Chapter 9
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An Overview on Pharmacological Effects of Few Phytopolyphenols from Dietary and Herbal Origins

Bharti Ahirwar [a*], Dheeraj K. Ahirwar [b], S. K. Lanjhiyana [a] and Sanmati K. Jain [a]

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ABSTRACT

The objective of the present chapter is to highlight the immunomodulation, antioxidant, anticancer, anti-inflammatory, antibacterial, and antiviral properties of phenolic compounds. Various research studies authenticated that these phytopolyphenols cause lesser side effects and toxicity in comparison to synthetic or chemical drugs of modern days in human subjects. These polyphenols were used in the form of dietary food, plant extracts, or active phytoconstituents compounds respectively. Today's world populations were directly or indirectly dependent on these polyphenols in the form of dietary or herbal medicines due to resultant healthcare benefits. The present chapter included a few types of polyphenols viz., flavonoids, lignans, phenolic acids and their analogs, tannins, quinines, etc. for the reasons of possible biological activities in human bodies.

Keywords: Dietary polyphenols; phytoconstituents; flavonoids; tannins; lignans; structure activity relationship; immunomodulators; anticancer; anti-inflammatory; antibacterial etc.

1. INTRODUCTION

In the current pandemic, conditions immunomodulators are playing a pivotal role and polyphenols or phenolic compounds are getting great attention due to their immunomodulation properties. Chemically, it is secondary plant metabolite possessing one or more aromatic rings with hydroxyl groups. Polyphenols derived from shikimate phenylpropanoid or polyketide pathway, without nitrogen-based functional group with 500 to 3000 Da molecular weight and water-soluble. These phenolic compounds involve in defence mechanism and germination process of plants. Apart from immunomodulation, antioxidant, anticancer, anti-inflammatory, antibacterial, and antiviral properties of phenolic compounds are attracting researchers. Most the nutraceuticals are rich in polyphenols or phenolics to prevent several oxidative stress-related diseases through antioxidant nature and promote health attracted researchers and nutraceutical manufacturers towards these wonderful secondary plant metabolites. Phenolic compounds with low molecular weight are used as antiseptics [1 – 5].

2. DIETARY POLYPHENOLS

Dark green and bright coloured vegetables, legumes, cereals, spices, and fruits are rich in polyphenols. Green and black tea contains about 30% phenolic compounds of their dry weight. Coffee contains chlorogenic acid and red wine consists of anthocyanin as phenolic compounds in high concentration [6 – 11].

3. TYPES OF POLYPHENOLS

Polyphenols are categorized on the basis of one or more aromatic rings which contain one or more hydroxyl groups. Flavonoids, lignans, phenolic acids, and their analogs, tannins, and quinines are

[a] *Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur (C.G.)- 495009, India.*
[b] *School of Pharmacy, Chouksey Engineering College, Bilaspur (C.G.)- 495001, India.*
**Corresponding author: E-mail: ah_bharti@yahoo.com;*

some types of polyphenols in which the number of phenolic rings and structural elements are linked with aromatic rings [4, 12, 13].

3.1 Flavonoids

Phenylbenzopyrone is the key skeleton of flavonoids in which 2 aromatic rings are connected with 3 oxygenated carbons in the C or pyran ring. These flavonoids can be grouped on the basis of saturation level and opening of the central pyran ring and they are categorized mainly into flavones, flavonols, flavanones, flavanols, anthocyanins, chalcones, isoflavonoids, and bioflavonoids. Flavonoids occur either in free or conjugated form in nature. Plants contain flavonoids in aglycone form while certain classes are colourless and some are coloured such as flower pigments [14 – 16].

3.2 Tannins

These polyphenolic compounds are water-soluble having a molecular weight from 500 – 4000. Tannins are classified into hydrolysable (gallo and ellegi) and condensed (proanthocyanidins) tannins. Hydrolysable tannins are complex polyphenols with polyester basic units degraded into sugars and phenolic acids through pH change, and enzymatic or nonenzymatic hydrolysis. Catechin or leucoanthocyanidins polymer is known as condensed tannins. These are constituted the main phenolic fractions that produce characteristics of astringency of vegetables and not hydrolysed by acid treatment [17, 18].

3.3 Chalcones and Coumarins

In food, chalcones are found as intermediate in the biosynthesis of flavonoids in the form of phloretin and its analogs such as glucoside phloridzin, chalconarigenin, and arbutin. Phloretin and phloridzin are the characteristics flavonoids of apple, chalconarigenin is for tomatoes and arbutin is for pears. Polyphenolic compounds with basic skeleton C6 and C3 are known as coumarins. These are lactones obtained by cyclization of cis-ortho-hydroxycinnamic acid. In nature, it is found as hydroxylated C7 coumarins. Hydroxylcoumarins, furocoumarin, isofurocoumarin, pyranocoumarins, bicoumarins, and dihydro-isocoumarins are some common coumarins. Coumarins or lactones are also formed by isomerization and hydroxylation of the structural analogs trans-hydroxycinnamic acid and derivatives [19, 20].

3.4 Lignans

Bioactive, non-nutrient, and non-caloric polyphenolic plant constituents are known as lignans found in flax and sesame seeds in the highest concentration whereas grains, fruits, vegetables, and other seeds contain in low concentration. Enterolignan is metabolite of food lignans found in human urine and plasma produced by human intestinal bacteria. Lignans are present in plants in free form and are derived from cis-o-hydroxycinnamic acid. Lignanolides, cyclolignanolides, bisepoxylignans, and neolignans are the main lignan components [21].

3.5 Phenolic Acids and Analogs

Phenolic acids are widely occurring in plants either in free or conjugated forms as amide or esters. Hydroxybenzoic acids (gallic acid, p-hydroxybenzoic acid, protocatechuic acid, vanillic acid, and syringic acid) and hydroxycinnamic acids (ferulic acid, caffeic acid, p-coumaric acid chlorogenic acid and sinapic acid) are the chief phenolic acids. Due to the structural similarity of capsaicin, rosmarinic acid, gingerol, gossypol, paradol, tyrosol, ellagic acid, cynarin, and salvianolic acid are considered as phenolic acids analogs [22].

3.6 Quinones

Nonesanthraquinones, phenanthraquinones, naphthoquinones, and benzoquinones are the natural quinones found in medicinal plants. Anthraquinones are the major class of natural quinones and

widely occur in medicinal and dietary plants than other natural quinones. The hydroxyanthraquinones normally have 1 to 3 hydroxyl groups on the anthraquinone structure [23].

4. PHARMACOLOGY OF INDIVIDUAL POLYPHENOLS

4.1 Flavonoids

The pharmacological actions of flavonoids are interrelated to their structures such as flavonoids produce chelate transition with metal ions which inhibits reactive species formation. Also, inhibit biomolecular damage, prevent carcinogen metabolic activation, induce apoptosis, promote differentiation, modulate multidrug resistance and inhibit proliferation and angiogenic process [24 – 31].

4.1.1 Antioxidant activity

More hydroxyl groups present in flavonols exhibit significant radical scavenging activity, for instant myricetin, quercetin, rutin, and quercetin are well-identified effective antioxidants. Flavanols contain an additional 3-galloyl group (catechol structure) which considerably improves antiradical activity. Furthermore, hydroxyl group glycosylation and substitution may also affect the antioxidant activity [32]. Several EGCG and EGC (catechins) exhibited noteworthy radical scavenging activity through metal ions chelation and avert free radical formation. Vicinal dihydroxy or trihydroxy of precise chemical structure add to their compelling antioxidant activity. EGCG could restrain telomerase, LOXs, and DNA methyltransferase; decrease the appearance of COX-2 (cyclooxygenase) and commencement of NF-κB and AP1; obstruct c-Jun N-terminal kinase (JNK) and p38 MAPK-related signalling pathways.

4.1.2 Antimutagenic activity

Genistein, luteolin, quercetin, ECG, EGCG, silymarin, and apigenin illustrate antiangiogenesis and antimutagenic properties.

4.1.3 Anti-inflammatory activity

As well 7 flavonoids and their analogs, daidzein, hesperetin, kaempferol, and myricetin all have anti-inflammatory. In accumulation, apigenin, genistein, quercetin, EGCG, and silymarin could stifle the commencement of NF-κB and AP1 and wedge signal transduction pathways. Silymarin also disallowed the initiation of apoptosis and dormant protein kinases and MAPKs [33, 34].

4.1.4 Antitumor activity

Genistein (soy isoflavone) is an angiogenesis inhibitor that could restrain the expansion of new blood vessels and showed antitumor and antiangiogenic activity in mouse models of melanoma and breast cancer. In addition, some isoflavones (e.g., genistein and daidzein) are phytoestrogens and could imitate the biological activity of estrogens and modulate steroid hormone metabolism. Consequently, they might play a significant role in breast cancer deterrence [35,36]. Quercetin is one of the most compelling antioxidants and has antioxidant, anti-inflammatory, antiproliferative, or apoptotic effects. At the molecular level, quercetin acts as an anticancer agent through cell cycle intonation, and antioncogenesis. Moreover, quercetin can restrain the activity of caspases-3, protein kinases, telomerase, lymphocyte tyrosine kinase, different tyrosines, and serine-threonine kinases; augment the expression of nicotinamide adenine dinucleotide phosphate (NADPH); reduce lipoperoxidation, NO production and iNOS (inducible nitric oxide synthase) protein expression, and levels of some oxidative metabolites; prevent lactate dehydrogenase (LDH) leakage.

4.2 Structure Activity Relationship

Flavonoids are well-known natural antioxidants. Structurally, the antioxidant action of flavonoids is due to the presence of hydroxyl groups in the 3’ and 4’ positions of the ring. These positions of the

OH group provide the high permanence to the formed radical through dislodgment of the electron and between C2 and C3 carbon double bond of ring C collectively at position C4 with the carbonyl group, which makes the disarticulation of an electron likely as of ring B. Furthermore, positions 3 and 5 of rings C and A respectively with joint carbonyl group in position 4, are as well significant for the antioxidant potential of these compounds [37, 38].

4.3 Toxic Effects

The popularity of flavonoids as antioxidants generally overlooked their toxicity. It acts as mutagens and pro-oxidants at higher doses. A high dose of flavonoids formed free radicals which inhibit the key enzymes implicated in hormone metabolism. Therefore, caution should be taken in ingesting flavonoids since the unfavourable effect may eclipse the useful ones. Further, if flavonoids cross the placenta, foetus may be at high risk [39 – 44].

4.4 Tannins

Antioxidant properties of tannins (Hydrolysable and condensed) depend on the size of the tannin molecule. As bigger tannin molecules possess powerful antioxidant action due to the presence of many OH groups or galloy and ortho-dihydroxyl groups. Tannins also exhibit significant antibacterial, antiulcer, anti-inflammatory, antileishmanial, antimutagenic, enzyme regulating, signal transduction pathways blocking, and apoptotic activities; therefore, they have wide paying attention for cancer therapy [45 – 49].

4.4.1 Anticancer activity

In colon cancer, gallotannin exhibited significant anticarcinogenic activity. Fraction of strawberry extract containing hydrolysable tannin was found most effective as a mutation inhibitor. Chebulinic acid regulates transcriptional activation of erythroid related genes (gamma-globin and NF-E2) and also inhibits acetylcholinesterase and hemoglobin synthesis in human leukemia K562 cells differentiation [50 – 52].

4.5 Stilbenes

Stilbenes, particularly resveratrol, have potential antioxidant, antibacterial, antiviral, anti-inflammatory, and anticancer activities. Resveratrol can influence the processes underlying all 3 stages of carcinogenesis i.e. tumor initiation, promotion, and progression, and also, stifle angiogenesis and metastasis. Widespread data in human cell cultures indicated that resveratrol could modulate multiple pathways involved in cell growth, apoptosis, and inflammation; and resveratrol and its hydroxylated analogs also possess antileishmanial activity [53 – 56].

4.5.1 Anticancer activity

Resveratrol and its analogs showed anticancer activity through triggering several intracellular pathways leading to arrest of cell growth, inhibition of PKC activation, preventing free radicals production, downregulation of β-catenin expression, biogenesis of mitochondria, inducing gene for oxidative phosphorylation, and inhibit NF-κB and AP1 mediated signal transduction pathways. Stilbenes also inhibit DNA topoisomerase III [57].

4.5.2 Lignans

Briefly, lignans have anti-inflammatory, antibacterial, antiviral, antiallodynic, antiangiogenesis, and antimutagenic properties through signal transduction pathways, and hormone metabolism. Lignans enhance detoxification and induce apoptosis by cell cycle arrest. It also reduces human breast cancer cell adhesion, invasion, and migration in vitro. Lignans are also considered phytoestrogen.

4.5.3 Anticancer and anti-inflammatory action

Sesamin is reported as an anticancer, anti-inflammatory, and antioxidant drug. Sesamin may be used to treat human leukemia, stomach, breast, and skin cancer cells through apoptosis and cell cycle arresting pathway. Podophyllotoxin is used as DNA topoisomerase II inhibitors to treat cancer.

Flaxseed contains 95% lignans as secoisolariciresinol diglucoside (SDG). It also contains omega-3 fatty acids, α-linolenic acid, lignan, and fibers. SDG used as an antiestrogenic agent which binds with cell receptors and decreases cell growth in breast cancerous cells. Omega-3 fatty acids and α-linolenic acids have been shown to suppress the growth, size, and proliferation of breast cancer cells. Flaxseed synergized the action of tamoxifen in tumor size reduction to a greater extent. Many clinical trials support the importance of flaxseed in breast cancer treatment mainly in postmenopausal women. Approximately 32 g daily consumption of flaxseed can reduce breast cancer jeopardy. Lignans as well diminish the risk of breast cancer. A study suggested that 70% of newly breast cancer patients should consume 52% of flaxseed and lignans-rich food at least once a week [58].

4.5.4 Coumarins

In human lung carcinoma cell lines, coumarin and 7-hydroxycoumarin have been shown to antitumor activity through cell proliferation inhibition and apoptosis (arresting cell cycle in the G phase). 6, 7-dihydroxy coumarin (Esculetin) has been exhibited inhibition on lipoxygenase activity in cell proliferation through modulating P signal transduction pathway in cultured rabbit vascular smooth muscle cells [59].

4.5.5 Anti-inflammatory and antipyretic activity

Coumarin inhibits histamine release from mast cells leading to mild adrenergic activity. Coumarin prevents noradrenalin metabolism by inhibiting the catechol-o-methyltransferase enzyme thus terminating adrenergic signals and producing a spasmolytic effect. Anti-inflammatory and antipyretic effects are also demonstrated by coumarin. Other significant pharmacological properties of coumarin and its derivatives are in the treatment of high protein lymphedema (HPLO), chronic infections, immune disorders, and cancer [60].

4.6 In Treatment of Melanoma

Many trials are tried to establish the effectiveness of coumarin in chemotherapy of melanoma. In 1954 FDA banned coumarin on the basis of animal study as indicated its hepatotoxicity.

4.6.1 Quinones

Hydroxyanthraquinones are one of the natural quinones with antioxidant properties. Quinones with orthodihydroxy structures such as hydroxyanthraquinones, purpurin, pseudopurpurin, and alizarin is more effective than those without orthodihydroxy structures such as emodin, chrysazine, rhein, chrysophanol, and aloe-emodin [61].

4.6.2 Cytotoxic effect

Quinines produced cytotoxicity through quinone redox cycling. Quinones are easily reduced into hydroquinones and semiquinones. Molecular oxygen oxidised semiquinones lead to the generation of reactive oxygen species (quinone redox cycling). These ROS lead to oxidative stress or oxidant-antioxidant imbalance and interacts with biomolecules (lipids, protein, RNA, and DNA) to cause irreversible damage in DNA strand breaks, DNA intra-strand breaks, and DNA protein cross-links. Oxidative stress induced through quinone redox cycling can cause DNA strand breaks, DNA intra-strand breaks, and DNA protein cross-links. It is well-known that these DNA lesions can activate apoptosis through p53, checkpoint kinase-1, and checkpoint kinase-2. ROS also breaks mitochondrial membranes leading to release the of pro-apoptotic agents (cytochrome c and Apoptosis Inducing Factor) which activate apoptosis. GSH (glutathione) level may deplete by a higher concentration of intra-cellular quinines leads to enhanced alkylation of SH dependent proteins which activate the pancreatic endoplasmic reticulum kinase pathway causing ER-stress-induced cell death. It is consequently obvious that quinone compounds can activate some intracellular signalling pathways to activate apoptosis. Quinines (emodin) may play a role as a biomarker in chemoprevention through inhibiting DNA binding and casein kinase-2 and inducing pRb-preventable G2/M cell cycle arrest and apoptosis. Also, block signal transduction pathway and modulate kinase function [62].

5. ANOTHER POLYPHENOLS AND THEIR BENEFICIARY EFFECT ON HUMAN

Carbohydrate-rich foods (potatoes and cereal) produced high levels of acrylamide after frying and baking. International Agency for Research on Cancer classified this acrylamide as carcinogenesis. Further various heterocyclic amines (HCAs) have been isolated as mutagens from a variety of thermally processed food materials (cooked meat and fish and pyrolysis products of amino acids and proteins). Numerous toxicological studies demonstrated earlier that acrylamide and HCA were genotoxic and carcinogenic.

Natural phenolic compounds obtained from plant extracts such as ginkgo, green tea, grape, soy, rosemary, bamboo, berries, and many more suppress the acrylamide and heterocyclic amines induced mutagenesis and carcinogenesis also, reduce the formation of acrylamide, polar and non-polar HCAs in various heat-treated cooked foods to varying extents. Polyphenols from tea and its epigallocatechin-gallate (EGCG) and theaflavin constituents inhibit tumorigenesis. Efficacy of phenolic compounds depends on the concentration of its active constituents in the target tissue and therefore route of administration and bioavailability of these compounds are carefully considered in the inhibitory effect in cancer tumors. Polyphenols significantly affect the intestinal microbiota, inflammation, and free radicals. These compounds are metabolized and biotransformed into simple aromatic carboxylic acids known as phenolic acids by intestinal microbiota. These metabolized bioactives are more active than polyphenols (precursors) in gastrointestinal diseases and colorectal cancer.

6. CONCLUSION AND PROSPECTS

Above all facts suggested that natural phenolics intervened at all the stages of cancer progression. Further, antioxidant property and inhibition of cancer development by polyphenolics rely on several fundamental cellular mechanisms and basic machinery. Furthermore, the extensive research on polyphenols and their active constituents will provide a plate form for their possible therapeutic effectiveness in oncology. Many clinical evidences have suggested that chemotherapy by natural polyphenolics is an economical, readily available and applicable, acceptable, and accessible approach to eradicating cancer. Many researchers had reported for bioactivity of dietary polyphenols and the multifaceted role of phyto-derived polyphenols in nano drug delivery systems has also been reported [63, 64]. Nevertheless, more scientific research on health benefits and the possible risks of polyphenols is needed to ensure their safety and efficacy.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Biography of author(s)

Dr. Bharti Ahirwar
Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur (C.G.) - 495009, India.

Research and Academic Experience: She has 22 Years of Experience.

Research Area: Her Research Area includes Pharmacognosy, Phytochemistry, Herbal Drug Technology and Herbal formulation development.

Number of Published papers: She has 70 Research Paper.
She has Granted 01 Indian Patent, and 03 Granted Australian Patent.

Special Award:
- 1st Chhattisgarh Young Scientist Award
- 2nd Chhattisgarh Young Scientist Award
- Research Award from UGC
- Distinguished woman Awards-VIWA 2018 in health and Medical sciences by Venus International Foundation, Chennai(T N)
- Women scientist of the year awards -2018, by IPG, Oriental University, Indore

Any other remarkable point(s):
Research Guidance:
1. Ph.D. Awarded – 02
2. M. Pharm. Awarded – 06

She is a Life member of:
1. Association of Pharmaceutical Teachers of India (APTI)
2. Indian Pharmaceutical Association (IPA)
3. Society and Pharmaceutical Education and Research (SPER)
4. Indian Society of Technical Education (ISTE)
5. Indian Society of Pharmacognosy

She has completed Research Projects:
CGCOST- MRP- 02
SERB -01

Prof. Dheeraj K. Ahirwar
School of Pharmacy, Chouksey Engineering College, Bilaspur (C.G.)- 495001, India.

Research and Academic Experience: He has 20 years of Experience.

Research Area: His Research Area includes Pharmacognosy, and Herbal Technology.

Number of Published papers: He has 80 Published papers.

Special Award: He received Chhattisgarh Young Scientist Award.

Any other remarkable point(s):

4 Patent Granted, Post doc. (UGC)) Ph.D. guided 8, M.Pharm. 22, funded Research Project 6 Completed
He is a Life member of:

1. Association of Pharmaceutical Teachers of India (APTI)
2. Indian Pharmaceutical Association (IPA)
3. Society and Pharmaceutical Education and Research (SPER)
4. Indian Society of Technical Education (ISTE)
5. Indian Society of Pharmacognosy(ISP)

Dr. S. K. Lanjhiyana
Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur (C.G.) - 495009, India.

Research and Academic Experience: He has 18 Years of Experience.

Research Area: His Research Area includes Pharmaceutics, Formulation development and characterizations, Colon specific drug delivery; Novel controlled and sustained drug delivery systems.

Number of Published papers: He has published 27 Research papers in national and international journals, and 05 Book chapters.

Any other remarkable point(s):
Research Projects Completed
UGC (Major Research Project)
AICTE (Major Research Project)
CGCOST (Minor Research Project)
Research Guidance:
1. Ph.D. Awarded – 01
2. Ph.D. Ongoing – 01
3. M. Pharm. Awarded – 17

He is a Life member of:
1. Association of Pharmaceutical Teachers of India (APTI)
2. Indian Pharmaceutical Association (IPA)
3. CGPCI

Dr. Sanmati K. Jain
Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur (C.G.)- 495009, India.

Research and Academic Experience: He has 20 Years of Experience.

Research Area: His Research Area includes Medicinal Chemistry, Computer Aided Drug Design (CADD).

Number of Published papers: He has 69 Published papers, and 5 Book Chapter.

Special Award: He received Prof. K. A. Thaker award for Best Paper published in 'Journal of Institution of Chemists (India).

Any other remarkable point(s):
Research Guidance:
1. Ph.D. Awarded – 02
2. M. Pharm. Awarded – 25
3. Ph.D. Submitted – 01
4. Ph.D. Registered - 01

He is a Life member of:
1. Association of Pharmaceutical Teachers of India (APTI)
2. Indian Pharmaceutical Association (IPA)
3. Society and Pharmaceutical Education and Research (SPER)