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Can We Cure the Coronavirus Disease 19 (COVID-19) by Using Rhus Coriaria (Sumac) Extract?

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Abstract:- The COVID-19 pandemic, first reported on 31 December 2019 detected in Wuhan, China, is now affecting 221 countries and territories around the world causing a global crisis. To the date there are 127,249,568 cases and 2,788,444 deaths and the numbers are still raising rapidly. Although vaccine trials are on-going, further studies are needed for a safe vaccine with a long term immunity. Moreover, there is no specific antiviral agent for this deathly disease. Thus an effective and quick treatment is immediately needed. Because the improvement of effective vaccines or a specific antiviral drug takes time, phytotherapy seems to be an option because of the easiness of finding the plants and are effective widely in the body dissimilar to specific therapeutic drugs. Thus, the antiviral effect of *Rhus Coriaria* has been demonstrated in clinical laboratory studies.

These laboratory studies suggest that sumac may be effective on COVID-19 virus. The aim of this review is to update the current knowledge of antiviral activity of *Rhus Coriaria* (Sumac) and question its potential effect in the fight against COVID-19.

Keywords:- *SARS-CoV-2, Sumac, Rhus Coriaria, Antiviral plants, Coronavirus*

I. INTRODUCTION

In the end of December, 2019, a new coronavirus was detected in Wuhan city of China, started a critical pandemic caused by a virus and it keeps rapidly spreading everywhere [1],[2].

One of the most common death reasons world-wide is viral enfections.[3]. Most human diseases are caused by viruses comprising cancer. Various deadly pathogenesis such as Alzheimer's disease and type 1 diabetes are caused by viruses and their infections [4]–[6]. Furthermore, because of enhanced rapid urbanization and global travel, epidemics associated with novel viruses present a crucial danger to community well-being, nominately if a useful treatment is not available. Instances contains the latest occurrence of measles virus, influenza virus, Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), West Nile virus and the most recently SARS-CoV-2 outbreaks [7]–[9].

Up to the present, nevertheless, many viruses can survive except a strong immunity and just a couple of antiviral medications are licensed for clinical use. Among the current antiviral therapeutic options, the majority is non-specific for certain viruses [2]. We urgently need a specific and effective treatment for this deadly disease. And the treatment also should be fast, deliverable and reachable to stop the pandemic [10].

However, vaccine trials have started at early stages of pandemic and there're several vaccines are approved for clinical use and some are on-going. Live Attenuated Vaccines (LAV) was the number one choice along other vaccines due to its huge potential. After vaccine treatment, infection rates were lower but at the same time, we need time and more clinical trials for determining possible side effects, allergenic reactions and their safety in long term [11].

Due to their rich source, herbal medications are frequently used for antiviral medications progress [12],[13]. According to a study, 105 different plants showed antiviral effects against different type of viruses [14]. Most of these plants were studied on herpes viruses [14]. Thus, herpes viruses, especially herpes simplex virus were the most reported viruses that were affected by the certain plants were reported. Besides herpes viruses, other viruses, for example human immunodeficiency virus 1 and 2, hepatitis and influenza have reported for their antiviral effects [14].

Today, it is thought that sumac extract has a very promising potential within the plant family it is found in. It has been proven that the sumac plant is a renewable biological product due to its biological properties [15]. Thus in this review, we purposed to take attention to the importance of sumac plant in medical use.

II. MATERIALS AND METHODS

For the progress of this review, first of all, keywords were determined. Including, COVID-19, SARS-CoV-2, Rhus Coriaria, Phytotherapy. Secondly, we made a detailed and particular literature search over the 6 months. We carefully decided on the researches that appropriate for our criterias

which are the values of certain paper and its compatibility with our paper. Thus, such databases like PubMed, Elsevier, Springer, Wiley and scientific websites such as ReserchGate and WHO (World Health Organisation) were reviewed in depth. Lastly we established the topic with our profession, dentistry. We concluded our paper by suggesting two different potentially alternative treatment option in the light of our research.

III. CORONAVIRUSES

A. Genomic Organisation of Coronaviruses

The largest group related to order Nidovirales is Coronaviruses [16]. Coronaviruses have a special crown-like conformation. These viruses can cause an infection in animals and humans and can cause principally enteric, neural and respiratory system problems [17]. The alphacoronavirus, betacoronavirus, gammacoronavirus, and deltacoronavirus are the 4 sub-members of coronavidae. The viruses were divided by aggregating clustering. Coronaviruses, which are RNA viruses, are enveloped, not segmented and positive sense, also RNA viruses with the largest genome [16].

The genome of coronaviruses is a single-stranded positive-sense RNA (+ssRNA) (~30 kb) with 5′-cap structure and 3′-poly-A tail. One reason for membrane assembly and receptor binding is spike glycoprotein (S protein). One of the properties of angiotensin-converting enzyme 2 (ACE2) is that it resides as a receptor on the surface of human cells and thus forms a link for SARS-CoV. It has been observed in recent studies that ACE-2 receptor plays a role in the entry of 2019-nCoV into human cells [18]–[20]. Another study demonstrated that, when compared to human SARS-CoV, the RBD of 2019-nCoV showed a lower affinity to ACE2 indicating a likely lower virulence of 2019-nCoV [21]. The genome is allowing to act as an mRNA for translation of the replicase polyproteins. On the 5′ end of the genome, there is a untranslated region (UTR) and leader sequence required for RNA replication and transcription [22].

B. Pathogenesis of Human Coronaviruses

For the first time, HCoV was described in 1960's in the patients with a common cold [23]. OC43 and 229E are the two coronaviruses that effect humans by causing cold [24]. In 2002-2003, at Guangdong, China, the Severe Acute Respiratory Syndrome (SARS) outbreak caused by SARS-CoV has occurred. In fact, SARS-CoV outbreak was the most common respiratory system disease caused by coronaviruses which resulted with 9% mortality rate until SARS-CoV-2 outbreak. It infects the lung epithelial cells. According to a study in China, some of the patients that effected by SARS-CoV has also showed nervous system, moreover, patients with SARS was damaged on brain tissue [25]. Nevertheless, It's been described the SARS-CoV also can effect dendritic cells but not cause an remarkable infection [26],[27]. However, infection of these cells may be substantial about inducing proinflammatory cytokines that may conduce to disease [28]. When someone infected proinflammatory by SARS-CoV, the chemokines of these cells rises in patients serum [29]. After the SARS pandemic, it was understood that human coronaviruses can cause more severe infections on respiratory system. Pneumonia in children and nearly %15 of colds are connected to human coronaviruses. Also the antibodies have a high prevalence [30]. The scientists succeed isolating HCoV-229E and HCoV-OC43 which are α-coronaviruses, roughly 50 years back [31],[32]. During SARS outbreak, beta coronaviruses, HCoV-NL63 and HCoV-HKU1 were just described [33],[34]. Human coronaviruses are causing 15–30 % of respiratory tract infections per year. They may cause more acute diseases in newborns, the older people, especially with chronical illnesses. HCoV-NL63 can also cause acute laryngotracheitis [35].

Number of SARS-CoVs that infect humans were identified from bats [36]. More importantly these viruses have high toleration to genetic instability. HCoV-229E examples from different areas in the world have only minimum sequence variation [37]. After this epidemic, in 2012, a new pandemic caused by MERS-CoV has accured in Middle East [29]. In fact, the MERS-CoV pandemic didn't occurred in 2013. In 2014 there have been 855 cases in total and the mortality rate was 40% according to the European Center for Disease Prevention and Control. There was a significant similarity between MERS-CoV and other coronaviruses, HKU4 and HKU5 [38]. It was showed in a study, MERS-CoV can infect several immune cells in the human body [17].

Lastly 2019-nCov caused another pandemic started in Wuhan, China and continue to rapidly spread all around the world [1],[39]. In the early stages of 2019-nCoV outbreak, the genome of the virus was explained. The genome sequence of 2019-nCoV was substantially similar to other 2 beta coronaviruses with 79% to SARS-CoV and 51.8% to MERS-CoV [36]. There is no specific medications or vaccines proven with long term immunity for this disease, so the treatment options are only supportive.

In conclusion, interferons (IFNs) are somewhat effective against coronaviruses [40]. However from the beginning of outbreak , studies are continuing [17].

C. Current treatment options for COVİD-19

There is currently no specific therapeutic agent proven with a long term immunity for COVID-19 [13],[41]. It's known that ribavirin has changeable activities on the replication of SARS-CoV. Moreover, ribavirin and corticosteroid combinations were used as the treatment of SARS-CoV patients but it has given poor prognosis [41]. However, It's been recently proven, in some countries, interferon alpha (IFN-α) and immunoglobulin showed a positive effect against COVID-19 when used together [42]. It has been stated that interferon beta (IFN-β) is more effective than IFN-α, moreover, polyethylene glycol-modified IFN-α changes the histopathology by preventing replication and consequently prevents SARS-CoV infection [43],[44].

Other drugs that may be effective on 2019-nCoV are thiamine cinnamon and cyclosporine, which have been used for the treatment of SARS. It is CsA which also is an immunosuppressive drug that prevents the nucleocapsid protein of the virus from binding to cyclophilin A (CypA) of

the host cell. On the other hand it has a peptidyl prolyl cis/trans isomerase (PPIase) activity, the combination of interferon and CsA can prevent infection in the lungs and bronchi caused by coronavirus by inhibiting replication and tissue damage [45].

Dexamethasone was significantly effective on mortality rates although the clinical use was limited because of it's immunosuppressive effects [11]. An antimalarial drug, chloroquine/hydrochloroquine (CQ/HCQ) was efficient on CoV but it's been used restrictively because it caused cardiac arrest when used in a combination with Azithromycin. Lopinavir/ritonavir did not cause a noticeable difference in mortality rates but it had positive effects on decreasing symptoms. Ivermectin, Favipiravir also has positive effects on SAS-CoV-2 and Oseltamivir (Tamiflu) is under clinical experiment for the treatment of COVID-19 [11].

On some coronaviruses, when used in conjunction with ribavirin, IFNs were more effective than single use of IFNs [46]. To a recent study, Remdesivir has shown the most promising effect against COVID-19 [47]. Nevertheless, vaccines are the most efficient way to fight against COVID-19. For the treatment of SARS-CoV, both Live Attenuated Vaccines (LAVs) and Inactivated Vaccines (IVs) were developed for prospective use but none of them are confirmed for clinical use [48].

IV. PHYTOTHERAPEUTIC APPROACH TO COVID-19: *RHUS CORIARIA*

A. History of Sumac Use

Medicinal plants have been used in many years for the treatment of infectious and viral diseases [13],[49].The genus Rhus (sumac) comprises over 250 species and is well characterized by triterpenes and phenolics. Rhus species grow in mild areas worldwide and have been used as a medical herb or spice for hundreds of years [49].

Rhus coriaria L. (Anacardiaceae), is a cooking plant, grow in the Mediterranean region. The mere form or in mixed with another herbs can be used as a seasoning spice [16]. Recently, sumac using has been increased all over the world [50]. Rhus Coriaria L. has been used in spice mixes and in conventional medicine for ages [16]. In traditional medicine, Rhus Coriaria has been used in the cure of cancer, stroke, diarrhea, hypertension, haematemesis, dysentery, ophthalmia, stomach ache, diuresis, atherosclerosis, diabetes, measles, smallpox, liver disease, aconuresis, teeth and gum ailments, headaches, animal bites, dermatitis [50],[51]. 'R. coriaria is known to have fever-reducing, non-mutagenic, DNA protective, antiseptic, antifungal, antibacterial, antioxidant, hypouricemic, anti-ischaemic, hypoglycaemic, and hepatoprotective qualities'[52],[53].

The extraction of R. coriaria fruits has a substantial resource of natural antioxidants phenolics, mostly tannins, which has a regulatory effect on muscle cells, offering an atheroprotective role for that substance. As its demonstrated that tannins have anticarcinogenic effects [53].

R. Coriaria fruits and seeds are immensely rich in vitamin A, C and antioxidants [54]. It's notable that high doses of vitamin C has proved effects on prevention and the treatment of COVİD-19 [55].

B. Antiviral Activity of Rhus Coriaria

The therapeutical features of R. Coriaria plant have been demonstrated for centuries. Thus, sumac have been used as a traditional property in the treatment of chronic symptoms of stroke, it was told in Canon of Medicine by Avicenna (Ibn-Sina) [56].

There's no clinical studies that have evaluated the antiviral effect of Rhus Coriaria (Sumac) on SARS-CoV-2. As It's recently suggested that Rhus coriaria extract is an important candidate in the treatment of COVİD-19 due to it's antimalarial activity. Because of Malaria and COVİD-19 are similar in the manner of their pathophysiological characteristics [47],[57].

According to a study in Iran, among 25 species, R. coriaria extract showed remarkable effects on HSV-1 and adenovirus type 5 [58]. In fact, four biflavones, viz. amentoflavone, hinokiflavone, agathisflavone, and sumaflavone, taken from the different parts of different sumac species. Interestingly, amentoflavone and agathisflavone have shown a remarkable antiviral effect against influenza A and B. Amentoflavone showed that decreased anti-HSV-1 and anti-HSV-2 activities with EC50 =18 and 48 μg/mL, in turn. However, the antiviral activities against HIV-1 reverse transcriptase of amentoflavone, hinokiflavone, and agathisflavone was remarkable [59]. It's been shown that the hinokiflavone from Podocarpus macrophyela has an antiviral effect exhibited by its inhibitory activity on Epstein-Barr virus genome expression in some specific cells and also has significant potential for this biflavone [60].

V.PHYTOTHERAPEUTIC APPROACH TO COVID-19: REFLECTIONS ON DENTAL PRACTICE

Dentistry is the most effected profession from pandemic according to New York Times [61]. Thus, in preventing from COVID-19 and decreasing the cases, dental professionals have a significant role [62]. The World Health Organization (WHO) has published a guidelines during pandemic for the all dentists around the world [63]. Under the guidance of WHO, dentists should apply all the rules, because dental clinics are highly risky in the spreading of the virus and infecting the patients due to aerosol reducing [61]. It's been advised taking the travel history of the physicians and patients, measuring the temperature before starting any protocol and gargling with 1% hydrogen peroxide water, using rubber-dam and high-volume suction in all kinds of applications and disinfecting door handles and chairs frequently after each procedure. Standard protocols such as cleaning and disinfecting open contact areas such as sinks also need to be considered [62]. As recommended in The American Dental Association (ADA) and some other guidelines, dentists should not admit patients or postpone their treatment for a while, except in emergencies. In

addition, it is aimed to reduce interpersonal contact, reduce the waiting period of patients and generally eliminate all kinds of factors that may cause patients who come to clinics for treatment to become infected [64],[65].

Beyond that, in the fight against infectious diseases, plants and herbs has been used as a traditional treatment option in dental practice mostly due to their antimicrobial, anti-inflammatory and antioxidant impacts to eliminate the chemicals using because of their cytotoxic effects [66],[67]. Medicinal plants, especially Sumac, as a highly effective medicinal plant, has been used in the treatment of root canals, dental caries, against dental plaques, preventing alveolar bone loss and reducing oral load [66],[68]. Sushma et. al. reported that, Sumac berry extract has shown a significant reduction in S. Mutans and E. Feacalis in oral load when compared to other plants. Moreover, Sumac extract was more effective than chlorhexidine [69]. In addition, Rhus Coriaria L. (sumac berry) extract has inhibited the most common oral bacterias i.e. S. Mutans, S. Sanguinis, S. Sobrinus, S. Salivarius and E. Faecalis, also inhibited bacterial biofilm on orthodontic wires [69]. When Rhus Coriaria used alone of it's alcoholic extract, it was also effective on S. Mutans and S. Sanguinis [68]. In another study, ethanol extract of sumac has reduced the bone loss through reducing RANKL/OPG (Receptor activator of nuclear factor kappa-B ligand/Osteoprotegerin) balance and TOS (Fully Automated Total Oxidant Status) and OSI (Oxidative stress index) levels was proved by Saglam et. al. [70].

It can be concluded that, medicinal plants can be used in dentistry as pharmaceutics and as mouthwashes in reducing and controlling oral infections and oral microbial load. However, more comprehensive studies are needed [66],[67].

VI.RECOMMENDATION FOR FUTURE STUDIES

According to latest studies of Sumac use as a medicinal treatment [56]–[58], in the non-toxic and non-allergic dose, we recommend 2 different methods for the clinical practice of this plant on COVID-19 patients or on the virus with in vitro studies [67]. Sumac fruit should be immersed in water (preferably 45°C for 12 hours) with different concentrations and tried on the patients by making a drinkable solutions or capsules. Another method is adding sumac as a spice on each meal of COVID-19 patients.

VII.CONCLUSION

Viral infections are a huge part of human infections and threatening the community health across the world since antiquity. Herbs have been used to treat infectious diseases for years. Nonetheless sumac has been used as a therapeutic agent around the world as a traditional and natural product. In many clinical laboratory studies, as suggested that this has severally therapeutic uses, such as antioxidant, anti-allergic, anti-inflammatory, antifungal, antibacterial, and potentially antiviral properties. Thus, medicinal herbs have rich resources for such infections and viral diseases. Furthermore, it can be concluded that the Rhus Coriaria extracts have antiviral potential that can be used to cure infectious diseases or moderate the symptoms. In this review we explored the recent antiviral research and the healing activity of Rhus Coriaria. Obviously, more extensive clinical studies are certainly needed to improve standard protocols for routine use.

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