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Nutritional Agonists of PPAR-γ: An Immunomodulatory Approach to Control Cytokine Storm in Covid19 Patients

Nadeem Siddiqui [a*], Shaik Mohammad Anjum [a], Sreeja Nannapaneni [a], Sri Sarvani Vemuri [a], Bhavana Potluri [a], Sreedhar Bodiga [b], Vijaya Lakshmi Bodiga [c] and Suryanarayana Veeravilli [d]

[a] Department of Biotechnology, Koneru Lakshmaiah Education Foundation, Guntur, Andhra Pradesh, India.
[b] Laboratory of Biochemistry, Department of Basic Sciences, Forest College and Research Institute Hyderabad, Mulugu, Telangana, India.
[c] Department of Biochemistry and Molecular Biology, Institute of Genetics & Hospital for Genetic Diseases, Osmania University, Begumpet, Hyderabad, Telangana, India.
[d] Department of Humanities and Basic Sciences, Aditya Engineering College, Kakinada, Andhra Pradesh, India.

Authors' contributions

This work was carried out in collaboration among all authors. Authors NS and SMA conceived and designed the study. Authors SN and SSV was responsible for data collection and acquisition of data. Authors BP and SB analysed and interpreted the data. Author VLB wrote the initial manuscript. Author SV critically revised the manuscript. All authors have read the final manuscript.

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Original Research Article

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ABSTRACT

Recent examinations express that multi organ failure is seen in Corona virus infected patients with different pathway. It has been shown in contemplates that increased levels of cytokines like IL-1B and INF gamma were observed. It is called as cytokine storm with higher convergences of CCL2

**Corresponding author: E-mail: siddiqui@kluniversity.in;*

and CXCL10. The cytokine storm is trailed by our immune system attacking own body which thus may cause numerous organ abnormalities and conclusive outcome being death. There is currently no specific treatment for viral illness, and this methodology is an optional path for focusing on specific qualities that may diminish cytokine storm. In such manner Peroxisome Proliferators Activated Receptors (PPARs) have a place with group of transcription factors which are known to manage the inflammatory mechanisms in body. This immunomodulatory approach is intended to focus PPAR-gamma ligands and their molecular docking studies. The activation or increased expression levels of PPAR gamma because of chosen agonists may reduce the cytokine storm in the covid patients. Thus, this is one such fascinating way to deal with neutralization of the cytokines exorbitantly elevated by use of substances like pomegranate, lemon grass and so on to activate PPARs reliably.

Keywords: PPAR; corona virus; cytokine storm; Covid; cytokines; immune system.

1. INTRODUCTION

The higher rate of mortality due to the corona virus outbreak has become a major threat to public health and number of cases is expected to grow exponentially [1]. Mononuclear inflammatory cells accumulation, pneumonocyte hyperplasia and alveolar damage are observed in patients infected severely with corona virus [2]. There are many mechanisms that are associated with the of the viral diseases and one among them is cytokine storm that causes threat to the patients [3]. The cytokine storm is due to the sudden outburst of the pro-inflammatory components [4]. The modulation of the aggressive release of the cytokines is important to reduce the multi-organ dysfunction in corona virus infected patients. Though many of the infected patients show mild symptoms nearly 20% need hospitalization and 7% of patients needed intensive care [5]. When the virus replicates inside the cells, ARDS acute respiratory distress syndrome is developed [6]. Similarly other problems like organ failure, kidney injury and sepsis are prevailed. The detailed examinations of studies and reports showed that it is due to elevated levels of cytokines like interferons and interleukin's [7]. When there is no known cure for corona virus infection, it is critical to investigate all other treatment options [8]. This article majorly focuses on the cytokine storm and its modulation by nutritional agonists. The remarkable role of PPAR-gamma increased expression also cooperates in reducing the cytokines risk [9].

1.1 Cytokine Storm and its Affects in Covid Patients

Cytokines are small secreted proteins that are discharged by cells with the end goal of intercellular communication and signaling [10]. Such cytokines are redundant in their activities, this means activities like autocrine, paracrine, endocrine movement and, through receptor binding, can bring out many responses, depending upon the target cell [11]. The control over cell expansion and differentiation are the major functions of cytokines. Prior to inspecting the effects of cytokine storms, it is significant to investigate the cytokines at the core of the cytokine storm. Severe lung diseases are considered best examples of severe lung diseases, in which nearby inflammation gushes out over into the circulatory system, delivering sepsis, as characterized by relentless hypotension, hyper-or hypothermia [12]. Viral, bacterial, and contagious aspiratory diseases all leads to the sepsis disorder and these etiological agents are hard to separate on clinical grounds [13]. Sometimes, cytokine storms in relation to tissue damage without microbial infection can also be persevered. Not with-standing lung infection, the cytokine storm is an outcome of extreme diseases in the gastrointestinal region, urinary tract and nervous system [14].

Patients with extreme sepsis show plasma cytokine profiles, which change after some time because of aspiratory or non-pulmonary infections. The intense reaction cytokines TNF and IL-1β and the chemotactic cytokines IL-8 and MCP-1 show up in the early minutes to hours after infection, trailed by a more continued increment in IL-6 [15]. The calming cytokine IL-10 shows up to some degree later, as the body endeavors to control the acute inflammation [16]. Infectious diseases remain as a severe threat all over the world accounting for increasing number of mortalities rates [17]. Against this scenery of antimicrobial resistance and the rise of new microbes, expanding interest has turned towards the advancement of medications that target on

the immune reaction to infection and it is logical to target this response in order to cut down the self-inflicted damage initiated by host cells [18].

1.2 Role of PPAR-γ

The activation and working of PPARs require the heterodimerization with another nuclear receptor, the retinoid X receptor of RXR (Fig. 1). The RXR family has three diverse isoforms (RXR-α, - β, - γ) that are initiated by endogenous 9-cis retinoic acid. Upon ligand binding, the PPAR-RXR complex moves into the nucleus, where it binds to the PPRE elements of target DNA [19-23]. The relationship with the ligand initiates conformational changes, co-repressor separation and co-activator association, prompting ligand-initiated trans-activation [24].

1.3 Nutritional Agonists Sources of PPAR-γ

Turmeric is derived from the plant Curcuma longa [25] primarily used as a food ingredient, but in recent years it has also been used as a treatment for inflammatory-related problems [26]. Curcumin, the phytochemical component of turmeric, can control the transcription factor expression, cytokines and enzymes related to inflammation [27]. The anti-inflammatory property of curcumin mediates the PPAR gamma gene, which therefore inhibits TNF-α, a cytokine associated with inflammation. The mechanism by which curcumin controls PPAR-γ has not yet been explained [28]. It was reported that, curcumin instigates an anti-inflammatory effect through the up-regulation of PPAR-γ, which leads to the inhibition of NF-κB, a favorable inflammatory mediator [29]. Rosemary and sage are spices that are fundamentally found in the Mediterranean zone; they are utilized in the kitchen as fragrant plants, yet before, they have been additionally utilized for their antiseptic and anti-inflammatory properties [30]. They contain dipertenoids, like carnosic acid and carnosol, which have been proved in having anti-inflammatory effects. In reality, carnosic acid and carnosol involve with the key pathways of inflammation, hindering the activation of NF-κB and the production ofCOX-2, eicosanoids, IL-1β, and TNF-α. Moreover, carnosic acid and, carnosol have been appeared to have agonistic impacts, consequently initiating PPAR-γ and its expression [31]. Lemongrass is a perennial herb utilized for the most part for the extraction of its oil, which is utilized for aroma in the kitchen and as a scent in beautifiers. Lemongrass has been utilized for quite a long time, particularly in Southeast Asia, for its pain relieving and anti-inflammatory properties [32]. Lemongrass oil contains citral, which gives it the particular smell and scent and is a combination of aldehydes that have the same molecular formula yet different structure, the trans isomer geranial and the cis isomerneral. Citral activates PPAR-γ, which represses the expression of cytokines, for example, IL-1β and IL-6, furthermore, suppresses the action of the COX-2 promotor [33]. Hot pepper is a member from the Solanaceae family; it is the widest spread spice on the planet, also, it is commonly utilized in cooking [34]. It contains capsaicin, the most present compound in hot pepper, which, along with different capsaicinoids, is responsible for the spicy taste [35]. Capsaicinoids have antifungal and antibacterial properties and have been utilized to treat joint pains. Capsaicin has anti-inflammatory properties. An examination has demonstrated that it represses the lipopolysaccharide mediated production of TNF-α, a provocative cytokine, by initiating PPAR-γ [36]. Pomegranate, a fruit grown primarily in Southeast Asia, the Mediterranean region, and in the USA [37]. It has been utilized for many years as a restorative natural product for its possible valuable properties; actually, the different parts of the organic product appear to contain antimicrobial, antifungal, cancer prevention agent, and anti-inflammatory properties [38]. Specifically, pomegranate seed oil contains punicic acid, which is a conjugated alpha-linoleic acid with anti-inflammatory and immunomodulatory capability. Punicic acid can inhibit expression of IL-6, IL-8, IL-12, and TNF-α, by modulating PPAR-gamma, which restrains the expression of the NF-κB pathway [39]. Polyunsaturated unsaturated fats are identified with the regulation of inflammation; specifically, they are responsible for the reduction of the pro-inflammatory cytokines (Fig. 2) by activating PPAR-γ [40]. Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are contained in ocean food and fish oil, and they are engaged with the inhibition of various aspects like leucocytes chemotaxis, eicosanoid production. Their cooperation with PPAR-γ prompts the hindrance of NF-κB, a key factor of pro-inflammatory cytokines [41].

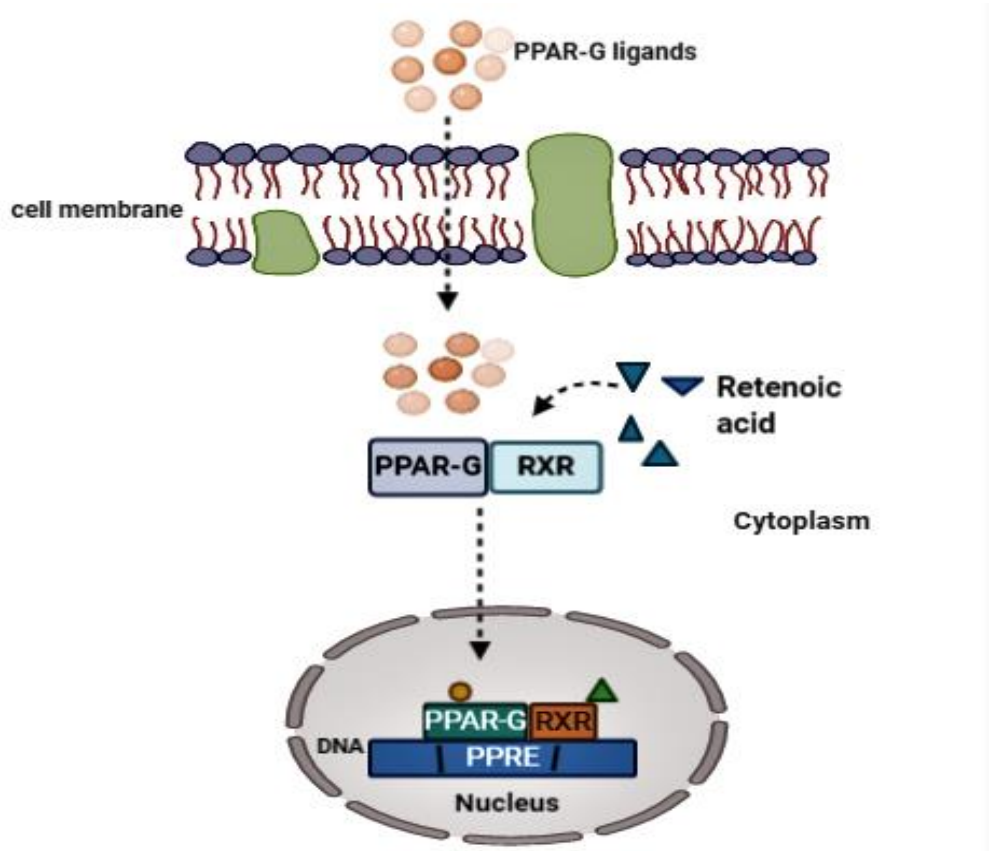

Fig. 1. PPAR-G and RXR signalling on binding of ligand

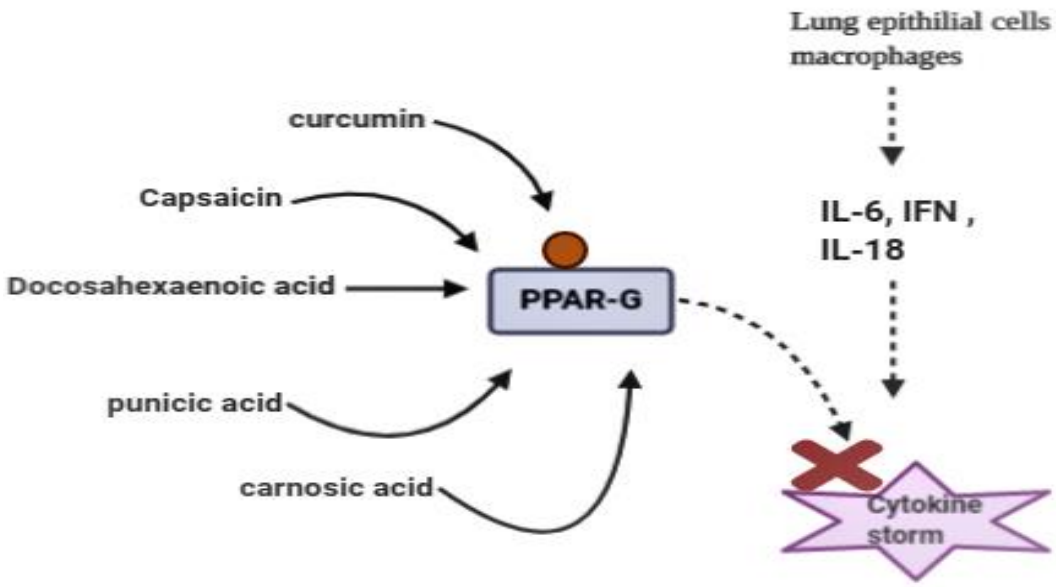

Fig. 2. The activation of PPAR-γ by above mentioned agonists showing regulatory role on cytokine storm. The pro-inflammatory cytokines released by macrophages and lung endothelial cells induce immune responses in turn PPAR—γ prevents over production of cytokines becoming target for immunomodulatory therapies in viral infections

2. MATERIALS AND METHODS

SwissDock is a docking web service platform in which the structure of the target protein, just as that of the ligand, can be automatically prepared for docking. Moreover, the bulky process of the docking system is hidden behind web interface giving sensible parameters as input records. All calculations are performed on the worker side, so that docking runs don't need any computational force from the client. The understanding of results and their interpretation into existing examination is encouraged by the consistent perception using UCSF Chimera. By using this online service high quality animations can be generated. The development is supported by National Institute of Health. Molinspiration for ADME analysis and PROCHECK.

2.1 Molecular Docking

Selection of target protein: In the target selection port within swiss dock PDB code or protein name is given as input (Fig. 3). If the selected target is unavailable then the PDB structure file can be uploaded. Selection of ligand: Ligand name is given as input and it retrieves the structure (Fig. 4) form zinc library or input can be Zinc Accession Number. If the ligand is unavailable then ligand can be downloaded from DrugBank or pubchem.

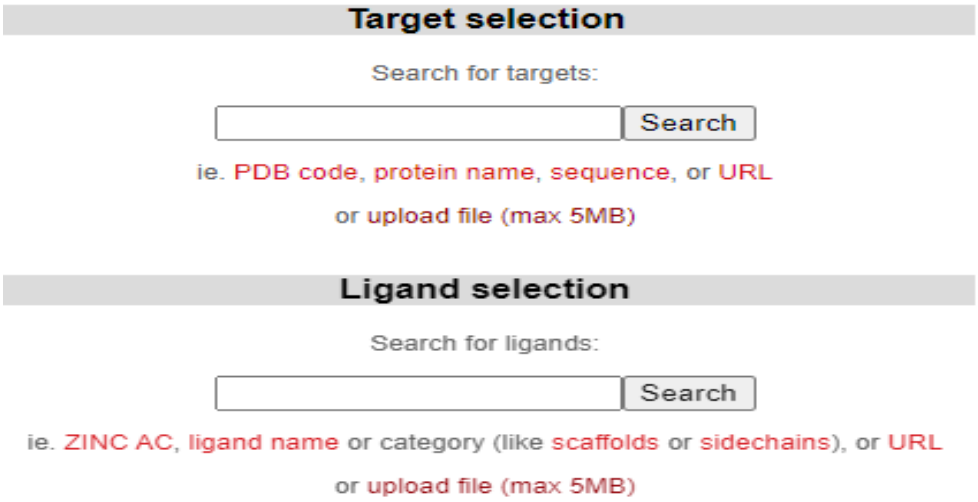

Fig. 3. Target and ligand selection in SwissDock

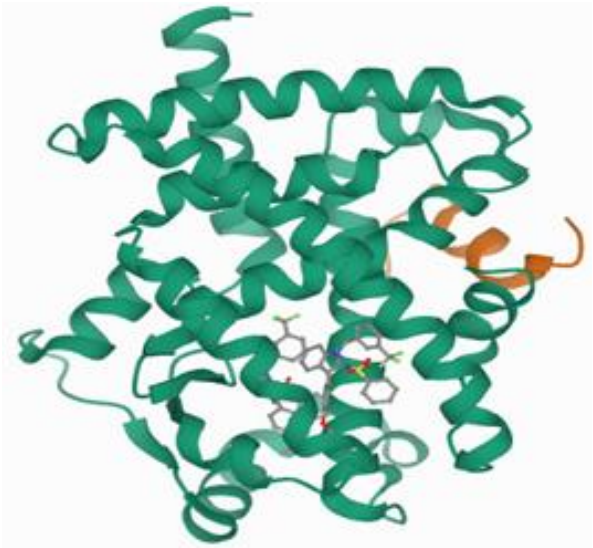

Fig. 4. Structure of PPAR-G complexed with ligand (Source PDB)

3. RESULTS AND DISCUSSION

On obtaining results from five selected ligands the best deltaG value is recorded for carnosol (-9.008968) with 3 hydrogen bonds and vanderwaal forces energy was recorded around -66.4635. Among curcumin, carnasol, citral, capsaicin and EPA; carnasol is assumed to have best agonistic property for PPAR-gamma and EPA is recorded with lowest ability of agonism (Table 1). Using chimera, the compounds were docked to obtain the 3D image (Fig. 5).

Table 1. Analysis of results using Chimera (Binding energy assessment)

Compound Name	Remark Full fitness	H Bonds	Delta G	Delta Gvdw
Curcumin	-3050.36	1	-8.782826	-53.0341
Carnasol	-3111.409	3	-9.008968	-66.4635
Citral	-3077.259	1	-6.735032	-25.7825
Capsaicin	-3083.72	2	-8.320375	-47.0803
Ecosapentanoic acid	-3030.526	1	-6.686183	-27.4205

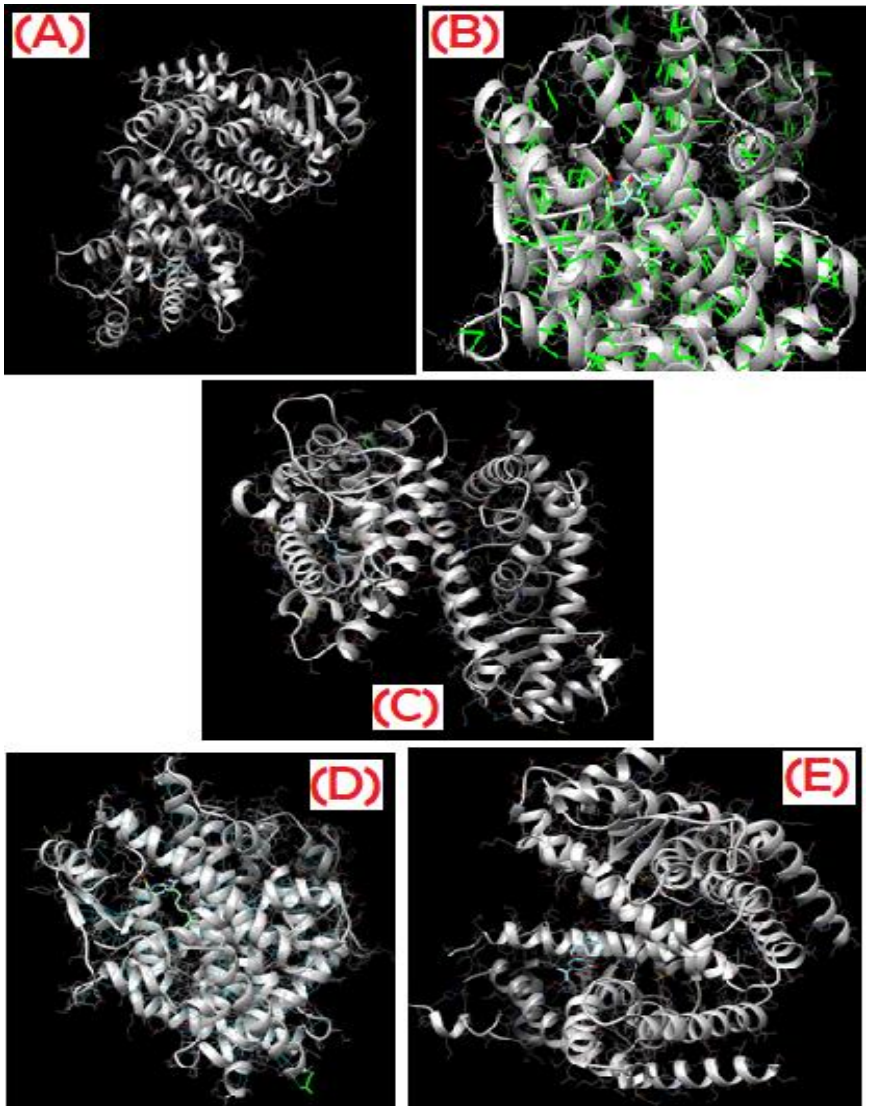

Fig. 5. Chimera based 3D image obtained after docking with (A) curcumin, (B) carnosol, (C) citral, (D) capsaicin and (E) EPA

Table 2. Absorption, Distribution, Metabolism, and Excretion (ADME) Prediction by Molinspiration

Name of ligand	Mol.Wt	nAtoms	N Violations	volume
Curcumin	368.38	27	0	332.18
Carnosol	302.12	20	0	331.12
Citral	152.24	11	0	169.74
Capsaicin	305.42	22	0	310.37
EPA	302.46	22	1	327.70

Since many drugs related projects come up short during clinical preliminaries because of poor ADME properties, it is a needy practice to do ADME tests at the beginning phases (Table 2). Different exploratory and computational techniques have been done to get ADME properties in an affordable way as far as time and cost. As in vitro and in vivo exploratory information on ADME have accumulated, the precision of in silico models in ADME increases and in this manner, numerous in silico models are currently broadly utilized in drug research. In light of the requests from drug discovery analysts, the advancement of Insilico models in ADME has become more dynamic (Fig. 6). Insilco ADME properties of the selected molecules were predicted using Molinspiration. Lipinski's rule stating the properties and their ranges molecular weight < to be less than 500, number of hydrogen bond donors < 5, number of hydrogen bond acceptors < 10, violations and total volume was also assessed, which helped in distinguishing between drug-like or non-drug like profiles of the selected candidates (Table 3). In this regard of given constraints and standard values, Citral is observed to have less molecular weight (152.24) and curcumin with very high molecular weight (368.38).

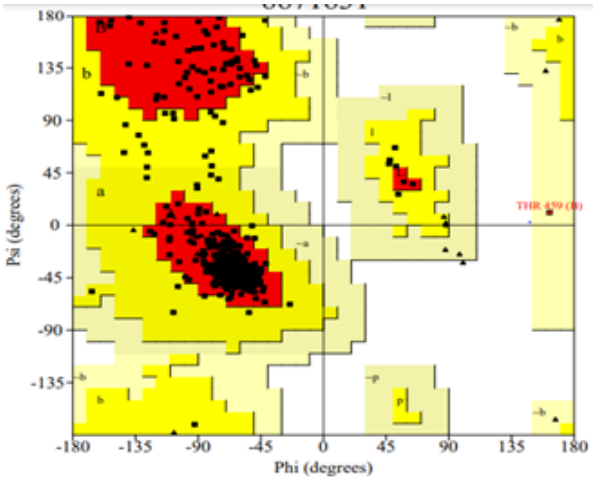

Fig. 6. Ramachandran plot obtained using PROCHECK

Table 3. The shaded region on the plot "core" regions represents the most favorable combinations of phi-psi values

Residues in most favorable regions	416	90.08%
Residues in additional allowed regions	41	9.0%
Residues in generously allowed regions	1	0.2%
Residues in disallowed regions	0	0.0%
Number of non-glycine and non-proline residues	458	100%
Number of end residues	12	
Number of glycine residues	22	
Number of proline residues	18	
Total	510	

Ideally, one would hope to have over 90% of the residues in these "core" regions. The percentage of residues in the "core" regions is one of the better guides to stereochemical quality. The percentage of residues in most favorable region is around 99.8% only 0.2% residues are present in generously allowed regions. 0% of disallowed regions (Table 3).

4. CONCLUSION

Currently the newly invaded corona virus infection represents a worldwide health problem. This made the national clinical systems go through stress. Somehow recent studies also proved the relation between the cytokine storm and hospitalization of patients infected with the corona virus. In this regard finding nutritional agonists for PPAR-gamma could be effective and best therapeutic strategy to reduce the elevated levels of cytokines. Characteristic nutritional compounds are proved as rich hotspot for the discovering novel PPAR-gamma ligands and many of them are basically assorted agonists from medicinal plants and from food products. Interesting activation pathways and Insilico approaches gives us the clear understanding of capabilities that nutritional ligands can have as agonists for increasing the expression of PPAR-gamma. The food products and compounds mentioned in previous sections would stand as the valid option for modulating the immune system mechanisms thereby reduce cytokine storm.

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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