seeing that the disease triggered strong organ and systemic inflammation, associated with episodes of micro- and macro-thrombosis, used NSAIDs in association with antithrombotic drugs (antiplatelet or low molecular weight heparins), plus gastric protection.

The poor response and organisation of local community level healthcare in Italy, in the face of the pandemic, led to the formation of several groups of volunteers, mainly doctors but also other healthcare and non-healthcare professionals, who joined forces in an attempt to remedy the situation that had been created and help healthcare facilities in the battle against the pandemic, providing great support to the disoriented and frightened public. The largest among the many groups set up at the time were the "*Early Home Therapy for COVID-19*" group (https://www.terapiadomiciliarecovid19.org), founded in March 2020 by a lawyer, Erich Grimaldi, and the "*Ippocrate.org*" group (https://ippocrateorg.org/), founded between May and July 2020 by Mauro Rango.

Both organisations have since treated thousands of cases of COVID-19 at home, also by remote monitoring, using personalized treatments with drugs, mainly non-steroidal anti-inflammatory drugs (NSAIDs) but also vitamins, dietary supplements and repurposed drugs such as hydroxychloroquine and ivermectin, administered, when possible, at the onset of the symptoms, in order to prevent clinical worsening and promote a full recovery. This type of approach, according to participating physicians, based on clinical observation, has led to excellent results, as documented by the clear drop in hospitalizations, the duration of symptoms and the number of deaths. Preliminary results with retrospective case histories of these experiences have already been published by our research groups [7, 8].

Lethality trend in Italy during the pandemic: Determining factors

When SARS-CoV-2 first appeared, COVID-19 was a virtually alien disease, the pathophysiological mechanisms of which were unknown, and which could even lead to the death of the infected person. Therefore, all useful measures had to be taken and implemented to clarify the relevant mechanisms and to investigate the nature of this disease as quickly as possible, in order to be able to treat it in the best possible way. To this end, autopsies of COVID-19 patients are certainly the quickest and most important of the various means at our disposal to understand the mechanisms and effects of the disease on our bodies. However, the circular of the Italian Ministry of Health of 1 April 2020, no. 11285 [9] (Page 3), reads as follows on the subject of autopsy examinations and diagnostic findings on deceased COVID-19 patients: "*For the entire period of the emergency phase, no autopsies or diagnostic findings should be carried out in con-firmed cases of COVID-19...*".

While not a blanket ban, this circular led to no or very few autopsies actually being carried out, precisely during the period when they would have been crucial to rapidly further our knowledge of the disease. In fact, it was precisely thanks to subsequent studies, carried out also using the autopsy method, that it became clear that one of the factors that aggravated the disease was endothelitis with the triggering of pulmonary micro- and macro-thromboses, as well as multi-district thrombosis [10]. It was precisely for this reason that a new circular of the Italian Ministry of Health, dated 11/01/2021, no.0000818 [11], corrected the aim by removing the wording that "advised against" performing autopsies.

Factors such as the significant impact of COVID-19 on the elderly population, the decision to manage the disease at an advanced stage only and exclusively in hospital settings, and the critical nature of the home treatment approach to people infected with SARS-CoV-2, may have contributed to the increase in the number of deaths from COVID-19 in Italy [12, 13]. The average lethality rate for COVID-19 in Italy was very high in 2020 (3.5%) and has gradually declined to 0.33% today, with an average figure for the entire pandemic period of about 1% (Table 1, data from Worldometers Coronavirus site). Vice versa, in countries such as Portugal, where the healthcare service responded particularly well, due to an excellent organisation at local community level, the average recorded lethality during the pandemic was 0.55%, i.e., still about 50% lower than in Italy [12], and this cannot be justified only by the fact that the over-65 segment of the population in Italy is 21%, while in Portugal it is 18%.).

Among the Western European countries, Italy recorded the highest lethality rate: in fact, Spain and Greece had an average lethality of 0.86%, Belgium 0.76%, Germany 0.53%, France 0.50%, Austria 0.44%, Luxembourg 0.43%, Switzerland 0.38%, and the Nether-lands 0.27%. Even

	Italy			Portugal		
Year	**2020**	**2021**	**2022***	**2020**	**2021**	**2022***
No. Cases	2,000,000	4,000,000	10,700,000	420,000	1,412,000	2,412,000
No. Deaths	70,000	62,300	29,500	6,197	12,083	3631
Lethality	3.5	1.55	0.32	1.64	0.85	0.15

* Until 18 of May 2022

Table 1: Lethality during the pandemic in Italy and Portugal compared (from Worldometers Coronavirus site, https://www.worldometers.info/coronavirus/).

Sweden, often accused of pandemic mismanagement for not applying strict restrictions during the various pandemic waves, recorded a lethality of 0.75%. On the other hand, according to the latest OECD iLibrary.org report, Italy is one of the tail-end countries in terms of per capita health expenditure, comparable to Greece, Spain and Portugal, which, however, recorded a much lower average lethality rate. (From OECD iLibrary.org, Health at a Glance: Europe 2020: State of Health in the EU Cycle) (Figure 1).

There are many likely causes of the important and progressive reduction in apparent lethality of COVID-19, from the beginning of the pandemic to the present day, although the most relevant seem to us to be the following:

NATURAL SELECTION: A relevant factor was the gradual reduction in the number of frail elderly people, who died in considerable numbers during the first months of the pandemic, with the average age of the sick decreasing and thus the number of cases destined to unfavorable evolution.

VACCINATION CAMPAIGN: The vaccination campaign, while failing to reduce the number of infections, probably conferred some degree of protection from serious illness and death for COVID-19 in elderly and more frail patients, thereby reducing lethality. However, in actual fact, the authorization studies on COVID-19 vaccines have not provided any evidence of a possible reduction in deaths from COVID-19

[14] since all-cause mortality was not substantially different over a six month period comparing subjects in whom was administered the BNT162b2 vaccine (15 deaths) with those who received placebo (14 deaths), and that there were more cardiovascular and sepsis related deaths in the first group (12 deaths) that in the second (6 deaths). However, a booster dose at least 5 months after a second dose of BNT162b2 added protection also against mortality [15], thus showing that, perhaps, the protection given by vaccination in the short term for deaths by COVID-19 may be lost in the long term as number of all-cause deaths, in the absence of subsequent booster. It should be noted that the effect of anti-covid-19 vaccines on public health should also be evaluated in the light of the emerging evidence of the multiple adverse effects caused by them, which are not always reported.

INCREASED DETECTION OF ASYMPTOMATICS: Swab testing became mandatory to access the workplace, public services and all indoor premises, such as restaurants, cinemas, theatres, etc., initially for those persons who did not wish to be vaccinated against COVID-19, but which was then extended also to vaccinated persons after it was realized that the COVID-19 jab did not provide protection against the spread of the virus. In order to be able to have a working and social life, or to travel, it was necessary to either complete the vaccination program or to have been cured of COVID-19 within the last 6 months or to have negatively
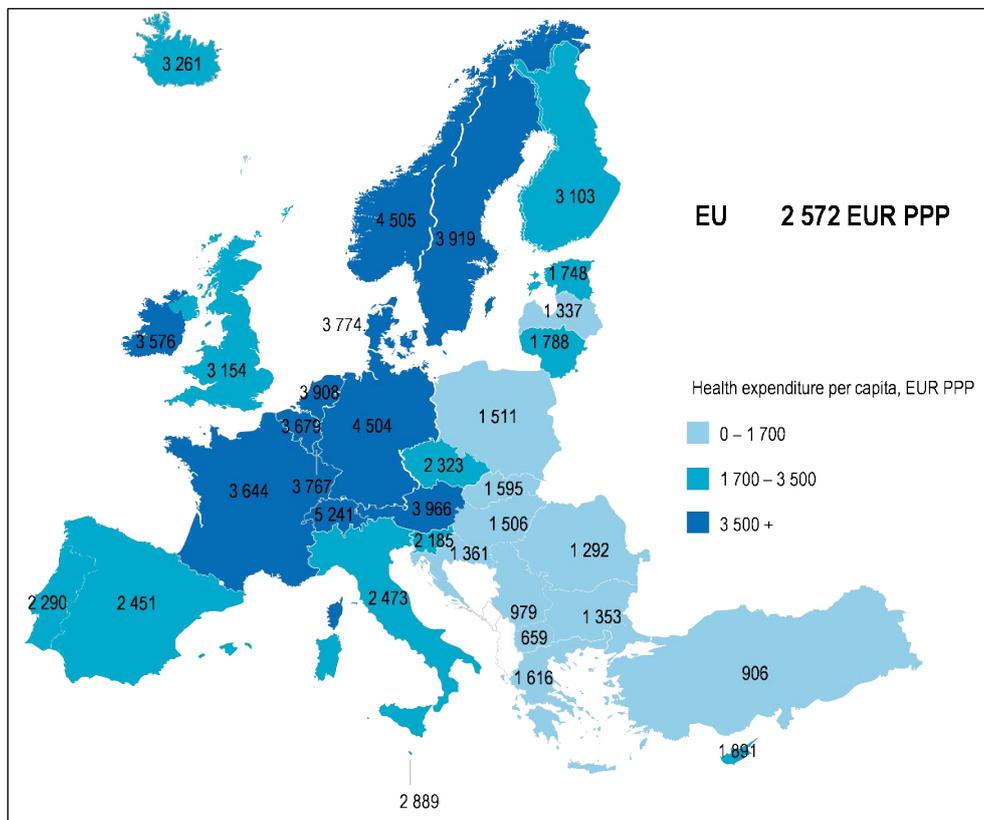

Figure 1: Per capita health expenditure in Europe, 2019 (From OECD iLibrary.org, Health at a Glance, Europe 2020)

antioxidants with chemical drugs in aid protocols to mitigate disease progression following SARS-CoV-2 infection.

Conclusions and Perspectives

The Italian approach to the pandemic by the public health institutions has revealed significant shortcomings and has proved to be partly mistaken, based on the contents of this paper, with the most prominent mistakes, in our opinion, being: the decision to tackle the pandemic only through the development of vaccines based on novel and experimental technology, with insufficient information as to the duration of their efficacy and their medium and long-term safety; the issuing of guidelines that discouraged doctors from adopting early home treatment therapy guided by science and conscience, using the drugs considered most appropriate for each patient; the decision to strongly recommend "*watchful waiting*" and symptomatic drugs alone, especially paracetamol, going so far as to sanction doctors who did not comply with the official recommendations; the refusal to enter into any form of dialogue with doctors who promptly treated thousands and thousands of patients at home, enormously reducing the number of hospitalizations. This inefficient management of the pandemic can be viewed as one of the factors whereby Italy is among the countries with most hospitalizations and deaths due to COVID-19.

Looking ahead, it is necessary to adopt a much more open and flexible approach, starting systematic and comparative studies between the different protocols that emerged from the experience of doctors who work at the patient's bedside or through telemedicine in the early stages of the disease. Since vaccine prevention and early treatment are not alternatives, it would be necessary, in the near future, for resources to be allocated to systematic and patient research of the various therapeutic approaches that have shown promising results, without focusing only on antiviral drugs in the belief that they can constitute a "silver bullet" capable of curing the disease in all instances. Relying only on "big pharma", which is engaged in researching next-generation antivirals, could prove yet another serious mistake in the face of a disease as complex as COVID-19.

Author Contribution:

Conceptualization, S.F., M.C., P.B.; methodology, F.M., E.Z.; validation, S.P., E.Z.; investigation, S.F., M.C., P.B., F.M.; writing—original draft preparation, S.F.; writing—review and editing, P.B.; All authors have read and agreed to the published version of the manuscript.

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References

1. Scotto Di Vetta M, Morrone M, Fazio S. COVID-19: Off-label therapies based on mechanism of action while waiting for evidence-based medicine recommendations. World J Meta-Anal 8 (2020): 173-177.

2. Amici C, Di CA, Ciucci A, Chiappa L, Castilletti C, Martella V, et al. Indomethacin has a potent antiviral activity against SARS coronavirus. Antivir Ther 11 (2006): 1021-1030.

3. Rezza GU, Urbani A. Circolare recante "Gestione domiciliare dei pazienti con infezione da SARS-CoV-2". Direzioni Generali della Programmazione Sanitaria e della Prevenzione Sanitaria, ed., Ministero della Salute, Roma (2020).

4. Fabiani M, Puopolo M, Morciano C, Spuri M, Spila Alegiani S, Filia A, et al. Effectiveness of mRNA vaccines and waning of protection against SARS-CoV-2 infection and severe covid-19 during predominant circulation of the delta variant in Italy: retrospective cohort study. BMJ 376 (2022): e069052.

5. Nyberg T, Ferguson NM, Nash SG, Webster HH, Flaxman S, Andrews N, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. Lancet 399 (2022): 1303-1312.

6. Nordstrom P, Ballin M, Nordstrom A. Risk of SARS-CoV-2 reinfection and COVID-19 hospitalisation in individuals with natural and hybrid immunity: a retrospective, total population cohort study in Sweden. Lancet Infect Dis 22 (2022): 781-790.

7. Fazio S, Bellavite P, Zanolin E, McCullough PA, Pandolfi S, Affuso F. Retrospective Study of Outcomes and Hospitalization Rates of Patients in Italy with a Confirmed Diagnosis of Early COVID-19 and Treated at Home Within 3 Days or After 3 Days of Symptom Onset with Prescribed and Non-Prescribed Treatments Between November 2020 and August 2021. Med Sci Monit 27 (2021): e935379.

8. Cosentino M, Vernocchi V, Martini S, Marino F, Allasino B, Balzola M, et al. Early outpatient treatment of COVID-19: a retrospective analysis of 392 cases in Italy MedXriv (2022): https://www.medrxiv.org/content/10.1101/2022.04.04.22273356v1.

9. D'Amario CR, Rossi P. Indicazioni emergenziali connesse ad epidemia COVID-19 riguardanti il settore funebre, cimiteriale e di cremazione. Direzione Generale

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della Prevenzione Sanitaria ed., Ministero della Salute, Roma (2020).

10. Wichmann D, Sperhake JP, Lutgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. Ann Intern Med 173 (2020): 268-277.

11. Rezza G. Indicazioni emergenziali connesse ad epidemia SARS-CoV-2 riguardanti il settore funebre, cimiteriali e della cremazione - Versione 11 gennaio 2021. Direzione generale della prevenzione sanitaria ed., Ministero della Salute, Roma (2021).

12. Pandolfi S, Valdenassi L, Bjorklund G, Chirumbolo S, Lysiuk R, Lenchyk L, et al. COVID-19 Medical and Pharmacological Management in the European Countries Compared to Italy: An Overview. Int J Environ Res Public Health 19 (2022): 19(7):4262.

13. Pandolfi S, Chirumbolo S, Ricevuti G, Valdenassi L, Bjorklund G, Lysiuk R, et al. Home pharmacological therapy in early COVID-19 to prevent hospitalization and reduce mortality: Time for a suitable proposal. Basic Clin Pharmacol Toxicol 130 (2022): 225-239.

14. Thomas SJ, Moreira ED Jr, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. N Engl J Med 385 (2021): 1761-1773.

15. Rohban T. BNT162b2 Vaccine Booster and Covid-19 Mortality. N Engl J Med 386 (2022): 1000.

16. Ma Q, Liu J, Liu Q, Kang L, Liu R, Jing W, et al. Global Percentage of Asymptomatic SARS-CoV-2 Infections Among the Tested Population and Individuals With Confirmed COVID-19 Diagnosis: A Systematic Review and Meta-analysis. JAMA Netw Open 4 (2021): e2137257.

17. Suter F, Consolaro E, Pedroni S, Moroni C, Pasto E, Paganini MV, et al. A simple, home-therapy algorithm to prevent hospitalisation for COVID-19 patients: A retrospective observational matched-cohort study. EClinicalMedicine 37 (2021): 100941.

18. Consolaro E, Suter F, Rubis N, Pedroni S, Moroni C, Pasto E, et al. A Home-Treatment Algorithm Based on Anti-inflammatory Drugs to Prevent Hospitalization of Patients With Early COVID-19: A Matched-Cohort Study (COVER 2). Front Med (Lausanne) 9 (2022): 785785.

19. Lin WT, Hung SH, Lai CC, Wang CY, Chen CH. The impact of neutralizing monoclonal antibodies on the outcomes of COVID-19 outpatients: A systematic review

and meta-analysis of randomized controlled trials. J Med Virol (2022): 94(5):2222-2229.

20. Vegivinti CTR, Evanson KW, Lyons H, Akosman I, Barrett A, Hardy N, et al. Efficacy of antiviral therapies for COVID-19: a systematic review of randomized controlled trials. BMC Infect Dis 22 (2022): 107.

21. Okoli GN, Rabbani R, Al-Juboori A, Copstein L, Askin N, Abou-Setta AM. Antiviral drugs for coronavirus disease 2019 (COVID-19): a systematic review with network meta-analysis. Expert Rev Anti Infect Ther 20 (2022): 267-278.

22. Kow CS, Ramachandram DS, Hasan SS. The use of neutralizing monoclonal antibodies and risk of hospital admission and mortality in patients with COVID-19: a systematic review and meta-analysis of randomized trials. Immunopharmacol Immunotoxicol 44 (2022): 28-34.

23. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. N Engl J Med 383 (2020): 2451-2460.

24. Marconi, F. Gestire la pandemia: linee guida e assistenza domiciliare al vaglio della giurisprudenza amministrativa. Il Diritto Amministrativo - Rivista Giuridica anno XIV, Luglio (2022). https://www.ildirittoamministrativo.it/Gestire-la-pandemia-linee-guida-e-assistenza-domiciliare-al-vaglio-della-giurisprudenza-amministrativa-Marconi/stu846.

25. Rezza, GU A. Circolare recante "Gestione domiciliare dei pazienti con infezione da SARS-CoV-2" aggiornata al 26 aprile 2021. Direzioni Generali della Programmazione Sanitaria e della Prevenzione Sanitaria, ed., Ministero della Salute Roma (2021).

26. Rezza GU, Urbani A. Circolare recante "Gestione domiciliare dei pazienti con infezione da SARS-CoV-2" aggiornamento del 10 febbraio 2022. Direzioni Generali della Programmazione Sanitaria e della Prevenzione Sanitaria, ed., Ministero della Salute, Roma (2022).

27. Cordon-Cardo C, Pujadas E, Wajnberg A, Sebra R, Patel G, Firpo-Betancourt, A, et al. COVID-19: Staging of a New Disease. Cancer Cell 38 (2020): 594-597.

28. Turk C, Turk S, Malkan UY, Haznedaroglu IC. Three critical clinicobiological phases of the human SARS-associated coronavirus infections. Eur Rev Med Pharmacol Sci 24 (2020): 8606-8620.

29. Alexander PE, Armstrong R, Fareed G, Lotus J, Oskoui R, Prodromos C, et al. Early multidrug treatment of SARS-CoV-2 infection (COVID-19) and reduced mortality among nursing home (or outpatient/ambulatory) residents. Med Hypotheses 153 (2021): 110622.

30. McCullough PA, Alexander PE, Armstrong R, Arvinte C,

Bain AF, Bartlett RP, et al. Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19). Rev Cardiovasc Med 21 (2020): 517-530.

31. Ravichandran R, Mohan SK, Sukumaran SK Kamaraj D, Daivasuga SS, Ravi S, et al. An open label randomized clinical trial of Indomethacin for mild and moderate hospitalised Covid-19 patients. Sci Rep 12 (2022): 6413.

32. Shekhar N, Kaur H, Sarma P, Prakash A, Medhi B. Indomethacin: an exploratory study of antiviral mechanism and host-pathogen interaction in COVID-19. Expert Rev Anti Infect Ther (2022): 20(3):383-390.

33. Desantis J, Mercorelli B, Celegato M, Croci F, Bazzacco A, Baroni M et al. Indomethacin-based PROTACs as pan-coronavirus antiviral agents. Eur J Med Chem 226 (2021): 113814.

34. Fazio S, Affuso F, Bellavite P. A Review of the Potential Roles of Antioxidant and Anti-Inflammatory Pharmacological Approaches for the Management of Mild-to-Moderate Symptomatic COVID-19. Med Sci Monit 28 (2022): e936292.

35. Sestili P, Fimognari C. Paracetamol-Induced Glutathione Consumption: Is There a Link With Severe COVID-19 Illness? Front Pharmacol 11 (2020): 579944.

36. Rushworth GF, Megson IL. Existing and potential therapeutic uses for N-acetylcysteine: the need for conversion to intracellular glutathione for antioxidant benefits. Pharmacol Ther 141 (2014): 150-159.

37. De Flora S, Balansky R, La MS. Rationale for the use of N-acetylcysteine in both prevention and adjuvant therapy of COVID-19. FASEB J 34 (2020): 13185-13193.

38. Bellavite P. Reappraisal of Dietary Phytochemicals for Coronavirus Infection: Focus on Hesperidin and Quercetin in *Antioxidants* (Waisundara, VY, ed) (2021) 473-487. DOI: 10.5772/intechopen.95529.

39. Zhang X, Wu X, Hu Q, Wu J, Wang G, Hong Z, et al. Mitochondrial DNA in liver inflammation and oxidative stress. Life Sci 236 (2019): 116464.

40. Bhargava A, Raghuram GV, Pathak N, Varshney S, Jatawa SK, Jain D, et al. Occult hepatitis C virus elicits mitochondrial oxidative stress in lymphocytes and triggers PI3-kinase-mediated DNA damage response. Free Radic Biol Med 51 (2011): 1806-1814.

41. 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 54 (2016): 312-319.

42. Saleh J, Peyssonnaux C, Singh KK, Edeas M. Mitochondria and microbiota dysfunction in COVID-19 pathogenesis. Mitochondrion 54 (2020): 1-7.

43. Suhail S, Zajac J, Fossum C, Lowater H, McCracken C, Severson N, et al. Role of Oxidative Stress on SARS-CoV (SARS) and SARS-CoV-2 (COVID-19) Infection: A Review. Protein J (2020): 39(6):644-656.

44. Keles ES. Mild SARS-CoV-2 infections in children might be based on evolutionary biology and linked with host reactive oxidative stress and antioxidant capabilities. New Microbes New Infect 36 (2020): 100723.

45. Delgado-Roche L, Mesta F. Oxidative Stress as Key Player in Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) Infection. Arch Med Res 51 (2020): 384-387.

46. Trujillo JA, Croft NP, Dudek NL, Channappanavar R, Theodossis A, Webb AI, et al. The cellular redox environment alters antigen presentation. J Biol Chem 289 (2014): 27979-27991.

47. Hati S, Bhattacharyya S. Impact of Thiol-Disulfide Balance on the Binding of Covid-19 Spike Protein with Angiotensin-Converting Enzyme 2 Receptor. ACS Omega 5 (2020): 16292-16298.

48. Dalan R, Bornstein SR, El-Armouche A, Rodionov RN, Markov A, Wielockx B, et al. The ACE-2 in COVID-19: Foe or Friend? Horm Metab Res 52 (2020): 257-263.

49. Roberts E, Delgado Nunes V, Buckner S, Latchem S, Constanti M, Miller P, et al. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. Ann Rheum Dis 75 (2016): 552-9.

50. Yadav DK, Singh A, Zhang Q, Bai X, Zhang W, Yadav RK, et al. Involvement of liver in COVID-19: systematic review and meta-analysis. Gut 70 (2021): 807-809.

51. Marin-Duenas I, Vega J, Carrillo-Ng H, Veramendi-Schult I, Zavaleta-Alva R, Vasquez-Elera L, et al. Alteration in liver function tests among patients hospitalized for COVID-19: a multicentric study in Peru. Rev Gastroenterol Peru 41 (2021): 86-93.

52. Santus P, Corsico A, Solidoro P, Braido F, Di MF, Scichilone N. Oxidative stress and respiratory system: pharmacological and clinical reappraisal of N-acetylcysteine. COPD 11 (2014): 705-717.

53. De FS, Grassi C, Carati L. Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term N-acetylcysteine treatment. Eur Respir J 10 (1997): 1535-1541.

54. Soltan-Sharifi MS, Mojtahedzadeh M, Najafi A, Reza KM, Reza RM, Moradi M, et al. Improvement by

N-acetylcysteine of acute respiratory distress syndrome through increasing intracellular glutathione, and extracellular thiol molecules and anti-oxidant power: evidence for underlying toxicological mechanisms. Hum Exp Toxicol 26 (2007): 697-703.

55. Poe FL, Corn J. N-Acetylcysteine: A potential therapeutic agent for SARS-CoV-2. Med Hypotheses 143 (2020): 109862.

56. Andreou A, Trantza S, Filippou D, Sipsas N, Tsiodras S. COVID-19: The Potential Role of Copper and N-acetylcysteine (NAC) in a Combination of Candidate Antiviral Treatments Against SARS-CoV-2. In Vivo 34 (2020): 1567-1588.

57. Zhou N, Yang X, Huang A, Chen Z. The potential mechanism of N-acetylcysteine in treating COVID-19. Curr Pharm Biotechnol (2020).

58. Luo P, Liu Y, Liu D, Li J. Perspectives for the use of N-acetylcysteine as a candidate drug to treat COVID-19. Mini Rev Med Chem (2020) 10.2174/138955752066620 1027160833 [doi].

59. Ibrahim H, Perl A, Smith D, Lewis T, Kon Z, Goldenberg R, et al. Therapeutic blockade of inflammation in severe COVID-19 infection with intravenous N-acetylcysteine. Clin Immunol 219 (2020): 108544.

60. Shi Z, Puyo, CA. N-Acetylcysteine to Combat COVID-19: An Evidence Review. Ther Clin Risk Manag 16 (2020): 1047-1055.

61. de Alencar JCG, Moreira CL, MÃ¼ller, AD, Chaves CE, Fukuhara MA, da Silva EA, et al. Double-blind, randomized, placebo-controlled trial with N-acetylcysteine for treatment of severe acute respiratory syndrome caused by COVID-19. Clin Infect Dis (2020): 5910353.

62. Carothers C, Birrer K, Vo M. Acetylcysteine for the Treatment of Suspected Remdesivir-Associated Acute Liver Failure in COVID-19: A Case Series. Pharmacotherapy 40 (2020): 1166-1171.

63. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 312 (1996): 71-2.

64. Allegri PMM A, Gulisano P, Burigana F, Ortolani R, Donzelli A, Valsecchi M, et al. La gestione dei pazienti COVID-19 in ambito domiciliare. Indirizzi operativi proposti dal gruppo di lavoro promosso da Luca Coletto, Capo Dipartimento Sanità Lega-Salvini premier in Documento depositato al Senato (Bagnai, LCaA, ed), Atti parlamentari Roma (2021). https://www.sanitainformazione.it/wp-content/uploads/2021/04/Terapia-domicliare-Covid.pdf.

65. Ravichandran R PP, Vijayaragavan S, Kalavakollu RT, Gaidhane S, Kumar RK. Efficacy and safety of indomethacin in COVID-19 patients. MedRxiv (2020). https://www.medrxiv.org/content/10.1101/2020.12.14.2 0245266v1

66. Zhou Q, Zhao S, Gan L, Wang Z, Peng S, Li Q, et al. Use of non-steroidal anti-inflammatory drugs and adverse outcomes during the COVID-19 pandemic: A systematic review and meta-analysis. EClinicalMedicine 46 (2022): 101373.

67. Bellavite P, Donzelli A. Hesperidin and SARS-CoV-2: New Light on the Healthy Function of Citrus Fruits. Antioxidants (Basel) 9 (2020). 10.3390/antiox9080742 [doi].

68. Ricordi C, Pacifici F, Lanzoni G, Palamara AT, Garaci E, Della-Morte D. Dietary and Protective Factors to Halt or Mitigate Progression of Autoimmunity, COVID-19 and Its Associated Metabolic Diseases. Int J Mol Sci 22 (2021).

69. Rizzuti, B; Grande, F; Conforti, F; Jimenez-Alesanco, A; Ceballos-Laita, L; Ortega-Alarcon, D, et al. Rutin Is a Low Micromolar Inhibitor of SARS-CoV-2 Main Protease 3CLpro: Implications for Drug Design of Quercetin Analogs. Biomedicines 9 (2021).

70. Colunga Biancatelli RML, Berrill M, Catravas JD, Marik PE. Quercetin and Vitamin C: An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19). Front Immunol 11 (2020): 1451.

71. El-Missiry MA, El-Missiry ZM, Othman AI. Melatonin is a potential adjuvant to improve clinical outcomes in individuals with obesity and diabetes with coexistence of Covid-19. Eur J Pharmacol 882 (2020): 173329.

72. Rondanelli M, Perna S, Gasparri C, Petrangolini G, Allegrini P, Cavioni A, et al. Promising Effects of 3-Month Period of Quercetin Phytosome((R)) Supplementation in the Prevention of Symptomatic COVID-19 Disease in Healthcare Workers: A Pilot Study. Life (Basel) 12 (2022).

73. Pawar A, Russo M, Rani I, Goswami K, Russo GL, Pal A. A critical evaluation of risk to reward ratio of quercetin supplementation for COVID-19 and associated comorbid conditions. Phytother Res (2022): 36(6):2394-2415.

74. Shohan M, Nashibi R, Mahmoudian-Sani MR, Abolnezhadian F, Ghafourian M, Alavi SM, et al. The therapeutic efficacy of quercetin in combination with antiviral drugs in hospitalized COVID-19 patients: A randomized controlled trial. Eur J Pharmacol 914 (2022): 174615.

75. Di Pierro F, Iqtadar S, Khan A, Ullah Mumtaz S, Masud Chaudhry M, Bertuccioli A, et al. Potential Clinical Benefits of Quercetin in the Early Stage of COVID-19: Results of a Second, Pilot, Randomized, Controlled and Open-Label Clinical Trial. Int J Gen Med 14 (2021): 2807-2816.

76. Di Pierro F, Derosa G, Maffioli P, Bertuccioli A, Togni S, Riva A, et al. Possible Therapeutic Effects of Adjuvant Quercetin Supplementation Against Early-Stage COVID-19 Infection: A Prospective, Randomized, Controlled, and Open-Label Study. Int J Gen Med 14 (2021): 2359-2366.