WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 9, 624-645. Review Article ISSN 2277– 7105

POLYPHENOLS IN CANCER: SIGNIFICANT ROLE IN PREVENTION OF MAMMARY CARCINOGENESIS

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Article Received on
02 July 2015,

Revised on 26 July 2015,
Accepted on 20 Aug 2015

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ABSTRACT

Polyphenols are the most abundant naturally occurring dietary antioxidants. Research in their role in chemoprevention has developed quickly over last few decades. This article reviews the recent studies on the prevention of carcinogenesis by polyphenols. Specifically focusing, the preclinical and clinical studies of polyphenols like naringin and daphnetin relevant to their anticancer potential against mammary carcinogenesis. Strong epidemiological evidences and current interest enlighten the benefits and uses of naringin, daphnetin and other polyphenols in various pathological conditions like cancer. This brings many molecules individually or crudely in practices of clinical trials. To establish safety and effectiveness of dietary polyphenols in cancer prevention in humans, 214 polyphenol based clinical trial studies were registered till May 2015 but only two from them are against breast cancer. Various factors affecting pharmacokinetics and bioavailability of these polyphenols are essentially being studied, as these are responsible for individual polyphenolic distribution and effect to specific organs and tissues. Many researchers come out with great discoveries and others are exploring with varying potential of polyphenols and mechanism of their anticancer activity against various cancer including mammary carcinoma. Rather than some common specified class of mechanisms, individual polyphenols exhibit various diversified mechanisms working for their activity against mammary cancer. *In-vitro* and *in-vivo* cancer studies give testimony to various hypotheses on protective activities of polyphenols in

biological system which may become a base for their access in research and clinical trials against various cancers.

KEYWORDS: Polyphenols, anticancer activity, mammary cancer.

INTRODUCTION

Natural plant-based diet has a key job in cancer aetiology and deterrence. Endogenously in plant, polyphenols exert a protective effect against various stress conditions like photosynthesis, reactive species induced, photosynthetic, UV radiation induced, wounds, herbivores and other variants.[1] The scientific substantiation consistently revealed contrary association of dietary intake of naturally occurring polyphenolic compounds and cancer biology. The magnitude of naturally occurring polyphenolic compounds in many diseases management is far and wide. The curiosity about the valuable effects and nutritional values of polyphenols has increased among nutritionists only in last few decades. The diversity and intricacy among their chemical structure are accountable for delayed research on polyphenols.

Naturally occurring polyphenols were classified on the basis of count of phenolic rings and structural moieties that binds them. Main classes comprises of flavonoids (flavanone (hesperidin, naringin etc.), flavonol (fisetin, catechin etc.), flavones (chrysin, leuteolin), flavanol (myricetin, quercetin etc.), flavanonol (taxifolin), iso-flavone (daidzein, genistein etc.) and antho-cyanidins (delphinidin, malvidin etc.),[2,3] phenolic acids (gallic acid, hydrobenzoic acids, hydrocinnamic acids), phenolic alcohols (tyrosol, hydroxytyrosol), stilbenes (resveratrol) and lignans (secoisolariciresinol).[4] Flavonoids are extensively stirring molecules in utilization as-well-as in research against various perilous disorders like neuro-, cardio- and metabolic disorders and human malignancies at many sites. Chemically they are molecules compile of a common phenylchromanone (C6-C3-C6) skeletal constitution, with single or added hydroxyl substitutions.[2,3] These are secondary metabolites and glycosidic occurrence of most of these flavonoids particular in terrestrial vascular plant range is testimony in literatures. Coumarins, are a vigorous class of phenolic phytoconstituents also known as benzopyrons. Constitutional arrangement of coumarins comprises of oxygen containing five carbon alpha (α) or gamma (γ) ring fused with parent benzene ring.[5] Coumarin related compounds habitually used in treatment and maintenance of a list of thrombotic, immunological, infectious and chronic disorders like cancer malignancies.[5]

These polyphenolic moieties bear arrays of biological activities at cellular and molecular level with credible chemo-preventive mechanisms and their interaction with signalling pathway mediators, receptors etc., which may account for their individual activities against many deteriorative damages, chronic diseases and anticancer potential in the body.[2]

The current review proposes the emphasised review on some specific polyphenols against cancer specifically mammary cancer prevention in preclinical and clinical studies. Author also intended to thrash out and compile numerous mechanistic oncological approaches and factors affecting pharmacokinetic and bioavailability of polyphenols, reported in various epidemiological studies and open new interventions left out so to carry requisite studies to overcome unrevealed cancer treatment pathways bear by these molecules.

POLYPHENOLS IN ANIMAL MODELS OF CANCER

Various investigators revealed the protective effects of different polyphenols against carcinogenesis on many animal models. The safety and efficacy of polyphenols is supported by various *in-vitro* and *in-vivo* animal experiments on different concentrations from nanogram to much higher than human consumption. Wang et. al., demonstrated reduction in tumour adenomas count and protection effects of theaflavin and tea preparation in NNK (nicotine derived nitrosamine ketone)-treated mice.[6] Ahmed and co-workers established potential of curcumin and naringin against DMBA-induced hepatic function, oxidative stress and histological integrity in rats.[7] They reported alleviation in antioxidant defence system. This may be due to antioxidant strength of naringin and increase in thiol pools.[7] Researchers reported naringin exhibits a potentiating effect on the antioxidant enzymes level as well as antioxidant action of cellular antioxidant enzymes in DEN-induced hepatic damage in rats[8] and efficiently reduces the cell proliferation and enhance apoptosis.[9] Naringin induces G1-phase cell cycle arrest via activation of the Ras/ Raf/ ERK signalling pathway in vascular smooth muscle cells isolated from SD rats.[10] In an animal study naringin evident to counteract DMBA-induced hepatic injury via enhancement of liver antioxidant defence system & suppression of oxidative stress and inflammation.[7] Daphnetin treatment to mice could downregulate ConA induced NF-κB and NFAT signal transduction pathway exerting immunosuppresion.[11] Shielding effect of caffeine in lung carcinoma in mice and rats was established earlier.[12] Tea polyphenols evident to inhibit the induction and progression of tumours at different organ sites in animal models through inhibiting enzyme activities and signal transduction pathways, resulting in the suppression of cell proliferation and

enhancement of apoptosis, as well as the inhibition of cell invasion, angiogenesis and metastasis.[12,13]

POLYPHENOLS IN CANCER CLINICAL STUDIES

The strong epidemiological evidences and current interest enlighten the benefits and uses of polyphenols. Human based investigations are winged in last decade. This brings many molecules individually or polyphenol rich food and beverages in practices of clinical trials. To establish effectiveness and safety of dietary polyphenols in disease prevention in humans, 214 polyphenol based clinical trial studies were registered till May 2015.[14] Many have finished with positive results and other are still continuing with varying interventions. Many have got it up to Phase II trials. About 32 clinical trials are registered for studying the beneficial and safety interventions of polyphenols on cancer. Two separate studies including the use of green tea polyphenols as dietary supplements in incidences of breast cancer and dietary anthocyanins on toxicity associated with radiotherapy of breast cancer has been registered. About 97 flavonoids based trials have been registered yet and 13 among them are cancer related. Only one study has been registered to study the safety and efficacy of flavonoids against breast cancer. Few studies on protection effect of naringin and naringenin individually or as adjuvant were registered. Although, having a number of patents on its name, daphnetin still has not reached the files of clinical trials.[14,15] Among several epidemiological studies the associations between increased polyphenol rich food intake and control on various cancer risk was evident.[16] In an cross sectional study of 219 adults, 70 years women suffering from hypertension, regular consumption of red wine and black tea relief their pathological conditions.[17] Likewise, many clinical trials has completed and many are ongoing, proving the promising role of polyphenols.

POLYPHENOLS IN CANCER EPIDEMIOLOGICAL STUDIES

A contrary relationship exists among polyphenolic intake and chronic disease risk in various epidemiological studies.[18,19] In cellular elements, after absorption polyphenols scavenge free radical by accepting one electron through phenolic group interrupt oxidative chain reactions.[20] Polyphenols rich food intake exert healthy effects by either occurrence of reductive polyphenols and metabolites in blood plasma enhancing its antioxidative potential, various specific effects of polyphenols on endogenous antioxidants or alteration of pro-oxidative food components in presence of polyphenols decreased lymphocytic DNA cleavage.[18] Various known and unexplored reasons in various epidemiological studies

evidently indicate bounded oxidative-induced degenerative disease with presence or increased polyphenol-rich food intake.[21,22,23] Duffy and co-workers demonstrated the beneficial effects of red wine and tea polyphenols against high fat diet induced endothelial dysfunction in rodents.[24] Naringin inhibit cholesterol-induced hepatic inflammation in rats by modulating MMP-2, 9 via inhibition of NF-κB pathway.[25] Daphnetin showed promising antiproliferative activity and inhibition of cell cycle progression in MCF-7 human breast cancer cell lines and several other tumour cell lines and proposed to be a potential anticancer agent. This breast cancer cell line response showed changes in cyclin D1 gene expression and can have potential against estrogen dependant tumours.[26] Daphnetin competitively to ATP and non competitively to peptide substract inhibit EGF receptor tyrosine kinase.[27] Daphnetin suggested to exhibit broad range of pharmacological activities including pyrexia,[28] antimalerial,[29] anti-arthritic, coagulation, stroke properties and founded to maintain cellular levels of enzymic antioxidant activity responsible for its antioxidant potential.[28,30] Daphnetin poses anti-proliferative activity against human renal carcinoma cells through P38-mitogen activated protein kinase mediation suggesting it act by cellular maturation.[5] Polyphenols from tea had been renounced to have antioxidant potential resulting in abilities to confiscate ionic metals and scavenging activity for reactive oxygen and nitrogen species which leads to cellular lipid membranes, proteins and nucleic acids protection.[31] Epigallocatechin gallate has expressed growth inhibitory effect besides human mammary and prostate cancer cells in athymic mice.[32] Naringin by downregulating VCAM-1 expression & increasing MIR-126 can potentially check migration and invasion if human chondrosarcoma.[33] In combination with tamoxifen, naringin demonstrated to impair proliferation and induce apoptosis in MCF-7 cells upto a greater extend.[34] In-vitro experiments by So and co worker provided evidence of anticarcinogenic properties of citrus flavonoids like naringin against breast cancer cell proliferation in vitro.[35]

POLYPHENOLS IN ANIMAL MODELS OF MAMMARY CARCINOGENESIS

The humoral equilibrium and regulations in rodents and humans are similar in normal female mammary gland.[36] Hence to study the effects of estrogen and estrogen-like substances on the mammary gland rodent are most suitable animal models. Documentation of anticancer potential of polyphenols are abundant. Polyphenols given prior to carcinogenic agent or human cancer cell line induction in rats and mice evident to reduce the count and growth of tumours at various sites and organs including alimentary canal, skin, mouth, breast involving diversified mechanisms.[37] Naringin could inhibit growth potential of triple-negative breast

cancer cell by modulating β-catechin pathway, can be used for potential supplement in breast cancer.[38] Green tea polyphenols (GTP) and its constituent Epigallocatechin Gallate (EGCG) treatment inhibits proliferation and induce apoptosis of MDA-MB-231 cells in-vitro and in-vivo.[39] Survival of breast cancer metastatic mice was increased significantly by dietary grape skin extract.[40] Black tea polyphenols were demonstrated to reduce DMBA-induced mammary carcinogenesis in high fat diet rats.[41] Natural compounds under several studies may also give treatment interventions for triple negative breast cancer. Epigallocatechin gallate (EGCG) possess antitumour activity against two triple negative breast cancer cell lines at very low doses MDA-MB-231 (30 µg/ml) and MDA-MB-468 (80 µg/ml) by inducing apoptosis as well as modulates various cell signalling pathways and reduces cell proliferation.[42]

PROPOSED MECHANISMS OF POLYPHENOLS AGAINST MAMMARY CARCINOGENESIS

Various diversified mechanistic oncological approaches have been proposed for anticancer potential of polyphenols.[43] Their ability to satiate free radicals is responsible due to their conjugated structure which gives delocalisation property for free radicals. Indeed, they scavenge a large number of reactive species including oxygen radicals, superoxide ion, nitrogen dioxide, nitroxide, peroxynitrite and hydrogen radical.[1]

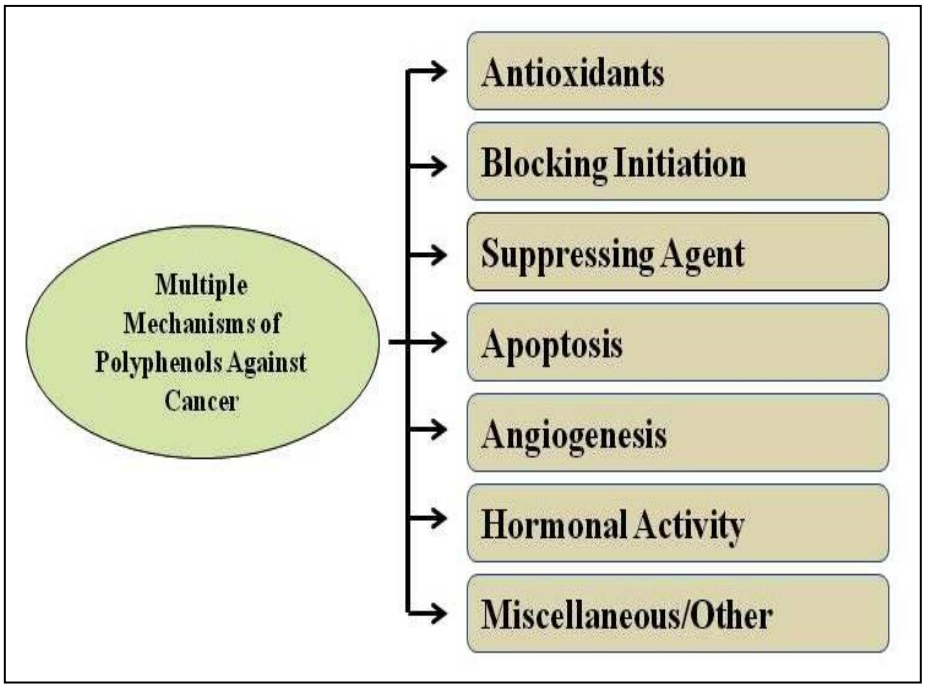

Figure 1.: Multiple mechanisms of polyphenols against cancer.

Antioxidant aptitude against lipid peroxidation and cellular component, antiplatelet and anti-inflammatory potentials of polyphenols are key motivations against deteriorative disease.[44] Also, most of them are capable to chelate metal ions reducing the liberation of free radicals and their scavenging.[1] There are evidence for improved endothelial function with polyphenol uptake. Polyphenols by altering endothelial cellular membrane components like MMP, inhibiting invasion, proliferation, restrain platelet aggregation (thrombosis) shows their healthy effect against cardiac diseases, cancer and metabolic disorders and are responsible for increase in quality and span of life.[17] The excellent binding affinity of polyphenols for proteins and nucleic acids is served by their superior hydrogen bond donor property. Hence, this group of naturally occurring diversified molecules gives various agents being studied & used for protein targeting.[1] Tea polyphenols were reported to have high affinity to proline rich salivary protein binding. There binding affinity for different membrane related changes, receptor and enzymes account for biological changes and activities of these polyphenols, investigated by different investigators.[12] Survivin, a inhibitor of apoptosis is highly expressed in breast cancer tumour as compared to normal breast tissue.[45] Tea polyphenols reported to induce apoptosis in breast cancer cells via downregulating survivin expression.[46] Various diversified mechanisms have been proposed for anticancer potential of polyphenols.[43] Based upon various epidemiological studies some of the major mechanisms can be quantified through figure 1. Polyphenols initially impede the metabolic activation of procarcinogens by altering the expression of metabolising P450 enzymes. Moreover, polyphenols enhance phase-II metabolising enzymes expression resulting in increased clearance of xenobiotics as well as toxic metabolites of polyphenol itself like quinines.[47] Also, they perform DNA repair functions to stuck the initiation of carcinogenesis.[48] Being suppressing agent, polyphenols are good for inhibiting the initiation (induction) and progression of cancer from affected cells *in-vitro* and *in-vivo* by various mechanisms.[18] Some work through protein kinases inhibition, AP-1 dependant transcriptional activity.[49] Some members are investigated extensively to develop potential novel cancer therapies. Single polyphenols was found to have activity against multiple kinases.[1] Apoptotic activity based on extracellular regulated kinase (ERK), c-Jun N-terminal kinas (JNK), cAMP dependant protein kinase (C) and protein kinase C are responsible for cytostatic, cytotoxic and various anticancer activity of esculatin , daphnetin and scopoletin.[1,27] Daphnetin was suggested to have cause cellular maturation and Antiproliferative effect on renal cell carcinoma intrinsically involving P38 MAP kinase cascade.[5] It also modulates intracellular signalling cascade including IKK/IKB, MAPKs and PI-3K/ AKT.[50] It also reported to

inhibit EGFR and serine/threonine-specific protein kinases, including cAMP-dependant kinases (PKA) and protein kinase C (PKC).[27] Multiple kinase affects of polyphenolic compounds enhance their efficacy by synergistic effect on cancer cells. Inhibiting expression of key enzymes including surviving,[46] aromatase, ornithin decarboxylase, involved in cell proliferation.[18] Altering the arachidonic acid metabolism has resulted in suppression of cell proliferation. Green tea polyphenols, curcumin and daphnetin founded inhibiting LPS-induced nitric oxide synthase and cycloxygenase-2 in mice.[18,51]

Phenolic phytoestrogens (isoflavones) exert a protective effect against breast and prostate cancers through their estrogenic properties or their capacity to affect the response to endogenous estrogens.[18]

Polyphenols reduces tumour cell growth via their apoptotic effect in *in-vitro* and *in-vivo* studies. But the mechanism is controversial as polyphenols ahve excitatory and inhibitory both effects.[18,52]

Polyphenols such as tea polyphenols, naringin exhibit anti-angiogenic effects resulting in reduced tumour growth.[3,18] Inhibition of MMPs are also found to be involved in reduction in cell growth or neovascularization.[53]

Rather than some common specified class of mechanisms, individual polyphenols exhibit various diversified mechanisms working for their activity against cancer. Inhibition of telomerase based activity of some polyphenols were also reported on nude mice responsible for reduction in growth of tumours.[54] Inhibition of transcription factor like NF-κB, TNF play essential role in protective effect of polyphenols on cancer.[55] Daphnetin was reported to significantly reduce the production of IL-1, TNF and macrophages inhibitory factors in arthiritic rats, interact with bovine serum albumin, and have significant anticancer activity.[56,57] Interactions of polyphenols with specific DNA sites cytotoxic effect on cancer cells inhibiting cell proliferation and causing cell death. Daphnetin evident to interact with adenine and thymine bases in the minor grooves of calph thymus DNA and bringing the conformational changes.[56]

PHARMACOKINETICS AND BIOAVAILABILITY OF POLYPHENOLS

Polyphenol based preparations are used widely as dietary supplements. Polyphenols claim to have health benefits and disease protective efficacy.[58] Availability to knowledge about

safety, biotransformation and bioavailability of polyphenols *in-vivo*, is necessary to distinguish their desired healthy effects.[59]

Pharmacokinetic and biological effects of these polyphenols can be altered by physiological and pathological conditions itself. Various studies demonstrated the variation in *in-vitro* study results and their extrapolation to *in-vivo*. Studies have reported about the pharmacokinetic and body distribution of polyphenols. But still satisfactory information on kinetics of polyphenols have not been yet reported.[58]

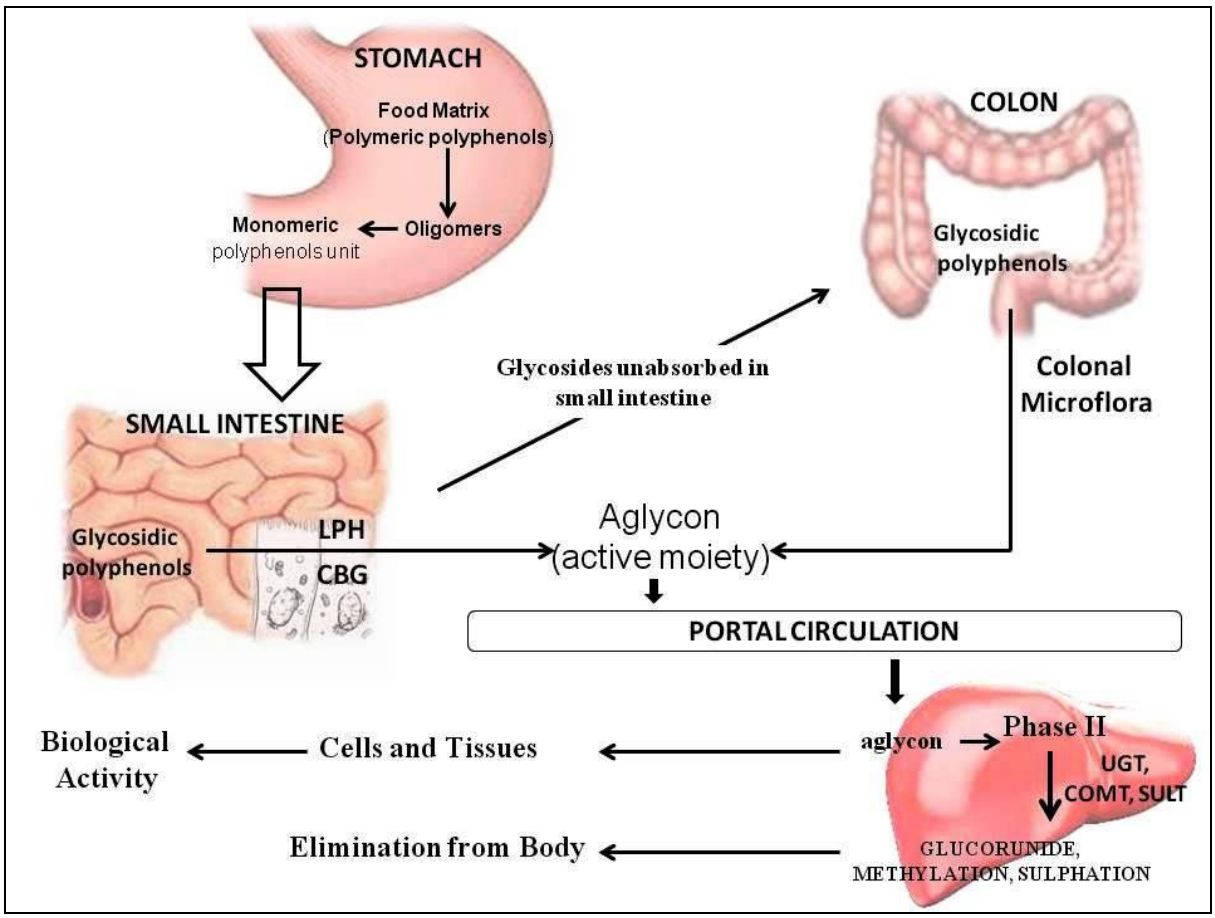

Figure 2.: Pharmacokinetic and bioavailability of polyphenols.

The kinetics and availability studies on plasma and urine samples in *in-vivo* studies for individual polyphenol or polyphenol based food are investigated.[60] All polyphenols posses variable kinetics and hence individual understanding and study reveals the relative interventions of polyphenols against specific health conditions. *In-vitro* and *in-vivo* studies show transformation of these polyphenolic compounds into other active or inactive molecules. To reveal real biological significance of individual polyphenols one need to determine its toxicity, kinetics and bioavailability. Widely held studies are performed on

animals, rodents and primates mainly. But, interspecies variations are of great importance and could be crucial to interpolate the physiological effects of polyphenols in human as compared to animals.[61] Many factors like inherent species, metabolic profiles, administration procedure, preparation method, extraction method, vehicle, dosage, gender, anaesthesia procedure, circulation and analytical procedure, polymorphism and many more are considerable in PK and BA studies. To describe the metabolic fate of polyphenols, PK studies are essential. BA of Polyphenolic compounds depends upon their metabolic fate, each can be revealed by elaborative PK studies with validated methodologies.[58] Efficient bioactive molecules in *in-vitro* studies may vary in their efficacy and potency *in-vivo*, depending upon its desired availability systemically. Bioavailability of polyphenol can be defined as the fraction of ingested polyphenol that can attain to systemic circulation and can exert its effect on tissue sites. The distributions of polyphenolic compounds are uneven in various food and beverages like citrus fruits, apple, wine, berries exhibit plenty of polyphenols from a range of few micrograms to few grams per kg.[62] Understanding the facts about bioavailability of polyphenols may assist to investigate protective healthy efficacy and potency of polyphenols correctly. Further, this will help for their precise human intake. To investigate and establish confirmatory evidences on administration, safety and efficacy of individual polyphenols among hundreds of them, their behaviour, distribution, structure and constitution essentially be defined. It is of vital importance to determine the factors involved in release of polyphenols from food, their absorption and metabolism while considering the diversity in the bioavailability of individual polyphenols.[4] Exhaustive studies had been done on bioavailability of polyphenols and established the general phenomenon of their absorption as aglycon from small intestine. Various polyphenols undergo hydrolysis by gastric flora and enzymes prior to absorption due to their ingestion in their native form of esters, glycosides, polymers etc. in food. The structural constitution of moieties in blood may differ from those available in food evident extensive metabolic transformations and modifications of polyphenols after absorption, responsible for their biological activities.[4] After administration of polyphenols, alteration in bioavailability occurs may affected by microfloral degradation of aglycon, their intestinal or hepatic conjugation leading to metabolic elimination. Individual organ penetration and availability of polyphenols to different vital and desired organ needs to be enlightened. Bioavailability of polyphenols is established by assessing the plasma and urine concentration of active and other metabolites after administration of food material or pure compound.[19] The most imperative use of bioavailability studies is to determine the correlation of availability of polyphenols in food and actual active and most bioavailable

polyphenol metabolite. Young et al 1999 evident the increase in antioxidant potency of plasma after gut wall absorption of polyphenolic rich food diet.[63] A number of factors affecting bioavailability of polyphenols make it difficult to conduct bioavailability study. Various potential factors are illustrated in figure 3. These factors by one way or another affect bioavailability at some stage and hence need to be considered. Preferably single-dose design is used in *in-vivo* studies. The increased level of polyphenols after absorption from food matrix containing polyphenols is measured. In regular intake condition the level of polyphenol may change variably in plasma as well as the cellular level.[64] Hence, various intrinsic and extrinsic can exert potential changes in bioavailability of polyphenols.

Environmental factors

various epidemiological studies involved direct plant parts or crude extracts containing polyphenolic compounds. Many factors like exposure of plants to various climatic conditions (sunlight, rain, temperature variations), stage of fruit at collection time etc. can cause alteration in phenolic content of plants and further to human consumption.[62] The anthocyanin content increases on ripening of fruits and phenolic acid decreased.[65]

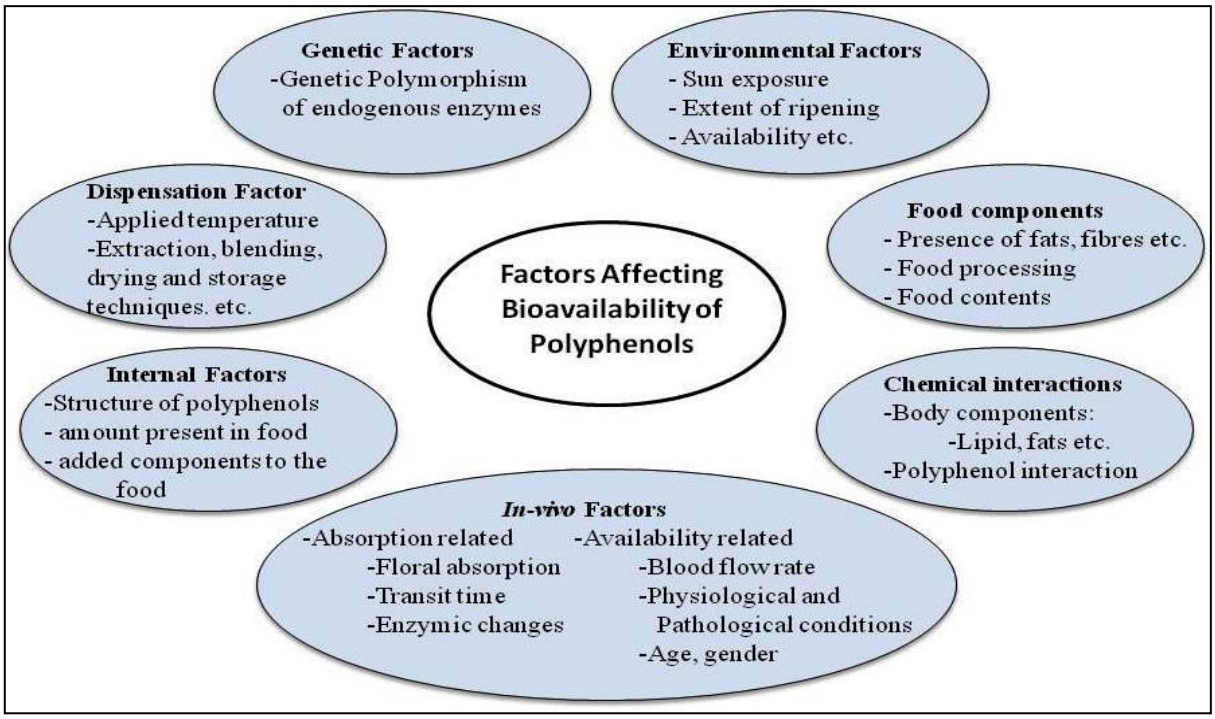

Figure 3.: Various factors affecting bioavailability of polyphenols.

Component of food matrix

Many studies reported about relation between polyphenolic component and other components like proteins, fats, carbohydrates, alcohols etc. bring changes in their systemic

availability.[62,66] Contradictory affects of milk on bioavailability of polyphenols has been reported.[67] Milk found to modify the phenolic metabolism in many study subjects as well as in humans.[68] Researchers showed the effect of sugar as glycoside content and polyphenolic bioavailability when compared with aglycon alone.[62] Studies showed enhanced absorption and digestibility of flavonoids and some phenol compounds with high fat content.[66] In some studies found that fat delay the absorption time of flavonoids as affecting transit time.[69] High absorption of phenolic compounds from virgin olive oil has been demonstrated in studies. Dietary fibres found to delay the absorption.[70]

Dispensing methods

Total phenolic contents as well as antioxidant activity were reported to be increased in several beans and legumes of various species after specific thermal treatment.[62,71] Whereas, it found that it decrease some specific phenolic contents in virgin olive oil.[72] Gastronomic preparations or cooking method exhibits specific changes in bioavailability of polyphenols as well as their biological activity. Food components and vegetables like carrot, broccoli, and artichokes oil, olive oil showed a remarkable change in their polyphenolic content depending upon their cooking procedure (frying, steaming, boiling etc.).[73] Raw vegetables are recommended generally but evidences showed increase in various protective compounds level in food after cooking including increased plasma level of naringenin and chlorogenic acid in cooked tomatoes.[74] Storage is one of the major considerations to be kept in mind while conducting a bioavailability study. Although controversial but some food material show a marked decrease in phenolic and polyphenolic content on long time storage whereas some show remarkable increase.[62,75] As demonstrated for lycopene and β-carotene, homogenization was found to have increasing effect on bioavailability.[76]

Internal Factors

chemical structure of polyphenols is a promising factor influencing their bioavailability. Natively, polyphenols exists as conjugated or polymerized form which undergoes hydrolysis by intestinal enzymes or colonal microflora that separate the glycon from aglycon part prior to absorption. As supported by studies exceptionally anthocyanins were absorbed as intact glycoside form.[77] Hence, the specific chemical structure of polyphenolic aglycon and sugar glycon moiety exerts effect on bioavailability.

Chemical interactions

Interaction of polyphenols with other intrinsic and extrinsic compounds and components may bring effects on their bioavailability. Some polyphenol posses high affinity for blood proteins that may results in their slow elimination and enhanced half life.[78,79] Some sulphotransferase enzymes influenced by polyphenols itself. SLUT1A1 (Phenol sulphotransferase 1A1) allele is inhibited by quercetin and coffee polyphenols.[81,82]

***In-vivo* factors**

These factors can be further divide into absorption related and availability related factors (figure 3). The intestinal physiology exhibits important role in ingestion and absorption of polyphenols. Most of the components depending upon their time of interaction are absorbed from small intestinal flora. Either by Lactase phloridizin hydrolase (LPH) or by Cytosolic *β*-glucosidase (CBG) enzyme within the epithelial cells of intestinal flora, polyphenols undergo transformation prior to absorption.[82] Components which are unabsorbed in the small intestine pass to colon where they undergo significant structural modifications. A very important factor for bioavailability and physiological activity of polyphenols takes place here. Colonal microflora hydrolyses glycosides into aglycon and shatter into phenolic acids.[83] Enormous individual variation exists for these metabolic reactions and hence varies the bioavailability and activity of polyphenols.[84] Before reaching to systemic circulation polyphenols undergo structural modifications in intestine and liver. Conjugation reaction that takes place in liver may work in both ways, they transform some polyphenols into active metabolites and some are eliminated from blood.[62] These metabolic reactions vary with various pathological states, age, gender of the individual.

Genetic Variations

It is well acknowledged that among huge population, large variation in bioavailability of individuals exists.[85] In bioavailability studies, intersubject variations are an important consideration and desired to be minimized. It has been estimated that genetic variations may fetch 20% - 95% of variability in drug disposition and their biological effects.[86] Various enzymes responsible for polyphenols metabolism may influenced by external factors like diet and some may show genetic polymorphism that may bring interindividual differences in toxicity, pharmacokinetics and bioavailability of polyphenols. Genetically, 5% of Europeans and 90% of Asians and Africans have LPH deficiency in adulthood.[64] Impotance of LPH in polyphenolic metabolism is discussed earlier. After separation of aglycon from Glycosidic

moiety of polyphenol, it may undergo many secondary biotransformation reactions. COMT (Catechol-O-methyl transferase) widely expressed in various tissues causes methylation of polyphenols. Functional genetic polymorphism in COMT gene results in threefold or fourfold difference in COMT enzyme activity.[87] UDP-glucuronyl transferase (UDPGT) involved in glucuronidation of polyphenols expressed primarily in intestine, liver and kidney. UDPGT1 specific for most of the polyphenol glucuronidation may show genetic polymorphism and can expressed variably in individuals.[64] Polymorphism in some enzymes like glutathione transferase, cytochrome P450 family, epoxide hydrolases, vitamin K epoxide reductase complex (VKORRC) subunits, thiopurine S-transferase (TPMT alleles), P-glycoproteins (PGP) and many more undergo genetic polymorphisms like single nucleotide polymorphism or multisatellite regions including genes relevant to organ transplantation may bring individual variations in molecular linkage, transformation, bioavailability and biological effect of drugs & chemicals like (warfarin, azathioprim, carotenoids, polyphenols (tannic acid, quercetin and derivatives etc.)).[85,88,89,90,91]

CONCLUSION

The hunt for efficient chemoprotective molecule with lesser side effects raises many hypotheses for use of herbals in medications. These various epidemiological, multiple mechanistic oncological based studies motivate the applications of polyphenols as polypharmacological agents having enhanced anticancer activities with reduced unwanted effects. But the most challenging task remains to demonstrate the effect of polyphenols in humans. *In-vitro* and *in-vivo* cancer models give testimony to these hypotheses on protective activities of polyphenols in biological system which became a base for their access in research and clinical trials.

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