

Review article

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

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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.

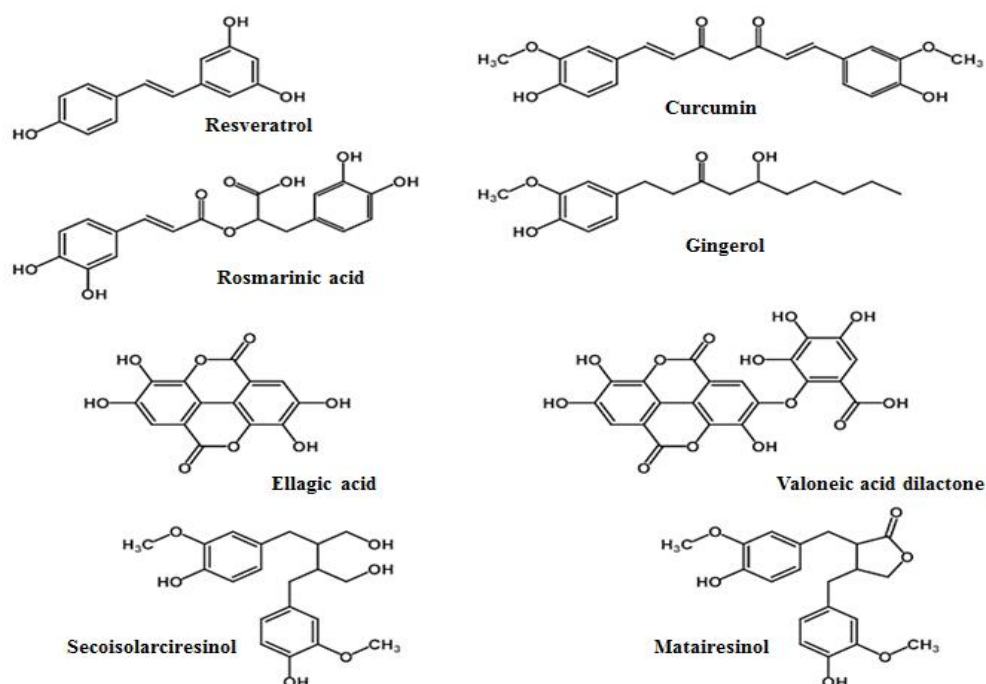


Fig. 1: Chemical conformation of polyphenol compounds

Polyphenol conformations vary based on the presence of substituents in their chemical structure. Examples of functional groups in polyphenols are cetic, 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).

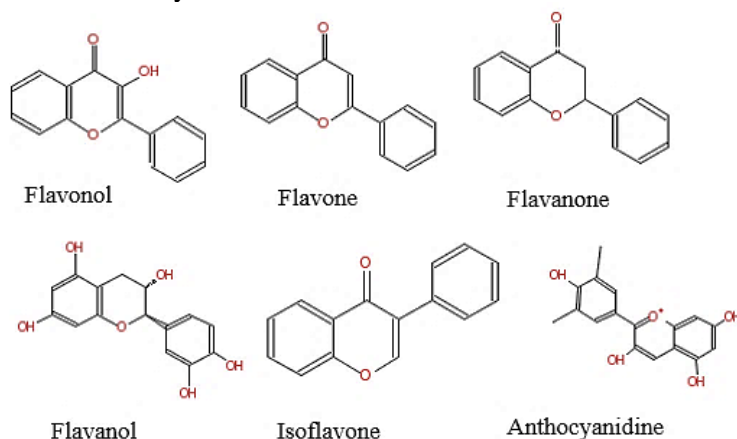


Fig. 2: Cyclic structures of common flavonoid-type polyphenols

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).

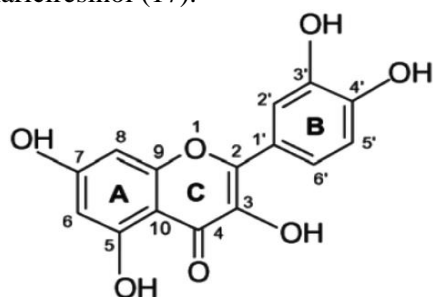


Fig. 3: General polyphenol cyclic representation and numbering

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- κ B 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.

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CONFLICT OF INTEREST

Authors declare no conflicts of interest.

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