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NATURAL HOME REMEDIES MAY ACT AS POTENTIAL IMMUNOMODULATORS TO PROTECT AGAINST SARS-COV-2 INFECTION

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ABSTRACT

Corona virus disease 2019 (COVID-19) is primarily caused by Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). The infection begins with flu like symptoms with respiratory problems but in severe cases it affects cardiovascular system and excretory systems. On March 11, 2020 World Health organization (WHO) announced this disease as pandemic. Researchers are working continuously to find a proper treatment in the form of an effective vaccine or drugs/medicines but till date these are not available in the market and mainly symptomatic treatment is provided to COVID-19 patients. Under these circumstances, Ministry of Health and AYUSH, India has released advisory to people to use natural home remedies as potential alternative treatment. Home remedies are easily available at home in the form of spices and herbs e.g. citrus fruits, garlic, ginger, turmeric, ashwagandha, mulethi, tulsi, oregano, ginseng etc and have immunomodulatory effects as evidenced by ayurvedic literature and scientific publications. As per WHO guidelines the use of herbs within permissible limit would be helpful to manage COVID-19 but its overuse may have harmful effects. In the present article authors attempted to draw the attention of readers about the easy availability and affordability of home remedies to boost immunity and general well being of our body to fight against COVID-19.

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1 Introduction

Corona virus disease 2019 (COVID-19) is primarily caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has presently caused a very severe pandemic affecting many countries across the globe and seeming to be challenging to control its spread (Dhama et al., 2020a; Rodriguez-Morales et al., 2020). It is believed that this disease originated from bats or pangolin and then got transmitted to humans (Zhou et al., 2020; Malik et al., 2020; Tiwari et al., 2020). For the first time it was noticed during December 2019 in China and gradually kept spreading to different countries. But the world came to know about its severity when WHO declared it as pandemic on March 11, 2020. Researchers worldwide are working hard to develop effective COVID-19 vaccines and drugs, few of these have entered in clinical trial stages (Rabaan et al., 2020; Yatoo et al., 2020). The disease begins with flu like symptoms and gradually becomes severe in some cases where immunity is not strong enough with symptoms like shortness of breath, respiratory problems and pneumonia leading to the multiple organ damage and finally death of the patient (Dhama et al., 2020b). There are two main factors that play a significant role in protecting our body from infectious viral diseases like COVID-19, dengue, swine flu and other deadly infectious diseases, viz. nutrition and immunity (Dhama et al., 2015; Dhama et al., 2018; Tiwari et al., 2018; Panyod et al., 2020). The immune system is considered as primary defense mechanism

against any type of infection inside our body. It is very important for each and every individual to boost its immunity. It is wisely suggested by nutritional expert that balanced diet containing rich amount of nutrients with use of natural home remedies can help to strengthen our immune system (Mahima et al., 2013; Rahal et al., 2014; Bailly & Vergoten 2020). These natural home remedies are rich source of vitamins, minerals, antioxidants and various other active ingredients that are very beneficial for boosting immunity (Dhama et al., 2018; Dhama et al., 2018; Tiwari et al., 2018). Herbs and medicinal plants like Tulsi, Marich, Sunthi, Dalchini, Ginger, Giloy and others are commonly used traditional medicines in home, and few of such traditional herbs have been suggested to be beneficial in countering SARS-CoV-2 infection and treating COVID-19 patients (Adithya et al., 2020). The Ministry of AYUSH, Government of India has recommended 'Ayush Kwath' for improving immunity and counter SARS-CoV-2 infection during COVID-19 pandemic owing to its immunomodulatory, antiviral and other modes of action (Gautam et al., 2020). In the present article authors attempted to draw the attention of readers about the use of easy available and affordable home remedies that can boost our immunity to fight against SARS-COV-2 infection. The article discusses the scientific basis of the ingredients present in each of the important natural home remedies playing a role in preventing SARS-CoV-2 infection. The Figure 1 depicts the different roles that natural remedies that may play crucial impacts to act as a shield against viral infection.

Figure 1 Natural home remedies may act as a shield against SARS-COV-2 infection

2 Important natural home remedies

2.1 Citrus Fruits

Citrus fruits include lemons, orange, clementines, tangerines, Grapefruit etc. They are rich sources of Vitamin C, flavanones and carotenoids etc. (Najmanová et al. 2019; Singh, 2020). Vitamin C is neither synthesized nor is stored inside our body. It is categorized as water soluble vitamin (Tiwari et al., 2018). The daily requirement of vitamin C in sufficient amount (75 mg for women and 90 mg for men) is important for keeping body healthy. Citrus fruits play a key role in maintaining immunity to our body to fight against various viral infections. The spike S protein of SARS-COV-2 virus enters the host cell by binding to ACE2 receptor of host epithelial cell (chiefly lung, gastrointestinal tract etc). It has been reported that Hesperidin is one of the flavones present in citrus fruit, which may block binding of S protein to ACE2 receptor (Bellavite & Donzelli, 2020). Apart from it, it promotes functioning of white blood cells, which plays key role in fighting infections (Maggini et al., 2007; Webb & Villamor, 2007; Chen et al., 2020). Vitamin C has been reported to play protective role in COVID-19 patients (Hoang et al., 2020). Figure 2 summarizes the different role of Vitamin C in immunomodulation (Carr & Maggini, 2017).

2.2 Oregano

It is used as a medicinal herb which is also known as *Lippia graveolens*. It is mainly found in the region of Central America and Mexico. Oregano contains an essential oil named Carvacrol (Pilau et al., 2011) which has antiviral properties as shown in various studies e.g. against Respiratory Syncytial Virus (RSV) (Chidgey & Broadley, 2005), Murine Norovirus (MNV) responsible for stomach flu (Gilling et al., 2014) and various other RNA and DNA viruses (Ball & Knipe, 2007; Pilau et al., 2011). So, it could be a very good option as a natural home remedy during this COVID-19 pandemic.

2.3 Ginseng

Ginseng is widely known for its antimicrobial properties. Various research articles showed its activity against pathogenic viruses. Additionally, it has a preventive role in the treatment of cancer, heart related diseases and also improves immune system (Kim et al., 2000). It is documented in various studies to have antiviral action against a number of viruses causing respiratory disorders (Lee et al., 2014a; Lee et al., 2015). For example against RSV, which shows similar symptoms like COVID-19 infecting the

Figure 2 Important roles of Vitamin C

respiratory system and finally leading to pneumonia and bronchiolitis (Kim & Park, 2011; Munoz, 2015), different types of Influenza virus (Claas et al., 1998; Neumann et al., 2009). It showed immunomodulatory effects in patients infected with viral infection like H1N1 and also neutralizes the reactive oxygen species (ROS) formed during infection (Lee et al., 2014b).

2.4 Garlic

Garlic is also known as *Allium Sativum L.*, is a popular traditional medicinal herb since ancient times and it is documented in ayurveda as antimicrobial and antiparasitic. The main odour of garlic is due to a number of sulphur compounds, the chief one is Allicin (diallylthiosulphonate) (Gruhlke et al., 2016). Allicin is reported to play a key role in formation of T-cell and B-cell (Salman et al., 1999); it stimulates CD8+ cells and T lymphocytes cells of immune system (Reinhart et al., 2009) against various viral infections like influenza A and B, HIV, HSV-1, viral pneumonia, and rhinovirus (Zhen et al., 2006; Sawai et al., 2008), and recently also suggested to be effective against SARS-CoV-2 infection (Donma & Donma, 2020). Garlic has contains fructo-oligosaccharides which exhibits important role in immunomodulation. The extract of garlic is reported to be anti-inflammatory, anti-atherosclerotic and regulates blood pressure (Arreola et al., 2015).

2.5 Ginger

Ginger, also known as *Zingiber Officinale Roscoe*. It is a famous spice which not only adds taste and flavour to food but also very rich in medicinal properties. Ginger tea or ginger extract is commonly used since ages to treat common cold or flu and sore throat (Chang et al., 2013). Its active constituent gingerol- is an antioxidant that boosts our immune system and has antiviral properties and helps in treatment of respiratory problems, and recently reported to be beneficial for COVID-19 patients (Aboubakr et al., 2016; Safa et al., 2020). It contains important enzymes like allinase, peroxidase, and myrosinase. Sulphur rich compounds like allicin, alliin, and ajoene are also among its important constituents. The presence of compounds like superoxide dismutase and glutathione peroxidase makes it a powerful antioxidant that plays a major role in the body defence mechanism against viral infections (Sharma, 2017). It is anti-inflammatory, analgesic, decreases blood cholesterol level and hence very useful in heart problems. A study showed hot water extract of ginger is very effective against respiratory syncytial virus (RSV), avian influenza, feline calicivirus (FCV) and norovirus. It prevents viral plaque formation in airways epithelium cells and blocks the viral attachment sites (Kim et al., 2006). The aqueous extract of ginger along with garlic and other herbs prevent food from being contaminated (Tripathi et al., 2020).

2.6 Ashwagandha

Ashwagandha also known as “Indian Ginseng”, is *Withania somnifera*. It is easily found in the Indian subcontinent and has many medicinal properties (Tiwari et al., 2014). The word Ashwagandha gets its origin from Sanskrit which means “Smell of Horse”. This Sanskrit meaning relates with the power and fast activity of a horse (Tripathi et al., 2020). Consumed in the powder form, it is famous for its therapeutic values in the treatment of arthritis, asthma, hypertension and inflammation (Singh et al., 2011). It is a powerful immunomodulator and enhances activity of T- helper cell (Singh et al., 2008). Ashwagandha is used as an anti depressant and stress reliever to improve physical health. It is also used as an anti-ageing medicine (Tripathi et al., 2020). It is also helpful in regulating blood glucose and cholesterol level in our body. This herb has been recently studied for its anti-SARS-CoV-2 potential (Shree et al., 2020). *Withania somnifera* (Indian ginseng) has been reported to inhibit SARS-CoV2 host entry and replication as deduced from an *in-silico* study (Chikhale et al., 2020). Ashwagandha contains bioactive compounds such as withanone (Wi-N) and Withanoside V which have ability to stop the replication of SARS-COV-2 (Tripathi et al., 2020). The various benefits of ashwagandha have been depicted in Figure 3.

2.7 Mulethi (Licorice)

Mulethi is scientifically known as *Glycyrrhiza glabra* t is a medicinal herb. It consists of rich amount of triterpenoids and huge variety of flavonoids of which the important ones are shown in Figure 4. It is known for its antiviral, antibacterial, anti inflammatory and anti tumour properties, and recently suggested to have anti-SARS-CoV-2 potential (Ahn et al., 2012; Adianti et al., 2014; Wang et al., 2015; Dhama et al., 2018; Sinha et al., 2020). In China it is popularly called as ‘sweet grass’ and was first time included in 2100 B.C (Wang et al., 2015). The predominant antiviral ingredients and its mode of action is represented in Table 1 while the ingredients exhibited as antifungal and antibacterial agent are given in Table 2.

2.8 Tulsi

It is scientifically named as *Ocimum sanctum Linn*. It is a religious herb, which is worshiped in many parts of India. It contains many flavonoids and phenolic compounds, the important ones are apigenin, eugenol, linalool and ursolic acid. Tulsi extract is antiviral and very effective against herpes, hepatitis B and enterovirus, Dengue and swine flu. The presence of linoleic acid makes it a powerful anti-oxidant and neutralizes free radicals produced by harmful toxicants causing cellular damage (Panda & Suresh, 2009). It is antibacterial, anti-inflammatory, anti-diarrheal, antipyretic, cardioprotective, reno-protective, hepato-protective, antimalarial and with immunomodulatory properties. It is effective to

Figure 3 : Various benefits of Ashwagandha (Kapoor, 1990; Vyas et al., 2011; Ven et al., 2012; Tripathi et al., 2020)

Figure 4 Beneficial ingredients of Mulethi (Licorice) (Wang et al., 2015)

Table 1 Antiviral ingredients in Mulethi and their working mechanism (Ahn et al., 2012; Adianti et al., 2014)

Table 1 Antiviral ingredients in Mulethi and their working mechanism (Ahn et al., 2012; Adianti et al., 2014)

Name of Virus	Active Ingredient	working mechanism
Hepatitis C	Glycyrrhizin	It stop release of virus when transmitted from one cell to another Prevents expression of viral genetic material
Herpes Simples		Reduces adhesion between cerebral capillary vessel endothelial cells and neutrophils
Cocksackie virus B3		Protects from Failure of nuclear factor inhibitor
Duck hepatitis virus		Helps in the formation of T-Cell
H5N1		Decreases production of C-X-C-L-5 by virus Decreases cell death due to virus
Influenza		Reduces the linking between HMGB1 and DNA Hampers functioning of viral polymerase enzyme
Cocksackie virus A16		Deactivates the virus
Herpes simplex 1		Stops virus multiplication
Rota virus	Glycyrrhetic acid	Reduces viral protein level
Human orthopneumovirus		Prevents viral attachment to cell Promotes production of interferon

Table 2 Antibacterial and antifungal ingredients in Mulethi and their mode of action (Wang et al., 2015)

Microbes	Ingredients in Mulethi	Mode of action
<i>Staphylococcus aureus</i>	18 β -Glycyrrhetic acid	Inhibits expression of viral genes (SaeRandHla)
<i>Candida albicans</i>		Aids T-helper cells
<i>Candida albicans</i>	Licochalcone A	Prevents biofilm formation stops transition of hyphae
<i>Staphylococcus aureus</i>	Licochalcone E	Decrease α toxin synthesis
<i>Candida albicans</i>	Glabridin	Stops transition of hyphae
<i>Staphylococcus aureus</i>	Liquiritigenin	Decrease α toxin synthesis

fight against cold, fever, diarrhoea, anxiety, cardiac and genitourinary problems (Pattanayak et al., 2010; Mohan et al., 2011; Mondal et al., 2011; Cohen, 2014). The anti-inflammatory and antioxidant properties of tulsi plant make it best natural home remedy for treatment of covid-19 infection (Suanarunsawat et al., 2011). It also works as an immunomodulator as it increases the formation of T helper cell and NK cells in the body (Lo et al., 2002; Mondal et al., 2011; Hemalatha et al., 2011). Recently, *O. sanctum* has been found to provide protection from SARS-CoV-2 infection (Dharmendra & Deepak, 2020; Shree et al., 2020). Figure 5 summarises various beneficial health effects of Tulsi.

2.9 Dalchini (Cinnamon)

It is a medicinal herb which is scientifically known as *Cinnamomum zeylanicum* Breyn. It is used as a natural immunity booster in flu, edema, cough and indigestion (Niphade et al., 2009). Its main chemical constituents are Cinnamaldehyde, Cuminaldehyde and Eugenol. Its bark consists of various beneficial compounds like benzaldehyde, cinnamaldehyde, cuminaldehyde and terpenes

(Valizadeh et al., 2015). It stimulates immunity i.e. cell mediated and humoral immunity, by increasing levels of immunoglobulins and phagocytic index (Niphade et al., 2009). It is reported as a regulator of cell mediated immunity due to its property of obstruction of NF- κ B which triggers signaling components, PDK1 and NF- κ B (Gautam et al., 2020). Dalchini also activate CD29 and CD43 leading to blocking of cell migration and induced attachment of one cell other cell. It reduces the production of nitric oxide and also upregulate level of CD80 and CD69 and specific receptors like TLR2 and CR3 that help in pattern recognition. Extract made by barks of dalchini decreases the amount of IFN- γ without impacting the IL-4 level or the IL-2 level. It also inhibits IFN- γ and IL-4 induced anti-CD3 antibody at the mRNA and secreted protein levels increase IL2 protein secretion at the cellular level, helping to minimize cell death. It inhibits the expression of IL-2 mRNA, inhibits p38, JNK, ERK1/2 and STAT4 mediated anti-CD3 activation, but does not degrade I κ B or STAT6 (Gautam et al., 2020). This demonstrates dalchini's immunomodulatory effect on cytokine secretion and its role in activated T cell signalling molecules. It also contributes to a reduction in the subG1 process and

Figure 5 Benefits of Tulsi (Pattanayak et al., 2010; Mondal, 2010; Mondal et al., 2011; Mohan et al., 2011)

Figure 6 Spices as natural home remedies: Garlic, Ginger, Dalchini and Kali Mirch,

Figure 7 Giloy and Turmeric with immunomodulatory effect

raises the ratio of necrotic to apoptotic cells. The constituents (cinnamaldehyde and cinnamophilin) are the receptor antagonist thromboxane A₂. It is anticoagulative and anti-atherosclerotic, thus avoiding unwanted platelet clumping (Tsui et al., 2018). Recently, SARS-CoV-2 inhibitors have been identified from *Cinnamon* via *in silico* studies (Prasanth et al., 2020).

2.10 Kali Mirch

Kali Mirch is scientifically known as *Piper nigrum*. It has antioxidant, anti-inflammatory, anti-parasitic, anti-asthmatic, anti-depressant, anti-carcinogenic, anti-diarrheal, anti-ulcer, anti-thyroid, anti-mutagenic, anti-apoptotic, anti-bacterial, anti-viral and immunomodulatory properties. It also increases the therapeutic efficacy of various drugs, vaccine and nutrients (Nahak & Sahu, 2011; Damanhour, 2014; Srivastava & Singh, 2017; Peterson et al., 2019). Its main ingredient is piperine, which is responsible for regulation of cytokines production of various types of immune cells like Th1, Th2, Th17 and Treg cells. It is responsible for decrease the aggregation of inflammatory cells as well, it avoids the expression of GATA3, IL-4, IL-6, IL-1 β , ROR, IL-17 A and TNF and increases the secretion of INF- and IL-10 in Broncho-alveolar lavage fluid. It also increases production of T cell and B cell and activate macrophage cells (Damanhour, 2014; Balkrishna et al., 2020; Gautam et al., 2020). Piperine is cytotoxic in nature. It reduces the amount of immunoglobulin Ig E, anti-OVA IgE, anti-OVA IgE1 and release of histamine in serum. It increases fibrosis and inflammatory cell infiltration. It also hampers Th2/Th17 response and

activates mast cell. It inhibits NF- κ B, c-Fos, cAMP response binding feature, Factor-2 transcription activation. It decreases the expression of PMA mediated MMP-9, inhibits PKCa / extracellular signal-regulated kinase (ERK) 1/2 and reduces the activation of NF- κ B / AP-1. It is also responsible for p-glycoprotein inhibition and the role of CYP3A4 (Zhai et al., 2016; Bui et al., 2019).

2.11 Giloy (*Tinospora cordifolia*)

Giloy is also known as *Tinospora cordifolia*. It is a curing climber plant in which stem is main part with many beneficial properties. It contains a significant number of alkaloids, polysaccharides, glycosides and steroids (Panchabhai et al., 2008). The immunomodulatory, anti-diabetic, antioxidant, antihepatotoxic and cytotoxic effects are popularly recognised (Sharma et al., 2012; Dhama et al., 2016). The active phytoconstituents responsible for its immunomodulatory activity are Tinocordioside, Cordifolioside A, Magnoflorine, and Syringin (Goyal et al., 2011). It is rich in antioxidants which neutralizes the free radicals and prevents inflammation. It effectively fights against harmful bacteria, fungus and viruses. It also flushes out toxins inside the body. The use of giloy kadha (juice) is very effective against harmful viruses. Anti-inflammatory properties help in the treatment of various types of respiratory problems like cold, cough and breathing problems. Its beneficial health properties have been suggested to inhibit SARS-CoV-2 and give relief to COVID-19 patients (Chowdhury, 2020; Dharmendra & Deepak, 2020; Krupanidhi et al., 2020; Shree et al., 2020). Figure 7 shows stems of Giloy and turmeric.

2.12 Turmeric (*Curcuma longa*)

It is commonly called as “Haldi” in India. Its active ingredient is polyphenolic compound known as Curcumin, which is anti-inflammatory, anti-microbial and has immunomodulatory effect in our body (Gupta et al., 2020; Zahedipour et al., 2020). It inhibits virus entry into the cell, inhibits virus and virus protease encapsulation, and modulates multiple cellular signaling pathways (Zahedipour et al., 2020). In the treatment of osteoarthritis and rheumatoid arthritis, it is also useful. Turmeric has been suggested to be a valuable option for treatment against COVID-19 (Babaei et al., 2020; Emirik, 2020). The main effects of curcumin on respiratory disorders are as follows.

2.12.1 Effect of Curcumin on Pulmonary Inflammation

Curcumin has its main role in the inhibition of inflammatory cytokines. Its presence blocks the critical signals controlling the expression of different pathways of pro-inflammatory cytokines such as nuclear factor B and MAPK (Ferreira et al., 2015). It has properties that are anti-inflammatory and anti-fibrotic. It reduces the expression of chemokines and cytokines, such as $\text{INF}\gamma$, MCP-1, IL-6, IL-10, involved in lung infection (Avasarala et al., 2013). By preventing viral replication, release of TNF alpha and down controlling phosphor-NF-alpha-B (Zahedipour et al., 2020), it demonstrates inhibitory effects against RSV infection.

2.12.2 Effect of Curcumin on Pulmonary Fibrosis

Pathways of curcumin inhibit apoptosis mediated by the p38MAPK route (Avasarala et al., 201).

2.12.3 Effect on Pulmonary Oedema

Pulmonary oedema is the condition when accumulation of fluid takes place in lungs. A recent study in SARS-COV-2 infection has shown that its envelope protein activates protein kinase C, thus reducing the activity of epithelial sodium channels of pulmonary epithelial cells resulting into pulmonary oedema (DeDiego et al., 2014). Recent research study (Tian et al., 2020) has demonstrated the use of Curcumin decreases the inflammation that results in the reduction in the influx of fluid in lungs in experimental animals (rat).

2.12.4 Effect of Curcumin in COVID-19 related heart problems

Respiratory problems are caused by the binding of the SARS-COV-2 virus spike protein to the ACE2 respiratory epithelium cell receptor. These complications are more pronounced in person with cardiac problems. The explanation may be that AEC2 is more commonly expressed in cardio patients (Zheng, 2020). By minimising c Jun N terminal Kinase and NF- κ B nuclear translocation phosphorylation, curcumin prevents myocardial ischemia-reperfusion injury. It also reduces immune cell infiltration and the expression in vascular cells of binding molecules and pro-inflammatory mediators (Li et al., 2017).

2.12.5 Curcumin 's effect on kidney problems associated with COVID-19

The occurrence of acute injury to the kidneys was seen in COVID-19. The high incidence in patients with diabetes may be due to the high expression of ACE2 in the kidneys (Ye et al., 2006) and may be the reason for renal damage. Curcumin up regulates AEC2 and ACE2 mRNA that contributes to the increase in flow of blood in kidneys in rat models (Xu et al., 2018). By reducing inflammation caused by MCP-1, NF- κ B, TNF, IL-1 β , COX-2 and COV-1, curcumin also decreases renal fibrosis at the stage of priming and activation. It decreases anti-inflammatory factors as well. In animal models, it targets MAPK / ERK, TGF- β / smads and PPAR-pathways (Sun et al., 2017).

Conclusion

Modern life style, laziness and undisciplined eating habits results in the increase of various types of disorders like diabetes, respiratory problems, heart related diseases, kidney dysfunctioning etc. These kinds of problems create serious problems to an individual during this COVID-19 pandemic. Natural home remedies are easily available at home, cheap and affordable and may prove to be very beneficial as alternative treatment in this pandemic time, when there is shortage in medical facilities, unavailability of any vaccine and specific medicines. These herbs, spices and citrus fruits are potent immunomodulator and can boost our body immunity to fight against harmful virus like SARS-CoV-2. The names described in the present article are just a tip of iceberg. There are many more medicinal plants, fruits, vegetables and spices whose inclusion in the present article is beyond the scope. It has been reported that some of the phytoconstituents viz. Withaferin A, Withanolide B, Tinocordioside, Somniferine A, Tinosporide, Withanolide, Orientin, Flavonol glucoside, Apigenin, Kempferol, withanone from medicinal plants like (Tulsi, giloy and Ashwagandha) show interaction with SARS-CoV-2 and other target proteins. Tulsi herb contains dihydrodieuginol B and Tulsinol A, B, C, D, E, F, G which can work as potential inhibitor for papain like protease and SARS corona virus main protease. Healthy body with good immunity has an ability to fight against attack of infections like COVID-19. More researches on the important herbs, spices and medicinal plants would pave way for providing a useful remedy to fight against COVID-19.

Conflict of interest

The authors declare that there is no conflict of interests.

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