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Curcumin (active component of turmeric): New therapeutic option against COVID-19.

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ABSTRACT

As the world has laid down its arms in the battle against the deadly Coronavirus, researchers around the world are trying their best to find a cure from this virus. Till date there is no specific antiviral therapy available to treat COVID-19 patients. Recent studies have shown that turmeric has potent antiviral properties. In India turmeric has been a quintessential part of Indian households. Right from its use in religious rituals to using it for medicinal purposes to using it as a spice for cooking, turmeric has been an inseparable part of our life. Since ages this spice has been used extensively as an immunity booster and for its health enriching properties. With the deadly Corona virus attack, this spice is being used more-than-ever to prepare medicines. Curcumin, the yellow pigment of turmeric is extensively used in our Indian traditional herbal medicines to cure many diseases associated with infection and inflammation for many decades. Curcumin exerts antiviral activities against broad spectrum of viruses including HIV, HSV-2, HPV viruses, Influenza virus, Zikavirus, Hepatitis virus and Adenovirus. It has shown promising efficacy against influenza A viral infections. Scientific evidence suggests that curcumin could have a potential role to treat COVID-19. Nutritional supplements of curcumin with vitamin C and zinc have showed promising results in boosting the natural immunity and protective defense against the CoV infections. Well-defined studies should be performed to evaluate the efficacy of curcumin against SARS-CoV-2 and assess its value as a possible treatment for this deadly virus.

Keywords: COVID-19, Turmeric, Curcumin, Influenza. Immunity booster.

INTRODUCTION

Highly contagious disease novel coronavirus (COVID19) that has recently emerged as epidemic in China in December 2019, spreads across the globe and becoming a pandemic (Zhang *et al.* 2020). The disease is caused by novel Coronavirus SARS-COV-2(severe acute respiratory syndrome coronavirus 2) belonging to the family coronaviridae. Coronaviruses are single stranded positive sense RNA viruses, transmitted to humans via respiratory droplets.

Majority of the severe SARS-CoV2 infected patients develop acute respiratory distress due to the elevated levels of proinflammatory cytokines and other clinical conditions like diarrhoea, when infection is transmitted through food (Zhang *et al.* 2020; Jean *et al.* 2020; Das *et al.* 2020).

Till date there is no specific antiviral therapy available to treat COVID-19 patients. Combination therapy has been considered by the clinicians which include antiviral agents, antibiotics and anti-inflammatory drugs (Jean *et al.* 2020) including hydroxychloroquine are widely used in developed countries. In the context of preventive and supportive therapy, several polyphenolic compounds extracted from natural products were identified with varied antiviral mechanisms such as targeting virus host specific interactions, viral entry, replication, and assembly. In connections with these findings, curcumin, is one of the natural compounds that had been widely investigated for its antiviral effects (Praditya *et al.* 2019).

However, a lot of research is still needed to prove the effectiveness of this potent antiviral spice in curing Corana virus, but the fact turmeric has antiviral properties shows that in future it can be a potential cure.

Curcumin, the active derivative of turmeric:

Turmeric (*Curcuma longa* L.) is a spice that is an integral part of Asian cooking and culture, and has been used in traditional medicine systems such as Ayurveda, Unani and Siddha for centuries, owing to its wide array of medicinal properties (Gupta *et al.* 2020). Curcumin, a natural polyphenolic compound extracted from roots of rhizome plant turmeric (Scientific name Curcuma longa belongs to family Zingiberaceae) (Manoharan *et al.* 2020).

To enhance the bioavailability of curcumin, newer technologies such as adjuvant, nanoparticles, liposomes, micelles and phospholipid complexes have been evaluated in the process of drug development. It is documented to be most efficacious in high doses at approximately 6–7 g/day orally, which is well tolerated (Gopinath and Karthikeyan, 2018). It has been widely used as a common household remedy for cough, sore throat and respiratory ailments in Asia (Gupta *et al.* 2020). Curcumin exhibits wide range of therapeutic properties including antioxidant, anti-microbial, anti-proliferative, anti-inflammatory, neuroprotective and cardioprotective properties. (Pang *et al.* 2015).

Anti-viral activities of Curcumin:

It is reported that, curcumin exerts antiviral activities against broad spectrum of viruses including HIV, HSV-2, HPV viruses, Influenza virus, Zikavirus, Hepatitis virus and Adenovirus (Das *et al.* 2020; Praditya *et al.* 2019).

Numerous curcumin derivatives have been evidenced to have antiviral properties. Studies using neuraminidase activation assay showed that five active curcumin derivatives decreased H1N1-induced neuraminidase activation in H1N1-infected lung epithelial cells (Lai *et al.* 2020). Tetramethyl curcumin and curcumin even downregulates nucleoprotein expression (Gupta et al 2020). Various researchers have found turmeric derivatives useful in the management of influenza virus infections (Richart *et al.* 2018). It has been observed that monoacetylcurcumin and curcumin both inhibited influenza virus infection, but via different pathways (Richart *et al.* 2018). Significant antiviral activity of turmeric against H5N1 (highly pathogenic avian influenza) virus in Madin–Darby canine kidney (MDCK) cells *in vitro* by interfering with viral haemagglutination (HA) activity has also been observed. The effects of anti-H5N1 virus activity by turmeric extracts were demonstrated by upregulation in the tested MDCK cells of the mRNA expression of the genes for tumour necrosis factor-α and interferon-β, which are potent antiviral agents (Richart *et al.* 2018).

Curcumin has been found to be beneficial in other viral disorders such as AIDS due to its inhibitory activity against HIV protease and integrase along with its synergistic action on other therapeutic drugs (Prasad and Tyagi, 2015). It has also been shown to inhibit other viruses such as hepatitis B, hepatitis C, zika, chikungunya and dengue. Respiratory distress syndrome with fulminant hypercytokinaemia and multiorgan failure is the leading cause of mortality with COVID-19. Curcumin has been found to attenuate influenza A virus-induced lung tissue injury by blocking nuclear factor κB signalling and inhibiting the production of inflammatory cytokines. Curcumin is a natural ligand of peroxisome proliferator-activated receptor-γ, which represses the inflammatory

process by reducing cytokine production; therefore, it might play a similar role in protecting against lung injury associated with COVID (Ciavarella *et al.* 2020).

Probable mechanisms of antiviral activities of Curcumin

Recent studies have indicated that alike original SARS-CoV, the SARS-COV2 also invades human host cells by targeting Angiotensin Converting Enzyme 2(ACE2) membrane receptor, an entry site for coronavirus. The binding of viral S protein to ACE2 receptor present on mucus membrane mediates the viral and membrane fusion and subsequent viral replication in host (Manoharan *et al.* 2020). A recent study showed that expression of ACE2 was detected in nasal epithelial cells, alveolar epithelial type II cells (AECII) of lungs and luminal surface of intestinal epithelial cells. Hence nasopharynx, lungs and intestine facilitate viral entry and serve as potential site of viral invasion (Jia *et al.* 2005). Most studies have shown that Angiotensin II exerts its biological activities by binding to two receptors namely angiotensin 2 type 1 receptor (AT1R) and angiotensin 2 type 2 receptor (AT2R). Angiotensin-converting enzyme 2 (ACE2) a homologue of ACE, sharing 61% sequence similarity with the ACE catalytic domain, hydrolyses Angiotensin II to Angiotensin (Keidar *et al.* 2006) and attenuates Angiotensin II-ATIR axis mediated vasoconstriction effects, thereby reducing the blood pressure through vasodilation (Keidar *et al.* 2006).

In line with the growing evidences of therapeutic properties of the curcumin, can be used as (1) potential inhibitory agent blocking the host viral interaction (viral spike protein—ACE2 receptor) at an entry site in humans and (2) as an attenuator via modulating the proinflammatory effects of Angiotensin II-AT1 receptor-signalling pathways reducing respiratory distress in the treatment of COVID19.

A study using Insilico approach involving docking and stimulation, demonstrated the dual binding affinity of polyphenolic compounds in which both the viral S protein and ACE2 binds to curcumin. Binding of curcumin to receptor binding domain (RBD) site of viral S protein and also to the viral attachment sites of ACE2 receptor, demonstrated that curcumin can act as potential inhibitory agent antagonizing the entry of SARS-CoV2 viral protein (Das *et al.* 2020). Moreover, emulsion form of topical application of curcumin may effectively prevent the SARS-CoV2 infection in humans, as the viral entry site of ACE2 receptor is predominantly distributed at the nasal cells, mucosal surface of respiratory tract and eyes (Jia *et al.* 2005).

Further, curcumin has been extensively studied for its role in the regulation of RAAS (renin–angiotensin–aldosterone system) components through which it is known to exert anti-oxidant, anti-inflammatory and antihypertensive effects. Animal studies have implicated the role of curcumin in the downregulation of ACE and AT1R receptor expression in brain tissue and vascular smooth muscle cells, respectively resulting inhibition of Angiotensin II-AT1R mediated effects of hypertension and oxidative stress in animals (Kim *et al.* 2019; Rachmawati *et al.* 2016; Li *et al.* 2017). Previous studies revealed high level of AT2R and ACE2 expression in myocardial cells treated with curcumin thus exhibiting the protective mechanism of curcumin via modulation of effects mediated by Angiotensin II receptors AT1R and AT2R. Upregulation of AT2R induces suppression of AT1R expression leading to Angiotensin II-AT2R mediated anti-inflammatory effects involving an inhibition of NF-κB activity and oxidative stress. Hence, treatment with curcumin attenuated the proinflammatory effects induced by Angiotensin II-AT1R axis leading to significant decrease in the level of pro infammatory cytokines TNF-α, IL-6 and reactive oxygen species (Manoharan *et al.* 2020).

Nutritional supplements of curcumin with vitamin C and zinc:

Nutritional supplements of curcumin with vitamin C and zinc have showed promising results in boosting the natural immunity and protective defense against the CoV infections have been noted in many hospitalized patients in Indian setting. It is also noted that pharmacological formulation of curcumin in nanoemulsion system proved increased solubility and bioavailability and with enhanced antihypertensive effect (Manoharan *et al.* 2020).

CONCLUSION

Turmeric has been used for centuries for its varied medicinal properties. Curcumin, the predominant derivative of turmeric has wide range of therapeutic properties inclu-ding antioxidant, anti-microbial, anti-proliferative, anti-inflammatory, neuroprotective and cardioprotective properties. Curcumin has been widely investigated for its antiviral effects. It has shown

promising efficacy against influenza A viral infections by regulating the immune response to prevent injury to pulmonary tissue.

Till date there is no specific antiviral therapy available to treat COVID-19 patients. Combination therapy has been considered by the clinicians which include antiviral agents, antibiotics and anti-inflammatory drugs including hydroxychloroquine are widely used in developed countries. As curcumin has antiviral properties it can be used to treat COVID-19 disease.

Nutritional supplements of curcumin with vitamin C and zinc have showed promising results in boosting the natural immunity and protective defense against the COVID-19 infections have been noted in many hospitalized patients in Indian setting. It is also noted that pharmacological formulation of curcumin in nanoemulsion system proved increased solubility and bioavailability and with enhanced antihypertensive effect.

Henceforth, it is clear that the biological properties including advance mode of drug delivery system of curcumin could be considered while formulating the pharmaceutical products and its application as preventive measure in the inhibition of transmission of SARS-COV2 infection among humans. However, further large-scale clinical trials are warranted to understand the usefulness of curcumin for the pharmacological application in nanoemulsion system. It can be concluded that curcumin could be used as a supportive therapy in the treatment of COVID19 disease in any clinical settings to circumvent the lethal effects of SARS-CoV-2. Thus, the use of curcumin in the clinical trial, as a new treatment option, should be considered.

Conflicts of interest: The authors stated that no conflicts of interest.

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