Curcumin as Adjuvant Therapy in COVID-19: Friend or Foe?

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Abstract

COVID-19, which is caused by SARS-CoV-2, quickly spreads in many countries and was declared as a pandemic. To date, there is no effective drug that is proven against COVID-19. Curcumin has various beneficial effects, including anti-inflammatory, antioxidant, antimicrobial, and antiviral properties. Curcumin containing herbal drink is famous to boost immune response, and curcumin was shown to bind to viral S1 protein, which is important for viral entry, in an in silico study. Therefore, administration of curcumin containing herbal drink may be beneficial to prevent COVID-19 and cytokine storm in severe form of COVID-19. However, high dose curcumin was showed to increase expression of ACE2 in myocardial fibrosis rat model. Therefore, there is a fear that curcumin may help viral entry into the cell, as ACE2 is the receptor for SARS-CoV-2 entry into cells. However, looking at the dose of curcumin in the herbal drink, it is unlikely that the dose will cause an increase in ACE2. In conclusion, curcumin may be beneficial as adjuvant to other drugs to prevent COVID-19 and cytokine storm in severe COVID-19, but studies are needed to get more robust prove, and to determine the optimal dose and timing of administration.

Review (J Int Dent Med Res 2020; 13(2): 824-829)

Keywords: Curcumin; COVID-19; SARS-CoV-2; ACE2; cytokine storm; anti-inflamatory.

Received date: 26 April 2020 **Accept date:** 11 May 2020

Introduction

Pneumonia cases of unknown origin were reported to the WHO by China Government in 31 December 2019. The cause was identified as a new corona virus i.e. 2019 novel coronavirus (2019-nCoV) that was named SARS-coronavirus 2 (SARS-CoV-2), while the disease it causes was named coronavirus disease (COVID-19)[1-4]. COVID-19 quickly spreads and cases were found in many countries. Therefore, on 11 March, the WHO declared COVID-19 as a pandemic[5].

Till to date, there is no proven effective treatment for COVID-19, though dozens of existing compounds were suggested to be tested. However, the WHO has chosen four compounds to be tested in global megatrials as potential drugs against COVID-19 to prevent serious harm and death, namely Remdesivir, Chloroquine and hydroxychloroquine, Ritonavir/lopinavir, and Ritonavir/lopinavir/interferon-beta combination[6].

One of the various candidates, which are not chosen to be tested as treatment for COVID-19, is curcumin. Curcumin as adjuvant to antiviral or other viral eliminating drugs might help in combatting COVID-19. Therefore this article discussed the pathogenesis of COVID-19, the role of curcumin in modulating COVID-19 pathogenesis, and prospect of curcumin as prevention of severe COVID-19.

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COVID-19 pathogenesis

SARS-CoV-2 is an RNA virus with several membrane bound proteins. The most important protein, which plays a role in COVID-19 pathogenesis, is spike glycoprotein (S protein) that is anchored at viral envelope. Based its sequence, SARS-CoV-2 spike protein contains a receptor binding motif (RBM) in a receptor binding domain (RBD) that binds to a host cell receptor. A study concluded that to enter a cell, host cell serine protease TMPRSS2 is needed for S protein priming, where the S protein is cleaved into S1 and S2. The S1 protein binds ACE2,

which acts as a receptor for SARS-CoV-2 entry into cells [7-10], and S2 protein facilitates viral and host cell membrane fusion, followed by viral material entry into the host cell and viral replication (Figure 1)[10]. ACE2 is a membrane bound enzyme that is found on cell surfaces, such as type 2 alveolar cells of lungs, oral mucosa, especially epithelial cells of the tongue, stratified epithelial cells of oesophagus, columnar epithelial cells of ileum and colon, cholangiocytes of liver, proximal tubule cells of kidney, bladder urothelial cells, and myocardial cells [11].

Further, ACE2, which protect from lung injury, is down regulated by S protein[7]. Upon entry and viral replication, various symptoms might develop from very mild to severe. In most cases, the body immune response develops and contained the disease. However, in severe cases, uncontrolled pro-inflammatory cytokine release (cytokine storm) occurs in response to the virus that may lead to multi organ failure and death[12].

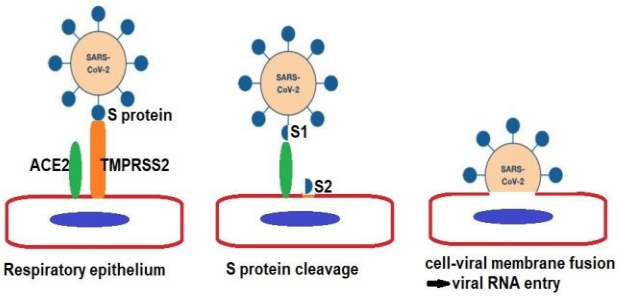

Figure 1. Mechanism of viral entry into cell.[10]

Curcumin and modulation of COVID-19 pathogenesis

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl) - 1,6 – heptadiene - 3,5 –dione), which is also called diferuloylmethane, is a phytochemical that can be extracted from the rhizome of turmeric (Curcuma longa L. and its related species). Turmeric is usually used as a spice in various kinds of foods and beverages in various countries, especially Asian countries. Moreover, it has been used as medicinal herb for around 4000 years, and has been documented in Ayurveda and Traditional Chinese Medicine to treat various diseases due to its various beneficial effects, including anti-inflammatory, antioxidant, antibacterial, antiviral, anti-mutation and anticancer properties [13].

Curcumin for treatment is available in various forms, which can be extracted from turmeric and its related species, either alone or in combination with other curcumin like substances, i.e. demethoxycurcumin (DMC) and bidemethoxycurcumin (BDMC) that have similar biological activity as curcumin and together they are known as curcuminoids. Curcuminoids contains curcumin (77%), DMC (17%), and BDMC (3%)[14].

Curcumin as friend: Prevention COVID-19 and modulation of severe COVID-19

In Indonesia, an Indonesian scientist has developed a curcumin containing herbal drink, to be used as adjuvant to western medicine [15]. The recipe to make the herbal drink is widely available and claimed to boost the immune system. The herbal drink contains various kinds of herbs including 100 g of curcumin rich fresh root of Curcuma Xanthorrhiza[16,17].

When SARS-CoV-2 infects an individual, several factors are responsible to determine development of COVID-19, i.e. viral (viral number and virulence), host (health state, host immune system, nutrition, etc.), and environment factors. When SARS-CoV-2 wins the battle, infection can range from mild to severe. Therefore, the use of curcumin containing herbal drink, which boosts the immune system, might help the body to win the battle against SARS-CoV-2, and thus prevent COVID-19 infection and might be used as prophylactic in health care providers.

Moreover, curcumin was showed to have antiviral property againt various kinds of viruses, i.e. zikavirus (ZIKV), chikungunya virus (CHIKV), human immunodeficiency virus (HIV), herpes simplex virus 2 (HSV-2), human papillomavirus (HPV), hepatitis viruses, influenza viruses, etc [18, 19]. A recent in-silico study showed that curcumin could bind to RBD of S protein [20]. Therefore, studies are needed to elucidate whether curcumin really can bind the S protein and therefore prevent SARS-CoV-2 infection, and whether the dose in the curcumin herbal drink is optimal for COVID-19 prevention, thus might be used as prophylactic in health care providers.

In severe form of COVID-19, acute respiratory distress syndrome (ARDS) may occur. The mechanism of ARDS is due to a large amount release of pro-inflammatory cytokine [12]. In various conditions with elevated inflammatory cytokines, curcumin was shown to reduce the inflammatory cytokines i.e. tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1β, IL-4, and monocyte chemoattractant protein-1 (MCP-

1) through various mechanisms, including by blocking nuclear factor-κB (NF-κB) activation, and its activator, TNF-α [13]. Moreover, antioxidant property of curcumin may prevent oxidative stress that is closely related to inflammation, and its antimicrobial property may prevent secondary bacterial infection[13]. Therefore, it is supposed that curcumin containing herbal drink as adjuvant may be beneficial to modulate cytokine storm, and to prevent secondary bacterial infection, so that severe form of COVID-19 can be prevented.

However, various studies of curcumin effect on inflammatory cytokines used various different doses[13] compared to those in the curcumin containing herbal drink. In addition, those studies combined curcumin/curcuminoid with piperine[21, 22] or lipid blend[23,24] to increase its bioavailability. A study on metabolic syndrome patients, which experienced increased inflammatory cytokines, used a dose of 500 mg curcumin in the form of curcumin C3 complex formula (curcuminoid) + 5 mg piperine twice a day (total curcuminoid dose 1g/day) and showed significant reduction in serum tumor necrosis factor-α (TNF-α), Interleukin-6 (IL-6), transforming growth factor-β (TGF-β), monocyte chemo-attractant protein-1 (MCP-1), and C-reactive protein (CRP) compared to placebo [21]. Ganjali et al[22] studied the effect of curcuminoids on obese patients and used the same dose of curcumicoids and piperine. Their study showed significant reductions in serum IL-1β, IL-4, and vascular endothelial growth factor (VEGF). However, no significant changes in serum IL-1α, IL-2, IL-6, IL-8, IL-10, interferon ɤ (IFNγ), TNFα, epidermal growth factor (EGF), and MCP-1 were observed.

Another study on healthy middle age people used a low dose lipidated curcumin (Longvida ®). The curcumin was a 400 mg optimized curcumin powder, which contained 80 mg curcumin, in a proprietary lipid blend to increase its bioavailability. After four weeks of daily curcumin consumption, C reactive protein, which is a marker of inflammation, was not changed[23]. This result might be due to the subjects, who were normal subject without any inflammatory condition. Mc Farlin et al[24] studied the effect of three doses of lipidated curcumin (Longvida ®), 200, 400 and 1,000 mg on inflammation due to muscle damage and showed that 400 mg was the optimal dose. Increasing to 1,000 mg did not give better result. Curcumin supplementation 400 mg/day showed significantly lower serum TNF-α and IL-6, but non-significantly lower IL-8 and IL-10 compared to placebo.

Finally, a systematic review and meta-analysis of curcumin effect on superoxide dismutase (SOD), which is an enzyme with anti-oxidant and anti-inflammatory properties, showed an overall increase in SOD after curcumin supplementation. Curcumin doses, which caused increases in SOD in the studies that were included in the systematic review, were: 1,000 mg/day (500mg curcumin C3 Complex + 5mg piperine, twice a day) (two studies), 1,500 mg/day (500mg curcumin C3 Complex + 5mg piperine, three times a day) (two studies), and 180 mg/day of lipidated curcumin (curcuminoids + soy phosphatidylcholine [lecithin] in 1:2 weight ratio) [25].

Curcumin as Foe: Facilitation of Viral Entry??

A study showed that oral curcumin (Sigma-Aldrich Co) 150 mg/kg body weight (BW)/day increased expression of ACE2 in myocardial fibrosis rat model [26]. Therefore, curcumin at a dose of 150 mg/kg BW may help viral entry into the cell, at the early stage of the disease, before the body immune system develops and copes with the disease. Therefore, Curcumin containing herbal drink should be used with caution if it was intended to prevent COVID-19 infection, when the dose of curcumin in the herbal drink reached 150 mg/kg BW (7,500 mg for a subject with 50 kg BW). However, the herbal drink is prepared using 100 g of fresh Curcuma xanthorrhiza[16, 17] that yields around 5 g of dry weight and contains a range of 3.60 – 7.99 % curcumin when planted in various cultivation conditions[27]. Thus a cup of herbal drink only contains 180 –400 mg of curcumin. It is suggested to take the herbal drink twice a day to boost the immune response, so that the curcumin dose/day is only 360 -800 mg, far below the dose of Pang et al study[26] that showed increased ACE2 expression after curcumin oral intake. Moreover, the herbal drink is prepared by boiling the ingredients in water until the water boils [16, 17], while curcumin has a lipophilic nature and is not readily soluble in water at room temperature[14, 28] boiling may increase curcumin solubility.

There are also questions, whether the curcumin containing turmeric, which is found in certain food and beverage, is of enough dosage to increase the expression of ACE2, and whether people who consume the curcumin containing food or beverage are more susceptible to contract COVID-19. The amount of turmeric in a dish is approximately 50 g fresh turmeric for 6 servings[29,30], and a cup of immune boosting turmeric golden milk is made using a half tea spoon (1 g) of turmeric powder [31]. The content of curcuminoids in fresh turmeric varies between 3.76-5.05 %[32], 2-9 %[33], and 1.33-1.92 %[34] depending on the source of turmeric, isolation and detection method. Therefore the content of curcumin in a dish of six servings is 0.67 – 4.50 g, and the content of curcumin per serving is only 110 –750 mg. Further, curcumin content may vary between various commercially available powders, but a study showed that pure turmeric powder contained 3.14% curcumin[35]. Therefore, a cup of turmeric golden milk, which uses 1 g of turmeric powder [31], contains only 30 mg of curcumin. In summary, curcumin content in food and beverage is far below the dose of Pang et al study [26] that showed increased ACE2 expression after curcumin oral intake.

Therefore, it is supposed that curcumin content in Indonesian immune boosting herbal drink or various curcumin containing food and beverage may not facilitate SARS-CoV-2 entry into the cells, or increase susceptibility to COVID-19. However, to be sure, studies are needed to know whether lower doses than those used by Pang et al[26] can cause increase in ACE2 expression, and the highest dose that is still safe.

Prospect of curcumin as prevention of both COVID-19 infection and its severe manifestation

Some clinical trials showed that doses between 4000 and 8000 mg/day and up to 12,000 mg/day had good tolerability and safety profile. Therefore, the use of curcumin and curcuminoids has been approved by the US Food and Drug Administration (US-FDA) and is regarded as safe. The Joint United Nations and World Health Organization Expert Committee on Food Additives (JECFA)[36] and European Food Safety Authority (EFSA)[37] reports had set an Allowable Daily Intake (ADI) value of curcumin to be 0–3 mg/kg BW. A high intake may result in several negative side effects, as several studies reported diarrhea, headache, rash and yellow stool after consuming 500 – 12,000 mg curcumin/day in a dose response study, and nausea, diarrhea, increased serum alkaline phosphatase and lactate dehydrogenase after consuming 450 to 3,600 mg curcumin /day for one to four months[13].

To prevent COVID-19, curcumin containing medicinal product (herbal drink) should contain a curcumin dose of less than 7,500 mg/day, to prevent increased expression of ACE2. Therefore, Indonesian curcumin containing herbal drink may be a suitable candidate, as it contains a low dose curcumin. However, in vitro and in vivo studies are needed to prove whether the herbal drink indeed can boost the immune system, and has an antiviral activity against SARS-CoV-2 to prevent SARS-CoV-2 infection. As curcumin content may vary according to various factors, i.e. geographical factors of cultivating region[32], soil factors, genus diversity[35], the use and type of fertilizers [32], developmental stage and time of harvest [38], standardization of optimal curcumin dose needs to be conducted.

To prevent cytokine storm, curcumin dose that exerts anti-inflammatory response is needed. Various studies showed that various doses below 7,500 mg/day were effective to significantly lower various cytokine levels, or boost anti-inflammatory responses in various conditions[13,21-25].

Therefore, to be used as adjuvant for prevention and modulation of cytokine storm in severe COVID-19, further studies are needed to determine the optimal dose, which may have anti-inflammatory effect, and timing of administration. As the dose to exert anti-inflammatory response may be higher than those needed for COVID-19 prevention, studies on special formulation that can increase curcumin bioavailability may be needed.

Conclusions

Curcumin may be beneficial to prevent COVID-19 infection by boosting the immune system, and to prevent and modulate cytokine storm in severe form of COVID-19. However, studies are needed to determine the optimal dose, formulation, and timing of administration for both prevention of infection and severe COVID-19.

Declaration of Interest

The authors report no conflict of interest.

References

1 Ma J. Coronavirus: China's first confirmed Covid-19 case traced back to November 17. South China Morning Post; March 13, 2020. Available at: https://www.scmp.com/news/china/society/article/3074991/coronavirus-chinas-first-confirmed-covid-19-case-traced-back. Accessed March 25, 2020

2 WHO. Emergencies preparedness, response. Pneumonia of unknown cause – China. WHO; January 5, 2020. Available at: https://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/. Accessed March 25, 2020

3 Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020; 382(8):727-33. doi: 10.1056/NEJMoa2001017

4 WHO. Naming the coronavirus disease (COVID-19) and the virus that causes it. WHO; February 11, 2020. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it. Accessed March 25, 2020

5 WHO. Virtual press conference on COVID-19 – 11 March 2020. WHO; March 11, 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/transcripts/who-audio-emergencies-coronavirus-press-conference-full-and-final-11mar2020.pdf?sfvrsn=cb432bb3_2. Accessed March 25, 2020

6 Kupferschmidt K, Cohen J. WHO launches global megatrial of the four most promising coronavirus treatments. Sciencemag; March 22, 2020. doi:10.1126/science.abb8497. Available at: https://www.sciencemag.org/news/2020/03/who-launches-global-megatrial-four-most-promising-coronavirus-treatments. Accessed March 25, 2020

7 Ortega JT, Serrano ML, Pujol FH, Rangel HR. Role of changes in Sars-Cov-2 spike protein in the interaction with the human ACE2 receptor: An in silico analysis. EXCLI J 2020; 19: 410-17. doi: 10.17179/excli2020-1167

8 Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020; 94(7):e00127-20. doi:10.1128/JVI.00127-20

9 Wang Q, Zhang Y, Wu L, et al. Structural and functional basis of 1 SARS-CoV-2 entry by using human ACE2. Cell 2020 Apr 7; S0092-8674(20)30338-X. doi: 10.1016/j.cell.2020.03.045

10 Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020; 181(2):271-80. doi:10.1016/j.cell.2020.02.052

11 Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020; 12(1):8 (5pages). doi: 10.1038/s41368-020-0074-x

12 Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal 2020 Mar 5.doi: 10.1016/j.jpha.2020.03.001

13 Hewlings SJ, Kalman DS. Curcumin: A Review of Its' Effects on Human Health. Foods 2017; 6(10): 92 (11 pages). doi:10.3390/foods6100092.

14 Kocaadam B, Şanlier N. Curcumin, an active component of turmeric (Curcuma longa), and its effects on health. Crit Rev Food Sci Nutr 2017; 57(13): 2889-95. doi: 10.1080/10408398.2015.1077195.

15 Setyorini DA. Professor Nidom: Ginger, turmeric, and "temulawak" is the best prevention of Corona virus [in Indonesian]. Berita Jatim; March 2, 2020. Available at: https://beritajatim.com/pendidikan-kesehatan/prof-nidom-jahe-kunyit-temulawak-pencegahan-terbaik-virus-corona/ Accessed March 31, 2020.

16 Kalbe Store. Recipe to make herbal drink [in Indonesian]. Kalbe Store; March 13, 2020. Available at: https://www.kalbestore.com/articles/resep-membuat-empon-empon/ Accessed April 13, 2020.

17 Yunita NW. Recipe of virus combatting herbal drink [in Indonesian]. Detik Food; March 5, 2020. Available at: https://food.detik.com/info-kuliner/d-4926382/resep-empon-empon-penangkal-virus-corona. Accessed April 13, 2020.

18 Praditya D, Kirchhoff L, Brüning J, Rachmawati H, Steinmann J, Steinmann E. Anti-infective Properties of the Golden Spice Curcumin. Front. Microbiol 2019; 10: 912 (16 pages). doi: 10.3389/fmicb.2019.00912.

19 Mathew D, Hsu W-L. Antiviral potential of curcumin. J Funct Foods 2018; 40: 692–9. doi: 10.1016/j.jff.2017.12.017

20 Jena AB, Kanungo N, Nayak V, Chainy GBN, Dandapat J. Catechin and Curcumin interact with corona (2019-nCoV/SARS-CoV2) viral S protein and ACE2 of human cell membrane: insights from Computational study and implication for intervention. Preprint from Research Square, 08 Apr 2020. doi: 10.21203/rs.3.rs-22057/v1 PPR: PPR148599

21 Panahi Y, Hosseini MS, Khalili N, et al. Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: A randomized controlled trial and an updated meta-analysis. Clin Nutr 2015; 34 (6): 1101–8. doi: 10.1016/j.clnu.2014.12.019

22 Ganjali S, Sahebkar A, Mahdipour E, et al. Investigation of the effects of curcumin on serum cytokines in obese individuals: A randomized controlled trial. Sci World J 2014; 2014: 898361 (6 pages). doi: 10.1155/2014/898361

23 DiSilvestro RA, Joseph E, Zhao S, Bomser J. Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people. Nutr J 2012; 11:79 (8 pages). doi: 10.1186/1475-2891-11-79

24 McFarlin BK, Venable AS, Henning AL, et al. Reduced inflammatory and muscle damage biomarkers following oral supplementation with bioavailable curcumin. BBA Clin 2016; 5: 72–8. doi: 10.1016/j.bbacli.2016.02.003

25 Sahebkar A, Serban M-C, Ursoniu S, Banach M. Effect of curcuminoids on oxidative stress: A systematic review and meta-analysis of randomized controlled trials. J Funct foods 2015;18 (Part B): 898–909. doi:10.1016/j.jff.2015.01.005

26 Pang X-F, Zhang L-H, Bai F, et al. Attenuation of myocardial fibrosis with curcumin is mediated by modulating expression of angiotensin II AT1/AT2 receptors and ACE 2 in rats. Drug Des Devel Ther 2015; 9:6043–54. doi: 10.2147/DDDT.S95333

27 Nihayati E, Wardiyati T, Retnowati R, Soemarno. The curcumin content of temulawak (Curcuma xanthorriza Roxb.) rhizome as affected by N, K and micronutrients B, Fe, Zn. Agrivita 2013; 35(3):218-26. doi: 10.17503/agrivita.v35i3.210

28 Kotha RR, Luthria DL. Curcumin: Biological, Pharmaceutical, Nutraceutical, and Analytical Aspects. Molecules 2019; 24 (16): 2930 (27 pages). doi: 10.3390/molecules24162930.

29 Febriyanti W. Simple spice chicken curry [in Indonesian]. Cookpad. Available at: https://cookpad.com/id/resep/3042872-kari-ayam-bumbu-sederhana. Accessed April 13, 2020.

30 Unilever food solution. Chicken curry [in Indonesian]. Unilever Food Solution 2020. Available at: https://www.unileverfoodsolutions.co.id/id/recipe/kari-ayam-R0073483.html. Accessed April 13, 2020.

31 Colon-Singh R. Here's How To Make Delicious Turmeric Golden Milk. Fine Dining Lovers; June 9, 2016. Available at: https://www.finedininglovers.com/article/heres-how-make-delicious-turmeric-golden-milk. Accessed April 13, 2020.

32 Madhusankha GDMP, Thilakarathna RCN, Liyanage T, Navaratne SB. Analysis of curcumin content in Sri Lankan and Indian turmeric rhizomes and investigating its impact on the colour. Int J Food Sci Nutr 2018;3 (4):3-5.

33 Priyadarsini KI. The Chemistry of Curcumin: From Extraction to Therapeutic Agent. Molecules 2014; 19 (12): 20091-112. doi:10.3390/molecules191220091

34 Gokhul V, Yuvapriya S, Chandramohan M, Muthukumaran P. Isolation and Extraction of Curcumin from Three Different Varieties of Curcuma Longa L - A Comparative Study. Int J Pharm Res Allied Sci 2015;4(2): 79-84.

35 Tayyem RF, Heath DD, Al-Delaimy WK, Rock CL. Curcumin Content of Turmeric and Curry Powders. Nutr Cancer 2006; 55(2): 126–31. doi: 10.1207/s15327914nc5502_2

36 Joint FAO/WHO Expert Committee on Food Additives (JEFCA). Curcumin. IPSC INCHEM; 2003. Available at: http://www.inchem.org/documents/jecfa/jeceval/jec_460.htm Accessed April 13, 2020.
37 European Food Safety Authority. Refined exposure assessment for curcumin (E 100). EFSA J 2014; 12(10):3876 (43 pages). doi: 10.2903/j.efsa.2014.3876.
38 Awin T, Mediani A, Maulidiani, et al. Phytochemical and bioactivity alterations of Curcuma species harvested at different growth stages by NMR-based metabolomics. J Food Compost Anal 2019; 77:66–76. doi: 10.1016/j.jfca.2019.01.004.