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Review Article

A Review Article on the Benefit of Melatonin in Ebola Virus Disease Treatment: A Summary of Available Evidence

Diriba Dereje[1]*, Urge Gerema[2], Bekalu Getachew[2] and Tesema Etefa[2]

[1]Department of Biomedical Sciences (Physiology), Institute of Health, Jimma University, Ethiopia

[2]Department of Biomedical Sciences (Anatomy), Institute of Health, Jimma University, Ethiopia

***Corresponding Author:** Diriba Dereje, Department of Biomedical Sciences (Physiology), Institute of Health, Jimma University, Ethiopia.

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Abstract

Ebola virus disease (EVD) is a viral infectious having high mortality rate. But, there is no yet available proven and recommended treatment. A severe EVD is characterized by insobriety, severe hemorrhages, disseminated intravascular coagulation and multiple organ failure with the development of severe shock. Melatonin application may act on and prevent each of those pathological alterations caused by the EVD. Melatonin possesses pro- and anti-inflammatory properties, limit coagulation problems, can prevent the oxidative stress and inflammatory injury that occurs in the infected endothelial cells, decreases the symptoms, and increases the survival rate after Ebola virus infection. Further clinical trials are mandatory and recommended to explore melatonin side effects, benefits, food and drug interactions, and route of administrations in Ebola virus disease management and prevention of complications.

Keywords: *Ebola Virus Disease; Melatonin; A Review*

Introduction

Melatonin (M) is the hormone, secreted from the pineal gland (PG). Main function of M is to regulate the sleep/wake cycle and other circadian rhythm. Additionally, it can also increase the ability of immune system to fight disease and it has cytoprotective effect [1-3]. The first case of EVD was reported from Sudan and Zaire in 1976, but the virus has only received real attention from scientists since 1995 [4].

The EVD case fatality rate varies from 25% to 90% in past outbreaks with an average around 50% [5,6]. Several efforts has been made, but Ebola was not eradicated yet and even new cases were detected soon in Democratic Republic of the Congo (DRC) [7,8]. This, indicates that it still needs a great attention. Despite new vaccines, therapeutics and the extensive lessons learned from the West African Ebola outbreak, the DRC's 2018-2020 outbreak has taken nearly 20 months to bring under control [9].

Progression to severe disease occurs when the virus causes an expression of pro-inflammatory cytokines, including interferons; interleukins (ILs) such as IL-2, IL- 6, IL-8, and IL-10; interferon inducible protein; and tumour necrosis factor α (TNF-α) in a host [10-12]. A severe EVD characterized by insobriety, severe hemorrhages, disseminated intravascular coagulation, and multiple organ failure with the development of severe shock [13,14].

M, pleiotropic molecule has anti-inflammatory, antioxidant and anticoagulopathic properties in addition to its endothelial protective effects [15]. The pathogenesis' mechanisms of EVD include interference with host immune response [16], inflammation, coagulopathy, and endothelial disruption [17]. In conclusion, this review explores and summates the available evidences on the beneficial effect of melatonin in management of Ebola virus disease.

Pathologies of Ebola virus

Three cells were identified as the central to the development of EVD. These include monocytes, macrophages, and dendritic cells. This is because, infection and/or interaction of these cells with Ebola virus stimulates the release of a variety of mediators and factors that trigger a host of downstream events which may be one of stimulation of the inflammatory response, activation of the coagulation system and disruption of the vascular endothelium. As explained in the previous work, because of its diverse and flexible benefit, M administration may act on the each of the pathological changes caused by the EVD, explained in figure 1 [17].

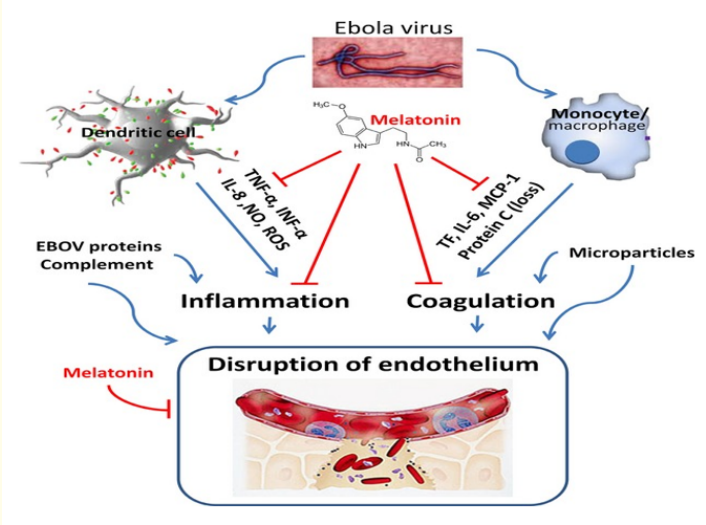

Figure 1: *The pathologies of Ebola virus infection and potential effects of melatonin [17].*

Melatonin in decreasing inflammation caused by Ebola virus disease

M possesses pro- and anti-inflammatory properties; regardless of these contradictory characteristics, it reflect more of anti-inflammatory benefits in advanced stages of inflammation in EVD [17]. Because of this, it is an active anti-inflammatory agent and a good free radical scavenger [18,19]. It suppresses the levels of TNF- α, interferon alpha (IFN- α), IL6, IL8, tissue factor (TF), monocyte chemo attractant protein one (MCP-1), vascular endothelial growth factor (VEGF), phosphorylation of c-Jun N-terminal kinase (JNK), and the degradation of the tight junctional proteins [20,21]. The cumulative effects of this all thing will result in limitation of harmful effect caused by the exaggerated response of inflammation severe disease which will result in unnecessary damage to the self. M may be the important promising chemical that can be applied in this kind of situation if adequate research will be conducted in the future.

Melatonin in decreasing coagulopathy caused by Ebola virus disease

Coagulation disorder is a major and life threatening condition in EVD. M has a capacity to prevent this in Ebola infection. In limiting this disorder M interact with the most important factor i.e. TF, in addition to the other mechanism, which has negligible effect [22]. Melatonin's effects on haemorrhage are mediated primarily by a decrease in pro-inflammatory cytokines [17]. TF, plays a key role in triggering the coagulation abnormalities in of Ebola virus infection [23]. Melatonin suppresses the level of this TF, there by decreases coagulation abnormalities [20].

Melatonin in decreasing endothelial disruption caused by Ebola virus disease

Endothelial disruption has several consequences, which cannot be limited to local area of blood vessel because it can cause a serious problem. The major mechanism in producing this endothelial damage is oxidative stress. M can decrease the oxidative stress (OS) and inflammatory damage that occurs in the affected endothelial cells and preserve their integrity of the cells [24]. Protecting against endothelial cell injury and preserving vascular structure and function are important to avoid the deadly hemorrhage in the late stage of EVD [17]. Melatonin also reduces endothelial apoptosis [20]. Additionally, it can be used to combat OS and inflammation which will decrease endothelial cell injury [25].

Future perspectives about melatonin in Ebola virus disease

According to WHO, supportive care and treatment of specific symptoms improves survival rate in EVD. However, there is no available effective, proven and standard treatment for EVD. But, a range of potential treatments which were said to have additional benefit and prevent complications were identified which include blood products, immune therapies and drug therapies are currently being evaluated now a day [6,26]. The main activities in treating EVD is to adjust alteration of homeostasis, to reverse disturbance in blood volume, to correct a change in water and electrolyte balance, to correct a change in acid-base, to correct a change in osmolar and oncotic pressure shortfall of blood components [13]. It was also suggested that although not targeted specifically to the treatment of the Ebola virus, M may decreases the symptoms and increases the survival rate of those infected with the Ebola virus [17].

Conclusion

EVD is a disease with a high case fatality rate with still no confirmed medication. It produces a very serious and life threatening conditions, which include altered immune response, abnormal inflammation, coagulopathy, and endothelial disruption. Melatonin application may act on each of the pathological alterations caused by the Ebola virus. Melatonin possesses pro- and anti-inflammatory properties, decreases coagulation abnormalities, can limit the oxidative stress and inflammatory injury that occurs in the infected endothelial cells, and decreases the symptoms and increases the survival of those infected with the Ebola virus. Further clinical trials are recommended to explore melatonin side effect and its benefit in EVD.

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