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## Role of phenol derived biometabolic compounds in bioregulation

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### ABSTRACT

Phenolic compounds are mostly abundant plant derived secondary metabolite. These compounds are heterogeneous and approximately 8000 known compounds are available. Irrespective of very low bioavailability polyphenols are doubtlessly considered for numerous biological functions and therefore poor bioavailability/high bioactivity paradox is affirmed. Most of the dietary polyphenols have different type of beneficial biological functions, working as antioxidants, free radical scavengers, and metal chelators; they also evince numerous physiological functions. Phenolic compound consumption is considered decisive for maintaining a good health.

**Keywords:** *Naturally occurring phenolic compounds, bioactivity, metabolites*

### 1. Introduction

Phenol and phenolic compounds are among the most abundant and diverse group of compounds obtained from plants. These are a type of plant derived secondary metabolites having aromatic rings along with other subgroups. Generally they are found within our daily eatable fruits, vegetables, nuts and seeds. These compounds are also present in stems and flowers. Plants based human diets are enriched with these phenolic phytometabolites. Phenolic compounds are mostly heterogeneous types of biochemical present in plant originated foods. Till now there are approximately 8000 well known phenolic and polyphenolic metabolic derivatives consisting of typical phenolic

aromatic ring comprised with one or more hydroxyl substitutes along with their functional derivatives<sup>1</sup>. Phenolic compounds include different classes belong to polyphenols commonly known as flavonoids, tannins and lignins. The term polyphenols include various subgroups of phenolic acids and flavonoids which differ notably within bioavailability, physiological functions and most importantly in their structure. The classification was done according to their structure and origin. Structurally natural phenolic compounds have wide variety from simple molecule of phenolic acid to explicitly polymerized compound i.e. tannin. Most commonly available classes of phenolic metabolites are

flavonoids and phenolic acids. Phenolic acids are falling into two main group, benzoic acid derivatives and cinnamic acid derivatives<sup>2</sup>. Their classification is done based upon the backbone of C1-C6 and C3-C6 respectively. Phenolic derivatives are secondary metabolites, formed via shikimic acid and pentose phosphate pathway by metabolization of phenylpropanoid. Till now over 2,000 flavonoids have been discovered and they are identified in different subgroups such as anthocyanins, flavan-3-ols, flavones, flavanones, flavonols, and more.<sup>3</sup> The structural features of flavonoids comprised of a C6-C3-C6 backbone along with two C6 rings of phenol. Biological functioning of different flavonoids are determined by their structure and pattern of glycosylation. Catechins are made up of flavanols or flavan-3-ols that are the isomers having *trans* configuration and *cis* configuration commonly known as epicatechins. Some polyphenolic amides bear N-containing functional substituents such as capsaicinoids. Other than phenolic and flavonoid there are other phenolic metabolites such as resveratrol occurs in grapes and red wine, from berries ellagic acid, flax gives lignans, turmeric provides curcumin, and herbs spices provide rosmarinic and ellagic acids. Phenolic compounds or polyphenols can serve as antioxidants because they are capable of scavenging singlet oxygen or free radicals produced in cells.<sup>1</sup> In plants, phenolic metabolites can execute multiple functions such as antimicrobials, natural pesticides, pollinator attractant, protection from abiotic

UV radiation, signal substances and insulating material and cell wall component such as lignin. However, animals, including humans are not capable of synthesizing phenolics in their cells and therefore they obtained them solely from intake of diet which are plant-based.

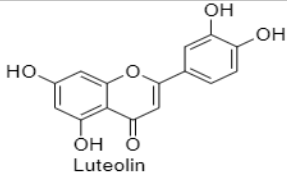
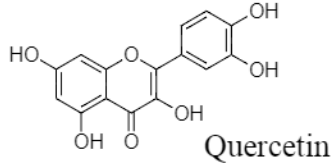
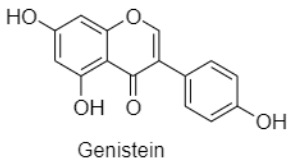
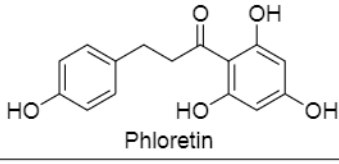
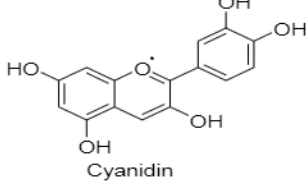
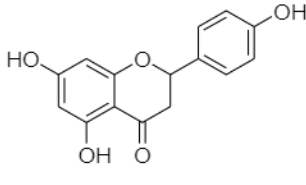
Chemical variability make the phenolic compounds useful for various functional application. These dietary polyphenols have attained attraction due to their beneficial biological functions. They work as antioxidants and metal chelators; they also display different physiological functions which include anti-inflammatory, antimicrobial, antiallergic, antihypertensive, anticarcinogenic and antiarthritic properties. Previous reports denote that dietary polyphenols are absorbed in the system poorly and they are metabolized with the help of phase-I and phase-II enzymatic actions in enterocytes and liver<sup>4</sup>. These biometabolites can undergo intensive biotransformation when gut microbiota acts upon them. It has been found that below 5% of the total consumed polyphenol is absorbed first before coming to the plasma as in unaltered form<sup>5</sup>. Irrespective of their low bioavailability polyphenols are no doubt considered for various biological functions and as a consequence low bioavailability/high bioactivity paradox is asserted. Phenolic compound consumption is considered decisive for maintaining a good health. The present review focuses on the role of phenolic bioactive metabolites in health benefits.

### **Structural overview of some common phenolic compounds**

There are different classes of flavonoids. Some of common flavonoid classes with examples are given below-

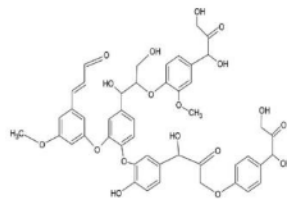
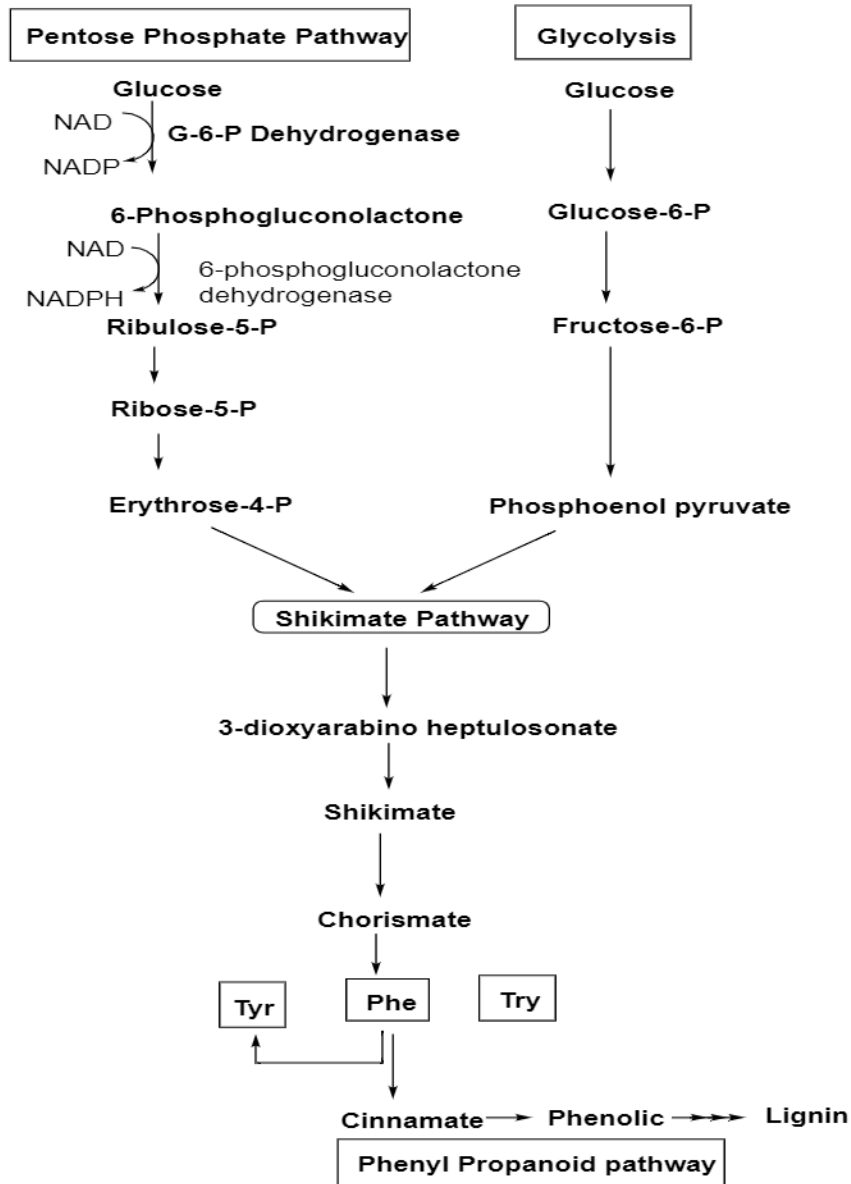
- i. Flavones- Luteolin;
- ii. Flavonols-Quercetin;

- iii. Isoflavones-Genistein;
- iv. Chalcones-Phloretin;
- v. Anthocyanins-Cyanidin;
- vi. Flavanones-Naringenin.

Class	Example of Flavonoid and Structure	Natural Sources
i. Flavones	 <p>Luteolin</p>	Carrots, Green Pepper, Broccoli, Dandelion
ii. Flavonols	 <p>Quercetin</p>	Vegetables, Fruits and spices
iii. Isoflavones	 <p>Genistein</p>	Soyabeans, Fava beans, Red Clover
iv. Chalcones	 <p>Phloretin</p>	Fruits and Vegetables
v. Anthocyanins	 <p>Cyanidin</p>	Fruits, Vegetables, Nuts and dried fruits
vi. Flavanones	 <p>Naringenin</p>	Fruits such as grapes

**Figure 1 :** Structures of some flavonoids with their classes.

**Biosynthetic pathway of phenol production**



**Figure 2:** General pathway depicting the production of phenolic derivatives in plants (adapted from Vattem et al., 2005).<sup>6</sup>

## 2. Discussion

### 2.1 Roles of Phenolic Metabolites in biological system

#### Antimicrobial Activity-

Now days the infections resulted due to multi-antibiotic-resistant pathogens are major concern for the worldwide community. It was found that lipophilic hydrocarbons accumulate in the membrane lipid bilayer, altering the structural integrity as well as functional properties of these membranes. As a result of these there is an increased permeability to protons and ions occur. This might cause unrepairable injury to the plasma membrane and coagulation of contents present inside the cell which can perturb actions and functions of intercellular enzymes. The interest is growing towards the identifications of molecules that can eliminate the bacteria other than impeding their growth. Bactericidal activity is generally termed as activity causing a reduction in 99.9% bacterial population and is measured by time-kill method or minimum bactericidal concentration (MBC) assay.<sup>7</sup> Reports of some membrane mimicking model denoted flavonoids can lead to aggregation and this effect was also observed in bacterial cells. The antibacterial activity may be attributable to the bacterial cell by three mechanistic processes. It includes damage in the plasma membrane created by puncture and/or a loss of membrane fluidity as mentioned earlier. Next to that pathway is the halting of nucleic acid synthesis by inhibiting topoisomerase activity and perturbation of metabolic processes of energy formulation by inhibition of NADH-cytochrome c reductase. Flavonoids can react by impeding together energy metabolism along

with synthesis of DNA. With the advancement of science there are some other mode of actions was noted for example in bacteria which are Gram-positive, there was report of perturbation of energy generation (ATP) process along with alternation of intracellular pH. Other phenolic compounds such as condensed phenylpropanoids-tannins might persuade impairments at the cytoplasmic membrane. There are numerous current studies which depicts augmenting the functional activity of the antibiotics by the flavonoids. Galloylflavan-3-ols such as epicatechin gallate caused reduction of minimum inhibitory concentrations (MICs) of  $\beta$ -lactam antibiotics toward few strains of methicillin-resistant *S. aureus* (MRSA) by 512 times.<sup>8</sup> Quorum sensing is a type of cell-cell cross talk process which bacterial species generally use for the regulatory directions of virulence, involving formation of biofilm. Current reports justify, flavonoids can distort interlinkage between acyl-homoserine lactones (a type signaling compound utilized by Gram-negative bacteria) and pertaining receptors. The pathogen of gastric track, *Helicobacter pylori* releases urease at the time of infection to ensure its survival at the very low pH environment of stomach. Toxins found to exhibit a significant function in the pathogenesis of bacteria, some instances lead to fatal disease after the pathogen kill themselves. Various reports suggest that flavonoids are capable of neutralizing these type virulence components. More over in inclusion to direct and synergistic

antibacterial functional action, there are developing instances where flavonoid molecules hinder many virulence factors of

### Antiviral Activity-

Intakes of antiviral drugs are capable of fostering the spreading of mutant virus variants. It is their inherent tendency by the virtue of which they are exerting this effect. There is a continuous effort by biomedical researchers for advanced antiviral drugs with least or minute sequel towards selection of mutant variants and they should not be harmful towards the host. Flavonoid antivirus studies have attracted attention in the beginning of 1980s, after the detection of human immunodeficiency virus type 1 (HIV-1). As an ameliorative agent plant products are used in human disease from time beginning of the civilization. But during the last couple of year the usage of plant derived biometabolites especially in

bacteria, encompassing toxins, enzymes and other receptors responsible for receiving signals.

the area of antiviral disease have been widely investigated. The plant flavonoids belonging to the catechin group mostly epigallocatechin gallate (EGCC) and proanthocyanidins (PACs) have shown promising anti inflammatory, antiviral activities.<sup>9</sup>. Based on the literature evidence it might not be unrealistic to postulate that some of the flavonoids would be able to perform synergistically as antimicrobial/ antiviral moieties. For investigating mechanism behind the flavonoid linked antiviral action the viral species in query (for example HIV-1, influenza, rotavirus, HSV, canine distemper virus, pseudorabies, HBV, Japanese encephalitis virus) were studied.



**Figure 3:** Structure of epigallocatechin gallate (EGCC) and proanthocyanidins (PACs)

An EGCG-linked reduction of viral infection was also observed in naked viruses e.g., enterovirus 71, adenovirus etc. Antiviral activities of various flavonoids vary according to its conformational property. It was found that the flavonol kaempferol (kae) and the flavone luteolin worked synergistically towards herpes simplex virus 1 in comparison with the sole

action of the mentioned flavonoids, whereas the antiviral property engaging in combinations of other flavonoids proved to be less efficacious in nature. The rabies virus comes from Rhabdoviridae family of Lyssavirus genus and comes under single strand negative sense RNA virus. Depending upon evidences, numerous alkaloids, flavonoids, polyphenols, saponins exhibited

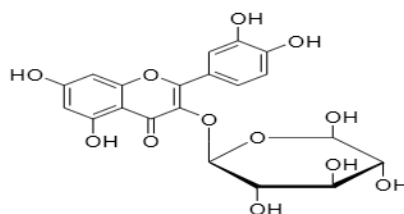
their ability to inhibit it by blocking adherence, duplication and/or maturation at the time of viral propagation. Studies with influenza virus infected mice showed, significant reduction of pro-inflammatory chemokine released in organ lungs after the oral administration of total alkaloids of

*Commelina communis*. The alkaloids belonging to the category of quinolizidine and isoquinoline have exhibited effect on synthetic machinery of proteins of virus whereas other category of alkaloids can augment on different replicative phases of virus.

### Effect on Cardiovascular system –

Polyphenols are plentiful constituents of human diet and they are found to attribute to prevent many degenerative diseases, which also includes cardiovascular diseases. Various *in vivo* and *in vitro* studies provide instances towards protective function of polyphenols against cardiovascular diseases. Polyphenols are metabolized in the tissue and they might exert their effect by modifying their native structures. In animal system the role of polyphenol enrich solution extracts (grape juice, pomegranate juice) exhibited reduction of the atherosclerotic lesion. Quercetin and resveratrol are found in red wine or natural grapes juice can reduce myocardial sufferings. Polyphenols are capable of affecting some markers of oxidative stress in a transient manner. Polyphenol intake caused to lower the level of total cholesterol, LDL-cholesterol, apolipoprotein B or lipoprotein (a), or an increment of high-density lipoprotein (HDL)-cholesterol and apolipoprotein A-I. This type of development in the lipid profiles were following the consumption of polyphenols out of olive oil (quercetin, oleuropein), cocoa (proanthocyanin), tea (rutin) or from

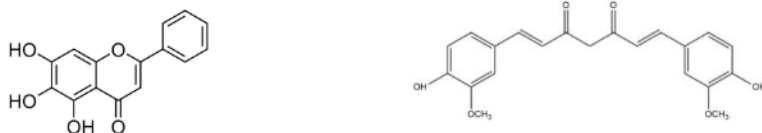
red clover (genistein). Whereas in case of both normo and hypercholesterolemic issues exhibited advancement or no alternation in the factors of lipid. Malfunction of vascular endothelial cells are normally calculated with the help of flow-mediated dilation (FMD) of the brachial artery. Studies also reported white wine revamped the weakened endothelium action in adults who suffers from coronary heart ailment. Such kind of progression of FMD was observed upon long-time intake of black tea in conditions of mild hyperlipemia. Several biomarkers measuring the risk of cardiac diseases are affected by the intake of phenol-rich supplements. Some of these polyphenols are hugely bioavailable whereas some are poorly absorbed via gut barrier. Moreover, each polyphenol may be present in foods in various forms, which can influence the absorption in the intestinal gut. Quercetin glucosides found in onions are absorbed highly. Whereas optimal doses of polyphenol required to prevent cardiovascular diseases could be more accurately determine by studying the bioavailability of the components.



**Figure 3:** Structure of Quercetin-3-glucoside**Role in Anti aggregation-**

Various derivatives of phenolic molecules have been shown to exhibit their anti aggregation property on amyloid formation. Various evidences denote that fibrilization of amyloid proteins engage in a vital role in amyloid-related malfunctions, including Alzheimer's disease, prion diseases, and type 2 diabetes.<sup>10</sup> Although the amino acid sequences are not related and tertiary conformations are unrelated, despite of these they can undergo unfolding and assemble themselves into fibrillar ultrastructures having similar biochemical characters, including long and branchless fibrils which is supplemented with  $\beta$ -sheet conformation. Treatment of amyloid-related disorders by preventing formation of amyloids and disruption of the assemblies of fiber are among newly proposed therapeutic strategies. Besides these inhibitors of enzyme, hormones, several antagonists, antibodies, various peptide fragments, synthetic ligands and natural polyphenols have been also screened rigorously for their potency as candidates of anti-amyloidogenic molecule. Various polyphenolic molecules such as naringenin, exhibited active roles in perturbing amyloid formation and disorganization of preformed fibrils of amyloids. The antioxidant characters of polyphenolic molecules are involved in the antiaggregation behavior of the molecules.

The relationship of structure–activity by polyphenol towards amyloidogenesis was investigated through in vitro studies on lysozyme model by using phenol, catechol, resorcinol and hydroquinone molecules. Studies suggested that catechol & hydroquinone are much prone to oxidative stress than resorcinol and phenol. The fact of catechol and hydroquinone effectively inhibited amyloid formation implicated lies on the matter that mainly quinone form, engaged in the anti-amyloidogenic function of phenols. Another systematic report depicted that polyphenols such as Cur, Baicalein, EGCG, and resveratrol in amalgamation with  $\beta$ -cyclodextrin act synergistically to inhibit  $\alpha$ S (alpha synuclein) aggregation. In vitro and in vivo reports with rifampicin exhibited that its phenolic structure is capable of inhibiting the low order oligomerization made of A $\beta$ , tau and  $\alpha$ S with the abatement of synapse loss and triggering of microglial cells. Besides these, the dietary polyphenols and bioactive metabolites which are formed by the gut microbiota are efficacious in altering the development and advancement of motor malfunction in an in vitro model system of  $\alpha$ -synucleinopathy. In future more elaborative studies with these polyphenolic compound could open a new arena in anti amyloidosis of protein.

**Figure 4:** Structure of Baicalein and Curcumin(Cur)

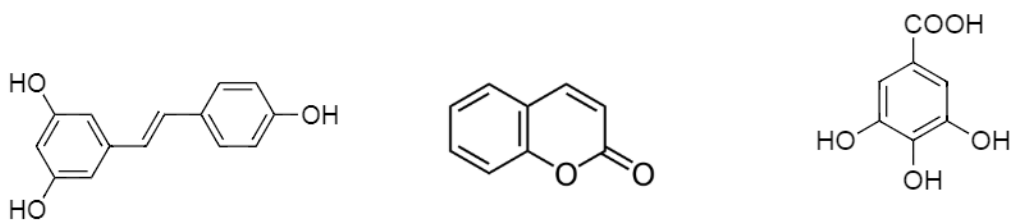


### Antioxidative property-

Radical species are generated within our body as a part of normal metabolic function. Radicals are compound with free/unpaired electrons. They can cause oxidative damage if they are not removed. They are very much reactive. Excess radicals can cause oxidative stress and it might lead to negative impact on cellular metabolism. Molecules which can scavenge radicals are regarded as antioxidant compound. Many molecules in food have antioxidant functions which are able to interact with reactive compounds. Among the vitamins C and E, provitamin  $\beta$ -carotene and the selenium a trace element are the major antioxidant nutrients. Besides these, other chemical molecules obtained from plant foods such as flavonoids and polyphenols (for example anthocyanins, coumarins and resveratrol) are also serve as strong antioxidants.

Many evidences suggest that generation of free radical species and oxidative stress are entailed in the pathogenesis of diabetes and in future it leads to the development of diabetic complications. Studies reported that supplementation of antioxidant can decrease the complication in diabetic individual.

Increased oxidative stress can negatively impact the integrity as well as the function of blood cell parameters. Seeds of fenugreek (enrich in gallic acid, caffeic acid, and chlorogenic acid) exhibited its defensive role against hydrogen peroxide ( $H_2O_2$ ) influenced oxidation in normal person and diabetic individual erythrocytes (RBCs). Some of the ailments are found to be linked with elevated tier of radicals in the cellular systems. In case of rheumatoid arthritis (RA), where joint tissues have an elevated level of activated neutrophils which are responsible for secreting radicals, such as  $O_2^-$ . Other disease conditions in which ROS are implicated involves atherosclerosis, myocardial infarction, adult respiratory distress syndrome (ARDS) and few types of cancer. These phenolic compounds are capable of maintaining intracellular  $Ca_2^+$  level and it is necessary for intracellular signaling and regulation of various processes. Hence, the capability to scavenge free radicals can perturb the outset of a disease, alter/delay the progression of the ailment or relieve some of its exhibited traits.



**Figure 5:** Structure of Resveratrol, coumarin and gallic acid.

### 3. Conclusion

In recent years the presence of bioactive phenolic molecules in food has gathered much attraction. Long-term consumption of bioactive compounds in fruits and vegetables may exert a protective effect on the organism and must be considered as part of an overall strategy against multifactorial disorders. Current investigation on medicinal chemistry suggests various structural configurations which ameliorate the antibacterial functions of flavonoids. Inception of such correlations is crucial if the activity of flavonoid is to be optimized. In inclusion to direct and synergistic

antibacterial role, there is increasing supports that flavonoids obstruct with different kinds of bacterial virulence components which includes enzymes, toxins and signal receptors. High phenolic antioxidant function denotes that some phenolic molecules are available in some species, which might evince to be favourable for human health as a portion of healthy diet. If the bioavailability of these phenolic compounds could be improved through some modification of the subgroups then it will be a boon for therapeutic supervisions.

### Conflicts of Interest

The authors declare no conflict of interest.

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