The Role of *Ganoderma lucidum* Uptake on Some Hematological and Immunological Response in Patients with Coronavirus (COVID-19)

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ABSTRACT

At the end of 2019, the novel coronavirus was discovered to cause pneumonia in Wuhan city in the Hubei Province, China. Later it has caused significant worldwide crises due to its fast transmission between humans, causing a widespread pandemic around the world. 150 patients with COVID-19 were collected from Shirqat hospital, their ages were between 35-55 years. The patients were divided into four groups. as follows: (1) The healthy control group: normal apparently healthy individuals, (2) G. lucidum group: Healthy individuals received G. lucidum orally, (3) COVID-19 Patients: patients infected with COVID-19, (4) Human convalescent plasma: this group treated Human convalescent plasma for intravenous injection, and (5) Patients COVID-19+ *G. lucidum* group: this group after infection and treated with *G. lucidum*, (6) COVID-19 Patients + Human convalescent plasma: this group treated with Human convalescent plasma for intravenous injection. The immunoglobulin (IgG and IgM) were positive in Patients with the COVID-19 group, whereas (IgG) only was positive in Patients COVID-19+G.lucidum and Patients COVID-19+ Human convalescent. The IgM was negative in Patients with COVID-19+G.lucidum and Patients with COVID-19+ Human convalescent groups. The result found that there was a significant change between the study groups (p<0.05) in total white blood cells, there was a less significant increase in G. lucidum group compared with control group. The lymphocyte was significantly decrease for patients with COVID-19 group compared with control group, while significant increase were seen in G. lucidum group and Human convalescent plasma compared with control group and the patients with COVID-19 + *G.lucidum* group results showed a significant increase compared with patients COVID-19 group. The result showed a significant decrease (p<0.05) in Patients with COVID-19 group of Hb, PCV, RBCs, and Platelet compared with the control group and Glucidum group, while there was no significant change in the Glucidum group and Human convalescent plasma group compared with the control group. Convalescent plasma together with the hyperimmune immunoglobulin have appositive effects on treating the COVID-19, as well as the G. lucidum has a great significant role in reducing the COVID-19 malicious effect on the studied hematological parameters. G. lucidum can be used to help in the treatment of COVID-19 infections.

INTRODUCTION

Coronaviruses (CoVs) are a group of RNA viruses that enveloped with a protein coat. it belongs to the Coronaviridae family of the Nidovirales order. CoVs were identified as a zoonotic that signifies its ability to transmit from animals to humans and cause a wide range of viral diseases. These infections appear as diverse symptoms ranging from the common cold to fatal diseases, such as enteric and central nervous system diseases, as well as respiratory syndrome. Two members of the COV family microorganisms have been caused two outbreaks in the past few years, the Severe Acute Respiratory Syndrome (SARS), and the Middle East Respiratory Syndrome (MERS). In 2002, SARS was identified in southern China, as for MERS was identified in Saudi Arabia for the first time in 2012. (Nakarin et al.,2020; Zhu et al.,2020).

At the end of 2019, the novel coronavirus was discovered to cause pneumonia, it has been designated as SARS CoV-2 at the beginning, in Wuhan city in the Hubei Province, China (Xu et al.,2020). It subsequently spread over China

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and the world to be a global health emergency. at the beginning of 2020 in February, the SARS-CoV-2 has been labeled as the 2019-nCoV by the World Health Organization (WHO). The 2019-nCoV infection mortality was recorded to be around 2% in China, less than that of MERS and SARS infection. Yet, it has caused significant worldwide crises due to its fast transmission between humans, causing a widespread pandemic around the world (Xu et al.,2020; WHO, 2020).

At the current time, there is no specific medication against this novel virus, supporting the organs of the symptomatic severely ill individuals are the main steps of the clinical treatment, however, some drugs have been used to restrain acute respiratory distress syndrome (ARDS) alongside the supplement. the recovered People developed natural immune defenses (antibodies) against the disease in their plasma (Yuan et al.,2020).

Ganoderma lucidum has been used widely in the east over the history for health promotion in Iraq, Japan, China, and other Asian countries. Itis a large, dark fungus that has a glossy exterior with a woody texture. (Moncalvo, 2000). The Ganodermataceae family described as a polypore basidiomycetous fungi with a basidiospore surrounded with a double-walls (Donk 1964). Ganoderma species contained protein, fats, carbohydrate, fiber, vitamins, and ash minerals such as with calcium, potassium, magnesium, phosphorus, iron, selenium, copper, and zinc (Borchers et al. 1999; Al-dulaimi et al., 2020). Some protease inhibitors of the virus have been isolated from some fungi strains. Lingzhi fungi (the chines designation for Ganoderma species) were acknowledged as a dietary supplement around the world because they have an attachment with long-term health safety and they own a wide range of medical properties (Nakarin et al., 2020). In addition, these fungi have a wide variety of biologically active molecules, like steroids, terpenoids, nucleotides, their derivatives, glycoproteins, phenols, and peptidoglycans, triterpenes, and polysaccharides. the proteins of these fungi hold all of the essential amino acids especially the lysine and leucine. The high content of the polyunsaturated fatty acids and the low proportion of the total fat contributes significantly to these fungi health value (Chang and Buswell 1996; Sanodiya et al. 2009; Abd-Alwahab and Al-dulaimi,2018: Zhou et al. 2007). Therefore, we aimed to evaluate the role of Ganoderma lucidum uptake on some hematological and immunological response in patients in patients with coronavirus.

Materials and Methods

Design of experiments

The study patients with COVID-19 were collected from Shirqat hospital. The plasma was collected from infected patients with COVID-19 and convalescent plasma were collected from the healed individuals after infection. G.lucidum was obtained from (DXN Company, Malaysia). The study performance period ranged from between April-June 2020. 150 patients, their ages were between 35-55 years, were divided into four groups. as follows: (1) The healthy control group: normal apparently healthy individuals, (2) G.lucidum group: Healthy individuals received *G.lucidum* orally (0.3g/1kg of body wt.), (3) COVID-19 Patients: patients infected with COVID-19, (4) Human convalescent plasma: this group treated Human convalescent plasma for intravenous injection (100µl /1kg of body wt. period 5 days), and (5) Patients COVID-19+G.lucidum group: this group after infection and treated with G.lucidum (0.3g/1kg of body wt.) daily for (10) days, (6) COVID-19 Patients + Human convalescent plasma: this group after infection and treated of Human convalescent plasma for intravenous injection (100µl /1kg of body wt. period 10 days). After the end of the experiment, blood was collected from all the study subjects via median cubital for laboratory analysis. Blood samples were analyzed using ELISA covid-19 test and complete blood count (CBC) by used Auto-hematology analyzer device, (Model: SPINAL3, Japan) (Haen, 1995; Aldulaimi et al.,2019; Yuan et al.,2020).

Statistical Analysis

The ANOVA analysis was used for the study data analyzed using the general linear model of the Statistically Analysis System (SAS). the level of significance was evaluated by using Duncan's multiple range test (Duncan,1955), and the significance level was P<0.05.

Results and Discussion

The results (Table 1) showed that immunoglobulin (IgG and IgM) were positive in Patients with the COVID-19 group, whereas (IgG) only was positive in Patients COVID-19+G.lucidum and Patients COVID-19+ Human convalescent. The (IgM) was negative in Patients with COVID-19+G.lucidum and Patients with COVID-19+Human convalescent groups. This positive result of immunoglobulin in Patients with COVID-19+G.lucidum and Patients COVID-19+Human convalescent groups. This positive result of immunoglobulin in Patients with COVID-19+G.lucidum and Patients COVID-19+ Human convalescent groups may be due to G.lucidum content many compounds that have inhibitory effects versus the protease activity of the COVID-19 including 3β -5 α -dihydroxy-6-methoxyergosta-7,22-diene, ganolucidic acid β , ganoderic acid A–C, ganodermanontriol, ganodermanondiol and lucidumol B (Lee et al.,1999; Li .,2005).

 Table 1. Effect of G.lucidum on IgG and IgM in Patients

 COVID 19

| Groups | Result | | | |
|--|--------|-------|--|--|
| | IgG | IgM | | |
| Control | 0.000 | 0.000 | | |
| G. lucidum | 0.000 | 0.000 | | |
| Patients COVID-19 | 2.300 | 6.200 | | |
| Human convalescent plasma | 0.012 | 0.017 | | |
| Patients COVID- 19+ <i>G.lucidum</i> | 5.200 | 0.080 | | |
| Patients COVID-19+ Human convalescent | 7.120 | 0.060 | | |

* Positive >0.1

* Negative<0.1

Table 2 showed the effects of *G.lucidum* on total and differential white blood cells in Patients. The result found that there was a significant changes between the study gropes (p<0.05) in total white blood cells, there was a less significant increase in *G.lucidum* group compared with control group. The differential white blood cells showed significant different in all groups, lymphocyte was significantly decrease for patients with COVID-19 group compared with control group, while significant increase were seen in *G.lucidum* group and Human convalescent plasma compared with control group and the patients COVID-19 + *G.lucidum* group results showed a significant increase compared with patients COVID-19 group.

Table 2. Effect of *G.lucidum* on Total and Differential white blood cells in Patients COVID-19.

| Parameter | Total ×10 ³ cell/mm ³ | Lymphocytes % | Monocytes % | Neutrophils % | Eosinophil % | Basophil % |
|------------|--|------------------|-------------|---------------|--------------|------------|
| Group | | | | | | |
| Control | 9.00±0.17 | 25.00±0.20 | 7.90±0.09 | 64.10±0.19 | 2.20±0.11 | 0.80±0.06 |
| | е | b | а | D | С | bc |
| G. lucidum | 9.20±0.11 | 28.10±0.12 | 8.20±0.20 | 61.80±0.32 | 1.22±0.24 | 0.65±0.10 |
| | d | а | а | Е | d | С |

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| Patients COVID- | 17.4±0.13 | 12.30±1.70 | 4.30±0.15 | 78.38±0.27 | 3.20±0.10 | 1.82±0.08 |
|-----------------|-----------|------------|-----------|------------|-----------|-----------|
| 19 | а | е | С | А | а | а |
| Human | 9.40±0.10 | 27.50±0.90 | 8.00±0.21 | 60.30±0.37 | 2.00±0.13 | 2.20±0.23 |
| convalescent | d | а | а | Е | С | а |
| plasma | | | | | | |
| Patients COVID- | 12.0±0.18 | 18.20±1.00 | 6.20±0.10 | 72.1±0.11 | 2.50±0.16 | 1.00±0.30 |
| 19+G.lucidum | С | d | b | В | bc | b |
| Patients COVID- | 13.1±0.12 | 21.30±0.17 | 6.50±0.22 | 68.2±0.23 | 2.70±0.21 | 1.30±0.07 |
| 19+ Human | b | С | b | С | b | b |
| convalescent | | | | | | |

*Different of letters mean significant difference at the level of significance (P<0.05).

The total white blood cells significant increase may have resulted from COVID-19 infection caused an inflammatory response, while the significant change for G.lucidum group was due to the contents of G.lucidum composition of polysaccharides that are responsible for immune activities-modulation that include phagocytic activity stimulation which in turn act as mediators of inflammation, and production of cytokine (Sadava et al.,2009; Saltarelli et al.,2009), The biologically active terpenoids in G. lucidum have been used widely used to treat many diseases as an antiviral.. (Sanodiya et al.,2009). These components express anti-infective and immunomodulating effects (Sato et al.,1986; Shang et al.,2009).

Most viruses infect animals and humans causing lymphocytosis because lymphocytes are the effector cells that fighting virus [Zhu et al.,2013]. The coronavirus family MERS, SARS, and SARS-CoV-2 all caused a decrease in a lymphocyte in the infected human (Rabaan et al.,2020; Al-Tawfiq et al.,2017), the mechanism of that may be due to the direct attack on lymphocytes by coronavirus or through apoptosis of lymphocytes (Chu et al.,2016; He et al.,2005).

several fungus species found to release immunomodulators, like G. lucidum. Flammulina velutipes, and Agaricus bisporus. G.lucidum was proved to produce a fungal immunomodulatory protein (FIP), these proteins have been used to repress the respiratory syncytial virus (RSV), which causes bronchiolitis. RSV replication, inflammation, and IL-6 expression were effectively decreased by FIP-fve by NF-B translocation inhibition and respiratory pathogenesis in mice infected with RSV. Interestingly, FIP-fve may be considered as a safe product to prevent viral infection and disease therapy (Chang et al., 2014). Immunomodulator proteins proved to be effective agents in relieving the pathological signs related to viral infections (Malemud, 2018). Table 3 showed the effects of G.lucidum on Hb, Pcv, RBCs, and Platelet in the study groups. The result showed a

and Platelet in the study groups. The result showed a significant decrease (p<0.05) in Patients with COVID-19 group of Hb, PCV, RBCs, and Platelet compared with the control group and G.lucidum group, while there was no significant change in the G.lucidum group and Human convalescent plasma group compared with the control group, also the result showed a significant increase in Patients with COVID-19 +G.lucidum group compared with HpCoV-19.

| Parameter | Hb g/dl | Pcv % | RBCs×10 ⁶ | Platelet ×10 ³ |
|---------------------------|-----------|---------|----------------------|---------------------------|
| Groups | 0, | | cell/mm ³ | cell/mm ³ |
| Control | 14.0±0.19 | 46±0.10 | 6.50±0.32 | 300.0±2.13 |
| | а | а | а | С |
| G. lucidum | 14.3±0.10 | 47±0.13 | 6.70±0.25 | 312.0±3.01 |
| | а | а | а | b |
| Patients COVID-19 | 12.8±0.20 | 42±0.21 | 5.00±0.16 | 145.0±0.91 |
| | С | С | С | f |
| Human convalescent plasma | 14.4±0.26 | 47±0.27 | 6.60±0.10 | 323.0±2.30 |
| | а | а | а | а |
| Patients COVID- | 13.6±0.09 | 45±0.10 | 5.75±0.28 | 159.0±1.93 |
| 19+G.lucidum | b | ab | а | е |
| Patients COVID-19+ Human | 13.5±0.17 | 44±0.25 | 5.70±0.23 | 200.0±1.20 |
| convalescent | b | ab | а | d |

Table 3. Effect of *G.lucidum* on Hemoglobin, Packed cell volume, Red Blood Cells and platelet in Patients COVID-19.

*Different of letters mean significant difference at the level of significance (P<0.05).

The G. lucidum includes enzymes and compounds like metalloprotease, nucleosides; nucleotides, and ergosterol (provitamin D2) that may result in a significantly increase in the hemoglobin, red blood cell, platelet counts of G.lucidum and Patients COVID-19 + G.lucidum groups. (Wasser,2005; Paterson,2006). Also, the novel 114-kDa hexameric lectin was isolated from the G. lucidum fruit body and mycelium which was revealed to be a glycoprotein with 9.3% neutral sugar and possess a hemagglutinating activity on human erythrocytes treated with proteinase. (Thakur et al. 2007).

The significant decrease in the platelet counts hemoglobin, red blood cell, of COVID-19 groups, is suggesting that the infection significantly inhibited the patients' hematopoiesis in the bone marrow (Prilutskiy et al.,2020).

Conclusions

Convalescent plasma together with the hyperimmune immunoglobulin have appositive effects on treating the COVID-19, as well as, the G. lucidum has a great significant role in reducing the COVID-19 malicious effect on the studied hematological parameters, as a result, G.

lucidum can be used to help in the treatment of COVID-19 infections.

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