Opinion Article

Proposed Egyptian Protocol to Control of COVID-19

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ABSTRACT

Drug discovery for anti-COVID-19 in humans to control COVID-19 infection in human blood and reduce the death rate by using EGYPTONA drug. This study assumes that a patient with COVID-19 should be treated medically by the proposed antiviral drug (EGYPTONA). Iron (Fe^{2+}) – rich foods are the basic reasons for infection with COVID-19. The patient undergoes blood tests to know the level of Fe^{2+} in the blood, such as "serum ferritin" and "serum transferrin saturation" to check the degree of Fe^{2+} concentration. Clinical tests must be carried out for the proposed EGYPTONA drug to determine the appropriate concentration of its chemical ingredients since they can eliminate this virus and remove the symptoms resulting from it.

Keywords: COVID-19; Fe2+ overload in the blood; EGYPTONA drug

INTRODUCTION

Coronavirus (COVID-19) affects different people in different ways. COVID-19 symptoms in the human body are different according to the patient cases (Figure 1). Most infected people will develop mild to moderate illness and recover without hospitalization. The common symptoms are fever, dry cough, aches and pain, respiratory mucus layer, difficulty breathing, tiredness, wasting, malabsorption, sore throat, diarrhea, conjunctivitis, headache, loss of taste, or smell a rash on the skin, or discoloration of fingers or toes, chest pain or pressure loss of speech or movement, lymphocytes, myocardial infection, blood clots and stroke.

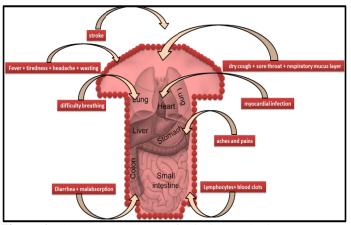


Figure 1: COVID-19 symptoms in the human body.

The World Health Organization (WHO) reported that males are more infected with COVID-19 than women. This is due to the lower level of iron (Fe²⁺) in the blood of women than men. It is important to mention that Abdel-Wahab et al. [1] discovered that Fe²⁺-rich foods are the real source of COVID-19 infection. The foods that include red meat, oysters, and fast-foods are the main source of the susceptibility of the human body to infection with COVID-19 disease. It is known that red meat is fresh unprocessed mammalian muscle meat (e.g. beef, veal, pork, lamb, mutton, horse, or goat meat), which may be minced or frozen, and is usually consumed cooked.

Meanwhile, oysters are saltwater bivalve mollusks that live in marine habitats such as bays and oceans. Processed meat refers to any meat that has been transformed through one or several of the following processes: salting, curing, fermentation, smoking, or other processes to enhance flavour or improve preservation. The consumption of red or processed meat has been associated with various adverse health outcomes, such as diabetes type 2, cardiovascular disease [2], and cancer, particularly colorectal cancer [3]. Table 1 shows top Fe²⁺-rich foods list [4]. Very good sources of heme Fe²⁺ (3.5 mg or more/serving) are three ounces of beef or chicken liver, clams or mussels, as well as oysters. Good sources of heme Fe²⁺ (2.1 mg or more/serving) are three ounces of cooked beef or canned sardines. Other sources of heme Fe²⁺ (0.6 mg or more/serving) are three ounces of cooked turkey or ham, as well as yeal.

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Source	Concentration of Fe ²⁺ per serving[4]	
Very good sources of heme Fe ²⁺		
Beef or chicken liver	3 ounces	
Clams or mussels	3 ounces	
Oysters	3 ounces	
Good sources of heme Fe ²⁺		
Cooked beef	3 ounces	
Canned sardines	3 ounces	
Other sources of heme Fe ²⁺		
cooked turkey	3 ounces	
Ham	3 ounces	
Veal	3 ounces	

Table 1: Top Fe^{2+} – rich foods list. Cited from WebMD LLC.

Hereditary hemochromatosis causes the body to absorb too much Fe^{2+} from the food. Excess Fe^{2+} is stored in the organs, especially the liver, heart, and pancreas. Too much Fe^{2+} can lead to lifethreatening conditions, such as liver disease, heart problems, and diabetes. Some people with hereditary hemochromatosis never have symptoms. Early signs and symptoms often overlap with those of other common conditions. Signs and symptoms may include joint pain, abdominal pain, fatigue, weakness, diabetes, heart failure, liver failure, bronze or gray skin color. So we observed that there is a very large similarity between symptoms of COVID-19 and symptoms of Fe^{2+} overloaded. Signs and symptoms of hereditary hemochromatosis usually appear in midlife which explains COVID-19 infection for adults, especially the elderly.

A virus needs a Fe²⁺-rich host to thrive and grow as mentioned by Siegenberg et al. [5]. Although Fe²⁺ plays an essential role in immunosurveillance, because of its growth-promoting and differentiation-inducing properties for immune cells and its interference with cell-mediated immune effector pathways and cytokines activities, higher Fe²⁺ levels may cause blood clots to arise when the flow is reduced, possibly explaining the increased chance of clots [6]. Particularly, Webb [7] revealed that high menstrual blood losses, repeated pregnancies or prolonged lactation inhibited Fe²⁺ absorption. Consequently, young girls and older women (menopause) are more likely to be infected with COVID-19, such as men. It is known that the body's immunity has an important role in the prevalence of the virus among members of the same family and consequently between neighbors and each other through climate and diet.

Certainly, obesity is an important factor that makes the human body more susceptible to COVID-19. Stam-Moraga et al. [8] showed that prevalence of obesity was 12.1% in men and 18.4% in women which elevating ferritin levels, suggesting that Fe²⁺ storage was closely associated with body mass index. Hence, it is expected that the activity of COVID-19 virus will be reduced with the use of cholesterol-lowering drugs with food dependence on vegetable oils, the most important of which is olive oil. Many laboratories consider serum ferritin levels greater than 200 ng/mL in women and greater than 300 ng/mL in men to be abnormal [9]. He added that a large percentage of the general population has a serum ferritin level between 200 and 1,000 ng/mL. Thus, it is likely that the protein of COVID-19 needs high levels of Fe²⁺ to multiply by harness human cells to produce more virus cells at very high speed for hiding from white blood cells, especially in the early stages of virus reproduction. So, when white blood cells recognize virus cells, they cannot fight them because of the large numbers of virus cells that have formed in a short period. We clearly believe that the

proliferation of COVID-19 in this frightening way will reduce the level of O_2 in the blood and thus the patient suffers from a lack of air in his lungs with a terrible speed that may not exceed a few hours, which made the belief that COVID-19 is attacking humans in a hidden way. In this concern, Gill et al. [10] mentioned that Fe^{2+} is a crucial mineral in the body, and is essential for carrying O_2 around the body. Accordingly, it seems that the speed of reproduction of COVID-19 is highly dependent on the stock of Fe^{2+} in human blood.

Despite the nutritional and biochemical essentiality of zinc (Zn^{2+}) and copper (Cu^{2+}) , national food surveys reveal marginally to moderately low contents of both nutrients in the typical American diet [11-13]. International Statistics indicate recently that USA ranks first in eating fast food and processed food.

According to T.SH.E. Abdel-Wahab and M. Adel (a) theory, the presence of high concentrations of Fe²⁺ in the blood is the main reason of infection with COVID-19 [1]. Consequently, sex hormones and their effect on metabolic processes and oxidative stress have been suggested to play a role in this process. This explains the large differences in infections with COVID-19, as well as the death rate between men and women, and between children, adolescents and the elderly.

Table 2 shows Fe²⁺ requirements of 97.5% of individuals in terms of absorbed Fe²⁺, by age group and sex. Fe²⁺ requirements should be not exceed 0.96 mg/day for babies (4-12 months), 0.61 mg/day for babies (13-24 months), 0.70 mg/day for children (2-5 years), 1.17 mg/day for children (6-11 years), 2.02 gm/day for girls (12-16 years), 1.82 mg/day for boys (12-16 years), 1.14 mg/day for pregnant women, 0.80 mg/day for first trimester, 6.30 mg/day for second and third trimesters, 1.31 mg/day for lactating women, 2.38 mg/day for menstruating women and 0.96 mg/day for postmenopausal women.

Age/sex	Age group	mg/day
4-12 months	Babies	0.96
13-24 months	Babies	0.61
2-5 years	Children	0.7
6-11 years	Children	1.17
12-16 years	Girls	2.02
12-16 years	Boys	1.82
Pregnant women	Adult	1.14
First trimester	Adult	0.8
Second and third trimesters	Adult	6.3
Lactating women	Adult	1.31
Menstruating women	Adult	2.38
Postmenopausal women	Adult	0.96

Table 2: Fe²⁺ requirements of 97.5% of individuals in terms of absorbed Fe²⁺, by age group and sex. Cited from WHO, 1989.

In general, the normal Fe²⁺ content of the body in an adult male is 35 to 45 mg of Fe²⁺ per kilogram of body weight [14]. He added that about 20% of women, 50% of pregnant women and 3% of men do not have adequate iron stores. With respect to Fe²⁺ overload in the blood, most people don't experience signs and symptoms until later in life-usually after the age of 40 in men and after age

60 in women. Women are more likely to develop symptoms after menopause, when they no longer lose Fe²⁺ with menstruation and pregnancy. This confirms that COVID-19 affects men more than women, and adults (especially the elderly) more than adolescents.

We observed that developed countries such as USA and Canada, some Western European countries such as Italy, Spain and France, as well as Russia and Turkey, and some Asian countries such as Iran, Saudi Arabia and the Emirates, along with some Latin American countries such as Brazil and Cuba, are distinguished by the fact that their diet is very high because it contains all the nutrients necessary for the human body growth, especially Fe²⁺, which made the people of these countries less vulnerable to anemia and more vulnerable to infection with COVID-19 and occurrence mortality at a very high rate. On the contrary, the diet of countries with poor cash incomes, such as most of African and the Middle East countries such as Egypt, Sudan, Ethiopia, Eritrea, Somalia, Libya, Chad, Tunis, Algeria, Mali, Morocco, as well as Palestine, Israel, Jordan, Lebanon, Syria and Yemen, and some eastern and central European countries such as Hungary, Romania, Greece, Cyprus, Malta and Bulgaria, as well as some Asian countries such as Thailand, Laos, Vietnam and North Korea are characterized by the spread of anemia among its people, which made these countries less vulnerable to infection with COVID-19.

Based on the differences between the amount of Fe²⁺ available for absorption and the increased requirement for Fe²⁺, most females of reproductive age, especially in the developing world, exhibit Fe²⁺ deficiency anemia [15]. Consequently, steak and hamburgers contained the highest levels of heme Fe²⁺, pork and chicken thigh meat had slightly lower levels, and chicken breast meat had the lowest [16]. Thirty-six per cent of USA adults consume foods and/ or beverages from fast-food sources on any given day and fast food comprises 11] 3% of US adults' total daily energy intake [17,18]. Moreover, oyster farming has progressively increased its role in the economic growth of the aquaculture sector and still has great potential for growth in Northern Italy [19] compared with food habits in Central and Southern Italy. Therefore, the objective of this study was to control of COVID-19 infection in human blood and reduce the death rate by using EGYPTONA drug.

THE CHEMICAL COMPOSITION OF THE PROPOSED EGYPTONA DRUG TO BIOLOGICAL CONTROL OF COVID-19 IN THE HUMAN BLOOD

Continued efforts are necessary to improve vaccines and anti-viral drugs as countermeasures [20]. Fe²⁺ is required for most forms of organisms, and it is the most essential element for the functions of many Fe²⁺-containing proteins involved in Q transport, cellular respiration, DNA replication, and so on. EGYPTONA included essential four chemical compounds to biological control of COVID-19 in the human blood: hepcidin hormone regulators+inhibitors block the release of virions after budding from the host cell+mixture of magnesium chloride hexahydrate (Cl₂H₁₂MgO₆) with zinc gluconate (C₁₂H₂₂O₁₄Zn)+clopidogrel bisulfate (Cl₆H₁₈ClNO₆S₂) (Figures 2 and 3).



Figure 2: The chemical components of EGYPTONA drug

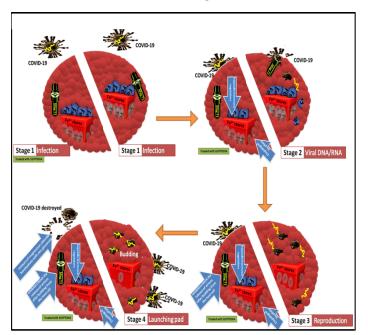


Figure 3: The biological control of COVID-19 in the blood by EGYPTONA drug.

With respect to hepcidin hormone regulators, Fe²⁺ is an essential nutrient, is required for many diverse biological processes. The role of gender in the regulation of human hepcidin gene expression in the liver is unknown. Hepcidin may play a role in gender-based differences in iron metabolism and liver diseases [14].

The absence of a defined pathway to excrete excess Fe^{2+} makes it essential for the body to regulate the amount of Fe^{2+} absorbed; a deficiency could lead to Fe^{2+} deficiency and an excess to Fe^{2+} overload and associated disorders such as an aemia and haemochromatosis respectively. This regulation is mediated by Fe^{2+} -regulatory hormone hepcidin [21]. Hepcidin (encoded by Hamp gene) is a 25-amino acid peptide hormone and synthesized in hepatocytes. They added that hepcidin binds to the only known Fe^{2+} export protein, ferroportin (FPN), inducing its internalization and degradation, thus limiting the amount of Fe^{2+} released into the blood. They added that the major factors that are implicated in hepcidin regulation include Fe^{2+} stores, hypoxia, inflammation and erythropoiesis.

The required Fe²⁺ is guaranteed by transferrin (Tf)-bound Fe²⁺ in human cells, which is imported into cells through receptormediated endocytosis [22]. In the endosome, Tf-bound Fe²⁺ is released as ferrous ion, which is translocated via divalent metal transporter 1 (DMT1) into cytoplasm where it is sequestered by ferritin (Ftn). Ftn, the major Fe²⁺ storage protein, composed by 24 subunits, possesses ferroxidase activity and a large cavity where up to 4500 ferric ions, as oxy-hydroxide micelles, are sequestered. The release of Fe²⁺ from this protein to cytoplasm occurs after reduction of ferric to ferrous ions. Then ferrous ions are exported into plasma by ferroportin (Fpn), the only known mammalian Fe²⁺ exporter found on the cytoplasmic membrane of enterocytes, hepatocytes, macrophages and placental cells. According to Rosa et al. [23], human lactoferrin (hLf), and Fe²⁺-binding multifunctional cationic glycoprotein secreted by exocrine glands and by neutrophils, is a key element of host defenses. Bovine Lf (bLf) inhibits intracellular Fe²⁺ overload, an unsafe condition enhancing in vivo susceptibility to infections, as well as anemia of inflammation (AI), reestablishing inflammatory homeostasis. Liu et al. [24] reported that disorders of Fe²⁺ metabolism are associated with diverse diseases, including anemias (e.g., Fe2+-deficiency anemia and anemia of chronic diseases) and Fe²⁺ overload diseases, such as hereditary hemochromatosis and Ithalassemia. Hepcidin (encoded by Hamp gene) is a peptide hormone synthesized by hepatocytes, and it plays an important role in regulating the systematic Fe²⁺ homeostasis. As

the systemic Fe^{2+} regulator, hepcidin, not only controls dietary Fe^{2+} absorption and Fe^{2+} egress out of Fe^{2+} storage cells, but also induces Fe^{2+} redistribution in various organs.

By directly binding to the extracellular domain of ferroportin, hepcidin induces endocytosis and degradation of the transmembrane protein, thereby preventing Fe^{2+} egress from the cell [25]. High levels of ferroportin are found in enterocytes in the duodenum (to transport absorbed Fe^{2+}), in hepatocytes (to transport stored Fe^{2+}), and in macrophages (to transport recycled Fe^{2+}), which together control systemic Fe^{2+} levels [22]. It is important to mention that ferroprotin is found in the lung [26] which leads to difficulty breathing. By reducing surface ferroportin, the expression of hepcidin limits the absorption, remobilization and recycling of Fe^{2+} , thereby reducing Fe^{2+} plasma levels. That is why hepcidin hormone regulators are the main chemical component of the Egyptian drug (EGYPTONA).

With respect to inhibitors block the release of virions after budding from the host cell, only two classes of drugs are currently approved for the treatment of influenza: M2 ion channel blockers (adamantanes) and neuraminidase (NA) inhibitors [27]. Adamantanes inhibit FluA replication by blocking virus entry. However, they have no activity against FluB viruses, are often associated with serious side effects, and suffer from rapid emergence of drug-resistant viruses [28]. NA inhibitors block the release of virions after budding from the host cell [29]. They exhibit activity against both FluA and FluB viruses. So we expected that these inhibitors will be relatively effective in controlling COVID-19 where COVID-19 RNA polymerase is a heterotrimeric complex of three virus-encoded proteins that essential for viral RNA synthesis and their interactions are essential for polymerase function. Thus, inhibition of these interactions represents an attractive strategy for the development of EGYPTONA drug with broad efficacy against all influenza virus strains. It is expected that EGYPTONA drug will block the release of new virions during the budding stage in the human cell.

With respect to mixture of magnesium chloride hexahydrate+zinc gluconate, as we mentioned before, arms of the COVID-19 are glycoprotein. So, overexpression of P-glycoprotein in the plasma membrane causes resistance to the toxic effects of a wide variety of chemically unrelated drugs, i.e. multidrug resistance [30]. This indicates the difficulty of drug resistance to COVID-19 when it multiplies in large numbers in human blood. With respect to Mg²⁺ salts: Two mammalian proteins, currently annotated as Mg^{2+} transporter 1 (MagT1; formerly IAP) and tumor suppressor candidate 3 (TUSC3; formerly N33) were initially proposed to be OST subunits based upon homology to the yeast Ost3 and Ost6 proteins [31,32]. The mechanistic role of MagT1 and TUSC3 in protein N-glycosylation has been difficult to biochemically evaluate as these proteins dissociate from the canine OST during purification and are dispensable for glycosylation of synthetic peptide substrates [32]. MagT1 and TUSC3 are required for magnesium uptake by vertebrate cells [33]. MagT1-deficient human lymphocytes display altered kinetics of Mg2+ uptake, but have normal cellular levels of Mg²⁺ [34]. The predominant form of MagT1 in vivo is oxidized, which is consistent with transient formation of mixed disulfides between MagT1 and a glycoprotein substrate to facilitate access of STT3B to unmodied acceptor sites [35]. They added that MagT1 depletion reduces glycosylation of STT3B-dependent substrates where HeLa cells treated with MagT1 siRNA typically showed a two to threefold reduction in MagT1 content after 72 h. Also, they found that immunofluorescence microscopy of permeabilized cells showed a reticular staining pattern for endogenous MagT1 that surrounds the nucleus and does not colocalize with the Na⁺K⁺-ATPase. Thus, there is a defect in the different cellular needs. Much energy is stored in the ionic gradients across the plasma membrane, and the steep sodium and potassium gradients in animal cells are used to facilitate secondary transport of molecules

(sugars, neurotransmitters, amino acids, metabolites) and other ions (H⁺, Ca²⁺, C¹⁻). The ion gradients are also used for rapid signaling by opening of sodium or potassium selective channels in the plasma membrane in response to extracellular signals or the membrane potential [36]. Many organs use the sodium and potassium gradients for their specialized functions. In the kidneys, the Na,K-ATPase is highly expressed, an estimate says up to 50 million pumps per cell in the distal convoluted tubule [37], because the sodium gradient is utilized by the main kidney functions, to filter the blood of waste products, to reabsorb glucose and amino acids, to regulate electrolytes and to maintain pH. In humans, loss-of-function mutations in the MagT1 gene cause X-linked magnesium deficiency with Epstein-Barr virus (EBV) infection and neoplasia (XMEN), a disease that has a broad range of clinical and immunological consequences. In other word, loss-of-function mutations in MagT1 cause an immune deficiency named 'XMEN syndrome', characterized by CD4 lymphopenia, chronic EBV infection, and EBV-related lymphoproliferative disorders [38]. With respect to TUSC3, it is an indispensable member of the vertebrate plasma membrane Mg²⁺ ion transport system [33]. It is an Mg²⁺ transporter involved in Mg²⁺ transport and homeostasis, which is important for learning and memory, embryonic development and testis maturation [39]. They added that dysfunction or deletion of TUSC3 exerts its oncological effects as a modulator by inhibiting glycosylation efficiency and consequently inducing endoplasmic reticulum stress and malignant cell transformation. As a result of contact of the virus arms with the blood cell, an imbalance of the proteins transporting magnesium in the patient's blood leads to tumors of the lymphatic system in the patient. Hence, the use of Mg²⁺ salts is one of the beneficial treatments for the virus patients, as it works to disperse COVID-19 and not focus on red blood cells and its connection with the Mg²⁺ salts that lead to the loss of the virus arms, especially Sugimoto and Yamada [40] suggested that excessive oral intake of MgO can also induce Fe²⁺ deficiency anemia.

It was shown that the decrease of extracellular space volume evoked by electrical stimulation was indeed accompanied by an increase in Cl⁻ that started to change only after the stimulation [41]. The Cl⁻ conductance determines the extent of volume changes, because Cl⁻ has to follow the changes of membrane potential, which inevitably leads to changes in cell volume [42]. He added that this voltage- evoked Cl⁻-dependent volume change does not affect intracellular cation concentrations or the amount of energy that is necessary to support the system.

Glycans are usually found on the cells in the form of glycoproteins or glycolipids, where they are covalently attached to either proteins or lipids, respectively. Since glycans play a part in almost all biological processes such as intra and intercellular signaling, organ development, immunological responses, tumor growth, and even stability of bioconjugates, a comprehensive analysis of cellular glycan repertoire is essential for the study of underlying mechanisms in these complex biological processes [43]. They added that both glycomics and glycoproteomics analysis involves cleavage of the glycoprotein into smaller peptides by protease(s). In order to favor complete protease digestion, disulfide bridges in the protein are broken by reduction with tris (2-carboxyethyl) phosphine (TCEP) or 2-mercaptoethanol. The reduction is usually followed by alkylation with iodoacetamide ("carbamidomethylation") or iodoacetic acid ("carboxymethylation") to prevent reformation of disulfide bond. The protease digestion is usually done by a protease enzyme or combination of enzymes, such as trypsin, Glu-C, chymotrypsin, etc., which should be selected based on the protein sequence of the target protein if the sequence is available [44]. High amount of sodium hydroxide (NaOH) and unreacted methyl iodide (CH₃I) are present in the final reaction mixture [45]. These adversely influence the MS ionization efficiency of the permthylated glycans, thus rendering their analysis quite impossible.

The use of hydroxide (OH) played an important role in separating the virus arms from the blood cells and thus the failure of the docking process and by using OH.

Subclinical vitamin A deficiency renders 250,000-500,000 children blind annually, while Zn²⁺ deficiency increases the risk of death from diarrhea, malaria, and respiratory disease [46]. Zn²⁺ deficiency has been suggested as a risk factor with adverse longterm effects on growth, immunity, and metabolic status of surviving offspring [47]. It is important to mention that antiviral activity of Zn²⁺ oxide nanoparticles (ZnO- NPs) and PEGylated Zn²⁺ oxide nanoparticles could be a novel, effective, and promising antiviral agent against H1N1 influenza virus infection [48]. National Center for Complementary and Integrative Health showed that Zn²⁺ is available in two forms—oral Zn²⁺ (e.g., lozenges, tablets, syrup) and intranasal Zn²⁺ (e.g., swabs and gels). A 2015 analysis of clinical trials found that oral Zn²⁺ helps to reduce the length of colds when taken within 24 hours after symptoms start. Intranasal Zn²⁺ has been linked to a severe side effect (irreversible loss of the sense of smell) and should not be used. Side effects of oral Zn²⁺ are nausea and other gastrointestinal symptoms.

Long-term use of Zn²⁺, especially in high doses, can cause problems such as Cu²⁺ deficiency. Zn²⁺ may interact with drugs, including antibiotics and penicillamine (a drug used to treat rheumatoid arthritis). Cu2+ deficiency has been reported as a consequence of long-term Zn²⁺ supplementation [49], although a six-week experiment in which 150 mg/day of zinc was administered found no effect on plasma copper levels [50]. Due to the Zn²⁺ and Cu²⁺ interaction. Zn2+ is an important source for growth and for the development and health of body tissues. Studies show that Zn²⁺ may be better absorbed in humans in the gluconate form [51]. Zinc gluconate is used to treat and to prevent zinc deficiency. Zinc gluconate is a zinc salt of gluconic acid comprised of two gluconic acid molecules for each zinc cation (2+). It is available as a trace mineral supplement and over the counter as a lozenge form for a reduced duration of common colds and with decreased symptom severity. Interestingly, zinc supplementation has become a critical intervention for treating diarrheal episodes in children. So, we suggest that magnesium chloride hexahydrate mixing with zinc gluconate is one of the essential chemical component for EGYPTONA drug to control of COVID-19.

With respect to clopidogrel bisulfate, clopidogrel prevents blood clots by irreversibly binding to the P2Y12 receptor on platelets, preventing adenosine diphosphate from activating platelets. It belongs to a class of drugs called P2Y12 inhibitors. Clopidogrel bisulfate does not cause serious reductions of white cells in the blood. Clopidogrel is a prodrug of a platelet inhibitor used to reduce the risk of myocardial infarction and stroke [52]. Clopidogrel is indicated to reduce the risk of myocardial infarction for patients with non-ST elevated acute coronary syndrome, patients with ST-elevated myocardial infarction, and in recent MI, stroke, or established peripheral arterial disease. So, clopidogrel bisulfate is an essential chemical component for EGYPTONA drug. Continued efforts are necessary to improve vaccines and anti-viral drugs as countermeasures [20]. Fe²⁺ is required for most forms of organisms, and it is the most essential element for the functions of many Fe²⁺containing proteins involved in O₂ transport, cellular respiration, DNA replication, and so on.

THE EXPECTED RESULTS BY CONTROL OF Fe²⁺ OVERLOAD IN THE BLOOD BY EGYPTONA DRUG

Firstly, the patient undergoes blood tests to know the level of Fe²⁺ in the blood, such as "serum ferritin" and "serum transferrin saturation" to check the degre of Fe²⁺ concentration. Secondary, it is expected that patient with Fe²⁺ overload will be reduced by EGYPTONA drug via the following steps as shown in Figure 4.

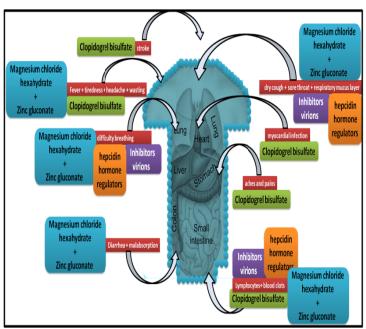


Figure 4: Role of the chemical constitutes of EGYPTONA drug.

- Hepcidin hormone regulator reacts with ferroportin (FPN) to induce its internalization and degradation, thus limiting the amount of Fe²⁺ released into the blood.
- Fe²⁺ overload reacts with hepcidin hormone regulator, zinc gluconate and magnesium chloride hexahydrate, as well as inhibitors that block the release of virions after budding from the host cell to treat dry cough, sore throat, respiratory mucus layer and difficulty breathing,
- Zinc gluconate and magnesium chloride hexahydrate, as well as clopidogrel bisulfate to treat fever, tiredness, headache and wasting.
- Zinc gluconate and magnesium chloride hexahydrate to treat diarrhea and malabsorption.
- Clopidogrel bisulfate to treat stroke, mycocardial infection, aches and pains.
- Fe²⁺ overload reacts with hepcidin hormone regulator, clopidogrel bisulfate, zinc gluconate and magnesium chloride hexahydrate, as well as inhibitors that block the release of virions after budding from the host cell to treat lymphocytes and blood clots.

CONCLUSION

It can be concluded that the proposed antiviral drug (EGYPTONA) that included hepcidin hormone regulators+inhibitors block the release of virions after budding from the host cell+mixture of magnesium chloride hexahydrate with zinc gluconate+clopidogrel bisulfate should be treated medically with patient. However, analyzes and clinical trials are necessary to determine the effective and appropriate dose of EGYPTONA drug to reduce the expected side effects.

REFERENCES

- Abdel-Wahab TI, Abdel-Wahab ShI, Abdel-Wahab Eman I, Adel Manal M. A Step forward to control of COVID-19. Int J Pharm Res. 2020; Suppl 1:1167 - 1190.
- 2. Micha R, Michas G, Mozaffarian D. Unprocessed red and processed meats and risk of coronary artery disease and type 2 diabetes-an updated review of the evidence. Curr Atheroscler Rep. 2012;14(6): 515–524.

- World Cancer Research Fund AIFCR. Food, nutrition, physical activity, and the prevention of cancer: A global perspective. Washington, DC: World Cancer Research Fund AIFCR. 2007.
- 4. WebMD LLC. Top Iron-Rich Foods List. 2020.
- 5. Siegenberg D, Baynes RD, Bothwell TH. Ascorbic acid prevents the dose-dependent inhibitory effects of polyphenols and phytates on nonheme-iron absorption. American J Clin Nutr. 1994;53: 537 541.
- Weiss G. Iron, Infection and anemia a classical triad. Wein Klin Wochenschr.2000;114:357–367.
- 7. Webb GP. Nutrition: A health Promotion Approach (3rd edn), Taylor and Francis Group, CRC Press. 2007.
- 8. Stam-Moraga MC, Kolanowski J, Dramaix M, De Backer G. Kornitzer MD. Sociodemographic and nutritional determinants of obesity in belgium. Int J Obes Relat Metab Disord. 1999;Suppl 1:1–9.
- 9. Adams P. Management of elevated serum ferritin levels. Gastroenterol Hepatol (N Y). 2008;4(5):333–334.
- Gill D, Brewer CF, Monori G, Trégouët DA, Franceschini N, Giambartolomei C, et al. Effects of Genetically Determined Iron Status on Risk of Venous Thromboembolism and Carotid Atherosclerotic Disease: A Mendelian Randomization Study. J American Heart Ass. 2019;8(15)
- 11. Pennington JAT, Young BE. Total diet study nutritional elements, 1982–J. Am Diet Assoc. 1989;91:179–183.
- 12. Wright HS, Guthrie HA, Wang MQ, Bernardo V. The 1987–88 Nationwide Food Consumption Survey: an update on the nutrient intake of respondents. Nutr Today. 1991;26:21–27.
- 13. Subar AF, Krebs-Smith SM, Cook A, Kahle LL. Dietary sources of nutrients among US adults, 1989 to 1991. J. Am. Diet. Assoc. 1998;98:537–547.
- 14. Harrison-Findik DD. Gender-related variations in iron metabolism and liver diseases. World J. Hepatol. 2010;2(8): 302 310.
- 15. Beard JL. Iron requirements in adolescent females. J. Nutr. 2000;130:440S-442S.
- 16. Cross AJ, Harnly JM, Ferrucci LM, Risch A, Mayne ST, Sinha R. Developing a heme iron database for meats according to meat type, cooking method and doneness level. Food Nutr Sci. 2012;3 (7): 905–913.
- 17. Powell LM, Nguyen BT, Han E. Energy intake from restaurants: demographics and socioeconomics, 2003–2008. Am. J. Prev. Med. 2012;43:498–504.
- 18. Fryar CD, Ervin RB. Caloric Intake From Fast Food Among Adults: United States, 2007–2010. Hyattsville, MD: National Center for Health Statistics; 2013. NCHS Data Brief no. 114.
- 19. Tamburini Elena, Fano Elisa, Castaldelli G, Turolla E. Life cycle assessment of oyster farming in the Po Delta, Northern Italy. Resources. 2019; 8 (170): 1 17.
- 20. Lambert LC, Fauci AS. Influenza vaccines for the future. Te New England j med. 2010;363: 2036 2044.
- 21. Rishi G, Wallace DF, Subramaniam VN. Hepcidin: regulation of the master iron regulator. Biosci Rep.2015;35 (3): e00192.
- 22. Donovan A, Lima CA, Pinkus JL, Pinkus GS, Zon LI, Robine S, et al. The iron exporter ferroportin/Slc40a1 is essential for iron homeostasis. Cell Metab. 2005;1:191–200.

- 23. Rosa L, Cutone A, Lepanto .S, Paesano R, Valenti P. Lactoferrin: A natural glycoprotein involved in iron and inflammatory homeostasis. Int. J. Mol. Sci. 2017; 18 (9): 1985.
- 24. Liu J, Sun B, Yin H, Liu S. Hepcidin: A promising therapeutic target for iron disorders. Medicine (Baltimore). 2016;95 (14): e3150.
- 25. Nemeth E, Tuttle MS, Powelson J, Vaughn MB, Donovan A, Ward DM, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science. 306 (5704): 2090 2093, Epub 2004 Oct 28.
- 26. Yang F, Haile DJ, Wang X, Dailey LA, Stonehuerner JG, Ghio AJ. Apical location of ferroportin 1 in airway epithelia and its role in iron detoxification in the lung. Am. J. Physiol. Lung Cell Mol. Physiol. 2005; 289: L14 L23
- 27. De Clercq E. Antiviral agents active against influenza a viruses. Nat. Rev. Drug Discov. 2006; 5: 1015 1025.
- 28. Hayden FG, Hay AJ. Emergence and transmission of influenza a viruses resistant to amantadine and rimantadine. Curr. Top Microbiol. Immunol. 1992;176: 119 130.
- 29. Colman PM, Varghese JN, Laver WG. Structure of the catalytic and antigenic sites in influenza virus neuraminidase. Nature. 1983;303: 41 44.
- 30. Gottesman MM, Pastan I. Biochemistry of multidrug resistance mediated by the multidrug transporter. Annu. Rev. Biochem. 1993, 62: 385 427.
- 31. MacGrogan D, Levy A, Bova GS, Isaacs WB, Bookstein R. Structure and methylation-associated silencing of a gene within a homozygously deleted region of human chromosome band 8p22. Genomics. 1996; 35: 55–65.
- 32. Kelleher DJ, Karaoglu D, Mandon EC, Gilmore R. Oligosaccharyltransferase isoforms that contain different catalytic STT3 subunits have distinct enzymatic properties. Mol. Cell. 2003; 12: 101–111.
- 33. Zhou H, Clapham DE. Mammalian MagT1 and TUSC3 are required for cellular magnesium uptake and vertebrate embryonic development. Proc Natl Acad Sci USA. 2009; 106:15750 15755.
- 34. Li FY, Chaigne-Delalande B, Kanellopoulou C, Davis JC, Matthews HF, Douek DC, et al. Second messenger role for Mg2+ revealed by human T-cell immunodeficiency. Nature. 2011;475:471–476.
- 35. Cherepanova NA, Shrimal S, Gilmore R. Oxidoreductase activity is necessary for N-glycosylation of cysteine-proximal acceptor sites in glycoproteins. J. Cell Biol. 2014; Vol., 206 (4): 525 539.
- 36. Clausen MV, Hilbers F, Poulsen H. The structure and function of the Na, K-ATPase isoforms in health and disease Front Physiol.
- 37. El Mernissi G, Doucet A. Quantitation of [3H]ouabain binding and turnover of Na-K-ATPase along the rabbit nephron. Am. J. Physiol. 1984; 247: F158–F167.
- 38. Ravell J, Chaigne-Delalande B, Lenardo M. X-linked immunodeficiency with magnesium defect, Epstein-Barr virus infection, and neoplasia disease: a combined immune deficiency with magnesium defect. Curr Opin Pediatr. 2014;26 (6): 713 719.
- 39. Yu X, Zhai C, Fan Y, Zhang J, Liang N, Liu F, et al. TUSC3: A novel tumour suppressor gene and its functional implications. J. Cell Mol. Med. 2017; 21 (9): 1711–1718.

- 40. Sugimoto H, Yamada U. Iron deficiency anemia induced by magnesium overuse: A case report. Biopsychosoc Med. 2019;13: 18.
- 41. Dietzel I, Heinemann U, Hofmeier G, Lux H. Stimulus-induced changes in extracellular Na+ and Cl concentration in relation to changes in the size of the extracellular space. Experimental Brain Research. 1982;46 (1): 73 84.
- 42. Dmitriev AV. The logic of ionic homeostasis: Cations are for voltage, but not for volume. PLoS Comput. Biol. 2019;L15(3): e1006894.
- 43. Shajahan A, Heiss C, Ishihara M, Azadi P. 2017. Glycomic and glycoproteomic analysis of glycoproteins: A tutorial. Anal Bioanal Chem., 409 (19): 4483 4505.
- 44. Chen R, Jiang X, Sun D, Han G, Wang F, Ye M, et al. Glycoproteomics analysis of human livertissue by combination of multiple enzyme digestion and hydrazide chemistry. J Proteome Res. 2009;8: 651–661.
- 45. Desantos-Garcia JL, Khalil SI, Hussein A, Hu Y, Mechref Y. Enhanced sensitivity of LC-MS analysis of permethylated N-glycans through online purification. Electrophoresis. 2011;32 (24): 3516–3525.
- 46. Tan Z, Ma G, Lin L, Liu C, Liu Y, Jiang J, et al. Prevalence of subclinical vitamin A deficiency and its affecting factors in 8 669 children of China. Zhonghua Yu Fang Yi Xue Za Zhi. 2002; 36 (3): 161–163. (in Chinese).

- 47. Brown KH, Rivera JA, Bhutta Z, Gibson RS, King JC, Lönnerdal B, et al. International Zinc Nutrition Consultative Group (IZiNCG) technical document #1. Assessment of the risk of zinc deficiency in populations and options for its control. Food Nutr Bull. 2004;25 (Suppl. 2): S99–S203.
- 48. Ghaffari H, Tavakoli A, Moradi A, Tabarraei A, Bokharaei-Salim F, Zahmatkeshan M, et al. Inhibition of H1N1 influenza virus infection by zinc oxide nanoparticles: another emerging application of nanomedicine. J Biomed Sci. 2019;26: 70 (2019).
- 49. Prasad AS, Brewer GJ, Schoomaker EB, Rabbani P. Hypocupremia induced by zinc therapy in adults. JAMA.1978;240(20): 2166-2168.
- 50. Samman S, Roberts DC. The effect of zinc supplements on plasma zinc and copper levels and the reported symptoms in healthy volunteers. Med J Australia. 1987; 146(5): 246-249.
- 51. Siepmann M, Spank S, Kluge A, Schappach A, Kirch W. The pharmacokinetics of zinc from zinc gluconate: A comparison with zinc oxide in healthy men. Int J Clin Pharmacol Ther.2005;43(12): 562 565.
- 52. Zhang YJ, Li MP, Tang J, Chen XP. Pharmacokinetic and Pharmacodynamic Responses to Clopidogrel: Evidences and Perspectives. Int. J. Environ. Res. Public Heal. 2017;14(3).