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Exploring Dermatological Complications of Drugs Used in Acute Respiratory Syndrome Coronavirus 2 Treatment: A Mini Review

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ABSTRACT

The COVID-19 pandemic has presented unprecedented challenges to governments and populations worldwide, triggering a global health crisis within months. In response, international health research organizations have highlighted various effects of chemical therapies, including dermatological complications. This mini-review explores the dermatological effects of drugs used in the treatment of COVID-19. This study examines the skin manifestations resulting from standard chemical treatments administered during the COVID-19 pandemic. Keywords were cross-referenced across multiple databases, including Web of Science, Scopus, PubMed, SID, Magiran, and Google Scholar. Search terms included COVID-19, coronavirus, SARS-CoV-2, chemical effects, neurological effects, and pandemic-related cardiac complications. The review encompasses a range of pharmaceuticals used in the treatment of COVID-19, such as hydroxychloroquine, remdesivir, azithromycin, dexamethasone, ribavirin/interferon, intravenous immunoglobulin (IVIG), oseltamivir, losartan, magnesium sulfate, and vitamin D3. Our investigation identifies various cutaneous manifestations, including rash, erythema, and ulceration. Additionally, early-onset nocturnal symptoms, somnolence, dyspnea, edema, arrhythmias, scleroderma, and other adverse effects are associated with the standard pharmacotherapy used to manage COVID-19.

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Intorduction

Coronaviruses are a group of viruses within the coronavirus family that induce respiratory infections in birds and mammals. While some strains may cause mild common colds, others, such as SARS, MERS, and COVID-19, can result in more severe diseases (Kumar et al., 2020; Xiu et al., 2020). Coronaviruses possess a relatively simple genome and, upon entering the host cell, directly target ribosomes associated with the endoplasmic reticulum, bypassing the cell nucleus. This direct interaction with the host cell machinery facilitates the production of viral proteins (Rahmani et al., 2020).

Coronavirus is a contagious respiratory disease that has been designated as a pandemic by the World Health Organization (McIntosh and Peiris, 2009). The novel virus causes respiratory illness in humans and can be transmitted from person to person. It was initially identified during investigations of an outbreak in Wuhan, China (Nishiura et al., 2020). Coronavirus is a global crisis, evolving rapidly and capturing worldwide attention due to its high transmissibility and mortality rate (Payvar et al., 2022). The most frequent symptoms of COVID-19 in Kuwait include fever, swelling, muscle weakness, nausea, sore throat, rash, and others (Ooi et al., 2022).

Antiviral therapies such as Paxlovid have demonstrated significant effectiveness in mitigating severe cases of COVID-19, reducing hospitalization rates and mortality when administered promptly after symptom onset to individuals at high risk (Akinosoglou et al., 2022). These therapies work by inhibiting key viral enzymes like the SARS-CoV-2 main protease (Mpro), thereby blocking viral replication (Li et al., 2023). Since the onset of the pandemic, a range of antiviral, anti-inflammatory, antibiotic, monoclonal antibodies, and other treatments have been utilized. The pandemic has spurred unparalleled initiatives in repurposing drugs and developing new treatments, resulting in the creation of numerous targeted antiviral, immunomodulatory, and antibody therapies aimed at addressing COVID-19 across its various disease severities, from mild to severe cases (Li et al., 2023; Murakami et al., 2023). The COVID-19 pandemic has prompted swift repurposing and development of diverse therapies. Although most are generally well-tolerated, dermatological adverse events may arise, particularly with prolonged use or in high-risk populations (Nordhorn et al., 2022; Martora et al., 2023).

The objective of the present study is to investigate the dermatological impacts of conventional pharmacological interventions employed for managing COVID-19 amid the coronavirus pandemic.

Results and Discussion

Hydroxychloroquine, remdesivir, azithromycin, favipiravir, dexamethasone, colchicine, ribavirin/interferon, intravenous immunoglobulin (IVIG), oseltamivir (Tamiflu), atazanavir, arbidol, lopinavir/ritonavir, ivermectin, losartan, zinc sulfate, magnesium sulfate, and vitamin D3, among others, are utilized in the treatment of COVID-19. Recorded instances of associated dermatological complications are summarized in Table 1.

Table 1. Dermatological Effects of Antiviral Medications

Drugs	Cutaneous Side Effects	Ref.
Hydroxychloroquine	Pruritic rashes, maculopapular eruptions, worsening of psoriasis and changes in skin pigmentation, epidermal necrolysis, vasculitis affecting small and large blood vessels presenting as ulcers, vesicles, and purpura, particularly in the vicinity of the ankles, urticaria, xerosis, alopecia, and potential graying of hair.	(Abou Assalie, Durcan et al. 2017, Martinez-Lopez, Cuenca-Barrales et al. 2020, Monte-Serrano, Cruañes-Monferrer et al. 2020, Türsen, Türsen et al. 2020, Nazari, Hesari et al. 2022)
Remdesivir	Non-specific pruritic rashes, the development of erythema, severe and occasionally painful inflammation in areas such as the armpits and groin.	(Kumar, Bhale et al. 2019, Bilovol, Tkachenko et al. 2020, Heck, Stichtenoth et al. 2021)
Azithromycin	Leukocytoclastic vasculitis, angioedema, ocular irritation, generalized non-specific skin rash, anaphylaxis, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome.	(Gautret, Lagier et al. 2020)
Favipiravir	Generalized rashes and instances of bilateral leg ulcers with significant depth.	(Kannan, Khan et al. 2015, Costanzo, De Giglio et al. 2020, Martinez-Lopez, Cuenca-Barrales et al. 2020)
Dexamethasone	Pruritus, burning sensation, folliculitis, rash resembling acne, skin thinning, edema, swelling, increased hair growth, stretch marks, and photosensitivity.	(Liu, Zhou et al. 2020, Mehta, An et al. 2021)
Colchicine	Hair shedding, pruritic rashes, erythema nodosum, and skin tenderness resembling Toxic Epidermal Necrolysis (TEN).	(Gürkan, Oguz et al. 2018, Mathur, Kottilil et al. 2018)
Ribavirin/ Interferon	Eczematous lesions, xerosis, worsening of psoriasis, pruritus, alopecia, and injection site reactions, including rash resembling acne and scleroderma.	(Arabi, Shalhoub et al. 2020)
Immunoglobin IVIG	Urticarial lesions and angioedema may occur during injection. Subsequent days may witness erythema multiforme, eczema, purpuric or ecchymotic rash. Cases of anaphylaxis, rash resembling Stevens-Johnson syndrome, and alopecia have also been reported.	(Bird, Olson et al. 2015, Jawhara 2020)
Tamiflu (Oseltamivir)	Instances of scaling, blistering, itching, and swelling involving the eyelids, lips, and tongue have been reported.	(Fabbiani, Gagliardini et al. 2018, Antipov and Pokryshevskaya 2019, Zuo, Wen et al. 2019, Gül 2020)
Ata Zanavir	Itching, hives, and yellowing of eyes and skin	(Avihingsanon, Tongkobpetch et al. 2015, Li, Liu et al. 2018)
Arbidol	Eruptive rash	(Darazam, Shokouhi et al. 2021, López-Medina, López et al. 2021)

Continued, Table 1		
Lopinavir/ritonavir	Rash, non-specific dermatitis, seborrheic dermatitis-like lesions, itching, and night sweats, along with uncommon side effects such as hair loss, capillaritis, and vasculitis. There is also a rare occurrence of Stevens-Johnson syndrome.	(Antipov and Pokryshevskaya 2019, Nazari, Hesari et al. 2022)
Ivermectin	Severe allergic reactions manifesting as hives, itching, and angioedema	(Rampur, Jariwala et al. 2016, Chandler 2018, Ketkar, Yang et al. 2019, Caly, Druce et al. 2020, Hoffmann, Kleine-Weber et al. 2020, Badary 2021)
Losartan	Itching	(Zarehoseinzade, Allami et al. 2021)
Zinc sulfate	Non-healing oral ulcers	(Cavell, Bryant et al. 2015, Dolcourt, Paxton et al. 2019)
Magnesium Sulfate	Skin infections, including those occurring during injection, as well as injection site pain, redness, and flushing attacks.	(Al-Shoha, Klair et al. 2015)
Vitamin D3	Urticaria lesions, itching, and non-specific skin rashes, along with mucous membrane dryness, reduced skin tone, and exacerbation of eczema, particularly atopic eczema.	(Lim and Thadhani 2020, Wang, Bao et al. 2020)

Scientists worldwide are diligently searching for effective drugs and designing vaccines to combat COVID-19. Many countries have used various drugs to treat the disease, despite being aware of potential side effects, particularly those affecting the skin. Hydroxychloroquine, for example, appears to prevent the virus from entering the cell by inhibiting glycerolysis in the host cell receptor, proteolytic processes, and endosomal acidification (Ahamed and Samad, 2020). However, despite its relative effectiveness in alleviating COVID-19 symptoms, hydroxychloroquine use has been associated with the occurrence of hives and skin itching (Srinivasa et al., 2017).

Remdesivir, an intravenous nucleotide prodrug, is metabolized into its active form, GS-441524 triphosphate. As an adenosine nucleotide analog, remdesivir interferes with viral replication by binding to the RNA-dependent RNA polymerase of the SARS-CoV-2 virus during RNA synthesis, thus inhibiting replication (Hasmono et al., 2022). Severe allergic reactions to remdesivir can manifest as skin rashes and itching (Hasmono et al., 2022).

Azithromycin, a macrolide antibiotic used to treat a wide range of bacterial infections, can cause dry skin as a side effect (Hopkins, 1991). Dexamethasone, an anti-inflammatory drug used to treat conditions such as arthritis, heart disease, kidney disease, and inflammatory pain, is also used in COVID-19 treatment. However, its use can lead to skin problems like acne and thin, shiny skin (Polderman et al., 2018). Oseltamivir, an antiviral drug, can also cause itching and skin rash (Kitching et al., 2009). Ivermectin, prescribed for treating parasites such as intestinal parasites in animals and scabies in humans, can cause itching and skin rashes when injected (Ottesen and Campbell, 1994).

Vitamin D3, or cholecalciferol, is a supplement used to treat vitamin D deficiency. If allergy symptoms such as skin spots, itching, and hives occur, its use should be discontinued (Sanaei et al., 2015; Abdi et al., 2019). Side effects of drugs are unexpected and unwanted reactions that occur in the body after taking medications. These side effects can range from mild and low-risk to serious and potentially dangerous. Managing medication side effects is crucial to minimizing adverse health effects. Common side effects of medications include nausea, vomiting, fatigue, dizziness, dry mouth, headache, itching, and muscle aches. While some side effects may be severe and require medical intervention, others may be mild and not cause significant concern. With anti-COVID-19 drugs, skin complications can occur, so careful consideration is necessary when selecting the appropriate medication.

COVID-19 is an infectious disease where the coronavirus interacts with target cells, stimulates the immune system, secretes inflammatory cytokines, and causes the death of infected cells. These processes collectively contribute to the development of oxidative stress (Chernyak et al., 2020). Hence, the use of antioxidants in COVID-19 treatment, particularly natural antioxidants or plants with high levels of antioxidant activity, may help reduce these side effects (Raimi et al., 2021). Many of these plants, in addition to their antioxidant properties, also possess anti-inflammatory effects (Saedeghi et al., 2023; Kim et al., 2024), which may offer additional benefits for COVID-19 patients.

Conclusions

While various treatments for COVID-19 demonstrate relative effectiveness, they are often associated with adverse side effects, particularly dermatological issues. Medications such as hydroxychloroquine, remdesivir, azithromycin, and dexamethasone can lead to skin complications like itching, hives, and dryness. Therefore, the use of anti-COVID-19 drugs should be approached with caution, taking these potential side effects into account. Additionally, incorporating natural antioxidants and medicinal plants, which possess both antioxidant and anti-inflammatory properties, may help mitigate oxidative stress and inflammation caused by the disease, thereby reducing the side effects associated with these treatments. This complementary approach could offer a more holistic strategy in the management of COVID-19.

Declarations

Conflict of interest

The authors declare no conflict of interest.

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Consent for publications

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Authors' contributions

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Ethical considerations

All ethical issues, including plagiarism, misconduct, data fabrication, falsification, double publication, or submission redundancy, have been fully observed.

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