Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy Dovepress
open access to scientific and medical research

Open Access Full Text Article

COMMENTARY

Beneficial Effects of Anti-Oxidative Herbal Medicines in Diabetic Patients Infected with COVID-19: A Hypothesis

This article was published in the following Dove Press journal:
Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

Ozra Tabatabaei-Malazy[1,2]
Mohammad Abdollahi[2,3]
Bagher Larijani[2]

[1]Non-Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran; [2]Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran; [3]Toxicology and Diseases Group, Pharmaceutical Sciences Research Center (PSRC), The Institute of Pharmaceutical Sciences (TIPS), and Department of Toxicology and Pharmacology, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

Abstract: During the pandemic of Coronavirus Disease 2019 (COVID-19), it is critical to introduce potential medical treatments. Anti-oxidative herbal medicines with evidence-based beneficial impacts in the treatment of diabetes mellitus can be suggested as an adjuvant therapy to its conventional treatments in patients infected with COVID-19.

Keywords: herbal medicine, COVID-19, anti-oxidative, diabetes mellitus

Introduction

The World Health Organization (WHO), declared a pandemic of the Coronavirus Disease 2019 (COVID-19) following its rapidspread after March 11, 2020.[1] As a viral disease, COVID-19 is characterized by some or all of the following symptoms: fever, dry cough, fatigue, dyspnea, pneumonia, and dysfunction of specific organs such as the respiratory tract, heart, liver, and kidney. Patients with underlying diseases such as diabetes mellitus, hypertension, severe obesity, and cardiovascular disease (CVD) have been proven to be at higher risk of complications and death than others.[2,3] According to recently published studies, patients suffering from type 2 diabetes mellitus (T2DM) have been hospitalized more than patients with non-T2DM, with severe forms and poor prognosis of COVID-19.[4–6] Based on the WHO situation report on July 21, 2020, the confirmed COVID-19 cases and deaths associated with COVID-19 were 14,348,858 and 603,691 worldwide, respectively.[7] Based on the 2019 International Diabetes Federation (IDF) report, the world prevalence of diabetes was 463 million, and is expected to reach 578 million in 2030, and 700 million in 2045.[8] It was estimated that nearly 20–50% of patients infected with COVID-19 have diabetes, much higher than the worldwide incidence rate of diabetes.[9]

Hyperglycemia and inflammation are the possible causes of severity and high mortality rates of COVID-19 in diabetic patients.[10] Hyperglycemia might worsen the prognosis and survival rate of COVID-19 and can be attended with a high proportion of inflammatory biomarkers and cytokines.[11,12] Abnormalities in the secretion and transportation of insulin within the tissues are associated with the changes in structure and function of endothelial cells and β cells as the result of cytokine secretions which lead to the apoptosis of the β cells, hyperglycemia, and insulin resistance. Furthermore, the cytokine storm might cause progressive failure of the liver and kidney functions.[13] Extensive damage of liver tissue in patients with

Correspondence: Bagher Larijani
Tehran University of Medical Sciences, No. 10, Next to Dr. Shariati Hospital, Jalal Al Ahmad Hwy., North Kargar Ave., Tehran 14117113119, Iran
Tel/Fax +982188631296-7
Email emrc@tums.ac.ir

submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/DMSO.S264824

COVID-19 reduces the production of glycogen and accelerates insulin resistance and hyperglycemia. Therefore, managing the hyperglycemia would result in the reduction of the cytokines serum level and improvement of the prognosis in COVID-19 patients.

Although some off-label drugs showed beneficial results in the treatment of COVID-19, no vaccine or specifically-approved drug is available to eradicate this disease, this necessitates the introduction of potential medical treatments or use of off-label drugs in this situation.[14,15] Therefore, considering alternative interventions such as traditional medicine as an adjuvant to the conventional treatments of diabetes in COVID-19 patients is required.

Oxidative stress, defined as an imbalance between reactive oxygen species (ROS) and anti-oxidative stress capacity, has been established as the primary pathologic mechanism of diabetes.[16] Changes in the activity and serum level of glucose-6-phosphate dehydrogenase (G6PD) as a marker of inflammation could generate nicotinamide adenine dinucleotide phosphate (NADPH) that induces oxidative stress and G6PD deficiency promotes folding, trafficking, and viral spread. In a study, a 12-fold higher viral production of coronavirus 229E was demonstrated. It shares sequence similarities with COVID-19 and clinically resembles it in human lung epithelial cells that have G6PD deficiency compared to control cells.[17,18] Acute lung injury in COVID-19 can result from the local generation of ROS. In patients infected with SARS-coronavirus (SARS-CoV), a significant increase in the production of oxidized lipids (oxLDL) was observed.[19] Caspase recruitment domain-containing protein 9 (CARD9)-dependent as a mediator of oxLDL in macrophages triggers the inflammatory signaling pathway in response to viral infection. The CARD9 could activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) that increase the expression of cytokines.[20] Therefore, respiratory viral infections have generally been associated with cytokine production, inflammation, apoptosis, and other pathophysiological processes known as oxidative stress.[21] Although in clinical studies a clear correlation was found between oxidative stress biomarkers and the severity of many viral diseases, this correlation for SARS-CoV has been seen in limited experimental studies.[22,23]

According to the literature, herbal medicines, especially those containing polyphenols, have shown strong antioxidant potential helpful for the treatment of diabetes.[24–26] However, rather than having hypoglycemic and antioxidant effects, some of these compounds have exhibited many other useful effects. Fruits and vegetables rich in flavonoids showed significant reductions in biomarkers of inflammation and improved microvascular reactivity through inhibition of NF-κB.[27,28] Beneficial effects of flavonoids were reported in the prevention and treatment of influenza viruses through suppression of neuraminidase, inhibition hemagglutinin activity, modifying cellular signaling pathways, and transcription factors that resulted in the reduction of viral replication.[29] These anti-influenza effects were observed after the administration of *Geranium sanguineum L.* extract in *in vitro* study of embryo fibroblast cells.[30] Another example is theaflavin derivatives (polyphenols from black tea) that their anti-influenza activities have been shown via down-regulation of IL-6 expression.[31]

Evidence suggest that the extract of *Scrophularia striata* has anti-oxidative, anti-cancer, anti-inflammatory, anti-asthmatic, and neuroprotective effects, secondary to its two flavonoid components, quercetin, and isorhamnetin 3-O-rutinoside.[32] The antiviral and antidiabetic effects of quercetin have been discussed in several studies.[25,33] Antiviral activity of quercetin against influenza virus and SARS-CoV was confirmed by inhibition of SARS-CoV 3-chymotrypsin-like protease (3CLpro) expression in Pichia pastoris.[33,34] It has been identified that 3CLpro has a vital role in viral replication. Therefore, 3CLpro can be considered as the targeted therapy. Due to the high similarity between the 3CLpro sequence of COVID-19 and that of SARS-CoV,[35] it could be hypothesized that quercetin may also exhibit antiviral effects on SARS-CoV-2.

Another example is curcumin – that is, the active ingredient of the dietary spice turmeric, from the plant *Curcuma longa* – has anti-inflammatory, anti-cancer, renal, cardioprotective, and antiviral effects, as well as cytokine suppression in both human and animal studies.[36] Inhibition of virus replication, 3CLpro activity, blocking the NF-κB signaling, and inhibition of bio-inflammatory markers production can mediate the antiviral impacts of curcumin.[37,38] In a clinical trial, daily dose of 1 gram curcuminoid for 8 weeks significantly increased serum level of superoxide dismutase (SOD) as an anti-oxidative biomarker, reduced serum level of malondialdehyde (MDA) as an oxidative biomarker, and decreased circulating C-reactive protein (CRP) concentration compared with placebo.[39]

In the recent viral outbreaks of COVID-19 and SARS-CoV, clinical pieces of evidence on the beneficial effects of Traditional Chinese Medicine (TCM) and certain

polyphenolic compounds have been suggested.[40,41] Positive improvement responses in clinical symptoms such as fever, quicker clearance of lung infection, better control of fungal infection, and decrease of mortality rate in SARS-CoV infected patients were observed in the intervention group (TCM with/without combination with conventional medicine) compared to control group.[41] The antiviral activity of TCM herbal extracts might be related to their active compounds such as baicalein and quercetin that are capable of COVID-19 inhibition by blocking 3CLpro activity and NF-κB signaling.[41] Besides, the TCM applied for the treatment of COVID-19 infected patients have shown anti-inflammatory effects through reduction of cytokine production.[41] All of these studies suggest that herbal medicines be used as adjuvant to currently prescribed drugs to treat COVID-19 in patients with diabetes and also can be considered as a suitable source to identify novel therapeutic agents for COVID-19. However, better designed experimental and clinical studies are urgently required to confirm their beneficial effects.

Disclosure

The authors certify that there is no conflict of interest.

References

1. WHO. WHO Director-General's opening remarks at the media briefing on COVID-19–11 March 2020; 2020. Available from: https://www.who.int/dg/speeches/detail/who-directorgeneral-s-opening-remarks-at-the-mediabriefing-on-covid-19-11-march-2020. Accessed April 08, 2020.
2. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis*. 2020;94:91–95. doi:10.1016/j.ijid.2020.03.017
3. Tootee A, Esfahani EN, Larijani B. Diabetes management during Ramadan amid Covid-19 pandemic. *DARU J Pharm Sci*. 2020. doi:10.1007/s40199-020-00357-6
4. Guan WJ, Ni ZY, Hu Y, et al. China medical treatment expert group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708–1720. doi:10.1056/NEJMoa2002032
5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506. doi:10.1016/S0140-6736(20)30183-5
6. Mantovani A, Byrne CD, Zheng MH, Targher G. Diabetes as a risk factor for greater COVID-19 severity and in-hospital death: a meta-analysis of observational studies. *Nutr Metab Cardiovasc Dis*. 2020;30(8):1236–1248. doi:10.1016/j.numecd.2020.05.014
7. WHO. Coronavirus disease (COVID-19) dashboard. Available from: https://covid19.who.int. Accessed July 21, 2020.
8. IDF Diabetes atlas, 9th edition 2019. Available from: https://www.diabetesatlas.org. Accessed July 21, 2020.
9. Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol*. 2020. doi:10.1016/s2213-8587(20)
10. Wang Q, Fang P, He R, et al. O-GlcNAc transferase promotes influenza A virus–induced cytokine storm by targeting interferon regulatory factor–5. *Sci Adv*. 2020;6:13. doi:10.1126/sciadv.aaz7086
11. Bode B, Garrett V, Messler J, et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. *J Diabetes Sci Technol*. 2020;14(4):813–821. doi:10.1177/1932296820924469
12. Kulcsar KA, Coleman CM, Beck SE, Frieman MB. Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection. *JCI Insight*. 2019;4. doi:10.1172/jci.insight.131774.
13. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507–513. doi:10.1016/S0140-6736(20)30211-7
14. Shojaei A, Salari P. COVID-19 and off label use of drugs: an ethical viewpoint. *Daru*. 2020;1–5. doi:10.1007/s40199-020-00351-y
15. Ayati N, Saiyarsarai P, Nikfar S. Short and long term impacts of COVID-19 on the pharmaceutical sector. *Daru*. 2020;1–7. doi:10.1007/s40199-020-00358-5
16. Rahimi R, Nikfar SH, Larijani B, Abdollahi M. A review on the role of antioxidants in the management of diabetes and its complications. *Biomed Pharmacother*. 2005;59:365–373. doi:10.1016/j.biopha.2005.07.002
17. Wu YH, Tseng CP, Cheng ML, et al. Glucose-6-phosphate dehydrogenase deficiency enhances human coronavirus 229E infection. *J Infect Dis*. 2008;197:812e816. doi:10.1086/528377
18. Li Y, Liu B, Cui J, et al. Similarities and evolutionary relationships of COVID-19 and related viruses. *arXiv*. 2020;2003:05580.
19. Imai Y, Kuba K, Neely GG, et al. Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury. *Cell*. 2008;133:235e49. doi:10.1016/j.cell.2008.02.043
20. Zhong X, Chen B, Yang L, Yang Z. Molecular and physiological roles of the adaptor protein CARD9 in immunity. *Cell Death Dis*. 2018;9:52. doi:10.1038/s41419-017-0084-6
21. Khomich OA, Kochetkov SN, Bartosch B, et al. Redox biology of respiratory viral infections. *Viruses*. 2018;10:E392. doi:10.3390/v10080392
22. van den Brand JMA, Haagmans BL, van Riel D, et al. The pathology and pathogenesis of experimental severe acute respiratory syndrome and influenza in animal models. *J Comp Pathol*. 2014;151:83e112. doi:10.1016/j.jcpa.2014.01.004
23. Lin CW, Lin KH, Hsieh TH, et al. Severe acute respiratory syndrome coronavirus 3C-like protease-induced apoptosis. *FEMS Immunol Med Microbiol*. 2006;46:375e380. doi:10.1111/j.1574-695X.2006.00045.x
24. Bule M, Abdurahman A, Nikfar S, et al. Antidiabetic effect of quercetin: a systematic review and meta-analysis of animal studies. *Food Chem Toxicol*. 2019;125:494–502. doi:10.1016/j.fct.2019.01.037
25. Tabatabaei-Malazy O, Larijani B, Abdollahi M. A systematic review of in vitro studies conducted on effect of herbal products on secretion of insulin from Langerhans islets. *J Pharm Pharm Sci*. 2012;15(3):447–466. doi:10.18433/J32W29
26. Naseri R, Farzaei F, Fakhri S, et al. Polyphenols for diabetes associated neuropathy: pharmacological targets and clinical perspective. *Daru*. 2019;27(2):781–798. doi:10.1007/s40199-019-00289-w
27. Macready AL, George TW, Chong MF, et al. Flavonoid-rich fruit and vegetables improve microvascular reactivity and inflammatory status in men at risk of cardiovascular disease–FLAVURS: a randomized controlled trial. *Am J Clin Nutr*. 2014;99:479–489. doi:10.3945/ajcn.113.074237
28. Gonzalez-Gallego J, Sanchez-Campos S, Tunon MJ. Anti-inflammatory properties of dietary flavonoids. *Nutr Hosp*. 2007;22:287–293.
29. Bahramsoltani R, Sodagari HR, Farzaei MH, et al. The preventive and therapeutic potential of natural polyphenols on influenza. *Expert Rev Anti Infect Ther*. 2016;14:57–80. doi:10.1586/14787210.2016.1120670

30. Lin LT, Hsu WC, Lin CC. Antiviral natural products and herbal medicines. *J Tradit Complement Med*. 2014;4:24–35. doi:10.4103/2225-4110.124335
31. Zu M, Yang F, Zhou W, et al. In vitro anti-influenza virus and anti-inflammatory activities of theaflavin derivatives. *Antiviral Res*. 2012;94:217–224. doi:10.1016/j.antiviral.2012.04.001
32. Azadmehr A, Hajiaghaee R, Zohal MA, Maliji G. Protective effects of Scrophularia striata in Ovalbumin-induced mice asthma model. *Daru*. 2013;21(1):56. doi:10.1186/2008-2231-21-56
33. Wu W, Li R, Li X, et al. Quercetin as an antiviral agent inhibits influenza A virus (IAV) entry. *Viruses*. 2015;8(1):pii: E6. doi:10.3390/v8010006
34. Nguyen TT, Woo HJ, Kang HK, et al. Flavonoid-mediated inhibition of SARS coronavirus 3C-like protease expressed in Pichia pastoris. *Biotechnol Lett*. 2012;34:831–838. doi:10.1007/s10529-011-0845-8
35. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395:565–574. doi:10.1016/S0140-6736(20)30251-8
36. Gupta SC, Patchva S, Koh W, Aggarwal BB. Discovery of curcumin, a component of golden spice, and its miraculous biological activities. *Clin Exp Pharmacol Physiol*. 2012;39(3):283–299. doi:10.1111/j.1440-1681.2011.05648.x
37. Wen CC, Kuo YH, Jan JT, et al. Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. *J Med Chem*. 2007;50:4087–4095. doi:10.1021/jm070295s
38. Ciavarella C, Motta I, Valente S, et al. Pharmacological (or synthetic) and nutritional agonists of PPAR-γ as candidates for cytokine storm modulation in COVID-19 disease. *Molecules*. 2020;25:E2076. doi:10.3390/molecules25092076
39. Panahi Y, Hosseini MS, Khalili N, et al. Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: a randomized controlled trial and an updated meta-analysis. *Clin Nutr*. 2015;34:1101–1108. doi:10.1016/j.clnu.2014.12.019
40. Chen Z, Nakamura T. Statistical evidence for the usefulness of Chinese medicine in the treatment of SARS. *Phytother Res*. 2004;18:592–594. doi:10.1002/ptr.1485
41. Yang Y, Islam MS, Wang J, et al. Traditional Chinese medicine in the treatment of patients infected with 2019-new coronavirus (SARS-CoV-2): a review and perspective. *Int J Biol Sci*. 2020;16(10):1708–1717. doi:10.7150/ijbs.45538