Journal of Pharmacognosy and Phytochemistry
Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
www.phytojournal.com
JPP 2021; 10(1): 1948-1951
Received: 28-11-2020
Accepted: 30-12-2020

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Traditional Sri Lankan plant, *Lantana camara*; Will it be a treatment against the hematological complications of COVID-19?

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DOI: https://doi.org/10.22271/phyto.2021.v10.i1aa.13636

Abstract
It is indisputable that COVID-19 virus interfered with the health status, education, socio economic impact on Sri Lanka and is threatening the entire world at present. Several vaccines are being developed; clinical trials are being performed aiming to eradicate the virus. The 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 current situation of COVID-19 infection in Sri Lanka, pathogenesis of the entry of COVID-19 virus to human red blood cells, hematological complications, existing laboratory diagnosis methods. We discuss the properties of traditional Sri Lankan plant, *Lantana camara* and how its activities are useful to act against the fatal pathophysiology that may associate with COVID-19 infected and post COVID-19 infected blood. Furthermore, we create a platform to discuss the possibilities of using *Lantana camara* in the management of COVID-19 patients in future.

Keywords: Covid-19, *Lantana camara*, hematological complications, red blood cells, medicinal plants

Introduction
The emergence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV 2) disease (COVID-19 infection) in China at the end of 2019 has caused a large global outbreak and is a major public health issue. The WHO declared COVID-19 as the sixth public health emergency of international concern [1]. This is the third time in recent history Sri Lanka had to fight a non-terrorist enemy after the Tsunami and dengue outbreak. As of current updated data on 16 January 2021 from the World Health Organization (WHO) there are 93,581,814 confirmed cases have been identified in 213 countries/regions, with 2,003,537 confirmed deaths being reported across the world [2]. This is the third time in recent history Sri Lanka had to fight a non-terrorist enemy after the Tsunami and dengue outbreak. A 44-year-old Chinese woman from China as the first confirmed case of the virus was reported in Sri Lanka on 27th January; she was admitted to the National Institute of Infection Diseases [3]. As of 16th January 2021, 51,594 confirmed cases were reported in the Sri Lanka with 255 deaths [2].

Entry of COVID-19 virus to human red blood cells
SARS CoV 2 is a known RNA virus and it has four sub types as α, β, γ and δ while α- and β-types of CoV 2 have the ability to infect humans [4]. This virus mainly spreads all through respiratory droplets expelled by patients who is infected with SARS CoV 2. The non-structural 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 [5]. Cosic *et al* 2020 have proposed that Band 3 Protein (B3P) present on the membrane of red blood cells is an entry point for the Corona virus into the cell [6]. The main function of B3P is to exchange Cl− by removing carbon dioxide as HCO_3^- through the RBC membrane. It is also responsible for acid balance, ion distribution and gas exchange [7]. In the structure of mature RBC, millions of B3P are present and they cross link with the other proteins present on the cytoskeleton and maintain the shape of the cell [7, 8].
Invasion of the SARS CoV 2 affects the circulating red blood cells as viral proteins interact with the β chain of hemoglobin to detach iron and form porphyrin [5, 9]. Initially 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 eventually oxidized into its ferric state. This deprives the process of binding oxygen to the heme and the red cell becomes non-

functioning causing hypoxia of the tissues. Further whilst the iron in its ferric state is toxic to the tissues and it also induces oxidative damage [5].

Laboratory diagnosis and hematological complications associated with COVID-19

Nasopharyngeal swab samples were normally used to detect COVID-19 viral RNA using real time polymerase chain reaction (RT qPCR) as the confirmatory test for the detection of infection in humans [8]. In addition the feasibility of using specific antibodies against nucleocapsid and spike proteins of the COVID-19 virus for the diagnosis was studied by Bruce *et al* 2020 and Elsande *et al* 2020 [8, 10] and both antibodies have shown a high specificity and sensitivity. Identifying the antibody responses by Enzyme Linked Immunosorbent Assay (ELISA) and lateral flow assays will be an advantage to find a vaccine for the disease.

As screening methods, major hematological findings were shown in studies conducted by using peripheral blood of COVID-19 patients. Full blood count has shown lymphopenia, normocytic anemia and normal platelet count whilst peripheral blood picture indicated normocytic anemia with occasional nucleated red blood cells, neutrophilia with left shifted myeloid cells, many smudge cells and large platelets in a study done by Mitra A *et al*. [11] Lymphopenia with remarked leucopenia and mild thrombocytopenia were shown with blood picture findings as reactive lymphocytes. Flowcytometry assay was done for peripheral blood lymphocytes in ICU patients have shown a lower amount of CD45+, CD3+, CD4+, CD8+, CD19+ and CD16/56+ counts on lymphocytes [12].

It was shown that the biochemical parameters like albumin, c reactive protein and lactate dehydrogenase (LDH) were raised up. Also, it was observed that the changes in hematological parameters as reduced neutrophil count, hemoglobin and increased values of serum ferritin, and erythrocyte sedimentation rate on majority of patients with COVID-19 infection [13]. Some studies have shown that the tendency to occur micro thrombus in lungs and in other organs caused by alterations in hypercoagulative state. Hypercoagulability is another fatal condition associated with COVID-19 in addition to acute respiratory failure. Limited data suggest pulmonary microvascular thrombosis may play a role in progressive respiratory failure and it may cause as a result of activation of megakaryocytes in the bone marrow with platelet aggregation and platelet-rich clot formation [14, 15]. Venothromboembolism (VTE) is a distinct feature of COVID-19 infections as it associates with hypercoagulable state. Continuous fibrin formation causes reduction in the coagulation factors and increased in fibrin degradation products (FDP). Therefore, D-dimer is increased in most of the patients, and also the non-specific acute phase reactant CRP increases [16].

Present condition of the treatment of COVID 19

The anti-malarial drug Chloroquine and Hydroxychloroquine are being used in the treatment of COVID-19. The mechanism of Chloroquine with COVID-19 is not clear and may be disrupting the virus's ability to enter a cell [17]. The drug Famotidine is being given in combination with the antimalarial Hydroxychloroquine to treat COVID infections in New York [18] World Health Organization has been performed the therapeutic trials for COVID-19 infection and it was found that the minute /no effect of Remdesivir, interferon, Lopinavir/Ritonavir and Hydroxychloroquine regimens on 28-day mortality or the in-hospital course among hospitalized patients [19].

At present there is no drug which have proven effectiveness in the treatment against COVID-19. Few vaccines have been developed and all of them are in a preliminary stage. The WHO report updated on December 2020 explains that various types of vaccines for COVID-19 are being developed. They can be behaved as inactivated or weakened virus vaccines, protein-based vaccines/RNA or DNA based vaccines produced by genetical engineering to attack the virus [20] Some of the vaccines are being used as clinical trials [21]. On December 2020, the U.S. government granted the permission for first authorization (EUA) for emergency use and distribution of vaccine against COVID-19 ; Pfizer-BioNTech COVID-19 [22]. Therefore, the challenge of today is to find out a drug that could act against the causative damage by the virus especially those who got infected to prevent the secondary complications.

Lantana camara

The plant *Lantana camara* (Verbanaceae) is the most widespread species of 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.

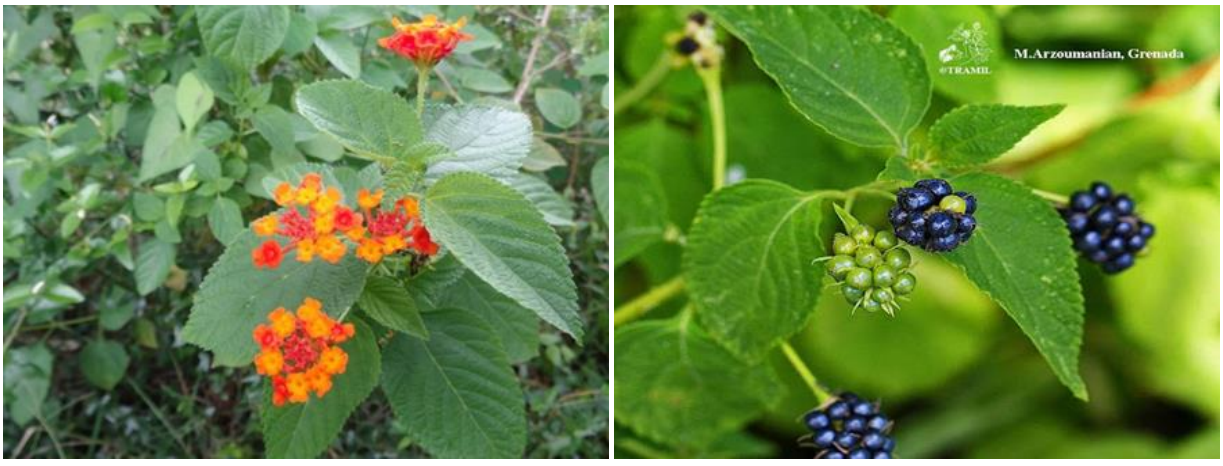

Fig *Error! No text of specified style in document.*: *Lantana camara* flowers (left) and leave and fruits (right).

Lantana camara has been used in many parts of the world to treat sores, chicken pox, measles, fevers, colds, rheumatism, asthma, and high blood pressure [23]. It has scientifically shown various therapeutic activities such as antiviral, erythrocyte membrane stabilization, antiplatelet aggregation, antioxidant, anti-inflammatory [23, 24].

Ethnopharmacological importance and mechanism of action

Empirical literature has claimed 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 [25]. Synthesis of a variety of 5,5-trans fused lactones, related to compounds found in extracts of *Lantana camara*, has provided a series of novel acylating inhibitors of human thrombin, trypsin, chymotrypsin and human leucocyte elastase [26]. Verbascoside is a phenylethanoid glycoside which exhibited activity against Respiratory syncytial virus (RSV). RSV is a cause of lower respiratory tract infection in infants and young children. In vitro these compounds had better antiviral activity than ribavirin, an approved drug for treatment of RSV infections in humans. Considerable interest has been shown in the anti-inflammatory action of some triterpenes such as oleanolic acid and ursolic acid as inhibitors of human leucocyte elastase. This enzyme involves in the destruction of elastin and plays a role in chronic disorders such as pulmonary emphysema, hepatitis, cystic fibrosis, and rheumatic arthritis [25].

Hematological properties

Al-Khafaj 2014 [27] has revealed that breeding rabbits who were fed by food mixed with dried powder of *Lantana camara* leaves for three weeks. They have shown the changes in hematological investigations as increased clotting time and bleeding time, reduced erythrocyte count, Hb concentration, and MCV, increased MCH, and percentage of monocytes while the other parameters were not changed compared with the control group [28]. revealed that blood of healthy rabbits treated with powder of lantana fruits and leaves for 14 days showed similar hematological parameters; reduction in the red blood cell counts, Hemoglobin & PCV, prolongation of bleeding and clotting times with normal leucocyte counts. It was found rats who were treated with different *Lantana camara* leave juice doses for 14 days presented with decreased absolute lymphocyte counts [29].

Membrane stabilizing potential

According to the available literature, membrane stabilizing profiles of various extracts of *L. camara* on red blood cells exposed to both heat and hypotonic induced lysis have been reported previously. A study conducted in Italy has confirmed the role of aqueous and methanolic extracts of *Lantana camara* in erythrocytes membrane stabilization [30]. Another study conducted in Nigeria has found that both ethanol and ethyl acetate contained principles have protected the erythrocyte membranes effectively in a concentration dependent fashion. Moreover, it has found the ethyl acetate fraction provided highest protection against induced lyses Besides, few studies were found that negative effects on membrane stability exert by the plant of interest [31]. It has been showed that blood treated with an aqueous extract of *Lantana camara* strengthen the erythrocyte membranes as it showed increased osmotic fragility with the alterations of the morphology of them which may be associated with pharmacological properties of the chemical compounds of *Lantana camara* extract [32].

Future Directions: Possibilities of *Lantana camara* to become a treatment for COVID-19

Many people with COVID-19 experience only mild symptoms in the early stages. It is possible to identify COVID-19 from someone who has just a mild cough and does not feel fever. According to WHO Some reports have indicated that people with no symptoms can transmit the virus [33, 34]. Following close contacts with similar levels of exposure to infection from primary cases can permit identification of the asymptomatic fraction and also, they may remain undiagnosed as a person's immune system remembers similar viruses. It is assumed that this asymptomatic transmission may create new clusters and worsen the pandemic condition silently.

Furthermore, though COVID-19 develops immunity in recovered patients, the evidence of how long the protection lasts is not clear [35]. Therefore, still there may be a risk of reinfection who had recovered from COVID-19 [35]. Indeed, as similar as to following any viral infection, COVID-19 also will be expected to have several organ damages and haematological changes too in the victims [36, 37]. Since the haematological changes are significant in COVID-19 infections [11–13] there is a timely need for a study that could screen the blood samples of post COVID-19 patients for such changes. Herbal medicine is becoming ever more popular in today's world as people seek out natural remedies. It would be beneficial as if a natural remedy could be used to alleviate possible abnormal changes in blood exert by the COVID-19 viral invasion. In view of that, it is proposed that the extracts of Sri Lankan *Lantana camara* L. (Verbenaceae) could be used against post corona viral haematological complications based on properties it possesses.

Conclusion

There is limited research available to find out the hematological complications and its behavior combining with traditional medicinal plants for COVID-19. In this review, we have created an ideal platform to discuss the possibilities of *Lantana camara* to address against the harmful effects by COVID-19 that leads it to become a future treatment for COVID 19. According to the current reports the situation in Sri Lanka coping up with the COVID-19 becoming critical with the increasing patients. Plenty of Lantana camara plants are available in Sri Lanka and the behavior of these extracts in human blood could well be studied in vitro. Finally, we conclude this review by opening the eyes of medical professionals to engage in research to find out how the traditional plants such as *lantana camara* suppress the harmful conditions caused by COVID-19 in human blood.

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