

# New intriguing possibility for prevention of coronavirus pneumonitis: Natural purified polyphenols

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**Keywords:** coronavirus, COVID-19, polydatin, resveratrol, tocilizumab

## 1 | INTRODUCTION

COVID-19 is an infectious disease characterized by several important systemic problems such as severe pneumonia. One of the mechanisms responsible for these systemic problems is the release of pro-inflammatory cytokines, such as interleukin (IL)-1 beta and IL-6 (Conti et al., 2020). The binding of virus to TLR (Toll-like receptor) can determine the release of pro-IL-1 beta with successive activation and production of active mature IL-1 beta, responsible for lung inflammation, fever, and fibrosis (Conti et al., 2020). The interstitial pneumonia is linked to an overproduction of IL-6. Based on this principle, several researchers started the use of an anti-arthritis drug, tocilizumab, for its anti-IL-6 action.

Technically, tocilizumab is an immunosuppressive drug used in tumor treatment (Dijkgraaf et al., 2015; Hirata et al., 2013; Kim et al., 2015) and acts reducing interleukin-6 production (Mihara et al., 2005). When the immune system is stimulated to fight the tumor, there is a side effect, which is respiratory distress, very similar to that induced by COVID-19. So, tocilizumab modulates the excessive and counterproductive action of the immune system. Therefore, a similar action could be useful in healthy subject in order to prevent the establishment of the pathogenic mechanism responsible for coronavirus pneumonia onset.

## 2 | NATURAL PRODUCTS AND COVID-19

Some natural products seem to be able to have an anti-IL-6 action, such as curcumin, resveratrol, and camellia sinensis (Theaceae) (Furst & Zundorf, 2014).

Resveratrol (3, 4', 5-trans-tri-hydroxy-stilbene) is a stilbene of plant origin belonging to the class of phytoalexins, molecules able to promote repair processes and defensive actions against biotic stresses, such as infections by pathogenic microorganisms, and abiotic stresses, such as oxidative ones.

Polydatin (3,5,4'-dihydroxystilbene-3-O-β-D-glucopyranoside) is a glucoside of resveratrol characterized by conformational changes, which are reflected in changes in biological properties. It is more resistant than resveratrol to enzymatic oxidation and can penetrate the cell through an active transport mechanism. The biological activities of resveratrol and its glucosidic derivatives, such as polydatin, can be summarized as follows:

1. powerful antioxidant activity, reducing the deleterious effects of oxidative stress on cells and exerting a strong protective action on the cardiovascular system;
2. Anti-inflammatory activity, for its ability to modulate the production of nitric oxide (NO) and the release of regulatory and pro-inflammatory cytokines;
3. Modulation of lipid synthesis by avoiding the storage of cholesterol and fats in liver;
4. Inhibition of platelet aggregation;
5. Powerful immunomodulatory effect on immune cells;
6. Antiviral and antibacterial action;
7. Strong anti-aging and neuroprotective activities;
8. Strong anti-mutagenic and anti-tumor action by inhibiting cellular events associated with the stages of initiation, promotion, and progression of the tumor.



**TABLE 1** In vitro and in vivo studies on the polydatin and resveratrol activities

Authors	Year	Compound	Type of study	Result
Yao et al.	2011	Polydatin	In vivo examination of potential inhibitory effects of polydatin on NF- $\kappa$ B pathway activation.	Polydatin reduces activity and expression of NF-kappaB p65 and myeloperoxidase activity, blocks the expression of TNF-alpha, IL-6, and IL-1 beta at both mRNA and protein levels.
Jiang et al.	2015	Polydatin	In vitro study on polydatin action on inflammatory cytokine production. In vivo study on polydatin activity about acute lung injury.	In vitro, polydatin inhibits the synthesis and release of inflammatory cytokines including IL-1 $\beta$ , IL-6, IL-8, and TNF- $\alpha$ in concentration-dependent manners in LPS-stimulated BEAS-2B cells. In vivo study of polydatin significantly inhibits the levels of polymorphonuclear activity, neutrophil number, TNF-alpha, IL-6, IL-1 beta, and reversed TLR4-MyD88-NF-kappaB signaling pathway in occasion of acute lung injury.
Pace et al.	2015	Polydatin	In vivo study on human subjects about the possible role of polydatin on serum parameters during chronic alcoholism.	In vivo study of polydatin reduces the same serum parameter markers of chronic inflammatory diseases.
Xu et al.	2016	Polydatin	In vitro examination of the antioxidant ability of polydatin (PD). In vivo study on the possible protective effect of PD on D-gal-induced liver and brain damage.	In vitro, polydatin has a remarkable free radical scavenging activity on 2,2-diphenyl-1-picrylhydrazyl. 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid radical ion), 38 hydroxyl and superoxide anion. In vivo, polydatin reduces serum levels of TNF-alpha, IL-1 beta, and IL-6.
Lin et al.	2017	Resveratrol	In vitro study of resveratrol activity on MERS-CoV.	In vitro study of resveratrol induces host cell death reduction and MERS-CoV replication inhibition.
Zaho et al.	2017	Resveratrol	In vivo study of resveratrol action on pseudorabies virus	Piglets, inoculated with pseudorabies virus and supplemented with resveratrol at different dose levels for seven days prior to infection, had significantly lower viral loads than the untreated group as well as significantly decreased death rates (90% survival in the resveratrol group, with no deaths in the higher dosed groups—30 mg/kg and 10 mg/kg had 100% survival; the low-dose group of 3 mg/kg had 90% survival)
Tang et al.	2018	Polydatin	In vitro study of the anti-inflammatory and chondroprotective effects of polydatin on interleukin (IL)-1 $\beta$ -induced human osteoarthritic chondrocytes. In vivo study on the action of polydatin on osteoarthritis in mice.	In vitro, polydatin can completely suppress the production of pro-inflammatory mediators, such as prostaglandin E2 (PGE2), TNF-alpha, nitric oxide (NO), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and IL-6. In vivo, polydatin attenuates the development of osteoarthritis in the mouse model.
Kamel et al.	2018	Polydatin	In vivo study on the possible therapeutic potential of polydatin on experimentally induced arthritis in rats.	In vivo, polydatin reduces levels of tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-6 (IL-6), interleukin-17 (IL-17), and matrix metalloproteinase-3 (MMP-3).
Cui et al.	2018	Resveratrol	In vivo study of the possible role of resveratrol in the control of viral infection (SARS-CoV-2 too)	In vivo study of resveratrol, added to the diet of piglets for 21 days, decreased TNF-alpha levels and diminished diarrhea due to rotavirus
Park et al.	2019	Polydatin	In vitro study of polydatin effect in hyperosmolarity-induced human dry eye disease conjunctival cells (HCCs) by using the CCK-8 assay. In vivo study of polydatin action on eye inflammatory processes induced by surgical removal of lacrimal glands.	In vitro, polydatin can inhibit inflammation induced by hyperosmolar stress reducing translocation of NF-kappaB to the nucleus and mRNA expression of TNF-alpha, IL-6, IL-1 beta, and MMP-9. In vivo, the study showed that polydatin eye dropping restored changes induced by the excision of lacrimal glands such as reduced tear fluid, severe corneal irregularity, damage, tear film break, and goblet cell loss as well as increased inflammation cytokine and NLRP3 expression in conjunctival tissue.
Gu et al.	2019	Polydatin	In vivo study of polydatin action on inflammatory cytokine.	In vivo, polydatin remarkably inhibited TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 production, MPO activity, and MDA content.

(Continues)

TABLE 1 (Continued)

Authors	Year	Compound	Type of study	Result
Li et al.	2019	Polydatin	In vivo study on protective effects and mechanisms of polydatin against lipopolysaccharide (LPS)-induced endometritis in mice.	In vivo, polydatin treatment remarkably inhibits the expression of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 by ELISA.
Baldassarre et al.	2020	Resveratrol	Study of resveratrol action in human infant common cold	In human study, intranasal resveratrol administered to infants decreases symptoms of the common cold

Some studies, in vitro and in vivo, verified the activities of polydatin and resveratrol on inflammatory processes (Table 1).

A study showed the ability of polydatin to reduce activity and expression of NF-kappaB p65, to block the expression of TNF-alpha, IL-6, and IL-1 beta at both mRNA and protein levels, to reduce myeloperoxidase activity (Yao et al., 2011). Another study showed that serum levels of TNF-alpha, IL-1 beta, and IL-6 were considerably reduced after polydatin administration in mice (Xu et al., 2016).

In vitro, polydatin can completely suppress the production of pro-inflammatory mediators, such as prostaglandin E2 (PGE2), TNF-alpha, nitric oxide (NO), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and IL-6 (Tang et al., 2018). Polydatin can inhibit inflammation induced by hyperosmolar stress reducing translocation of NF-kappaB to the nucleus and mRNA expression of TNF-alpha, IL-6, IL-1 beta, and MMP-9 (Park et al., 2019). Other studies concerning mice showed the ability of polydatin to reduce IL-6 production (Gu, Liu, Xu, & Lu, 2019; Kamel, Gad, Mansour, Safar, & Fawzy, 2018; Li et al., 2019).

An interesting study on lung showed that polydatin significantly inhibits the levels of polymorphonuclear activity, neutrophil number, TNF-alpha, IL-6, IL-1 beta, and reversed TLR4-MyD88-NF-kappaB signaling pathway in occasion of acute lung injury (Jiang et al., 2015).

Zaho et al. showed that piglets, inoculated with pseudorabies virus and supplemented with resveratrol at different dose levels for seven days prior to infection, had significantly lower viral loads than the untreated group as well as significantly decreased death rates (90% survival in the resveratrol group, with no deaths in the higher dosed groups—30 mg/kg and 10 mg/kg had 100% survival; the low-dose group of 3 mg/kg had 90% survival) (Zhao et al., 2017).

Another study showed on humans that intranasal resveratrol and carboxymethyl-beta-glucan mixture administered to infants decreased symptoms of the common cold (Baldassarre et al., 2020).

As a final example of the possible role of resveratrol in the control of viral infection (SARS-CoV-2 too), resveratrol, added to the diet of piglets for 21 days, decreased TNF-alpha levels and diminished diarrhea due to rotavirus (Cui et al., 2018).

Although there are no data for using resveratrol in humans infected with SARS-CoV-2, the above studies demonstrate that this compound may be an adjunctive antiviral agent to consider, especially based on the data published by Lin et al. showing activity against MERS-CoV in vitro (Lin et al., 2017).

### 3 | CONCLUSION

Currently, no specific anti-virus drugs or vaccines are ready for fighting this lethal disease. Actually, the principal possible actions are supportive care and non-specific treatment of symptoms (Yang, Islam, Wang, Li, & Chen, 2020). Tocilizumab is one of these new therapeutic possibilities in the treatment of COVID-19. In fact, treatment guidelines by China's National Health Commission provided tocilizumab for its ability to reduce IL-6 production. This drug is not useful for the preventive treatment, also for its high risk of side effects (Tarp et al., 2016).

Traditional Chinese medicine (TCM) is used by People's Republic of China in the campaign to contain and eradicate coronavirus pandemic (Yang et al., 2020). In several provinces, Health Commission officially declared that TCM can be used in combination with conventional medicine in the treatment of these patients (Yang et al., 2020). On February 17, Chinese National Health Commission reported that 60,107 confirmed COVID-19 patients (85.20% of total confirmed cases) had been treated with TCM (China, 2020). At the date of March 1, a total of 303 clinical trials aiming to evaluate the efficacy and safety of treatments for COVID-19 patients are active in China (Yang et al., 2020) and 50 of these trials (16.5%) are about TCM, including 14 trials (4.6%) that have the purpose to evaluate the effect of combined treatment with TCM and Western medicine (Yang et al., 2020).

For all these reasons, it is necessary to provide complementary and alternative treatments for coronavirus patients or to prevent the infection. This is the occasion to verify the true value of natural products or nutraceuticals in preventing/treating emerging contagious diseases. Several randomized, double-blind, and placebo-controlled studies are necessary in order to verify the real efficacy of these agents for their use in the prophylaxis or therapy of infectious diseases. For this reason, polydatin can be a preventive measure for people professionally exposed to the risk of contagion, and/or positive patients not in intensive care; it has no contraindications. Naturally, it is necessary to start a trial on large number of subjects; polydatin was just used in clinical protocol with interesting results in oxidative metabolic stress (Pace et al., 2015). In this difficult moment, every possible hypothesis must be tested, and none can be discarded a priori.

## CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

## AUTHOR CONTRIBUTION

**Lorenzo Lo Muzio:** Conceptualization; Data curation; Methodology; Visualization; Writing-original draft; Writing-review & editing. **Maria Eleonora Bizzoca:** Conceptualization; Data curation; Methodology; Visualization; Writing-original draft; Writing-review & editing. **Giampietro Ravagnan:** Conceptualization; Data curation; Methodology; Visualization; Writing-original draft; Writing-review & editing.

## PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/odi.13518>.

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## REFERENCES

Baldassarre, M. E., Di Mauro, A., Labellarte, G., Pignatelli, M., Fanelli, M., Schiavi, E., ... Laforgia, N. (2020). Resveratrol plus

- carboxymethyl-beta-glucan in Infants with common cold: A randomized double-blind trial, *Heliyon*, 6, e03814. <https://doi.org/10.1016/j.heliyon.2020.e03814>
- China, N. H. C. o. t. P. s. R. o (2020). *Transcript of press conference in 17, February 2020*. <http://www.nhc.gov.cn/xcs/s3574/202002/f202012a202062d202010c202002a202048c206895cedf202002faea202006e202001f.shtml>
- Conti, P., Ronconi, G., Caraffa, A., Gallenga, C. E., Ross, R., Frydas, I., & Kritas, S. K. (2020). Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): Anti-inflammatory strategies. *Journal of Biological Regulators and Homeostatic Agents*, 34(2), 1–3. <https://doi.org/10.23812/CONTI-E>
- Cui, Q., Fu, Q., Zhao, X., Song, X. U., Yu, J., Yang, Y. I., ... Yin, Z. (2018). Protective effects and immunomodulation on piglets infected with rotavirus following resveratrol supplementation. *PLoS One*, 13(2), e0192692. <https://doi.org/10.1371/journal.pone.0192692>
- Dijkgraaf, E. M., Santegoets, S. J., Reyners, A. K., Goedemans, R., Wouters, M. C., Kenter, G. G., ... Kroep, J. R. (2015). A phase I trial combining carboplatin/doxorubicin with tocilizumab, an anti-IL-6R monoclonal antibody, and interferon-alpha2b in patients with recurrent epithelial ovarian cancer. *Annals of Oncology*, 26(10), 2141–2149. <https://doi.org/10.1093/annonc/mdv309>
- Furst, R., & Zundorf, I. (2014). Plant-derived anti-inflammatory compounds: Hopes and disappointments regarding the translation of pre-clinical knowledge into clinical progress. *Mediators of Inflammation*, 2014, 146832. <https://doi.org/10.1155/2014/146832>
- Gu, L., Liu, J., Xu, D., & Lu, Y. (2019). Polydatin prevents LPS-induced acute kidney injury through inhibiting inflammatory and oxidative responses. *Microbial Pathogenesis*, 137, 103688. <https://doi.org/10.1016/j.micpath.2019.103688>
- Hirata, H., Tetsumoto, S., Kijima, T., Kida, H., Kumagai, T., Takahashi, R., ... Kumanogoh, A. (2013). Favorable responses to tocilizumab in two patients with cancer-related cachexia. *Journal of Pain and Symptom Management*, 46(2), e9–e13. <https://doi.org/10.1016/j.jpain.symman.2013.01.009>
- Jiang, Q., Yi, M., Guo, Q., Wang, C., Wang, H., Meng, S., ... Chen, T. (2015). Protective effects of polydatin on lipopolysaccharide-induced acute lung injury through TLR4-MyD88-NF-kappaB pathway. *International Immunopharmacology*, 29(2), 370–376. <https://doi.org/10.1016/j.intimp.2015.10.027>
- Kamel, K. M., Gad, A. M., Mansour, S. M., Safar, M. M., & Fawzy, H. M. (2018). Novel Anti-arthritis Mechanisms of Polydatin in Complete Freund's Adjuvant-Induced Arthritis in Rats: Involvement of IL-6, STAT-3, IL-17, and NF-small ka, CyrillicB. *Inflammation*, 41(5), 1974–1986. <https://doi.org/10.1007/s10753-018-0841-4>
- Kim, N.-H., Kim, S.-K., Kim, D.-S., Zhang, D., Park, J.-A., Yi, H., ... Shin, H.-C. (2015). Anti-proliferative action of IL-6R-targeted antibody to-ciluzumab for non-small cell lung cancer cells. *Oncology Letters*, 9(5), 2283–2288. <https://doi.org/10.3892/ol.2015.3019>
- Li, R., Maimai, T., Yao, H., Liu, X., He, Z., Xiao, C., ... Xie, G. (2019). Protective effects of polydatin on LPS-induced endometritis in mice. *Microbial Pathogenesis*, 137, 103720. <https://doi.org/10.1016/j.micpath.2019.103720>
- Lin, S. C., Ho, C. T., Chuo, W. H., Li, S., Wang, T. T., & Lin, C. C. (2017). Effective inhibition of MERS-CoV infection by resveratrol. *BMC Infectious Diseases*, 17(1), 144. <https://doi.org/10.1186/s12879-017-2253-8>
- Mihara, M., Kasutani, K., Okazaki, M., Nakamura, A., Kawai, S., Sugimoto, M., ... Ohsugi, Y. (2005). Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R, but not by the receptors of other members of IL-6 cytokine family. *International Immunopharmacology*, 5(12), 1731–1740. <https://doi.org/10.1016/j.intimp.2005.05.010>
- Pace, M. C., Passavanti, M. B., Aurilio, C., Sansone, P., Aurilio, R., Maria, S. D. E., ... Stiuso, P. (2015). Polydatin administration improves serum



- biochemical parameters and oxidative stress markers during chronic alcoholism: A pilot study. *In Vivo*, 29(3), 405–408.
- Park, B., Jo, K., Lee, T. G., Hyun, S. W., Kim, J. S., & Kim, C. S. (2019). Polydatin Inhibits NLRP3 Inflammasome in dry eye disease by attenuating oxidative stress and inhibiting the NF-kappaB Pathway. *Nutrients*, 11(11), 2792. <https://doi.org/10.3390/nu11112792>
- Tang, S., Tang, Q., Jin, J., Zheng, G., Xu, J., Huang, W., ... Liu, H. (2018). Polydatin inhibits the IL-1beta-induced inflammatory response in human osteoarthritic chondrocytes by activating the Nrf2 signaling pathway and ameliorates murine osteoarthritis. *Food & Function*, 9(3), 1701–1712. <https://doi.org/10.1039/c7fo01555k>
- Tarp, S., Amarilyo, G., Foeldvari, I., Christensen, R., Woo, J. M. P., Cohen, N., ... Furst, D. E. (2016). Efficacy and safety of biological agents for systemic juvenile idiopathic arthritis: A systematic review and meta-analysis of randomized trials. *Rheumatology (Oxford)*, 55(4), 669–679. <https://doi.org/10.1093/rheumatology/kev382>
- Xu, L. Q., Xie, Y. L., Gui, S. H., Zhang, X., Mo, Z. Z., Sun, C. Y., ... Xie, J. H. (2016). Polydatin attenuates d-galactose-induced liver and brain damage through its anti-oxidative, anti-inflammatory and anti-apoptotic effects in mice. *Food Function*, 7(11), 4545–4555. <https://doi.org/10.1039/c6fo01057a>
- Yang, Y., Islam, S., Wang, J., Li, Y., & Chen, X. (2020). Traditional Chinese Medicine in the Treatment of Patients Infected with 2019-New Coronavirus (SARS-CoV-2): A review and perspective. *International Journal of Biological Sciences*, 16(10), 1708–1717. <https://doi.org/10.7150/ijbs.45538>
- Yao, J., Wang, J.-Y., Liu, L., Zeng, W.-S., Li, Y.-X., Xun, A.-Y., ... Wang, L.-S. (2011). Polydatin ameliorates DSS-induced colitis in mice through inhibition of nuclear factor-kappaB activation. *Planta Medica*, 77(5), 421–427. <https://doi.org/10.1055/s-0030-1250462>
- Zhao, X., Cui, Q., Fu, Q., Song, X., Jia, R., Yang, Y., ... Yin, Z. (2017). Antiviral properties of resveratrol against pseudorabies virus are associated with the inhibition of IkappaB kinase activation. *Scientific Reports*, 7(1), 8782. <https://doi.org/10.1038/s41598-017-09365-0>

**How to cite this article:** Lo Muzio L, Bizzoca ME, Ravagnan G. New intriguing possibility for prevention of coronavirus pneumonitis: Natural purified polyphenols. *Oral Dis*. 2022;28(Suppl. 1):899–903. <https://doi.org/10.1111/odi.13518>