

## THYMULIN – A HOPE OUT OF THE BOX IN COVID-19 DISASTER

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### ABSTRACT

The COVID-19 pandemic is a challenge to medical science. Till date we do not have any definitive treatment for it nor do we have vaccines available against SARS-CoV-2. Cytokine storm syndrome, through immune dis-regulation is the most important mechanism in the death of serious patients of COVID-19. Regulating the immune system may reduce mortality in COVID-19 cases. In this review, we see Thymulin, a thymic peptide as a modality for treatment of serious COVID-19 cases through control of cytokine storm.

**KEYWORDS:** Thymulin, COVID-19, cytokine storm.

### INTRODUCTION

The COVID-19 pandemic is challenging to medical science and to humanity as well. The world is still trying to understand COVID-19 disease and SARS-CoV-2 virus. Both disease and virus are regularly surprising us with different pathogenesis, pathophysiology and immunogenicity in hosts of different age groups and gender. As of today we do not have any definitive treatment for the COVID-19, nor do we have any kind of preventive vaccines against SARS-CoV-2 virus. Cytokine storm syndrome, through immune dis-regulation is the most important mechanism in the death of serious patients of COVID-19. Regulating the immune system may reduce mortality in COVID-19 cases.

In research literature, Thymulin peptide has been researched and studied as an immuno-modulator, during the last 3-4 decades with no definitive medical recommendations and use in humans till date. Here we are trying to open a window of hope in severe cases of COVID-19 through reviewing Thymulin peptide molecule to protect against severe cytokine storm of the disease.

### Search strategy

Data articles for this review were searched online through Google scholar, Pubmed, references of relevant

articles using term Thymulin, Thymulin functions, Thymulin as immunomodulator, COVID-19 and cytokine storm. Only online available English literature included in the review.

### Thymus and Thymulin

Thymus is considered a lymphoid organ with internal milieu consisting of thymocytes, thymic epithelial cells and thymic stromal cells. Many hormones like ACTH, TSH, Prolactin and LH exert their regulatory influence on thymic functions.<sup>[1-3]</sup> Thymulin also called as Nonathymulin, Serum thymic factor.<sup>[4]</sup> It is a zinc dependent nonapeptide, one of the hormones produced by thymus involved in intrathymic and extrathymic T cell differentiation.<sup>[5,6]</sup> It has a tridimensional role as an interface in neuro-immuno-endocrine messaging.<sup>[7]</sup> Thymulin also plays a hypophysiotropic role through feedback loop on neuroendocrine targets postnatally and as an important physiological mediator for neuroendocrine maturation during perinatal period.<sup>[2]</sup> W. Savino, in his review discussed thymus physiology and its bidirectional interaction with neuroendocrine structures, confirming importance of thymulin as immunomodulator in the system of internal homeostasis.<sup>[3]</sup> Thymulin seems to be in role of natural remedy for body. Production of thymulin has been observed in extrathymic cells on exposure to oxidative stress, apoptosis and necrosis.<sup>[8]</sup> So it will be interesting

to evaluate the effect of Thymulin on stress induced by cytokine storm in COVID-19 cases.

### **Pathogenesis And Pathophysiology Of Covid-19 Disease**

The treatment guidelines of COVID-19 are frequently changing because of the new insights on pathogenesis and pathophysiology of disease and the causative virus. Whole world is evaluating both and finding definitive solution. Qin *et al.* evaluated 452 adult cases of COVID-19 retrospectively, of which 286 were of severe infection. He found to have variable laboratory data depending on severity. He documented lower levels of both helper T cells and suppressor T cells along with regulatory T cells in severe cases. Inflammatory markers and inflammatory cytokines were high in severe cases.<sup>[9]</sup> Based on published data, D. Giannis, *et al.*, quotes coagulation disorder- prothrombotic state and DIC in severe COVID-19 cases. Viral infections elicit systemic inflammatory responses in severe illnesses, leading to high level of D dimer and thrombocytopenia.<sup>[10]</sup> There is a diffuse alveolar damage, pulmonary edema, hyaline membrane formation and interstitial mononuclear infiltrate in severe cases causing death.<sup>[11]</sup> All these suggest high activity of inflammatory processes which is uncontrolled and unregulated.

### **Cytokine Storm in Covid-19 Diseases**

Cytokine storm syndrome, also called as cytokine release syndrome, is a state of severity with similar clinical phenotype triggered by diverse conditions like autoimmune diseases, malignancies and viral infections.<sup>[12]</sup> It is characterized by severe uncontrolled inflammation, multi-organ failure, coagulation defect with high levels of inflammatory markers.<sup>[12]</sup> Ruan Q *et al.* analyzed data of 150 patients of COVID-19, admitted in two hospitals from Wuhan. There were high levels of C reactive protein, mayoglobin, cardiac troponin and interleukin 6, in death cases as compared to discharged cases, leading to conclusion that cytokine storm syndrome may contribute to mortality in COVID-19.<sup>[13]</sup> Chaolin Huang *et al.* found high level of prothrombin time and D dimer among ICU COVID-19 patients compared to that of non-ICU patients. He also documented higher concentrations of GCSF, IP10, MCP1, MIP1A, and TNF $\alpha$  in ICU COVID-19 patients, suggesting role of cytokine storm in disease severity.<sup>[14]</sup> Another pre published data of 20662 COVID-19 patients shows fibrinolytic hyperactivity with high level of C-reactive protein, erythrocyte sedimentation rate, interleukin-6 and serum ferritin suggesting inflammatory storm.<sup>[15]</sup> This way cytokine storm syndrome plays crucial part in outcome of severe COVID-19 cases.

### **Thymulin and Cytokine Storm**

All over the world, tiny diffuse blood clots were the one of major unresolved puzzles, in mortality of COVID-19 patients.<sup>[16]</sup> Coagulation disorder with thrombotic complication and DIC were described in patients infected by SARS-COV-2.<sup>[10]</sup> Thymulin significantly reduces

activity of FIX, FXI and FXII in intrinsic coagulation pathway and imposes a distinct tendency of hypo-coagulability.<sup>[17]</sup> In this manner, Thymulin may play a crucial role in prevention of complications and decreasing mortality in COVID-19 patients.

Thymulin levels are low in immunodeficiency and autoimmune diseases. It plays important role in the interaction between the immune system and the neuro-endocrine system.<sup>[18]</sup> Thymulin has a protective role in lung diseases. It induces selective immunomodulatory effect by enhancing anti-inflammatory and inhibiting pro-inflammatory cytokines. It suppresses p38 (implicated in glucocorticoid-resistance) and inhibits NF- $\kappa$ B activation, which has an important pathogenic role in several lung diseases.<sup>[19]</sup> Effect of Thymulin 5CH, on BCG induced granuloma in male adult Balb/c mice, showed improvement in the granuloma inflammatory process and the infection remission, by modulating local and systemic phagocyte differentiation.<sup>[20]</sup> Thymulin as an anti-inflammatory medication, inhibits the endotoxin induced nuclear activation of NF-B and the transcription factor required for the expression of proinflammatory cytokines gene, in the hippocampus.<sup>[21]</sup> In mice with acute septic inflammation, Thymulin increases the anti-inflammatory activity of a specific inhibitor of the NF- $\kappa$ B signaling pathway, I $\kappa$ B kinase (IKK) inhibitor XII.<sup>[22]</sup> In a study done on lipopolysaccharide treated mice, Thymulin suppressed the proinflammatory response, reduced fever, apoptosis, increased splenic cell number, and decreased cytokine production.<sup>[23,24]</sup> Thymic endocrine function (thymulin production) is the important part of chronobiological organization of immune system.<sup>[25]</sup> Thus Thymulin is experimentally proven to be effective in controlling the situation of uncontrolled, unsynchronized hyperactivity of inflammatory mediators in cytokine storm and bring order to the system.

### **Thymulin and Covid-19**

COVID-19 is showing gender and age bias in mortality. Deaths are more in males than women.<sup>[26]</sup> Female hormone, Prolactin can stimulate Thymulin synthesis and secretion through Prolactin-Thymulin axis.<sup>[2]</sup> This may be the reason that plays protective role for women in COVID-19 patients. Children are diagnosed of SARS-COV-2 infection mostly by contact tracing. Majority of younger age group are asymptomatic.<sup>[27-29]</sup> Immaturity of immune system may be the one factor but higher titer of Thymulin and lower levels of thymulin inhibitory molecule in younger children compared to adolescent age group may be the explanation.<sup>[30]</sup>

Thymus peptide, Thymosin alpha 1 has been shown to reduce mortality in COVID-19 patients.<sup>[31]</sup> Compared with untreated group, T $\alpha$ 1 treatment significantly reduces mortality of severe COVID-19 patients (11.11% vs. 30.00%,  $p=0.044$ ). Likewise Thymulin may also be beneficial in decreasing deaths in COVID-19 cases.

### Thymulin as Drug

Most of the studies of Thymulin in humans were conducted during the period of 1980s in rheumatoid arthritis, multiple sclerosis, Di-George syndrome, nephrotic syndrome, immunodeficiency and systemic lupus erythematosus cases.<sup>[32-37]</sup> Thymulin has short half-life of 30-60 min with, with longer duration of drug effect on T lymphocytes (24-48 hour).<sup>[32]</sup> Oscar J. Cordero et al. recommends use of thymic peptides in immunotherapy.<sup>[38]</sup> Amor B. et al. conducted two open trials in rheumatoid arthritis, one with 150 ug and another with 1 mg thymulin (Choay, Paris, France) dose, given subcutaneously, once each day for 2 weeks and then 3 times a week for 4 months. Cases with 1 mg

schedule had better results with no documented side effects.<sup>[39]</sup> Amor B. et al. also did two double blind placebo control trial on rheumatoid arthritis cases with Nonathymulin in different doses (1mg, 5mg and 10 mg) by subcutaneous route once a day for 2 weeks and 3 times a week for 6 months. Side effects were minimal in all the groups, though 5mg of Thymulin was the most efficient dose.<sup>[32]</sup> Nonathymulin was also studied in multiple sclerosis by Roulett E et al, no significant side effects were recorded in study group.<sup>[33]</sup> Synthetic Serum Thymic Factor was used with positive outcome in immunodeficient children. Route of administration was intravenous.<sup>[34]</sup>

### Thymulin is commercially available under different forms and names.<sup>[40-44]</sup>

Company name	Country	Product name	Website link
LKT Labs	USA	Thymus factor	<a href="https://lktlabs.com/product/thymus-factor/">https://lktlabs.com/product/thymus-factor/</a>
Samson-MED LLC	Russia	Thymalin	<a href="https://samsonmed.ru/en/portfolio-items/thymalin/">https://samsonmed.ru/en/portfolio-items/thymalin/</a>
Hangzhou Go Top Peptide Biotech	China	Thymalin	<a href="https://www.gtpeptide.com/generic-peptide/thymalin-cas-no-63958-90-7.html">https://www.gtpeptide.com/generic-peptide/thymalin-cas-no-63958-90-7.html</a>
Homeopathic Educational Services	USA	Thymuline 9C	<a href="https://homeopathic.com/product/thymuline-pellet-form-helping-strengthen-bodys-defenses/">https://homeopathic.com/product/thymuline-pellet-form-helping-strengthen-bodys-defenses/</a>
Abcam	USA	Human Thymulin peptide	<a href="https://www.abcam.com/human-thymulin-peptide-ab42294.html">https://www.abcam.com/human-thymulin-peptide-ab42294.html</a>

### Thymulin Over Other Immunomodulators

Thymulin is naturally occurring peptide in the body which is nontoxic and can be administered easily. Synthetic forms are available in the market. It is safe, easy manufacturing possible in large quantity, and cheap as compared to other available immunomodulators.

Considering the size of pandemic and patients load, we are at desperate need of answers. Over thousand years of development, our body has evolved fine regulatory mechanism of immunity. Thymulin is the key to body's internal regulation. We can learn from it and use it against COVID-19.

### Possibilities and Need

SARS-CoV-2 is a tough challenge for humans and medical science alike. No definitive treatment is available in hand. Development of vaccines will take time with questionable success. While the world economy is at its most vulnerable state, medical science is trying to find a solution. Within the closet of our scientific development, Thymulin is the one possibility which needs to be brought into the treatment box of COVID-19.

### CONCLUSION

Thymulin is a promising molecule, effective in cytokine storm, yet to be tested against COVID-19. Serious cases of COVID-19 may benefit from it. Indeed Thymulin may decrease morbidity and mortality in COVID-19.

### RECOMMENDATIONS

Serious consideration should be given to prevent cytokine storm syndrome with Thymulin, in symptomatic patients of COVID-19. Human trial should be started using Thymulin on symptomatic COVID-19 cases to protect against cytokine storm, as a priority and on urgent basis.

### CONTRIBUTORS

#### All the authors contributed equally

AK, conceived the idea. VC and AK planned the study design. VC and RK did collection of data, writing of manuscript. AK and VC did data analysis and screening of manuscript.

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### CONFLICTS OF INTEREST

None.

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