

## Medicinal herbs and manufactured drugs: for treatment of COVID-19 and its complications in Aden -Yemen

Nashwan Saleh Al-ashwal

Al-Nasr General Hospital and Al-ashwal Clinic for Medical and Cardiac Disease || Adhale || Yemen

**Abstract:** Aims: To detect the herbs benefits in treatment of COVID-19 patients. To discover the effect of *coronavirus-2* on the clinical and subclinical diseases that has accompanied with/ or caused by *H. pylori* infection or vice versa.

Results: A study of observational clinical trial with randomly selected patients, enrolled to it 775 patients; 35 of them, have suffered of *chikungunya and dengue* fevers, and the remaining 740 patients were of confirmed and highly suspected COVID-19 cases. They were divided into six groups; four of them have a manifestations of COVID-19 of confirmed and suspected cases, the 5<sup>th</sup> group was for patients with other viral causes; *chikungunya and dengue* fevers, and the sixth was a group of extra-pulmonary manifestations, and each one was subdivided into two subgroups except group D that was subdivided into three subgroups. The patients that were giving an *Echinacea* syrup had treated within 48 – 72 hours; clinically and para-clinically, earlier than the patients that were giving a combination of herbs; such as *Curcuma*, *Ginger* and *Cissus rotundifolia* whose had got a recovery after 7 days, while the patients that were giving *clarithromycin* tabs and *Echinacea* syrup had recovered earliest, i.e. after 24 hours, it achieved a highest percentage of success that reached 98%, 100% and 100% respectively, i.e. the medicinal substances of *Echinacea purpurea* have an antiviral effect on CoV-2, that evidenced by the fast and complete cure of COVID 19 manifestations, if compared with the clinical effect of Remdesivir or hydroxychloroquine. The combination therapy; *Echinacea* syrup, *Ginkgo biloba* tabs and the *H. pylori* therapeutic and preventive program, has achieved a successful effect on patients' illness of severe COVID-19 or those with accelerated or aggravated diseases that accompanied with/caused by *H. pylori* infection, in post covid-19 period. The patients with *chikungunya and dengue* fevers haven't responded to the *Echinacea* herbal therapy; i.e. *Echinacea* has no benefit in these two diseases but it has an efficient effect against COVID-19.

Conclusion: This study proves the following: I) The medicinal extracts from *Echinacea purpurea* have an efficient effect against novel-CoV-2 disease, faster than *Curcuma*, *Ginger* and *Cissus rotundifolia*, but the *Echinacea* and *clarithromycin* have a fastest remedy from the COVID-19. II) The combination of *Echinacea*, *H. pylori* therapeutic and preventive program, and *Ginkgo biloba*, is a successful regime for treating of patients with severe Covid-19, and whose suffered of post covid-19 extra-pulmonary diseases, allowed them to return to their work after 7 days of treatment only "Inshaa Allah". III) Coronavirus-2 had accelerated the subclinical and aggravated the clinically apparent diseases that has accompanied with /caused by *H. pylori* infection.

**Keywords:** COVID-19, *Echinacea*, accelerated, *H. pylori*, *Ginkgo biloba*.

أعشاب طبية وأدوية مصنعة لعلاج مرضى كوفيد-19 ومضاعفاته في عدن، اليمن

نشوان صالح الأشول

الملخص: الأهداف: الكشف عن فوائد الأعشاب الطبية في علاج مرضى كوفيد-19. اكتشاف تأثير فيروس كورونا-2 على أمراض الحلزونية البابية السريرية وتحت السريرية او العكس.

النتائج: الدراسة تجربة سريرية قائمة على الملاحظة مع مرضى تم اختيارهم عشوائياً، ضمت هذه الدراسة 775 مريضاً؛ عانى 35 منهم من حصى الشيكونوغونيا وحصى الضنك، بينما الـ 740 الباقون من حالات كوفيد-19 المؤكدة والمشتبه فيها بشدة تم تقسيمهم إلى ست مجموعات: اربعاً منها لمرضى الكوفيد-19 والخامسة كانت لمرضى الشيكونوغونيا وحصى الضنك أما السادسة فهي مجموعة المرضى اللذين لديهم أعراض خارج رئوية بعد عدة أسابيع من الشفاء من حصى الكوفيد-19. كل مجموعة قسمت إلى مجموعتين فرعيتين ماعدا مجموعة (د) فقد قسمت إلى ثلاث مجموعات فرعية. تم علاج المرضى اللذين تناولوا شراب القنفذية خلال 48-72 ساعة؛ أي تحسناً سريرياً ودون السريري، وفي وقت مبكر عن المرضى اللذين كانوا يُعطون مزيجاً من الأعشاب، مثل: الكركم، الزنجبيل، والحلق واللذين تحسنوا بعد 7 أيام، في حين أن المرضى اللذين تناولوا أقراص الكالاريثرومايسين وشراب القنفذية قد تماثلوا للشفاء بوقت أبكر من سابقهم أي بعد 24 ساعة، وكانت نسبة النجاح 98%، و100% على التوالي. أي أن القنفذية لها تأثيراً مضاداً للفيروس التاجي المستجد-2، والذي يتضح من خلال الشفاء السريع والكامل سريرياً وما دون السريري إذا ما قورنت بتأثير الهيدروكسي كلوروكوين والرامديسيفير. أما العلاج المركب من شراب القنفذية، الجنكوبيلوبا والبرنامج العلاجي والوقائي من مرض الحلزونية البوابية فله تأثيراً ناجحاً على حالات مرضى كوفيد-19 الوخيمة ومضاعفاتها وأمراض الحلزونية البوابية المتسارعة والمتفاقمة الخارج رئوية محققاً نجاحاً 100%. وهذا مصداقاً لقول النبي عليه الصلاة والسلام: ما أنزل الله من داء إلا وأنزل له شفاء.

**الخلاصة:** 1- حقق المستخلص الدوائي من عشبة الزهرة القنفذية نجاحاً عالياً في معالجة حالات كوفيد-19 الطفيفة ومتوسطة الخطورة خلال 48-72 ساعة، وهي أكثر سرعة وفاعلية في التأثير عليه من مجموعة الأعشاب المستخدمة: الكركم، الزنجبيل والحلق بحسب الجرعات وطريقة الاستخدام الموضحة في الدراسة. 2- استخدام مستخلصات الزهرة القنفذية والجنكوبيلوبا بالإضافة إلى برنامج معالجة أمراض الجرثومة الحلزونية البوابية والوقاية منها أثبتت فاعلية كبيرة في معالجة حالات كوفيد-19 الوخيمة ومضاعفاتها، وعودة المرضى إلى أعمالهم في أقل من 7 أيام. 3- الفيروس التاجي-2 المستجد يعمل على تسريع وتيرة المرض تحت السريري ويفاقم الأمراض المرافقة لوجود أو التي تسببها الجرثومة الحلزونية البوابية الظاهرة سريرياً.

**الكلمات المفتاحية:** كوفيد-19، الزهرة القنفذية، تسريع، الجرثومة الحلزونية البوابية، الجنكوبيلوبا.

## INTRODUCTION:

The recent world catastrophe due to COVID – 19 outbreaks; that initiated firstly at Wuhan – China on late December 2019 then to other cities in China and many other countries as it reported in 114 countries, with occurrence of rapid spread during 75 days that evoked later the WHO on the 76<sup>th</sup> day, to declare it as a pandemic on March 11, 2020<sup>[1]</sup>, it constitute a big challenge to all the world, due to its effect on social, economic and health levels, particularly with the continuing increase in numbers of COVID-19 patients in spite of all the protective measures and the proper hand hygiene<sup>[2,3,4,5,6]</sup>, Its transmission occur via two modes; respiratory droplets and contacts<sup>[7]</sup>, i.e. it spread via airborne, and touching the fomites which contaminated the hands and then reached to the nose by any way, particularly, when there was a recording about presence of viable SARS-CoV-2 in urine and stool<sup>[8,9]</sup>, as shedding of SARS-CoV-2 had detected in stool samples from patients with covid-19 in a quantity of 10<sup>7</sup> RNA copies/g faeces one week after symptom onset and decreased to 10<sup>3</sup> RNACopies/g three weeks after onset<sup>[10]</sup>, thus, Increasing circulation of the coronavirus-2 in the population will increase the virus load into the sewer system<sup>[11]</sup>, and as it detected in samples of sewage water that had got from 29 of 300 sewage treatment plants in Dutch in the Netherlands in April and May, 2020<sup>[12]</sup>, and also in water and wastewater<sup>[13]</sup>, with a success of

coronavirus-2 culturing from stool samples of patients with covid-19 that be infectious to others<sup>[14]</sup>. Actually, the aforesaid results had risen a suspicion about the role of sewage treated water in case of persistently increased numbers of covid-19 patients, but because there is no any reporting that peoples have infected via sewage, the WHO declared the sewage water is unlikely to become an important transmission pathway for coronaviruses like SARS-CoV-2<sup>[15]</sup>, however, a hypothesis "that proposed the sewage water as a hidden way of transmission of coronavirus-2 because it increased more in the countries that reclaims the water from the sewages even for human use", which evidenced by the following: if the chemical disinfectant effect have killed a 99.9% of viruses and bacteria, so when its concentration became more diluted in the sewage water, that consist approximately of many billions of Cubic meters of water, it permits a survives of more than 0.1% of microorganisms as the coronavirus-2 and others, resulting in increase of coronavirus-2 growing in a directly proportional manner, particularly, in the presence of global outbreaks, especially when the incubation period of COVID-19 hasn't a fixed duration and estimated to be up to 14 days from the time of exposure, with a median of 4 to 5 days, to the appearance of its manifestations<sup>[16, 17, 18]</sup>, that make the presence of asymptomatic cases<sup>[19]</sup>, as an additional factor to overbalance the increasing loads of coronavirus-2 that reached to the sewage water, this argument could evidence more by the hypothesis of " the mutant abilities of coronavirus-2 afford resistance to their new generations against the environmental factors during its evolutions". This hypothesis could evidence by the following: *Casanova et al. (2009)* said: COVID-19 virus could remain an infectious in a water contaminated with faeces for days to weeks<sup>[20]</sup>, and others said: the virus survival at room temperature required only 10 days to result in 99.9% of reduction of coronavirus in filtered tap water, while at 4°C this level of virus inactivation would require over 100 days, and as *Hurst et al. (in 1980) and John and Rose (in 2005)* said: the Coronavirus survival decrease with increasing temperature<sup>[13]</sup>, but *Gundy P. et al. (in 2009)*, the gastroenteritis coronavirus demonstrated a 99.9% die-off in from 2 days at 23°C<sup>[8]</sup>, to 2 weeks at 25°C as said by *Casanova et al. (2009)*<sup>[20]</sup>, this mean the coronaviruses had been developing its own protective properties against the environmental factors (as its survival in 1980 – 2005 had decreased with increasing temperature to die-off in 2 days at 23 Celsius degree but in 2009 it survived up to 2 weeks with increasing temperature to 25 Celsius degree) and possibly may did it against the chemical disinfectant (if taking its detection at sewage treatment plants, seriously.), and also for contagious ability. All of these make the sewage transmission mode more possible, indirectly; through our use of treated sewage water, as in the case of *H. pylori* transmission that happened via the infected milk that came from infected Cow's, because it had been eating a grass that irrigated by this type of water or drunk a water that contaminated with the remnant of dairy products or the water of their washing up<sup>[21]</sup>, or by ate a vegetables that irrigated by sewage or by treated water that also be used for foodstuffs processing<sup>[22]</sup>. This mode of transmission also resulted in Co-existence of infection; such as the *H. pylori*, this transmission occurred due to the absence of highly sophisticated equipment's to investigate the whole quantities of treated sewage water,

at its surface and deep, with 100% of investigating abilities, and because of humans believes that they had been knowing everything's about microorganisms, they decided to reclaim the sewage water, yet, the covid-19 outbreaks had been exposing the humans knowledge, exactly, as said by the Professor Steven Oppenheimer: " the world's scientific community does not and will not know all the toxic agents and carcinogens that may be able to make it through the indirect reclaimed water process to drinking water. Also, there is simply no technology to detect them."<sup>[23]</sup>, surely, also the microorganism no one knowing everything about it. Thus, if we are imagining that the animals or birds had been getting their water needs from/near to the sewage treatment plants, so really, they harbored the coronavirus-2, that has a mutation abilities and produce new generations of more developed strains that could be more durable and resistible to the environmental factors and the chemical destructions, so, it will be becoming more vigorous than the novel-COVID-19, according to the evolution history; because as written in C. Li, and B. H. Xu study; SARS-CoV-2 shared 96.2% identical genomic sequence to a bat coronavirus, while 80.26% identity to SARS-CoV and 51.8% identity to MERS-CoV<sup>[24]</sup>. i.e. they have developed itself more and more within and after each outbreak, that clearly understood from the appearance of extra-pulmonary manifestations<sup>[25]</sup>, after few weeks from appearance of respiratory manifestations. The rapid and continuous evolution of the coronavirus-2, heralding some ominous years, that evidenced by curtailments of the time that needed by the virus to serialize its appearance with occurrence of some changes in the genetic characteristics, such as the 2002 to 2012 and last but not least the 2019 outbreaks. It will be coming necessarily, if we don't cut the transmission recycling; animals to humans and vice versa. Hence, with the absence of definitive drugs against coronavirus-2, while the scientists are continuing search for definitive drug with an effortless working to find a specific anti-CoV-2 in the advanced countries, and until that time, my study will provide a chance to everybody not only for fast and effective remedies from COVID-19 mild or critical but also to prevent disease progression as well, and fasten the early returning to work, by using of these herbs that described in detail in the context, in addition to the effect of combined therapy; by using of both; herbs and manufactured drugs, to make the human systems free of viral-bacterial takeovers control, in particular, if it has accompanied by prevention of sewage treated water use for foodstuffs manufacturing or preparing. This benefits of medicinal herbs are considering as a gift from the Creative of everything's; as the Prophet of Allah said: "There is no disease that Allah has created, except that He also created its treatment"<sup>[26]</sup>.

## Material & Methods:

To detect the herbs benefits in treatment of COVID-19 patients and to discover the effect of coronavirus-2 on the clinical and subclinical diseases that has accompanied with/ or caused by H. pylori infection or vice versa, an observational study of patients that had randomly selected, and information was entering into MS, after collected it from observing, examining and follow up of patients clinically and

para-clinically, with exclusion of patients that haven't a history of exposure with a confirmed case of covid-19 disease, within one week before presentation. A total number was 775 patients, three of them had positive nasopharyngeal COVID-19, PCR-results, and 737 patients with highly suspected COVID-19, and lastly 35 cases with other viral fevers. Place of study: Dr. Al-ashwal clinic, Adhale Governorate in the period from 15 June 2020 to 15 October 2020. The study consists of six Groups; five of them subdivided into two subgroups for each one, and the sixth into three subgroups. Group A n=296; in A1 n=168; (148 M and 20 F), and A2 n=128; (103 M and 25 F), group B n=165; B1 n=113; (80 M and 33 F), and B2 n=52; (40 M and 12 F), group C, n=18; (C1 n=12; (6 M and 6 F), and C2 n=6; (4 M and 2 F), and group D, n=204, it subdivided into three subgroups; D1 n=130; (M=100 & F=30), D2 n=65; (M=30 & F=35), and D3 n=13; (M=9 & F=4), *Chikungunya and Dengue* fevers group; n= 35 (M= 30 and F= 5): it subdivided into *chikungunya* and *dengue* subgroups n= 19 & n= 16 respectively, and lastly the Extra-pulmonary group; n= 57 ( F= 30 and M= 27), it subdivided into two subgroups; n=20 for symptomatic and specific drugs and n=37 for therapeutic regime of D3 subgroup. Patients in group A, presented after 3 to 5 days, while that in group B, had presented after 1 - 5 days and patients in group C, presented after 7 - 10 days of appearance of their manifestations, and these in group D; presented after taken medications for 2 to 10 days with poor response to it and their conditions had worsened rapidly. The group of extra-pulmonary manifestations contained those in whom an aggravation of previous diseases and/or appearance of new extra-pulmonary manifestations had occurred, as shown in table (1), and they have revealed a positive result of *H. Pylori* Antigen or Antibody. Laboratory results as shown in table (2), X- rays of chest as shown in photo (1), and ultra-sonographic imaging of the lung via the intercostal spaces by horizontal and long axis view, as shown in photos (2, 3 & 4), measurements of oxygen saturation in all fingers bilaterally by Oximeter, as shown in table (3). Trial treatments in the study consist of three lines, Herbal: I- folk medicine sources as *Curcuma* 2.5 ml powder mixed with 250 ml of warm water, at night, *Ginger* juices as 10 gram of raw roots parts that mixed with 750 ml of plain water; at morning, and *Cissus rotundifolia* (from the *Genus Cissus & Fam. Vitaceae*); non-parched fresh leaves in quantity of 10 to 20 leaves per day of moderate sizes, boiled in water then they have eaten it a once time per day; at afternoon with 2 hours apart from the previous or next drug(s) time, for three days (for B1 and B2 subgroups). II- herbal drugs from pharmacies as *Echinacea* syrup of two regimes 20 ml; each 5 ml contains 37.5 mg of root extracts (for A1, C1 and D1 subgroups) and 40 ml/dose (for D1 started dose only, and for D2, D3 subgroups, *chikungunya and dengue fever* group and group of extra-pulmonary manifestations; all the doses); each 5 ml of it contains 37.5 mg also, it was giving at 6 hours interval per day for 7 days in the following way: washing the mouth by each dose for 2-3 minutes then swallowed it, lastly, *Ginkgo biloba*; (Tebofortin, Marcyrl), tablets 40 mg three times per day as a sublingual (modified) for two doses or more then by swallowing for 7 days (for D3 subgroup and the D3 regime subgroup among the extra- pulmonary manifestations group). The determination of herbal drugs doses in this study depended on three things, herbs effects, modified traditional doses and

palatability of patients' to their taste as resulted from previous trial therapy for many diseases, such as respiratory tract infection, in chronic cough post pertussis or in complicated common cold, and in controlling of diabetic state for patients with irregular use of hypoglycemic drugs, and in patients with arthritis; by use of *Curcuma*, and also for patients with endemic fever with no response to drugs; by use of *Cissus rotundifolia*. Secondly, manufactured drugs; antibiotics such as: *Azithromycin* (AZ), in a dose of 500mg/tablet per day for 6 days (for A2, C2 and B2 subgroups) or *Clarithromycin* tablets 500mg x 12 hours x 7 days (for D2 subgroup), *Clarithromycin* and *amoxicillin* cap each one in dose of 500mg every 12 hours (for D3-subgroup and extra-pulmonary manifestations group), both gave for 7 days, and lastly immunosuppressive or immunoregulator drugs as *Azathioprine* (for D3 subgroup and group of extra-pulmonary manifestations), in a starting dose of 75 mg then 1.5 mg/kg daily in divided doses, via sublingual route every 12 hours for 7 days. Patients in D3 subgroup, at first gave the drugs as the following: 1<sup>st</sup> two gave them an *Echinacea* syrup 40 ml; in the same way of use, 2<sup>nd</sup> two gave them *Clarithromycin* and *Amoxicillin* 500mg each one, 3<sup>rd</sup> two gave them *Azathioprine* 75 mg sublingual, last seven patients had given the *Clarithromycin* 500mg and *Amoxicillin* 500mg, then after half an hour the *Echinacea* syrup gave as 40ml per dose, and after 15 minutes the *Ginkgo biloba* tablets (Tebofortin 40mg) had taken sublingually, thus, regime of herbal and manufactured drugs was applying to all the 13 patients in D3 subgroup and 37 patients among the extra-pulmonary manifestations group. Third line: contains specific drugs against the diseases that shown in table (1), In addition to the supportive treatments.

Patients monitoring have done clinically by recording the changes in their symptoms and signs; measurement of temperature in the axillaries and external auditory canal, and percent of fingers Oxygen saturations with chest auscultation, every 15 minutes, and para-clinically by test of complete blood count, and sonographic examination of chest every 24 hours, and other investigations every 3 – 7 days.

Parameter of success is I) starting the appearance of benefits within 24 hours (i.e. when they feel of some clinical improvements with no need for antipyretic drugs after 24 hours) and be completed within one to two weeks.

## RESULTS:

All patients among groups A, B, C, D, and extra-pulmonary manifestations have a different percentage of reduced oxygen saturation by using of fingers Oximeter, that corresponded to the diseased areas of the lung, as shown in table (3), while the *chikungunya and dengue* group has 99% in all fingers. Patients in subgroups A1 and C1 were 168 and 12, respectively, their responding by clinical improvements to *Echinacea* syrup as the following: after one an hour of the first dose there was improvement in breathing process with patients feeling of comfortable air entrance through nasal, tracheal into the whole chest, this accompanied by increase in the breathing sound (by auscultation), and oxygen saturation also increased rapidly from 66% & 94% to 91% & 96%, as shown in table (3), the patients said: "our breathing

is improve" or "our chest became open slightly" with decrease in fever intensity from 38.8°C-to-37.8°C, and subsided of shivering that returned the same again after 5 hours of the first dose but it rapidly responded to antipyretic paracetamol infusion of 500mg; after 15 minutes, in addition to the decrease in nausea, vomiting, and diarrhea frequencies that manifested among (18.4% & 50% of patients in A1 & C1 respectively), then after 12 hours, patients temperature decreased in response to paracetamol tablet of 500 mg only, that recorded 37.3°C at the end of the first 24 hours, then they have felt well at the end of the 48 hours with no use of paracetamol infusions or tablets, returned of smell and taste senses also, and on the third day they have felt better; their laboratory results revealed improvement in their values as shown in table (2), and oxygen saturation also improved in all fingers with recording of 99% by Oximeter. So, they returned to their work activities after 72 hours, and continued the therapeutic duration of 7 days. The side effect that recorded due to herbal *Echinacea* syrup intake is a feeling of heartburn that had recorded by two patients from A1 subgroup, therefore, they had discontinued drug intake by themselves at the 2<sup>nd</sup> day of therapy and their conditions had deteriorated more after two days, that they have suffered of severe breathlessness and chest tightness which accompanied with decreased in oxygen saturation to 66%, severe lymphopenia with 5% of  $16 \times 10^9/L$ , bilateral pleural effusions of 1200 ml and 790 ml on right and left sides respectively, then they transferred to other regime. also, one patients from subgroup C1, had suffered of allergic wheezing, then herbal *Echinacea* syrup stopped. The patients in group A2 and C2 (n= 128 , n= 6 respectively ), they responded as the following: from A2; ninety patients (n= 90, i.e.=70.3%) of them, had felt of improvement in their coughing and chest tightness but fever, body ache, dizziness and nausea stayed for more than 3 days, and oxygen saturation was below 90%, and thirty-eight of them (n=38, i.e.=29.68%) had no improvement as a whole after 72 hours with an increase in their breathing shortness and decreased of oxygen saturation from 94% to 81%), chest crepitation and rhonchi that had become more pronounced during recurrence of fever that associated with experiencing of cutting-like pain that had originated at their pelvic and extended down to the thighs, while those in subgroup C2 (n=6) had no improvement in their conditions; fever, cough, breathing shortness (with oxygen saturation of 88%), body ache, and diarrhea that increased at the 5<sup>th</sup> day, then they transferred to other therapeutic regime. The patients in group B, n= 165; (B1 = 113 & B2= 52), had used the paracetamol tablets frequently for 3 days, and shortness of breathing slightly improved (oxygen saturation increased from (88% & 91%) to (92% & 97%), but body aching, fatigue, and dizziness were outstaying but with less discomfort and the diarrhea decreased in frequency and quantity from 6 times per day to 3 times. In this group the patients after longtime of improvement; such as from four weeks up to 16 weeks, they have developed some different manifestations, as shown in table (1). The patients in Group D; in D1, its patients (n=130), all of them had responded to the herbal *Echinacea* syrup (40 ml started then 20 ml per each dose), with increased oxygen saturation from (90% & 97%) to (95% & 99%) with no failure, no side effects or complications. These in D2; n=65, each dose of *Echinacea* syrup was 40 ml, and they have

infected with *H. pylori* (positive antigen and antibody), therefore they gave an antibiotic *clarithromycin* tablets and they felt an improvement after 24 hours, achieved a 95.38%; n=62, of success, with increased of Oxygen saturation from (66% & 94%) to (91% & 100%) and a failure was a fortune of 4.6%; n=3, of its patients, because they had severe involvements of lung and rapidly deteriorated to respiratory failure within 24 hours, they had died at the second day, in spite of increase in the values of oxygen saturations from 66 & 80% to 75 & 85% after one an hour of ingestion of the first dose of *Echinacea* syrup, and because they had a fluctuated levels of oxygen saturations particularly during speech, the oxygen supply was giving and it resulted in increasing of oxygen saturation to 91% & 97% during its flow, but oxygen saturation returned the same again after few minutes of out of oxygen. The patients in D3 subgroup; responded as the following: firstly, two patients after had given 40 ml of *Echinacea* syrup, they had felt of improvement after 2 hours as a decrease in symptoms intensity; fever, breathing difficulty, abdominal pain, and dizziness, then they suffered again after one an hour but with an increased intensity, secondly, the 2<sup>nd</sup> two patients had experienced the same scenario, after one an hour, and the 3<sup>rd</sup> two patients had responded to *azathioprine* tablets after 30 minutes as the following: temperature was increased in chest, arms and neck with increased breathlessness, and the last seven patients; after 15 minutes of the *ginkgo biloba* tablets taken, they had felt some improvements that be more comfort after 2 hours, and the former 6 patients also improved in the same way as them after taken the drugs in the same sequence, and so on, this improvement was increasing with time, for example; they be able to lie on supine or lateral decubitus for 10 to 15 minutes, that reached a goodwill level after 90 minutes with improvement in sleeping, speech, feeding, and bathroom times, without apparent discomfort, and they be able to walk for 50 meters to and from with no tiredness after 48 hours had elapsed, and reached a maximum of 170 meters also to and from, with normalization of blood pressure and oxygen saturation (98% to 100%), and they weren't suffering after 7 days, in addition to the decrease in pleural effusion levels from 1700 ml and more to 190 ml and less without aspiration or diuretics. Their Laboratory results, as shown in table (2); have revealed a decline in ferritin, CRP, ESR levels and normalization of lymphocytes, neutrophils, cholesterol, triglyceride & LDL-cholesterol ratio, and decreased in levels of pre-prandial and post-prandial sugar, with declining of 21.8% weekly from the total HbA1C. In *Chikungunya and Dengue* group; their patients hadn't responded to *Echinacea* syrup 40 ml per dose every 6 hours for 48 hours, but instead they developed leucopenia with transient improvement in counts of thrombocyte, but with no feeling of clinical improvement by the patients; fever stayed at high levels with severe headache that had decreased for 1-2 hours only post intravenous infusion of paracetamol, then returned the same again. The extra-pulmonary group; their patients were responding well to D3 subgroup regime, they experienced a feeling of comfort after one an hour of taken a drugs for example; decreased swelling of severely enlarged tonsils, decreased joints restriction and patients be able to climb stairs, decreased blood pressure, such as from 220/110mmhg to 160/100 mmhg with equalization of both arms measurements, normalization of free prostatic surface



antigen (f-PSA), improvement in manifestations of patient with severe hypothyroidism; facial dullness, amnesia, and speech difficulty with feeling of heavy tongues, this improvement was progressing well from the 1<sup>st</sup> week till achieving a goodwill results after two weeks, in some patients; as stopping of antihypertensive, hypolipidemic and hypoglycemic drugs, but the part of patients among the subgroup of specific and symptomatic drugs hadn't responded to the increase in their drugs doses nor to the new prescribed drugs.

### Discussion:

The Prophet of Allah; said: "There is no disease that Allah has created, except that he also has created its treatment"<sup>[26]</sup>. So, in our world we are surrounded by a natural plants of various types that could be differ from one country to another, and it have a benefits in their medicinal substances to humans and animals, that mean Allah didn't create various plants in vain. I was depending in this study on trial of natural herbs alone and in combination with manufactured drugs from two categories; as a sources for therapy of COVID-19 the confirmed and the suspected cases with mild to severe severity, which have given an excellent results, as will discuss in details; for example, if we notice the effect of *Echinacea* syrup on patients in subgroups A1, C1, and D1; we find that the clinical improvement was achieving in a short time, started from after one an hour to be completed after 48 hours in mild and moderate severity with returning of patients smell and taste at the second day by 40.6%; n=126 and a 90%; n=279 of patients on the fourth day of treatment, resulting in a total success of (98.0%; n=304); for the three subgroups. The patients in A2 & C2 (the *Azithromycin* subgroups, have a 67%; n=90 of success), had got some improvement in coughing frequency and intensity, shortness of breathing and chest tightness intensity, on the 3<sup>rd</sup> day of treatment, and (28.3%; n=38) of A2 and C2, have no improvement. The patients in group B; (B1; n=113), with herbal combinations of *Curcuma*, *Ginger* and *Cissus rotundifolia*, and the patients in B2; (n= 52) all of them have some improvement after 3 days, but also with residual symptoms that caused some discomfort to the patients such as: dizziness, body aching, fatigue and mild nasal dryness, it subsided after 7 to 10 days, i.e. these three herbs have achieved a success after 7 days, which could be due to the use of small doses from their powders in this study, and according to the effect of their medicinal substances, if used with a large doses could be result in rapid clinical improvement, as they exerted their effect on interleukins (the pro and anti-inflammatory); for example, the curcumin reduced levels of IL-1beta, IL-6, IL-8, MMP1, MMP3 and MMP13, in addition to the antiviral activities, and did not show an involvement of NF-kB, but it down regulated TLR2 expression and inhibited the MAP kinase JNK while activating p38 and ERK, while the *Curcuma* targeting NF-kappa-B pathway, up-regulating the IL-10, and both of them caused an up-regulation of TNF-alpha, beside the antiviral activity in vitro against SARS-CoV-3CL protease activity by *curcuma*, which is essential for its replication<sup>[27,28]</sup>, i.e. there are different and similar activities exerted by the *Curcuma* medicinal substances which evidence the importance of the

comprehensive effect of the medicinal herbs that differentiate it from the manufactured drugs, and explained the benefits of the whole herb substances such as the exertion of a complementary therapeutic action. the *Ginger* exerted its effect through inhibition of T cells activation and proliferation, targeting T helper-1 via inhibiting IL-12, and inhibit LPS induced macrophage activation and function<sup>[29]</sup>, also it decreased activity of NF-kappa-B, and induce T helper-2 (IL-4 and IL-10 production and up-regulation)<sup>[30, 31]</sup>, while the *Cissus rotundifolia*, has an analgesic, anti-inflammatory and anti-ulcerative activities, beside using it in Yemeni traditional medicine for treating fever and digestive ailments<sup>[32]</sup>, it need further and advanced analysis to elicit the biochemical content of its medicinal substances. while, *azithromycin* had exerted only a partial beneficial effect on 70.3% (n=90) of patients in A2 subgroup, with failure in both C2 100% (n=6), and part of A2 (29.68%;n=38) patients, this effect have elicited a suspicion about its benefits for patients in B2 subgroup, because it hadn't a benefit for severely diseased patients as result in study of *Azithromycin* for severe COVID-19<sup>[33]</sup>, it has different effect on anti-inflammatory interleukins; for example, *azithromycin* was down regulates inflammatory cytokine production by M1 polarized CF alveolar macrophages but didn't modified its production in alveolar macrophages that stimulated with LPS alone, and significantly reduced pro-inflammatory cytokine expression (IL-1beta, CCL-2 or TNF-alpha) in M1- induced CF and wild type alveolar macrophage, but its anti-inflammatory effect seemed to be limited to alveolar macrophage because it was unable to influence IL-1beta, CCL-2, or TNF-alpha expression in M1 activated peritoneal macrophage, and it didn't modified expression of M2 markers ( Arg-1, FIZZ-1, Ym1-2) and that of anti-inflammatory IL-10 cytokine<sup>[34]</sup>, but it affect the IL-10 production; increased it, from dendritic cells and naïve T cells<sup>[35]</sup>, thus, whereas it has only an effect on M1 plus LPS-activated alveolar macrophage and no effect on only LPS-activated alveolar macrophage or that from other tissues, its failure to bring about complete clinical improvement in mild to moderate cases over and above the severe cases of covid-19, that may be caused by viral LPS - macrophage activation which probably it differ from the EPS (pure lipopolysaccharide) that extracted from roots of *Echinacea purpurea* and bring about alternative macrophage activations that could be initiate a different orders by macrophages, because the macrophages as *Meyer, Huaux, Gavilanes, and et al. (2009)* said: may play a cardinal role in the orchestration of inflammatory responses, and macrophages control switches of the immune system by securing the balance between pro- and anti-inflammatory reactions<sup>[34]</sup>, all of these make the effect of *Echinacea* medicinal substances on macrophages as a re-programming effect. The patients in D2 (n=65) subgroup; three of them had died due to acute respiratory failure while the remaining responded to 40 ml of *Echinacea* syrup, the same as above, and the *Clarithromycin* was added due to co-existence of *H. pylori* infection, and because they were suffering of diffused chest crepitation, and had experienced of aggravation of their chronic diseases; as diabetic, dyslipidemia and hypertension, and also to observe the result of *H. pylori* eradication beside the effect of the *Echinacea* syrup that revealed better result than the *Echinacea* alone with achievement of clinical improvement within 24

hours; probably this occurred because as *Sugiyama K. et al. (2007)* said: about *clarithromycin* effect on interleukins the following: the *Clarithromycin* has an effect on cytokines through CTLA-4 up-regulation, as it inhibits production of IL-2 and IL-6 by T cells, that co-cultured with dendritic cells (DCs), also it down-regulate the LPS-induced TLR4 expression<sup>[35]</sup>, and decreased IL-8 production by bronchial epithelium that stimulated by TNF-alpha<sup>[36]</sup>, and whereas the *H. pylori* LPS be able to induce little NF-kB activation through TLR4, that shown to induce IL-12 and IL-18 responses, which are thought to be pro-inflammatory<sup>[37]</sup>, thus, *clarithromycin* by its effect as a down-regulator of TLR4 expression, be able to inhibit the induction of IL-12 and IL-18, thereafter, re-regulate the IFN-gamma functions. The IFN-gamma as *Akdis et al. (2011)* said: has antiviral properties and regulate the local leukocyte-endothelial interactions, and more was mentioned in this reference<sup>[38]</sup>, and the *clarithromycin* also decreased production of IL-2 that may participate in the systemic response and hyper-gamma globulinaemia that observed in patients with cystic fibrosis<sup>[39]</sup>, therefore, it has a beneficial effect in reducing the high level of IL-2 in COVID-19 patients with severe lymphopenia, because in spite of its functional role; as said by *Akdis et al. (2011)* it induce proliferation and differentiation of T lymphocytes, NK and Naïve cells<sup>[38]</sup>, it lost this function and more probably it acted to the side of COVID-19 pathological process, this interpretation evidenced by correction of the leucocytes count of white and the neutrophils to lymphocytes ratio, on the 3<sup>rd</sup> day of therapy of patients with mild to moderate covid-19 severity, and because the lymphopenia has considered as a sign of poor prognosis in covid-19 patients, the presence of high levels of IL-2 and IL-7 with persistence and progression of the inflammatory process that caused more deterioration points to the presence of takeovers control of human immune system by CoV-2, that clarified more if we know the function of IL-7 as described by *Hickman Cj. et al. (1990)*, whose said: the IL-7 regulate the human cytotoxic T lymphocyte development<sup>[40]</sup>, a function that also lost in COVID-19 patients, as evidenced also by the presence of progressive and severe lymphopenia, which culminated in the failure of the immune system to stop the inflammatory cascade and save the body organs, as clearly understand by review of the plasma levels of interleukins in COVID-19 patients as the following: for example, a retrospective analysis that had demonstrated the initial plasma levels of interleukins in COVID-19 patients which are IL-1beta, IL-1RA, IL-7, IL-8, IL-10, IFN-gamma, monocyte chemoattractant peptide (MCP)-1, macrophage inflammatory protein (MIP)-1beta, granulocyte-colony stimulating factor (G-CSF), and tumor necrosis factor-alpha (TNF-alpha), are increase in patients with COVID-19, (this increase in IL-10, IL-1ra and IL-7 could be as a functional role to counteract the high levels of the pro-inflammatory cytokines, that will result in containments of the virus and its inflammatory process ). But, a further analysis has shown that the plasma concentrations of IL-2, IL-7, IL-17, IL-10, MCP-1, MIP-1alpha, and TNF-alpha, in ICU patients are higher than non-ICU patients<sup>[41]</sup>, i.e. the IL-1RA, antagonized the IL-1beta, and IL-10 antagonized the IL-8 but IL-2 and IL-7 had increased with persistence decrease in count of lymphocytes and persistence increase in IL-17, this events are points to the presence of another inducer. Moreover, the plasma levels of

IL-2, IL-6, IL-8, IL-10, and TNF-alpha observed in severe infections, are prominently greater than those in non-severe infection<sup>[42]</sup>, also few retrospective studies have revealed that the lung injury reported with Murray score is strongly associated with the levels of IL-1alpha, IL-1ra, IL-2, IL-7, IL-10, IL-17, IFN-gamma, inducible interferon protein (IP)-10, G-CSF, and MCP-3, and these cytokines and chemokines excluding MCP-3 are positively related to SARS-CoV-2 viral load<sup>[43]</sup>, (it mean, that the secretion of cytokines persisted and IL-17 was higher in ICU patients and associated with lung injury; i.e. its secretion may be a compensatory to counteract the decreased levels of IL-1, IL-6 and IL-8 and others, which mean a viral effect on Th1, and presence of highly specialized dominant cells that lie under the viral control to perpetuate the pathological process by re-production of the inflammatory cytokines via another activation as IL-17 signaling, that explained its secretion in a higher levels among ICU patients). The plasma level of IL-6 considered as a significant cytokine contributing to MAS, severe patients have significantly higher level of IL-6 than mild or non-severe patients, the large area of lung injury ( $\Rightarrow$ 50%) is closely correlated with the increased level of IL-6 and the subgroup of lymphocytes in the peripheral blood<sup>[44]</sup>, also the total count of lymphocytes and subsets of T cells are reduce in patients with SARS-CoV-2 infection<sup>[45, 46]</sup>, and its systemic inflammation and hypoxic respiratory failure is associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin<sup>[47-50]</sup>, with a confirmed relationship between inflammatory markers, including ESR, CRP, and IL-6 and the subset of lymphocytes<sup>[51]</sup>. This reduction in peripheral lymphocytes occurred in spite of the presence of IL-2, IL-10 and IL-7, which are the anti-inflammatory cytokines that induce proliferation and differentiation of T and B lymphocytes and natural killer (NK) cells, to increase their cytolytic functions<sup>[52]</sup>, which be in favor of the existed pathological process, exactly as what occurred by HIV infection, as explained by the study of *Gulati K, et al. (2016)* who said: in HIV, the secretion of cytokines such as IL-2 and IFN-gamma is decrease while production of Th2 cytokines IL-4, IL-10 and pro-inflammatory cytokines like IL-1, IL-6, IL-8 and TNF-alpha is increase, in addition to stimulation of HIV replication in T cells and monocytes derived macrophages (MDM), by TNF-alpha, TNF-beta, IL-1 and IL-6, and whereas IL-2, IL-7, and IL-5 up-regulates HIV-1 in T cells, while macrophage colony stimulating factor (M-CSF) stimulates HIV in MDM<sup>[53]</sup>, also IL-10, and IL-13 inhibits it in MDM only, but the IFN-gamma, IL-4 and GM-CSF, are bi-functional cytokines, have an inhibitory and stimulatory effect for HIV infections<sup>[54]</sup>, but in case of *Coronavirus-2* instead of stimulating its replication in the respiratory system; because it spontaneously cleared from nasopharyngeal region at the 8<sup>th</sup> day of infection as it resulted from the stander of care (SOC) arm and hydroxychloroquine (HCQ) arm study<sup>[47, 55]</sup>, it stayed long time in gastrointestinal tract and continued its shedding in the stool, as aforesaid, therefore, more probably it had been stimulating the *H. pylori* pre-programmed cells, and result in recurrence of the previously treated *H. pylori* complications, as occurred after many weeks among patients in group B, but not among patients who're using an *Echinacea*, that heralded an increase in presentations of the known diseases but with an increased resistance to treatment. Hence, co-existence of

*H. pylori* and *coronavirus-2* in the same patients, increased the complexity of the disease, as happened in group D among patients that enrolled in D3 subgroup; whereas, its patients had suffered of paradoxical effect to *azathioprine*, *Echinacea* and *clarithromycin*, that improved after 30 minutes of sublingual administration of *Ginkgo biloba* tablets; these effect will explain by understanding of their effect on cytokines: firstly; the *Echinacea* medicinal extracts exerted their actions via the activation of macrophages in independent way of any cooperative effect with lymphocytes, by purified polysaccharide (EPS); that prepared from herb and root, and has no effect on T lymphocytes with moderate effect on B lymphocytes) to produce IL-1 and secrete Oxygen radicals<sup>[56]</sup>, and has anti-inflammatory activity via the following: Enzyme 5-lipoxygenase (5-LOX)<sup>[57,58]</sup>, polar caffeic acid fraction that enhanced arginase activity (which is an active participant in anti-inflammatory action), in addition to the Alkamides that prevented NO and iNOS production which are a mediator of inflammation<sup>[59]</sup>, also antioxidant activity by Caffeoyl derivatives and methanol extracts of freeze-dried roots that has an activity for scavenged the hydroxyl, 1, 1-diphenyl-2-picrylhydrazyl(DPPH) and ABTS radicals, antifungal activity<sup>[60, 61]</sup>, and Antiviral activity against influenza-A2, herpes simplex<sup>[62]</sup>, anti-androgenic<sup>[63]</sup>, Cannabinoidomimetic<sup>[64]</sup>, anti-tumor<sup>[65]</sup>, and radioprotective activities<sup>[66]</sup>, i.e. integral effect on multiple sites at the same time due to overall actions of the herb medicinal substances. But in other studies; as *Megha Gupta et al. (in 2012)*, said: purple coneflower extract did not prove to be successful in prevention of upper respiratory tract infection and in the treatment of common cold in other study, while in 3-double-blind, placebo-controlled trial *Echinacea purpurea* root in combination with other herbal drugs was reported to be successful in reducing symptoms severity of common cold flue<sup>[67]</sup>, nevertheless, 10 patients in group of extra-pulmonary manifestations, after 5 weeks of their cured from COVID-19, they had caught a cold that relieved at the end of 48 hours in spite of their continuing use of D3 subgroup drugs regime, but this could be due to a common cold cause that may be a coronavirus as it constitute one cause of common cold, and failure of *Echinacea* in treating common cold as aforesaid either could be due to different causes of common cold other than coronavirus, or due to different soil and type of water irrigation of *Echinacea* herbs; for example, as said in the presented reference; water standing on the field for a day or two will injure plants, and as this study depend on *Echinacea* type that cultivated in Canada under the following characteristics; type of water irrigation preferable from the pond that filled completely by rain or snow, and other sources must be get a license and has low sodium and/or iron levels<sup>[58]</sup>, therefore, using of sewage treated water will result in land dampness, in addition to the damages that could be caused by the multiple chemical substances and bacteria that present in this type of water, or that failure may be due to poor absorption of *Echinacea* medicinal substances from gastrointestinal system as result of pathological barrier formed in small intestine like that formed due to *H. pylori* infection and enhanced some water collection in intestinal lumen; that has an ultrasonographic and physical characteristics; for example, physically, it has soft texture by palpation like silky thin tissues and has a dark green colored, after 5 hours of its dryness it was

regained its characteristics if putting it upon a water surface for few minutes, it had resulted in decreased absorption of vitamins A, D and E<sup>[22]</sup>, that had evidenced by increase in their absorption after sublingual administration. Thus, *Echinacea* effect as explained by *Zili Zhai et al. study (in 2010)*, who said; once macrophages are activated by effect of alcohol extracts of *Echinacea*, the induced nitric oxide synthase (iNOS)-gene transcription is initiated about one an hour after activation, whereas its protein expression occurs some 3-4 hours later<sup>[68]</sup>, and whereas in this study, the clinical effect started to appear after one an hour, and about 40 minutes if increased the dose, i.e. at the time of initiation of iNOS gene transcription, a result that points to the presence of multiple effects occurred at the same time due to an integral actions by all the medicinal substances of *Echinacea*, a properties that not present in the manufactured drugs. *Echinacea* enhanced arginine synthesis, so due to insufficiency of endogenous arginine (because arginine is the source of nitrogen atom in nitric oxide<sup>[69]</sup>), as a result of infection and inflammation<sup>[70]</sup>, thus, it induce arginase activity for synthesis of enough amounts of arginine, via up-regulation of inducible nitric oxide synthase for synthesis of nitric oxide that help in production of citrulline that in turn can be recycled to arginine in a pathway known as the Citrulline-NO Cycle, and then the arginine availability for metabolic functions is determined by activities of its transporters in the plasma and mitochondrial membranes, that can be changed in response to arginine concentration and to specific stimuli<sup>[71]</sup>, as the anti-inflammatory activity of *Echinacea* via alkamides fraction, that possibly inhibits the inducible nitric oxide synthase, via down-regulation of the (Cationic amino acid transporter-2 (CAT-2), because as reported by Sidney M and Morris Jr, 2007: failure to induce cationic amino acid transporter-2 (CAT-2) can limit arginine availability for induce NO synthesis to varying degrees, depending on cell type<sup>[72, 73, 74]</sup>), therefore, the GM-CSF that also produced in high levels in covid-19 patients, as evidenced by the severe neutrophilia, act as stimulator for CAT-2<sup>[75]</sup>, which actually inhibited by *Echinacea* effect, that evidenced in the study by correction of patients white blood cells ratio after 48 hours of *Echinacea* intake in cases with mild and moderate severity, and possibly this anti-inflammatory effect achieved by the anti-inflammatory effect of *Echinacea* medicinal substances, because as *Zhai et al. (in 2010)* said: anti-inflammatory effect of *Echinacea* is via alkamides fraction, or as a synergistic action of both alkamides and caffeic acid derivatives that act together to drive macrophages to alternative activation as anti-inflammatory activity, or via inhibition of nuclear expression of multiple pro-inflammatory transcription factors including NF-kB and STATs, as what occurred in a viral model<sup>[68]</sup>, as *Echinacea* has a direct effect on some viruses as aforementioned, and as it result in cure of patients with mild to moderate severity within 48 to 72 hours, an effect that not related only to inflammatory cytokines stoppage, but possibly related to antiviral activity against CoV-2, that clearly evidence clinically by its effects on patients in A1, C1, and D1 subgroups that have given only an *Echinacea* syrup, and the anti-inflammatory property by the paradoxical effect that produced after its intake by patients in D3 subgroup that have a progressed COVID-19 process. Also, the *Ginkgo biloba* has an anti-inflammatory properties; in opposite to *Echinacea* as inhibition of production of

IL-1beta, and TNF-alpha; and characterized by other multiple effect, as the following: adjust the balance of peripheral T lymphocyte subsets, increasing production of anti-SRBS antibodies, and reducing expression of IL-8, prevent the increase in IL-6 levels and ameliorate the unbalanced Th17/Treg response with maintaining of normal ratio, in addition to reducing corticotrophin-releasing hormone and sympathetic activities, also reduced the number of ventricular extra-systoles, and has a regulation effect on proteins and cell cycle progression, also has anti-mutagenic properties, and inhibit free radical release and prostaglandin PG12 and it down-regulating NF-kappa-B' (similar to *Echinacea* effects ), and down-regulate prostaglandin E2, also it has fibrinolytic effect equivalent to that of streptokinase, in addition to up-regulation of gene expression of vasoactive substances, also up-regulates gene expression of IL-10 in addition to IL-10 receptor and activating enzyme nitric oxide synthesis (eNOS), hemorrheological regulation<sup>[76, 77]</sup>, that also differed in some aspects from *Echinacea* effect, and it hasn't an effect on endogenous cannabinoid like *Echinacea*, while the *Azathioprine* has unique effect such as it depend on the immunosuppressing of immune cells and anti-RAC1 anti-inflammatory activity via its metabolite 6-mercaptopurine (6-MP), that has a protective role in endothelial cell activation as an anti-inflammatory effect, because they block activation of GTPase Rac1 in T lymphocytes, vascular endothelium and other tissues, resulting in inhibition of monocytes/macrophage adhesion to activated endothelium and inhibit endogenous Rac1 activation via a GTP-dependent mechanism resulted in effective suppression of TNF-alpha induced activation of the transcriptional factors c-Jun, ATF2, and NF-kB, i.e. potently, they can reduce the mRNA-expression level of pro-inflammatory cytokine IL-12 and chemokines CCL2 and CCL5; known as MCP-1 and RANTES, respectively, IL-6, IL-8, and protein-10(IP-10), but not IL-1beta m-RNA, resulting in reduced VACM-1 protein, and not affect the ICAM-1 protein level but instead of that they block the maturation of ICAM-1-induced docking structures lead to prevention of monocytes and neutrophil transmigration across endothelial cells<sup>[78]</sup>, i.e. *azathioprine* metabolite 6-MB, successfully inhibited most of the cytokines and chemokines that involved in COVID-19 mild to critical severity, IL-6, IL-8, TNF-alpha, IL-12, MCP-1, and even the IP-10 that increased in lung injury stage, but has no effect on IL-18 (that inhibited by help of *Clarithromycin*, that also down-regulated expression of TLR4 and thus inhibit production of IL-12 and IL-18, but it like *Azathioprine* hasn't an effect on IL-17; that inhibited by help of *Ginkgo biloba*, a property that made it beneficial because as *Meng et al. (in 2012)* said: the IL-17 signaling facilitated production of IL-1, IL-6, and TNF-alpha, and increased the expression of transforming growth factor-1, fibrogenic cytokine, and directly induced production of collagen type I in hepatic stellate cells by activating the signal transducer and activator of transcription 3 (stat3) signaling pathway<sup>[79]</sup>, and whereas, IL-17 was increasing more in covid-19 patients with lung injury, thus its inhibition by *Ginkgo biloba* effect, in addition to effects of other drugs simultaneously prevented the paradoxical effect, as it block the initiating( activation of macrophage by lipopolysaccharide), and perpetuating (activation of inflammatory cells by IL-17 signaling) stages of inflammations in addition to cut the synergistic activity

between *H. pylori* and CoV-2. Withdrawn of *azathioprine* result in re-appearance of manifestations, that disclosed a co-existence of viral and bacterial activities via the GTPase RAC1 pathway, in endothelial cells and other tissues, as proved by treatment of *Helicobacter pylori* syndrome. Also omitted doses of *Clarithromycin* and ingestion of foodstuffs that processed with sewage treated water led to return of manifestations, which subsided after prevention of its intake in addition to oblige to *clarithromycin* doses, this results has elicited also the importance of the TLR4 receptor expressions, and IL-12 and IL-18 roles in perpetuating the pathological process, as a result of the continuous *H. pylori* messages, as proved by the poor response to the three drugs without *clarithromycin* treatment or re-use of this kinds of foodstuffs, by adding of this result to the cure of patients in group of extra-pulmonary manifestations, after use of *H. pylori* therapeutic and preventive program that proved by clinical, laboratory and ultrasonographic results to be effectively efficient in treating of *H. pylori* diseases and the associated systematic chronic pathological process, that has explained in detailed in this reference<sup>[22]</sup>, in addition to the use of herbal drugs to treat *Coronavirus-2* or *Covid-19*, that success in treating patients whose infected with *coronavirus-2*, in spite of their use of *H. pylori* therapeutic and preventive program for treating of *Helicobacter pylori* syndrome, that also explained in the former reference, all of these proved the role of *coronavirus-2* in aggravation and acceleration of diseases that accompanied with the presence of *H. pylori* infection and/or that caused by its pathological process. The *Echinacea* has no benefits to patients with other viral fever that presented in our region, as *Chikungunya* and *Dengue fevers*, because no clinical improvement had detected within 48 hours of started therapy, but instead of that, their conditions have worsened, i.e. not all fevers can be treated by using of *Echinacea*, but its effect on COVID-19 cases with mild and moderate severity making it a herbal drug of clinically proved antiviral activity; if compared with the clinical effect of *hydroxychloroquine* or *Remdesivir*, it's the best and also it has an anti-inflammatory and partial immunoregulator activities, as evidenced in the study, in addition to what aforementioned about its activities.

## Conclusion:

This study proves the following: I) The medicinal extracts from *Echinacea purpurea* have an efficient effect against novel-CoV-2 disease, in a faster way than *Curcuma*, *Ginger* and *Cissus rotundifolia*, but the *Echinacea* and *clarithromycin* have a fastest remedy from COVID-19. II) The combination of *Echinacea*, *H. pylori* therapeutic and preventive program, and *Ginkgo biloba*, is a successful regime for treating of patients with severe Covid-19, and whose suffered of post covid-19 extra-pulmonary diseases, allowed them to return to their work after 7 days of treatment only "Inshaa Allah". III) *Coronavirus-2* accelerated the subclinical and aggravated the clinically apparent diseases that accompanied with/caused by *H. pylori* infection.



## Recommendations:

Herbal therapy by using the studied herbs is a beneficial remedy if used earlier in the symptomatic stage of COVID-19, that must be used frequently as an emergent therapy to prevent disease progression in addition to its curable effect; in particular, the *Echinacea* syrup, in the aforementioned route of use, especially in the presence of *Coronavirus-2* mutagenic ability, that permitting a recurrent infection, and forming a synergistic pathological effect with *H. pylori*.

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I thank my GOD; Allah, for these results, that reveals the herbal benefits in treating COVID-19 patients and abolish the dangers of its pathological process. There is no any support from anywhere and mention of *Echinacea* and *Ginkgo biloba* trademarks, aimed only to detect the sources of the used herbal drugs in the study.

## Competing interests:

There are no competing interests

Table (1) represents the pre and post treatment clinical manifestations of patients with confirmed and highly suspected COVID-19.

Clinical manifestations of patients with confirmed and suspected COVID-19, in Aden-Yemen 2020.					
Manifestations (pre-treatment)*	Patients		Manifestations (post-treatment)**	Patients	
	n=775	%		n= 57	%
Fever	775	100	- Facial pain	2	3.5
Cough	496	64	- Electrical sensation in trigeminal distribution	2	3.5
Coldness and shivering	558	72	- Something Move from head to nasal root	-	-
Laryngeal pain	155	20	- Dyslipidemia	3	5.2
Shortness of breathing	651	84	-Aggravated blood pressure	-	-
Breathlessness	10	1.29	5	8.77	
Nasal	2	20(0.26)	-Aggravated blood sugar	3	5.2
Chest	6	60(0.77)	-Accelerated Subclinical Atherosclerosis	-	-
Abdominal heaviness	2	20(0.26)	- thyroid papillary CA. metastatic to spinal cord	2	3.5
Nasal flue	10	1.29	-	3	5.2
Loss of taste	635	81.9	***	-	-
Loss of smell	630	81.2	- Hepatoma like lesion	1	1.75
			- Aggravated ascites in	-	-

Clinical manifestations of patients with confirmed and suspected COVID-19, in Aden-Yemen 2020.					
Chocking sensation	5	0.64	cirrhotic patients	-	-
Thyroid pain	4	0.51	-narrowing of spinal canal	2	3.5
Tinnitus	7	0.90	-Enlarged lymph-nodes	-	-
Dizziness	23	2.96	- non responded (gastro- esophagitis)	3	5.2
Nausea	37	4.77	-Matted intestines	-	-
Vomiting	30	3.9	-severe unusual Uteritis	1	1.75
Diarrhea	37	4.77	- diffuse breasts	-	-
Constipation	2	20(0.26)	lymphadenopathy	2	3.5
Abdominal pain	21	2.7	- Aggravated arthritis	-	-
Renal pain	17	2.19	-Amnesia and limb tremor (unilateral)	1	1.75
Inflammation	16	2.06	- Spondylosis of thoracic and lumber vertebra,	2	3.5
Polyps	1	0.129	-ankylosing spondylitis and sacroiliitis	2	3.5
Acute hepatitis with ascites	1	0.129		7	12.28
Stroke	3	0.387		-	-
Angina	2	20(0.26)		1	1.75
				-	-
				8	14.0
				-	-
				-	-
				5	8.77

\*in the acute episode of the disease accompanied with fever. \*\*after few to many weeks of improvements. \*\*\* patient was suffering of electrical sensation in limbs and unable to sit down or standing even 5 steps with bilateral support but after treatment with regime of D3 subgroup, she was able to do it with heaviness.

Table (2) represents the laboratory results of patients with confirmed and highly suspected COVID-19.

The laboratory results of patients with confirmed and suspected COVID-19. Aden-Yemen 2020						
Investigations	Pre-treatment			Post-treatment		
	Values	n=775	%	Values	n=775	%
A) Blood						
1) -White blood cells x 10 <sup>9</sup> /L counts:						
I- counts: a- leucopenia	2.5-3.2	045	5,8	4.5 – 5.6	010	1,29
b- leukocytosis	8.0-17.5	020	2,58	5.0 – 5.5	020	2,58

The laboratory results of patients with confirmed and suspected COVID-19. Aden-Yemen 2020						
c- normal WBC	4.0-6.7	710	91,6	5.0 – 5.6	710	91,6
II- differential%: a- neutrophil*	25 - 83	775	100	45 – 63	734	94,7
b- lymphocytes**	05 - 58	775	100	36 - 58	734	94,7
2) thrombocytes x 10 <sup>9</sup> /L	90-120	045	5,8	220– 350	740	95,48
3) C-reactive protein (CRP) reactive	1/96	700	90,3	1/12	740	95,48
4)Erythrocyte Sedimentation	50-135	740	95,4	25-35	772	99,6
Rate(mm/hr.)	<150	092	11,87	< 100	092	11,87
5)Ferritin (ng/ml.)	290 - 350	239	30,8	< 280	520	67,09
	>350 - 673	431	55,6	290– 320	150	19,35
	700 – 1150	013	1,67	>=150	013	1,67
6)d-Dimer (microgram/ml)	<0.5	062	8	< 0.5	772	99,6
	0.5	700	90,3	-	-	-
	>0.5 - 5.0	013	1,67	-	-	-
7)AST (unite per liter)	>= 60	683	88,1	< 48	755	97,41
8)ALT (unite per liter)	>= 37	674	86,96	< 36	755	97,41
9)LDH (unite per liter)	560 - > 800	703	90,7	< 400	745	96,1
10)Creatinine (mg/dl)	> 1.3	065	8,38	1.0 – 1.3	740	95,48
11)Lipid profile (mg/dl)	-	-	-	-	-	-
I- Cholesterol	>= 220	023	2,96	150 - 189	772	99,6
II- Triglyceride	>= 360	064	8,25	100 - 141	772	99,6
III- LDL	>= 100	020	2,58	56 – 94	772	99,6
IV- HDL	40 - 55	668	86,1	40 – 48	772	99,6
V- TG/HDL rate	>= 6.5	064	8,25	2.5 – 2.9	772	99,6
12)Blood sugar (mg/dl)	>=250mg/dl	113	14,5	120 – 135	772	99,6
13)HbA1C%	>=10.5	038	4,9	6.5 – 7.8	772	99,6
14) COVID-19 NP-PCR	Positive	003	0,387	Negative	003	0,387
15) Chikungunya IgM	Positive	019	2,45	Positive	019	2,45
16) Dengue IgM	Positive	016	2,06	Positive	016	2,06
II) Urine	-	-	-	-	-	-
High red blood cells	Many/HPF	157	20,25	0 – 1/HPF	035	4,51
High white blood cells	Many/HPF	157	20,25	2 – 3 /HPF	035	4,51
Granular casts	1-2 plus	073	9,41	NO	772	99,6
Nitrite	2-3 plus	021	2,7	NO	772	99,6
Urobilinogen	Positive	017	2,19	NO	772	99,6
Protein	Trace-2 plus	016	2,06	NO	772	99,6

\*patients with covid-19 had at 1<sup>st</sup> and 2<sup>nd</sup> days 4% less than lower normal limit of neutrophil or equal to lower limit and 10 - 13% more than upper limit of lymphocytes, then rapid progression of lymphopenia with disease progression. \*\*patients with chikungunya had lymphocytosis and neutropenia

(21 – 28% lymphocytes and 70 – 76% neutrophilia) while these with dengue fevers had similar percentage to 1<sup>st</sup> and 2<sup>nd</sup> days of covid-19 patients' values.

**Table (3) represents the Oximeter oxygen saturation values and corresponding lung surface areas for patients with confirmed and highly suspected COVID-19.**

Oximeter oxygen saturation values with corresponding lung surface areas for COVID-19 confirmed and highly suspected cases in Aden – Yemen – 2020												
of patients of a total number = 775 Percent of oxygen saturations										Areas of decreased breathing sound by auscultation, and confirmed by sonographic imaging.	Number of pts. (n=) <sup>+</sup>	Percentage (=%) <sup>+</sup>
Hand fingers	Pre-treatment	Post treatment by <i>Echinacea</i> alone and by combination*				After 1 an hour** next to deterioration and re- control		Rt.	Lt.			
		One an hour		48 hours								
Oxygen saturation%												
	Rt.	Lt.	Rt.	Lt.	Rt.	Lt.	Rt.	Lt.				
Thumb	86	91	91	97	93** – 96	94** - 96	94 - 96	94 – 96	Apical	63	8,1	
	96	95	98	99	99	99	No	No		100	12,9	
Index	90	87	93	91	92** – 97	89** – 96	96- 97	92 – 96	Anterior	150	19,3	
	95	99	98	99	99	99	No	No		70	9,0	
Middle	86	81	93	92	91** – 97	96**	95 - 97	98	Sub-axillary	250	32,2	
	98	98	99	99	99	99	No	No		133	17,1	
Ring	66	80	94	92	91** – 97	95**	95 - 97	98	Anterior to Scapula	523	67,4	
	96	96	99	99	100	99	No	No		148	19,0	
Little	76	86	91	97	92**	98**	96	99	Lower basal (back)	263	33,9	
	97	98	98	98	99	99	No	No		63	8,1	

\*Herbal drugs that has effects on Oxygen saturations, with more and fast effect achieved by *Echinacea syrup*. \*\*patients' intake milk and white tea before 14 hours of recording a decreased value of oxygen saturation by 4%, with fluctuated values. \*\*after one an hour of doubling the regime doses of D3 subgroup, there were increasing in the values of lower limits also by increment of 4%. <sup>+</sup> few patients have one or two regions of lung surface areas with decreased breathing sound while the majority have more than two regions.

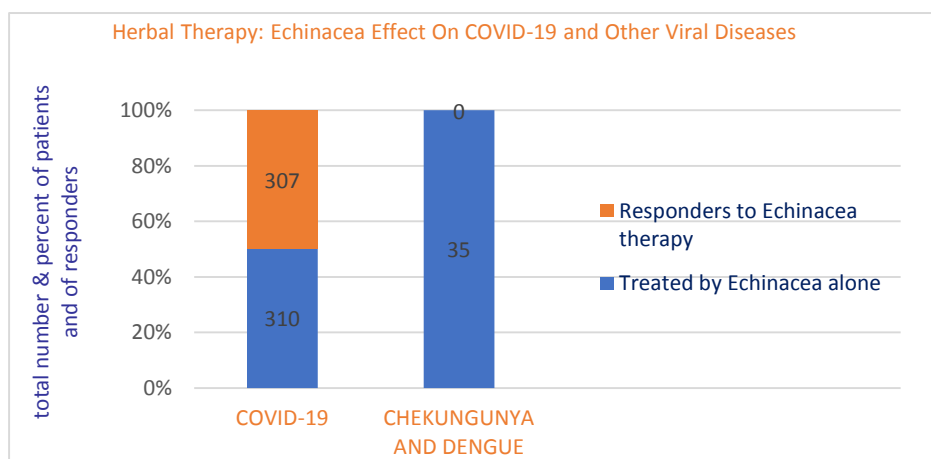


Figure (1) Represent the Successful Effect Of Echinacea Syrup Alone On COVID-19 & No Effect On Chekungunya and Dengue Fevers At The time of COVID-19 Pandemic-2020, Aden-Yemen.



Photo (1) chest x- ray PA view reveals bilateral ground glass opacities; for highly suspected patients that is similar to confirmed covid-19 patients



Photo (2) ultrasonographic imaging reveals decreased air depth with presence of thickened arterial walls and narrowing of lumens that are more apparent at the bottom for patients with confirmed covid-19.



Photo (3) ultrasonographic imaging of lung for highly suspected covid-19 patients reveals decreased depth of air flow inside the left lung with decreased in the air width as shown in the left of the photo in compare with that at the right.

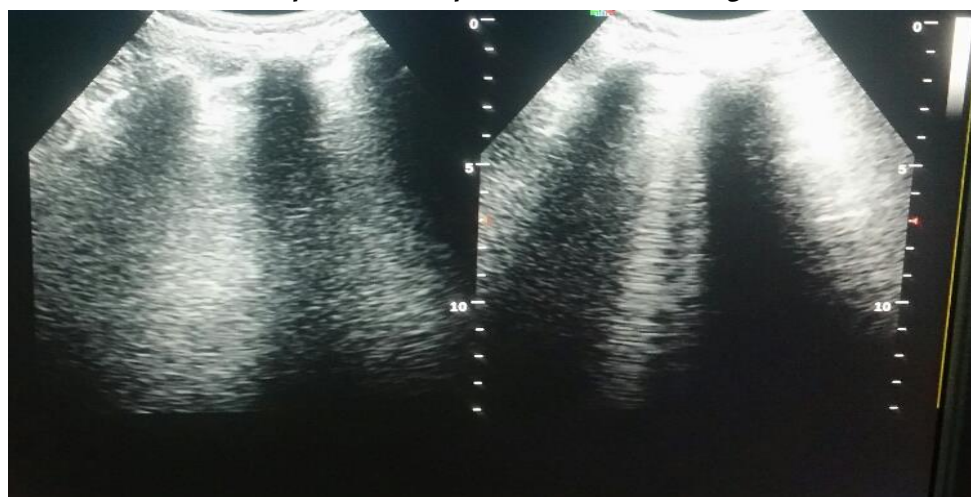


Photo (4) ultrasonographic imaging of patients in the early symptomatic period of confirmed covid-19, reveals mild decrease in the width of the air flow as shown in the left side of the photo with presence of round shapes characterized by hyper-echogenic reflection to the right of the left middle air column, and peri-arterial opacities with walls thickening in both sides.

#### REFERENCES:

- 1- WHO Director-General's *opening remarks at the media briefing on COVID-19*: (2020 March 11). Published 2020 March 11. [last accessed 19 November 2020].
- 2- Coronavirus disease 2019 (*COVID-19*) *Situation Report – 66* [https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200326-sitrep-66-covid-19. Pdf? sfvrsn=81b94e61\\_2](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200326-sitrep-66-covid-19.pdf?sfvrsn=81b94e61_2). [last accessed 19 March 2020].
- 3- Liu J, Liao X, Qian S, *et al.* (2020) *Community transmission of severe acute respiratory syndrome coronavirus 2, Shenzhen, China, 2020*. *Emerg Infect Dis.* doi.org/10.3201/eid2606.200239.

- 4- Ong SW, Tan YK, Chia PY, Lee TH, Ng OT, Wong MS, *et al.* (2020). *Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient.* JAMA.2020 March 4.
- 5- COVID- 19 and Food Safety: *Guidance for Food Businesses: interim guidance (2020 April 7).* [last accessed 19 March 2020].
- 6- Infection Prevention and control SAVE LIVES: *Clean Your Hands, (2020 May 5)* <https://www.who.int/infection-prevention/campaigns/clean-hands/en/>. [last accessed 19 March 2020].
- 7- <https://www.who.int/emergencies/diseases/nove-coronavirus-2019/technical-guidance/infection-prevention-and-control>. [last accessed 19 March 2020].
- 8- <https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions>. [last accessed 19 March 2020].
- 9- Wang W, Xu Y, Gao R, *et al.* (2020). *Detection of SARS-CoV-2 in different types of clinical specimens.* JAMA; 323 (18): 1843-1844. doi:10.1001/jama.20203786.
- 10- Woelfel R, Corman V, Guggemos W, Seilmaier M, Zange S, Mueller MA, Niemeyer D, Vollmar P, Rothe C, Hoelscher M, Bleicker T, Bruenink S, Schneider J, Ehmann R, Zwirgmaier K, Drosten C, Wendtner C. (2020) *Clinical presentation and virological assessment of hospitalized cases of coronavirus disease-2019 in a travel-associated transmission cluster.* medRxiv; 03.05.20030502; <https://doi.org/10.1101/2020.03.05.20030502>.
- 11- Gertjan Medema, Leo Heijnen, Goffe Elsinga, Ronald Italiaander. *Presence of SARS-Coronavirus-2 in sewage.* (2020). medRxiv preprint doi: <https://doi.org/10.1101/2020.03.29.20045880>.
- 12- <https://www.rivm.nl/en/novel-coronavirus-covid-19/research/sewage>. [last accessed 20 March 2020].
- 13- Gundy P, Gerba CP, Pepper IL, (2009) *Survival of coronavirus in water and wastewater.* Food Environ Virol. 1:10-14. Doi;10.1007/s12560-008-9001-6.
- 14- Yong Zhang Y, Chen C, Zhu S, Shu C, Wang D, Song J, Song Y, Zhen W, Feng Z, Wu G, Xu J, Xu W. *Isolation of 2019-nCoV from a stool Specimen of a Laboratory-Confirmed Case of the Coronavirus Disease 2019 (COVID-19).* (2020). J China CDC Weekly; 2(8): 123-124.
- 15- World Health Organization & United Nations Children's Fund (UNICEF). (2020). *Water, sanitation, hygiene and waste management for the COVID19 virus, Interim guidance, 23 April 2020.* World Health Organization. <https://apps.who.int/iris/handle/10665/331846>. [last accessed 20 Nov 2020].
- 16- Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, Azman AS, Reich NG, Lessler J. *The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application.* (2020 May 5). Ann Intern Med; 172(9):577-582. Doi:10.7326/M20-0504. (2020 Mar 10). PMID: 32150748; PMCID: PMC7081172.

- 17- Guan WJ, Ni ZY, Hu Y, *et al.* (2020 April 30). *Clinical characteristics of coronavirus disease 2019 in China*. N Engl J Med; 382(18):1708-1720. Doi: 10.1056/NEJMoa2002032. Epub 2020 Feb 28. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32109013>. [last accessed 20 November 2020].
- 18- Li Q, Guan X, Wu P, *et al.* *Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia*. (2020 Mar 26). N Engl J Med; 382(13):1199-1207. Doi: 10.1056/NEJMoa2001316. Epub 2020 Jan 29. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31995857>. [last accessed 20 November 2020].
- 19- Heneghan C, Brassey J, Jefferson T. (2020 April 6). *COVID-19: what proportion are asymptomatic?* University of Oxford, Centre for Evidence-Based Medicine. Available at: <https://www.cebm.net/covid-19/covid-19-what-proportion-are-asymptomatic/>. [last accessed 20 November 2020].
- 20- Casanova L, Rutalal WA, Weber DJ, Sobsey MD. (2009). *Survival of surrogate coronaviruses in water*. Water Res;43(7):1893-8. Doi: 10.1016/j.watres.2009.02.002.
- 21- Mohammed. (2018 December). *The effect of dairy products on the therapeutic regimen of patients with Helicobacter pylori*. AJSRP; 2(4), 89-98. Doi:10.26389/AJSRP.N110518.
- 22- Al-ashwal Nashwan Saleh. *Diagnosis of Helicobacter pylori: A guide to diagnosis of Helicobacter pylori by clinical and ultrasonography approaches*. (2020). AGH. <https://aghpublishing.com/product/book-02-3112020>. [last accessed 19 March 2020].
- 23- Professor Oppenheimer, Steven. (no year). *think before you agree to drink, is sewage a source of drinking water?* <https://www.valscan.com.au>. [last accessed 19 March 2020].
- 24- C. Li, B. H. Xu. *The viral, epidemiology, clinical characteristic and potential therapy options for COVID-19*. (2020). European Review for Medical and Pharmacological Sciences; 24: 4576-4584.
- 25- Aakriti Gupta, Mahesh V. Madhavan, Kartik Sehgal, *et al.* *Extrapulmonary manifestations of COVID-19*. (2020 July 26). Nature Medicine. 1017-1032.
- 26- Sahih Bukhari. (no year) – *medicine* – English (translation); 7(71)582. Available at: [al-Islamic.net/hadith/Bukhari/76](http://al-Islamic.net/hadith/Bukhari/76). [last accessed 24 September 2020].
- 27- Quero L, Klawitter M, Klasen J, Nerlich A, Boos N, Wuertz K. *Curcuma extracts and curcumin reduce proinflammatory cytokines and matrix degrading enzymes in human intervertebral disc cells by possibly influencing TLR2 expression and JNK activity*. (2012 Aug 21). J Inflamm (Lond);9(1):29. Doi: 10.1186/1476-9255-9-29.
- 28- Liu Z and Ying Y. *The inhibitor effect of Curcumin on virus-induced cytokine storm and its potential use in the associated severe pneumonia*. (2020). Front Cell Dev Bio 8:479. Doi: 10.3389/fcell.2020.00479.
- 29- Tripathi S., Bruch D. and Kittur D.S. (2008). *Ginger extracts inhibits LPS induced macrophage activation and function*. BMC Complementary and Alternative Medicine. 8:1. Doi: 10.1186/1472-6882-8-1.



- 30- Lantz RC, Chen GJ, Sarihan M, Solyom AM, Jolad SD, Timmermann BN. (2007). *The effect of extracts from ginger rhizome on inflammatory mediator production*. Phytomedicine. 14: 123-128.
- 31- Aryaeian N, Tavakkoli H. (2015). *Ginger and its effects on inflammatory diseases*. Adv Food Technol Nutr Sci. Open J. 1(4): 97-101.
- 32- Said A. A., Aboutabl E. A., El Awdan S. A., and Raslan M. A. *Proximate analysis, phytochemical screening, and bioactivities evaluation of Cissus rotundifolia (Forssk.) Vahl. (Fam. Vitaceae) and Sansevieria cylindrical Bojer ex Hook. (Fam. Dracaenaceae) growing in Egypt*. (2015). Egypt Pharm J 14: 180-186. DOI: 10.4103/1687-4315.172864.
- 33- Oldenburg, C. E., and Doan, T. *Azithromycin for severe COVID-19*. (2020 October 3). The Lancet; 396(10256). [https://doi.org/10.1016/S0140-6736\(20\)31863-8](https://doi.org/10.1016/S0140-6736(20)31863-8)
- 34- Meyer, Huaux, Gavilance, et al. (2009). *Azithromycin and Macrophage Polarization in CF*. American Journal of Respiratory Cell and Molecular Biology; vol. 41.
- 35- Sugiyama K., Shirai R., Mukae H., Ishimoto H., Nagata T., Sakamoto N., Ishii H., Nakayama S., Yanagihara K., Mizuta Y. and Kohno S. (2007). *Differing effects of clarithromycin and azithromycin on cytokine production by murine dendritic cells*. Clinical and Experimental Immunology, 147: 540-546.
- 36- Kovaleva A. A., Remmelts H. H. F., Rijkers G. T., Hoepelman A. I. M., Biesma D. H. and Oosterheert J. J. (2012). *Immunomodulatory effects of macrolides during community-acquired pneumonia: a literature review*. J Antimicrobial Chemother; 67: 530-540. Doi:10.1093/jac/dkr520.
- 37- Ihan A. and Gubina M. *Immune response to H. pylori*. Food Technol. (2014). Biotechnol; 52 (2) 204-209.
- 38- Akdis et al. (2011). *interleukins, from 1 to 37, and interferon-gamma: receptors, functions, and roles in diseases*. J Allergy Clin Immunol; 127:701-21.
- 39- Greally P, Hussain MJ, Vergani D, et al. (1993). *Serum interleukin-1 alpha and soluble interleukin-2 receptor concentration in cystic fibrosis*. Arch Dis Child; 68:785-7.
- 40- Hickman CJ, Crim JA, Mostowski HS, et al. (1990). *regulation of human cytotoxic T lymphocyte development by IL-7*. J Immunol; 145:2415-2420.
- 41- Huang C, Wang Y, Li X, Ren L, Zhao J, et al. (2020). *Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China*. Lancet (London, England); 395 (10223): 497-506. Doi: 10.1016/s0140-6736(20)30183-5.
- 42- Qin C, Zhou L, Hu Z, Zhang S, Yang S, et al. (2020). *Dysregulation of immune response in patients with COVID-19 in Wuhan, China*. Clinical Infectious Diseases: an official publication of the Infectious Diseases Society of America. Doi: 10.1093/cid/ciaa248.
- 43- Yang Y, Shen C, Li J, Yuang J, Yang M, et al. (2020). *Exuberant elevation of IP-10, MCP-3 and IL-1ra during SARS-CoV-2 infection is associated with disease severity and fatal outcome*. MedRxiv. Doi:10.1101/2020.03.02.20029975.

- 44- Wang W, He J, Lie P, Huang I, Wu S, *et al.* (2020). *The definition and risks of cytokine release syndrome-like in 11 COVID-19 infected pneumonia critically ill patients: disease characteristics and retrospective analysis.* MedRxiv. Doi:10.1101/2020.02.26.20026989.
- 45- Li T, Qiu Z, Zhang L, Han Y, He W, *et al.* (2004). *Significant changes of peripheral T lymphocyte subsets in patients with severe acute respiratory syndrome.* The Journal of Infectious Diseases; 189 (4): 648-651. Doi:10.1086/381535.
- 46- Cecere TE, Todd SM, Leroith T. (2012). *Regulatory T cells in arterivirus and coronavirus infections: do they protect against disease or enhance it? Viruses*; 4 (5): 833-846. Doi:10.3390/v4050833.
- 47- COVID-19 Treatment Guidelines Panel. *Coronavirus Disease 2019 (COVID-19) Treatment Guidelines.* National Institutes of Health. Available at <https://www.covid19treatmentguidelines.nih.gov/>. [last accessed 21 November 2020].
- 48- Zhou F, Yu T, Du R, *et al.* (2020). *Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.* Lancet;395(10229):1054-1062. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32171076>. [last accessed 21 November 2020]
- 49- Huang C, Wang Y, Li X, *et al.* (2020). *Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.* Lancet; 395(10223):497-506. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31986264>. [last accessed 21 November 2020]
- 50- Wang Z, Yang B, Li Q, Wen L, Zhang R. (2020). *Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China.* Clin Infect Dis. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32176772>. [last accessed 21 November 2020]
- 51- Wang F, Nie J, Wang H, Zhao Q, Xiong Y, *et al.* (2020). *Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia.* The Journal of Infectious Diseases. Doi: 10.1093/infdis/jiaa150.
- 52- Akdis *et al.* (2016). *interleukins (from IL-1 to IL-38), interferons, transforming growth factor beta, and TNF-alpha: receptors, functions, and roles in diseases.* J Allergy Clin Immunol; 138:984-1010.
- 53- Gulati K, Guhathakurta S, Joshi J, Rai N, Rai A. (2016). *Cytokines and their role in health and disease: A brief overview.* MOJ Immunol. 4 (2):00121. Doi: 10.15406/moji.2016.0400121.
- 54- Kedzierska K, Crowe SM. (2001). *Cytokines and HIV-1: Interactions and clinical implications.* Antivir Chem Chemother, 12 (3): 133-150.
- 55- Tang W, Cao Z, Han M, *et al.* (2020). *Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomized controlled trail.* BMJ; 369:m1849. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32409561>. [last accessed 21 November 2020]
- 56- Stimpel M, Proksch A, Wagner H, Lohmann-Matthes ML. (1984). *Macrophage activation and induction of macrophage cytotoxicity by purified polysaccharide fractions from plant Echinacea purpurea.* Infec Immun; 46: 845-849.

- 57- Wagner H, Breu W, Willer F, Wierer M, Remiger P, Schwenker G. (1989). *In vitro inhibition of arachidonate metabolism by some alkamides and prenylated phenols*. *Planta Med*; 55:566-567.
- 58- Muller – Jakic B, Breu W, Probstle A, Redl K, Greger H, Bauer R. (1994). *In vitro inhibition of cyclooxygenase and 5-lipoxygenase by alkamides from Echinacea and Achillea species*. *Planta Med*; 60: 37-40.
- 59- Zili Z, Avery S, Lankun *et al.* (2009 February). *Echinacea increases arginase activity and has anti-inflammatory properties in RAW 264.7 macrophage cells indicative of alternative macrophage activation*. *J Ethnopharmacol*; 25; 122(1): 76-85.
- 60- Binns SE, Purgina B, Bergeron C, Smith ML, Ball L, Baum BR, Arnason JT. (2000). *Light mediated antifungal activity of Echinacea extracts*. *Planta Med*; 66: 241-2.
- 61- Beuscher N, Bodinet I, Willigmann D, Egert. (1995). *Immunomodulierende Eigenschaften von Wurzelextrakten verschiedenen Echinacea-Arten*. *Z Phytother*; 16: 157-166.
- 62- Hu C, Kitts DD. *Studies on the antioxidant activity of Echinacea root extract*. (2000). *J Agric Food Chem*; 48: 1466-1472.
- 63- Skaudickas D, Kondrots AJ, Baltrusaitis K, Vaitiekaitis G. (2003). *Effect of Echinacea (Echinacea purpurea (L.) Moench) preparations on experimental prostate gland*. *Medicina (Kaunas)*; 39: 761-766.
- 64- Raduner S, Majewska A, Chen JZ, Xie XQ, Hamon J, Faller B, Altmann KH, Gertsch J. (2006). *Alkylamides from Echinacea are a new class of cannabinomimetics. Cannoid type 2 receptor-dependent and independent immunomodulatory effects*. *J Biol Chem*; 281: 14192-14206.
- 65- Chicca A, Adinolfi B, Martinotti E, Fogli S, Breschi MC, Pellati F, Benvenuti S, Nieri P. (2007). *Cytotoxic effects of Echinacea root hexanic extracts on human cancer cell lines*. *J Ethnopharmacol*; 110: 148-153.
- 66- Aboueilla AM, Shahein YE, Tawfik SS, Zahran AM. (2007). *Phytotherapeutic effects of Echinacea purpurea in gamma-irradiated mice*. *J Vet Sci*; 8: 341-351.
- 67- Gupta M. *et al. A Review On Purple Cone Flower (Echinacea purpurea L. Moench)*. (2012). *Journal of pharmacy research*, 5(8), 4076-4081.
- 68- Alberta agricultural, food and rural development: (2005). *Commercial Echinacea Production*. Canada. [www.agric.gov.ab.ca/publications](http://www.agric.gov.ab.ca/publications). ISBN 0-7732-6074-9. [last accessed 29 November 2020].
- 69- Beaumier L, Castillo L, Yu Y-M, Ajami AM, Young VR. Arginine. (1996). *new and exciting development for an "old" amino acid*. *Biomed Environ Sci*; 9: 296-315.
- 70- Flynn NE, Meininger CJ, Haynes TE, Wu G. (2002). *The metabolic basis of arginine nutrition and pharmacotherapy*. *Biomed Pharmacother*; 56:427-38.
- 71- Sidney M. Morris Jr. (2007). *Arginine metabolism: Boundaries of our knowledge*. *J. Nutr*; 137: 1602S-1609S.

- 72- Manner CK, Nicholson B, MacLeod CL. (2003). *CAT2 arginine transporter deficiency significantly reduces-mediated NO production in astrocytes*. J Neurochem; 85: 476-82.
- 73- Nicholson B, Manner CK, Kleeman J, Macleod CL. (2001). *Sustained nitric oxide production in macrophages requires the arginine transporter CAT2*. J Biol Chem; 276:15881-5.
- 74- Nicholson B, Manner CK, MacLeod CL. (2002). *Cat2 L-arginine transporter deficient fibroblasts can sustain nitric oxide production*. Nitric Oxide; 7: 236-43.
- 75- Martin L, Comalada M, Marti L, Closs EL, Macleod CL, Martin Del, Rio R, Zorzano A, Modolell M, Celada A, et al. (2006). *Granulocyte-macrophage colony-stimulating factor increases L-arginine transport through the induction of CAT-2 in bone marrow-derived macrophages*. Am J Physiol Cell Physiol; 290: C1364-72.
- 76- Xia S, Sun Q, Zou Z, Liu Y, Fang X, Sun B, Wei S, Wang D, Zhang A, and Liu Q. (2020). *Ginkgo biloba extract attenuates the disruption of pro-and anti-inflammatory T-cell balance in peripheral blood of arsenicosis patients*. Int J Biol Sci; 16(3): 483-494. Doi: 10.7150/ijbs.39351. Available from <https://www.ijbs.com/v16p0483.htm>. [last accessed 21 November 2020]
- 77- Labkovich M., Jacobs E. B., Bhargava S., Pasquale L. R., and Ritch R. (2020). *Ginkgo biloba extract in ophthalmic and systemic disease with a focus on normal tension glaucoma*. Asia-Pac J Ophthalmol (Phila); 9:215-225.
- 78- Marinkovic G., Kroon J., Hoogenboezem M., Hoeben K. A., Ruiter M. S., Kurakula K., Rubio I. O., Vos M., de Vries C. J. M., van Buul J. D. and de Waard V. (2014). *Inhibition of GTPase Rac1 in endothelium by 6-Mercaptopurine results in immunosuppression in nonimmune cells: New Target for an Old Drug*. J Immunol; 192: 4370-4378. Doi: 10.4049/jimmunol.1302527.
- 79- Meng F, Wang K, Aoyama T, Grivennikov S. I., Paik Y, Scholten D, Cong M, Iwaisako K, Liu X, Zhang M, Osterreicher C. H., Stickel F, Ley K, Brenner D. A., and Kisseleva T. (2012). *Interleukin-17 signaling in inflammatory, kupffer cells, and hepatic stellate cells exacerbates liver fibrosis in mice*. Gastroenterology; 143(3): 765-776.e3.doi: 10.1053/j.gastro.2012.05.049. Epub 2012 Jun 8.