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Dexamethasone, Interleukin 6, and the Adrenal Gland are the Real Battles for COVID-19: Our Molecular Docking, Physiological, and Immunological Explanations of Why the Clinical Benefit of Dexamethasone is More Evident in Males

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

More than two years have passed since the pandemic and despite all the efforts of researchers, the pathogenesis of the SARS-CoV-2 has not yet been resolved. The SARS-CoV-2 coronavirus that causes COVID-19 has high ability of mutation resulting in different variants of the virus. This mutation helps the virus bypass the body's immune defenses such as innate and adaptive immunity. Interleukin (Il-6), neutrophils, high ferritin, and high D dimer are crucial markers for all sorts of cells on the lengthy path to treatment of COVID-19. IL-6 is one of the key mediators of

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inflammation and viral cytokine storm in COVID-19 patients. In humans, interleukin (IL)-6 is a strong stimulator of the hypothalamic-pituitary-adrenal (HPA) axis at all levels, and it appears to have a pathogenic role in chronic stress and physiological aging. The adrenal glands have earned further recognition as key modulators of immune function, because secretory products of the adrenal glands. Dexamethasone inhibits TNF-α–induced IL-6 mRNA expression and protein secretion by reducing IL-6 mRNA stability. Although Dexamethasone provides benefits in patients with coronavirus disease but there is sex linked difference between male and female at response to this drug. It was showed that this drug might indeed have an effect in treating covid-19 but the clinical benefit of dexamethasone is more evident in males. Here we propose a testable hypothesis that dexamethasone may be effective in men better than female owing to two factors the first is the ability of males to induce high secretion of adrenal hormone under stress vs female. In males both stressors induced a significant increase, whereas in female adrenal e excretion remained on the same level under the two stress conditions. Both Adrenal e hormones and dexamethasone are hypothesized to promote blood neutrophil levels by increasing neutrophil exit from bone marrow, delaying neutrophil outflow from circulation, and lengthening the half-life of circulating neutrophils. Neutrophils a type of white blood cells that can downregulate interferon-stimulated genes, i.e., suppress their activity. When male patients received the steroid treatment, the dysregulated interferon signals went away quickly. But in female patients, the proportions of neutrophils were not as high and they did not react to the steroids in the same way. The second factor is that ACTH response to il-6 is stronger in males than females and ACTH was found to induce il-6. Therefore, male interact with dexamethasone better than females. Additionally, dexamethasone does not affect Il-6 secreted from the adrenal cortex, which allows Il-6 to be produced during stress and increase neutrophil ratio leading to stronger response in males. We need a new classification of IL-6 at physiological and pathological aspects, as the stimulatory factors are different. it was found that ACTH is h Endocrine Il-6 is stimulated by ACTH, but immune Il-6 is stimulated by il-1β and angiotensin II. Of note, dexamethasone critically saves COVID-19 patients but has no effect on Il-6 of endocrine (ACTH stimulated) origin, either basal or stimulated. We studied the molecular docking of dexamethasone with interleukin-6 and showed that the binding interaction of dexamethasone with interleukin-6 was with high binding affinity (-6.7 Kcal/mol)

Keywords: Dexamethasone; acth; endocrine; interleukin 6; Lbt4; COVID-19; cortisol; adrenal gland; resistive breathing.

ABBREVIATIONS

NSAIDs	*Nonsteroidal Anti-inflammatory Drugs*
DEX	*Dexamethasone*
ACTH	*Adrenocorticotropic Hormone*
AP-1	*Activator Protein 1*
ASM	*Airway Smooth Muscle*
CBG	*Corticosterone Binding Globulin*
CIRCI	*Critical Illness-Related Corticosteroid Insufficiency*
CRH	*Corticotropin-Releasing Hormone*
GCs	*Glucocorticoids*
HPA	*Hypothalamic-Pituitary–Adrenal*
HTPA	*Hypothalamic-Pituitary–Adrenal*
IFN-g	*Interferon-g*
IL	*Interleukin*
LPS	*Lipopolysaccharide*
PGE2	*Prostaglandin E2*
COPD	*Chronic Obstructive Pulmonary Disease*

1. INTRODUCTION

As of February 10, 2021, there were >106 million cases of coronavirus disease 2019 (COVID-19) in 223 countries, which had resulted in nearly 2,320,000 confirmed deaths [1]. Most patients experience mild to moderate disease, although 5–10% of cases progress to severe or critical disease, which can involve pneumonia and acute respiratory distress syndrome (ARDS) [2]. Severe COVID-19 cases typically involve a mild-to-moderate presentation followed by secondary respiratory failure at 9–12 days after the first onset of symptoms [2,3]. The concept of cytokine storm syndrome emerged early in the pandemic to explain critically ill patients with COVID-19 [4]. However, accumulating evidence challenges the single cytokine storm model and suggests that severe COVID-19 is a dysregulated host response of inflammation, immunity, and interferon signaling [5,6], the host immune response is thought to play a key role in the pathophysiology of organ failure. Inflammatory organ injury may occur in severe Covid-19, with a subgroup of patients having markedly elevated levels of inflammatory markers, including C-reactive protein, ferritin, interleukin-1, and interleukin-6 [7,8] Several therapeutic interventions have been proposed to mitigate inflammatory organ injury in viral pneumonia, but the value of glucocorticoids has been widely debated [9,10]. A large group of cytokines has been recognized as significantly increased in severe COVID-19 patients: interleukin-1β (IL-1β), IL-1RA, IL-2, IL-6, IL-7, IL-8 (CXCL8), IL-9, IL-10, IL-17, IL-18, tumor necrosis factor (TNF-α), interferon-gamma (IFN-gamma), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein 1 (MIP-1alpha/CCL3), monocyte chemoattractant protein-1 (MCP-1/CCL2), interferon gamma-induced protein 10 (IP-10/CXCL10), and fibroblast growth factor (FGF) [11,12].

Of all the upregulated cytokines that may represent selective therapeutic targets, IL-6 has been regarded as particularly important in the COVID-19 pathogenesis and may be antagonized by existing drugs. IL-6 is an inflammatory interleukin mainly produced by macrophages and T lymphocytes in response to pathogens and is pivotal to controlling several viral infections [13,14]. While homeostatic values of IL-6 contribute to the resolution of infections and tissue lesions, its exacerbated production contributes decisively to cytokine storms.Dexamethasone is currently the only agent that can provide a survival benefit in COVID-19 cases [15]. This survival benefit was greater for patients who were receiving supplemental oxygen or mechanical ventilation and was not observed among patients who were not receiving oxygen. Also, it seems that Dexamethasone survival benefits is greater in men than women [16]. Although critical for host defense, innate immune cells are also pathologic drivers of acute respiratory distress syndrome (ARDS). Innate immune dynamics during Coronavirus Disease 2019 (COVID-19) ARDS, compared to ARDS from other respiratory pathogens, is unclear. Moreover, mechanisms underlying the beneficial effects of dexamethasone during severe COVID-19 remain elusive Here we will propose a novel hypothesis for this difference

2. OUR HYPOTHESIS

Here we propose a testable hypothesis that dexamethasone may be effective in men better than female owing to many factors that could induce neutrophils which is discussed as follow:

The first is the ability of males to induce high secretion of adrenal hormone under stress vs female, the pattern of adrenal e excretion, however, differed between sexes: in males both stressors induced a significant increase, whereas in females adrenal e excretion remained on the same level under the two stress conditions as during relaxation [17]. Moreover, It was shown that men in normal state have greater level of il-6 than women [18]. Furthermore, mean cortisol responses were 1.5- to 2-fold higher in men compared with women [19]. It is well known that interleukin 6 (IL6) has the ability to activate the hypothalamo-pituitary–adrenocortical (HPA) axis influencing each level of the axis. IL6 stimulates corticotrophin-releasing hormone (CRH) release from the hypothalamus of rats in a dose-dependent manner [20,21]. IL6 also directly stimulates corticotrophs, even in CRH knockout animals [22,23]. In humans, acute administration of IL6 increases adrenocorticotropin (ACTH) and cortisol concentrations [24]. Also, a dose-dependent increase in ACTH and cortisol is seen in response to IL6 administration [25]. IL6 also acts directly on the adrenal cortex, stimulating glucocorticoid release. However, in the absence of ACTH, IL6 fails to elicit glucocorticoid response. Consequently, ACTH is a necessary permissive factor, enabling direct cytokine actions on the adrenal gland [26]. As IL6

augments ACTH stimulation of the adrenal cortex, higher IL6 levels should be correlated with increased cortisol response to ACTH stimulation.Both Adrenal e hormones and dexamethasone are hypothesized to promote blood neutrophil levels by increasing neutrophil exit from bone marrow, delaying neutrophil outflow from circulation, and lengthening the half-life of circulating neutrophils. Neutrophils a type of white blood cells that can downregulate interferon-stimulated genes, i.e., suppress their activity. When male patients received the steroid treatment, the dysregulated interferon signals went away quickly. But in female patients, the proportions of neutrophils were not as high and they did not react to the steroids in the same way. The second factor is that ACTH response to il-6 is stronger in males than females and ACTH was found to induce il-6 [27]. Therefore, male interact with dexamethasone better than females. Additionally, dexamethasone does not affect Il-6 secreted from the adrenal cortex, which allows Il-6 to be produced during stress and increase neutrophil ratio leading to stronger response in males.

Surviving SARS-CoV-2 depends on striking a temporal balance between inciting viral clearance immune programs during the early stage and subsequently restraining those same programs at later stages to limit immunity-induced damage. IFN signaling stands at the nexus between anti-viral immunity and overactive effector immune programs that inadvertently compromise tissue function and threaten survival [28]. It was showed that a stable neutrophil state with signature downstream IFN signaling is selectively expanded during late-stage COVID-19 infection. Inborn errors [28] and suppressed early-stage [29]. IFN signaling predict COVID-19 severity, and increased IFNactive neutrophils in females correlated with decreased mortality [30]. Thus, early initiation of IFN therapy has been suggested to mitigate disease severity [31,32]. Given these observations, one might posit that IFN activity in neutrophils represents a concerted host anti-viral program. Interestingly, immunosuppression with dexamethasone, a corticosteroid known to improve mortality in patients hospitalized with COVID-19 [ref.33], was associated with global alteration of neutrophils as well as suppression of neutrophilic IFN networks and preferential depletion of COVID-19-enriched IFNactive neutrophils. These altered neutrophil states shared striking resemblances to bacterial ARDS, suggesting that installation of generalized microbicidal programs ameliorate the overzealous neutrophil responses during COVID-19 (and perhaps during other viral infections). Although neutrophil ISG activation might promote anti-viral immunity during early stages of SARS-CoV-2 infection, sustained IFN activation during late stages (for example, patients admitted to the ICU with severe disease) could drive immunopathology of COVID-19. Indeed, positive correlation between neutrophil type 1 IFN programs and COVID-19 severity [34,35], paired with our observation that IFNactive neutrophils dominate the bronchoalveolar microenvironment during severe COVID-19 [ref. 36], support this view. Another neutrophil state that emerged with COVID-19 (and was absent in healthy controls) was an ARG1+ immature and immunosuppressive state with immunomodulatory properties [37,38,39,40,41]. This state was significantly expanded with dexamethasone, suggesting a second route of effect of dexamethasone on both neutrophils and systemic innate immune response. Male COVID-19 patients exhibited a larger proportion of IFNactive neutrophils than female patients and favored steroid-induced immature neutrophil development, which might affect outcomes. "Specifically, in men, we detect an increased neutrophil interferon response that is greatly inhibited when a patient is given dexamethasone," Biernaskie said. Females, on the other hand, "had a considerably more tempered neutrophil interferon response, therefore dexamethasone had less impact." Dexamethasone showed different effects according to sex, which could have serious consequences for sex-dependent findings and treatment impact in serious COVID-19 symptoms [42]. Research published in the journal Nature found that dexamethasone halted nearly a third of deaths in severe COVID-19 patients. Steroids, however, showed little impact on patients with moderate instances of COVID-19. Researchers hypothesize that the anti-inflammatory response of dexamethasone may be connected to its therapeutic impact on severely sick COVID-19 patients. However, the vast majority of serious cases suffer from crucial illness-related corticosteroid insufficiency (CIRCI), and dexamethasone's therapeutic potential might be due to its increase in the cortical role [43].

Table 1. Types of interleukins 6 according to the stimulatory effect

Immune IL-6	Endocrine IL-6	Type I adrenal steroid receptors	Type II adrenal steroid receptors
IL-1α, IL-1β angiotensin II	ACTH stimulated	Mineralocorticoid receptors	Glucocorticoid receptors
Dexamethasone effect	No dexamethasone effect	High affinity for endogenous cortisol	High affinity to synthetic glucocorticoids dexamethasone
Zona glomerulosa	Zona glomerulosa	Aldosterone agonists significantly decrease levels of plasma neutrophils and natural killer (NK) cells	Significant increase in neutrophils and natural killer cells after application of type ii receptors agonists RU28362

Glucocorticoids are potent regulators of the immune response. The arrangement of adrenal steroid receptors differs between kinds of immune cells, as do the effects of adrenal steroids on the immune modulator reflex or synthesis. Adrenal steroids function to defend the body by blocking overshooting immune responses. During infection, the hypothesis is that elevations in adrenal steroids help immune system cells hurry their fight regions at the time of infection or metastasis of cancer cells [44,45].

As B lymphocytes, lacking from the lung beneath regular conditions, and B cells are the maximum delicate lymphocytes for glucocorticoids, and glucocorticoids impact the dissemination of lymphocytes withinside the body, it is far possible that B lymphocytes are probably defenseless toward stress-instigated heights of glucocorticoids [46].

Dexamethasone is not tied to corticosteroid proscribing globulin (CBG) and thus has equal admittance to each unmarried invulnerable compartment. New statistics suggest that interleukin-12 (IL-12) and IFN-γ – (kind II interferon) are probably communicated extraordinarily earlier than withinside the cytokine course [47], accordingly for the duration of viral contaminations, pinnacle IL-12 and (IFN-γ) came about for the duration of the middle degree with the shift to IL-four at past due degree, endogenous glucocorticoids may improve this shift and can expect a component at IFN initiated rearrangement of lymphocytes from dissemination to neighborhood lymph hubs and splenic white mash regions and one extra activity of glucocorticoids is probably extensive for the duration of starting degree is a reallocation of mononuclear cells from fringe blood to lymphoid compartments [48,49,50,51]. In viral infections, acute immunopathology can result from excess production of cytokines. Utilizing portions of trial murine viral fashions for concentrating at the enlistment and potential of steroids as intranasal contaminations with flu contamination observe good-sized lung pathology and the insusceptible response arises to feature to something like a volume of this harm [52,53,54,55,56] as against intraperitoneal sicknesses with LCMV [57,58] which display decrease negligible pathology so extra damage befell with an intranasal version so fashions supply tremendous statistics approximately diverse pathways of steroid popularity all through infections.

The accessibility of coursing corticosteroids organically to adrenal receptors in exclusive invulnerable tissues is directed with the aid of using corticosteroid proscribing globulin (CGB) and liver - inferred plasma protein and it is far giant spotlight intensifies that dexamethasone and several engineered corticosteroids are not restrained with the aid of using CBG so why electricity of those synthetic steroids in vivo comparative with cortisol or corticosterone so beneath Neath standard situations over 90% of flowing corticosteroid is sure to CBG so the extent and appropriation of CBG is the important thing in guiding principle of prescribing of endogenous chemical substances to adrenal steroid receptors that is the cause the dexamethasone is quite extreme in obtaining access to insusceptible booths like spleen [59].

Pregnancy is a variable that adjusts the CBG level, as estrogen upregulates CBG creation, which serves to generally balance the raised cortisol creation present at present.

As of the hour of the day on adrenal receptor enactment, increased admittance of glucocorticoids to secure compartment recognized with dull as Diurnal modifications

withinside the dispersion of fringe blood insusceptible cells which same adjustments in coursing tiers of corticosterone are likewise constant with the increased admittance of glucocorticoids to this secure compartment [60].

Generally, the assessed adrenal steroid receptor actuation became extra distinguished in thoughts than in pituitary or invulnerable tissue, and internal a selected tissue, there has been an extra noteworthy stage of assessed enactment of the adrenal steroid excessive fondness kind I receptor than of the type II receptor. There became an extra noteworthy actuation of thought kind II receptors via basal corticosterone to withinside the PM (30-35%) compared with the AM (5-15%). As excessive stress added comparative stages of receptor enactment on the two times of day (45-half), the internet alternate in kind II receptor initiation withinside the thoughts later excessive stress became plenty extra modest withinside the PM than withinside the AM. This suggests that there are probably diurnal contrasts within the task of kind II receptors in corticosterone-bad complaints at the hypothalamic-pituitary-adrenal pivot. In susceptible tissues, kind II receptor enactment via means of excessive stress became especially heterogeneous, contingent upon each the resistant category and the hour of the day, recommending that those are significant factors including a difference in the influence of corticosterone on invulnerable reactions in the course of excessive stress. Taken together, our effects propose that the phasic and tonic actions of corticosterone on the course tissue reactions no longer simply with the diurnal and strain emission examples of corticosterone but moreover with target tissue factors, such as type I and sort II receptor articulation and chemical bioavailability. These elements are uploaded to massive precision of response for the foundational chemical corticosterone [61].

The conditions that are known to stimulate the hypothalamic-pituitary-adrenal axis, such as mycobacteria, viral infections, strenuous exercise, or academic stress, may affect leucocyte glucocorticoid sensitivity, which decreases. This explains why dexamethasone has no effect on interleukin-6 stimulated by ACTH during HPA axis stimulation during viral infections, and the inhibitory effect of dexamethasone on both IL-6 and TNF-α secretion was significantly reduced following exercise because this exercise was accompanied by HPA axis activation and increased ACTH, which stimulated IL-6 secretion immediately after exercise. Resistance to dexamethasone may occur, as there are interindividual differences in GC responsiveness. Additionally, intraindividual differences have been reported, suggesting dynamic regulation of GC sensitivity, so such decreased responsiveness could have therapeutic consequences when occurring in inflammatory disorders [62].

Therefore, activation of HPA by cytokines through the release of glucocorticoids has been found to play a critical role in restraining and shaping immune responses. Thus, cytokine-HPA interactions represent a fundamental consideration regarding the maintenance of homeostasis and the development of disease during viral infection [63].

2.1 Role of Inhaled Dexamethasone on il-6 Stimulated by Resistive Breathing

(Resistive breathing, interleukin-6, pulmonary edema, dexamethasone is interlocked:

Resistive breathing is breathing against increased airway resistance and issimilar to exercise for respiratory muscles and is linked with high negative intrathoracic pressures, increased mechanical stress promoting high permeability and pulmonary edema, and inflamed lungs [64]. Inspiratory resistive breathing or strenuous contractions of the respiratory muscles occurred at many chronic respiratory diseases like COPD, asthma especially during attacks increases the plasma levels of proinflammatory cytokines like tumor necrosis factor (TNF-α). Interleukin 1β (IL-1β) and interleukin il-6, and stimulate the HPA axis which results in β-endorphin that affect breathing brain functions including sleeping and sensation of fatigue, also if resistive breathing continued can injure the respiratory muscles and acute lung injury [65], the study by Dimitris et al; give the possibility that the increased permeability of the alveolar-capillary membrane and pulmonary edema formation was noted earlier than inflammation after resistive breathing, [63,66] the pathophysiology of this mechanism is similar to what's happening of pulmonary edema at severe covid-19 cases where a study by Xinyu Cui et al; review the mechanisms which induce pulmonary edema and lead to severe critical cases of covid-19 patients and fluid accumulation in the alveolar airspace which cause mortality [67] preliminary

results from the study by Vassilakopoulos T et al; suggest that inspiratory resistive breathing leads to an increase of IL-6 in the induced sputum of healthy volunteers [68] the origin of resistive breathing -stimulated plasma cytokines what's the origin?

data obtained by the study speculated that the origin of resistive breathing-induced plasma cytokines is not from monocytes but respiratory muscles so resistive breathing as a form of exercise restricted to respiratory muscles and antioxidants supplementation dramatically blunt the il-6 response and (TNF-α). and 1β (IL-1β) were undetectable [69].

the results of 2 studies show the beneficial effect of short term inhaled dexamethasone or intravenous on improving pulmonary functions, decreasing the respiratory resistance, and decreasing the inflammation for preterm infants at risk of bronchopulmonary dysplasia [70,71] on the resistive airflow properties studied by M Pappagallo et al; and intravenous dexamethasone by Yoder MC et al; [69, 72].

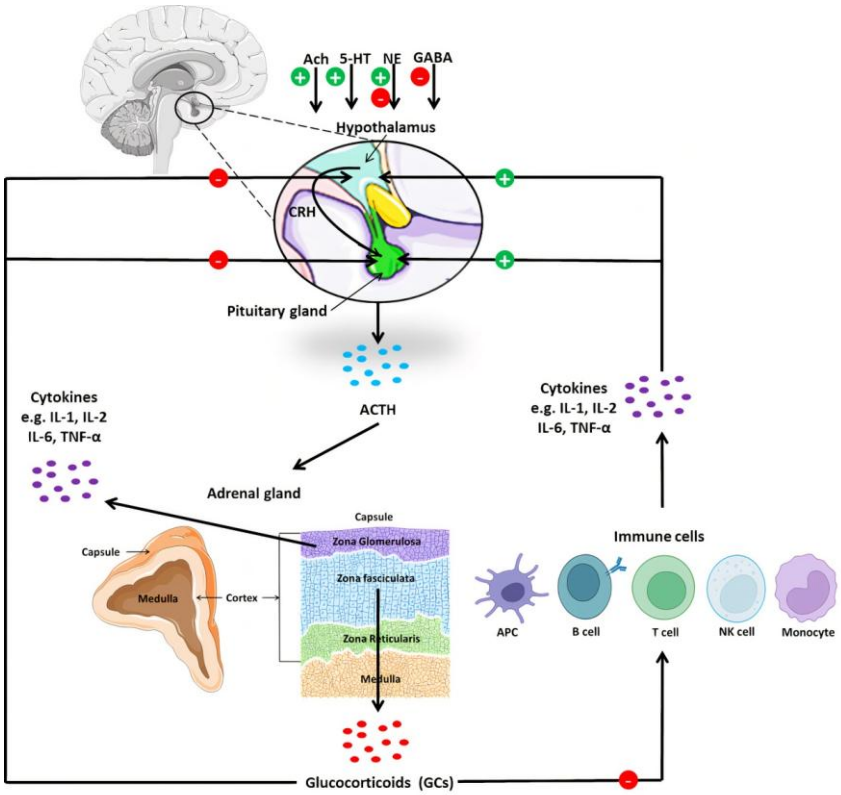

Fig. 1. Schematic illustration of the hypothalamic-pituitary-adrenal axis (HTPA axis) and the immunomodulation pathway

Corticotropin-releasing hormone (CRH) from the hypothalamus is responsible for pituitary activation and releasing of adrenocorticotropic hormone (ACTH) which stimulates the adrenal cortex to secrete glucocorticoids (GCs). GCs (or dexamethasone as a synthetic example) have a critical role in immune suppression by blocking the secretion of proinflammatory cytokines (especially IL-6 released from endocrine origin or stimulated by ACTH) secreted by immune cells. On the other hand, dexamethasone suppresses the production of IL-6 in many different tissues, however, it has no impact on IL-6 produced in the adrenal cortex [1]. NE, Norepinephrine; GABA, gamma-Aminobutyric acid; 5-HT, 5-hydroxytryptamine; Ach, Acetylcholine; IL, Interleukins; TNF-α, Tumor necrosis factor

3. IN SILICO MOLECULAR DOCKING OF DEXAMETHASONE WITH IL-6

Using AutoDock Vina, the molecule dexamethasone was docked with the receptor interleukin-6 and analyzed for binding energy and protein-ligand interactions. The binding affinity was found at -6.7 Kcal/mol. PyMOL was used to create complex receptor and ligand files, while Discovery Studio was used to find interactions.

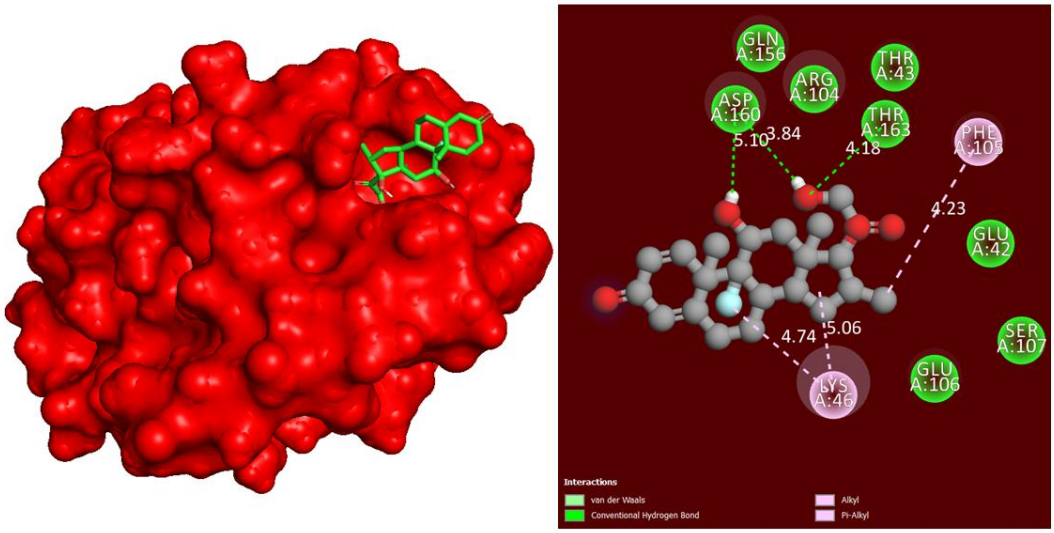

Fig. 2 Binding interaction of dexamethasone with interleukin-6

It shows the binding pocket of protein in 3D and 2D. Important binding residues making different kinds of interactions present in the binding site are shown in the 2D image

4. CONCLUSIONS

In excessive cases, COVID-19 is a multisystemic indicator of infection with a cytokine typhoon signal. Dexamethasone is a exquisite weapon in opposition to cytokine typhoon in coronavirus illness, as dexamethasone is incredibly sturdy toward the insusceptible framework with the aid of using its inability to tie to CBG and gaining access to each resistant compartment. Therefore, all secure tissues displayed equal and vast type II receptor enactment depending upon the fact that dexamethasone went in opposition to endogenous glucocorticoids since it is not impacted while of day ether dim or dynamic period. Adrenal receptor enactments infringe blood lymphocytes with the aid of stress-induced heights in corticosterone take place at dim periods. With the aid of atomic docking, dexamethasone was combined with interleukin-6. It indicates limiting liking turned into found - 6.7 Kcal/mol. Be that because it may, dexamethasone does not affect ACTH-stimulated Il-6 discharged from the adrenal cortex. LTB4 may have a role in respiratory failure and water in the lung, as it is a milestone at the metabolite of arachidonic acid and plays a role in the HPA axis, so more clinical studies are needed about its role in HPA axis stimulation. Resistive breathing produces cytokines like strenuous exercise which also induces a plasma cytokine response. Resistive breathing may be the hallmark at the critical stage of covid-19 and progressing to pulmonary edema.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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