ISSN No:-2456-2165

Review: Combat against COVID-19 Complications - Traditional Plant *Lantana camara*

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Abstract:- A remarkable step has taken to rescue lives from COVID-19 virus with the development of vaccines. At present, a few vaccines have been developed and dispensed to the patients. In parallel to this process, clinical trials are being performed aiming to develop advanced therapies. This review paper is being written in the period when the vaccine for COVID-19 was administered first time to health professionals in Sri Lanka. Any therapeutic method used against COVID-19 should address the main complications that may associate with the disease state. As a tropical country with rich vegetation throughout the year, application of traditional medicinal plants as treatments of patients or as supportive therapies is a common topic being discussed today. In this review, we discuss the condition of COVID-19 infection in Sri Lanka at the beginning of the administration of vaccine, entering of COVID-19 virus to human red blood cells, abnormal hematological findings, laboratory diagnosis methods available. We discuss the properties of the traditional Sri Lankan plant, *Lantana camara* and how its potentials to act against the abnormal pathophysiology that may arise because of COVID-19 infected and post COVID-19 infected blood. Furthermore, we discuss the potentials of using *Lantana camara* in the management of COVID-19 patients in future.

Keywords:*-COVID-19, Lantana camara, hematological complications, red blood cells.*

I. INTRODUCTION

A silver line has been shined for the entire world with the invent of vaccines against COVID-19. COVID-19 vaccine "AstraZeneca" is now authorised across Europe[1]and for the first time it has been administered to selected Sri Lankan health professionals. Rest of the health professional to be treated with the vaccine and vaccination is about to continue to cover the entire people in Sri Lanka stepwise in near future. According to the current updated data on 31stJanuary 2021 from the World Health Organization (WHO) there are 102,059,807 confirmed cases have been identified in 213 countries/regions, with 2,201,428 confirmed deaths being reported across the world.At the same time, 63,293 confirmed cases were reported in the Sri Lanka with 313deaths.[2]

A. Entry of covid-19 virus to human red blood cells

This virus mainly spreads all through respiratory droplets expelled by patients who is infected with SARS CoV 2. The non-structural outer surface proteins called spike proteins produced because of the replication process of the RNA of the SARS CoV 2virus inside the host cell have an ability to capture other cellular pathways.[3]Cosic et al. 2020 have proposed that Band3 Protein (B3P) present on the membrane of red blood cells is an entry point for the Corona virus into the cell [4].Invasion of the SARS CoV 2using its outer membrane protein, spike proteins affects the circulating red blood cells as viral proteins interact with the β chain of hemoglobin to remove iron and form porphyrin.[3],[5]Thereafter, it disturbs the exchange of oxygen and carbon dioxide and it affects the transportation

of oxygen to other organs. It releases iron from the porphyrin ring and oxidized into its ferric state allowing it to withdraw the process of binding oxygen to the heme and the red cell becomes non-functioning causing hypoxia of the tissues. The released iron in its ferric state becomes toxic to the tissues and it also causes oxidative damage.[3]

B. Mechanism of action of covid-19 vaccine AstraZeneca

Since COVID-19 virus uses proteins on its outer surface, called spike proteins, to enter the red blood cells the vaccine has been prepared by targeting spike protein.[1]For this, COVID-19 vaccine AstraZeneca has been made using a virus of the adenovirus family (a common cold virus). It has been modified to activate the gene encoding for the same spike protein that present on the SARS-CoV-2. Since the adenovirus itself cannot replicate theoretically, it cannot cause disease. Once it has been injected, the vaccine sends the SARS-CoV-2 gene into cells in the body. The cells that treated with new modified virus will use the gene to produce the spike protein. Then the person's immune system will trigger and identify this spike protein as non-self and produce antibodies. The memory cells produced by this exposure will activate once the same person is infected by COVID-19 virus. Then the rapidly secreting antibodies with the combination of T cells will attack and destroy it.[6]

C. Laboratory diagnosis and hematological complications associated with COVID-19

RT qPCR is the recommended diagnostic laboratory test to detect COVID-19 virus. In addition, the rapid antigen test is used to screen the patients in the population. [7] In both instances the material that are used is nasopharyngeal swab samples.[7], [8]

The prominent hematological abnormalities in association with COVID-19 revealed by Mitra et al. 2020[9] are lymphopenia, normocytic anemia with occasional nucleated red blood cells and normal platelet count. In the study done by Fan et al (2020) mentioned that peripheral blood film contains few reactive lymphocytes in lymphopenia patients and neutrophilia with left shifted myeloid cells. Smudge cells and large platelets were also present. They have conducted the study using COVID-19 infected ICU and Non-ICU patients. Most ICU patients have shown a reduced hemoglobin level and flowcytometry based analysis of peripheral blood lymphocytes have shown a significantly lower amount of the markers of lymphoid lineage ; CD45, CD3, CD 4 and CD 8.[10] Some COVID-19 patients were associated with neutrophilia, low hemoglobin and increased values of serum ferritin, and high erythrocyte sedimentation rate.[11] Hypercoagulability is a critical condition associated with COVID-19 with the tendency to occur micro thrombus in lungs and in other organs. It is suggested that the pulmonary microvascular thrombosis may play a role in progressive respiratory failure and it may cause as a result of platelet aggregation and platelet-rich clot formation.[12], [13]Venothromboembolism (VTE) is a prominent feature of COVID-19 infections as it associates with hypercoagulable state. Consumption of coagulation factors due to excess fibrin formation causes bleeding at the latter stages increased in fibrin degradation products (FDP) in early stages. Therefore, the test D-dimer is increased in most of the patients in the first phase with the increasing levels of acute phase reactant CRP.[14]

D. Vaccination for COVID-19 and post complications

According to WHO report updated on December 2020 explains that various types of vaccines for developed against COVID-19 can be acted as totally inactivated or partially weakened virus vaccines, RNA or DNA based vaccines, protein-based vaccines, vaccines produced by genetical engineering.[14] However, it is obvious that vaccination always associates with complications starting from simplest fatigue, swelling or pain around the injection site, fever, headache, redness to serious complications like allergic shock.[15] Furthermore, certain vaccines are not recommended to treat with the adults over 65 years; e.g., Vaccine AstraZeneca.[7] Furthermore, vaccination may cause delayed hypersensitivity reactions sometimes to be fatal.[16] Therefore, the challenge of today is to develop an innovative treatment that could act against the complications by the virus by giving minimum side effects to an individual. Moreover, the individuals who got infected and susceptible to have a recurrence should be managed by the treatment by preventing the second attack.

II.LANTANA CAMARA

The plant *Lantana camara*(Verbanaceae) is a shrub containing mixture of triterpenes. It contains certain important bioactive molecules in its different parts including;lantadenes, urosolic acid, oleonolic acid. (figure 1).[17] It is the most widespread species of

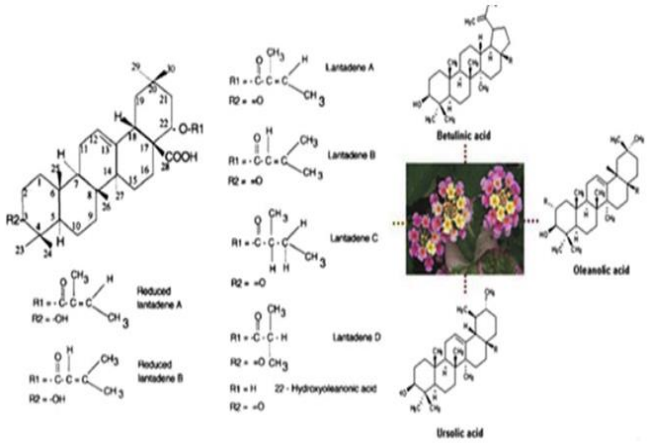

Fig.II. *Bioactive compounds of Lantana*

This genus and it is a woody straggling plant with various flower colours, red, pink, white, yellow, and violet. It is also generally known as wild or red sage. phytochemical screening revealed that leaf, stem and root of Lantana camara contained tannin, catachin, saponin, steroids, alkaloids, phenol, anthroquinone, protein, several tri-terpenoids, flavonoids, alkaloids, glycosides and reducing sugar which are mainly responsible for exerting diverse biological activities.[18]

The evidence found in literature to prove that *Lantana camara* is used as an herbal medicine from ancient era. All parts of this plant have been used in traditional medicine in the different parts of the world.[18], [19] The plant extracts have been used for the treatment of cancers, chicken pox, measles, asthma, ulcers, swellings, eczema, tumors, high blood pressure, bilious fevers, catarrhal infections, tetanus, rheumatism and malaria.[20] Further, used for the treatment of skin itches, as an antiseptic for wounds, and externally for leprosy in folk medicine.[18]

A. Mechanism of action of Lantanacamara

Lantana's Antimicrobial and antibacterial activity is exerted by Lantadene A (LA), Lantadene B (LB), oleanolic acid, ursolic acid, 4- acid and 24-Hydroxy-3-oxours-12-en-28-oic acid and its Protein kinase C inhibiting activity via Verbascoside.[20] Moreover, Verbascosides exhibit activity against some viruses such as Respiratory syncytial virus (RSV) In vitro these compounds had better antiviral activity than ribavirin, an approved drug for treatment of RSV infections in humans.[21] this antiviral activity exerted by Lantadene A, Lantadene B, Lantadene C, Reduced Lantadene A, Reduced Lantadene B and 22beta-Hydroxy-3-oxolean-12-en-28-oicacid contained in *lantana*.[20], [22] Further, literature suggests that Lantana camara exhibited thrombin inhibitory activity via acylation of the active site Ser 195 residue of thrombin due to the presence of euphane lactone triterpenes in the leaves.[21]

B. Impact of Lantana camara on hematological parameters

Hematological changes were shown by ingestion of *Lantana camara* extracts and it was proved in some animal studies. The rabbits were divided into three groups as 05 rabbits for each as exposed for fruit extract, exposed for leave extract and control group and then hematological changes were detected in each group and compared. Important result was the reporting of no toxic signs in first and second groups. It was found that the prolonged clotting time and bleeding time, decreased erythrocyte count, Hb concentration, and Mean Cell Volume (MCV), increased Mean Cell Hemoglobin (MCH), and percentage of monocytes in rabbits who were fed by diet mixed with dehydrated powder of *Lantana camara* leaves and fruits for 14 days.[23] Also, the same researcher has conducted a study with a member and there they have used 10 healthy rabbits and fed them by diet with dried powder of leaves. it was revealed that similar hematological parameters; reduction in the red blood cell counts, Hemoglobin & PCV, prolongation of coagulation tests with normal leucocyte counts.[24]

C. Membrane stabilizing potential

It was reported that membrane stabilizing profiles of various extracts of *Lantanacamara* on red blood cells lysis in some literature. Maiworm et al., (2008) have done a study using 10mg/ml extract of L. camara leaves and performed osmotic fragility test and morphological analysis of mouse red blood cells. It was found that the changes in red cell morphology and increase hemolysis by increasing osmotic fragility. It means compound has strengthen the erythrocyte membranes as it showed increased osmotic fragility.[25] The role of aqueous and methanolic extracts of Lantana camara on RBC membrane stability was discussed by a study conducted in Italy.[26] It was found the same results in the study done in Nigeria as effective protection of erythrocyte membranes by the extract while the ethyl acetate fraction has provided better protection than ethanol.[27]

III. INNOVATIONS: *LANTANA CAMARA* TO BECOME A TREATMENT FOR COVID-19

The most critical episode of the disease is the recurrence. It has been reported that the reappearance of 6 COVID -19 cases in Brazil.[28], [29] It has been shown that at least one recent major clinical sign of COVID-19 including fever or chills, febrile flu-like-syndrome, dyspnoea, anosmia, or dysgeusia was observed with a positive SARS-CoV-2 RT-PCR test.[30] In addition, According to WHO Some reports have indicated that people with no symptoms can transmit the virus.[31], [32]And this asymptomatic transmission may create new clusters and worsen the pandemic condition silently. Although certain groups have been recovered by self-immunity, the testimony of how long the protection lasts is not evident. Therefore, there may still be a risk of reinfection from COVID-19.[33] It is possible to have several organ damages and haematological changes following any viral infection and in COVID-19 the same could be expected.[34], [35] Since the haematological changes are significant in COVID-19 infections [14], [36], [13] more attention to be paid to screen the blood samples of post COVID-19 patients for such changes.

Herbal medicine is becoming ever more popular in today's world. As a country who does have varieties of plants throughout the year it is feasible to develop a treatment method using natural remedies. It is time for a widen study to make use of *Lantana camara* first as a treatment of COVID-19 patients' blood samples in-vitro with the controls. Since Sri Lankan Lantana camara L. (Verbenaceae) possesses most of the actions against the complications associated with COVID-19 it is expected that their extracts could be used against post corona viral haematological and other complications.

IV. CONCLUSION

Although vaccines are being developed and clinical trials are being performed there is still a gap to be fulfilled especially due to post COVID -19 complications and the recurrence of the disease. The remedies of traditional medicine still have an opportunity of filling this gap. However, there is limited research available to find out the human blood associated complications and its behavior combining with traditional medicinal plants for COVID-19. In this review, we suggested a traditional plant *Lantana camara* to use up against the harmful effects by COVID-19 by aiming it to become an innovative treatment for COVID 19 in future. According to the current trend the entire world including Sri Lanka is blessed with the vaccines being

developed and expecting more vaccines to be available. It is high time to experiment with the traditional plant *Lantana camara* plants that are freely available in Sri Lanka against COVID-19. With this message, we conclude this review by directing the researchers to engage in advanced traditional medicinal plants-based research for COVID-19.

ACKNOWLEDGMENT

We thank General Sir JohnKotelawalaDefence University for the support provided in all aspects.

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