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Potential Effects of Natural Antioxidants in The Treatment of Some Viral Diseases : Review

Nareman Adeem Shnaa Aljazy [a)] and Alaa R. Abdulstar [b)]

Department of Food Science, College of Agriculture, University of Basrah, Iraq.
[a)] naremanadeem@gmail.com
[b)] Corresponding Author: alaa.abdull_sattar@uobasrah.edu.iq

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Abstract. Viruses have a high ability to resist drugs and adapt to all conditions. This has encouraged the scientific community to develop new therapeutic agents by using antioxidant compounds that are naturally present in foods and medicinal plants. Cellular harm caused by free radicals (Reactive Oxygen Spescies ROS) leads to many From the diseases such as diabetes, virus inflammation, impregnability diseases, and digestive diseases. ROS are created during Metabolism of complex chemical compounds. Some plants are characterized by their antioxidant and antiviral activity which increases their ability to fight viruses, therefore plants with antioxidant capacity protect cells by stopping the oxidation chain reaction, and also can contribute significantly to offsetting oxidative stress caused by viral disease. Essential oils extracted from plants may serve as potential alternative sources for treating diseases caused by certain viruses. This study aims to show the potential effect of natural antioxidants found in some foods, herbs and their essential oils in treating some viral diseases, as well as how they work in boosting immunity and inhibition of free radicals

Keywords. Natural antioxidant, Herbalists, Natural antivirals, Nedicinal plants, Scavengers .

I. INTRODUCTION

The immune system of human is the first line of defense against viruses and the process of maintaining it lies by relying on a diet rich in natural antioxidants, vitamins, minerals and other nutrients that the body needs. To strengthen the immune system. In the cell , the mitochondria work a dais for natural impregnability. A mitochondria's antiviruses signaling (MAVS) are necessary proteins of antiviral innate immunity, these stimulates the immune response and eliminates viruses [1]. Antioxidants enhance the work of the immune system by regulating the work of mitochondria, It is found in fruits and vegetables , which are healthy foods rich in effective antioxidant ingredients . Antioxidants have the ability to stop oxidative stress by binding with free radicals and neutralizing their harmful effects (the biggest alarm for many diseases , including viral infections) through several chemical mechanisms created by natural active compounds to combat free radicals and stop their harmful effects on cells .Among the most important of these mechanisms are ; the hydrogen atom transfer (HAT), Single electron transfer (SET) [2]. As antioxidants donate a hydrogen atom or an electron to unstable free radicals and make them more stable and suppression their harmful effect on cellular tissue [3]. Depending on their activity ,antioxidants can be classified into antioxidant enzymatic and non-enzymatic , enzymatic antioxidants convert dangerous oxidative products into hydrogen peroxide (H_2O_2) and then into water(H_2O) in existence of auxiliary factors such as Fe ,Cu and Mg .Non-enzymatic antioxidants work by interrupting free radical chain reaction , for example, vitamin C , plant phenols and Carotenoids , Another way to classify antioxidant depends on their solubility in water or lipid , the water soluble antioxidant (vitamin C) and the lipid soluble antioxidant (vitamin E) [4]. Pharmaceutical are used as antimicrobial agents to maintain the health , but they can cause many side effects, particularly when raise free radicals in the body [5, 6] . The ROS species extremely dangerous to human health and caused the production of various types of cancers[7–9] . Furthermore, they can increase potential health risks [10]. Many plant extracts contribute to the treatment of many microbial and viral diseases and some cancers due to their high content of biologically active compounds [11–13] .

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II. ANTIOXIDANT MEDICINAL HERBS

Medicinal plants are characterized by their natural components that are responsible for preventing viruses from entering the target cells or indirectly by stimulating the immune response, so they have been the subject of many scientific studies

- *Silymarin*

Silymarin (*Silybum Marianum*) It is a medicinal plant characterized by its red flowers and green leaves. It is native to Asia and Europe, and its cultivation has now spread to almost all countries [14] . The silybin structure is divided into two halves. The first is based on a flavononol group in flavonoids called taxifolin. The second is a phenylpropanoid unit, which is conyferil alcohol in this example. An oxeran ring connects these two pieces to form a single structure [15]. Silybin is one of the active biological compounds in the Silymarin plant. It is a natural antioxidant that can play an important role in reducing the oxidative$_c$ stress of cells and thus inhibiting or preventing the growth of a Mayaro virus[16, 17]. In view of the recent studies and reviews published , Recent studies have indicated the Prophylactic effects of the herb silymarin. Silymarin is extracted from dried seeds[18]. It is a complex mixture of flavonols, including silybin, silidianin, silicristin and isosilybin [19]. The flavonoid silybin complex is one of the most important compounds of silymarin, being a natural antioxidant that neutralizes free radicals resulting from metabolic processes, Silymarin also boosts the levels of endogenous antioxidants including GSH-Px and SOD [20]. These isomers are :(Silybin, Isosilybin , Silydianin , Silychristin and dehydrosilybin) and a few flavonoids mainly taxifolin [21]. The use of silymarin has been shown to protect against a variety of liver illnesses, as well as toxic and viral hepatitis, cirrhosis, and damage to liver cells caused by a variety of toxic substances. Apart from its hepatoprotective qualities, it is also said to have anticancer effects and to protect numerous essential organs, including the lungs, kidneys, and liver [22]

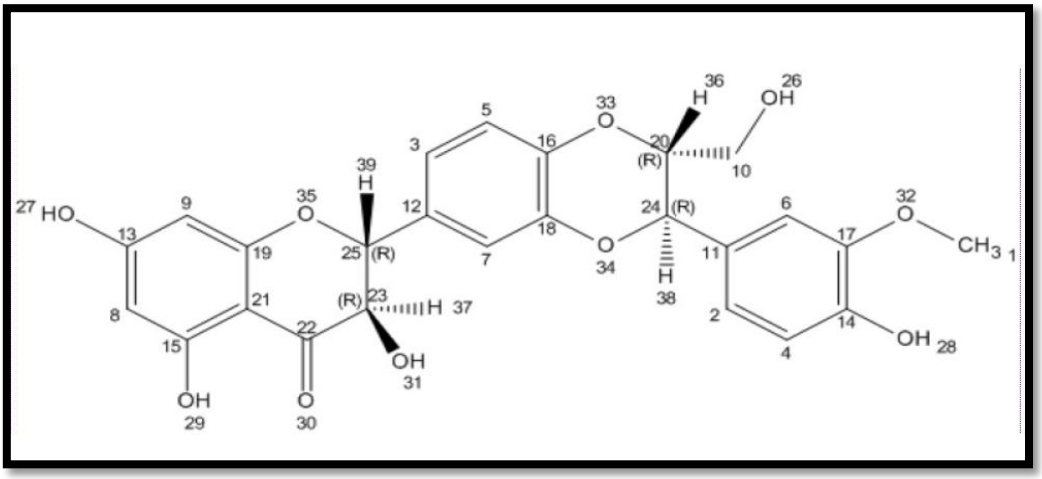

FIGURE 1. Chemical structure of silybin.

Silymarin is one of the 10 top most popular natural products and the botanical medicine reported the importance of silymarin in the treatment of chronic hepatitis C patients [23] . Free radicals caused by oxidative stress reduce levels of Glutathione, it is a natural antioxidant that plays an important role in the protection and recycling of immune cells and has an antiviral effect [24]. Silymarin increases natural antioxidant enzymes including glutathione peroxidase GPx and superoxide dismutase SOD, which protect cells from ROS toxicity, Furthermore, silymarin has been used in numerous clinical investigations as an adjuvant and safe medicine with no adverse effects [25]. Silymarin can be used as a preventive and pharmacological treatment against SARS-CoV-2, it is a safe drug and does not have any toxic effects even at large doses [26] .

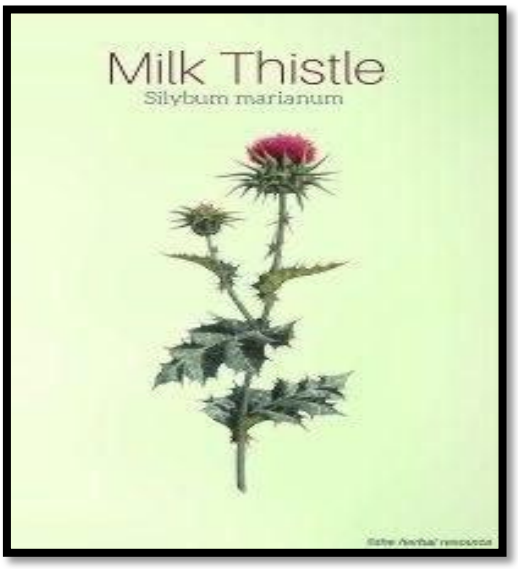

FIGURE 2. Silymarin (*Silybum Marianum*).

- *Astragalus*

Astragalus (*Astragalus membranaceus*) is an energy-boosting plant that supports the immune system,it is amazing herb that has been considered for 4000 years as a revitalizing herb in traditional Chinese medicine , and for its stimulant and anti-inflammatory properties in the body and is considered excellent for supporting the immune system in depth as it has exceptional properties to stimulate and strengthen the immune system ,it is ideal for the prevention of viral and bacterial diseases ,and it activates killer T cells for complete immune defense ,it increases the production of resistant red and white blood cells. Astragalus is rich in antioxidant flavonoids that are responsible for scavenging free radicals , including superoxide and hydroxyl radicals . Polysaccharide, one of the most biologically active ingredients in Astragalus, is a natural antioxidant that supports the immune system by increasing the number of lymphocytes in the body [27]. In addition to its ability to produce interferon, which contributes to the activation of the body's protective impulses, thus protecting the body from bacterial and viral infections [28] . The components of astragalus ,especially the antioxidant flavonoids , have a cellular protective properties against pathological changes in the heart ,blood vessels ,level ,lungs and kidneys[29]. These properties will naturally increase the immune system's resistance to viral infections. Astragalus enhances the immune response by increasing the number of cytokines in addition to stimulating Macrophage cells and natural killer cells [30]. The methanolic aqueous extracts of the root of Astragalus showed antiviral activity against the bird flu virus, while the concentrations used did not record any toxic effect on the embryos of the chickens under study [31] .

FIGURE 3 . Astragalus (*Astragalus membranaceus*).

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- *Clove*

Clove (*Syzygium aromaticum*) is a powerful antibacterial and antioxidant plant from the Myrtaceae family. This plant is a traditional plant found predominantly in Asia and Africa. Definition of components and their biological activity [32] . Cloves have been used since ancient times to treat many diseases due to their high content of natural antioxidants,Previous studies have demonstrated that clove extract and oil are effective antibacterial agents versus a wide range of bacteria [33]. It also has antiviral and antifungal properties [34]. The ethanol extract of cloves tested as an antiviral, which was obtained from the flower buds of the plant. The researchers showed clear inhibition of Herpes simplex virus (HSV). The clove extract, interestingly, has a direct inactivating effect on the particles of the standard HSV strain. Furthermore, after treatment with the extract, the overall HSV virus production after 30 hours decreased [35]. Another study showed a high inhibitory activity of the methanolic clove extract towards HCV protease, with an inhibition rate of 90% at a dose of 100 g/ml [36] .

FIGURE 4 . Clove (*Syzygium aromaticum*).

- *Sambucus Nigra*

Sambucus nigra Returns to the family Caprifoliaceae. S. nigra may have antiviral properties against the human immunodeficiency virus (HIV), herpes simplex virus (HSV1), and influenza, according to recent studies [37] . According to certain research, two flavonoids found in S. nigra are capable of combating the influenza virus strain (H1N1) and reducing viral penetration into cells [38]. The lectins in S. nigra fruits lead to an important role in preventing influenza infection[39]. In vitro, sambucol has been shown to prevent influenza fourfold to sixfold depending on the strain [40]. *S. nigra* efficiency against infection has also been discovered through research because of immune system activation [41–43]. Peptic polysaccharides, polyphenolic chemicals, and flavonoids found in *S. nigra* may have a role in viral suppression as well. The fruit extract from *S. nigra* has been shown to be effective in treating a variety of viral illnesses [44]. Since ancient times, S. nigra has been used to cure a variety of ailments, including urinary tract infections, epilepsy, rheumatism, blood sugar control, HSV infections and HIV infection [45, 46].

(a) **(b)**

FIGURE 5 . Sambucus nigra, A : Leaves and B: fruits

- *Spirulina*

Spirulina is a filamentous blue –green algae that belong to the oscillatiriaceae family. It contains Carotenoids and Phycocyanins PC an active protein of Spirulina it has an anti-oxidant effect [47]. Spirulina provides protection against oxidative stress induced by arsenic ,and this activity is largely related to phycocyanin ,it is contains a tetra pyrrole phycocyanobilin ,which is responsible for its antioxidant properties [48]. Spirulina is characterized by its high nutritional value due to its high protein content, similar to animal proteins found in meat, milk and fish, as well as its content of vitamins and mineral elements, which made it a biologically active substance against some viruses such as the human immunodeficiency viruses (HIV) [49]. The antioxidant activity of spirulina is applied through several mechanisms including activation of cellular antioxidant enzymes ,inhibition of lipid peroxidation ,DNA damage ,free radical removal and increased activity of Catalase [50]. for its health benefits , it has attracted a lot of interest in therapeutic applications of proteins , in addition to providing new ideas for future implants . Prevention is one of the best solutions to inhibition viruses and reduce its harmful effect , Some foods are characterized by their high content of natural antioxidants, which play an important role in combating some viruses, especially respiratory viruses such as COVID 19 , Spirulina is used as a popular nutritional supplement due to its biological activates and nutritional importance in this immune modulation thanks to its components of Vitamins ,Carotenes ,Iron ,Phenolic acids and Linoleic acid [51]. Spirulina's antiviral effect is due to its good content of phycocyanin and polysaccharides , which is one of the most important substances that encourage the formation of white and red blood cells, thus enhancing the immune strength of the body [52]. The major components in Spirulina that reinforcement the immune system are: Phycocyanin, Phycocyanobilinallo, Calcium Spirulina ,Cyanovirin - N(CV-N) and Sulpholipid . [53, 54] .

- *Nigella Sativa*

Nigella sativa L. is a plant grown in Mediterranean countries , The original home of this plant is eastern Europe and western Asia, and cultivation has spread in almost all countries due to its great therapeutic benefits due to its high content of effective biological compounds such as Beta-carotene thymoquinone , tocopherols ,vitamin A and C and. Past and present use to treat many aliments , including inflammation ,coughing and influenza . High in thymoquinone TQ content ,its biological activity is related to controlling the oxidative stress and reduction system through the removal of ROS and Modification of biocomposites systems [55] . Several scientific studies have discussed the effectiveness of N.sativa in strengthening the immune system against many microbial and viral causes [56]. The components of N. sativa, especially thymoquinone, strengthen the body's immunity, thus eliminating viruses early [57]. In addition to increasing number of CD4-positive cells [55]. More recently, thymoquinone analogues (chloroquine and hydroxychloroquine) have been used as potential therapeutic drugs for the COVID-19 [58]. Studied [59] effect of Nigella sativa L in the treatment of hepatitis C virus, where the experiment was conducted on a group of people with the same disease, treated with a concentration of (450 mg three times daily) for three months, the results showed a clear improvement In patients who return to the role of N. sativa in reducing the number of free radicals.

FIGURE 6. Nigella sativa L.

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- *Yogurt*

It is a product formed by the fermentation of milk with the action of lactic acid bacteria(LAB) ,*Lactobacillus bulgaricus* and *Streptococcus thermophilus* [60]. It is a food source rich in biologically active and antioxidant compounds, in addition to being an excellent source of protein, vitamins B_1 B_2 , B_{12}, B_9 , metallic elements Ca , P Mg and Zn [61]. Several studies have reported that preventive nutrition is the starting point for boosting immunity and disease resistance. Fermented milk is characterized by its good content of peptides that have an inhibitory effect on the enzyme angiotensin , which is one of the causative factors of COVID-19 [62]. In addition to enhancing the intestinal microflora with beneficial bacteria known for their antiviral effect [63, 64]. Probiotics have the ability to form some compounds that are known for their antiviral capabilities, such as lactic acid [65]. where this acid reduces the acidity of the medium and thus the medium becomes unsuitable for the growth of many viruses [66]. H_2O_2 is one of the important products of probiotics, which has shown an antiviral role, especially respiratory viruses [67]. AIDS virus types I and II [68]. Consuming yogurt is a more appropriate way to diminish viral infections by enhancing the functions of the immune system by increasing the production of Cytokines ,Antibodies , T-Cell and large granular lymphocytes (LGL) [69] .

III. ANTIVIRAL EFFECTS OF ESSENTIAL OILS

Essential oils are one of the most effective natural antioxidant and remedies for viruses . Essential oils cause cell wall damage by establishing a membrane potential across the cell wall and disrupting ATP assembly. Essential oils can potentially disrupt the electron transport system (ETS) route by dissolving mitochondrial membranes. Essential oils largely damage bacterial pathogens' cellular architecture, causing membrane integrity to break down and disturbing a variety of cellular functions, including energy generation and membrane transport. Essential oils can cause membrane rupture, resulting in cellular component leakage and ion loss. Several essential oils have antiviral properties, making them effective against a variety of RNA and DNA viruses[70]. Bergamot oil has been demonstrated to have anti-influenza viral action in vitro (100 percent inhibition of A H1N1 at a concentration of 0.3 %). Furthermore, after 10 minutes of exposure to bergamot oil vapor, these researchers discovered a 95% suppression of the H1N1 virus[71]. Essential oil (*Pelargonium graveolens*) and Rosa damascene (*Rosa damascene*) showed anti-effect of adenovirus35 [72] . Lemon balm oil has antiviral activity, especially avian influenza A virus (H9N2), due to its good content of active compounds such as generally 85%. linalool (up to 9.0%), citronellal (0.7- 20.3%), geraniol (up to 23.2%), β-caryophyllene (up to 11.3%), and caryophyllene oxide (0.4-31.7%) [73]. Tea tree oil inhibited influenza A (H1N1) virus 100 percent at a concentration of 0.01 percent and had a median inhibitory concentration (IC50) of 6 ppm [74, 75] . In addition, after 30 minutes of exposure to tea tree oil vapor, the type A (H11N9) virus was completely inhibited [76]. With IC50 values of 25, 12, and 250 ppm, the components of tea tree oil, terpinen-4-ol, terpinolene, and -terpineol, have exhibited anti-influenza viral activity against type A (H1N1) influenza virus[75]. Lavender *Lavandula angustifolia* L. and *Salvia officinalis* L. are perennial woody sub-shrubs in the family *Lamiaceae* widely used in food application , these essential oil have promising biological activities. Such as antioxidant and antiviral [77]. In a recent study conducted to evaluate the effectiveness of oil from lavender and salvia against the H5N1 virus, both oils showed a clear inhibition against H5N1 at IC50 0.11µg/ml lavender and 0.41 µg/ml for salvia[78]. Angiotensin-converting enzyme 2 (ACE2) is the entry point of the COVID-19 virus into the host cells, as geranium and lemon oils showed inhibitory effects on the activity of ACE2, which decreased from 17.68 ng/ml to 1.43 ng/ml and 4.34 ng/ml, respectively [79].

FIGURE 7. Salvia officinalis L.

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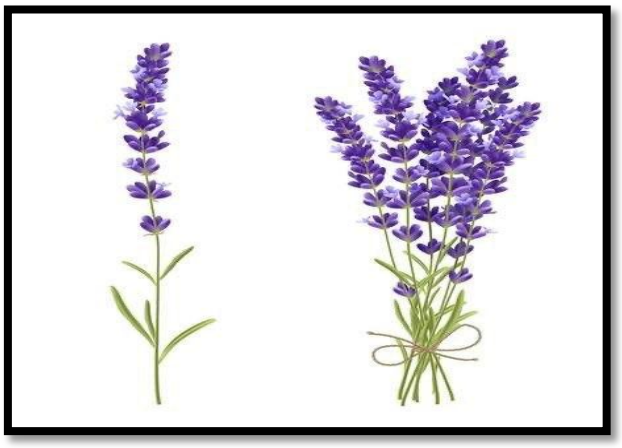

FIGURE 8. Lavandula angustifolia L.

CONCLUSION

Sometimes , the electrons spilt apart in your body from oxidative stress , the resulting unstable atoms called free radicals , The main culprits of oxidative stress are fried foods , alcohol ,tobacco smoke and air pollutions .At the cellular level ,Free radical can cause a change in the genetic material DNA , which in turn leads to a decrease in immunity and accelerates the occurrence of disease and viral infection . Research shows that treatment with free radical scavengers "Antioxidant" that are able to interact with and neutralize free radicals has a major role in combating the spread of disease and strengthen immunity . Many studies have focused on searching for antioxidant and immune – boosting drugs with fewer side effects . Antibiotics and chemical agents can inhibit the growth of viruses and strengthen immunity , but they also lead to the generation of reaction oxygen species. Plants medicines such Silymarin , Astragalus ,Lavender ,Salvia and Nigella sativa ,eliminate viruses by removing free radicals, Also, the presence of biologically active ingredients in the extract indicates the strong antioxidant and antiviral properties together, This strength increases with the increase in the concentration of these components. Yogurt ,with its high content of antioxidant peptides and probiotics , plays a vital role in strengthening immunity and fighting viruses , so it should be included with the diet to increase immunity in general .Hence ,this review suggests using herbal agents as an antioxidant instead of synthetic because of their dual antioxidant and antiviral activity ,so it is suggested that these biological materials be used against a virus COVID 19 and to speed up healing .

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