Acta Biologica Marisiensis sciendo

THERAPEUTIC ASPECTS OF CATECHIN AND ITS DERIVATIVES – AN UPDATE

Sanda COȘARCĂ[1], Corneliu TANASE[1*], Daniela Lucia MUNTEAN[1]

[1]University of Medicine, Pharmacy, Science and Technology of Târgu-Mureș, Faculty of Pharmacy, 38 Gheorghe Marinescu Street.

*Correspondence:
Corneliu TANASE
tanase.corneliu@umfst.ro

Received: 1 May 2019; **Accepted:** 20 June 2019; **Published:** 30 Iune 2019

Abstract: Catechin and its derivatives are polyphenolic benzopyran compounds. The condensation of catechin units leads to the formation of condensed tannins. It is found in appreciable amount in green tea leaves, cocoa, red wines, beer, chocolate, etc. It possesses important antioxidant, antibacterial, antifungal, antidiabetic, anti-inflammatory, antiproliferative and antitumor properties. The present review outlines recent updates and perspectives of the effects of catechins and the pharmacodynamic mechanisms involved.

Keywords: catechin, antitumor, antioxidant, antibacterial, hypolipidemic.

1. Introduction

Catechins are flavanols which belong to polyphenolic compounds. Condensed or non-hydrolyzable tannins are formed by the condensation of catechin (epicatechin and a catechin epimer) (**Fig. 1**). Catechin, together with epicatechin and epigallocatechin gallate, are the main flavonoids which are found in the composition of green tea (Li et al., 2018). Many research results have highlighted that catechins have an important role in protection against degenerative diseases (Ide et al., 2018). Other studies have demonstrated an inverse reaction between catechin intake and the risk of cardiovascular diseases (Ikeda et al., 2018). It has been reported that catechins appear to produce greater antibacterial activity against Gram-positive bacteria than Gram-negative ones (Ajiboye et al., 2016; Gomes et al., 2018).

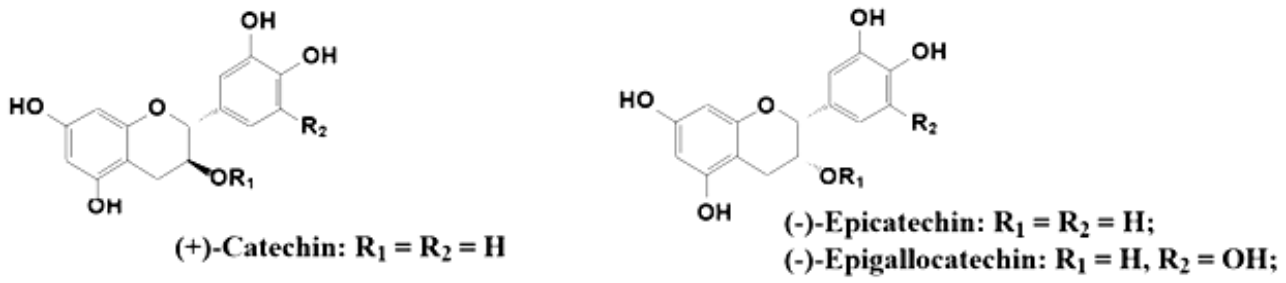

Fig. 1. Chemical structure of catechin and its derivatives

The present paper is a critical review of the recent literature on therapeutic aspects and pharmacodynamic mechanisms of catechin and its derivatives.

2. Bioavailability and biological effects of catechin and its derivatives

The bioavailability of catechin and its derivatives differs significantly depending on the form under which it is found (**Table 1**). When administered in esterified form with gallic acid, the absorption is much slower. Methylated forms were identified as a result of metabolization in the case of epigallocatechin. In another study, the plasma concentration of 4'-O-methyl-epigallocatechin was determined, whose value was 5 times higher in plasma and 3 times higher in urine than the concentration of epigallocatechin (Rothwell et al., 2018). Epigallocatechin gallate is the only flavonol form which is present in plasma in a significant percentage (48-55%).

The other catechins are detected as the glucoronidated or sulphated form. The main epicatechin metabolites are: epicatechin-3'-O-glucuronide, 4'-O-methylepicatechin-3'-O-glucuronide, 4'-O-methyl-epicatechin-5- or 7-O-glucuronide, 4'-O-methylepicatechine and epicatechin aglycone (Liao et al., 2018; Casanova et al., 2019). Metabolization leads to metabolites that can extend the beneficial effect of catechins, having a longer half-life (5 hours for epigallocatechin-3-gallate). In this case, renal excretion of catechins is very rapid (Manach et al., 2005; Ikeda et al., 2018).

Catechin influences molecular mechanisms involved in angiogenesis, extracellular matrix degradation, regulation of cell motility, and multiple resistance to cancers and associated disorders.

Based on epidemiological and experimental studies, a correlation between green tea consumption rich in catechins and cardiovascular health has been highlighted by several antioxidant, antihypertensive, anti-inflammatory, antithrombogenic, hypo-lipidemic, etc. effects (Rothwell et al., 2018). It was also shown that catechin and its derivatives, namely epigallocatechin gallate, would inhibit platelet aggregation. These effects were explained by the inhibition of cytoplasmic calcium growth (Lill et al., 2003; Watson et al., 2014). Catechins also have an important role in maintaining homeostasis (Matsui, 2015), their cardioprotective and antidiabetic effects have been demonstrated by several studies (Thielecke et Boschmann, 2009; Hashemipour et al. 2017).

3. Antiallergic properties

New studies have been conducted on the anti-inflammatory and anti-allergic effects of catechin (Hussein et al., 2015). The pharmacological effects of catechin in mice with allergic rhinitis were determined by performing haematoxylin and eosin staining and Giemsa staining of the nasal tissues essential in observing the allergic symptoms. The results showed that catechin, at 75, 150 or 300 mg/kg bodyweight, reduced the allergic symptoms in mice with allergic rhinitis, such as sneezing and nasal rubbing. Catechin could reduce interleukin-5, interleukin-13 and ovalbumin E serum concentrations and restore T helper type 2 / T helper type 1 cell balance. Catechin has efficiently decreased the inflammation in allergic rhinitis. The mechanism of action would be that catechin inhibited the expression of TSLP (lymphatic stromal lymphopoietin) in epithelial cells by influencing the NF-κB / TSLP pathway (Pan et al., 2018).

4. Cardiovascular effects

Recent evidence demonstrates that catechins can be key mediators in cardiovascular health through mechanisms underlying blood pressure reduction,

vasodilation, and atherosclerosis (Mangels et al, 2017).

The prevalence of coronary heart disease in Asian people is demonstrated to be very low due to their increased tea consumption (Shahid et al., 2016; Li et al., 2018). Also, recent studies have demonstrated that, due to their antioxidant effect, they have the ability to reduce cytotoxicity produced by amiodarone (commonly used antiarrhythmic drug) in human lung fibroblast cells (Cooper et al., 2005; Santos et al., 2017).

5. Antioxidant and anti-tumor effect

Clinical trials conducted so far have shown the beneficial effects of catechin due to its antioxidant action. The ability of catechins to cross the blood-brain barrier has led to increased interest related to their antioxidant properties beneficial for the prevention and treatment of neurodegenerative diseases.

Catechin and other catechins in green tea block carcinogenesis and help modulate signal transduction pathways related to proliferation, transformation, inflammation and metastasis of cells. It also has a chemopreventive potential (Grzesik et al, 2018; Yang et al., 2018; Baranowska et al., 2018) and catechin nanohybrids significantly improve the anti-tumour effect by inducing apoptosis of WM266 human melanoma versus free catechin (Di Leo et al., 2017). Also, the loading of catechin with PLGA (poly (1-lactide-co-glycolide)) fibers had a high effect of reducing the reactive oxygen species, so processing of catechin in controlled release forms could allow future localized applications of great importance in the fields of tissue engineering and wound healing (Ghitescu et al., 2018).

Oxidative stress plays a central role in the degeneration of neurons by activating intracellular signaling cascades, which have a role in autoimmune apoptosis and extracellular modulation (Suryavanshi et al, 2017, Bhatt et al., 2012) processes. Generation of ROS in neuronal cells activates inflammatory mediators like TNF-α, COX-2, NF-κβ as well as proapoptotic mediators such as Bcl-2 and caspase-9 (Suryavanshi et al, 2017; Kimura-Ohba et al., 2016). Catechin directly or indirectly decreases neuronal damage by reducing oxidative stress, scavenging ROS and improving antioxidant enzymes (Shai et al 2015; Xiang et al., 2016).

6. Lipid-lowering effects

Studies in rats have shown that catechin in green tea can reduce the risk of cardiovascular disease (CD). The effect has been attributed to the antioxidant and anti-inflammatory properties of catechin. Also it is suggested that catechin reduces the risk of cardiovascular disease by lowering cholesterol and triglyceride levels (Cooper et al., 2005). In vitro and in vivo studies show that catechins in green tea inhibit intestinal absorption of dietary lipids, by interfering with lipid digestion and their solubilization (the critical steps involved in the intestinal absorption of dietary fats, cholesterol and other lipids). Based on the information available so far, it is clear that green tea and its catechins effectively reduce the intestinal absorption of lipids (Ikeda et al., 1992). The mechanism of action of catechin is based on the fact that it inhibits the absorption of lipids. This effect appears to be associated with its ability to form complexes with lipids and lipolytic enzymes, thereby interfering with emulsification, hydrolysis, micellar solubilization processes and subsequent absorption of lipids. These mechanisms are not fully clarified and further studies are needed to define mechanisms underlying lipid absorption inhibition (Shishikura et al.; 2006; Koo et al., 2007).

7. Antibacterial and antiviral effect

Polyphenols are among the most abundant compounds in the plant kingdom. They have been reported to be associated with a number of organoleptic properties of drinks and foods.

Table 1. The effect of catechin and its derivates

Compound	Effect	Reference
epicatechin gallate epigallocatechin-3-gallate	beneficial role in muscles regeneration	Kim AR et al.,2017
epigallocatechin, epicatechin, epigallocatechin-3-gallate, epicatechin-3-gallate	antioxidant cardioprotective	Ikeda et al., 2018
epigallocatechin gallate	antibacterial	Miyamoto et al., 2017
epicatechin, epigallocatechin, epicatechin gallate, epigallocatechin gallate, gallocatechin gallate	bactericidal effects on oral bacteria, *Aggregatibacter actinomycetemcomitans*	Chang et al., 2019
epicatechin epicatechin gallate epigallocatechin epigallocatechin gallate	antioxidant	Grzesik et al., 2018
catechin	antioxidant, anti-inflammatory, beneficial effect in the management of diabetic autonomic neuropathy in rats	Addepalli V et Suryavanshi SV, 2018
catechin	antibacterial	Gomes et al., 2018
catechin	antioxidant	Caro et al., 2019
catechin	hepatoprotective	Akinmoladum et al., 2018
catechin	cytotoxic	Di Leo et al., 2017
catechin	anti-microbial	Chunmei et al., 2010
epigallocatechin-3-gallate	antioxidant,	Roychoudhur et al., 2017
epigallocatechin-3-gallate	antibacterial	Founier-Larente et al., 2016
catechin	antioxidant, antibacterial	Akiboye etal., 2016
catechin	antibacterial	Diaz-Gomez et al., 2013
catechin	antibacterial	Diaz-Gomez et al., 2014
catechin	antibacterial antioxidant	Li et al., 2018
catechin	antibacterial	Zhang et al., 2016
catechin	antifungal	Saito et al., 2013s
epigallocatechin gallate	antibacterial	Nakayama et al., 2013

Several authors have highlighted the antibacterial effect of polyphenols against bacteria that can cause gastrointestinal diseases.

Several studies associate catechin with different antibiotics. It has been observed that the combination of antibiotics like catechin-imipenem, catechin-erythromycin, catechin-tetracycline would have a synergistic inhibition effect against *Eschericia coli*, which suggests that polyphenols may be considered promising alternatives for the treatment of bacterial and viral infections, thus the catechin can be used for the prophylaxis of influenza and A (H1N1) infection (Gomes et al., 2018; You et al., 2018; Diaz-Gomez et al., 2013). Other studies demonstrate that black tea consumption would influence the incidence of Helicobacter pylori infection due to its catechin content (Boyanova et al., 2015; Naveeda et al., 2018; Diaz-Gomez et al., 2013).

8. Antidiabetic effect

Certain studies have pointed out that catechin would have a significant potential to reduce blood glucose, body weight and body mass index (BMI) in both elderly and obese subjects by stimulating thermogenesis (Hashemipour et al., 2017; Pastoriza et al., 2017; Addepalli et al., 2018). Catechins control plasma glucose levels by modulating the glucose transport system (Grzesik et al., 2018).

9. Immunostimulatory effect

Catechin also intervenes in immune function modulation through humoral and cellular mechanisms. It has been emphasized that catechin decreases cyclophosphamide-induced myelosuppression (Ganeshpurkar et al., 2018).

Conclusions

Catechin and its derivatives represent a class of phenolic compounds with a very wide therapeutic potential. At present, not all the mechanisms of action are fully known, but studies have shown that these compounds would be worthwhile investigating.

Numerous studies have shown positive effects of green tea and tea-based products due to their content of catechin and its derivatives. These compounds would also be beneficial for the improvement of degenerative, metabolic and cardiovascular diseases as well as the quality of life in elderly population. Studies on cell lines highlight the effects of catechin on cancer chemopreventive activity. However, catechins and their derivatives must be given full attention due to numerous effects, for the development of new, more efficient and more stable drug structures. There are currently no food supplements with catechin or its derivatives in pure form, but most of the green tea extract supplements are based on its effects and its derivatives.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Addepalli V, SV (2018) Catechin attenuates diabetic autonomic neuropathy in streptozotocin induced diabetic rats. Biomedicine & Pharmacotherapy 108:1517-1523.
2. Akinmoladun AC, Oladejo CO, Josiah SS, Famusiwa CD, Ojo OB, Olaleye MT, Catechin (2018) quercetin and taxifolin improve redox and biochemical imbalances in rotenone-induced hepatocellular dysfunction: Relevance for therapy in pesticide-induced liver toxicity? Pathophysiology 25(4):365-371.
3. Ajiboye TO, Aliyu M, Isiaka I, Haliru FZ, Ibitoye OB, Uwazie JN, Muritala HF, Bella SA, Yusuf II, Mohammed AO (2016) Contribution of reactive oxygen species to (+)- catechin-mediated bacterial lethality. Chemico-Biological Interaction 258:276-287.
4. Baranowska M, Suliborska K, Chrzanowski W, Kusznierewicz B, Namieśnik J, Bartoszek A (2018) The relationship between standard reduction potentials of catechins and biological activities involved in redox control. Redox Biology 17:355-366.
5. Bhatt LK, Addepalli V (2012) Potentiation of aspirin-induced cerebroprotection by minocycline: a therapeutic approach to attenuate exacerbation of transient focal cerebral ischaemia. Diabetes Vasc. Dis. Res. 9:25-34.
6. Boyanova L, Ilieva J, Gergova G, Vladimirov B, Nikolov R, Mitov I (2015) Honey and green/black tea consumption may reduce the risk of helicobacter pylori infection. Diagn. Microbiol. Infect. Dis. 82 (1):85-86.
7. Caro AA, Davis A, Fobare S, Horan N, Ryan C, Schwab C (2019) Antioxidant and pro-oxidant mechanisms of (+) catechin in microsomal CYP2E1-dependent oxidative stress. Toxicology in Vitro 54:1-9.
8. Casanova E, Salvado J, Crescenti A, Gilbert-Ramos A (2019) Epigallocatechin gallate modulates muscle homeostasis in type 2 diabetes and obesity by targeting energetic and redox pathways: A narrative review. International Journal of Molecular Sciences 20:532.
9. Chang EH, Huang J, Lin Z, Brown AC (2019) Catechin-mediated restructuring of a bacterial toxin inhibits activity. BBA - General Subjects 1863:191-198.
10. Chunmei D, Jiabo W, Weijun K, Cheng P, Xioache X (2010) Investigation of antimicrobial activity of catechin on Escherichia coli growth by microcalorimetry. Environmental Toxicology and Pharmacology 30:284-288.
11. Di Leo N, Battaglini M, Berger L, Giannacinni M, Dente L, Hampel S, Vittorio O, Cirillo G, Raffa V (2017) A catehin nanoformulation inhibits WM266 melanoma cell proliferation, migration and associated neo-angiogenesis. European Journal of Pharmaceutics and Biopharmaceutics 114:1-10.
12. Diaz-Gomez R, Lopez-Solis R, Obreque-Slier E, Toledo-Araya H (2013) Comparative antibacterial effect of gallic acid and catechin against Helicobacter pylori. LWT-Food Science and Technology 54:331-335.
13. Diaz-Gomez R, Toledo-Araya H, Lopez-Solis R, Obreque-Slier E (2014) Combined effect of gallic acid and catechin against Eschericia coli. LWT-Food Science and Technology 59:896-900.
14. Fournier-Larente J, Morin MP, Grenier D (2016) Green tea catechins potentiate the effect of antibiotics and modulate adherence and gene expression in

Porphiromonas gingivalis. Archives of Oral Biology 65:35-43.
15. Ganeshpurkar A, Saluj AK (2018) Protective effect of catechin on humoral and cell mediated immunity in rat model. International Immunopharmacology 54:261-266.
16. Gomes FMS, da Cunha XJ, dos Santos JFS, de Matos YMLS, Tintino SR, de Freitas TS, Coutinho HDM (2018) Evaluation of antibacterial and modifying action of catechin antibiotics in resistant strains. Microbial Pathogenesis 115:175-178.
17. Grzesik M, Naparlo K, Bartosz G, Sadowska-Bartosz I (2018) Antioxidant properties of catechins: Comparison with other antioxidants. Food Chemistry 241:480-492.
18. Hashemipour MA, Lotfi S, Torabi M, Sharifi F, Ansari M, Ghassemi A, Sheikhshoaie S (2017) Evaluation of the effects of three plant species (Myrtus Communis L., Camellia Sinensis L., Zataria Multiflora Boiss.) on the healing process of intraoral ulcers in rats. J. Dent. 18 (2):127–135.
19. Ide K, Matsuoka N, Yamada H, Furushima D, Kawakami K (2018) Effects of Tea Catechins on Alzheimer's Disease: Recent Updates and Perspectives. Molecules 23:2357.
20. Ikeda A, Iso H, Yamagishi K, Iwasaki, M Yamaji T, Miura T, Sawada N, Inoue M, Tsugane S (2018) Plasma tea catechins and risk of cardiovascular disease in middle-aged Japanese subjects: The JPHC study. Atherosclerosis 277:90-97.
21. Kim AR, Kim KM, Byun MR, Hwang JH, Park JI, Oh HT, Kim HK, Jeong MG, Hwang ES, Hong JH (2017) Catechins activate muscle stem cells by Myf5 induction and stimulate muscle regeneration. Biochem Biophys Res Commun. 489(2):142-148.
22. Kimura-Ohba S, Yang Y (2016) Oxidative DNA Damage Mediated by Intranuclear MMP Activity Is Associated with Neuronal Apoptosis in Ischemic Stroke. Oxid. Med. Cell. Longev. http://dx.doi.org/10.1155/2016/6927328
23. Koo SI, Noh SK (2007) Green Tea as Inhibitor of the Intestinal Absorption of Lipids: Potential Mechanism for its Lipid-Lowering Effect. J Nutr Biochem. 18(3):179-183.
24. Li F, Jin H, Xiao J, Yin X, Liu X, Li D, Huang Q (2018) The simultaneous loading of catechin and quercetin on chitosan-based nanoparticles as effective antioxidant and antibacterial agent. Food Research International 111:351-360.
25. Liao Y, Fu X, Zhou H, Rao W, Zeng L, Yang Z (2019) Visualized analysis of within-tissue spatial distribution of specialized metabolites in tea (Camellia sinensis) using desorption electrospray ionization imaging mass spectrometry. Food Chemistry 292: 204-210.
26. Lill G, Voit S, Schro K, Weber AA (2003) Complex effects of different green tea catechins on human platelets. FEBS Letters. 546:265-270.
27. Manach C, Williamson G, Morand C, Scalbert A, Remesy C (2005) Bioavailability and bioefficacy of polyphenols in humans, I. Review of 97 bioavailability studies. Am J Clin Nutr 81:230-242.
28. Mangels DR, Mohler ER (2017) Catechins as Potential Mediators of Cardiovascular Health. Arterioscler Thromb Vasc Biol. 37(5):757-763.
29. Matsui T (2015) Condensed catechins and their potential health benefits. European Journal of Pharmacology 795:495-502.
30. Miyamoto T, Zhang X, Ueyama Y, Kitichalermkiat AK, Nakayama M, Suzuki Y, Ozawa T, Mitani A, Shigemune N,

Shimatani K, Yui K, Honjoh K (2017) Development of novel monoclonal antibodies directed against catechins for investigation of antibacterial mechanism of catechins. Journal of Microbiological Methods 137:6-13.

31. Nakayama M, Shimatani K, Ozawa T, Shigemune N, Tsugukuni T, Tomiyama D, Kurahachi M, Nonaka A, Miyamoto T (2013) A study of the antibacterial mechanism of catechins: Isolation and indentification of Escherichia coli cell surface proteins that interact with epigallocatechin gallate. Food Control 33:433-439.
32. Naveeda M, BiBi J, Kamboh AA ,Suheryani I, Kakar I, Fazlani SA, Fang XF, Kalhoro SA, Yunjuan L, Kakar MU, El-Hackk MEA, Noreldin AE, Zhixiang S, LiXia C, Hui ZX (2018) Pharmacological values and therapeutic properties of black tea (Camellia sinensis): A comprehensive overview, Biomedicine & Pharmacotherapy 100:521-531.
33. Pan Z, Zhoua Y, Luoa X, Ruanb Y, Zhoua L, Wanga Q, Yanc Y, Liua Q, Chend J (2018) Against NF-κB/thymic stromal lymphopoietin signaling pathway, catechin alleviates the inflammation in allergic rhinitis.International Immunopharmacology 61:241-248.
34. Pastoriza S, Mesías M, Cabrera C, Rufiánhenares JA (2017) Healthy properties of green and white teas: an update. Food Funct. 8:2650-2662.
35. Rothwell JA, Madrid-Gambin F, Garcia - Aby M, Andres-Lacueva C, Logue C, Gallagher AM, Mack C, Kulling SE, Gao Q, Pratici G, Dragsted LO, Scalbert A (2018) Biomarkers of intake for coffee, tea, and sweetened beverages. Genes&Nutrition doi: 10.1186/s12263-018-0607-5
36. Roychoudhury S, Agarwal A, Virk G , Cho CL (2017) Potential role of geen tea catechins in the management of oxidative stress-associated infertility. Reproductive Biomedicie Online 34:487-498.
37. Saito H, Tamura M, Imai K, Ishigami T, Ochiai K (2013) Catechin inhibits Candida albicansi dimorphism by distructing Cek1 phosphorylation and cAMP synthesis. Microbial Pathogenesis. 56:16-20.
38. Santos LFS, Stolfo A, Calloni C, Salvador M (2017) Catechin and epicatechin reduce mithochondrial dysfunction and oxidative stress induced by amiodarone in human lung fibroblasts. Journal of Arrythmia 33:220-225.
39. Shahid A, Ali R, Ali N, Hasan SK, Bernwal P, Afzal SM, Vafa A, Sultana S (2016) Modulatory effects of catechin hydrate against genotoxicity, oxidative stress, inflammation and apoptosis induced by benzo(a)pyrene in mice. Food and Chemical Toxicology 92:64 -74.
40. Shay J, Elbaz HA, Lee I, Zielske SP, Malek MH, Hüttemann M, Molecular mechanisms and therapeutic effects of (−)-epicatechin and other polyphenols in cancer, inflammation, diabetes, and neurodegeneration. Oxid. Med. Cell. Longev. http://dx.doi.org/10.1155/2015/181260
41. Shishikura Y, Khokhar S, Murray BS (2006) Effect of tea polyphenols on emulsificat on of olive oil in a small intestine model system. J Agric Food Chem 54:1906-13.
42. Suryavanshi SV, Kulkarni YA (2017) NF-κβ: a potential target in the management of vascular complications of diabetes, Front. Pharmacol. 8:1-12.
43. Thielecke F, Boschmann M (2009) The potential role of green tea catechins in the prevention of the metabolic syndrome-A review. Phytochemistry 70:11-24.

44. Watson RR, Preedy VR, Zibadi S (2014) Polyphenols in Human Health and Disease. Imprint Academic Press https://doi.org/10.1016/C2011-1-09286-X
45. Xiang LP, Wang A, Ye JH, Zheng XQ, Polito C, Lu JL, Li QS, Liang YR (2016) Suppressive effects of tea catechins on breast cancer. Nutrients 8(8) https://doi.org/10.3390/nu8080458.
46. Yang H, Xue X, Li H, Apandi SN, Tay-Chan SC, Ong SP, Tian EF (2018) The relative antioxidant activity and steric structure of green tea catechins-A kinetic approach. Food chemistry 257:399-405.
47. You HL, Huang CC, Chen CJ, Chang CC, Liao PL, Huang ST (2018) Anti-pandemic influenza A (H1N1) virus potential of catechin and gallic acid. Journal of the Chinese Medical Association 81:458-468.
48. Zhang H, Jung J, Zhao Y (2016) Preparation, characterization and evaluation of antibacterial activity of catechins and catechins-Zn complex loaded β-chitosan nanoparticles of different particle sizes. Carbohydrate Polymers 216:82-91.