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Review Article

Prevention of Side effects associated with COVID 19 Vaccinations: A Review

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A B S T R A C T

Globally, the new SARS-CoV-2, which is responsible for COVID-19, represents a considerable burden on both health and the economy. Although there have been a great number of clinical investigations, there is not yet a single therapy or medicine that has been licensed for successful treatment. Over 300 million people have lost their lives as a result of the COVID-19 epidemic, and there is an increasing demand for anti-viral medication. Following the COVID-19 pandemic, extensive international research has led to the development of effective vaccines. However, due to the crisis, some potential side effects have been overlooked. Common complications include cerebrovascular disorders, transient ischemic attacks, intracerebral hemorrhage, ischemic stroke, and demyelinating disorders. These effects are often acute and transient but can be severe and even fatal in a few cases. This review examines the immunological and autoimmune adverse events associated with COVID-19 vaccines, highlighting their frequencies, reported cases, and associations with specific vaccine classes. The concept of vaccine-induced immune thrombotic thrombocytopenia is crucial in addressing vaccine skepticism. Healthcare professionals and public health agencies must actively monitor and address these adverse events promptly disclose suspicious incidents, take measures to mitigate dangers, and inform the public with transparency and accurate information. Continuing research and surveillance are essential for understanding the underlying mechanisms of these adverse events and developing strategies to minimize their occurrence.

Keywords: COVID-19; SARS-Cov-2; Natural Medication; Traditional Medicine; Vaccines.

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INTRODUCTION

The emergence of a novel coronavirus outbreak designated "Severe Acute Respiratory Syndrome Coronavirus 2" (SARS-CoV-2) was first observed in December 2019 in Wuhan City, Hubei Province, China. This epidemic is the cause of the 2019 Coronavirus Disease (COVID-19), a global health threat (1). As of December 13, 2020, the World Health Organisation (WHO) provides detailed information on the global spread of COVID-19 as a pandemic. The outbreak has spread to over 215 countries, with 72,645,205 confirmed cases and 1,616,908 confirmed deaths (2). SARS-CoV-2 enters the host cell by attaching S protein (spike proteins) to ACE2 (angiotensin-converting enzyme 2, which is mediated by the serine protease TMPRSS211 (transmembrane serine protease 211) produced by the host cell (Figure 1) (3). Investigate potential drug candidates by examining their target location on virion and host cells, with a particular emphasis on key proteins and their mechanisms of dissemination. For example, by inhibiting the binding of ACE2 and TMPRS211 proteins, producing polyclonal antibodies against the viral S protein, and preventing virus replication within the host cell (4). The transmission of microbial pathogens by a variety of animals is the cause of infectious diseases. It was discovered that these pathogens exhibited a certain level of resistance to certain antibiotics and antiviral medicines. Genomics is crucial in a wide range of biotechnological applications, such as the development of antipathogenic pharmaceuticals and therapies (5–7). Regrettably, there are currently no approved potential medications or vaccine candidates for the prevention of COVID-19. The substantial rise in the number of progressive cases among confirmed COVID-19 patients suggests that there is a pressing need to create a prospective and preventive acute anti-COVID medication or therapy (8).

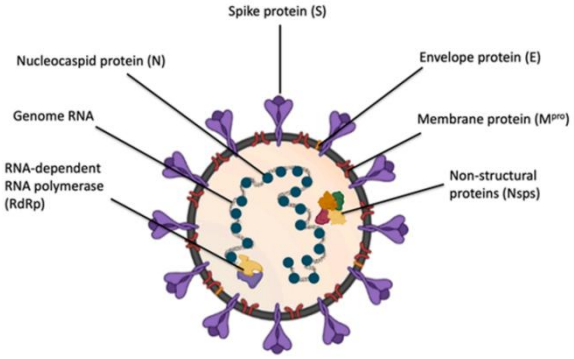

Figure 1: Structural representation of SARS-CoV-2

The current pandemic of coronavirus disease 2019 (COVID-19), which is the sixth public health emergency of international significance, has resulted in a total of 505,035,185 cases and 6,210,719 fatalities around the globe over the course of the past two years. According to the World Health Organisation. Pandemic warnings have been issued on many occasions due to the presence of the Alpha, Beta, Gamma, and Delta versions of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is responsible for COVID-19. According to Nasreen et al., on November 24, 2021, the unique Omicron (South Africa) variety was confirmed for the very first time, which is quite concerning. Despite this, it quickly became the most prevalent strain on a global scale within a short period of time due to its enhanced likelihood of transmission and its capacity to circumvent the immune system (9). As at this moment, the Omicron form, which is extremely destructive, has spread to virtually every country. For the purpose of lowering the rate of human-to-human transmission, it is essential to implement efficient measures such as vaccines (10), traditional medicine (11, 12), and small-molecule inhibitors (13, 14). In light of the fact that SARS-CoV-2 is extremely infectious, vaccinations are the most critical public health actions that can be taken to prevent individuals from exposure to COVID-19 (Table 1).

Table 1: Approved COVID 19 Vaccine

Common name	Type	Country of origin	First authorization
Oxford-AstraZeneca	Adenovirus vector	United Kingdom	December 2020
Pfizer-BioNTech	RNA	Germany, United States	December 2020
Janssen	Adenovirus vector	United States, the Netherlands	February 2021
Moderna	RNA	United States	December 2020
Sputnik V	Adenovirus vector	Russia	August 2020
Novavax	Subunit/virus like particle	United States	December 2021
Sanofi-GSK	Subunit	France	November 2022
EpiVacCorona	Subunit	Russia	October 2020
ZyCoV-D	DNA	India	August 2021
COVAX-19	Subunit	Australia, Iran	October 2021
Turkovac	Inactivated	Turkey	December 2021
CoVLP	Virus like particle	Canada, United Kingdom	February 2022

A number of steps are involved in the process of conducting vaccine trials. These phases include preclinical testing on animals to evaluate the safety and efficacy of the vaccine, followed by clinical trials with human volunteers. These clinical trials are carried out in a series of stages, beginning with a limited number of volunteers and gradually expanding the number of participants in order to collect further information on the safety and effectiveness of the treatment (15). Anaphylaxis, blood clots, myocarditis, pericarditis, differences in hearing, and tinnitus are some of the rare side effects that can occur as a result of receiving a COVID-19 vaccination. The overall risk of anaphylaxis is relatively low, and the occurrence of severe responses following immunisation is something that only a tiny fraction of people experience. In order to protect the health and safety of those who get vaccines, medical professionals carefully monitor and manage any adverse reactions that may occur (16).

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Side effects or adverse effects associated with COVID 19 Vaccination

Vaccines have been created in order to prevent the spread of the SARS-CoV-2 virus; nevertheless, these vaccines have resulted in significant adverse effects in a variety of organ systems. These reactions include migraines, fever, tiredness, reactions at the injection site, and circulatory issues (17). Myocarditis, pericarditis, thrombotic events, arrhythmias, hypertension, acute coronary syndrome, cardiac arrest, and anaemia are all examples of adverse effects that can occur in the circulatory system during treatment. Figure 2 illustrates that these side effects are extremely uncommon and only manifest themselves in a small fraction of the people who get the COVID-19 vaccination. Nevertheless, the possible dangers that are linked with these undesirable effects are far outweighed by the advantages of vaccination in terms of averting serious disease and hospitalisation among individuals. Individuals who are getting the vaccination are subjected to attentive monitoring and management of probable adverse reactions by medical specialists in order to guarantee their safety and protect their well-being (18)

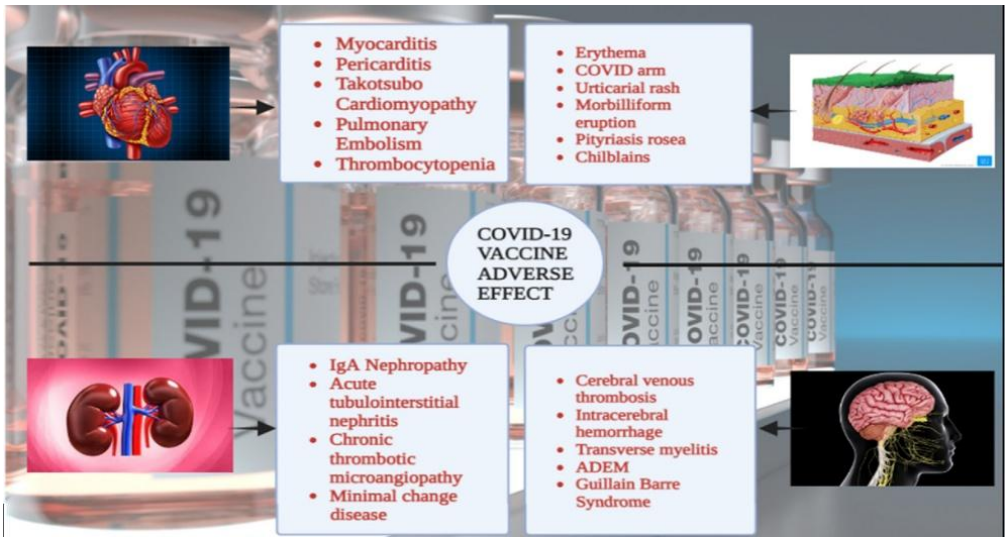

Figure 2: Various adverse effects associated with COVID-19 vaccines

The World Health Organization (WHO) reports that inactivated virus-based vaccines, particularly Sinopharm, can cause local and systemic adverse reactions such as injection site reactions, fatigue, fever, headache, and allergic dermatitis (19). These reactions are self-limiting and do not require hospitalization. However, rare reports have been published on these side effects. Vaccine reactivity is linked to a temporary increase in infammatory cytokines, causing a fu-like syndrome for several consecutive days after vaccination (20). A recent report on the Sputnik vaccine reported headache, joint pain, fever, and fu-like symptoms. It is crucial to evaluate the effectiveness of the Sputnik vaccine and publish relevant data to determine its side effects. COVID-19 vaccination can have severe side effects on the nervous system, including the brain, spinal cord, cranial nerves, and peripheral nerves. Two main mechanisms for the pathogenicity of vaccines are ectopic immune reactions and molecular mimicry (21). Some of the common side effects are as follow:

Headache

Te first and most common systemic side effect of COVID-19 vaccines is headache, which is mild to severe and is felt in the frontal area of the head. Post-vaccination headaches can be caused by stress, vascular spasm, and intracerebral or subarachnoid hemorrhage. Vaccines based on mRNA and adenovirus has been reported to be most likely to cause headaches (22).

Vascular Complications in the Brain

COVID-19 vaccines can cause thrombocytopenia, cerebral venous sinus thrombosis, ischemic stroke, and intracerebral hemorrhage due to the immune system's activity. The mechanism for thrombocytopenia is the synthesis of IgG antibodies against platelet factor 4, activating platelets and blood clots in large venous arteries. Adenovirus-based vaccines are at the forefront of causing this complication due to the transfer of nucleic acids encoding the viral spike protein. Venous sinus thrombosis is associated with excessive coagulation, and vaccine viral antigens activate platelets or indirectly cause blood clotting. These complications are more common in women aged 30-50 than men (23).

Side effects associated to Integumentary system

Vaccine-associated adverse effects, such as cutaneous reactions, are generally minor. Systemic reactions, more frequent and severe, can cause symptoms. Well-tolerated reactions, such as inflammation and skin irritation at the injection site, usually resolve. Common skin adverse effects include local injection site reactions, urticaria, morbilliform reactions, erythromelalgia, herpes zoster lesions, chilblains, and burning foot sensations (24). Rare cases of severe allergic reactions, such as anaphylaxis, have been reported. These reactions can manifest symptoms beyond cutaneous effects, such as difficulty breathing, swelling of the face and throat, and decreased blood pressure. Immediate medical attention is necessary to prevent further complications. Healthcare providers should educate patients about potential allergic reactions and emphasize seeking medical attention if any concerning symptoms arise (25).

Approach to deal with the Side effects associated with the COVID 19 Vaccination

Venenum Bufonis

Venenum Bufonis, (ChanSu), is a traditional medicine animal secretion used in China to treat various diseases, including heart failure, infections, toothaches, and cancers. ChanSu injection, a valuable anticancer agent, has been used in tumor treatment for over 30 years. ChanSu's main active constituents are bufadienolides with an unusual 2-pyrone ring, which contribute to their pharmacological activities by inhibiting Na+/K+ ATPase. Jin et al. (2021) demonstrated that six bufadienolides (bufalin, bufotalin, cinobufagin, cinobufotalin, resibufogenin, and telocinobufagin) have potent broad-spectrum antiviral activities in vitro. Experiments showed that bufalin could inhibit virus replication in the nanomolar range, including MERS-CoV, SARS-CoV, and SARS-CoV-2 at a half-maximal inhibitory concentration (IC50) of 0.018 μM, SARS-CoV at an IC50 of 0.016 μM, and SARS-CoV-2 at an IC50 of 0.019 μM. Subsequent dose toxicity studies revealed that bufalin and

cinobufagin have strong toxicity in the mouse model, while telocinobufagin has lower toxicity, better metabolic stability, excellent oral bioavailability, and proper anti-SARS-CoV2 activity. Telocinobufagin might be a more promising broad-spectrum inhibitor among bufadienolides, worthy of multifaceted properties investigation from in vitro studies to clinical practice (26- 29).

Nigella sativa

Nigella sativa extract and thymoquinone have shown significant effectiveness in an animal influenza virus infection model. They reduce virus division and survival, regulate nitric oxide, reactive oxygen species, and TGF-β1 production, and protect multiple organ dysfunction syndromes. Thymoquinone and nigellimine offer beneficial spectra for COVID-19 treatment by blocking virus introduction to host pneumocytes, improving zinc consumption, enhancing the host immune response, and suppressing viral replication. Thymoquinone, the main active ingredient of Nigella sativa, exhibits numerous therapeutic properties, including immune-regulatory, anti-inflammatory, anti-oxidant, antimicrobial, antitumor, analgesic, antiAlzheimer, and hepatoprotective. Thymoquinone-mediated inhibition of cytokines in bronchoalveolar lavage fluid increased immune cell numbers in lung tissue. Its anti-inflammatory activities are regulated by higher production of hem oxygenase in human keratinocyte cells. Its anti-oxidant properties are linked to the redox activities of quinone structure and its ability to cross significant barriers to cellular nich (30- 33).

Caffeic acid

Caffeic acid, (((E)-3-(3,4-dihydroxyphenyl)prop-2-enoic acid) with a molecular mass of 180.16 g/mol.), a polyphenol found in various foods and medicine, is a potent and abundant hydroxycinnamic acid. Studies have shown that caffeic acid, its derivatives (CAFDs), and Caffeic Acid Phenethyl Ester (CAPE) have various immune-modulatory properties, including anti-oxidant, anti-inflammatory, anti-bacterial, and anti-viral effects. These properties make them suitable candidates for clinical studies. Caffeic acid has been reported to have potential anti-viral properties against various viruses, including influenza, herpes simplex, and severe fever with thrombocytopenia syndrome. CAPE has shown high efficacy against HIV and hepatitis C virus, with an EC50 of 1.17 ± 0.75 µg/mL. Caffeic acid, CAPE, and CAFDs have been found to inhibit virus attachment to host cells and suppress the viral 3CL protease enzyme, preventing viral replication. The scientific basic and antiviral mechanisms of CA, CAPE, and CAFDs may differ depending on the type of virus (34-39).

Thymol

Thymol (2-isopropyl-5-methylphenol) is the phenolic monoterpene in thyme species and the main constituent of thyme essential oils. Other than the medicinal plant thyme (Thymus vulgaris), thymol is also extracted from plants such as Ocimum, Origanum, Monarda genera, and other plants, for instance, the members of Verbenaceae, Scrophulariaceae, Ranunculaceae, and Apiaceae families. Thymol, a traditional medicine agent, has been found to have multiple therapeutic applications, including anti-viral, anti-bacterial, antibiofilm, antifungal, anti-inflammatory, antithelial, and anti-cancer agents. Recent studies have shown that thymol compounds can also be used as antioxidants, local anesthetics, anti-carcinogenesis agents, and growth enhancers (40). Kulkarni et al. conducted an in-silico study on eighteen well-reported anti-viral phytochemicals to determine if they could prevent SARS-CoV-2 infection. The study predicted the structure of a host protein, TMPRSS2, which cleaves the spike protein of SARS-CoV-2, aiding viral internalization. The catalytic domain of TMPRSS2 was docked against the selected phytochemicals, and the target-inhibitor complex's stability was analyzed using molecular dynamic simulation (41). Unique phytocompounds thymol could physically bind SARS-CoV-2 spike glycoproteins, SARS-CoV-2 B.1.351 South Africa variant of spike glycoprotein (7NXA), and ACE2 to prevent the SARS-CoV-2 binding to the host ACE2, TMPRSS2, and neutrapilin-1 receptors. Qazi et al. elucidated the epigenetic mechanism of SARS-CoV-2 and its impact on the environment, suggesting that thymol compounds can inactivate the virus from surfaces when sprayed without harming the biological environment (42).

Rosmarinic acid

Rosmarinic acid (3,4-dihydroxyphenyllactic acid) is a polyphenol molecule commonly found in many culinary herbs, such as rosemary, perilla, sage, mint, and basil. It is found to be slightly soluble in an aqueous medium whereas very well in most organic solvents. Rosmarinic acid, a phytoconstituent with numerous biological and pharmacological properties, is found in medicinal plants, herbs, and spices. It serves as a defense molecule and has health-promoting effects, including rheumatic, diuretic, and antiepileptic agents. However, it has been linked to a remarkable carcinogenesis progression (43). The primary amino acids L-phenylalanine and L-tyrosine, along with eight enzymes and co-factors, are required for rosmarinic acid biosynthesis (44). Tegen et al. predicted the use of phyto-compounds as COVID-19 therapeutics, with medicinal plants containing rosmarinic acid, ursolic acid, and others being promising compounds for treating COVID-19. Natural compounds, including rosmarinic acid, have shown potential to enhance the expression of ACE-2 and exacerbate SARS-CoV-2 infection by degrading host receptors aiding viral endocytosis. A molecular docking study found that rosmarinic acid and ursolic acid interacting successfully with the Nsp15 viral protein, suggesting their potential role in inhibiting SARS-CoV-2 replication (45-46).

CONCLUSIONS

The COVID-19 pandemic has significantly increased vaccine reactogenicity, with most people experiencing adverse reactions after immunization. A survey found that 65% of participants experience adverse reactions, while only a few studies have reported severe effects. Individuals with a history of SARS-CoV-2 infection have stronger vaccination reactogenicity than those without such history. Over 95% of individuals had moderate and self-limiting side effects, with only 5% requiring medical evaluation and hospitalization. Most reported adverse effects were minor and required no therapy or care at home. Younger people, women, and those with comorbid conditions are more likely to experience negative, potentially systemic, adverse effects after

immunization with an inactivated vaccine. Despite the risks, vaccination remains the most efficient method for fighting the pandemic's broad effects. Healthcare professionals closely monitor and assess vaccine safety and efficacy to ensure continued vaccination in combating the pandemic. In light of the current unfavorable conditions of COVID-19, there is an immediate need to create antiviral medications or therapeutic alternatives. There is a significant amount of time required for the identification and development of novel medications, as well as additional validation and clinical studies to verify their efficacy and effectiveness. Phytoconstituents from medicinally significant plants, such as thymoquinone, quercetin, caffeic acid, ellagic acid, ursolic acid, thymol, vanillin, and rosmarinic acid, have the potential to offer a wide range of therapeutic applications against side effects associated with the COVID-19 vaccination. However, the dose of these substances at greater concentrations may be harmful beyond a specific threshold due to potential toxicity. Initial research should focus on chemicals previously authorized by the FDA or considered safe for use in therapeutic formulations, such as polyphenolic components, to build a successful COVID-19 treatment.

Conflict of Interest

None

REFERENCES

1. Zhao W, Zhang J, Meadows ME, Liu Y, Hua T, Fu B (2020) A systematic approach is needed to contain COVID-19 globally. Sci Bull 65(11):876–878.
2. WHO Coronavirus Disease (COVID-19) Dashboard. World Health Organisation (WHO). 2020;
3. Patel SKS, Lee JK, Kalia VC (2020) Deploying biomolecules as antii-COVID-19 agents. Indian J Microbiol 60:263–268.
4. Rishi P, Thakur K, Vij S, Rishi L, Singh A, Kaur IP, Patel SKS, Lee JK, Kalia VC (2020) Diet, gut microbiota and COVID-19. Indian J Microbiol 60:420–429.
5. Kalia VC, Raju SC, Purohit HJ (2011) Genomic analysis reveals versatile organisms for quorum quenching enzymes: acyl-homoserine lactone-acylase and-lactonase. Open Microbiol J 5:1–11.
6. Kalia VC, Wood TK, Kumar P (2014) Evolution of resistance to quorum-sensing inhibitors. Microb Ecol 68:13–23.
7. Kumar P, Patel SKS, Lee JK, Kalia VC (2013) Extending the limits of Bacillus for novel biotechnological applications. Biotechnol Adv 31:1543–1561.
8. Lythgoe MP, Middleton P (2020) Ongoing clinical trials for the management of the COVID-19 pandemic. Trends Pharmacol Sci 41(6):363–382.
9. Desai A, Kulkarni A, Rajkumar SV, Gyawali B (2020) Clinical trial endpoints in severe COVID-19. Mayo Clin Proc 95(8):1578–1580.
10. Kupferschmidt K, Cohen J (2020) WHO launches global megatrial of the four most promising coronavirus treatments? Sci Mag.
11. Nile SH, Nile A, Qiu J, Li L, Jia X, Kai G (2020) COVID-19: pathogenesis, cytokine storm and therapeutic potential of interferons. Cytokine Growth Factor Rev 53:66–70.
12. Joppi R, Bertele V, Vannini T, Garattini S, Banzi R (2020) Food and drug administration vs European medicines agency: review times and clinical evidence on novel drugs at the time of approval. Br J Clin Pharmacol 86:170–174.
13. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R (2020) COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. J Adv Res 24:91–98.
14. Xian Y, Zhang J, Bian Z, Zhou H, Zhang Z, Lin Z, Xu H (2020) Bioactive natural compounds against human coronaviruses: a review and perspective. Acta Pharma Sin B 10(7):1163–1174.
15. Tian, H. Y., Ruan, L. J., Yu, T., Zheng, Q. F., Chen, N. H., Wu, R. B., et al. Bufospirostenin A and Bufogargarizin C, steroids with rearranged skeletons from the toad Bufo bufo gargarizans. J. Nat. Prod. 2017; 80 (4), 1182–1186.
16. Shen, Y., Cai, H., Ma, S., Zhu, W., Zhao, H., Li, J., et al. Telocinobufagin has antitumor effects in non-small-cell lung cancer by inhibiting STAT3 signaling. J. Nat. Prod. 2022; 85 (4), 765–775.
17. Panggabean, J. A., Adiguna, S. B. P., Rahmawati, S. I., Ahmadi, P., Zainuddin, E. N., Bayu, A., et al. Antiviral activities of algal-based sulfated polysaccharides. Molecules 2022; 27 (4), 1178.
18. Prassas, I., and Diamandis, E. P. Novel therapeutic applications of cardiac glycosides. Nat. Rev. Drug Discov. 2008; 7 (11), 926–935.
19. S. Banerjee, A.O. Kaseb, Z. Wang, D. Kong, M. Mohammad, S. Padhye, F. H. Sarkar, R.M. Mohammad, Antitumor activity of gemcitabine and oxaliplatin is augmented by thymoquinone in pancreatic cancer, Cancer Res. 69 (13) (2009) 5575–5583.
20. K. Chaieb, B. Kouidhi, H. Jrah, K. Mahdouani, A. Bakhrouf, Antibacterial activity of Thymoquinone, an active principle of Nigella sativa and its potency to prevent bacterial biofilm formation, BMC Complement. Altern. Med. 11 (2011) 29.
21. Ahmad, R.K. Mishra, A. Vyawahare, A. Kumar, M.U. Rehman, W. Qamar, A. Q. Khan, R. Khan, Thymoquinone (2-Isoprpyl-5-methyl-1, 4-benzoquinone) as a chemopreventive/anticancer agent: Chemistry and biological effects, Saudi Pharm. J. 27 (8) (2019) 1113–1126.
22. M. Khader, P.M. Eckl, Thymoquinone: an emerging natural drug with a wide range of medical applications, Iran. J. Basic Med. Sci. 17 (12) (2015) 950–957.
23. M. El Gazzar, R. El Mezayen, J.C. Marecki, M.R. Nicolls, A. Canastar, S.C. Dreskin, Anti-inflammatory effect of thymoquinone in a mouse model of allergic lung inflammation, Int. Immunopharmacol. 6 (7) (2006) 1135–1142.
24. K. Ikeda, K. Tsujimoto, M. Uozaki, M. Nishide, Y. Suzuki, A.H. Koyama, H. Yamasaki, Inhibition of multiplication of herpes simplex virus by caffeic acid, Int. J. Mol. Med. 28 (4) (2011) 595–598.
25. J.J. Meyer, A.J. Afolayan, M.B. Taylor, D. Erasmus, Antiviral activity of galangin isolated from the aerial parts of Helichrysum aureonitens, J. Ethnopharmacol. 56 (2) (1997) 165–169.
26. J.R. Weng, C.S. Lin, H.C. Lai, Y.P. Lin, C.Y. Wang, Y.C. Tsai, K.C. Wu, S.H. Huang, C.W. Lin, Antiviral activity of Sambucus FormosanaNakai ethanol extract and related phenolic acid constituents against human coronavirus NL63, Virus Res. 273 (2019), 197767.
27. G.F. Wang, L.P. Shi, Y.D. Ren, Q.F. Liu, H.F. Liu, R.J. Zhang, Z. Li, F.H. Zhu, P. L. He, W. Tang, P.Z. Tao, C. Li, W.M. Zhao, J.P. Zuo, Anti-hepatitis B virus activity of chlorogenic acid, quinic acid and caffeic acid in vivo and in vitro, Antivir. Res. 83 (2) (2009) 186–190.
28. M.A.I. Al-Hatamleh, M.M. Hatmal, K. Sattar, S. Ahmad, M.Z. Mustafa, M.D. C. Bittencourt, R. Mohamud, Antiviral and immunomodulatory effects of phytochemicals from honey against COVID-19: potential mechanisms of action and future directions, Molecules 25 (2020) 21.
29. D.D. Singh, D.K. Yadav, TNBC: potential targeting of multiple receptors for a therapeutic breakthrough, nanomedicine, and immunotherapy, Biomedicines 9 (2021) 8.
30. A.A. Turab Naqvi, G.M. Hasan, M.I. Hassan, Targeting tau hyperphosphorylation via kinase inhibition: strategy to address Alzheimer's disease, Curr. Top. Med. Chem. 20 (12) (2020) 1059–1073.
31. Kowalczyk, M. Przychodna, S. Sopata, A. Bodalska, I. Fecka, Thymol and thyme essential oil-new insights into selected therapeutic applications, Molecules 25 (2020) 18.
32. S.A. Kulkarni, S.K. Nagarajan, V. Ramesh, V. Palaniyandi, S.P. Selvam, T. Madhavan, Computational evaluation of major components from plant essential oils as potent inhibitors of SARS-CoV-2 spike protein, J. Mol. Struct. 1221 (2020), 128823.
33. P.K. Yadav, A. Jaiswal, R.K. Singh, In silico study on spice-derived antiviral phytochemicals against SARS-CoV-2 TMPRSS2 target, J. Biomol. Struct. Dyn. (2021) 1–11.
34. R. Rolta, D. Salaria, P. Sharma, B. Sharma, V. Kumar, B. Rathi, M. Verma, A. Sourirajan, D.J. Baumler, K. Dev, Phytocompounds of Rheum emodi, Thymus serpyllum, and Artemisia annua inhibit spike protein of SARS-CoV-2 binding to ACE2 receptor: in silico approach, Curr. Pharmacol. Rep. (2021) 1–15.
35. S. Qazi, K. Sheikh, K. Raza, In silico approach to understand the epigenetic mechanism of SARS-CoV-2 and its impact on the environment, Virusdisease (2021) 1–12.
36. M. Ghasemzadeh Rahbardar, H. Hosseinzadeh, Effects of rosmarinic acid on nervous system disorders: an updated review, Naunyn Schmiede Arch. Pharmacol. 393 (10) (2020) 1779–1795.
37. S. Kumar, P. Kashyap, S. Chowdhury, S. Kumar, A. Panwar, A. Kumar, Identification of phytochemicals as potential therapeutic

agents that binds to Nsp15 protein target of coronavirus (SARS-CoV-2) that are capable of inhibiting virus replication, Phytomedicine 85 (2020), 153317.
38. J. Selvaraj, U.V. Rekha, S.F. Jh, V. Sivabalan, R. Ponnulakshmi, V. Vishnupriya, M. Kullappan, R.N. Sreekandan, S.K. Mohan, Molecular docking analysis of SARSCoV-2 linked RNA dependent RNA polymerase (RdRp) with compounds from Plectranthus amboinicus, Bioinformation 17 (1) (2021) 167–170.
39. M. Petersen, M.S. Simmonds, Rosmarinic acid, Phytochemistry 62 (2) (2003) 121–125.
40. C. Colica, L. Di Renzo, V. Aiello, A. De Lorenzo, L. Abenavoli, Rosmarinic acid as potential anti-inflammatory agent, Rev. Recent Clin. Trials 13 (4) (2018) 240–242.
41. M. Hitl, N. Kladar, N. Gavari´c, B. Bo˘zin, Rosmarinic acid-human pharmacokinetics and health benefits, Planta Med. 87 (4) (2020) 273–282.
42. A.G. Junior, S. Tolouei, F.A. Dos Reis Lívero, F. Gasparotto, T. Boeing, P. de Souza, Natural agents modulating ACE-2: a review of compounds with potential against SARS-CoV-2 infections, Curr. Pharm. Des. 27 (13) (2021) 1588–1596.
43. S. Banerjee, A.O. Kaseb, Z. Wang, D. Kong, M. Mohammad, S. Padhye, F. H. Sarkar, R.M. Mohammad, Antitumor activity of gemcitabine and oxaliplatin is augmented by thymoquinone in pancreatic cancer, Cancer Res. 69 (13) (2009) 5575–5583.
44. J. Selvaraj, U.V. Rekha, S.F. Jh, V. Sivabalan, R. Ponnulakshmi, V. Vishnupriya, M. Kullappan, R.N. Sreekandan, S.K. Mohan, Molecular docking analysis of SARSCoV-2 linked RNA dependent RNA polymerase (RdRp) with compounds from Plectranthus amboinicus, Bioinformation 17 (1) (2021) 167–170.
45. D.D. Singh, I. Han, E.H. Choi, D.K. Yadav, Recent advances in pathophysiology, drug development and future perspectives of SARS-CoV-2, Front. Cell Dev. Biol. 8 (2020), 580202.
46. D.D. Singh, I. Han, E.H. Choi, D.K. Yadav, Immunopathology, host-virus genome interactions, and effective vaccine development in SARS-CoV-2, Comput. Struct. Biotechnol. J. 18 (2020) 3774–3787.