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Degradation of Some Purines Compounds in the Samples of COVID-19 Patients

A Thesis

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بسم الله الرحمن الرحيم

يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ وَاللَّهُ بِمَا تَعْمَلُونَ خَبِيرٌ

صدق الله العظيم

سورة المجادلة – الاية (١١)

Dedication

To my mother's soul that left us too early that we still miss during the minute details of our life ….

To my heart's soul … My Father

To My Husband and my Children

(Apple of my eye)

To my brothers and sisters

To the homeland we are looking for, and we yearn to see it one day as we wish it safe and upright

To all those whose spring butterflies dance to those who open the anemones and yasin ..... to the martyrs

Zinah

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Summary

The aim of study to estimation serum level of xanthine oxidase, hypoxanthine, CRP, uric acid, allantoin, Xanthine and Potassium in patients with COVID – 19. In this study, 150 blood samples were collected from Hila Teaching Hospital and Murjan Medical City, 50 of them were collected from healthy people who visited the blood bank for the purpose of donating blood(control group), 50 of them were from patients infected with Covid 19 who had been immunization by the Pfizer vaccine previously(vaccinated group), and 50 samples were collected from people who were admitted to the hospital Being infected with COVID-19 and not immunized with any type of COVID-19 vaccines(unvaccinated group), the healthy group had an average lifespan of (41.02±10.8), the vaccinated group (39.5±12.26) and the unvaccinated group (47±12.9) . The study was done in the University of Babylon/College of science WSCI /Department of Chemistry. The study lasted for the period from 1-11-2021 to 1-6-2022. The target parameters were (xanthine oxidase, xanthine, hypoxanthine, CRP, uric acid, allantoin and potassium). The following parameters (xanthine oxidase, and hypoxanthine) were measured by the ELISA technique. Xanthine and allantoin were measured by HPLC. CRP was measured by I-Chroma instrument (full automated device). Uric acid and Potassium were measured by spectrophotometers. The result showed: xanthine oxidase increased significantly in the group of patients infected with Covid 19 who were unvaccinated compared to the other groups. Xanthine oxidase levels in three groups (control, vaccinated and unvaccinated) were 6.8±12.7, 31.3±38.5

and 159.1±167.6 ng/ml respectively. Hypoxanthine showed no significant difference between Control and vaccinated group It's were 13.5±5.7, 14.8±6.8 and 29±17.6 pg/ml respectively. The CRP showed no significant difference between Control and vaccinated group It's were 2.9±1.07, 6.6±2.5 and 36.4±25.7mg/dl respectively. The uric acid showed significant increase in unvaccinated group difference. They were 4.8±0.8, 6.5±0.8 and 8.2±0.7mg/dl respectively. The results showed that the concentration of allantoin increased significantly in the group of patients infected with Covid-19 who were unvaccinated compared to the other groups. Allantoin levels were 1.1±0.01, 2.1±0.04 and 8.1±0.03mmol/L respectively.

Xanthine also increased significantly in the group of patients infected with Covid-19 who were unvaccinated compared to the other groups. Xanthine levels were 0.83±0.01, 0.68±0.01and2.16±0.02µmol/L respectively. Potassium showed decrease in unvaccinated group with no significant difference. It was 4.2±0.66, 4.0±0.5 and 3.3±0.64mg/dl respectively. Positive correlation is significant at the 0.01 level amongst all parameters except potassium showed negative correlation for all parameters.

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Abbreviations	Details
ACE2	Angiotensin converting enzyme receptor-2
ARDS	Acute respiratory distress syndrome
ACIP	The Advisory committee on Immunization Practices
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
BMI	Body Mass Index
COVID-19	Coronavirus disease 2019
CDC	The centers for disease control
CRP	C-reactive protein
$C_5H_4N_4O_2$	Molecular Formula for xanthine
$C_5H_4N_4O$	Molecular Formula for Hypoxanthine
$C_5H_4N_4O_3$	Molecular Formula for Uric acid
$C_4H_6N_4O_3$	Molecular Formula for Allantoin
COPD	Chronic obstructive pulmonary disease
cAMP	Cyclic adenosine monophosphate
DNA	Deoxyribonucleic acid
ELISA	Enzyme – linked immunosorbent assay
HPLC	High-performance liquid chromatography
HRP	Horseradish Peroxidase
HGPRT	Hypoxanthine-guaninephosphoribosyltransferase
IBMX	3-isobutyl-1-methylxanthine
IMP	Inosine monophosphate
LNS	Lesch–Nyhan syndrome
MERS-CoV	Middle East respiratory syndrome –coronavirus
MS	Multiple sclerosis
mRNA	Messenger Ribonucleic acid
OSAS	Obstructive sleep apnea syndrome
OD	The optical density
PKA	Protein kinase A
RNA	Ribonucleic acid
SARS-CoV-2	The severe acute respiratory syndrome coronavirus 2
SD	Significant differences
SEM	Stander error mean
T-cx cells	T-cytotoxic cells
TNF-α	Tumor necrosis factor alpha
TMB	Tetramethylbenzidine

tRNA	Transfer Ribonucleic acid
WHO	World Health organization
XO	Xanthine oxidase
XDH	Xanthine dehydrogenase
2019-nCOV	2019 novel coronavirus

Chapter One

Introduction and Literature review

1. Introduction

1.2. COVID – 19 Virus

Coronavirus disease 2019 (COVID-19), often known as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), is a kind of coronavirus. (Huang *et al.*, 2020), An enveloped RNA beta Coronavirus belonging to the Coronaviridae family has been discovered. It has been linked to a variety of respiratory illnesses, from mild to severe. (Lippi and Plebani, 2020).

It is a new infectious agent, according to the World Health Organization (WHO), that creates worldwide public health problems. SARS-CoV-2 has grown into a pandemic too quickly, since it was merely an epidemic outbreak when it was initially discovered in Wuhan, China. The first patient with SARS-CoV-2 was diagnosed on February 24, 2020, at Najaf, Iraq; thereafter, further cases werepublicly registered. (WHO,2021)

SARS-CoV and Middle East respiratory disease (MERS) have greater fatality rates than SARS-CoV-2; nevertheless, SARS-CoV-2 is more deadly than seasonal flu. (Smilowitz *et al.*, 2021). SARSCoV-2 is more likely to kill immunocompromised individuals with chronic conditions and theelderly, although younger patients with no severe underlyinginfections or disorders may still develop potentially deadly consequences such as disseminated intravascular coagulopathy and fulminant myocarditis. (Madjid *et al.*, 2020).

C-reactive protein (CRP) is an acute-phase protein produced by the liver in response to the inflammatory cytokine interleukin-6 (IL-6) and is a frequently used biomarker of inflammation. C-reactive protein has also been linked to severe illness in H1N1 influenza pneumonia patients, and a number of recent studies have shown a link between higher CRP levels and increased disease severity in COVID-19 patients. (Smilowitz *et al.*, 2021).

Coronavirus Disease 2019 is a respiratory infection that may lead to thrombotic complications. Patients with coronavirus disease 2019 (COVID-19) have varying signs and symptoms at the onset of illness (Poudel *et al.*, 2021).

In the early phases of viral infection, detecting and controlling the pro-inflammatory response is critical. Over the past few months there has been a significant increase in COVID-19 cases. virus found to be transmitted among birds and mammals, rather humans being were not being apart for such infection and transmission as was seen previously in the severe acute respiratory syndrome-coronavirus (SARS-CoV) in 2002 and the Middle East respiratory syndrome-coronavirus (MERS-CoV) in 2012 (Di Yacovo et al., 2013). During patient monitoring, the unknown reaction to COVID-19 medication is critical. After activated macrophages, IL-6 is one of the most important cytokines. As a result, controlling systemic IL-6 levels in SARS-CoV-2 infected individuals might be a COVID-19 disease parameter. (Vatansever andBecer, 2020).

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Gao *et al.*, 2020). The disease was first reported in December 2019 from Wuhan, Hubei province, China and has since spread throughout the world (Rimsan *et al.*, 2020). The World Health Organization declared a global pandemic on March 11, 2020. As of October 28, 2020 there were over 44 million confirmed cases of COVID-19 and over 1.1 million deaths reported globally. In the United States, confirmed cases as of October 28, 2020 is nearly 9 million with over 227,000 deaths. Presentations of COVID-19 have ranged from asymptomatic/mild symptoms to severe illness and mortality (Alpaydin *et al.*, 2021; Organization and Others, 2020; Rossato *et al.*, 2020) .

Coronaviruses are enveloped, positive single- stranded large RNA viruses that infect humans Coronaviruses were first described in 1966 by Tyrell and Bynoe, who cultivated the viruses from patients with common colds, but also a wide range of animals (Tian *et al.*, 2022; Velavan and Meyer, 2020). Coronaviruses are large, roughly spherical particles with unique surface projections. Their size is highlyvariable with average diameters of 80 to 120 nm. Extreme sizes are known from 50 to 200 nm in diameter. The total molecular mass is onaverage 40,000 kDa. They are enclosed in an envelope embedded witha number of protein molecules. The lipid bilayer envelope, membraneproteins, and nucleocapsid protect the virus when it is outside the hostcell. The viral envelope is made up of a lipid bilayer in which the membrane (M), envelope (E) and spike (S) structural proteins are

anchored (Lalchhandama, 2020; Lu *et al*., 2022; Tian *et al*., 2022), figure (1-1).

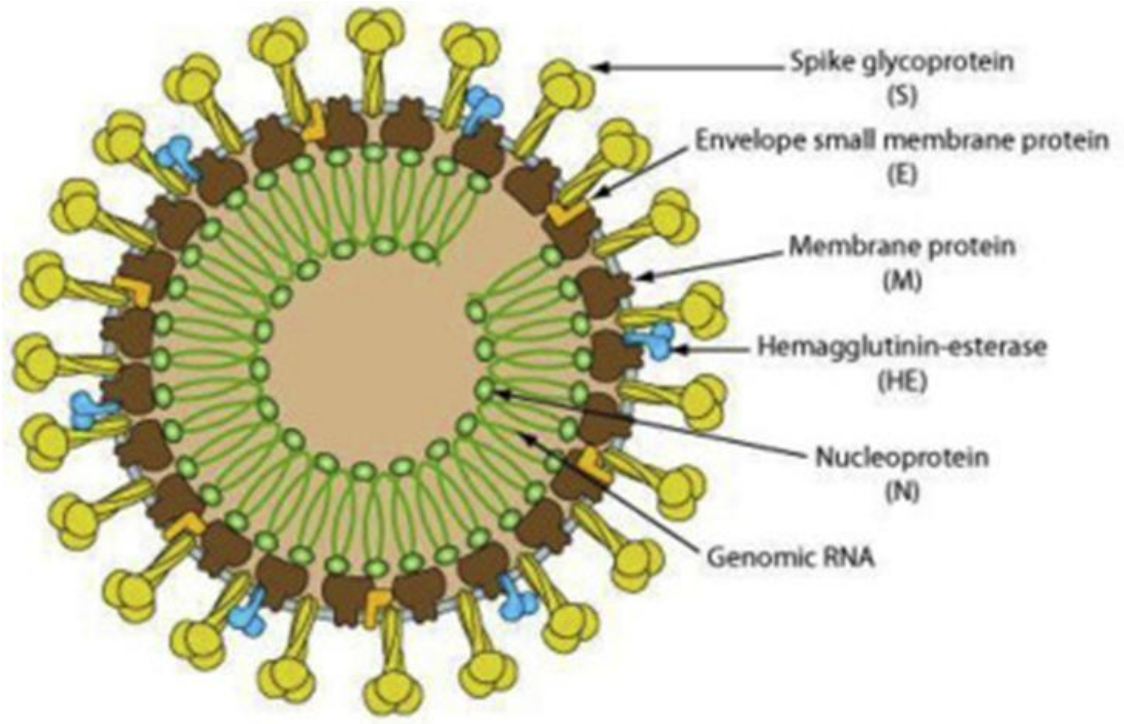

Figure (1-1) : The morphology structure of coronavirus (Mousavizadeh and Ghasemi, 2021).

Based on their morphology as spherical virions with a core shell and surface projections resembling a solar corona, they were termed coronaviruses (Latin: corona = crown). Four subfamilies, namely alpha-, beta-, gamma- and delta- coronaviruses exist (Miller, 2020). While alpha- and beta- coronaviruses apparently originate from mammals, in particular from bats, gamma- and delta- viruses originate from pigs and birds. The genome size varies between 26 kb and 32 kb (Kamel Boulos and Geraghty, 2020). Among the seven subtypes of coronaviruses that can infect humans, the beta-coronaviruses may cause severe disease and fatalities, whereas alpha-

coronaviruses cause asymptomatic or mildly symptomatic infections (Zhou *et al.*, 2020).

Four human coronaviruses produce symptoms that are generally mild, even though it is contended they might have been more aggressive in the past: [Human coronavirus OC43 (HCoV-OC43), β-CoV], [Human coronavirus HKU1 (HCoV-HKU1), β-CoV)], [Human coronavirus 229E (HCoV-229E), α-CoV] and [Humancoronavirus NL63 (HCoV-NL63), α-CoV–]. Three human coronaviruses produce potentially severe symptoms: Severe acute respiratory syndrome coronavirus (SARS-CoV), β-CoV (identified in2003) , Middle East respiratory syndrome-related coronavirus (MERS- CoV), β-CoV (identified in 2012) and Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), β-CoV (identified in 2019) .These cause the diseases commonly called SARS, MERS, and COVID-19 respectively (Nnadi *et al.*, 2021).

The first patient with COVID-19 was reported in Iraq on 24 February 2020 for the Iranian student. Iraq has shown a cure rate lower than those reported by Iran, Turkey and Jordan; are higher than Saudi Arabia and Kuwait (Sarhan *et al.*, 2020).In 2002, coronavirus infections (SARS-CoVes) spread in Guangdong,south China, causing high fever, breathlessness and pneumonia, and rapidly spread to various regions around the world. The infection has spread in 26 countries, resulting in about 8096 cases and 774 deaths (Barbisch *et al.*, 2015).

On 16 March 2020, the disease affected more than 150 countries and territories around the world (Gudbjartsson *et al.*, 2020). Over the past few months there has been a significant increase in COVID-19 cases.

2020 (Khalil *et al.*, 2020). virus found to be transmitted among birds and mammals, rather humans being were not being apart for such infection and transmission as was seen previously in the severe acute respiratory syndrome-coronavirus (SARS-CoV) in 2002 and the Middle East respiratory syndrome-coronavirus (MERS-CoV) in 2012 (Di Yacovo *et al.*, 2013).

The current virus outbreak was initially named as 2019 novel coronavirus (2019-nCOV) by the World Health organization. Later on it was updated as SARS-CoV-2 and they named its disease as coronavirus disease- 2019 (COVID-19)(Chen *et al.*, 2020). On March 12 of current year, WHO has declared COVID-19 as a worldwide pandemic after infection began to spread rapidly across many countries whose reported the cluster of cases including Iraq (Koch *et al.*, 2021). Figure (1-2) .

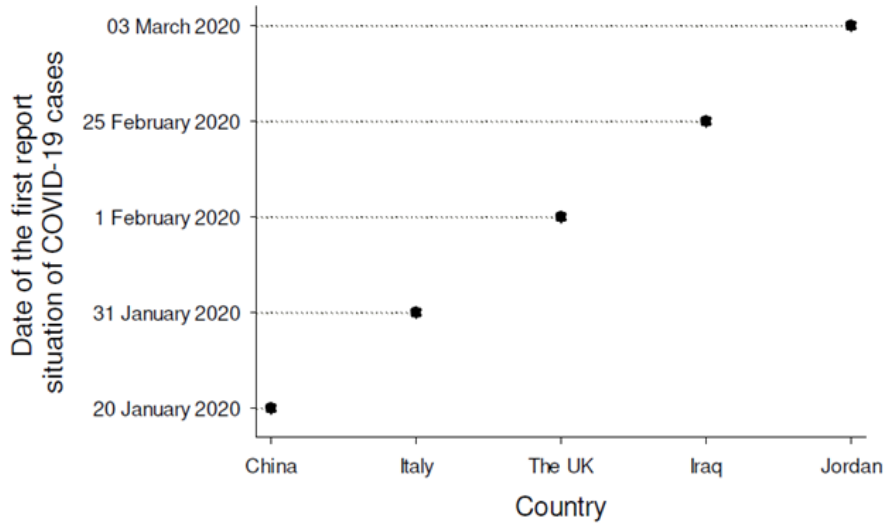

Figure (1-2): The first situation report of COVID-19 cases in each country recorded by WHO (Jebril.,2020).

1.2.1. COVID-19 Transmission

The first key to Corona's contact with human cells is the "angiotensin-converting enzyme receptor-2" (ACE2), which was monitored by several studies, most notably a previous study that compared the new Corona virus and its closest relative from the coronavirus family, which is the SARS virus (Inokuchi *et al.*, 2021). Corona has the ability to bind to the future more tightly, and this helped it spread to a greater degree than SARS To infect humans, coronavirus must first attach to the surface of human cells lining the respiratory or intestinal tracts (Hosseini *et al.*, 2022).

Once attached, it invades the cell and then replicates itself in multiple copies, accelerating the spread of the virus in the body (Sung *et al.*, 2021).

The second key is a protein called Neuropilin-1, which is found in cells lining the nasal cavity, making it suitable for the virus to establish refuge inside bodies, and to reproduce to form a viral family, before spreading by moving to a new host (Bisgin *et al.*, 2021; Zhu *et al.*, 2020) . Figure (1-3).

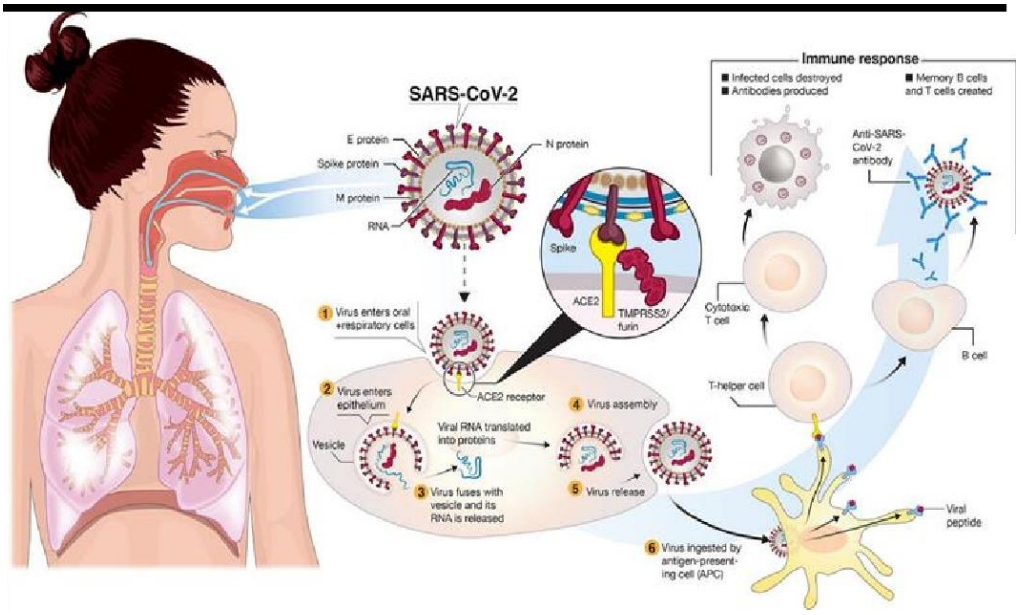

Figure (1-3) : Transmission and life-cycle of SARS-CoV-2 causing COVID-19 (Trougakos *et al.*, 2021) .

1.2.2. COVID-19 Symptoms

Patients with coronavirus disease 2019 (COVID-19) have varying signs and symptoms at the onset of illness. However, most patients will experience the following: Fever (83-99%), Cough (59-82%), Fatigue (44-70%), Anorexia (40-84%), Shortness of breath (31-40%), Sputum production (28-33%), Myalgia's (11-35%) (Yang *et al.*, 2020) .

Coronavirus disease 2019 (COVID- 19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS- CoV- 2), is a disease characterized by pneumonia. The main clinical presentations are fever, dry cough, and fatigue, but in addition to respiratory symptoms, a minority of patients may present only with muscle soreness, gastrointestinal symptoms, or dispiritedness in the early stages (Eastin and Eastin, 2020). According to limited pathological autopsy results, in addition to lung involvement, the heart, liver, kidneys, spleen, hilar lymph nodes, bone marrow, and even brain

tissues are also affected in patients with COVID- 19 (Li, Zhu, *et al.*, 2021; Martins and Felo, 2022; Wong *et al.*, 2021).

1.2.2.1 Epidemiology

Fewer cases of coronavirus disease 2019 (COVID-19) have been diagnosed in children than in adults, and the majority of the pediatric cases have been mild. Whereas children comprise 22% of the US population, approximately 14% of all cases of COVID-19 reported to the Centers for Disease Control and Prevention (CDC) were among children (as of May 12, 2021). The number and rate of cases in children in the US have been steadily increasing (Liu, Zhang, *et al.*, 2020). The American Academy of Pediatrics reports children represent 14% of all confirmed cases in the 49 states reporting by age (Xu, Li, *et al.*, 2020).

To date, data on COVID-19 in children and adolescents remain scarce, despite the number of confirmed COVID-19 cases now exceeding 8 million globally (Grant *et al.*, 2020). Most published data originate from China, which cannot necessarily be extrapolated to children in Europe and elsewhere. Also, existing papers from China contain very few clinical data on children, and most lack details

regarding supportive measures required by children with COVID-19. Similarly, recent epidemiological reports from Europe and North America contra in little clinically relevant information. Determining the level of support required by children is essential for pediatric service planning during the ongoing COVID-19 pandemic (Team *et al.*, 2020) .

The innate immune system represents the first line of defense against viruses, which can inhibit virus replication, improve virus clearance, promote tissue repair, and activate a prolonged adaptive immune response against the viruses. Viruses, such as CoV, could affect the function of the immune system in different ways, such as dysregulation of the macrophage antiviral response, induction of excessive cytokine-mediated immune system responses, and the activation of complement and coagulation cascades, which may result in enhanced infectivity and worse outcomes (Alpaydin *et al.*, 2021).

1.2.3. Risk Factors of COVID – 19

The risk factors for SARS-CoV were established after analyzing data collected from the World Health organization between 2012 and 2018, where males seemed to be more affected than females, and also age over 30 years-old or the presence or comorbidities. (Mph *et al.*, 2020).

1.2.3.1Clinical Risk Factors

1.2.3.1.1 Cigarette Smoking

In a recent editorial published on tobacco and COVID-19, the Sociedade Portuguesa de Pneumologia raises doubts and caution about the data coming from the medical and scientific community regarding the hypothesis that cigarette smoking or nicotine could be “protective” against COVID-19, recommending that this information should not be taken as an invitation to start smoking or to delay giving it up to avoid

SARS-CoV-2 infection or its complications. (Goel *et al.*, 2021). (Rossato and Di Vincenzo 2021) The role of cigarette smoking/nicotine (or whatever else is contain within cigarette smoke) in the scientific discussion on COVID-19 ignores the fact that smoke cessation has to be discouraged to avoid COVID 19 pulmonary complications (this seems obvious for scientists and physicians) but references the scientific importance of the strong epidemiological data coming from all the countries that hospitalized patients with SARS-CoV-2 related pneumonia show quite low percentages of active smokers . (Silva *et al.*, 2014; Tenembaum *et al.*, 2016). While another study indicated that a person with a past with smoking compared to non-smokers significantly increases the incidence of adverse health outcomes in patients with the Corona virus. Figure (1-4)

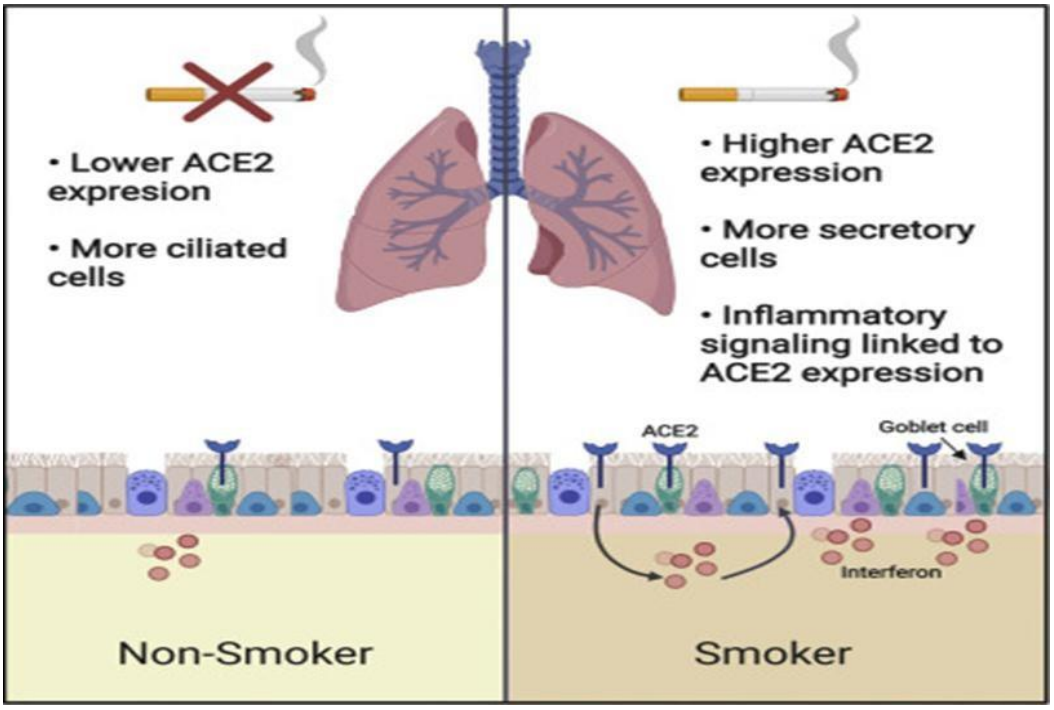

Figure (1-4) : Cigarette Smoking Exposure and Inflammatory Signaling Increase the Expression of the SARS-CoV-2 Receptor ACE2 in the Respiratory Tract . (JC smith *et al.*, 2020).

1.2.3.1.2. COVID – 19 with other diseases

Data from China and Italy show that a majority of COVID-19 deaths occurred in adults aged ≥60 years and in persons with serious underlying health conditions (Moriarty *et al.*, 2020; Wu *et al.*, 2020). Early age-stratified COVID-19 death rates in the United States, reported by the Centers for Disease Control and Prevention (CDC), also suggest that persons aged ≥65 are at highest risk. Additional factors associated with severe disease include male sex and the presence of comorbidities including hypertension, obesity, diabetes mellitus, cardiovascular disease, and chronic lung disease (Garg *et al.*, 2020).

Severe COVID-19 infection is characterized by a high inflammatory burden, and it can cause viral pneumonia with additional extra pulmonary manifestations and complications including acute respiratory distress syndrome (ARDS) (Xu, Shi, *et al.*, 2020) , Studies have also documented high rates of heart damage, cardiac arrhythmias and blood clots in COVID-19 patients. Patients with severe diseasecan suffer respiratory failure and failure of other vital systems, leadingto death (Bai *et al.*, 2020)

1.2.4. The immune system and COVID – 19

The body contains the organs of the immune system, which protects against diseases. It plays a key role to maintain health and pathogenesis. It also protects the body from harmful substances, germs, and cell changes (neoplasm). .(Frühwirt et al., 2020; Stanbury, 2022)The key player in the immune system is the white blood cells, which can travel throughout the body through the blood vessels. To monitor for invading microbes. (Berry, 2001).

The immune response associated with COVID-19 is complex. Most people who are infected mount a successful anti-viral response, which results in few, if any, symptoms. (Poon *et al.*, 2021).

In a minority of patients, however, there is evidence that the immune system overreacts. This leads to a flood of immune cells and to chronic inflammation and damage to multiple organs, often resulting in death. (Maggi *et al.*, 2020) .

That profound alterations in many immune cell types oftenpersisted for weeks or even months after SARS-CoV-2 infection. These problems resolved themselves very differently depending on thetype of immune cell. Some recover while some remain markedly abnormal, or show only limited recovery, even after systemic

inflammation has resolved and patients have been discharged from hospital. (Schultze and Aschenbrenner, 2021).

Because there is no registered medicine or vaccine against COVID-19, the immune system is the best defense because it supportsthe body's natural ability to defend against pathogens (eg, viruses, bacteria, fungi, protozoan, and worms and resists infections. As long as the immune system is functioning normally, infections such as COVID-19 go unnoticed. (Koppenol and Hider, 2019) The three types of immunity are innate immunity (rapid response), adaptive immunity (slow response), and passive immunity. Passive immunity has two types: natural immunity, received from the maternal side, and artificial immunity, received frommedicine. Skin and inflammatory responses begin when the body is affected. However, when the body encounters germs or viruses for thefirst time, the immune system cannot work properly, and illness can occur. This scenario is what has occurred in the case of COVID-19. (Islam *et al.*, 2022)

When the cells of the immune system become educated, they complete their jobs by recirculating between central and peripheral lymphoid organs and migrating it and from sites of injury via blood (Figure 1-5). Blood carries naïve and educated immune cells from onesite to another, as it flows throughout the body, and acts as a pipeline for the immune system. The cells again enter into the bloodstream to be transported to tissues throughout the body after exiting these nodesthrough outgoing lymphatic vessels. (Chowdhury *et al.*, 2020)**.**

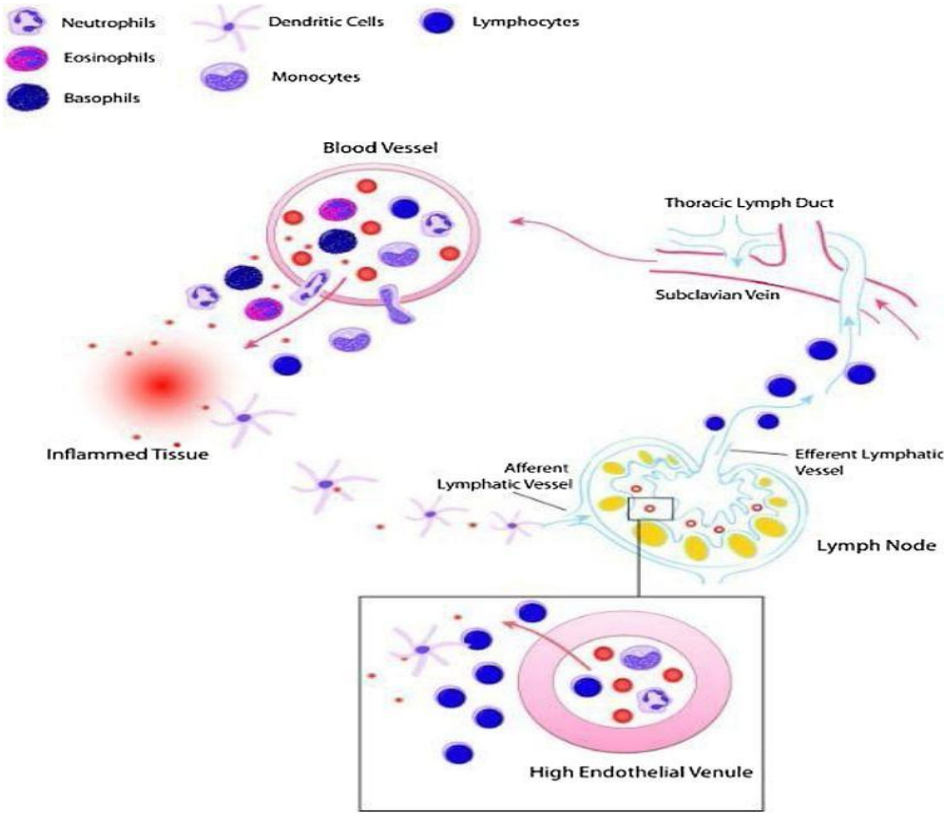

Figure (1-5) : Blood in the pipeline of the immune system (Chowdhury *et al.*, 2020).

Researchers are attempting to improve the immune system against COVID-19 and here some of the data reviewed. Ten proteins are encoded by the COVID-19 genome; one of them is the S protein , because a glycoprotein exists in the virus-infected region . The S protein is a significant therapeutic target, ensured its location, and targetable using antibodies. The formation ofneutralizing antibodies' immunization animals with S protein-oriented vaccines is very effective in preventing infection by homologous coronavirus. (Rijkers *et al.*, 2021).

1.2.5 COVID-19 management

Coronavirus disease 2019 (COVID-19) is a rapidly emerging disease caused by a highly contagious virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and this disease has affected millions of people across the world and led to hundreds of thousands of deaths worldwide (Kamel Boulos and Geraghty, 2020; Ortiz-Prado *et al.*, 2020). Nutrition is a key factor related to this disease, and nutritional status may determine the risk and outcomes of SARS-CoV-2 infection. Its antioxidant and anti-inflammatory activity is attributed to its role in immunity. Therefore, antioxidants are important in viral infections and can play a vital role in supporting coronavirus disease 2019 (COVID-19) (Lima *et al.*, 2021) . Antioxidants are compounds that inhibit oxidation, a chemical reaction that can produce free radicals and chain reactions that may damage the cells of organisms. Antioxidants such as thiols or ascorbic acid (vitamin C) may act to inhibit these reactions To balance oxidative stress. Dietary supplements marketed as antioxidants have not been shown to improve health or prevent disease in humans (Azab *et al.*, 2019).

Some vitamins and minerals have antioxidant properties and these include vitamins and minerals: (Vitamin E) Vitamin E helps thebody perform its normal functions, and it also has a role in reducing the production of free radicals. Vitamin E is found in 8 different chemical forms in food, but the only form that meets human needs forvitamin E is alpha-tocopherol. Foods rich in vitamin E include: wheatgerm oil, sunflower seeds or sunflower oil, almonds, and beans (Alpert, 2017; Suleman *et al.*, 2019). (Vitamin C) Vitamin C helps protect against various diseases and increase the body's immunity, andVitamin C also acts as an effective antioxidant. Foods rich in vitamin

C include: orange juice, red pepper, kiwi, and grapefruit juice (Shakeri *et al.*, 2020).

(Copper) Copper is a powerful antioxidant. Foods rich in copper include: oysters, kidney beans, soy protein powder, and tomato paste. (Zinc) Zinc is one of the most important elements for the body, and zinc has anti-inflammatory properties and acts as an antioxidant. Zinc plays a useful role in the activity of nearly 100 enzymes in the body. Foods that contain zinc include beef, fortified cereals, and shellfish (Akram *et al.*, 2020; Gharibzahedi and Jafari, 2017). The main role of antioxidants is to promote overall health and to fight and eliminate free radicals efficiently. Free radicals are unstable compounds and molecules that the body produces in response to environmental factors and stressors, such as pollution, exposure to ultraviolet rays, and cigarette smoke. (Akram *et al.*, 2020; Gharibzahedi and Jafari, 2017) (figure 1-6)

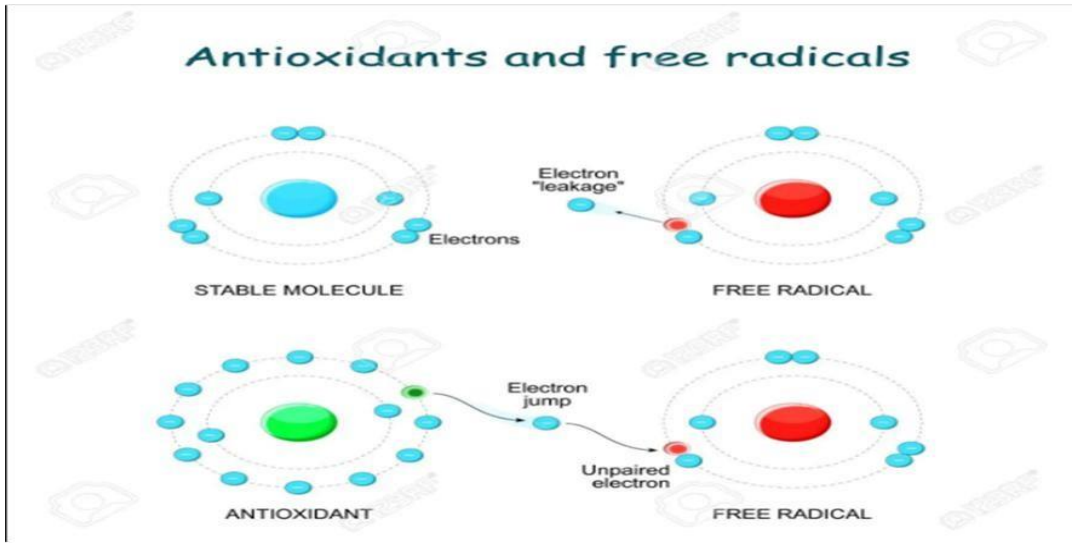

Figure (1-6): Chemically reactive unpaired electron + electron donation: stable electron pair is formed, free radical is neutralized

The presence of large amounts of iron in patients will lead to the formation of hydroxyl root through a known reaction is the reaction of Fenton reaction. (Pieczykolan *et al.*, 2016)

$$Fe^{+2} + H_2O_2 \rightarrow HO^- + HO\bullet + Fe^{+3}$$

Free radicals attack and destroy cell components to cause serious damage to their genetic material and cellular functions. As the accumulation of free radical's increases, many diseases such as degenerative diseases, cardiovascular disease, cancer, aging and others emerge in normal cells, there is an effective equilibrium between oxidants and antioxidants, but this equilibrium can change toward the primary oxidants when the production of active oxygen species increases significantly (after taking certain chemicals or drugs) or when the levels of antioxidants are weakened or decreased When inhibiting the enzymes. (Qin *et al.*, 2020; Taysi*et al.*, 2019)

1.2.6. COVID-19 Vaccine

By July 2021 there were 184 COVID-19 vaccine candidates in pre-clinical development, 105 in clinical development, and 18 vaccines approved for emergency use by at least one regulatory authority. These vaccines include whole virus live attenuated or inactivated, protein-based, viral vector, and nucleic acid vaccines (Higdon *et al.*, n.d.). By mid-2021 three billion doses of COVID-19 vaccine have been administered around the world, mostly in high-income countries. COVID-19 vaccination provides hope for an end to the pandemic, if and only if there would be equal access and optimal uptake in all countries around the world (Nagy and Alhatlani, 2021;

Sell *et al.*, 2021). The COVID-19 vaccines are in four primary categories using different platforms: whole virus vaccines, protein-based vaccines, viral vector vaccines, nucleic acid vaccines (Sung *et al.*, 2021).

Live attenuated vaccines use a weakened form of the virus, which can still grow and replicate but does not cause illness (Rabaan *et al.*, 2020). Inactivated vaccines contain viruses whose genetic material has been destroyed by heat, chemicals, or radiation, so they cannot infect cells and replicate but can still trigger an immune response (Rodrigues *et al.*, 2015). Vector vaccines deliver the construction plan for a part of the virus (Johnson and Pause, n.d.). Produced in a laboratory, this construction plan consists of DNA. Forthe COVID-19 vaccine, the construction plan carries the instructions to produce the spike protein of the coronavirus. This protein covers thesurface of the virus like spikes and is therefore easily recognizable byour immune system (Dull *et al.*, 2019; Mendonça *et al.*, 2021; Rihn *etal.*, 2021). In s the case of the vector vaccine, the DNA is inserted intoinactivated (and therefore harmless) adenoviruses so that the instructions can gain entry to the cells of our body (Wang *et al.*, 2020). After the vaccine has been injected into the muscle, the adenovirusesenter our cells and transport the DNA instructions to the cell nucleus, where proteins transcribe the DNA into mRNA (Doerfler, 2021). The mRNA then serves as a template for the ribosomes outside the cell nucleus to produce the spike proteins (Malone *et al.*, 2022).

The spike proteins are subs sequentially transported to the cell surface where they can be detected as intruders by our immune cells (Wei and Hui, 2022). This activates the immune system and antibodies against the spike protein are produced. Moreover, an immunological

memory is created in the form of memory B cells that offer protection against later infection (Roy *et al.*, 2022). figure (1- 7)

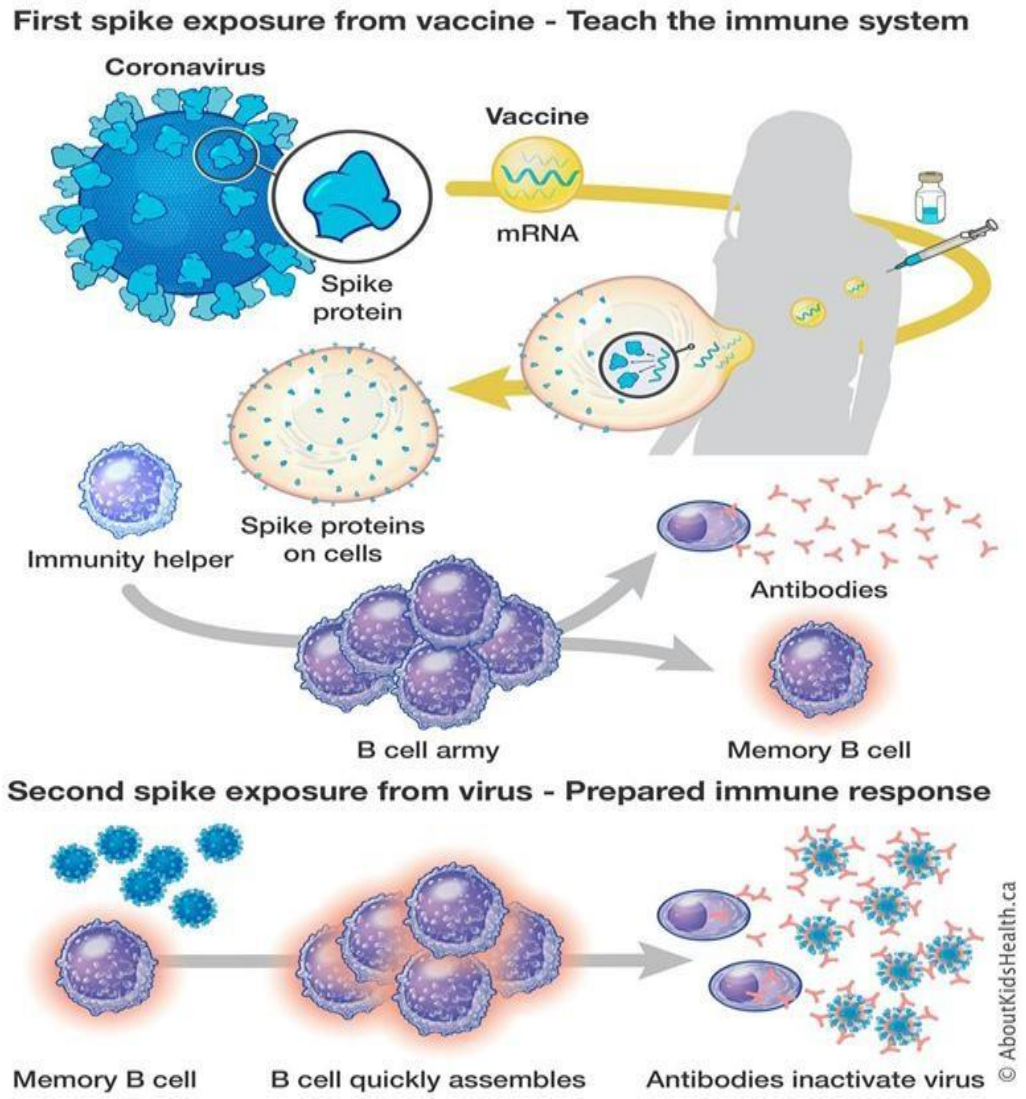

Figure (1- 7): COVID -19 Vaccines general information

(Kourlaba *et al.*, 2021).

1.2.7. Types of COVID -19 vaccines

1.2.7.1 Pfizer-Biontech Covid-19 Vaccine

On December 11, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the Pfizer-BioNTech COVID-19 (BNT162b2) vaccine (Pfizer, Inc.;Philadelphia, Pennsylvania), a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine encoding the perfusion spike glycoprotein of SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19) (Oliver *et al.*, 2020). Vaccination with the Pfizer-BioNTech COVID-19 vaccine consists of 2 doses (30 μg, 0.3 mL each) administered intramuscularly, 3 weeks apart. On December12, 2020, the Advisory Committee on Immunization Practices (ACIP) issued an interim recommendation* for use of the Pfizer-BioNTech COVID-19 vaccine in persons aged ≥16 years for the prevention of COVID-19 (Dooling *et al.*, 2020).

From the SARS- CoV-2 virus, the mRNA (able to translate and codify for the superficial spike proteins of the virus involved in the human pathogenicity) by working from the way backwards of s-proteins, is isolated and included in a lipid nanoparticle. This nanoparticle is injected intramuscularly into the human body and once attached to the host cells, inserts its mRNA into the cytoplasm (not in the nucleus) in such a way as to reach the ribosomes and use them for synthesizing the viral spike proteins. (Mascellino *et al.*, 2021). This process is called translation. Proteins then achieve the cellular membrane and evolve in two types:the MHC-2 (antigen presenting cells) and the MHC-1 related to another antigen which is present in all the nucleated cells of our body.The MHC-2 complex is only found in particular kind of cells: B-cells,macrophages and dendritic cells. These are activated by the s-protein

and attract the cells of the immune system. In particular, the T-helper (Th) cells which have a particular type of membrane protein (TCR) that binds to the viral s-protein. (Mascellino *et al.*, 2021). Other proteins called CD4 produced by the Th cells interact with the complex MHC-2. The stronglyactivated Th cells begin to produce cytokines such as IL-2, IL-4 and IL5. These interleukins cause the B-cells of our body to differentiate into plasma-cells that begin to produce a huge amount of antibodies against the viral spike proteins, able to neutralize or destroy the virus.Meanwhile, the interleukins also stimulate Th cells to proliferate the memory T cells. Another group of cells called T-cytotoxic cells (Tcx cells) interact with the MHC-1 protein on the cell membranes throughtheir TCR and produce CD8 proteins. (Wouters *et al.*, 2021). These proteins are very dangerous because may allow the Tcx cells to generate unsafe molecules which lead the cells to death if infected with the virus in thefuture but not the cells, which are currently processing the vaccine. Conversely, these Tcx cells are also able to produce substances that amplify the aforementioned immune response. (Wieczorek *et al.*, 2017) (Figure 1- 8)

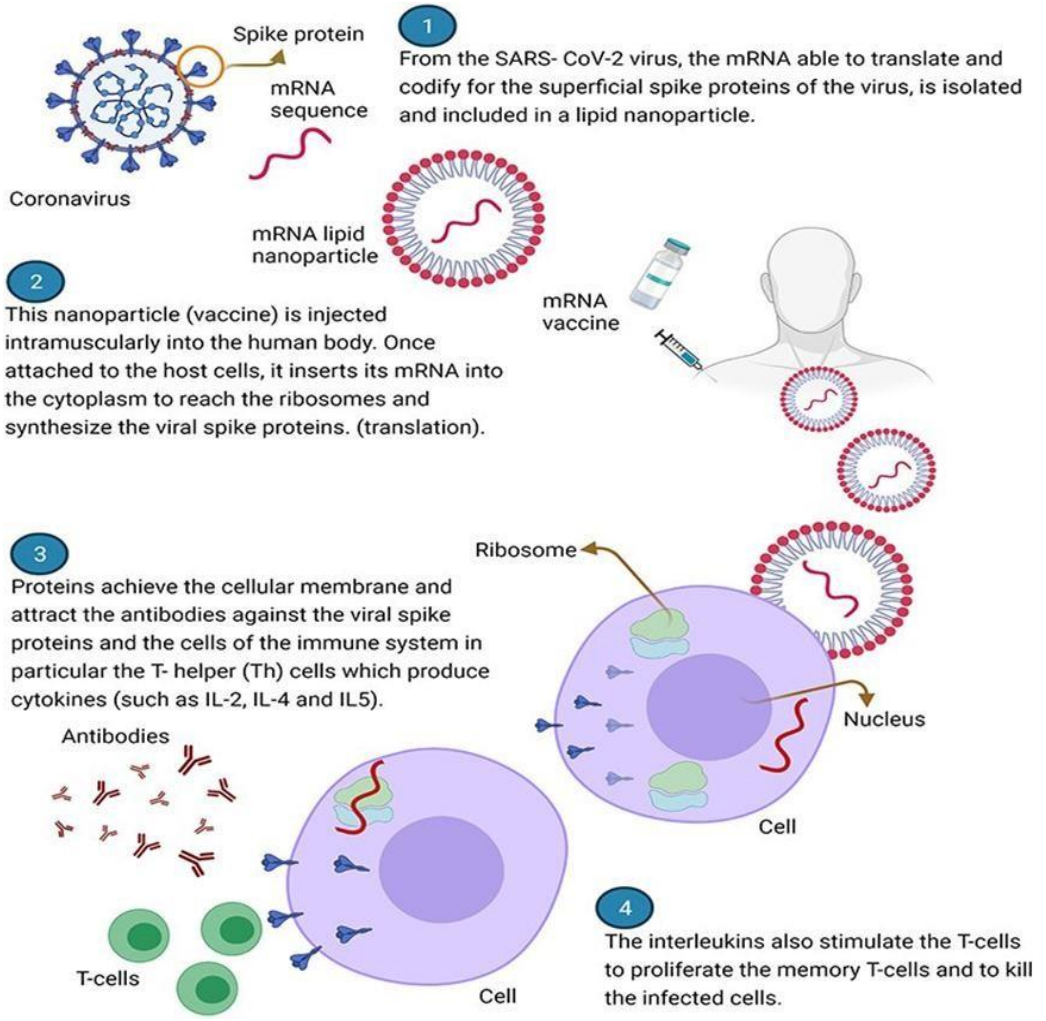

Figure (1-8) : Scheme of mechanism of action of vaccines Pfizer-BioNTech (Mascellino *et al.*, 2021)

1.2.7.2. Sinovac Vaccine Against Covid-19

The WHO Strategic Advisory Group of Experts on Immunization (Immunization Expert Group) has issued interim recommendations for the use of the inactivated COVID-19 vaccine, Sinovac – CoronaVac , developed by China National Pharmaceutical Group/Sinovac (McIntyre and Walls, 2020)

The Sinovac vaccine (SinoVac–CoronaVac vaccine) is 2-dose β-propiolactone-inactivated, aluminium hydroxide-adjuvanted COVID-

19 vaccines. It is recommended that the vaccine not be given to people under the age of 18, pending the results of further studies related to this age group. Available data on the immunization of pregnant women with the Sinovac-CoronaVac (anti-Covid-19) vaccine are insufficient to assess the efficacy of the vaccine or the risks associated with it in pregnancies (Spadaro, 2021).

1.2.7.3. The Oxford/Astrazeneca Covid-19 Vaccine

The ChAdOx1 nCoV-19 vaccine, commonly known as the Oxford-AstraZeneca vaccine, Covishield, or Vaxzevira, is one of three vaccines that has received conditional approval for the prevention of COVID-19 in the U.K. (March 2021) (Mahase, 2020) . The Oxford-AstraZeneca vaccine has received regulatory approval in over 100 countries as of late March 2021, and approximately 50 million doses have been administered across the U.K., the E.U., and India (Mallapaty and Callaway, 2021). This vaccine makes use of a novel technology that relies on a Chimpanzee Adenovirus-vector (ChAdOx) to encode the production of the SARS-CoV-2 spike protein, which induces an immune response (Wang *et al.*, 2022).

1.2.8. Relation of some parameter to COVID-19

1.2.8.1Xanthine

Xanthine (3,7-dihydropurine - 2,6-dione) is a purine base found in most tissues and fluids of the human body and other biota. Figure (1-9)

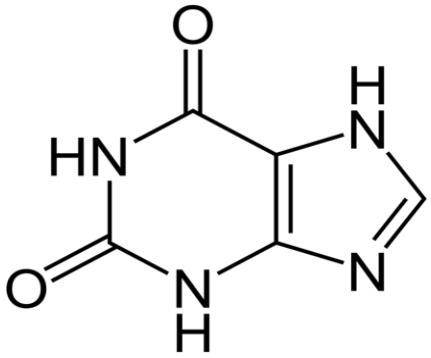

Figure (1- 9) : structure of Xanthine (Caramori *et al.*, 2019).

The properties of Xanthine are Molecular Formula: ($C_5H_4N_4O_2$) - Molar mass :(152.11 g/mol) - Appearance: (White solid) -Melting point: (decomposes) - Solubility in water: (1 g/ 14.5 L at 16 °C -1g/1.4 L at 100 °C) .

A number of stimulants such as caffeine and theobromine are derived from it. It is the result of the breakdown of purines. It is converted to uric acid by the enzyme oxidizing casein (Pundir and Devi, 2014). Xanthine consists of a benzene (hexagonal) ring linked toa pentagonal ring. The bonds are distributed as in the figure, and theyare three bonds of the -HN group, one nitrogen bond and two oxygen bonds. It is noted that the benzene ring is all monovalent except for one which is divalent and is related to the pentavalent ring (Tosato *etal.*, 2016).

Xanthine's, have been used in the treatment of asthma for approximately 150 years, which was first prescribed for the treatmentof asthma in 1937, is still widely used for asthma and chronic obstructive pulmonary disease (COPD) and still remains a very useful add-on therapy (Yazdanparast *et al.*, 2019).

Xanthine's don’t open airways as well as the previously described inhaled bronchodilators. But xanthine's, working via mechanisms of action that are still not well understood, produce

several effects that are beneficial to patients with Chronic obstructive pulmonary disease (COPD) and asthma (Thomas *et al.*, 2009). They decrease diaphragmatic muscle fatigue, increase mucociliary clearance, block centrally mediated hypoventilation, and decrease capillary leakage. At the same time, at high doses they stimulate heart rate and force of contraction, can generate cardiac arrhythmias, and can lead to convulsions (Rezaeinasab *et al.*, 2019).

1.2.8.1.1. Clinical significance of xanthine

Derivatives of xanthine (known collectively as xanthines) are a group of alkaloids commonly used for their effects as mild stimulants and as bronchodilators, notably in the treatment of asthma or influenza symptoms (Aguilar *et al.*, 2021). In contrast to other, more potent stimulants like sympathomimetic amines, xanthines mainly act to oppose the actions of adenosine, and increase alertness in the central nervous system (Seow *et al.*, 2020).

But Methylxanthines (methylated xanthines), which includecaffeine, aminophylline, IBMX (3-isobutyl-1-methylxanthine), paraxanthine, pentoxifylline, theobromine, and theophylline, affect not only the airways but stimulate heart rate, force of contraction, and cardiac arrhythmias at high concentrations (dePaula and Farah, 2019).In high doses, they can lead to convulsions that are resistant toanticonvulsants. Methylxanthines induce gastric acid and pepsin secretions in the gastrointestinal tract. Methylxanthines are metabolized by cytochrome in the liver (Ocaña *et al.*, 2022).

If swallowed, inhaled, or exposed to the eyes in high amounts, xanthines can be harmful, and may cause an allergic reaction if applied topically.

In vitro pharmacological studies, xanthines act as both competitive nonselective phosphodiesterase inhibitors which raise intracellular cAMP (Cyclic adenosine monophosphate), activate PKA (protein kinase A), inhibit TNF-α (tumor necrosis factor alpha) and leukotriene synthesis, and reduce inflammation and innate immunity and nonselective adenosine receptor antagonists which inhibit sleepiness-inducing adenosine (Lang, 2018) (Monteiro *et al.*, 2016).

1.2.8.2. Hypoxanthine

Hypoxanthine (1,9-Dihydro-6H-purin-6-one) is a naturally occurring purine derivative. The properties of Hypoxanthine are Chemical formula: (C5H4N4O) -Molar mass: (136.112 M) (Hu *et al.*, 2018). (Figure 1- 10)

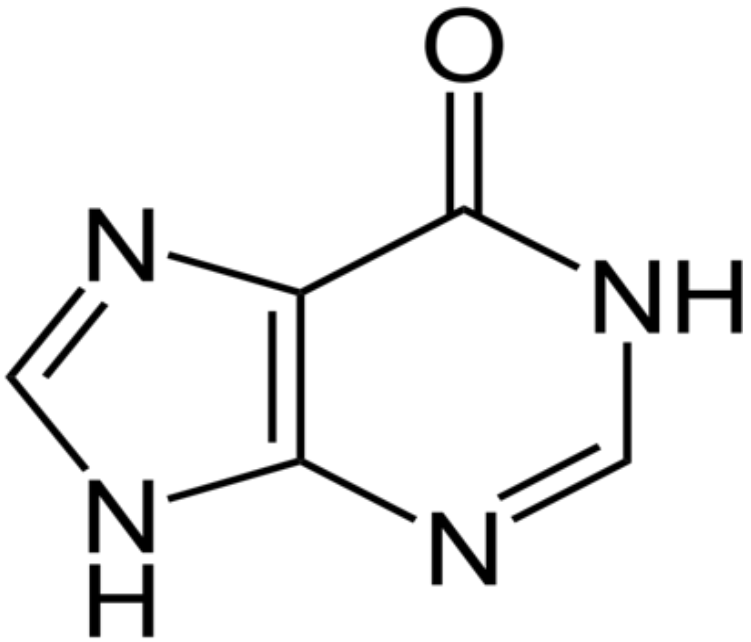

Figure (1- 10) : Hypoxanthine structure (Schmalle et al., 1988).

It is occasionally found as a constituent of nucleic acids, where it is present in the anticodon of tRNA in the form of its nucleoside inosine. It has a tautomer known as 6-hydroxypurine. Hypoxanthine is a necessary additive in certain cell, bacteria, and parasite cultures as a substrate and nitrogen source. For example, it is commonly required reagent in malaria parasite cultures, since Plasmodium requires a source of hypoxanthine for nucleic acid synthesis and energy metabolism (Ty *et al.,* 2019).

In August 2011, a report, based on NASA studies with meteorites found on Earth, was published suggesting hypoxanthine and related organic molecules including the DNA and RNA components adenine and guanine, may have been formed extra terrestrially in outer (Michaelian, 2021) .

Tissue hypoxia due to repeated apneas among patients of obstructive sleep apnea syndrome (OSAS) leads to cumulative oxidative stress. It is established that an increased plasma level of hypoxanthine/xanthine may serve as a criterion of tissue hypoxia (Hira *et al.,* 2014). It has been known for more than 40 years that the concentration of uric acid in plasma and its excretion in the urine is increased during anaerobic conditions. found that there was an increased liberation of hypoxanthine into the coronary circulation an

increased catabolism of high energy purines to uric acid (Lee *et al.*, 2018). During the past years a series of other papers have confirmed these results. As oxygen is needed for the transformation of hypoxanthine into uric acid, the reaction will probably be slowed down when the availability of oxygen is reduced. Hence we can imagine that during hypoxia there will be accumulation of hypoxanthine (Nagao *et al.*, 2018).

1.2.8.2.1Clinical significance of Hypoxanthine

Hypoxanthine is a potential free radical generator and could be used as an indicator of hypoxia. Hypoxanthine seems to play a role in post hypoxic re-oxygenation cell injury through oxygen radical production and is therefore involved in the pathogenesis of a number of diseases. Hypoxanthine also modulates a number of other processes because it reacts with benzodiazepine receptors and inhibits phosphodiesterase in the brain. Hypoxanthine inhibits the effect of several cytotoxic drugs and may therefore influence treatment with such drugs (Drummond *et al.*, 2019).

1.2.8.3 Xanthine and Hypoxanthine

Xanthine and hypoxanthine are important as they are used as analytes due to their significance in the clinical and food science, together with the conventional methods of analysis. A large section covers methods for the electrochemical hypoxanthine and xanthine sensing. It is divided into subsections according to the nanomaterials used including carbon nanomaterials, meal oxide nanoparticles, metal organic frameworks, conductive polymers, and bio-nanocomposites (Chausali *et al.*, 2022).

A further large section covers optical methods for hypoxanthine and xanthine sensing, with subsections on nanomaterials including

carbon nanomaterials, nanosheets, nanoclusters, nanoparticles, and their bio-nanocomposites. A concluding section summarizes the current status, addresses current challenges, and discusses future perspectives (Díez-Pascual and Rahdar, 2021). The main difference between xanthine and hypoxanthin is that xanthine is an oxidized form, whereas hypoxanthin is a reduced form from xanthine. Xanthine is formed from the oxidation of hypoxanthine. Therefore, xanthine contains two carbonyl atoms while hypoxanthine contains only one carbonyl atom (Mehmood *et al.*, 2019).

Another difference between xanthine and hypoxanthine is that xanthine contains two oxygen atoms in its chemical structure, while hypoxanthine contains only one oxygen atom. Xanthine is formed as a product of the purine hydrolysis pathway. There are three main reactions that xanthine can create. (Nagao *etal.*, 2018). From guanine by guanine deaminase, from hypoxanthine by xanthine oxidoreductase, and from xanthosine by purine nucleoside phosphorylase While hypoxanthin is formed when the enzyme xanthine oxidase acts on xanthine. It is alsoformed as a product of spontaneous deamination of adenine (Cheviet *et al.*, 2019).

1.2.8.4 Xanthine oxidase

Xanthine oxidase (XO, sometimes 'XAO') is a form of xanthine oxidoreductase, a type of enzyme that generates reactive oxygen species. These enzymes catalyze the oxidation of hypoxanthine to xanthine and can further catalyze the oxidation of xanthine to uric acid. These enzymes play an important role in the catabolism of purines in some species, including humans (Ardan *et al.*, 2004).

The following chemical reactions are catalyzed by xanthine oxidase:

- hypoxanthine + H_2O + O_2 ↔ xanthine + H_2O_2
- xanthine + H_2O + O_2 ↔ uric acid + H_2O_2
- Xanthine oxidase can also act on certain other purines, pterions, and aldehydes. For example, it efficiently converts 1- methyl xanthine (a metabolite of caffeine) to 1-methyluric acid, but haslittle activity on 3-methylxanthine.
- Under some circumstances it can produce superoxide ion RH + H_2O + 2 O_2 ↔ ROH + 2 O_2^- + 2 H^+. Figure (1 -11).

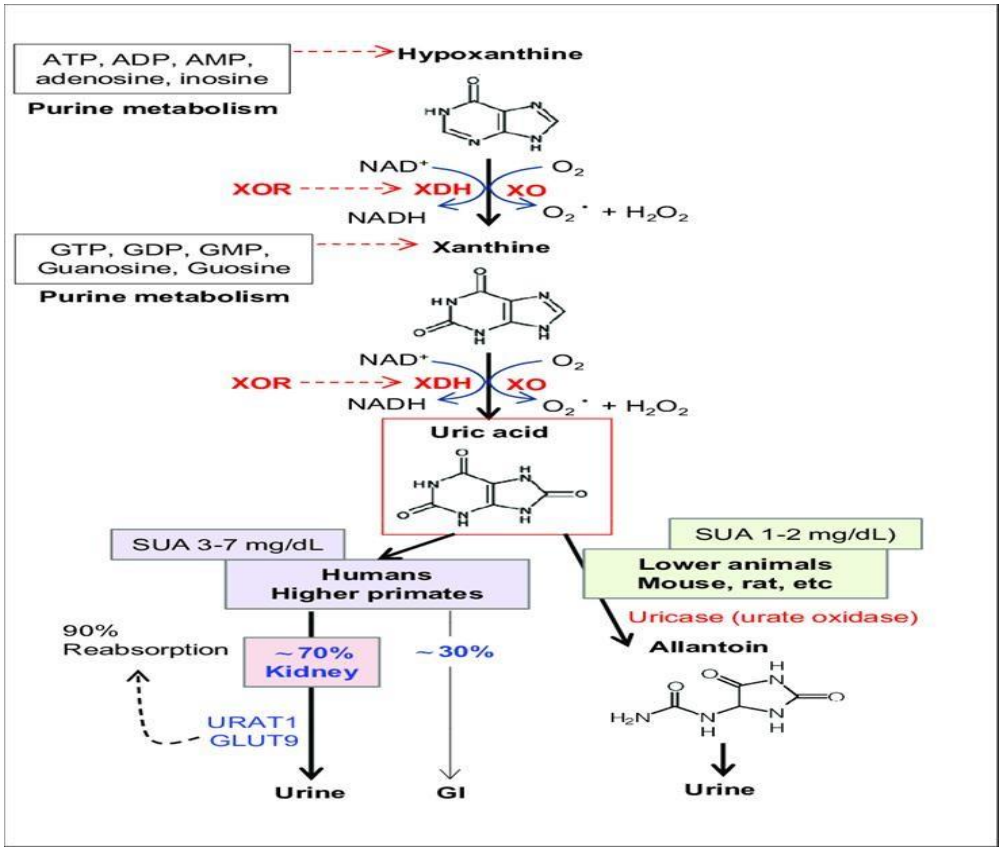

Figure (1-11): Generation of uric acid and superoxide anion byxanthine oxidase. XO indicates xanthine oxidase; XDH, xanthine dehydrogenase; O 2 – ·, superoxide anion; and ROS, reactive O_2 species (Masuoka *et al.*, 2015).

Xanthine oxidase is a superoxide-producing enzyme found normally in serum and the lungs, and its activity is increased during a infection. During severe liver damage, xanthine oxidase is released into the blood, so a blood assay for XO is a way to determine if liver damage has happened.(Juan *et al.*, 2021). The lack of xanthine oxidase leads to high concentration of xanthine in blood and can cause health problems suchas renal failure (Stiburkova *et al.*, 2018).

Inhibition of xanthine oxidase has been proposed as a mechanism for improving cardiovascular health. A study found that patients with chronic obstructive pulmonary disease (COPD) had a decrease in oxidative stress, including glutathione oxidation and lipid peroxidation, when xanthine oxidase was inhibited using allopurinol. Oxidative stress can be caused by hydroxyl free radicals and hydrogen peroxide, both of which are byproducts of XO activity (Qadir *et al.*, 2018).

1.2.8.5 Uric acid

Uric acid is a compound of carbon, nitrogen, oxygen, and hydrogen with the formula $C_5H_4N_4O_3$. The properties of Uric acid are Chemical formula ($C_5H_4N_4O_3$) -Molar mass (168.112 $g \cdot mol^{-1}$) - Appearance (white crystal) - Melting point (300 °C (572 °F; 573 K) - Solubility in water - 6 mg/100 mL (at 20 °C) (95). Figure (1-12).

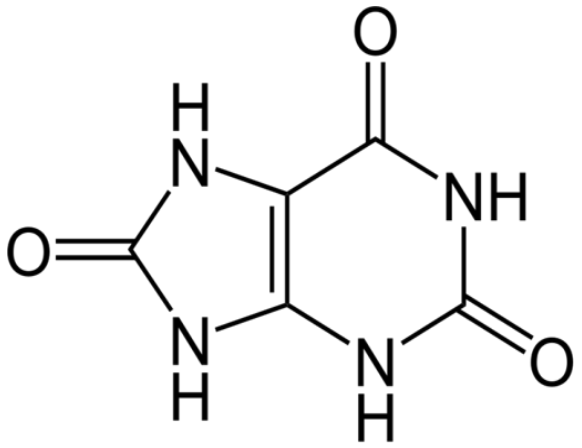

Figure (1-12): Uric acid structure. IUPAC name (7,9-Dihydro- 1H-purine-2,6,8(3H)-trione) (Banihani, 2018).

It forms ions and salts known as urates and acid urates, such as ammonium acid urate. Uric acid is a product of the metabolic breakdown of purine nucleotides, and it is a normal component of urine. High blood concentrations of uric acid can lead to gout and are associated with other medical conditions, including diabetes and the formation of ammonium acid urate kidney stones (Sekimoto *et al.*, 2022).

Uric acid displays lactam–lactim tautomerism (also often described as keto–enol tautomerism). Although the lactim form is expected to possess some degree of aromaticity. Uric acid is a strongperoxynitrite scavenger and antioxidant. One clinical observation thatmay speak to uric acid's antioxidative effect is the near absence of multiple sclerosis (MS) in gout patients (Jiménez and Alderete, 2005).

It is believed that the peroxynitrite is responsible for myelin degradation in MS, and peroxynitrite production can be blocked by higher uric acid levels. Conversely, there is a strong association of low serum uric acid levels with increased incidence of MS. In both humans

patients and a murine MS model (experimental autoimmune encephalomyelitis), high serum uric acid levels can reverse the disease progress. It also has been suggested that modest uric acid levels are protective in ischemic stroke. In human blood plasma, the reference range of uric acid is typically 3.4–7.2 mg per 100 mLl (200–430 μmol/l) for men, and 2.4–6.1 mg per 100 ml for women (140–360 μmol/l) (Campbell *et al.*, 2016).

Uric acid concentrations in blood plasma above and below the normal range are known as, respectively, hyperuricemia and hypouricemia. Likewise, uric acid concentrations in urine above and below normal are known as hyperuricosuria and hypouricosuria. Uricacid levels in saliva may be associated with blood uric acid levels (Zhao and Huang, 2015) . Hyperuricemia (high levels of uric acid), which induces gout, has various potential origins:

- Diet may be a factor. High intake of dietary purine, high, and sucrose can increase levels of uric acid (Aiumtrakul *et al.*, 2021).
- Serum uric acid can be elevated by reduced excretion via the kidneys (Mahor *et al.*, 2016).
- Fasting or rapid weight loss can temporarily elevate uric acid levels (Al-Kandari *et al.*, 2009) .
- Certain drugs, such as thiazide diuretics, can increase blood uric acid levels by interfering with renal clearance.
- Tumor lysis syndrome, a metabolic complication of certain cancers or chemotherapy, due to nucleobase and potassium release into the plasma Low uric acid (Hypouricemia) can have numerous causes . Low dietary zinc intakes cause lower uric acid levels. This effect can be even more pronounced in women taking oral contraceptive

medication. (Dong *et al.*, 2014).

hyperuricemia frequently associates with respiratory diseases, patients with severe coronavirus disease 2019 (COVID-19) and severe acute respiratory syndrome (SARS) can show marked hypouricemia. Previous studies on the association of serum uric acid with risk of adverse outcomes related to COVID-19 have produced contradictory results (Chen *et al.*, 2021).

Serum uric acid is increased in respiratory disease, especially inthe presence of hypoxia and systemic inflammation. Evaluated serum uric acid as a biomarker for prediction of mortality and future acute exacerbation of chronic obstructive pulmonary disease (AECOPD) (Bartziokas *et al.*, 2014).

1.2.8.6 Allantoin

Allantoin is a chemical compound with formula ($C_4H_6N_4O_3$) . The properties of Allantoin are Chemical formula ($C_4H_6N_4O_3$) -Molar mass (158.117 $g \cdot mol^{-1}$) -Appearance (colourless crystalline powder) -Density (1.45 g/cm^3) (Ke *et al.*, 2016) It is also called 5-ureidohydantoin or glyoxyldiureide. Allantoin is a major metabolic intermediate in most organisms including animals, plants and bacteria. It is produced from uric acid, which itself is a degradation product of nucleic acids, by action of urate oxidase (uricase) (Pizzichini *et al.*, 1996) .

Allantoin is an imidazolidine-2,4-dione that is 5-aminohydantoin in which a carbamoyl group is attached to the exocyclic nitrogen. It has a role as a vulnerary, a human metabolite. (Xi *et al.*, 2000).

Allantoin was first isolated in 1800 by the Italian physician Michele

Francesco Buniva (1761–1834) and the French chemist LouisNicolas Vauquelin, who mistakenly believed it to be present in the amniotic fluid. In 1821, the French chemist Jean Louis Lassaigne found it in the fluid of the allantois; he called it (acid allantoique). In 1837, the German chemists Friedrich Wöhler and Justus Liebig synthesized it from uric acid and renamed it (allantoin) (Johnson *et al.*, 2009).

Uric acid is an enzymatic end product of endogenous and dietarypurine nucleotide metabolism and a power antioxidant and scavenger of free radicals in humans. Uric acid is converted to allantoin by enzymatic oxidation in vitro and in vivo. Allantoin, which is one froma number of uric acid oxidation products, a metabolic compound in most organisms including animals, plants and bacteria (Zitnanová *et al.*, 2004).

Allantoin has an important role in skin soothing and rapid regeneration of skin cells. It removes corneocytes by loosening the intercellular kit or the desmosomes that maintain the adhesion of corneocytes to each other. Due to these activities, allantoin has been used in cosmetic industry in various forms (e.g. some lotions, creams, shampoos, lipsticks, and different aerosol preparations), as well as in topical pharmaceutical agents for treatment of skin diseases nowadays (Klaunig, 2019).

1.2.8.7 Potassium

Potassium is a chemical element with the symbol K (from Neo-Latin kalium) and atomic number 19. Potassium ions are vital for the functioning of all living cells. The transfer of potassium ions across nerve cell membranes is necessary for normal nerve transmission; potassium deficiency and excess can each result in numerous signs and symptoms, including an abnormal heart rhythm and various electrocardiographic abnormalities. Fresh fruits and vegetables are good dietary sources of potassium (Kovesdy, 2019). The body responds to the influx of dietary potassium, which raises serum potassium levels, with a shift of potassium from outside to inside cells and an increase in potassium excretion by the kidneys. Potassium is the eighth or ninth most common element by mass (0.2%) in the human body, so that a 60 kg adult contains a total of about 120 g of potassium (Al-Musawi, 2018) .

The body has about as much potassium as sulfur and chlorine, and only calcium and phosphorus are more abundant (with the exception of the ubiquitous CHON elements) Potassium ions are present in a wide variety of proteins and enzymes. Potassium disturbances are one of the most common factors among confirmed Covid-19 cases. Both high and low serum potassium levels were found to be important factors independently influencing disease prognosis. Determining the effect of potassium may lead to impaired balance in affected patients (Noori *et al.*, 2022).

1.2.8.8 C-Reactive Protein

C-reactive protein (CRP) is an annular (ring-shaped) pentameric protein found in blood plasma, whose circulating concentrations rise in response to inflammation. CRP is used mainly as an inflammation

marker. Serum C-reactive protein (CRP) level is an indicator of disease severity during COVID-19 infection compared to other hematological and inflammatory markers. Previous studies have indicated that the aberrant host immune response and cytokine storm may play an important role in the severity of COVID-19 (Pepys and Hirschfield, 2003).

CRP is an acute-phase protein that serves as an early marker of inflammation or infection. The CRP serum level is routinely measured in early diagnosis of pneumonia, and some Chinese publications have reported the prognosis value of CRP (Liu, Li, *et al.*, 2020)

Aims of study

The aims of present study are:

1-Measure serum level of xanthine oxidase in patients with COVID – 19, healthy control subject and patient with vaccine and to assess the correlation with other parameters.

2- Measure serum level of hypoxanthine in patients with COVID – 19, healthy control subject and patient with vaccine and to assess correlation with other parameters

3- Measure serum level of CRP in patients with COVID – 19, healthy control subject and patient with vaccine and to assess the correlation with other parameters.

4- Measure serum level of uric acid in patients with COVID – 19, healthy control subject and patient with vaccine and to assess the correlation with other parameters.

5- Measure serum level of allantoin in patients with COVID – 19, healthy control subject and patient with vaccine and to assess the correlation with other parameters.

6- Measure serum level of xanthine in patients with COVID – 19, healthy control subject and patient with vaccine and to assess the correlation with other parameters.

7- Measure serum level of Potassium in patients with COVID – 19, healthy control subject and patient with vaccine and to assess the correlation with other.

Chapter Two

Materials and methods

2.Materials and Methods

2.1. Materials

2.1.1. Instruments and Tools

All instruments and tools that have been used in this study are listed in table (2-1)

Table (2-1) : Instruments and their suppliers .

NO	Instruments	Company and country
1	Centrifuge Tube	Sigma / Germany
2	ELISA reader and printer	Bio Tek / USA
3	Freezer	Liebhe / Austria
4	Micropipettes 100 – 1000 mL	Dragon lab / Chine
5	Micropipettes 5-50 mL	Dragon lab / Chine
6	Spectrophotometer	OPTIMA / Japan
7	Plane Tube	Jorden
8	Eppendorf	Jorden
9	Incubator	Memmert / Germany

10	**Filter paper**	**Broche / Turkey**
11	**HPLC model**	**SYKAMN / Germany**
12	**Tips (10 ul., 200 ul., 1000 uL),**	**CO.ltd / Chine**
13	**SSSGT**	**Vacutube / Chine**
14	**i-chroma**	**Boditech / Korea**

2.1.2. Chemicals and suppliers

Kit that are used in this study with their sources are listed in the Table (2-2).

Table (2-2) Kits and their sources:

NO	Chemicals	Company and country
1	**CRP KIT**	**Boditech / Korea**
2	**Human Hypoxanthine ELISA Kit**	**SUNLONG / Chine**
3	**Human Xanthine oxidase ELISA Kit**	**SUNLONG / Chine**
4	**Potassium Kit**	**Biosam / UAE**
5	**Uric Acid Kits**	**BIOLABO / France**

2.2. Methods

2.2.1. Patients Selection & Blood Sampling

This study included 150 Iraqi subject with aged ranged (15-65) years old and with normal BMI . The subjected in this prospective case – control study included three groups as following:

1-Group (G1) : consist of (50) apparently healthy subjects as control .

2-Group (G2) : consist of (50) patients with COVID-19 with vaccine (P-Fizer) .

3- Group (G3) : consist of (50) patients with COVID -19 .

The Group (G2) and group (G3) were attended from Mirjan Medical city in Babylon Province , Hilla city , from December . 2021 till March 2022.

Five Milliliters of blood were collected from all subjects' venipuncture. The Gel tube was incubated at 37 ^{0}C for 15 min to clot then centrifuge at 4000 rpm for 10 min. The serum which was obtained was divided into 500 µL for determination of Hypoxanthine, 500 µL for determination of Xanthine, 500 µL for determination of Xanthine oxidase , 500 µL for determination of Uric acid, 500 µL for determination of CRP, 500 µL for determination of Potassium and 500 µL for determination of Allatoin . All of the above serum has been kept in Freeze until analysis. All subjects were smoker or exo-smoker males and females in order to increase. Homogeneity of the study population.

2.2.2. Study design

2.2.3 Exclusion criteria

Any disease that may result in change level of parameters as follow:

Cardiovascular co – morbidities like hypertension, ischemic heart disease. Diabetes mellitus disease. Arthritis. Smoker. Hepatic cirrhosis. Pregnancy woman. Patients with tuberculosis, malignancy or connective tissue disorders. The diagnoses of patient with COVID – 19 depend on history, clinical examination and pulmonary function tests.

.

2.2.4 Inclusion criteria

Age (15 – 65) year. exo-smoker males and females in orderto increase homogeneity of the study population, Normal BMI.

2.2.5. Biochemical Measurement

2.2.5.1. Determination Xanthine oxidase (pg/ml)

2.2.5.1.1. Principle

This ELISA kit uses Sandwich-ELISA as the method. The Micro Elisa strip plate provided in this kit has been pre-coated with an antibody specific to XOD. Standards or samples are added to the appropriate Micro Elisa strip plate wells and combined to the specific antibody. Then a Horseradish Peroxidase (HRP)- conjugated antibody specific for TLR6 is added to each Micro Elisa strip plate well and incubated. Free components are washed away. The TMB substrate solution is added to each well. Only those wells that contain XOD and HRP conjugated XOD antibody will appear blue in color and then turn yellow after the addition of the stop solution. The optical

density (OD) is measured spectrophotometric ally at a wavelength of 450 nm. The OD value is proportional to the concentration of XOD. You can calculate the concentration of XOD in the samples by comparing the OD of the samples to the standard curve.

2.2.5.1.2. Reagents preparation

Dilution of Standards:

The standard was diluted by small tubes first, then pipette the volume of 50ul from each tube to microplate well, each tube use two wells, total ten wells. Figure (2-1).

300µl Original Standard + 150µl Standard diluents	**Standard No.1**	**1800pg/L**
300µl Standard No.1 + 150µl Standard diluents	**Standard No.2**	**1200pg/L**
150µl Standard No.2 + 150µl Standard diluent	**Standard No.3**	**600pg/L**
150µl Standard No.3 + 150µl Standard diluent	**Standard No.4**	**300pg/L**
150µl Standard No.4 + 150µl Standard diluent	**Standard No.5**	**150pg/L**

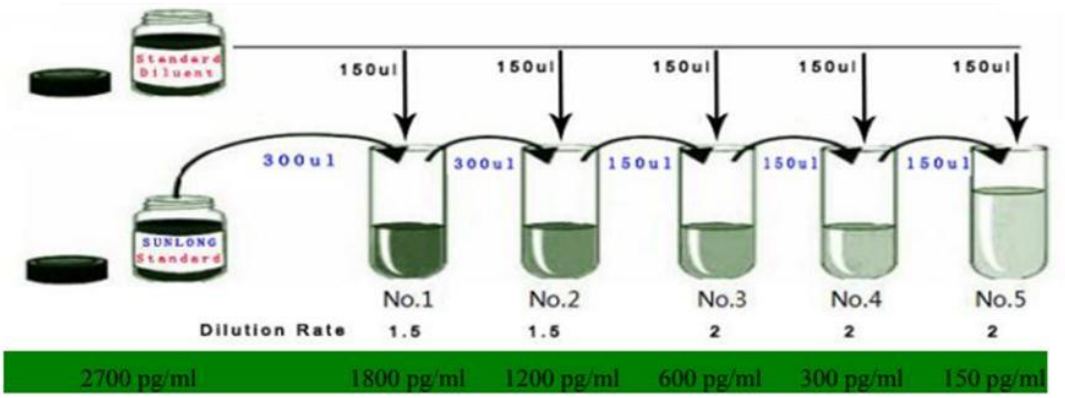

Figure (2-1): The standard reference of dilution method for Xanthine oxidase.

2.2.5.1.3. Procedures

1. In the Micro Elisa strip plate, leave a well empty as blank control. In sample wells, 40µl Sample dilution buffer and 10µl sample are added (dilution factor is 5). Samples should be loaded onto the bottom without touching the well wall. Mixed well with gentle shaking.

2. Incubation: incubate 30 min at 37℃ after sealed with Closure plate membrane.

3. Dilution: dilute the concentrated washing buffer with distilled water (30 times for 96T).

4. Washing: carefully peel off Closure plate membrane, aspirate and refill with the wash solution. Discard the wash solution after resting for 30 seconds. Repeat the washing procedure for 5 times.

5. Add 50 µl HRP-Conjugate reagent to each well except the blank control well.

6. Incubation as described in Step 3.

7. Washing as described in Step 5.

8. Coloring: Add 50 µl Chromogen Solution A and 50 µl Chromogen Solution B to each well, mixed with gently shaking and incubated at 37℃ for 15 minutes. Light was avoided while coloring.

9. Termination: add 50 µl stopped solution to each well to terminated the reaction. The color in the well changed from blue to yellow.

10. The absorbance O.D. was read at 450nm using a Micro titer Plate Reader. The OD value of the blank control well is set as zero. The Assay was be carried out within 15 minutes after adding stop solution.

2.2.5.1.4. Reference range

Result	**Human Xanthine oxidase**
Intra-Assay	**CV<10%**
Inter-Assay	**CV<12%**
Assay range	**30 pg/ml - 2000 pg/ml**

2.2.5.1.5. Calculation Of The Results

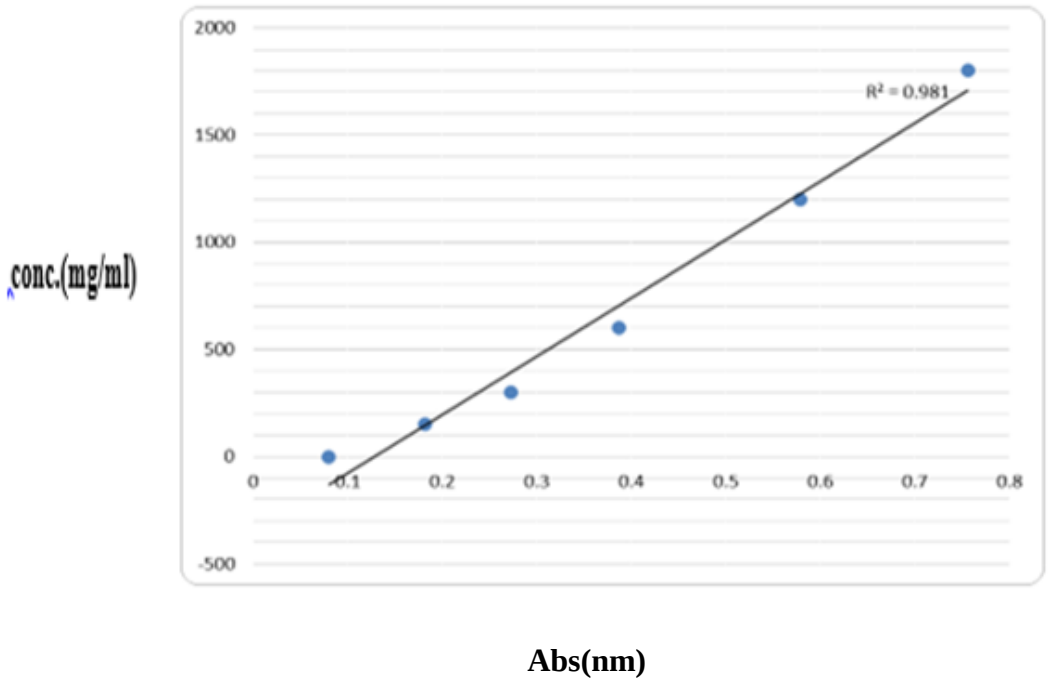

Figure (2-2): The standard curve for Xanthine oxidase

2.2.5.2. Determination Hypoxanthine (ng/ml)

2.2.5.2.1. Principle

This ELISA kit uses Sandwich-ELISA as the method. The Micro Elisa strip plate provided in this kit has been pre-coated with an antibody specific to Hypoxanthine. Standards or samples are added to the appropriate Micro Elisa strip plate wells and combined to the specific antibody. Then a Horseradish Peroxidase (HRP)-conjugated antibody specific for Hypoxanthine is added to each Micro Elisa strip plate well and incubated. Free components are washed away. The TMB substrate solution is added to each well. Only those wells that contain Hypoxanthine and HRP conjugated Hypoxanthine antibody will appear blue in color and then turn yellow after the addition of the stop solution. The optical density (OD) is measured spectrophotometric ally at a wavelength of 450 nm. The OD value is

proportional to the concentration of Hypoxanthine. You can calculate the concentration of Hypoxanthine in the samples by comparing the OD of the samples to the standard curve.

2.2.5.2.2. Reagents preparation

Dilution of Standards

The standard was diluted by small tubes first, then pipette the volume of 50ul from each tube to microplate well, each tube use two wells, a total ten wells.

300µl Original Standard + 150µl Standard diluents	**Standard No.1**	**180ng/L**
300µl Standard No.1 + 150µl Standard diluents	**Standard No.2**	**120ng/L**
150µl Standard No.2 + 150µl Standard diluent	**Standard No.3**	**60ng/L**
150µl Standard No.3 + 150µl Standard diluent	**Standard No.4**	**30ng/L**
150µl Standard No.4 + 150µl Standard diluent	**Standard No.5**	**15ng/L**

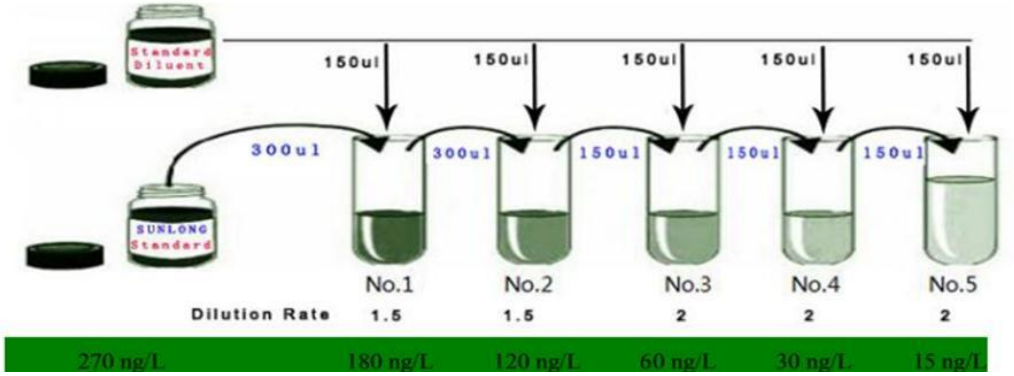

Figure (2-3). The standard reference of dilution method forHypoxanthine.

2.2.5.2.3. Procedures

1. In the Micro Elisa strip plate, leave a well empty as blank control. In sample wells, 40µl Sample dilution buffer and 10µl sample are added (dilution factor is 5). Samples should be loaded onto the bottom without touching the well wall. Mixed well with gentle shaking.

2. Incubation: incubate 30 min at 37℃ after sealed with Closure plate membrane.

3. Dilution: dilute the concentrated washing buffer with distilled water (30 min times for 96T).

4. Washing: carefully peel off Closure plate membrane, aspirate and refill with the wash solution. Discard the wash solution after resting for 30 seconds. Repeat the washing procedure for 5 times.

5. Add 50 µl HRP-Conjugate reagent to each well except the blank control well.

6. Incubation as described in Step 3.

7. Washing as described in Step 5.

8. Coloring: Add 50 µl Chromogen Solution A and 50 µl Chromogen Solution B to each well, mixed with gently shacked and incubated at 37℃ for 15 minutes Light was avoided while coloring.

9. Termination: add 50 µl stopped solution to each well to terminated the reaction. The color in the well changed from blue to yellow.

10. The absorbance O.D. was read at 450nm using a Microtiter Plate Reader. The OD value of the blank control well is set as zero. The Assay was carried out within 15 minutes after adding a stop solution.

2.2.5.2.4. Reference range

Human Hypoxanthine	**Result**
CV<10%	**Intra-Assay**
CV<12%	**Inter-Assay**
6 ng/L - 260 ng/L	**Assay range**

2.2.5.2.5. Calculation of the results

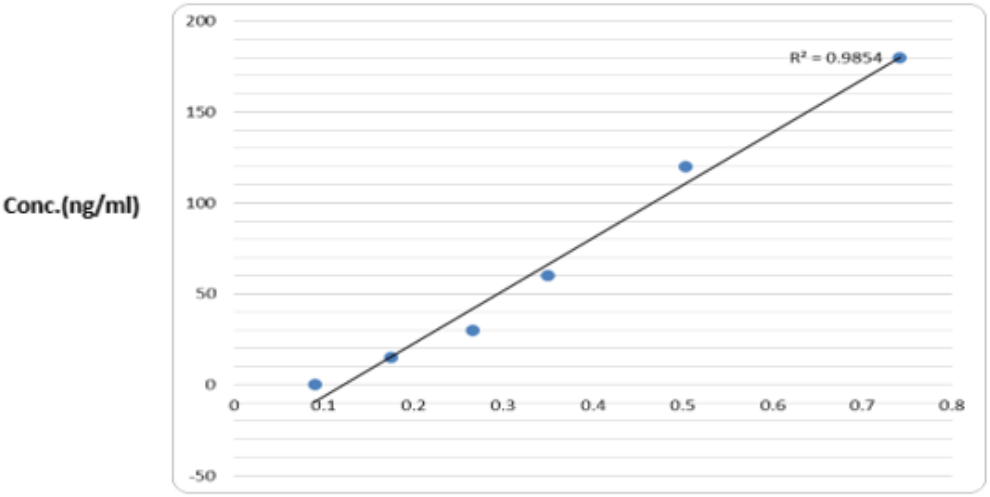

Figure (2-4) : The standard curve for Hypoxanthine concentration .

2.2.5.3. Determination CRP (mg/dl)

The C-RP was determined using a ichroma™ full automated device and a close system laboratory kit (Pepys, M.B.,1981).

Procedures

1) Puncture was made on the top of a detection buffer by inserting an empty sample collector.

2) ten µL was drawn (Human serum) of the sample with a sample collector.

3) The sample collector and the detection buffer were assembled into one.

4) Sample was shaken 10 times or more until the out of the sample collector by inversion. The mixture of the buffer and the sample has to be used within 30 seconds.

5) The cap off the top of the assembled tube was removed.

two drops of reagent were discarded onto the paper towel before applying to a cartridge.

6) Two drops only loaded from the mixture onto the sample well of the cartridge.

7) The cartridge was left at room temperature for 3 min before inserting the device into the holder. The sample-loaded cartridge was scanned immediately when the incubation time was over. If not, it will causeinaccurate test results.

8) To scan the sample-loaded cartridge, it was inserted into the cartridge holder of the instrument for ichroma™ tests.

9) The 'START' button was Selected on the instrument for ichroma™ tests to start the scanning process.

10) Instrument for ichroma™ tests started and scanned the sample-loaded cartridge immediately.

11) The test result was Reading on the display screen of the instrument for ichroma™ tests. Figure (2-5)

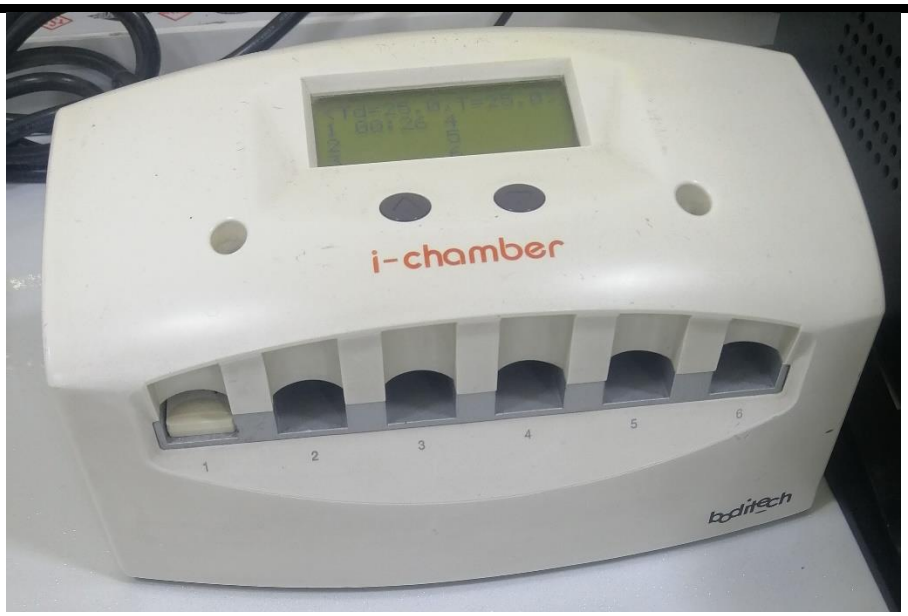

Figure (2-5): Scheme of i-chroma Determination of CRP Concentration.

2.2.5.4. Uric acid

2.2.5.4.1. Principle

Uricase acts on uric acid to produce allantoin, carbon dioxide and hydrogen peroxide. Hydrogen peroxide in the presence of peroxidase reacts with a chromogen (amino-antipyrine) and dichlorohydroxybenzene sulfonate) to yield quinoneimine , a red coloured complex. The absorbance measured at 505 nm is proportional to the amount of uric acid in the specimen (TIETZ N.W. *et al*., 1999).

Vial R1 Enzymes	
Potassium hexacyanoferrate (II)	**42 µmol/L**
Peroxidase	**≥450U/L**
Amino-antipyrine	**0.150 mmole/L**
Uricase	**≥ 120 U/L**
Vial R2 BUFFER	
Dichlorohydroxybenzen sulfonate	**2 mmol/L**
Tris pH 8.0 at 25°C Preservative	**50 mmol/L**
Vial R3 STANDARD	
Uri acid	**10 mg/dL (595 µmol/L)**

2.2.5.4.2. Reagents preparation

Use a non-sharp instrument to remove aluminium cap. Add promptly the contents of vial R1 into vial R2. Mix gently until complete dissolution. Vial R3: Ready for use .

2.2.5.4.3. Manual Procedure

1. Serum, plasma, or urines diluted (1+9) with demineralized water.

2. Specific procedures are available upon request for automated instruments Please contact BIOLABO technical support

3. Kenza applications and other applications proposal are available on request.

Figure (2-6): Scheme of spectrophotometer Determination of Uric Acid Concentration.

2.2.5.4.4. Calculation

Calculate the results as follows:

Result = {Abs (Assay) /Abs (Standard)} x Standard concentration

Diluted urines (1+ 9): Multiply the above result by dilution factor 10.

2.2.5.5. Determination Allantoin (mmol/L)

2.2.5.5.1Sample preparation:

A serum sample (100 µm) was mixed with 400 µm of solvent C (KH2PO4/H3PO4-buffer with 50 mmol/1 phosphates, pH 4.60) then filtered through a membrane filter with a pore diameter of 0.22 µm (Germany). Analiquot (50 µm) of the filtrate was directly injected into the injector of the

HPLC device. The quantification of is based on the peak areas calculated for the wavelength.

2.2.5.5.2. Preparation of standard solutions:

2 mg of each standard was taken and placed in a volumetric flask (25 ml) and the volume was supplemented with methanol (HPLC 99.9 %) to the mark where the stock solution concentration (80 ppm). By using the dilution law C 1 V 1 = C 2V 2, the concentrations that injected into the HPLC were prepared.

HPLC Condition:

High Performance Liquid Chromatography HPLC model SYKAMN (Germany) It was used to analyses add detection of Vincristine and vinblastine . The mobile phase was an isocratic acetonitrile–0.1M phosphate buffer containing 0.5% glacial acetic acid (30 : 70) at flow rate at 1.2 mL/min , column was C18 – ODS (25 cm* 4.6 mm) and the detector UV

– 360 nm.

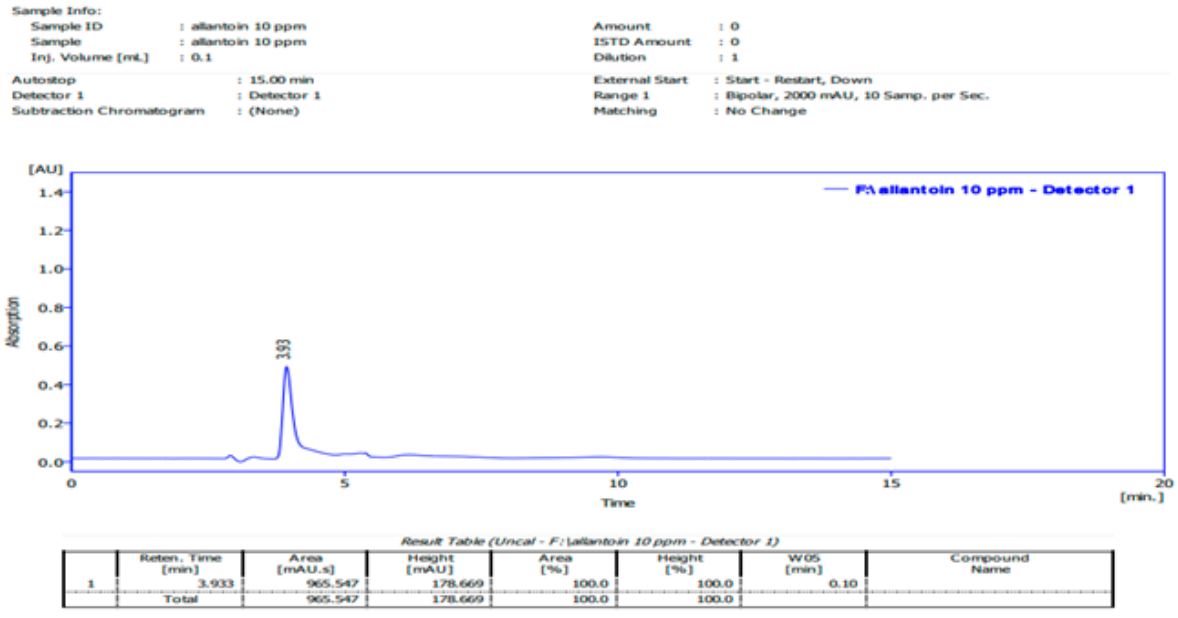

Figure (2-7): Typical chromatogram of prepared allantoin (stander materials) that used in HPLC technique.

2.2.5.6. Xanthine

High performance liquid chromatography

The HPLC was performed on a Bruker Model LC-31 Chromatograph

equipped with Rheodyne injection valve (100 µl injection-loop), 20x4 mm RP-18 guard-column, 250x4mm RP-18 analytical column, both packed with LiChrosorb RP-18, 5 µl material from Merck (Darmstadt, Germany). The guard column had to be replaced every 30 injections to avoid significant reduction of the separation properties. UV-detection was performed using the following settings: wavelength range 200—400 nm, resolution 2nm, 1 scan per second, The eluents used were:

Solvent A: demineralized water
Solvent B: K2HPO4/KH2PO4/H3PO4-buffer with 100 mmol/1 phosphate, pH ranging from 2.50 to 7.50

Solvent C: KH2PO4/H3PO4-buffer with 50 mmol/1 phosphates, pH 4.60 Solvent

D: tri-sodium-citrate 30 mmol/1, sodium-acetate 27.7 mmol/1, pH 4.75, methanol, volume fraction 0.25 The flow-rate was 1 ml/min, corresponding to a back-pressure of 130-145 bar. Procedures and measurements Preparation of the stock-standards. Xanthine was detected at 264 nm. Figure (3-8)

Figure (2-8): Scheme of HPLC Determination of XANTHINE and Allantoin Concentration.

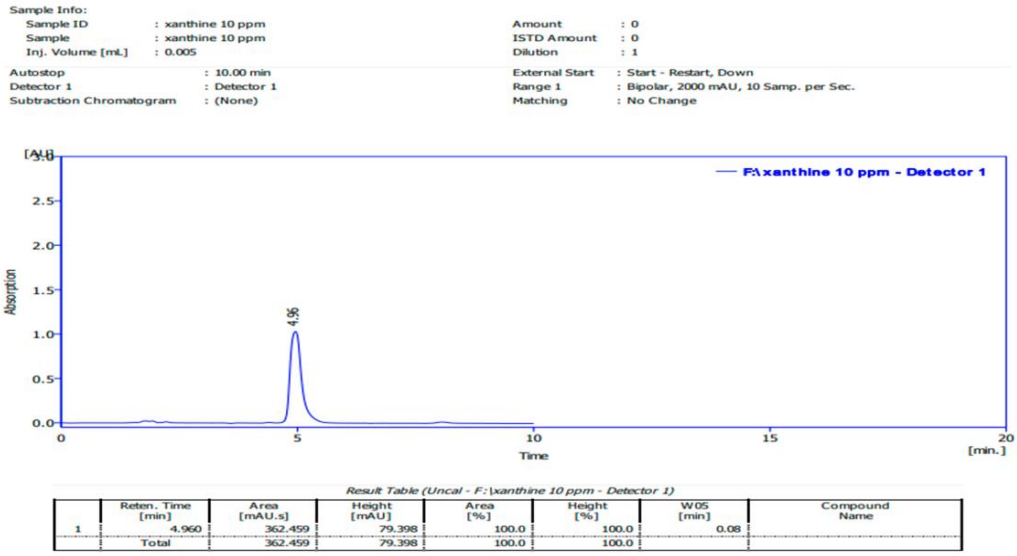

Figure (2-9): Typical chromatogram of prepared xanthine (stander materials) that used in HPLC technique.

2.2.5.7. Potassium

2.2.5.7.1. Principle

Potassium reacts with sodium tetra phenol boron in a specially prepared buffer to form a colloidal suspension. The amount of the turbidity produced is directly proportional to the concentration of potassium in the sample (Stone MS. *et al*., 2016)

2.2.5.7.2. Assay Procedure

Pipette into clean dry test tubes labeled as Blank (B), Standard (S), and Test (T) :

Mix well and incubate at RT for 5 mins. Measure the absorbance ofStandard (Abs.S) and Test (Abs. T) against reagent blank at 630 nm.

2.2.5.7.3. Calculation

NORMAL VALUES: Serum/Plasma: 3.5 - 5.5 mEq/L

2.3. Statistical analysis

Data analysis was performed using SPSS 24 for Windows (SPSS Inc., Chicago IL., USA). Data were expressed as mean, SD, and range, and were evaluated by one – way analysis of variance (ANOVA) followed by KOTI test. The Kolmogorov Smirnov test was used to verify of data followed normal distribution. The statistical significance level was considered at $P \leq 0.005$. correlations between study parameters are tested by correlation coefficient (Steel and Torrie , 1960) .

Chapter Three

Results and Discussion

3.Results and Discussion

3.1. Age and Gender

In this study, 150 blood samples were collected from Hilla Teaching Hospital and Murjan Medical City, 50 of them were collected from healthy people who visited the blood bank for the purpose of donating blood(control group), 50 of them were from patients infected with Covid 19 who had been immunization bythe Pfizer vaccine previously(vaccinated group), and 50 samples were collected from people who were admitted to the hospital Being infected withCOVID-19 and not immunized with any type of COVID-19 vaccines(unvaccinated group), the healthy group had an average lifespan of (35), the vaccinated group (42) and the unvaccinated group (39).As shown in table (4-1) and Figure (3-1) .

Table (3-1): The mean and standard divisions of age for the control , vaccinated and unvaccinated groups.

	Control	vaccinated	unvaccinated
Age	**41.02±10.8[a]**	**39.5±12.26[b]**	**47±12.9[c]**

All data recorded as Means and Standard division. Groups with the same letters have no significant difference

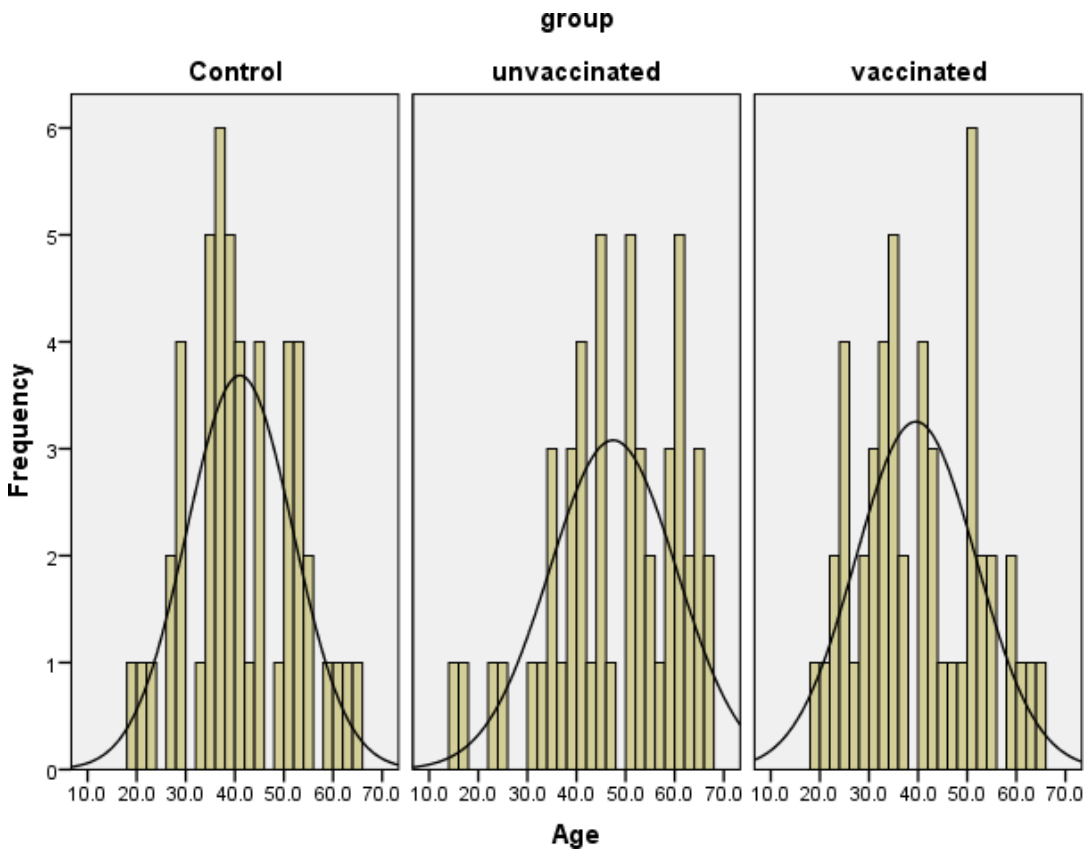

Figure (3-1): chart illustrate the age for three group control,vaccinated and unvaccinated groups.

As for gender, the current study collected equal samples from both sexes for all groups .As showed in Table (3-2).

Table (3-2) The mean and standard divisions of age for the control , vaccinated and unvaccinated groups.

Gender	Control	vaccinated	unvaccinated
Male	25	25	25
Female	25	25	25

3.2. Biochemical Measurement

3.2.1. Levels of Xanthine Oxidase in Serum

Xanthine oxidase was measured in three three groups (n=150 each group 50): control group consist of healthy peoples, vaccinated group consist covid-19 patients whose were immunizations with pfizer vaccine and unvaccinated group consist covid-19 patients whose have not immunizations with covid-19 vaccine. The results showed that the concentration of xanthine oxidase increased significantly in the group of patients infected with Covid 19 who were unvaccinated compared to the other groups. Xanthine oxidase levels (µmol/L) were (6.8±12.7, 31.3±38.5 and 159.1±167.6) respectively. as shown in Table (3-3).

Table (3-3) Xanthin oxidase concentration (µmol/L) in three groups.

Parameter	Control means±SD	Vaccinated means±SD	Unvaccinated means±SD
Xanthine oxidase	6.8 ± 12.7^{a}	31.3 ± 38.5^{b}	159.1 ± 167.6^{c}

All data recorded as Means and Standard division. Groups with the same letters have no significant difference

The xanthine oxidase levels were increased in unvaccinated group than othergroups with a significant difference. Xanthine oxidase (XO) is an enzyme that catalyzes the production of uric acid and superoxide radicals from purine bases xanthine also expressed in respiratory epithelial cells.

Urci acid, which is also considered a danger associated molecular pattern (DAMP), could trigger a series of inflammatory responses by activating theinflammasome complex path and NF-κB within the endothelial cells and by inducing proinflammatory cytokine release (Pratomo *et al.*, 2021). This means that there is a positive relationship between xanthine oxidase and inflammatory factors, and the higher its concentration, the greater the intensity of inflammation. This shows the effective role of the vaccine in reducing the severity of the infection, as the concentration of xanthine oxidase in the vaccinated group was almost equal to the control group.

Xanthine oxidase showed positive correlation is significant at the 0.01 levelfor all parameters except potassium showed negative correlation. The r values for (xanthine, hypoxanthine, CRP, uric acid, allantoin and potassium) were (0.581, 0.939, 0.880,0.547,0.550 and -0.684) respectively. As shown in table (3-4).

Table (3-4) Correlation between xanthine oxidase and other parameters

Parameters		**Xanthine**	**Hypoxanthine**	**CRP**	**Uric. Acid**	**Allantoin**	**Potassium**
Xanthine Oxidase	**r**	**0.581****	**0.939****	**0.880****	**0.547****	**0.550****	**-0.684****
**** Correlation is significant at the 0.01 level .**							

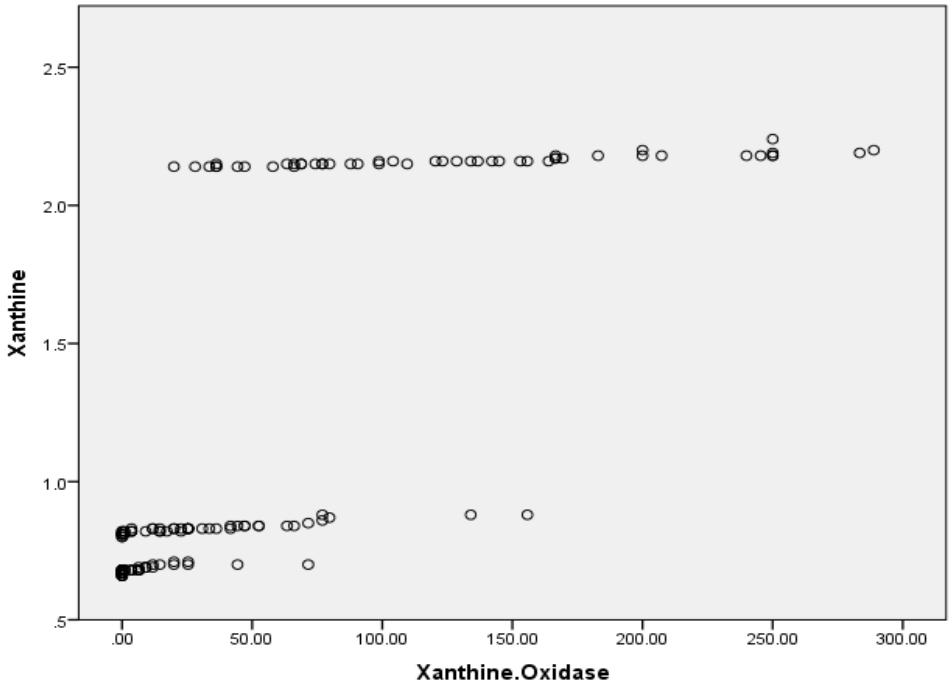

Figure (3-2): Correlations test between xanthine oxidase and xanthine.

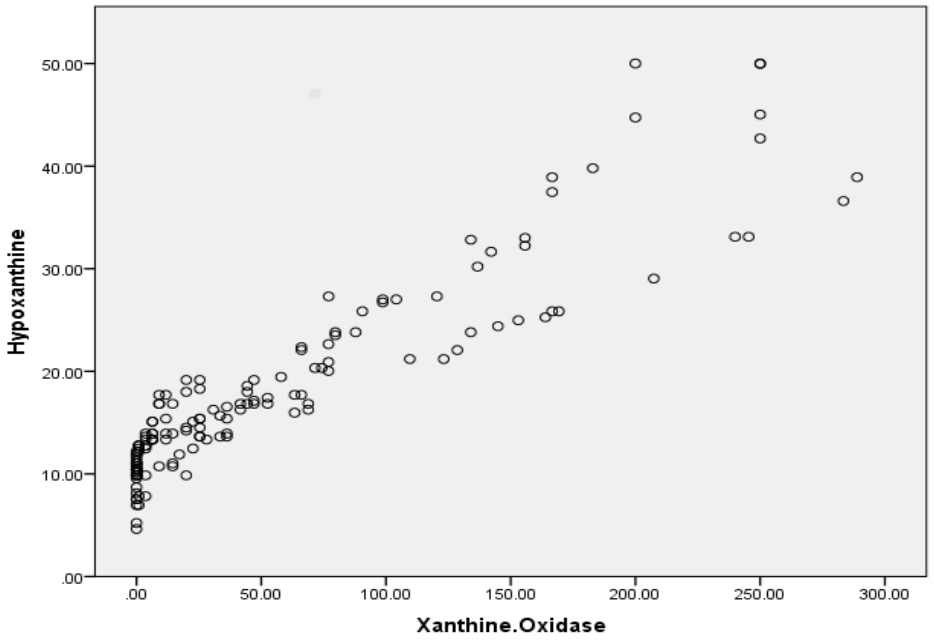

Figure (3-3): Correlations test between xanthine oxidase and Hypoxanthine.

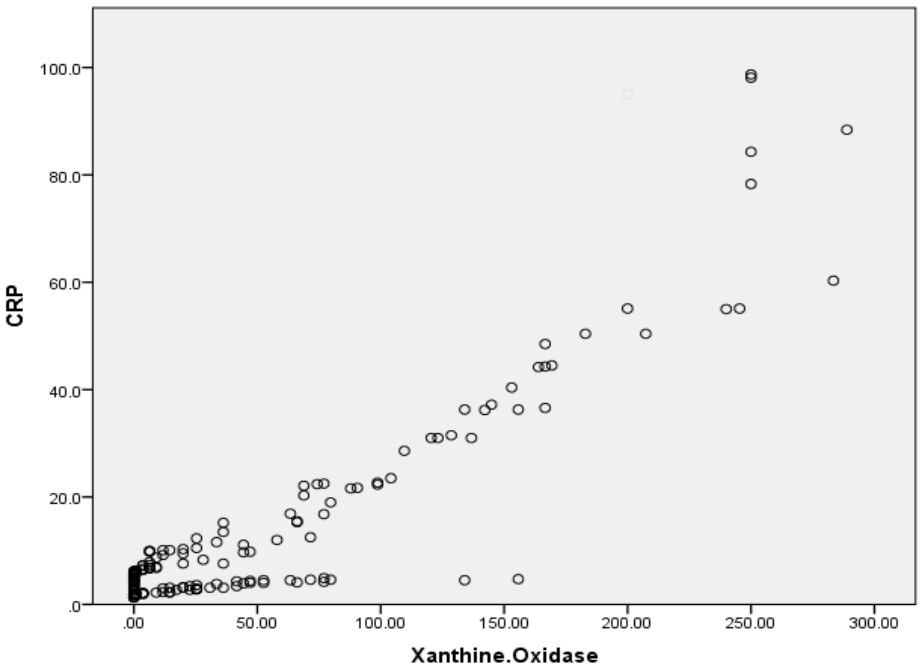

Figure (3-4): Correlations test between xanthine oxidase and CRP.

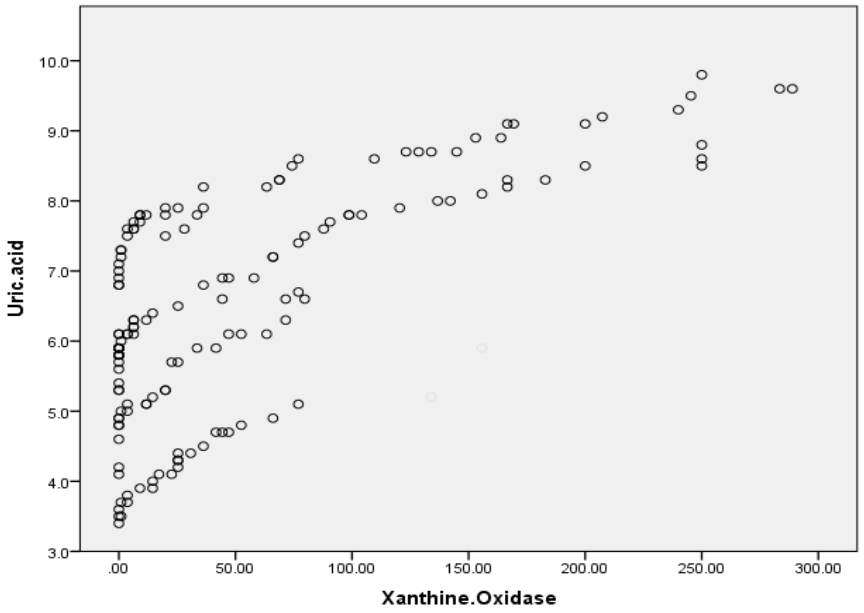

Figure (3-5): Correlations test between xanthine oxidase and uric acid.

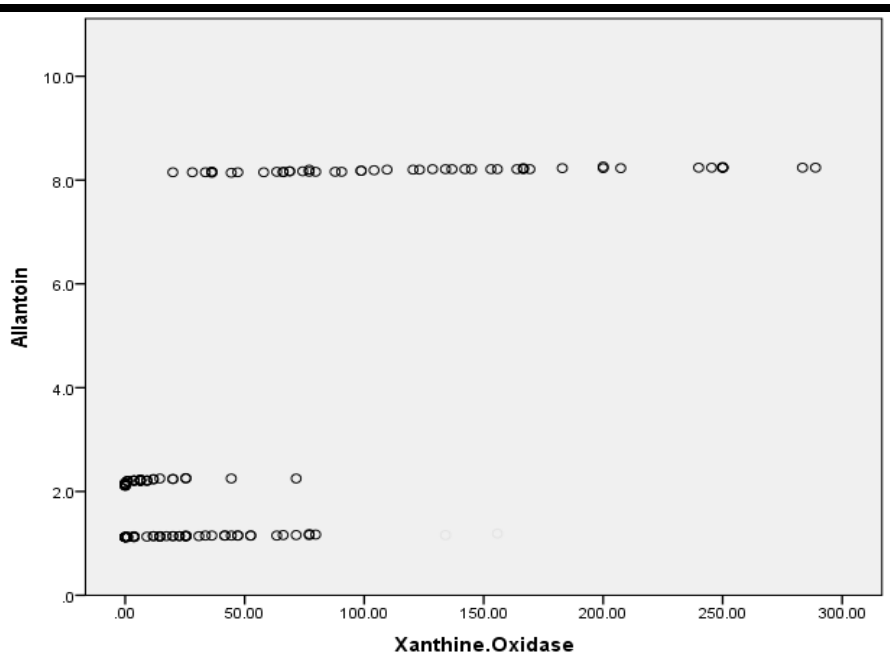

Figure (3-6) : Correlations test between xanthine oxidase and allantoin .

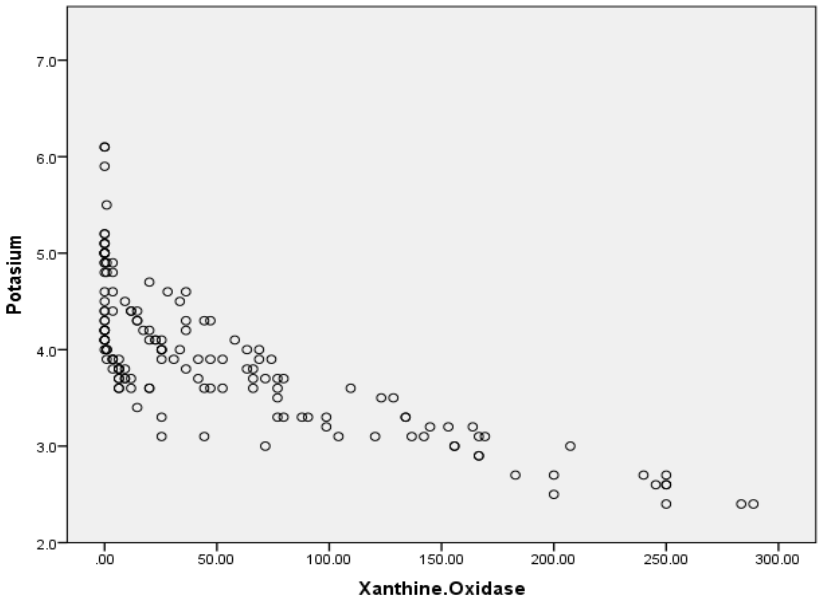

Figure (3-7): Correlations test between xanthine oxidase and Potassium.

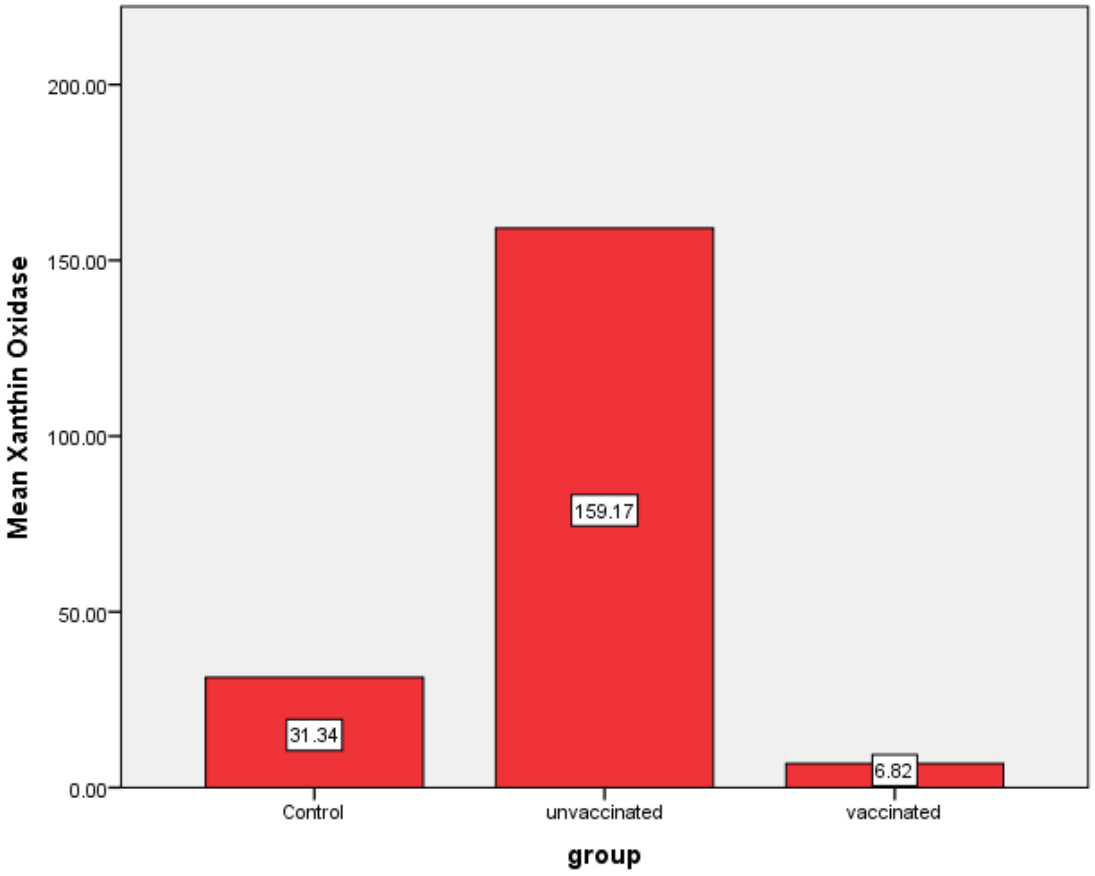

Figure (3-8): chart illustrates the mean of xanthine oxidase in three groups.

3.2.2. Levels of Xanthine in serum (µmol/L)

Three groups of Xanthine were measured (n=150, each group 50): Healthy individuals make up the control group. The vaccinated group consists of covid-19 patients who have had vaccinations with the pfizer vaccine, whereas the unvaccinated group consists of covid-19 patients who have not received vaccinations with the covid-19 vaccine. The findings demonstrated that, in comparison to the other groups, the patients with Covid- 19 infections who had not had a vaccination had considerably higher concentrations of xanthine. Xanthine levels were (0.83±0.01, 0.68±0.01 and 2.16±0.02) respectively. as shown in table (3-5)

Table (3-5) : Xanthin concentration(µmol/l) in three groups.

Parameter	Control means±SD	Vaccinated means±SD	Unvaccinated means±SD
Xanthine	0.83±0.01[a]	0.68±0.01[b]	2.16±0.02[c]

All data recorded as Means and Standard division. Groups with the same letters have no significant difference

The current study found an increase in the concentration of xanthine in the group of unvaccinated patients more than the rest of the groups in the current study. This means two important things, the first is that the concentration of xanthine is related to the severity of inflammation, and the second is that the vaccine has an effective role in reducing the symptoms of the disease, as the proportion of xanthine decreased in patients.

There are no previous studies specialized in the relationship between xanthine and vaccine or xanthine and Covid 19, so the study was limited to citing old previous studies regarding the relationship of inflammation in general with xanthine levels. A previous study found a significant increase in the level of xanthine in people who suffer from arthritis more than healthy people (Gudbjörnsson *et al*., 1991).

Perhaps the reason is that inflammation increases cell death and thus increases the metabolism of purines, and thus increases xanthine as a byproduct.

Or because xanthine oxidase enzyme is absent. During catabolism hypoxanthine is converted to xanthine and then to urate by xanthine oxidase. If this enzyme was absent in the inflammations, xanthine and hypoxanthine would be the end products of purine metabolism. Xanthine oxidase was previously thought to be almost exclusively found in the liver and

intestinal mucosa (Aziz and Jamil 2021).

Xanthine showed positive correlation is significant at the 0.01 level for all parameters except potassium showed negative correlation. The r values for (hypoxanthine, CRP, uric acid, allantoin and potassium) were (0.544, 0.710, 0.714,0.974 and -0.518) respectively. As shown in table (4-6).

Table (3-6): Correlation between xanthine and other parameters.

Parameters		Hypoxanthine	CRP	Uric. Acid	Allantoin	Potassium
Xanthine	r	0.544**	0.710**	0.714**	0.974**	-0.518**
** Correlation is significant at the 0.01 level .						

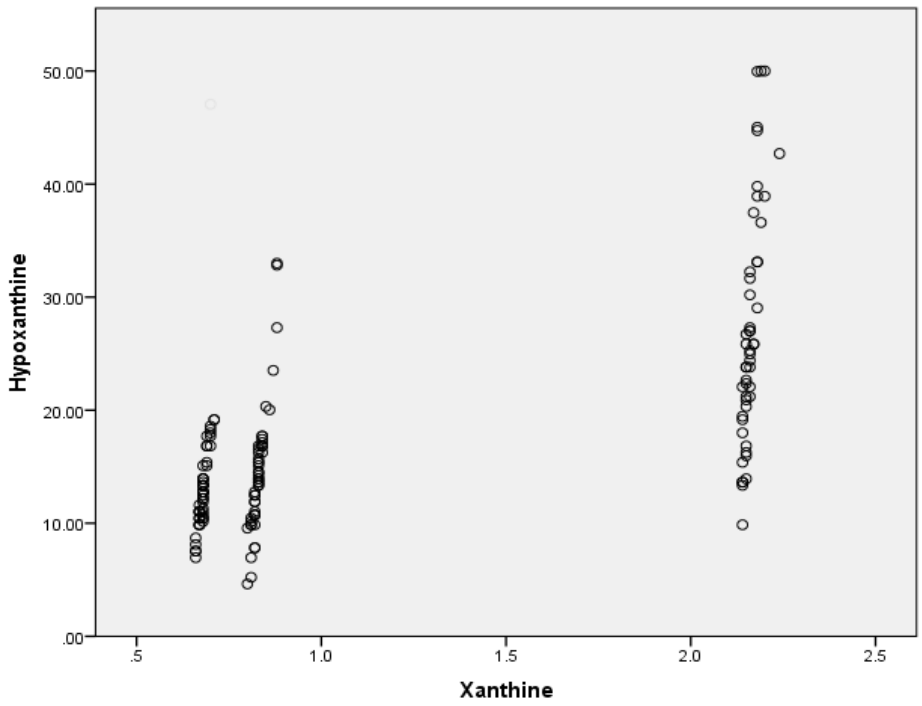

Figure (3-9) : Correlations test between xanthine and hypoxanthine.

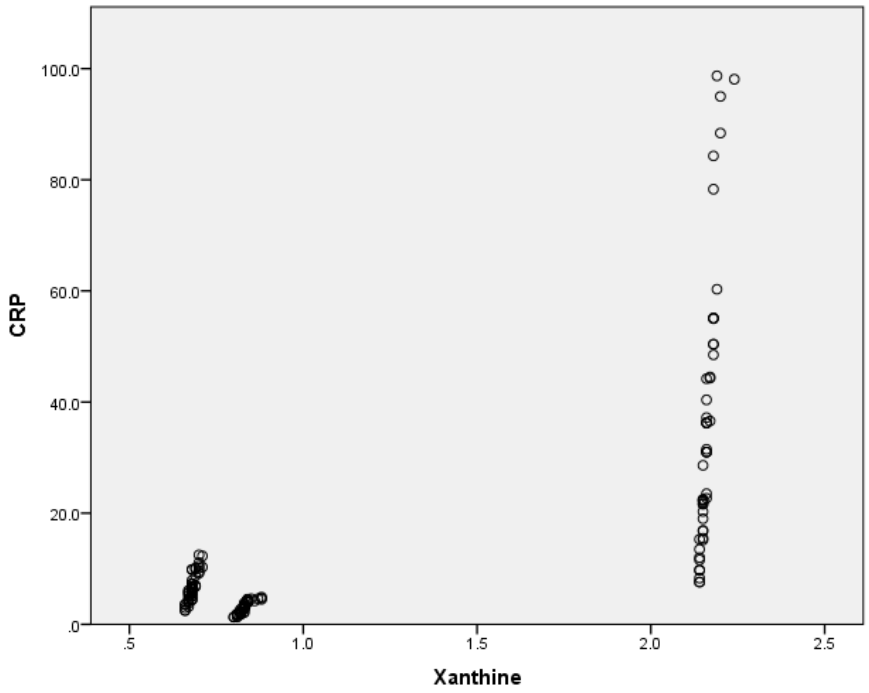

Figure (3-10): Correlations test between xanthine and CRP.

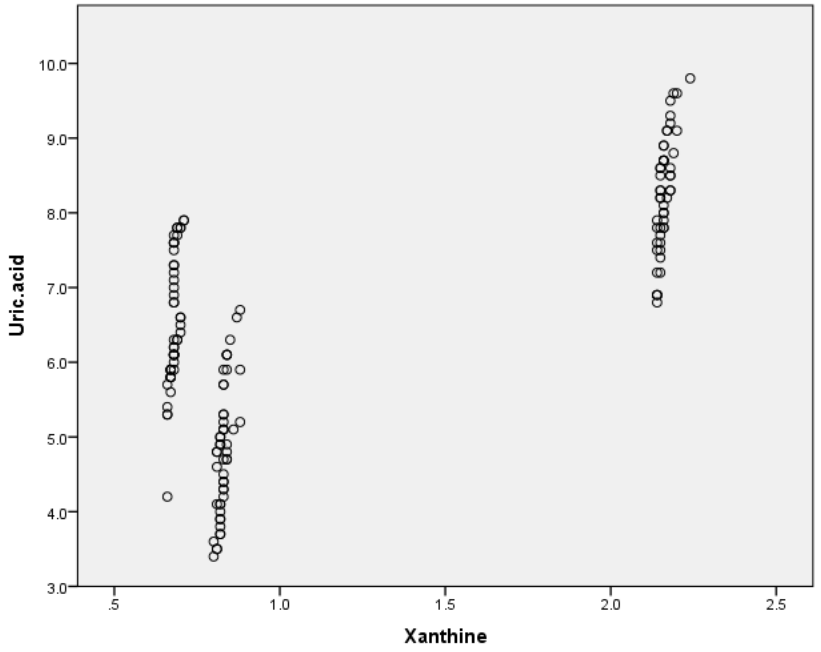

Figure (3-11): Correlations test between xanthine and uric acid.

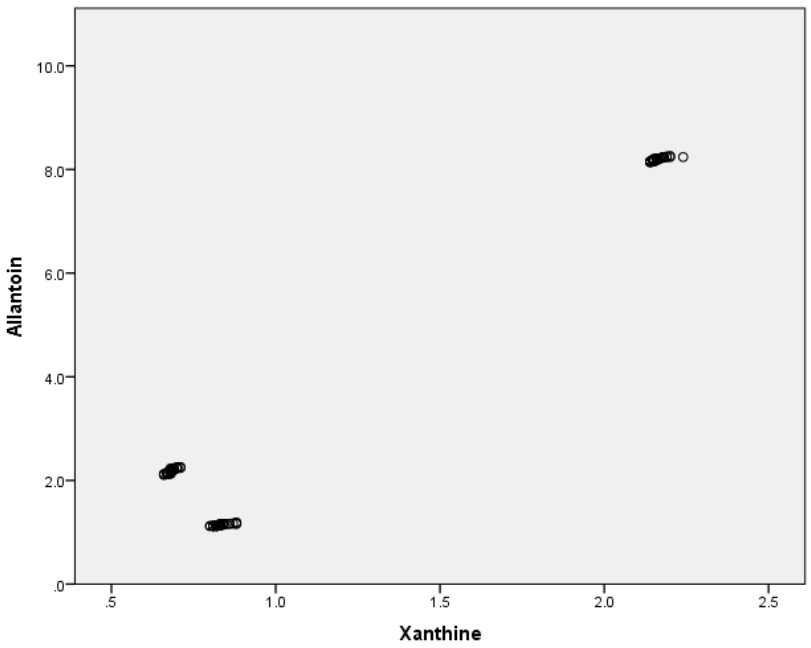

Figure (3-12): Correlations test between xanthine and allantoin.

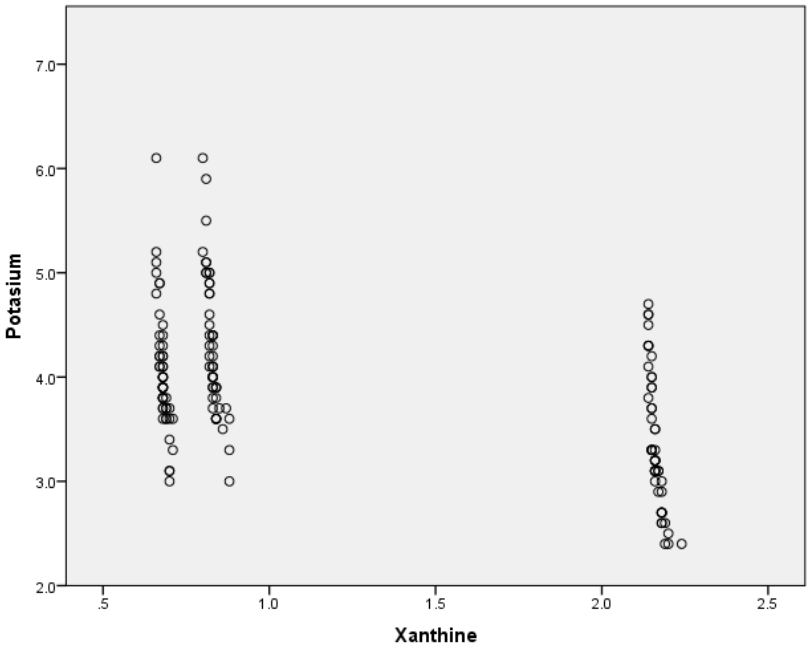

Figure (3-13): Correlations test between xanthine and potassium.

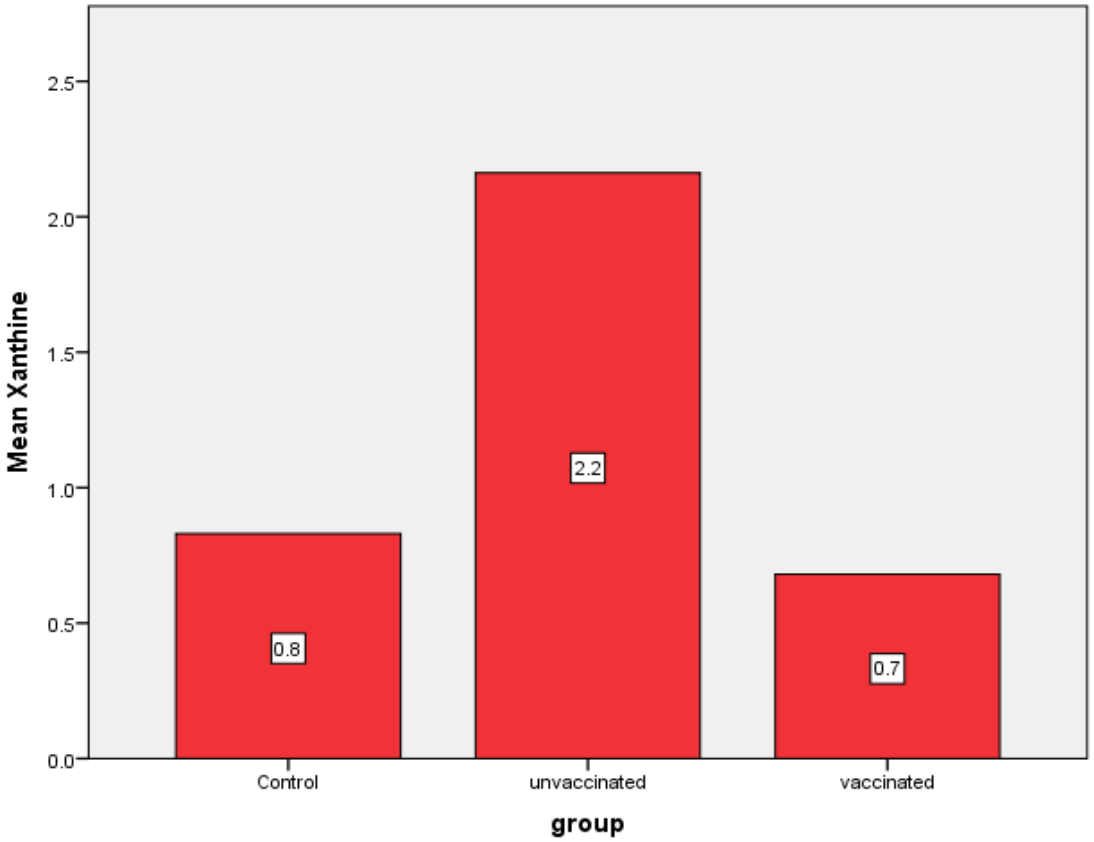

Figure (3-14) : chart illustrates the mean of xanthine (µmol/L) in three groups.

3.3. Levels of Hypoxanthine in serum (pg/ml)

This assay was done for three groups (n=150, each group n=50): control group consist of healthy peoples, vaccinated group consist covid-19 patients whose were immunizations with pfizer vaccine and unvaccinated group consist covid-19 patients whose have not immunizations with covid-19 vaccine. The results showed that the concentration of hypoxanthine increased significantly in the group of patients infected with Covid 19 who were unvaccinated compared to the other groups. Control and vaccinated group showed no significant difference. Its were (13.5±5.7, 14.8±6.8 and 29±17.6) respectively. Also the results showed no significant differences between control and vaccinated group as shown in table (3-7).

Table (3-7) : Hypoxanthine concentration(pg/ml) in three groups.

Parameter	Control means±SD	Vaccinated means±SD	Unvaccinated means±SD
Hypoxanthine	**13.5±5.7^{a}**	**14.8±6.8^{a}**	**29±17.6^{c}**
All data recorded as Means and Standard division. Groups with the same letters have no significantdifference			

In physiological conditions, hypoxanthine and xanthine concentrations in the cell ranged around 1–3 μM, while in hypoxic conditions, the concentrations of hypoxanthine and xanthine increase to about 50–100 μM and cause pH reduction to 7 (Cantu-Medellin and Kelley, 2013). In that condition, this enzyme undergoes a post translational modification in the 535th and 992nd cysteine residues or proteolysis, resulting in XDH conversion into XO (Kuwabara *et al.*, 2003).

Hypoxanthine showed positive correlation is significant at the 0.01level for all parameters except potassium showed negative correlation. Ther values for (xanthine, CRP, uric acid, allantoin and potassium) were (0.544,0.838, 0.550, 0.523 and -0.717) respectively. As shown in table (4-8).

Table (3-8) Correlation between hypoxanthine and other parameters.

Parameters		Xanthine	CRP	Uric. Acid	Allantoin	Potassium
	Sig.		0.00	0.00	0.00	0.00
Hypoxanthine	r	0.544**	0.838**	0.550**	0.523**	-0.717-**
** Correlation is significant at the 0.01 level .						

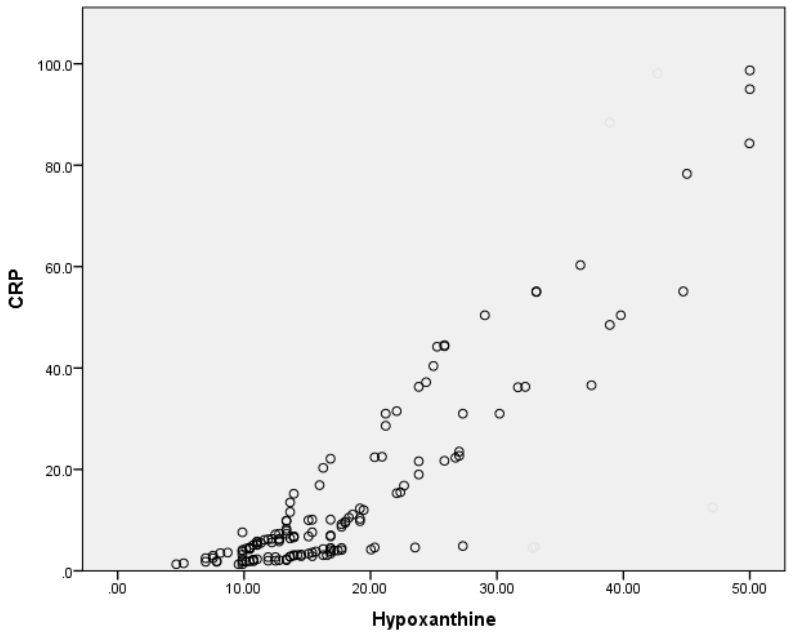

Figure (3-15): Correlations test between hypoxanthine and CRP.

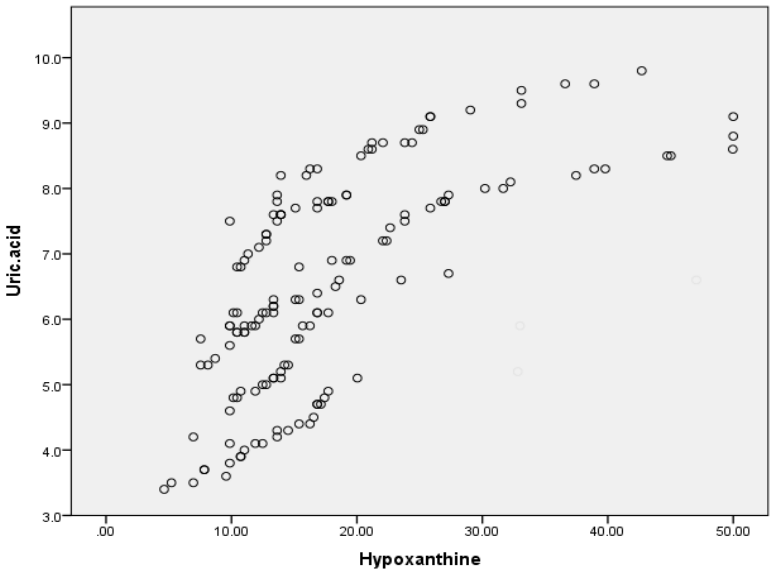

Figure (3-16): Correlations test between hypoxanthine and uric acid.

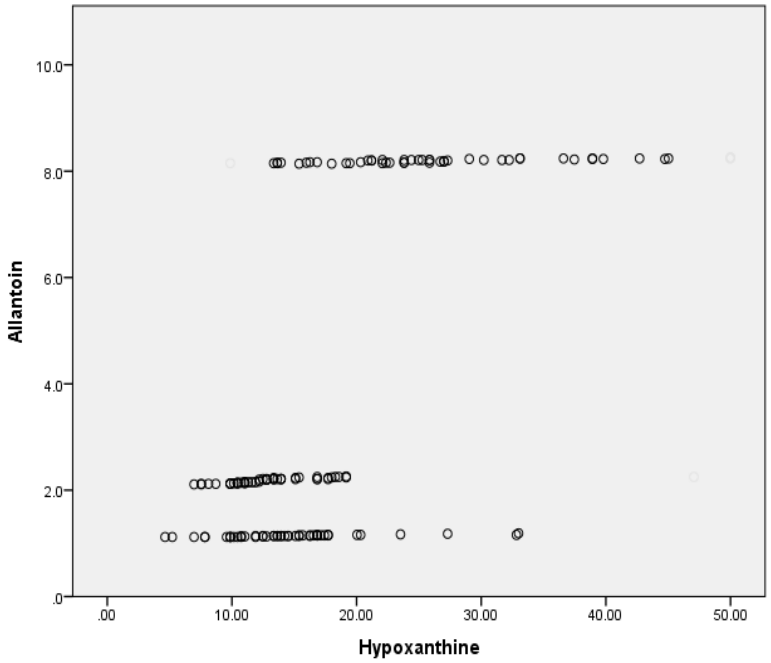

Figure (3-17) : Correlations test between hypoxanthine and Allantoin.

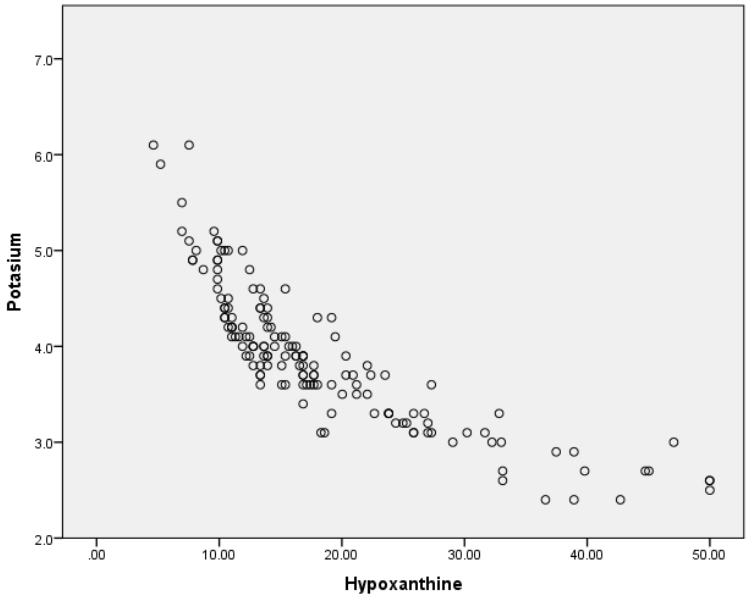

Figure (3-18): Correlations test between hypoxanthine and potassium.

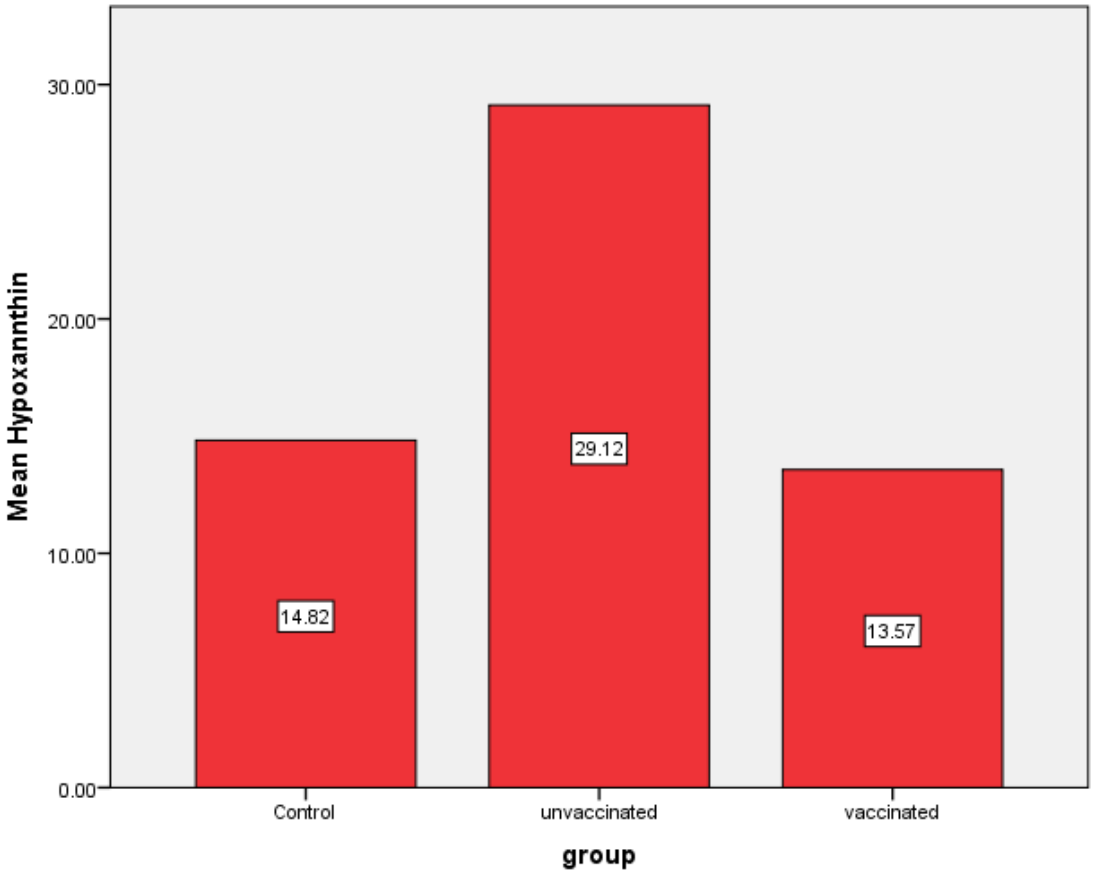

Figure (3-19): Chart illustrates the mean of hypoxanthine in three groups.

3.3.1.C-reactive protein

The CRP was measured for three groups. The results showed that the concentration of CRP increased significantly in the group of patients infected with Covid 19 who were unvaccinated compared to the other groups. Control and vaccinated group showed no significant difference. Its were (2.9±1.07, 6.6±2.5 and 36.4±25.7) respectively. Also the results showed no significant differences between control and vaccinated group as shown in table (3-9).

Table (3-9) CRP concentration (mg/dl) in three groups.

Parameter	Control mean±SD	Vaccinated means±SD	Unvaccinated means±SD
CRP	**2.9±1.07[a]**	**6.6±2.5[a]**	**36.4±25.7[b]**
All data recorded as Means and Standard division. Groups with the same letters have no significant difference			

Blood levels of the prototypic acute phase reactant, C-reactive protein (CRP), which is hepatically synthesized and released in response to interleukin-6 stimulation, is markedly elevated in patients with COVID-19. Markedly high CRP levels correlate with poor prognosis for survival. Insights into CRP structure–function relationships have uncovered both pro- and anti-inflammatory isoforms that may be used to monitor the extent of tissue damage associated with COVID-19 pathologies and prognoses (Potempa *et al.*, 2020).

A current study showed an increase of CRP in patients who are not immunized with vaccines than other groups with significant differences, that means these parameters may be utilize as indicator for estimation of vaccines activity.

CRP showed positive correlation is significant at the 0.01 level for all parameters except potassium showed negative correlation. The r valuesfor (xanthine, hypoxanthine, uric acid, allantoin and potassium) were (0.710, 0.838, 0.716, 0.716 and -0.703) respectively. As shown in table (3-10).

Table (3-10) Correlation between CRP and other parameters.

Parameters		Xanthine	Hypoxanthine	Uric. Acid	Allantoin	Potassium
CRP	r	0.710**	0.838**	0.716**	0.716**	-0.703-**
** Correlation is significant at the 0.01 level .						

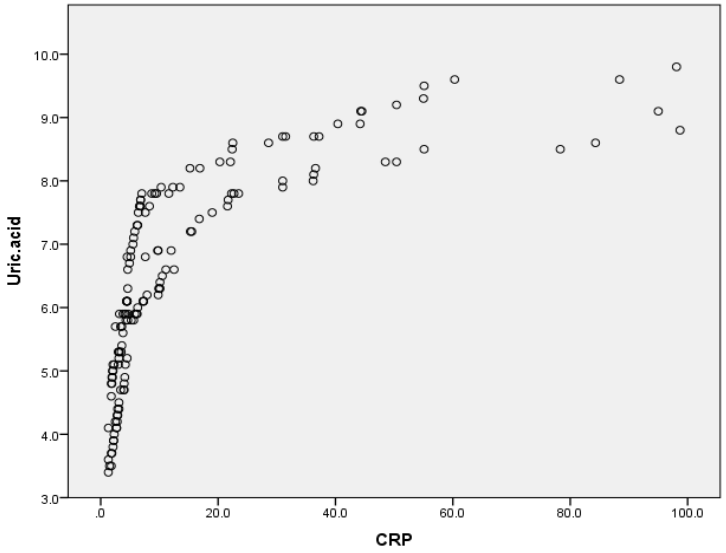

Figure (3-20): Correlations test between CRP and uric acid.

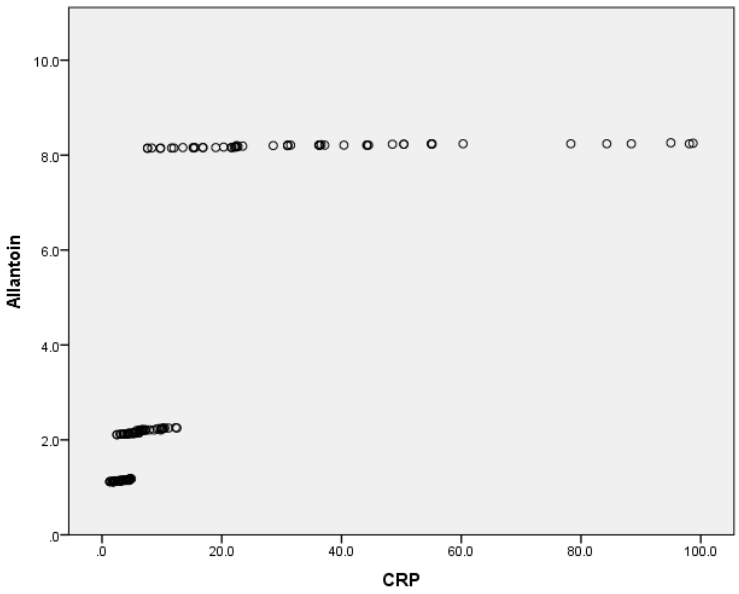

Figure (3-21) : Correlations test between CRP and allantoin.

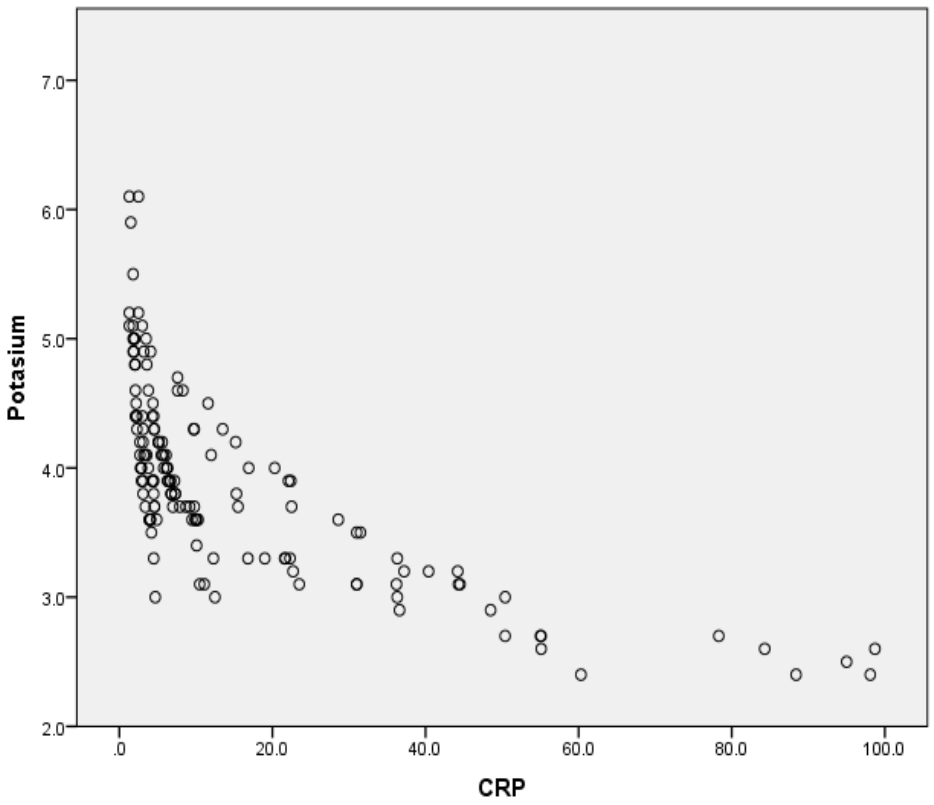

Figure (3-22): Correlations test between CRP and potassium.

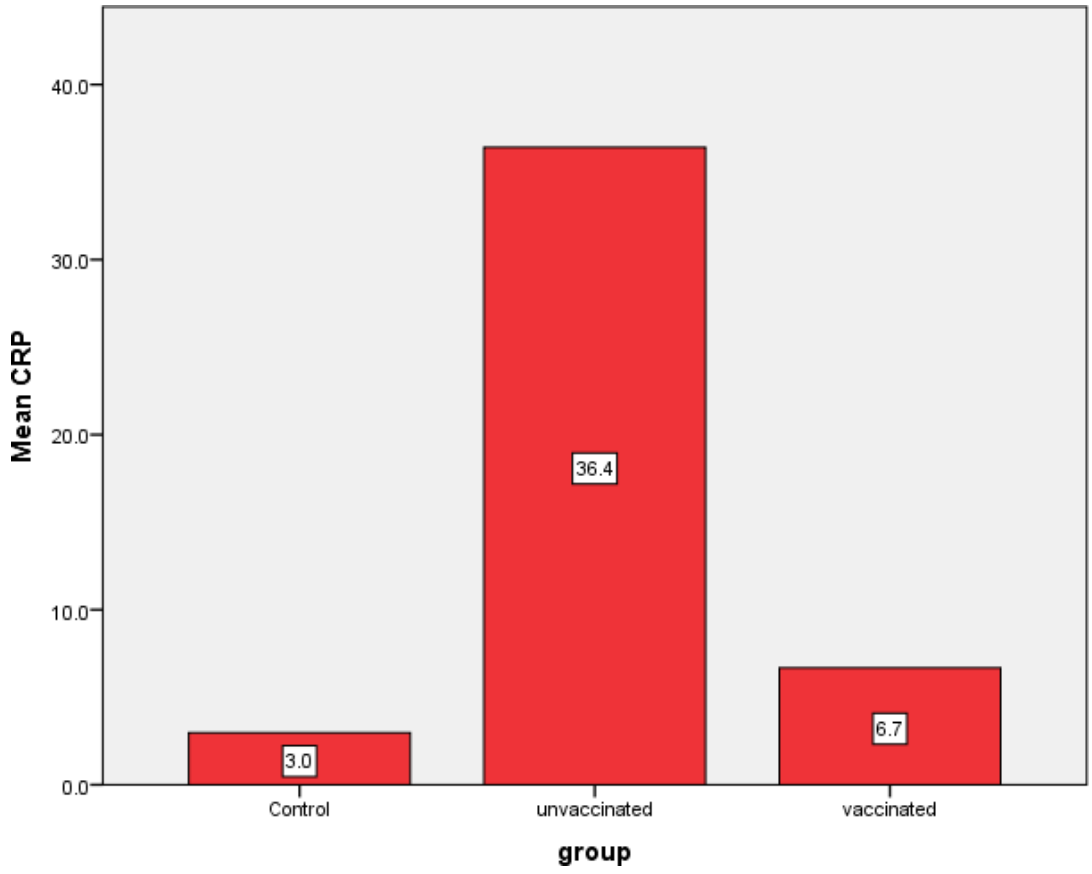

Figure (3-23): Chart illustrates the mean of CRP (mg/dl) in three groups.

3.3.2. Levels of Uric Acid in serum (mg/dl)

The uric acid was measured in groups. The results showed that the concentration of hypoxanthine increased significantly in the group of patients infected with Covid 19 who were unvaccinated compared to the other groups. The uric acid showed significant increase in unvaccinated group difference. Its were (4.8±0.8, 6.5±0.8 and 8.2±0.7) respectively . Also the results showed no significant differences between control and vaccinated group as shown in table (3-11)

Table (3-11) Uric Acid concentration (mg/dl) in three groups

Parameter	Control means±SD	Vaccinated means±SD	Unvaccinated means±SD
Uric Acid (mg/dl)	**4.8±0.8[a]**	**6.5±0.8[b]**	**8.2±0.7[c]**
All data recorded as Means and Standard division. Groups with the same letters have no significant difference			

Uric acid also showed significant increase in unvaccinated group than other groups that indicated to severity of infection in this group. and other groups showed normal values of these parameters.

Previous study aimed to explore whether uric acid can independentlyact as a prognostic factor and critical marker of COVID-19. A study determined that the lowest concentration of UA during hospitalization canbe used as a prognostic indicator and a marker of disease severity in severepatients with COVID-19 (Li, Wu, *et al.*, 2021).

Therefore, this parameter is of great importance in determining the severity of infection with Covid-19, as the results of the current study showedthat the group of vaccinated patients did not suffer from any rise in uric acidand it was within the normal range, and this explains two important things,the first is that the vaccine is effective, and the second is that this parameteris important Monitoring disease severity or vaccine efficacy.

Uric acid showed positive correlation is significant at the 0.01 level for all parameters except potassium showed negative correlation. The r values for (xanthine, hypoxanthine, CRP, allantoin and potassium) were (0.714, 0.550, 0.716, 0.803 and -0.705) respectively. As shown in table (4-12)

Table (3-12) Correlation between uric acid and other parameters.

Parameters		Xanthine	Hypoxanthine	CRP	Allantoin	Potassium
Uric. Acid	r	0.714**	0.550**	0.716**	0.803**	-0.705-**
** Correlation is significant at the 0.01 level .						

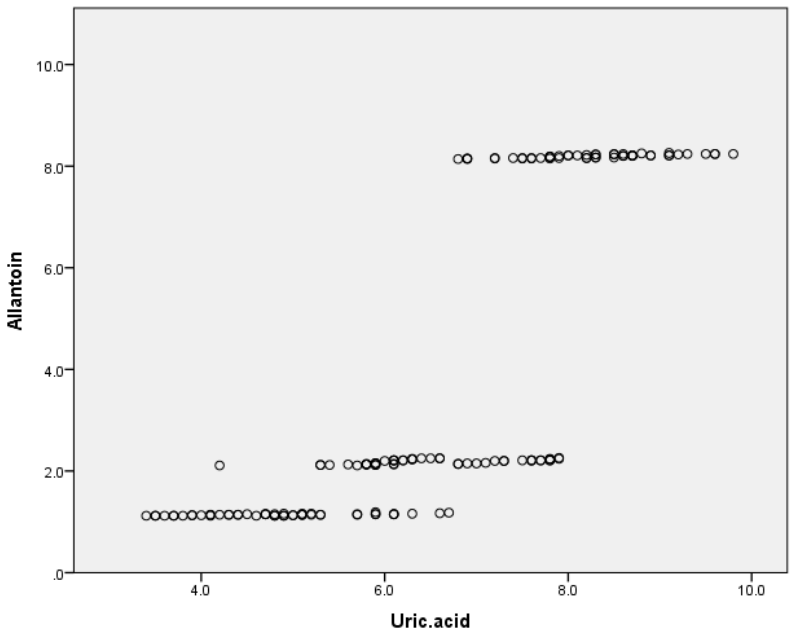

Figure (3-24) : Correlations test between uric acid and allantoin.

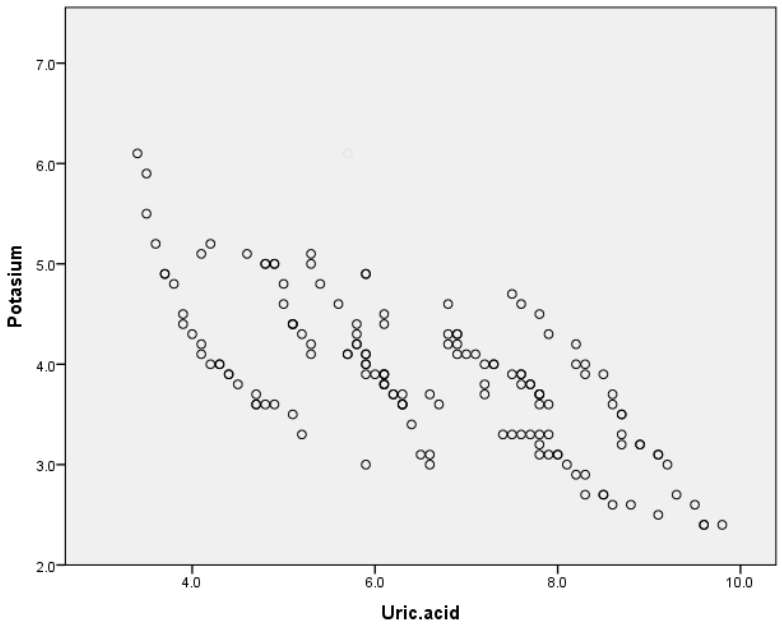

Figure (3-25) Correlations test between uric acid and potassium.

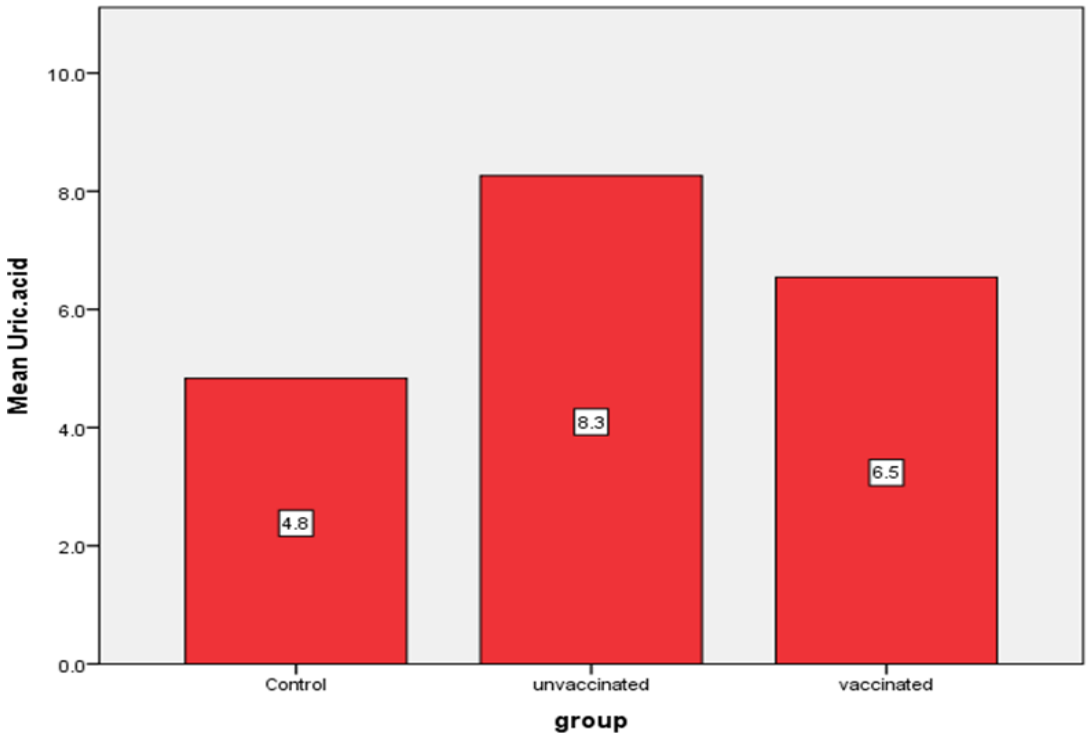

Figure (3-26): Chart illustrates the mean of uric acid (mg/dl) in three groups.

3.3.3. Levels of Allantoin in serum (mmol/L)

Allantoin was measured in three three groups (n=150 each group 50): control group consist of healthy peoples, vaccinated group consist covid-19 patients whose were immunizations with pfizer vaccine and unvaccinated group consist covid-19 patients whose have not immunizations with covid-19 vaccine. The results showed that the concentration of allantoin increased significantly in the group of patients infected with Covid -19 who were unvaccinated compared to the other groups. Xanthine levels were (1.1±0.01, 2.1±0.04 and 8.1±0.03) respectively. as shown in table (3-13).

Table (3-13) Allantoin concentration (mmol/L) in three groups.

Parameter	Control means±SD	Vaccinated means±SD	Unvaccinated means±SD
Allantoin (mmol/L)	1.1±0.01[a]	2.1±0.04[b]	8.1±0.03[c]
All data recorded as Means and Standard division. Groups with the same letters have no significant difference			

The results of this parameter showed a significant increase in the unvaccinated group with a significant difference from the rest of the groups. As for the vaccinated group, the parameter level was within the normal range.

Uric acid is the end product of purine metabolism in humans. It has been pointed out that uric acid acts as an antioxidant and is capable to reactwith biologically relevant oxidants to form allantoin (Kand'ár *et al.*, 2006).

Allantoin, the major oxidation product of urate, has been suggestedas a candidate biomarker of oxidative stress because it is not produced metabolically (Gruber *et al.*, 2009).

Allantoin showed positive correlation is significant at the 0.01 level for all parameters except potassium showed negative correlation. The r values for (xanthine, hypoxanthine, CRP, uric acid and potassium) were (0.974, 0.523, 0.716, 0.803 and -0.535) respectively. As shown in table (3-14).

Table (3-14) Correlation between allantoin and other parameters.

Parameters		Xanthine	Hypoxanthine	CRP	Uric. Acid	Potassium
Allantoin	r	0.974**	0.523**	0.716**	0.803**	-0.535-**
** Correlation is significant at the 0.01 level .						

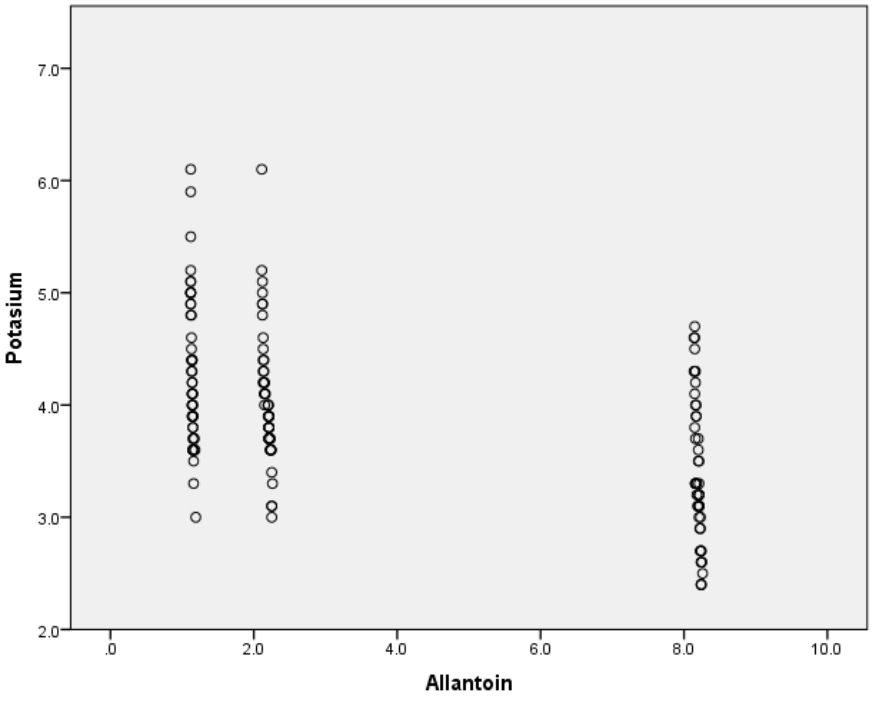

Figure (3-27) : Correlations test between allantoin and potassium .

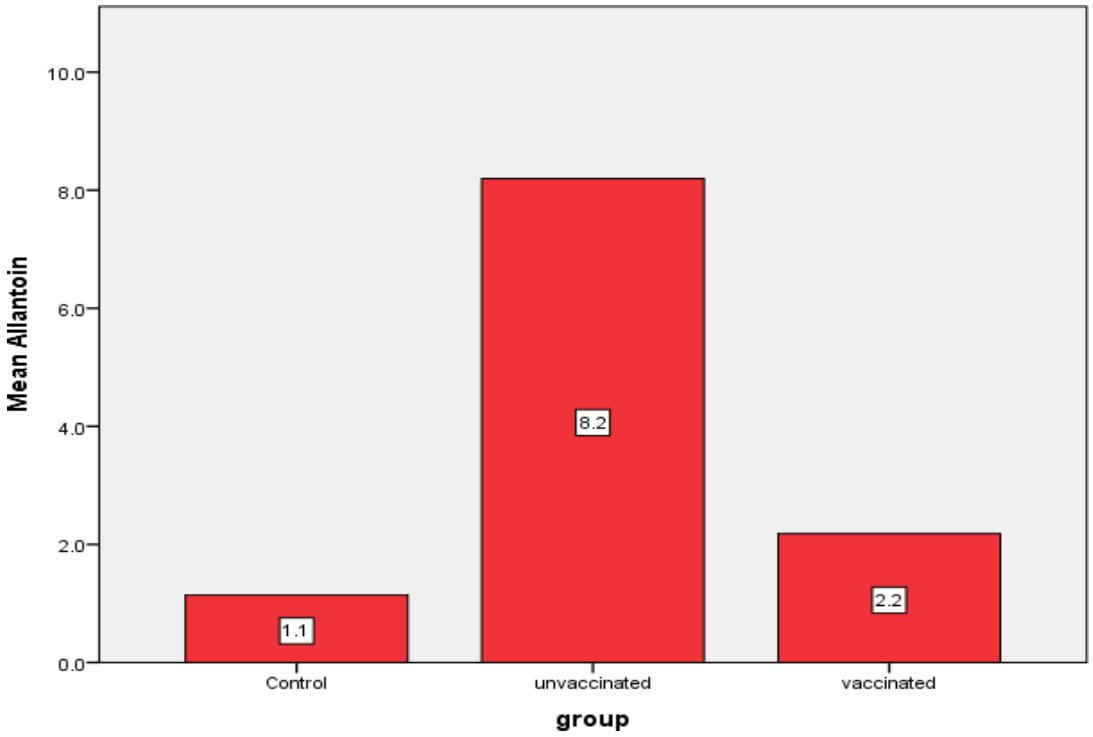

Figure (3-28): Chart illustrates the mean of allantoin (mmol/L) in three groups.

3.3.4. Levels of Potassium in serum (mg/dl)

This assay was done for three groups (n=150, each group n=50): control group consist of healthy peoples, vaccinated group consist covid-19 patients whose were immunizations with pfizer vaccine and unvaccinated group consist covid-19 patients whose have not immunizations with covid-19 vaccines. The results showed that the concentration of potassium decreased with not significant effect in the group of patients infected with Covid 19 who were unvaccinated compared to the vaccinated groups. Potassium showed decrease in unvaccinated group with no significant difference. Its were (4.2±0.66, 4.0±0.5 and 3.3±0.64) respectively. Also the results showed a significant difference between control and vaccinated group as shown in table (3-15).

Table (3-15) Potassium concentration (mg/dl) in three groups.

Parameter	Control means±SD	Vaccinated menas±SD	Unvaccinated means±SD
Potassium (mg/dl)	**4.2±0.66[a]**	**4.0±0.5[b]**	**3.3±0.64[b]**
All data recorded as Means and Standard division. Groups with the same letters have no significant difference			

Covid -19 infection results in a range of symptoms from mild pneumonia to cardiac arrhythmias, hyper activation of the immune response, systemic organ failure and death. However, the mechanism of action has been hard to establish. Elevated urinary loss of potassium is associated with disease severity, and the response to electrolyte replenishment correlates with progression toward recovery (Causton, 2021). These findings suggest possible diagnostic opportunities and therapeutic interventions. They provide insights into comorbidities and mechanisms associated with infection by COVID 19 and other RNA viruses that target activate cytokine-mediated immune responses in a potassium-dependent manner.

A previous study to investigate the effects of dietary magnesium, potassium, and sodium on children's lung function, the study showed, low magnesium and potassium intakes were associated with lower lung volumes and flows (Gilliland *et al.*, 2002).

Potassium showed negative correlation is significant at the 0.01 level for all parameters. The r values for (xanthine, hypoxanthine, CRP, uric acid and allantoin) were (-0.518, -0.717, -0.70, -0.70 and -0.535) respectively. As shown in table (3-16).

Table (3-16) Correlation between potassium and other parameters.

Parameters		Xanthine	Hypoxanthine	CRP	Uric. Acid	Allantoin
Potassium	r	-0.518**	-0.717**	-0.70**	-0.70**	-0.535**
** Correlation is significant at the 0.01 level .						

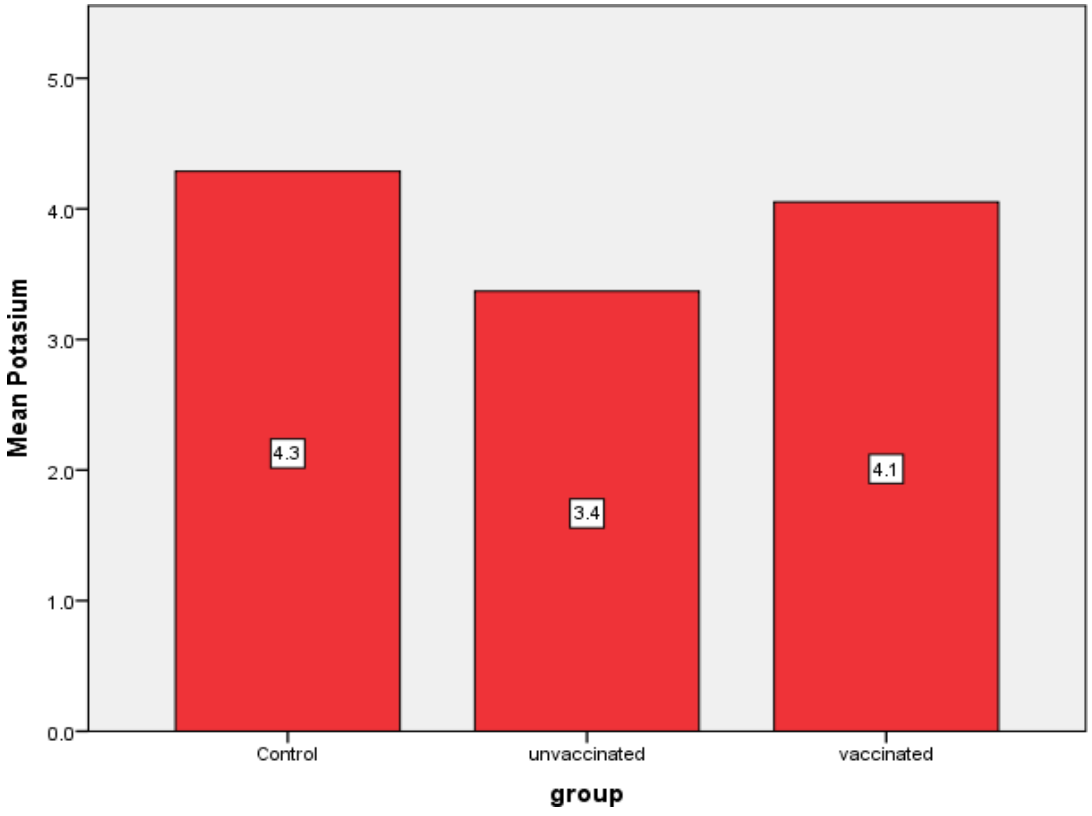

Figure (3-29): Chart illustrates the mean of potassium (mg/dl) in three groups.

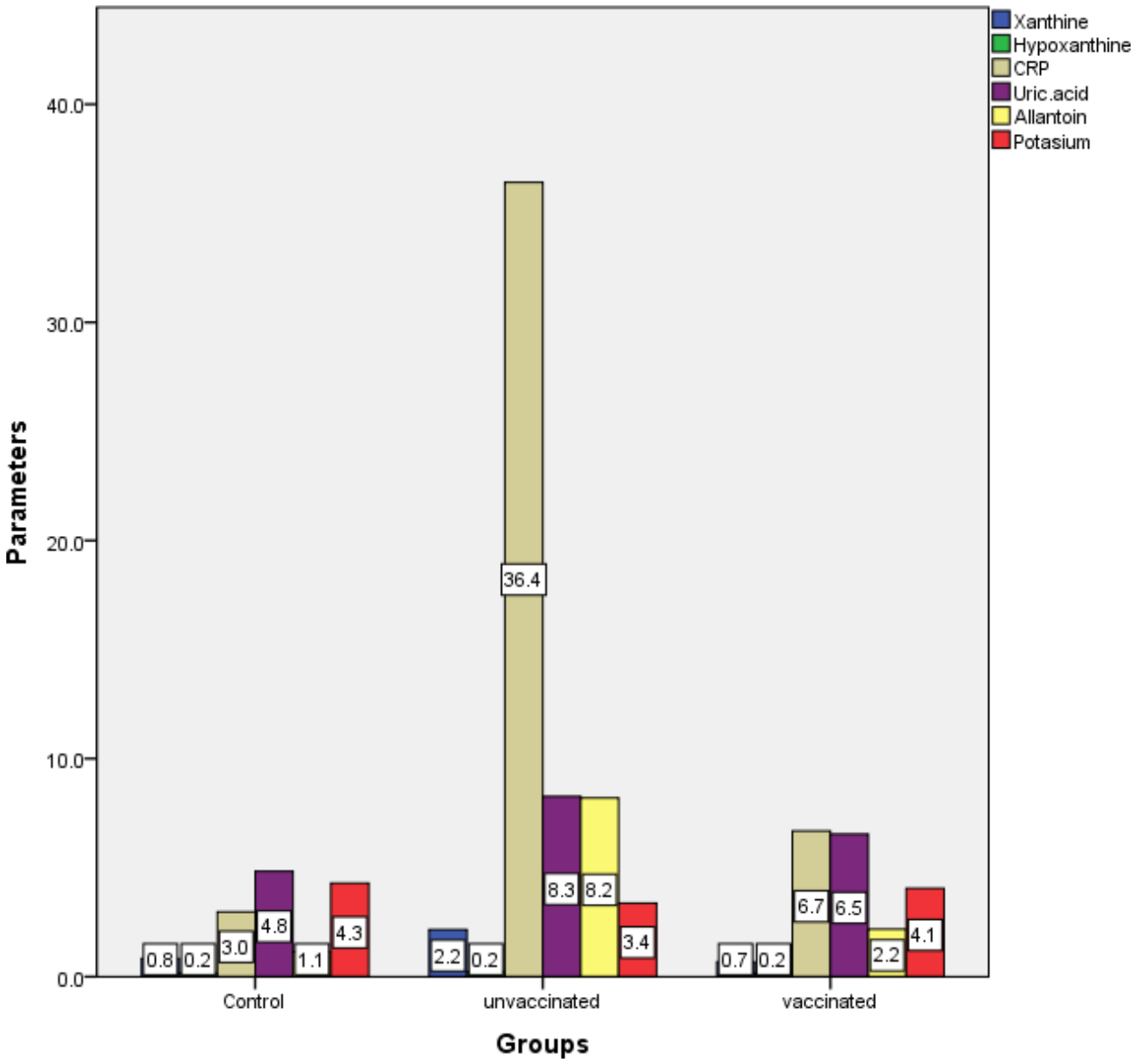

Figure (3-30): Serum levels of (xanthine,hypoxanthine, CRP, uric acid , allantoin and potassium) in three groups (n=150 each group 50): control group consist of healthy peoples , vaccinated group consist covid-19 patients whose were immunizations with pfizer vaccine and unvaccinated group consist covid-19 patients whose have not immunizations with covid-19 vaccine.

3.4. Conclusions and Recommendations

3.4.1. Conclusions

The conclusions of this study indicate that Xanthine oxidase, Hypoxanthine, CRP, uric acid, allantoin, and xanthine levels are elevated inpatients group with COVID-19 when compared with control group and vaccinated group.

While Potassium levels are decrese in patients with COVID-19 when compared with control group and vaccinated group. While Xanthine oxidase a significant with other parameter (positive correlationwas found between xanthine oxidase with xanthine, uric acid, allantoin, CRP) and (a significant negative correlation between xanthine oxidase withpotassium) in patients.

3.4.2. Recommendations

1. Monitoring the level of xanthine oxidase, xanthine, hypoxanthine, uric acid, allantoin and potassium should be considered in the diagnosing and treating COVID-19.
2. Determination of xanthine oxidase, xanthine, hypoxanthine, uric acid , allantoin and potassium in patients with COVID-19 in according to severity of COVID-19 .
3. Study the correlation of xanthine oxidase, xanthine , hypoxanthine , uric acid , allantoin and potassium with age .
4. A significant correlation between parameter and age (positive correlation age with xanthine oxidase, Hypoxanthine, CRP, uric acid, allantoin) and (a significant negative correlation between age with Potassium) in patients.
5. These results may be earlier signs for further diseases that can emerge in the advanced stages in patients with covid-19, evaluating the patients not only with the pulmonary function and also systemically , contributes to minimizing the mortality and morbidity.

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الخلاصة

الهدف من الدراسة تقدير مستوى اوكسيديز الزانثين، هيبوزانثين ،CRP ، وحامض اليوريك ، الانتوين ،الزانثين ، البوتاسيوم في امصال مرضى كوفيد - 19 في هذه الدراسة ، تم جمع 150 حالة دم من مستشفى الحلة التعليمي ومدينة مرجان الطبية ، 50 منهم تم جمعها من الأشخاص الأصحاء الذين زاروا المستشفى- بنك الدم لغرض التبرع بالدم (مجموعة الاصحاء) ، 50 منهم من مرضى مصابين بفايروس كورونا تم تطعيمهم بلقاح فايزر سابقًا (المجموعة الملقحة) ، وتم جمع 50 عينة من الأشخاص الذين تم إدخالهم إلى المستشفى كونه مصابًا بفايروس كورونا ولم يتم تحصينه بأي نوع من لقاحات كورونا (مجموعة غيرملقحة) ، كان متوسط عمر المجموعة الصحية (41.02 ± 10.8) والمجموعة الملقحة (39.5±12.26) والمجموعة غير الملقحة (47±12.9). تمت الدراسة في جامعة بابل / كلية العلوم للبنات / قسم الكيمياء. استمرت الدراسة في الفترة من 1-11-2021 إلى 1-6-2022. كانت المعلمات المستهدفة (زانثين أوكسيديز ، زانثين ، هيبوزانثين ، CRP ، حمض اليوريك ، ألانتوين ، بوتاسيوم). تم قياس المعلمات التالية (زانثين أوكسيديز ، وهيبوزانثين) بواسطة أداة ELISA. تم قياس Xanthine و الانتوين بواسطة HPLC. تم قياس CRP بواسطة أداة I-Chroma (جهاز آلي كامل). تم قياس حامض اليوريك والبوتاسيوم بمقاييس الطيف الضوئي. وأظهرت النتائج: زيادة أوكسيديز الزانثين بشكل ملحوظ في مجموعة المرضى المصابين بفيروس كوفيد 19 الذين لم يتم تلقيحهم مقارنة بالمجموعات الأخرى. وأظهرت النتائج: زيادة أوكسيديز الزانثين بشكل ملحوظ في مجموعة المرضى المصابين بفيروس كوفيد 19 الذين لم يتم تلقيحهم مقارنة بالمجموعات الأخرى. كانت مستويات أوكسيديز الزانثين في ثلاث مجموعات (مجموعة تحكم ، مُلقحة وغير مُلقحة) 6.8 ±12.7 ،31.8 ± 38.5 و159.1 ± 167.6 نانوغرام / مل على التوالي. . لم يظهر الهايبوزانثين أي فرق معنوي بين مجموعة الاصحاء والمحصنة فقد كانت 13.5± 5.7و14.8± 6.8 و29 ±17.6 بيكوغرام / مل على التوالي . لم يظهر CRP فرق معنوي بين المجموعة الضابطة والمحصنة كانت 2.9 ± 1.07 ، 6.6 ± 2.5 ، 36.4 ± 25.7 ملجم / ديسيلتر على التوالي. أظهر حامض اليوريك زيادة معنوية في فرق المجموعة غير المحصنة. كانت 4.8 ± 0.8، 6.5 ±0.8 و 8.2 ± 0.7 ملغ / ديسيلتر على التوالي. أظهرت النتائج أن تركيز آلانتوين زاد بشكل ملحوظ في مجموعة المرضى المصابين بكورونا الذين لم يتم تلقيحهم مقارنة بالمجموعات الأخرى. كانت مستويات الانتوين

1.1 ± 0.01 ، 2.1 ± 0.04 و 8.1 ± 0.03ملي مول / لترعلى التوالي. كما زاد الزانثين بشكل ملحوظ في مجموعة المرضى المصابين بكورونا . كانت مستويات الزانثين 0.83 ± 0.01 ، 0.68 ± 0.01 و 2.16 ± 0.02 ميكرومول / لتر على التوالي . أظهر البوتاسيوم انخفاضاً في المجموعة غير المحصنة مع عدم وجود فرق معنوي. كانت 4.2 ± 0.66 ، 4.0 ± 0.5 و 3.3 ± 0.64 ملغ / ديسيلتر على التوالي. كان الارتباط الموجب معنويا عند مستوى 0.01 بين جميع البارامیتیرزما عدا البوتاسيوم وأظهر ارتباط سلبي لجميع البارامیتیرز.

جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جامعة بابل /كلية علوم البنات
قسم الكيمياء

تحلل بعض مركبات البيورينات في عينات مرضى فايروس كورونا

رسالة مقدمة الى مجلس

كلية علوم البنات / جامعة بابل و هي جزء من متطلبات نيل درجة الماجستير

في علوم الكيمياء

من قبل

زينة حبيب سليم العمار

بكالوريوس علوم كيمياء

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