Review article

Chemical properties of polyphenols: a review focused on anti-inflammatory and anti-viral medical application

Beatriz A. Cano-Avendaño1, Juan C. Carmona-Hernandez1,2, Ricardo E. Rodriguez3, Gonzalo Taborda-Ocampo4, Clara H. González-Correa2

1Grupo de Investigación Médica, Universidad de Manizales, Manizales, Colombia
2Grupo de Investigación Nutrición, Metabolismo y Seguridad Alimentaria, Universidad de Caldas, Manizales, Colombia
3Dean of Arts and Sciences, Texas Wesleyan University, Fort Worth - USA
4Grupo de Investigación en Cromatografía y Técnicas Afines, Universidad de Caldas, Manizales, Colombia

(Received: September 2020 Revised: January 2021 Accepted: February 2021)

Corresponding author: Juan C. Carmona-Hernandez. Email: jucaca@umanizales.edu.co

ABSTRACT

Polyphenols are attributed to multiple biological activities that provide nutritional and therapeutical benefits. The present paper is a descriptive review focused on polyphenolic chemical structural aspects contributing to explain biological and biochemical functions offered by these phytochemicals. Element conformation differences, ring modifications, the presence of specific functional groups, and the tridimensional chemical arrangement are fundamental to explain specific effects presented by polyphenols. The anti-oxidant and anti-inflammatory actions of polyphenols suggest that basic chemical reactions and element re-organization are important in understanding their function, well-known polyphenols such as quercetin, curcumin, and catechin have been evaluated in multiple studies. Moreover, anti-bacterial and anti-viral activities have been proven to be dependent on hydroxylation, methoxylation, and alkylation of several polyphenol ring components. Polyphenols extracted from tea, like catechins, proved to inhibit efficiently hepatitis C, Zika, and Chikungunya viruses. They have also acted as promising prophylactic and therapeutic agents against SARS-CoV-2. Epicatechin extracted from the hawthorn tree showed antiviral activity on several bacteria such as Escherichia coli and Salmonella typhimurium. The inclusion of these natural components in daily diets is of primary nutritional benefit and importance in the prevention of several diseases.

Keywords: Chemical conformation; polyphenols; biological function; therapeutical application

INTRODUCTION

Polyphenols are the most numerous phytochemicals known today (1). Around 8000 polyphenols are presently identified with flavonoids as their most numerous subgroup. Rich polyphenol diets benefit human health and execute specific actions according to their structural characteristics (2-4). The cyclic structure, covalent bond arrangement, and different chemical functional groups are relevant factors for diverse reactions and biochemical functions. Polyphenols are involved in the regulation of oxidative stress and control of reactive oxygen species; they also have functional similarity, or related-action, to enzymes and vitamins (4, 5). In the last 40 years, polyphenols started to attract more attention from nutritionists, industrial engineers, food engineers, and health professionals (5). Recent studies report benefits in the prevention of cancer, diabetes, cardiovascular and neurodegenerative diseases (5-8). Polyphenol actions are related to their structural variations and chemical arrangements (5).

Polyphenol actions are related to their structural variations and chemical arrangements (1,6). These phytochemicals participate in different biological and biochemical pathways; the most active subclass of polyphenols are flavonoids, found in all parts of the plants like roots, stem, leaves, flowers, and seeds (5, 6). Polyphenols are responsible for colour and flavour in plants. They act as defence mechanisms, oxidative stress regulators, water and luminous stimuli controllers, and as ultraviolet (UV) radiation protectors (3, 4). The present review focuses on structural aspects and chemical characteristics in polyphenols related to biological functionality and medical applications. These characteristics can contribute to explaining several biochemical aspects in polyphenols. And they invite to include more polyphenols in regular diets considering that polyphenols like luteolin, genistein, quercetin, curcumin, among several others, act as antiapoptotic, anticancer, and antioxidant agents (7, 8).

Chemical structure and reactivity

Functional groups and classification

The main backbone in phenolic structures is characterized by the presence of a benzene ring (C6H6) with a hydroxyl group (-OH) (6). Phenols are slightly soluble in polar solvents due to the single OH group that gives low polarity to the cyclic structure. Polyphenol hydro solubility depends on the possibility of making hydrogen-bonding based on the number and type of substituents in the chemical conformation (7). Fig. 1 shows the variety of chemical substituents in polyphenolic structures.
Polyphenol conformations vary based on the presence of substituents in their chemical structure. Examples of functional groups in polyphenols are cetonic, carboxylic groups, and mono or disaccharides (8). Most polyphenols appear in nature as glucosides joined to glucose or a galactose molecule. Some polyphenols are aglycones, structures without carbohydrate rings attached. The main classes of polyphenols are hydrocinnamic acids, hydroxybenzoic acids, flavonoids, lignans, and stilbenes. Flavonoids are the most numerous polyphenol-type compounds. They include subclasses like flavonols, flavones, flavanones, isoflavones, flavonols, and anthocyanidins (9). Fig. 2 represents examples of several flavonoid structures.

Around 4000 flavonoids are currently identified (8). This chemical group characterizes by the presence of phenolic rings and variable tridimensional modifications. The chemical reactivity of flavonoids is wide and varied. Subgroups of plant flavonoids allow for different reactions and several functions (8).

Chemical arrangement of polyphenols

Several studies report polyphenols as natural antioxidants, highlighting that their structure is fundamental in free radical control, active participation of oxido-reducing reactions, cyclooxygenases inhibiting, and cell aging regulation (1,10,11). Several factors make polyphenols active and efficient antioxidants, like the inclusion of several hydroxyl groups, the incidence of single and double covalent bonding, and the electronic resonance (10).

Polyphenols participate in polymeric reactions common in pharmacological synthesis (10); they can inhibit specific points of the arachidonic pathway acting directly on enzymes like the cyclooxygenase type I (2,10). Polyphenols functionality depends in part on the location and number of hydroxyl groups;
ring substitution in orientations ortho-meta- and para-depend on electron movement and free orbital availability (10).

This structural dynamic and mobility offer the cyclic structure more stability and resistance (11). Deprotonation of the –OH group allows oxygen to achieve a higher electronic density and free p orbitals leading to the opening of spaces to relocate electrons. This way, polyphenol reactivity can be stimulated due to ring modification and the entrance of more substituents (12). Therefore, reactions like addition, substitution and reorganization can be achieved (13).

Other structural modification in polyphenols is polymerization and increased molecular weight caused by more phenolic rings. The antioxidant property of polyphenols tannins, which are composed of multiple rings with several hydroxyl substituents, is reported in several studies (14,15). Due to efficient electronic transferring, tannins are highly effective in oxido-reducing reactions based on their capability of making hydrogen bonding, rapid electron movement, and hydroxyl group rearrangement (13-15).

**Presence of multiple rings**

Polyphenols comprise more than one benzene ring and several hydroxyl groups. Their general structure has a representation C6-C3-C6, where the rings are labelled as A, B, and C (15). Rings A and B join to ring C by a heterocyclic pyrane (16). Fig. 3 represents the general cyclic polyphenol structure. Polyphenol variety depends on substitutions in ring C; different functions depend on the modifications in rings A and B (16). Hydroxybenzoic acid derivatives as hydroxytyrosol, tannins, and gallic acids are examples of polyphenols with a single structure represented as C6 (15). Caffeic and cumaric acids are double-ringed polyphenols (C6-C3) related to hydroxycinnamic acid. There are polyphenols composed of three rings (C6-C2-C6), like resveratrol, stilbenes, and polydatin. Lignans are four-ringed (C6-C4-C6) polyphenols; one example of them is secoisolariciresinol (17).

Fig. 3: General polyphenol cyclic representation and numbering

Most polyphenols have the -OH group in position 5 or 7 (C5 or C7) in ring A. Ring B has the same groups in positions 3 and 4 (16). Variations in these places and the presence of more functional groups allow for multiple chemical reactions and several biological activities (16).

**Contribution to biological and biochemical processes**

Natural components have benefited humans throughout the centuries. Plants serve as antimicrobial agents; several studies focus on the use of natural polyphenols to tackle infectious diseases (18-20). Antimicrobial effects in plants are due to simple phenolic groups, polyphenols, tannins, and essential oils (18). Their mechanism of action degrade and increase the permeability of the cytoplasmic membrane causing lysis, allowing bacteria to be vulnerable to the immune attack, altering the enzymatic systems related to energy production, damaging the synthesis of structural components, and inhibiting the synthesis of nucleic acids (19, 20).

Defence mechanisms in plants are also dependent on polyphenol structural modifications and covalent bonding organization (19). Covalent bonding interchange and nucleophilic substitution are fundamental aspects for effective enzyme action. This chemical action is common in peroxidases and polyphenol oxidases against pathogens (19). Polyphenol oxidases are also responsible for aroma and flavour in different parts of the plant (20). Polyphenols are antibacterial, anti-inflammatory, antiallergenic, and antithrombotic agents (1, 8).

Polyphenols are the most abundant natural antioxidants. They are ten times better antioxidants than vitamin C and approximately 100 times better than vitamin E and carotenoids (20). Polyphenols are important in preventing degenerative and cardiovascular diseases, and in regulating different types of cancer (18, 19). Table 1 cites more biological contributions evaluated in polyphenols from multiple natural sources.

**Table 1: Biological activity proven in polyphenols**

| Biological action | Polyphenol | References |
|-------------------|------------|------------|
| Antiapoptotic | Apigenin, luteolin | (20) |
| Anticancer | Genistein, apigenin | (18) |
| Anti-inflammatory | Quercetin, kaempferol | (21) |
| Antioxidant | Lutein, tannins, curcumin | (22) |
| Antimicrobial | Catechin, gallic acid | (23) |

**Effect to medical applications**

**Anti-inflammatory activity**

Different studies have explored the anti-inflammatory effects of polyphenols involving multiple inflammatory mediators and pathways (22, 24). Continuous inflammation links to different human disorders involving cancers, diabetes type 2,
obesity, arthritis, and neurodegenerative and cardiovascular diseases; therefore, clinical trials have assessed the anti-inflammatory benefits of dietary polyphenols (24). Studies report a significant decrease in interleukin-8 (IL-8), interleukin-6 (IL-6), interleukin-10 (IL-10), tumour necrosis factor-α (TNF-α), and interleukin-12p70 (IL-12) after a short time consuming different types of pigmented rice, a known source of polyphenols, with phenolic acids, flavonoids, anthocyanins, and proanthocyanidins content (25, 25).

A compelling reduction in C-reactive protein (CRP) and TNF-α with healthy subjects after a single dose of a famous Mediterranean tomato-based sauce, “Tomato Sofrito,” was inversely correlated with the urinary excretion of total polyphenols (26). Resveratrol, for instance, a natural polyphenol found in various plants, has been studied extensively, decreases the expression and the activity of some matrix metalloproteinases (MMP-2 and MMP-9), well-known inflammatory mediators, via multiple mechanisms, including the inhibition of the transcription factor NF-κB activation also a pivotal mediator of inflammatory responses (27).

Polyphenol chemical structural aspects are crucial; it is worthwhile mentioning some polyphenols present in extra virgin olive oil for their antioxidant and anti-inflammatory properties (21, 22). For example, lignans are fibre-associated polyphenols whose structure bases on a 2,3-dibenzylbutane complex, derived from the dimerization of two cinnamyl acid residues (2). Thyrosol-derived compounds, such as oleuropein and hydroxytyrosol, are the main polyphenols in extra virgin olive oil. Thyrosols have a phenethyl alcohol moiety with a hydroxyl group in position 4 of the benzene group (2).

Polyphenol activity depends on their absorption rate and bioavailability of derivative metabolites. Once ingested, polyphenols interact with other nutrients such as proteins, sugars, fats, fibre, and the intestinal microbiota generating active metabolites (28). Polyphenol absorption is due to glycoside moieties. Anthocyanins are absorbed intact, while others are hydrolyzed to aglycones in the small intestine brush border or within epithelial cells in the colon (28-30). Aglycones get to the circulation system in conjugated forms, such as sulphate, glucuronide, and methylated metabolites (1). Finally, aglycones undergo ring fixation with the production of bioactive metabolites, like phenolic acids and hydroxycinnamates, detected in plasma after 12–48 h from polyphenol ingestion (31).

**Anti-viral and anti-bacterial activity**

Various studies report the anti-viral and anti-bacterial activity of polyphenols. For instance, moderate therapeutic activities of different flavonoids against influenza virus (32, 33). Tea polyphenols inhibit hepatitis C virus entry, Zika virus entry, Chikungunya virus, and also show possible and promising prophylactic as well as therapeutic agents against SARS-CoV-2 based on polyphenol properties to dock to various active sites of the new coronavirus (24, 25, 36, 37).

Another study in hawthorn tree extracts, a widely cultivated Chinese plant containing epicatechin, procyanidin B2, chlorogenic acid, and quercetin, reported antibacterial activity on *Staphylococcus aureus*, *Escherichia coli*, *Shigella dysenteriae*, and *Salmonella typhimurium* (38). Researchers suggested that polyphenols against *Staphylococcus aureus* caused membrane depolarization and permeabilization, affecting intracellular-enzyme activities and increasing intracellular reactive oxygen species (ROS) levels, leading to cell apoptosis and bacterial death (38).

The therapeutic activity of polyphenols against bacteria and viruses depends on polyphenol structure modifications such as glycosylation hydroxylation, methoxylation, and alkylation (35-37). For instance, fruit flavonoids in aglycone forms or the 3-O-glycoside flavonoids can modulate the antibiotic-resistance in *S. aureus*. This inhibitory action is not possible in the 7-O-glycoside form that lowers the interaction with the target bacteria (38, 39).

**DISCUSSION**

Fruits, vegetables, grains, chocolate, tea, and wine are important sources of polyphenols (30, 31, 34). Polyphenols exhibit varied chemical structures and multiple biological and biochemical actions. The presence of different functional groups, the degree of oxidation, and the arrangement of chemical bonds are fundamental for their activity (22). Both for plants and for humans polyphenols contribute in several ways. They are considered efficient antioxidants, anti-inflammatory, antiviral, and antimicrobial agents (22, 23).

The functionality of polyphenols relies upon structural and organizational differences. The presence of hydroxyl groups in several parts of the cyclic arrangement is essential for electron movement and free radical regulation (10, 11). This chemical characteristic helps plants to control UV radiation, to regulate growth and cellular differentiation (40). The generation of hydrogen bonds and the attraction to other molecules are imperative to explain the inhibition of inflammatory factors and active enzymes in pathological processes (12).

Element arrangement, unsaturation covalent bonding, and hydrogen bonds provide polyphenols stable and active cyclic structures (14). Polyphenols attach to water molecules, mono, and disaccharides, proteins, and lipoproteins (12). These chemical properties give more resistance to the vegetable cell, making it more
tolerable to water shortage or extreme temperature changes. The anti-inflammatory and anti-bacterial action of polyphenols relates to different chemical participation (21, 23). Polyphenol glycosylation hydroxylation, methoxylation, alkylation, ring substitutions, conjugations, and structural arrangement are major chemical mechanisms contributing to specific polyphenol biological and therapeutical actions.

CONCLUSION

The assessment of polyphenol structural characteristics to explain differences in their biological and biochemical activity is fundamental to understand their contribution to human health. The identification, quantification of new plant polyphenols, and the mechanism of action are relevant to explore their nutritional and physiological benefits leading to medical approaches with therapeutical applications. Regular inclusion of fruits, vegetables, and polyphenol-rich drinks in current diets is recommended for effective nutritional processes and the prevention of multiple diseases.

ACKNOWLEDGEMENTS

Authors thank Universidad de Manizales in Caldas (Colombia) and COLCIENCIAS (Bogota – Colombia) for their support and financial contribution to this project.

CONFLICT OF INTEREST

Authors declare no conflicts of interest.

REFERENCES

1. Luca, S. V., Macovei, I., Bujor, A., Miron, A., Skalicka-Woźniak, K., Aprotsosiea, A. C., et al. Bioactivity of dietary polyphenols: The role of metabolites. Critical Reviews in Food Science and Nutrition. 2020 Feb 21; 60(4): 626-659.
2. Magrone, T., Magrone, M., Russo, M. A., Jirillo, E. Recent advances on the anti-inflammatory and antioxidant properties of red grape polyphenols: in vitro and in vivo studies. Antioxidants. 2020 Jan; 9(1): 35.
3. Gori, A., Nascimento, L. B., Ferrini, F., Centritto, M., Brunetti, C. Seasonal and diurnal variation in leaf phenolics of three medicinal Mediterranean wild species: What is the best harvesting moment to obtain the richest and the most antioxidant extracts? Molecules. 2020 Jan; 25(4): 956.
4. Araújo, M., Pimentel, F. B., Alves, R. C., Oliveira, MBPP. Phenolic compounds from olive mill wastes: Health effects, analytical approach and application as food antioxidants. Trends in Food Science & Technology. 2015 Oct; 45(2): 200-211.
5. Chaudhary, A., Jaswal, V. S., Choudhary, S., Sonika., Sharma A., Beniwal, V., et al. Ferulic acid: A promising therapeutic phytochemical and recent patents advances [Internet]. 2019 [cited 2020 Aug 29]. Available from: https://www.ingentaconnect.com/content/ben/iaid/2019/00000013/00000002/art00005#.
6. Kurikawa, Y., Togo, M., Murata, M., Matsuda, Y., Sakata, Y., Kobayashi, H., et al. Mechanistic insights into visible light-induced direct hydroxylation of benzene to phenol with air and water over pt-modified wo3 photocatalyst. Catalysts. 2020 May; 10(5): 557.
7. Sas, O. G., Domínguez, I., González, B., Domínguez, Á. Liquid-liquid extraction of phenolic compounds from water using ionic liquids: Literature review and new experimental data. [C2mim]FSI. Journal of Environmental Management. 2018 Dec 15; 228: 475-482.
8. Durazzo, A., Lucarini, M., Souto, E. B., Ciaca, C., Caiazzo, E., Izzo, A. A., et al. Polyphenols: A concise overview on the chemistry, occurrence, and human health. Phytotherapy Research. 2019; 33(9): 2221-2243.
9. Rothwell, J. A., Knaze, V., Zamora-Ros, R. Polyphenols: dietary assessment and role in the prevention of cancers [Internet]. 2017 [cited 2020 Aug 30]. Available from: https://www.ingentaconnect.com/content/wk/coCRM/2017/ 00000002/00000006/art00004.
10. Zhang, H., Tsao, R. Dietary polyphenols, oxidative stress and antioxidant and anti-inflammatory effects. Current Opinion in Food Science. 2016 Apr; 8: 33-42.
11. Siddiqui, R., Naz, S., Sayeeda, S. A., Ishteyaque, S., Haider, M. S., Tarar, O. M., et al. Antioxidant potential of the polyphenols in Grewia asiatica, Eugenia jambolana and Carissa carandas. Journal of Agricultural Science. 2013 Feb 17; 5(3): 217.
12. Subramanyam, M. D., Pai, S. R., Upadhya, V., Ankad, G. M., Bhagwat, S. S., Hegde, H. V. Total polyphenolic contents and in vitro antioxidant properties of eight Sida species from Western Ghats, India. Journal of Ayurveda Integrative Medicine. 2015; 6(1): 24-28.
13. Lucarini, M., Pedulli, G. F. Free radical intermediates in the inhibition of the autoxidation reaction. Chem Soc Rev. 2010 May 25; 39(6): 2106-2119.
14. Furia, E., Marino, T., Russo, N. Insights into the coordination mode of quercetin with the Al(III) ion from a combined experimental and theoretical study. Dalton Transactions. 2014 Apr 15; 43(19): 7269-7274.
15. M’hiri, N., Ioannou, I., Ghoul, M., Boudrioua, N. M. Phytochemical characteristics of citrus peel and effect of conventional and nonconventional processing on phenolic compounds: A review. Food Reviews International. 2017 Nov 2; 33(6): 587-619.
16. Xiao, J., Ni, X., Kai, G., Chen, X. Advance in dietary polyphenols as adolse reductases inhibitors: structure-activity relationship aspect. Critical Reviews in Food Science and Nutrition. 2015 Jan 2; 55(1): 16-31.
17. Anand, U., Jacobo-Herrera, N., Altimimi, A., Lakhssassi, N. A comprehensive review on medicinal plants as antimicrobial therapeutics: potential avenues of biocompatible drug discovery. Metabolites. 2019 Nov; 9(11): 258.
18. Estrela, J. M., Mena, S., Obrador, E., Benlloch, M., Castellano, G., Salvador, R., et al. Polyphenolic phytochemicals in cancer prevention and therapy: bioavailability versus bioeficacy. J Med Chem. 2017 Dec 14; 60(23): 9413-9436.
19. Abbaszadeh, H., Keikhaei, B., Mottaghi, S. A review of molecular mechanisms involved in anticancer and antiangiogenic effects of natural polyphenolic compounds. Phytotherapy Research. 2019; 33(8): 2002-2014.
20. Hazafa, A., Rehman, K-U., Jahan, N., Jabeen, Z. The role of polyphenol (Flavonoids) compounds in the treatment of cancer cells. Nutrition and Cancer. 2020 Apr 2; 72(3): 386-397.
21. Harbeoui, H., Hichami, A., Wannes, W. A., Lemput, J., Toumi, M. S., Khan, N. A. Anti-inflammatory effect of grape (Vitis vinifera L.) seed extract through the downregulation of NF-κB and MAPK pathways in LPS-induced RAW264.7 macrophages. South African Journal of Botany. 2019 Sep 1; 125: 1-8.
22. Habyarimana, E., Dall’Agata, M., Franceschi, P. D., Baloche, F. S. Genome-wide association mapping of total antioxidant capacity, phenols, tannins, and flavonoids in a panel of Sorghum bicolor and S. bicolor × S. halepense populations using multi-locus models. PLOS ONE. 2019 dic; 14(12): e0225979.
23. Sousa, V., Luís, Â., Oleastro, M., Domingues, F., Ferreira, S. Polyphenols as resistance modulators in *Arcobacter butzleri*. Folia Microbiol. 2019 Jul 1; 64(4): 547-554.

24. Cardoso, R. R., Neto, R. O., dos Santos D’Almeida, C. T., do Nascimento, T. P., Pressete, C. G., Azvedo, L., et al. Kombuchas from green and black teas have different phenolic profile, which impacts their antioxidant capacities, antibacterial and antiproliferative activities. Food Research International. 2020 Feb 1; 128: 108782.

25. Callcott, E. T., Blanchard, C. L., Snell, P., Santhakumar, A. B. The anti-inflammatory and antioxidant effects of pigmented rice consumption in an obese cohort. Food and Function. 2019; 10(12): 8016-8025.

26. Hurtado-Barroso, S., Martínez-Huélamo, M., De Álvarenga, J.F.R., Quifer-Rada, P., Vallverdú-Queralt, A., Pérez-Fernández, S., et al. Acute effect of a single dose of tomato sofrito on plasmatic inflammatory biomarkers in healthy men. Nutrients. 2019; 11(4).

27. Kodarahmian, M., Amidi, F., Moini, A., Kashani, L., Shabani Nashtaei, M., Pazhohan, A., et al. The modulating effects of Resveratrol on the expression of MMP-2 and MMP-9 in endometriosis women: a randomized exploratory trial. Gynecological Endocrinology. 2019; 35(8): 719-726.

28. Jakobek, L. Interactions of polyphenols with carbohydrates, lipids and proteins. Food Chemistry. 2015 May 15; 175: 556-567.

29. Eran Nagar, E., Okun, Z., Shipigelman, A. Digestive fate of polyphenols: updated view of the influence of chemical structure and the presence of cell wall material. Current Opinion in Food Science. 2020 Feb 1; 31: 38-46.

30. Tian, L., Tan, Y., Chen, G., Wang, G., Sun, J., Ou, S., et al. Metabolism of anthocyanins and consequent effects on the gut microbiota. Critical Reviews in Food Science and Nutrition. 2019 Mar 26; 59(6): 982-991.

31. Kumar, N., Goel, N. Phenolic acids: Natural versatile molecules with promising therapeutic applications. Biotechnology Reports. 2019 Dec 1; 24: e00370.

32. Rakers, C., Schwertfeger, S. M., Mortier, J., Duwe, S., Wolff, T., Wolber, G., et al. Inhibitory potency of flavonoid derivatives on influenza virus neuraminidase. Bioorganic and Medicinal Chemistry Letters. 2014; 24(17): 4312-4317.

33. Zima, V., Radilová, K., Kožišek, M., Albiñana, C. B., Karlukova, E., Brynda, J., et al. Unraveling the anti-influenza effect of flavonoids: experimental validation of luteolin and its congeners as potent influenza endonuclease inhibitors. European Journal of Medicinal Chemistry. 2020 Aug 22; 112754.

34. Ciesek, S., von Hahn, T., Colpitts, C. C., Schang, L. M., Friesland, M., Steinmann, J., et al. The green tea polyphenol, epigallocatechin-3-gallate, inhibits hepatitis C virus entry. Hepatology. 2011; 54(6): 1947-1955.

35. Chowdhury, P., Sahuc, M. E., Rouillé, Y., Rivière, C., Bonneau, N., Vandeputte, A., et al. Theaflavins, polyphenols of black tea, inhibit entry of hepatitis C virus in cell culture. PLoS ONE. 2018; 13(11).

36. Carneiro, B. M., Batista, M. N., Braga, ACS, Nogueira, M. L., Rahal, P. The green tea molecule EGCG inhibits Zika virus entry. Virology. 2016; 496: 215-218.

37. Lu, J. W., Hsieh, P. S., Lin, C. C., Hu, M. K., Huang, S. M., Wang, Y. M., et al. Synergistic effects of combination treatment using EGCG and suramin against the chikungunya virus. Biochemical and Biophysical Research Communications. 2017; 491(3): 595-602.

38. Zhang, L. L., Zhang, L. F., Xu, J. G. Chemical composition, antibacterial activity and action mechanism of different extracts from Hawthorn (*Crataegus pinnatifida* Bge.). Scientific Reports. 2020; 10(1): 1-13.

39. Xiao, J., Muzashvili, T. S., Georgiev, M. I. Advances in the biotechnological glycosylation of valuable flavonoids. Biotechnology Advances. 2014; 32(6): 1145-1156.