in airway mucosa.[1,2] These changes include lipid peroxidation, increased airway reactivity, increased nasal mucosal sensitivity and secretions, production of chemoattractant molecules, increased vascular permeability, and congestion.[1–7] Hydrogen peroxide is known to increase inflammatory cytokines, including interleukin (IL)-6 in both the nasal cavity and lungs.[1,8,9] Our group has previously demonstrated that proinflammatory cytokine levels were decreased by treatment with sodium pyruvate, which correlated with decreased ROS.[10] Furthermore, the inhalation of sodium pyruvate in mice produced statistically significant reductions in IL-6 and IL-1β over the inhalation of saline.[11]

Allergic rhinitis (AR) is a type I hypersensitivity reaction mediated by immunoglobulin E responses to specific inhaled antigens.[12] Although not generally life threatening, AR can significantly impact quality of life and can exacerbate other diseases like chronic obstructive pulmonary disease (COPD). In fact, 40%–80% of COPD patients have nasal symptoms, including AR.[13] Thus, treatment of AR has the potential to impact other respiratory diseases too. AR is typically treated with over-the-counter medications, including antihistamines and topical nasal decongestants.[12] However, rebound AR can happen with prolonged use of decongestants.[14] Therefore, new therapeutic avenues are needed to treat this chronic disease.

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One potential add-on therapeutic option to current therapies for AR is to administer early and sufficient doses of antioxidants to strengthen the body's antioxidant defenses. This can play a major role in prevention and intervention of inflammatory responses.[15,16] Clinically, sodium pyruvate has a good safety profile and has been given to patients for a variety of disorders ranging from Friedreich's ataxia[17] to open heart operations.[18] It has been administered via several routes, including intravenous,[18] topical administration,[19] dietary supplementation,[20] and intranasally.[15,16] The purpose of the five studies presented here was to test the therapeutic value of sodium pyruvate to improve nasal inflammation in patients with AR.

Methods

Clinical trials

Informed consent was obtained before enrollment in all five studies. The studies have been performed with adherence to applicable ICH guideline E6 for Good Clinical Practice and Requirements provided for in 21 CRF parts 50 and 56 and in accordance to standard operating procedures and applicable protocols. All studies were performed under FDA approved protocols, and all data were submitted and subsequently reviewed for safety and efficacy by the FDA under FDA IND 50089. There were 311 patients participating in 5 different clinical trials (Table 1). Specific details for each trial are given below. If the patients were using other nasal sprays as part of their normal therapy, those nasal sprays were eliminated. For all studies, during the initial visit, a medical history was obtained and physical examination performed by a staff physician. Blood was collected and routine analysis performed. Vital signs (pulse rate, respiratory rate, and blood pressure) were monitored, and a urine pregnancy test was given to all women of childbearing age. Inclusion criterion for all studies was a clinical diagnosis of AR. For all studies, the exclusion criteria were as follows:

1. Lung diseases other than COPD or pulmonary fibrosis.
2. Clinically significant cardiac disease, including uncontrolled congestive heart failure and unstable angina.
3. Pregnancy.
4. Females of childbearing potential age not on adequate contraception.
5. Lactating females.
6. Systemic corticosteroid treatment within one month of screening visit.
7. Inhaled corticosteroid treatment within 15 days of screening visit.
8. Younger than 18 years of age (except study 3, where the exclusion was younger than 12 years of age).
9. Hospitalization within last 6 months due to acute exacerbation of airway disease.
10. Escalating dose of immunotherapy.
11. Clinically significant abnormal chest X-ray within the past 12 months.
12. Medication changes within 1 month.
13. Participation in another investigational drug treatment study within the last month.
14. Current history of alcohol or recreational drug abuse.
15. Use of vitamins with antioxidant properties (E or C) or dietary supplements containing pyruvate within 24 hours before the screening visit.

Studies 1–5. In these five studies, patients (Table 1) used a 20 mM sodium pyruvate nasal spray in 0.9% sodium chloride with 0.02% benzalkonium chloride, pH 7.2 (N115). They were compared to either a baseline no treatment (NT) control (trials 1 and 2) or a placebo control with 0.9% saline and 0.02% benzalkonium chloride (trials 3–5). Both N115 and saline controls were delivered by a Mistette Mark II (MeadWestvaco, Richmond, VA, USA) nasal spray pump that delivers a 0.1 mL metered dose from a 30 mL polypropylene bottle.

Subjects were removed from their regular nasal sprays (mostly steroids) and given N115 or saline nasal spray to use during the trials. The subjects were instructed that they could only use the study-issued nasal spray during the test period. In addition, they were instructed to contact laboratory staff immediately if they experienced any problems or adverse events. Before, and at the end of the study period, the subjects' nostrils were examined by a registered nurse for mucosal fragility, lesions, erythema, and edema using a rhinoscope. Nasal characteristics were rated on a five-point scale from zero to four. Rating = 0 (No Inflammation or Erythema), 0.5 (Barely Perceptible), 1 (Mild Inflammation or Erythema), 2 (Moderate Inflammation or Erythema), 3 (Marked Inflammation or Erythema), and 4 (Severe Inflammation or Erythema).

1. Study 1: The study was a phase I, open-label, baseline-controlled trial conducted at Consumer Product Testing, Fairfield, NJ, USA, and ST&T Clinical Research Center, San Francisco, CA, USA. Each patient's nasal passages were evaluated at baseline. Then, the patients self-administered N115 nasal spray, 2–3 sprays per

Table 1. Patient Demographics and Study Design

Study	*Gender*	*Age, average (range)*	*Patient's stated ethnicity*	*Study design*
1	F = 9 M = 9	54 (21–76)	Caucasian = 13 Hispanic = 2 Black = 3	Open-label baseline control
2	F = 11 M = 6	49 (28–81)	Caucasian = 15 Hispanic = 2	Open-label baseline control
3	F = 71 M = 59	36 (12–78)	Hispanic = 22 Black = 11 Asian = 3 Caucasian = 94	Double-blind placebo-control
4	F = 41 M = 39	46 (18–62)	Asian = 63 Caucasian = 37	Open-label placebo-control
5	F = 34 M = 26	52 (19–79)	Asian = 29 Caucasian = 31	Double-blind placebo-control

nostril, 3 times daily, for 1 week, and nasal inflammation was reevaluated on day 7. Patients completed a patient log to verify adherence to the protocol. Eighteen subjects with a clinical diagnosis of AR were enrolled, and all completed the study successfully.

2. Study 2: The study was a phase I, open-label, baseline-controlled trial conducted at Consumer Product Testing, Fairfield, NJ, USA, and ST&T Clinical Research Center, San Francisco, CA, USA. Each patient's nasal passages were evaluated at baseline. Then, the patients self-administered N115 nasal spray, 2–3 sprays per nostril, 3 times daily, for 1 week, and nasal inflammation was reevaluated on day 7. Patients completed a patient log to verify adherence to the protocol. Twenty patients with a clinical diagnosis of AR were enrolled in the study, but three did not complete treatment because of noncompliance (failed to use product daily as instructed and/or missing data). Thus, only 17 patients had complete data for the data analysis.
3. Study 3: Patients were enrolled in a double-blinded, computer randomized, placebo-controlled phase II/III study conducted at Consumer Product Testing, Fairfield, NJ, USA, and ST&T Clinical Research Center, San Francisco, CA, USA. Product and placebo packaging were numbered so that patients and clinicians were blinded to the treatment. Two hundred patients with a clinical diagnosis of AR were recruited and 146 completed prescreening. Another 16 did not comply with instructions and used another nasal spray the day before or in the morning of testing. No data were collected from these patients. Thus, 130 completed the study with saline placebo or N115 (65 patients per group).

All patients were initially treated with 2–3 sprays of saline nasal spray per nostril and baseline nasal inflammation measurements were obtained. After 1 hour, 65 patients were treated with 2–3 sprays of saline again and 65 patients were treated with 2–3 sprays of N115, and their nasal inflammation scored again after 1 more hour. All treatments were performed, and data collected in the clinic.

4. Study 4: The study was an open-label placebo-controlled phase II/III study conducted at the Department of Otolaryngology, North China Hospital, Beijing, China. Patients with a clinical diagnosis of AR were randomized into two groups; 38 patients were treated with saline, and 42 patients were treated with N115. Each patient's nasal inflammation was evaluated at baseline. Then, the patients self-administered either N115 nasal spray or saline placebo, 2–3 sprays per nostril, 3 times daily, for 1 week, and nasal inflammation was reevaluated on day 7. Patients completed a patient log to verify adherence to the protocol. Of the 88 originally enrolled, 8 subjects failed to complete the trial (use of other medications or missing data) and the incomplete data prevented their inclusion in the analysis.
5. Study 5: Patients with a clinical diagnosis of moderate AR were enrolled in a double-blind placebo-controlled phase II/III study conducted at Nanjing Hospital of Chinese Medicine (NHCM), Jiangsu Province, China. Product and placebo packaging were numbered so that patients and clinicians were blinded to the treatment using a computer-generated randomized number set. Thirty patients received N115 and 30 received saline placebo control. Each patient's nasal inflammation was evaluated at baseline. The patients then self-administered either N115 nasal spray or saline placebo, 2–3 sprays per nostril, 3 times daily, for 1 week, and nasal inflammation was reevaluated on day 7. Patients completed a patient log to verify adherence to the protocol. Of the 64 patients enrolled, 60 completed the study and were included in the data analysis. Four of the patients had missing information and could not be included.

Statistical analyses

All statistical analyses were performed using GraphPad Prism 6. The primary endpoint for all five trials was nasal inflammation score. Statistical analysis was performed using a paired (trial 1–2) or unpaired (trial 3–5) two-tailed Student's *t*-tests. The data are presented as the mean ± standard deviation, and $p < 0.05$ was considered statistically significant. Analyses for specific data sets are indicated in Table 2.

Results

Reduction of nasal inflammation and congestion in five human studies of N115

Study 1: Significant improvements in nasal inflammation were observed on day 7 of N115 treatment. Patients also reported that the nasal spray relieved nasal congestion immediately upon use. Pretreatment nasal inflammation scores were 2.35 ± 0.57 and N115 posttreatment scores were 1.09 ± 0.58 ($p < 0.0001$) (Table 2).

Study 2: Significant improvements in nasal inflammation were also observed on day 7 in this trial. Patients further reported that the nasal spray relieved nasal congestion upon use. Pretreatment nasal inflammation scores were 3.45 ± 0.70 and N115 posttreatment scores were 2.05 ± 0.60 ($p < 0.0001$) (Table 2).

Study 3: One-hour posttreatment, the N115 sodium pyruvate nasal spray significantly reduced nasal inflam-

Table 2. Nasal Inflammation and Congestion with 20 mM Sodium Pyruvate Nasal Spray (N115)

Clinical trial (patient numbers)	*Nasal inflammation and congestion scores*		p
	N115	*Control*	
1. AR (18)	1.09 (± 0.58)	2.35 (± 0.57) N.T.	<0.0001
2. AR (17)	2.05 (± 0.60)	3.45 (± 0.70) N.T.	<0.0001
3. AR (65/65)	0.77 (± 0.9)	2.08 (± 1.0) saline	<0.0001
4. AR (42/38)	2.0 (± 1.0)	3.57 (± 0.9) saline	<0.0001
5. AR (30/30)	0.98 (± 0.39)	2.8 (± 0.68) saline	<0.0001
Total (311)			

The data listed were collected over multiple years and include data from five nasal spray clinical trials. Patients presented with mild to severe AR with inflammation, edema, erythema, and congestion. The data are compared to either the baseline measurements (NT = no treatment) or against a saline placebo control (saline). The severity of nasal inflammation was scored on a scale of 0–4 with 4 being the worst. Statistical analysis was performed using a paired two-tailed Student's *t*-test for studies 1–2 and an unpaired two-tailed Student's *t*-test for studies 3–5. $p < 0.05$ was considered statistically significant.

AR, allergic rhinitis.

mation and congestion when compared to the saline placebo, with most patients obtaining relief from congestion in 30 seconds or less. The saline posttreatment nasal inflammation scores were 2.08 ± 1.0 and the N115 posttreatment scores were 0.77 ± 0.9 ($p < 0.0001$) (Table 2).

Study 4: After 7 days, saline placebo-treated patients had nasal inflammation scores of 3.57 ± 0.9 and the N115-treated patients had scores of 2.0 ± 1.0. ($p < 0.0001$) (Table 2).

Study 5: The nasal inflammation scores of saline placebo treated patients on day 7 were 2.8 ± 0.68 and N115-treated patients had scores of 0.98 ± 0.39 ($p = 0.0001$) (Table 2).

No adverse reactions were reported in any of these trials.

Discussion

We previously showed in Pulmonary Fibrosis patients that treatment with N115 nasal spray for 21 days significantly improved nasal inflammation.[15] Here, we demonstrate that sodium pyruvate can also decrease inflammation in the nasal tissues in five clinical trials with AR patients. Importantly, in study 3, sodium pyruvate treatment significantly improved nasal inflammation with a single treatment within 1 hour. The data presented have some limitations.

Studies 1, 2, and 4 were open-labeled studies. Also, patients were compared to a baseline and not a saline placebo control in studies 1 and 2. Although bias is a confounding factor in these studies, the data are still informative as they agree with the data in studies 3 and 5, where clinical staff and patients were blinded (patients were assigned to groups by computer randomization), and a saline placebo was used as a control. Therefore, the totality of the results from the five studies reported here suggests that sodium pyruvate can improve nasal inflammation.

The association between chronic inflammation and oxidative stress is well documented.[3–7] ROS such as superoxide anion, peroxynitrite, free hydroxyl radical, and hydrogen peroxide are toxic to various mammalian tissues,[21] including the lungs,[22–24] and have been implicated in many human diseases.[25] One of the body's natural endogenous antioxidants is sodium pyruvate. It is secreted by cells, readily enters cells, and can react with oxygen radicals and peroxide to ''detoxify'' them.[26–28] Sodium pyruvate has protective antioxidant activity[28–32] and can protect organs from damage caused by oxygen radicals.[33,34] Sodium pyruvate is also known to prevent nitric oxide from reacting with hydrogen peroxide producing toxic peroxynitrite and both are elevated in AR causing inflammation and congestion.[4–7]

Based on our previous findings that sodium pyruvate can decrease ROS,[10] we propose this as a possible mechanism for reducing inflammation in AR patients. Additional double-blinded, placebo-controlled trials are needed in the future to confirm these findings. Further studies are also needed to confirm the antioxidant mechanism for reducing nasal inflammation by examining ROS in nasal passages as well as inflammatory cytokines.

In conclusion, these five human trials demonstrate that nasal administration of sodium pyruvate (N115) has potential for treating AR. These findings could also have an impact on the treatment of COPD, pulmonary fibrosis, COVID-19, and long COVID, since patients with these diseases often suffer from nasal inflammation.[13,15,16]

Authors' Contributions

A.M.: conceptualization (lead), data curation (lead), project administration (lead), resources (lead), funding (lead), methodology (supporting), supervision (lead), validation (equal), writing-original draft (lead), writing-review and editing (equal), and formal analysis (supporting). C.L.: Validation (supporting), writing-original draft (supporting), writing-review and editing (equal), visualization (lead), and formal analysis (lead). R.A.: validation (equal), writing-original draft (supporting), supervision (supporting), and formal analysis (supporting).

Acknowledgments

We thank the patients who participated in the clinical trials. We also thank Dr. Thrall, University of Connecticut for the help with data collection.

Author Disclosure Statement

A.M. is the CEO of Emphycorp/Cellular Sciences, Inc., and has a financial stake in the company. C.L. receives research funding and consultation fees from Emphycorp/Cellular Sciences, Inc. R.A. is an employee of Emphycorp/Cellular Sciences, Inc., and has a financial stake in the company.

Funding Information

This research was funded by Emphycorp/Cellular Sciences, Inc.

References

1. Yao L, Hu DN, Chen M, et al. Subtoxic levels hydrogen peroxide-induced expression of interleukin-6 by epidermal melanocytes. *Arch Dermatol Res* 2012;304(10):831–838; Doi: 10.1007/s00403-012-1277-6.
2. Ogasawara H, Yoshimura S, Kumoi T. Hydrogen peroxide generation by eosinophils in allergic rhinitis. *Auris Nasus Larynx* 1991;18(2):133–143; Doi: 10.1016/s0385-8146(12)-80217-3.
3. Bowler RP, Crapo JD. Oxidative stress in allergic respiratory diseases. *J Allergy Clin Immunol* 2002;110(3):349–356; Doi: 10.1067/mai.2002.126780.
4. Dekhuijzen PN, Aben KK, Dekker I, et al. Increased exhalation of hydrogen peroxide in patients with stable and unstable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;154(3):813–816; Doi: 10.1164/ajrccm.154.3.8810624.
5. Dohlman AW, Black HR, Royall JA. Expired breath hydrogen peroxide is a marker of acute airway inflammation in pediatric patients with asthma. *Am Rev Respir Dis* 1993; 148(4):955–960; Doi: 10.1164/ajrccm/148.4_Pt_1.955.
6. Kietzmann D, Kahl R, Muller M, et al. Hydrogen peroxide in expired breath condensate of patients with acute respiratory failure and with ARDS. *Intensive Care Med* 1993; 19(2):78–81; Doi: 10.1007/BF01708366.
7. Sznajder JI, Fraiman A, Hall JB, et al. Increased hydrogen peroxide in the expired breath of patients with acute hypoxemic respiratory failure. *Chest* 1989;96(3):606–612; Doi: 10.1378/chest.96.3.606.

8. Klemens C, Rasp G, Jund F, et al. Mediators and cytokines in allergic and viral-triggered rhinitis. *Allergy Asthma Proc* 2007;28(4):434–441; Doi: 10.2500/aap.2007.28.3017.
9. Alper CM, Li-Korotky HS, Lo CY, et al. Nasal secretion concentrations of IL-5, IL-6, and IL-10 in children with and without upper respiratory tract viruses. *Arch Otolaryngol Head Neck Surg* 2010;136(3):281–286; Doi: 10.1001/archoto.2010.14.
10. Abusalamah H, Reel JM, Lupfer CR. Pyruvate affects inflammatory responses of macrophages during influenza A virus infection. *Virus Res* 2020;286:198088; Doi: 10.1016/j.viruses.2020.198088.
11. Reel JM, Christopher R. Lupfer. Sodium pyruvate ameliorates influenza A virus infection in vivo. *Microbiol Res* 2021;12(2):258–267; Doi: 10.3390/microbiolres12020018.
12. Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and rhinology: Allergic rhinitis. *Int Forum Allergy Rhinol* 2018;8(2):108–352; Doi: 10.1002/alr.22073.
13. Bergqvist J, Andersson A, Olin AC, et al. New evidence of increased risk of rhinitis in subjects with COPD: A longitudinal population study. *Int J Chron Obstruct Pulmon Dis* 2016;11:2617–2623; Doi: 10.2147/COPD.S115086.
14. Ramey JT, Bailen E, Lockey RF. Rhinitis medicamentosa. J Investig Allergol Clin Immunol 2006;16(3):148–155; Doi: 10.1081/9780826179340.0342.
15. Lupfer CR, Nadler R, Amen R, et al. Inhalation of sodium pyruvate to reduce the symptoms and severity of respiratory diseases including COVID-19, long COVID, and pulmonary fibrosis. *Eur J Respir Med* 2021;3(3):229–237; Doi: 10.31488/EJRM.121.
16. Martin A, Lupfer C, Amen R. Inhalation of sodium pyruvate to reduce hypoxemia and dyspnea associated with chronic respiratory diseases—A multi-study retrospective analysis. *Eur J Respir Med* 2022;4(1):258–261; Doi: 10.31488/EJRM.124.
17. Dijkstra U, Gabreëls F, Joosten E, et al. Friedreich's ataxia: Intravenous pyruvate load to demonstrate a defect in pyruvate metabolism. *Neurology* 1984;34(11):1493–1497; Doi: 10.1212/wnl.34.11.1493.
18. Giannelli S, McKenna JP, Bordiuk JM, et al. Prevention of increased hemoglobin-oxygen affinity in open-heart operations with inosine-phosphate-pyruvate solution. *Ann Thorac Surg* 1976;21(5):386–396; Doi: 10.1016/s0003-4975(10)63886-6.
19. Levy SB, Goldsmith LA. Sodium pyruvate treatment for hyperkeratotic disorders. South Med J 1979;72(3):307–310; Doi: 10.1097/00007611-197903000-00022.
20. Stanko RT, Robertson RJ, Galbreath RW, et al. Enhanced leg exercise endurance with a high-carbohydrate diet and dihydroxyacetone and pyruvate. *J Appl Physiol* (1985) 1990; 69(5):1651–1656; Doi: 10.1152/jappl.1990.69.5.1651.
21. Jamieson D. Oxygen toxicity and reactive oxygen metabolites in mammals. Free Radic Biol Med 1989;7(1):87–108; Doi: 10.1016/0891-5849(89)90103-2.
22. Baldwin SR, Simon RH, Grum CM, et al. Oxidant activity in expired breath of patients with adult respiratory distress syndrome. *Lancet* 1986;1(8471):11–14; Doi: 10.1016/s0140-6736(86)91895-7.
23. Ward PA, Till GO, Hatherill JR, et al. Systemic complement activation, lung injury, and products of lipid peroxidation. *J Clin Invest* 1985;76(2):517–527; Doi: 10.1172/JCI112001.
24. Perkowski SZ, Havill AM, Flynn JT, et al. Role of intrapulmonary release of eicosanoids and superoxide anion as mediators of pulmonary dysfunction and endothelial injury in sheep with intermittent complement activation. *Circ Res* 1983;53(5):574–583; Doi: 10.1161/01.res.53.5.574.
25. Cross CE, Halliwell B, Borish ET, et al. Oxygen radicals and human disease. *Ann Intern Med* 1987;107(4):526–545; Doi: 10.7326/0003-4189-107-4-526.
26. Bunton CA. Oxidation of α-diketones and α-keto-acids by hydrogen peroxide. *Nature* 1949;163(4142):444–444; Doi: 10.1038/163444a0.
27. Melzer E, Schmidt HL. Carbon isotope effects on the decarboxylation of carboxylic acids. Comparison of the lactate oxidase reaction and the degradation of pyruvate by H_2O_2. *Biochem J* 1988;252(3):913–915; Doi: 10.1042/bj2520913.
28. O'Donnell-Tormey J, Nathan CF, Lanks K, et al. Secretion of pyruvate. An antioxidant defense of mammalian cells. *J Exp Med* 1987;165(2):500–514; Doi: 10.1084/jem.165.2.500.
29. Andrae U, Singh J, Ziegler-Skylakakis K. Pyruvate and related alpha-ketoacids protect mammalian cells in culture against hydrogen peroxide-induced cytotoxicity. *Toxicol Lett* 1985;28(2):93–98; Doi: 10.1016/0378-4274(85)90015-3.
30. Varma SD, Morris SM. Peroxide damage to the eye lens in vitro prevention by pyruvate. *Free Radic Res Commun* 1988;4(5):283–290; Doi: 10.3109/10715768809066893.
31. Nath KA, Enright H, Nutter L, et al. Effect of pyruvate on oxidant injury to isolated and cellular DNA. *Kidney Int* 1994;45(1):166–176; Doi: 10.1038/ki.1994.20.
32. Brunkhorst R, Mahiout A. Pyruvate neutralizes peritoneal dialysate cytotoxicity: Maintained integrity and proliferation of cultured human mesothelial cells. *Kidney Int* 1995; 48(1):177–181; Doi: 10.1038/ki.1985.282.
33. Shah SV. Role of reactive oxygen metabolites in experimental glomerular disease. *Kidney Int* 1989;35(5):1093–1106; Doi: 10.1038/ki.1989.96.
34. Paller MS, Hoidal JR, Ferris TF. Oxygen free radicals in ischemic acute renal failure in the rat. *J Clin Invest* 1984; 74(4):1156–1164; Doi: 10.1172/JCI111524.

Received on April 29, 2022
in final form, July 1, 2022

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