Section A-Research paper
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Mucor and Mucormycosis: An *in silico* perspective of drug toxicity

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Abstract
Mucor infections in humans are known as mucormycosis or zygomycosis, and can be serious and potentially life-threatening if left untreated. Mucormycosis is triggered by molds called Mucoromycetes. It is a rare, difficult-to-diagnose, and non-communicable disease that might affect the mucous membrane in the lungs, brain, eyes, skin, etc. Early diagnosis and treatment are essential for recovery. Mucormycosis treatment typically combines antifungal medication with surgical debridement. The specific approach to treatment depends on the level of the fungal infection. Knowledge regarding the side effects of drugs used for treatment is limited. Potential side effects of these drugs should be carefully weighed against their therapeutic benefits, and treatment should be tailored to the individual's specific circumstances. In this study, ProTox-II was used for the *in silico* estimation of toxicity levels of the recommended medications for mucormycosis using toxicity endpoints such as hepatotoxicity, cytotoxicity, carcinogenicity, mutagenicity and immunotoxicity. A close monitoring and management of potential side effects will ensure optimal outcomes in management of this life-threatening disease.

Keywords: Drugs, *Mucor*, Mucormycosis, Pathogenesis, Toxicity, ProTox-II, SARS-CoV-2 virus

Introduction

Mucor is a type of filamentous fungus that is ubiquitous [1]. Around 50 species of *Mucor* are reported worldwide. *Mucor* species are common and predominantly saprotrophs [2]. Mucor can colonize and thrive on organic substrates, including soil, vegetation surfaces, fruit and vegetable waste, animal manure, and agricultural remains, to varying degrees. It is associated with flora, fauna, and humans as opportunistic pathogens [3]. Additionally, dust particles and decomposing plant matter are all potential habitats for this thermotolerant fungus [4]. Fungi colonize the surface of the hosts and obtain sugar and amino acids as nutrient sources [5].

Fungi within the order Mucorales includes a number of economically significant and versatile species [6]. Some of these fungi are involved in the production of certain food products and drinks like tempeh and sake [7]. However, they can also cause significant economic losses as food spoilage organisms, particularly in fruits, vegetables, and dairy products [8]. Mucorales fungi can also act as plant parasites, causing diseases such as mucor rot in crops such as

strawberries, grapes, and tomatoes. In addition, some species are potentially fatal for humans [9].

Mucorales are the 3rd most widespread source of IFIs or intrusive fungal infections in persons having weakened immune systems or underlying medical conditions [1, 10]. Fungal infections can happen when someone breathes in spores, eats spoiled food, or comes into contact with contaminated objects while suffering from an open cut or burn [11]. When infected, the blood vessels of the host get constricted as the hyphae grow out from the spores, causing tissues in the vicinity to swell and eventually die. The infection of fungi can affect the brain, lungs and skin etc. The severity of the fungal infection depends on the immunity and health conditions of the individual [1].

Paucity of effective antifungal drugs against the causative agent for Mucormycosis has recently increased lethal incidences caused by the fungi of class Zygomycetes [12]. A group of molds known as Mucoromycetes are the source of the deadly but uncommon fungal infection known as mucormycosis (formerly known as zygomycosis) [13, 14].

Mucorales and the Entomophthorales are two disease-causing orders of Zygomycetes fungi [15]. Some examples of these disease-causing fungi are *Absidia corymbifera, Rhizomucor pusillus*, and *Rhizopus arrhizus*. The onset of Mycoses disease, in most cases, is sudden and it affects primarily patients with pre existing ailments [16, 17].

The disease is linked to people with a weak immune system, such as acidotic diabetes [18]. Gastrointestinal mucormycosis is associated with malnourished children [19], and primary cutaneous mucormycosis is manifested in patients with severe burns and tissue trauma [19, 20, 21]. Mucormycosis was also identified in patients having cancer and AIDS [1]. The fungus *Mucor*, which causes "black fungus," primarily affects patients with weakened immune systems or those who have chronic kidney illness or diabetes [22].

Economic importance

Mucor species are important biotechnologically due to their rapid growth rates and potential for secondary metabolite production (e.g., antibiotics) [23]. Fungi of the order Mucorales are important as fermenting agents, and as producers of enzymes [5]. In the biobased economy, fungi are important for efficient and sustainable utilization of resources [24].

Fungi help produce renewable substitutes from fossil resources, and economically important products from agricultural and food processing industries wastes [25]. They can also play a role as a bacterial antagonist, strengthening the gut biota and counteracting lifestyle diseases [26]. They make crop plants more resilient to climate change [27]. Fungi are also used in the development of novel biological medicines [27, 28]. The genus *Mucor* comprises around 40-50 recognized species, of considerable economic importance and are promising candidates for discovering new drugs and value-added bio-based products [29].

Mucor species have important biotechnological potentials; they produce enzymes like amylase, lipase, pectinase, polygalacturonase, and protease [30, 31]. *Mucor indicus* is a mold that has a high economic value and is utilized in the production of industrial products such as ethanol lactic acid, amylases, rennin, and organic products such as fumaric acid, chitosan, oil (single-cell oils), and polyunsaturated fatty acids [32]. It is also a rich nutritional source, which is utilized as fish feed [32].

As an alternate fuel (or oxygenate alternative) to the conventional fossil fuels, ethanol has attracted a lot of attention in recent decades. Bioethanol (ethanol from a renewable resource) can be formed by *M. indicus* & *R. oryzae* from the cellulose component of lignocellulosic wastes like straw of rice, which is one of the world's richest lignocellulosic wastes [33]. Additionally, *Mucor circinelloides* has attracted significant attention for production of ethanol [34]. *Mucor indicus* could be beneficial to clean up oil spills and can be utilized in heavy metal removal from *wastewaters* [35]. Chinese cheese called sufu is prepared from

soybeans with the help of the mucor [36]. *Mucor circinelloides, Mucor indicus,* and *Mucor subtilissimus* are examples of zygomycetes that can degrade cellulose and grow on lignocellulose, a mixture of hexose and pentose [37].

Taxonomy and current classification

The taxonomy of the phylum Zygomycota has undergone significant changes in recent years due to advances in molecular phylogenetics [6, 38]. It is important to note that the taxonomy of Zygomycota is still evolving, and new research may lead to further changes in the future.

Zygomycosis encompasses two pathologically and clinically distinct conditions, mucormycosis (caused by Mucorales) and entomophthoramycosis (caused by Entomophthorales) of Zygomycota [39, 19]. Phylum Zygomycota includes Mucorales and Entomophthorales, amongst other orders. Both classes are pathogenic members [39]. In the decreasing order of severity, the mucormycosis causing genera (i.e. members of order Mucorales) are *Mucor, Cunninghamella, Apophysomyces, Lichtheimia, Saksenaea*, and *Rhizomucor* [39, 40].

Basidiobolus (causes subcutaneous tissue infection) and *Conidiobolus* (causes chronic rhinofacial infection) belong to the Entomophthorales and are also pathogenic fungi that cause basidiobolomycosis and conidiobolomycosis respectively [41].

The Mucorales and the Entomophthorales are two orders of Zygomycetes that are known to cause infectious disease in humans [42]. Zygomycosis has been used interchangeably with mucormycosis. The fungi that cause the diseases, formerly referred to collectively as zygomycosis, are now recognised independently as mucormycosis (caused by *Mucor*), conidiobolomycosis (caused by *Conidiobolus*), and basidiobolomycosis (caused by *Basidiobolus*) [43].

The clinical histopathology of the tissue infected with the three fungi plays a crucial role in diagnosis. All of them have marked phylogenetic differences but they are morphologically similar in terms of having coenocytic or non-septate hyphae. Clinical outcome of the tissue histopathology has profound effects on the diagnosis and the ensuing treatment [43].

The phylum Zygomycota has been demonstrated to be polyphyletic through molecular-phylogenetic evaluation, and the taxa that were formerly included in Zygomycota have been moved to the separate phylum Glomeromycota and four subphyla with still unresolved positioning. The newly established classification has a significant impact on the designation of the medical condition because the classification of the Zygomycota (Zygomycetes), in which the fungal members responsible for the condition had been categorized, served as the foundation for the nomenclature of the disease zygomycosis (39, 44). Zygomycosis was traditionally defined as an umbrella term for two distinct medical conditions with distinct clinicopathological manifestations: mucormycosis, produced by fungi included within the order Mucorales of Zygomycota, and entomophthoromycosis, attributed to the fungal species included within the order Entomophthorales of the former Zygomycota (39, 44). The term "zygomycosis," however, has been utilized more frequently as an alternative name for mucormycosis alone without modification of the original definition. Based on the evolution of our understanding of its etymology, revisions in the taxonomic classification and the medical condition, the traditional names "mucormycosis" and "entomophthoramycosis" are preferable to "zygomycosis."(39, 44).

The disease caused by these genera referred to as ‘zygomycosis’ or ‘mucormycosis’ has led to a lot of confusion. Both mucormycosis and entomophthoramycosis [39, 44] are types of zygomycosis caused by different fungi in the same order, but they have some differences in terms of the populations they affect, the parts of the body they commonly affect, and the severity of the infection [17, 42, 43, 45.]. *Actinomucor elegans, is* an invasive mucormycosis-causing fungus [46].

Morphological features

Mucor species have a highly developed mycelium and branched hyphae [47]. The hyphae in Mucor are generally coenocytic, rarely septate [25]. The cytoplasm of the hypha appears granular. Mucor has been cultured and grows on agar [44] Initially colonies appear cottony and become dark grey, after growth of sporangia [48]. Sporangiophores are straight or rarely circinate and repeatedly sympodial branches are hyaline, grey or brownish [2]. Sporangia are round, black, and filled with sporangiospores [25, 49, 50].

Within infected tissues, the strains that cause pathogenesis only manifest in the form of hyphae (without a yeast phase) [51, 52]. Non Septation of hyphae means hyphal cells are mixed and nuclei float in the cells [53].

Following Candidiasis and Aspergillosis, Mucormycosis is the most common aggressive fungal-infection [1]. The fungus is found in soil, dust, manure, decaying fruits and vegetables and as bread mold. Interestingly the pathogen can be cultured from the mouth, nose, throat, and stools of healthy people without infections. Fungal spore inhalation, contact with contaminated tissue via trauma, ingestion, or direct inoculation are the usual causes of infection in an immunocompromised individual [54].

The lungs, digestive tract, kidneys, and skin are prominently the primary infection sites. Diabetics frequently suffer from infections that begin in the nasal lining and extend to the hypopharynx, eyes, and brain [55].

Pathogenic potential of Mucorales and Entomophthorales

In total, 27 species of Mucorales (representing 11 genera) have been associated with the mucormycosis infection [56]. People with compromised immune systems, untreated diabetic ketoacidosis, chemotherapy, haematological disease, and other potentially life-threatening conditions are more likely to develop a Mucorales infection swiftly [56]. Twenty-one of the 27 species have complete genomic sequence databases that can be accessed. Several different types of fungi, including *Rhizopus, Mucor, Lichtheimia* (formerly *Absidia*), *Cunninghamella, Rhizomucor,* and *Apophysomyces*, are responsible for the spread of mucormycosis infection [57, 19].

"Entomophthoromycosis" are infections caused by Entomophthorales [58]. *Conidiobolus* spp. elicit rhinofacial entomophthoramycosis in immunocompetent and in immunocompromised hosts. In immunocompetent patients, *Basidiobolus* spp. infection induces subcutaneous entomophthoromycosis of the limbs, chest, back, and the buttocks. Pulmonary, nasal, retroperitoneal and GI tract infections caused by *Basidiobolus* spp. are becoming more common in various parts of the world. Laboratory diagnosis relies on contaminated tissue culture. However, molecular analysis approaches, using DNA probes, and RT-PCR are increasingly being employed to detect and identify these species in the tissue. Antifungal triazoles dominate treatment. Depending on the location of the infection, surgery may be required to treat entomophthoromycosis [58, 59].

Mucormycosis is a lethal invasive infection spread by the fungus of the subphylum and order Mucoromycotina and Mucorales respectively [60, 61]. Mucormycosis has emerged as the third most prevalent form of fungal infection to spread through the blood and cause mortality [11]. Pulmonary and zygomycosis infections are perhaps the most common infection, and these two types of mucormycosis were observed in patients during the COVID-19 pandemic [62, 63]. Despite the use of antibiotics, mortality rates among immunocompromised patients remained high, at around 70% [64]. Angioinvasion and necrosis of tissue are the early signs of progression of the disease that promotes the spread of the fungus through the bloodstream, resulting in deeper infections and less effective antifungal drugs are the reason for high mortality [19, 44]. There is an urgent need to better understand the molecular mechanisms that drive the disease in order to develop new methods of curing and preventing

mucormycosis due to the paucity of current treatment options and the high morbidity of extremely disfiguring surgical procedures [61, 65].

Fungus can enter our body through cuts, scrapes, wounds, or other forms of trauma in the dermal layer of the skin [48]. Mucormycosis is not a transmittable disease. It is a lethal contamination with a pathogenesis that is not completely understood. It was demonstrated that Fungi of the order Mucorales secrete a toxin called mucoricin that contributes to the pathogenicity of the disease they cause [66, 60].

Mucormycosis is associated with several species of *Rhizopus, Mucor, Lichtheimia* and *Cunninghamella, etc. Rhizopus* and *Mucor* are common agents for spreading of mucormycosis [56]. It is reported to be much more prevalent in emerging countries, as compared to established economies. Haematological cancers and transplants are the two most prevalent illnesses in the advanced countries. *Mucor* spp. was reported to be responsible for many more mucormycosis cases amongst organ transplant recipients, followed by *Rhizopus* spp. and *Lichtheimia* [11].

Mucorales are resistant to voriconazole and have been associated with breakthrough infections in patients receiving prophylactic voriconazole treatment. The other risk factors are intravenous drug abuse and under nourishment [67, 44].

Mucormycosis:

- The outcome of infection by fungi of order Mucorales, e.g.: *Rhizopus* or *Mucor*.
- Usually affects people with low immunity, diabetes, cancer and HIV.
- The sinuses, brain, and lungs are particularly vulnerable.
- Possible fatality unless promptly diagnosed and treated.

Entomophthoromycosis:

- Caused by fungi in the order *Entomophthorales*, such as *Basidiobolus* or *Conidiobolus*.
- Typically affects healthy people, particularly those who live in tropical or subtropical areas.
- Most commonly affects the skin and subcutaneous tissues, but can affect other organs, eyes and gastrointestinal tract.
- Tends to be less aggressive than mucormycosis, and the prognosis is generally better.

Mucormycosis: Diagnosis and Management

Mucormycosis is hard to identify and treat successfully because it can be identified only after a biopsy [68]. Tissues are analysed by advanced molecular methods in pathology [69]. Prompt diagnosis and early treatment are critical [70]. The saprophytic fungus begins by attacking the sinuses, subsequently it spreads to the mouth, eye orbit and to the lungs, leading to an acute phase wherein there is an inadequate supply of blood to the affected tissue which ultimately leads to tissue necrosis [62]. If it is left untreated, it can cause a loss of vision (temporary or permanent), fever, headache, redness in face, allergy etc.[71]. There are a number of laboratory assessments that can be performed, such as a tissue biopsy, a CT scan, and a reverse transcriptase-PCR [72]. Amphotericin B and Micafungin are the most prescribed medicines against these fungi [73]. Mucormycosis is an acute, potentially fatal, extremely aggressive fungal infection that can be treated by surgically removing the contaminated tissue. The infection originates within the nose and then moves on to infect the paranasal sinuses, followed by orbit/brain infiltration. conventional treatments involve antifungal medication and surgical removal of the infected region. Infection of the nose, internasal sinuses, neck regions by mucormycosis can be highly dangerous and even lead to death sometimes [19, 59, 71, 74]. There are numerous reports available which indicate that surgical excision of the afflicted areas successfully cures patients of the infection if it had

only spread locally [68, 75]. Hence, there has been a sudden demand in the search for a cure to mucormycosis [75, 76].

In silico prediction to treat mucormycosis disease

As a consequence of the recent advancements in the field of computational research, *in silico* approaches can potentially provide substantial advantages for conducting risk assessments in compliance with the regulatory standards, for evaluating safety profile of a plethora of experimental compounds that can specifically target a particular disease, in the pharmaceutical industry [77].

Compounds having the strongest docking scores in the screening process may represent effective therapies [78]. Prior to these chemicals being potentially utilised by the pharmaceutical industry, however, toxicity must be meticulously evaluated in preclinical research [79]. Preclinical toxicological analysis of substances to ensure ultimate outcome and also to determine side effects is expensive as well as complicated with ethical challenges throughout drug development, which can take up to 12 years [80]. In order to better direct further toxicity studies and chemical selection, toxicity prediction based on computational methods can be employed for preliminary screening to identify relevant toxicity endpoints [81].

Prior to COVID-19, mucormycosis had a death rate of about 50% [82] but widespread occurrence of the two infections together caused 85% of deaths [83] The worst-case situation for any person was to have both widespread mucormycosis and SARS-CoV-2 [83, 84]. Steroids that were given to COVID-19 patients to lower inflammation in their lungs, resulted in raising their blood sugar levels, making them more susceptible to mucormycosis infection [85].

The immunological irregularity initiated by the SARS-CoV-2 virus, and excessive consumption of antibiotics, in patients with uncontrolled blood sugar levels, diabetic ketoacidosis, are considered to have led to the spike in mucormycosis infected cases whilst the 2nd peak of the COVID-19 infection was going on, and the disease had been acknowledged as an epidemic in various regions in the country. It was called "black fungus" because of the black coloration it imparted to dead and dying tissue [86].

Many studies have been conducted all over the world to try materials that could be used to treat mucormycosis.

Materials and Methods

In Silico Prediction Methods to measure the extent of Toxicity of Drugs used to cure Mycosis [77].

For *in silico* methods, an online ProTox-II system served as the platform [77]. PubChem-name of the molecules are used for the analysis [87].

This platform is grounded in the following five steps:

Step	Classification	Models for prediction
1	Acute toxicity (oral toxicity)	6 classes of toxicity
2	Toxicity against Fatal Organs	1
3	Toxicological endpoints	4
4	Toxicological different pathways	12
5	Toxicological targets	15

ProTox-II tool is based on molecular similarity index and techniques of ML (machine learning) [77].
A set of 33 models used in order to predict various toxicity types including - acute toxicity, organ toxicity, adverse-outcomes (Tox21) pathways and their toxicity targets [88].

Prediction for Oral Toxicity

PubChem name of compound analyse, were entered in ProTox prediction pane and clicked on Start-Tox prediction, depending on the Lethal-Dose$_{50}$ (mg/kg body-weight), chemicals or mycotoxins were placed under 5 different toxicity classes [89], categorised as:

Class-I.: Lethal upon consumption of Lethal-Dose$_{50}$ of $\leq$ 5.0 mg/kg;
Class-II.: Lethal upon consumption of 5mg/kg<Lethal-Dose$_{50}$ of $\leq$ 50.0 mg/kg;
Class-III.:Toxic upon consumption of 50mg/kg<Lethal-Dose$_{50}$ of $\leq$300.0 mg/kg;
Class-IV.: Injurious upon consumption of 300mg/kg<Lethal-Dose$_{50}$ of $\leq$ 2000.0 mg/kg;
Class-V.: Maybe injurious upon consumption, of 2000 mg/kg < Lethal-Dose$_{50}$ of $\leq$ 5000.0 mg/kg.

Prediction of Toxicity of Drugs against various Organs

We have compiled the drugs that are used to treat Mycosis by *in silico* methods. Drug toxicity studies were performed using the ProTox-II platform.
In this prediction, models were based on data available on ProTox server from *in vivo* and *in vitro* investigations and the input data compared with available data.

Prediction Toxicological Pathways

Two different class of Toxicological Pathways are available for analysis in ProTox tool:
1) Nuclear receptor signalling pathways: In these, class 7 pathways are available [90].
2) Stress response pathways: In this, class 5 pathways are available [91, 92].

Result and Discussion

In Silico Toxicity Prediction - All the drugs used in treatment may be harmful if swallowed as it is seen that they either belong to toxicity class 4 or class 5 none of them are fatal (See Table 1).

Table 1 In Silico Toxicity Prediction for all drugs used to treat Covid-19

S.NO	Drugs used for Covid-19 and Mucormycosis	Analysed LD_{50} Value (mg/kg)	Analysed Toxicity Class	Analysed Similarity (%)	Analysed accuracy (%)
1.	Enoxaparin	5000	5	58.14	67.38
2.	Methylprednisolone	160	4	100	100
3.	Dexamethasone	3000	5	100	100
4.	Remdesivir	1000	4	40.93	54.26
5.	Favipiravir	1717	4	39.16	23
6.	Isavuconazole	1000	4	37.66	23
7.	Itraconazole	320	4	100	100
8.	Micafungin	1000	4	45.13	54.26

Organ-toxicity and toxicity endpoints:

With the online (web server) ProTox-II system, the organ-toxicity of different drugs that were used to treat Covid-19 & Mucormycosis, it was observed that Isavuconazole, Enoxaparin, Isavuconazole, Itraconazole, Micafungin cause toxicity to the liver whereas other drugs such as Methylprednisolone, Dexamethasone, IItraconazole, Micafungin are immunotoxic, Favipiravir is carcinogenic and none of them are mutagenic or cytotoxic.

Table 2 Result of Organ toxicity by ProTrox-II web server for different Drugs used for treatment of Covid-19 Mucormycosis

Ligands	Organ Toxicity endpoints (Possibility/Probability)				
	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
Enoxaparin	+	-	-	-	-
Methylprednisolone	-	-	+	-	-
Dexamethasone	-	-	+	-	-
Remdesivir	-	-	-	-	-
Favipiravir	-	+	-	-	-
Isavuconazole	+	-	-	-	-
Itraconazole	+	-	+	-	-
Micafungin	+	-	+	-	-

+ : Active, - : Inactive

Toxicological pathways

(i) **Nuclear Receptor Signalling pathways**

Table 3 Nuclear receptor signalling pathways analysed by ProTrox-II web server for different Drugs used for treatment of Covid-19 Mucormycosis

Ligand	Different receptor and signalling pathways (Possibility/Probability)						
	Aryl Receptor	Androgen Receptor	Androgen Receptor Ligand Binding Domain	Aromatase	Estrogen Receptor Alpha	Estrogen Receptor Ligand Binding pathway	Peroxisome Proliferator Activated Receptor pathway
Enoxaparin	-	-	-	-	-	-	-
Methylprednisolone	-	+	+	-	-	-	-
Dexamethasone	-	+	+	-	-	-	-
Remdesivir	-	-	-	-	-	-	-
Favipiravir	-	-	-	-	-	-	-
Isavuconazole	-	-	-	-	-	-	-
Itraconazole	-	-	-	-	-	-	-
Micafungin	-	-	-	-	-	-	-

(ii) In **Stress response pathways**, five different stress pathways were analysed by ProTox II. Predictions results indicated that all the analysed drugs showed to interact with stress pathways mentioned in the table 4.

According to the analysed result of drugs obtained against Nuclear receptor signalling pathways, it is concluded that Methylprednisolone and Dexamethasone could interact with Androgen Receptor and Ligand Binding Domain both showed maximum probabilities.

Table 4 Different Stress response pathways result using the ProTrox-II web server for different Drugs used for treatment of Covid-19 & Mucormycosis

Ligands	Stress response pathways (Possibility/Probability)				
	Nuclear factor (antioxidant responsive element)	Heat shock factor	Mitochondrial Membrane Potential	Tumor Suppressor factor (p53)	ATPase family (AAA domain-factor)
Enoxaparin	-	-	-	-	-
Methylprednisolone	-	-	-	-	-
Dexamethasone	-	-	-	-	-
Remdesivir	-	-	-	-	-
Favipiravir	-	-	-	-	-
Isavuconazole	-	-	-	-	-
Itraconazole	-	-	-	-	-
Micafungin	-	-	-	-	-

+ : Active, - : Inactive

Conclusions

Mucormycosis is a rare fungal disease that can spread rapidly and may ultimately prove lethal. The rarity of the illness implies that few people have experienced it or understand it, hence it remains untreated, and proves fatal.

All the drugs used in its treatment may be harmful if swallowed, as it is seen that they either belong to toxicity class IV or class V and none of them are fatal. Results showed that all of the drugs interacted with all five stress-related pathways, such as antioxidant response pathways, heat-shock-factor-pathways, mitochondrial membrane-potential pathways, and p53 suppressor gene pathways. However, Methylprednisolone and Dexamethasone could interact with the Receptor-Signalling-pathways such as Androgen-Receptor Ligand Domain and Androgen-Receptor pathways. The effects of a drug binding to the androgen receptor or its ligand binding domain depend on the specific drug and the context in which it is used, for example, if the drug blocks the AR and prevents its activation, it can be used to treat androgen-dependent diseases such as prostate cancer, which rely on AR signalling for their growth and survival. And if the drug binds to the AR and activates its signalling pathway, it can promote the growth and development of androgen-dependent tissues, such as the prostate gland and male external genitalia. This can be beneficial in certain medical conditions, such as hypogonadism or delayed puberty, where androgen therapy can help to restore normal physiological functions. So we may conclude that it is important to carefully evaluate the risks and benefits of Methylprednisolone and Dexamethasone as anti Covid drugs and each individual patient needs to be closely monitored for their response to such treatment.

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