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# Metabolic and colonic microbiota transformation may enhance the bioactivities of dietary polyphenols

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ABSTRACT

Epidemiological evidences throughout the years have indicated that consumption of phytochemicals may play important functions in the regulation of pathological and normal biological processes. Polyphenols are one of the large and ubiquitous groups of phytochemicals. Dietary polyphenols are naturally present in a wide variety of fruits and vegetables, and potentially contribute to the maintenance of human health. However, growing information has indicated that the bioactive compounds from polyphenols may exert beneficial effects in part by their metabolites. The bioactive metabolites were converted by the gut microflora, liver microsomes and hepatocytes, and identified in intestinal, plasma, feces, and urine after dietary ingestion. Surprisingly, recent studies suggested that many metabolites possess more active biological functions than their precursors. In order to explore the possibilities of metabolites in food bioactive compounds, more clear understanding of the metabolic pathways and the molecular targets responsible for health promotion and diseases prevention are needed. In this review, we first summarize the distribution and beneficial health activities of metabolites from dietary polyphenols. We also discuss the available evidence on the relationship between metabolites bioefficacy and bioavailability of their parent polyphenol compounds. We hope that this knowledge will lead to future research to discover and develop new bioactive compounds as possible chemopreventive agents.



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## 1. Introduction

Plant polyphenols are secondary metabolites found abundantly in a wide variety of foods, such as fruits, vegetables, herbs, seeds and cereals and in beverages, such as coffee, tea cocoa and wine (Vinson, Su, Zubik, & Bose, 2001). In recent years, polyphenols have been shown to have the capacity to influence pathological and physiological processes via multiple mechanisms, including free-radical scavenging, metal chelation, regulation of enzymatic activity, inhibition of cellular proliferation and alteration of signaling transduction pathways (Liu, 2004; Vanden, 2012). Epidemiological and experimental studies have highlighted the association between the consumption of polyphenol-rich foods and their beneficial health effects (Kussmann, Affolter, Nagy, Holst, & Fay, 2007). Other evidences have also indicated that dietary intake of polyphenols contributes to the prevention of chronic diseases, such as cancers, diabetes, ulcer, cardiovascular, and other degenerative disorders in humans (Pan, Lai, & Ho, 2010).

Bioavailability is a complex process involving multiple stages of liberation, absorption, distribution, metabolism and excretion (Rein et al., 2013). The healthful properties of bioactive polyphenol compounds depend on their bioavailability for intestinal absorption, metabolism, and subsequent interaction with target tissues (Stahl et al., 2002). However, dietary polyphenols are mostly poorly absorbed and extensively biotransformed, which lead to a reduction in their bioavailability. However, it is interesting that even with low bioavailability, most polyphenols still exhibit biological functions. Recent research has demonstrated that metabolites from dietary polyphenols might have more profound biological activities than their precursors (Delmas et al., 2011; Monagas et al., 2010). The present review focuses on the potential health effects and bioactivities of metabolites from dietary polyphenols, including resveratrol, daidzein, genistein, 6-shogaol, rutin, apigenin, quercetin, theaflavin-3,3′-digallate (TFDG), curcumin and nobiletin, and discuss molecular mechanisms on the modulation of cellular signaling events by their bioactive metabolites.

*Abbreviations*: AA, arachidonic acid; AD, Alzheimer's disease; AMPK, AMP-activated protein kinase; AP-1, activator protein-1; ASCVD, atherosclerotic cardiovascular disease; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; BID, BH3 interacting-domain; BMD, bone mineral density; C3, complement protein 3; CAT, catalase; CDKs, cyclin-dependent kinases; CDKIs, Cdk inhibitors; C/EBP, CCAAT/enhancer binding protein; C4HE, *cis*-4-hydroxyequol; CML, $N^{\varepsilon}$-carboxymethyllysine; CNS, central nervous system; COX-2, cyclooxygenase-2; CpG, cytosine phosphate guanine; CREB, cAMP response element binding protein; CV, capillary vascularity; Cx-43, connexin-43; CYP-450, cytochrome P-450; DA, dopamine; DAT, dopamine transporter; 3,4-DHPAA, 3,4-dihydroxyphenylacetic acid; 3,4-DHT/4MC, 3,4-dihydroxytoluene/4-methylcatechol; DHT, dihydrotestosterone; DMBA, 7,12-dimethylbenz(a)anthracene; 3′-DMN, 3′-demethylnobiletin; 4′-DMN, 4′-demethylnobiletin; EGF, endothelial growth factor; EPCs, endothelial progenitor cells; ER, estrogen receptor; ERK, extracellular-signal-regulated kinase; ET, endothelin; EZH2, enhancer of zeste homolog 2; FASN, fatty acid synthase; GCL, glutamate–cysteine ligase; GDNF, glial cell line-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GI, gastrointestinal; GM, gentamicin; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; GSK-3-3β, glycogen synthase kinase-3β; GST, glutathione S-transferases; GSTT2, glutathione S-transferase T2; 3′-HD, 3′-hydroxydaidzein; 6-HD, 6-hydroxydaidzein; 8-HD, 8-hydroxydaidzein; HEK, human embryonic kidney; HFA, human flora associated; 3′-HG, 3′-hydroxygenistein; 6-HG, 6-hydroxygenistein; 8-HG, 8-hydroxygenistein; HMGB1, high mobility group box 1 protein; HMG-CoA, hydroxy methylglutaryl coenzyme A; HO-1, heme oxygenase-1; $H_2O_2$, hydrogen peroxide; Homovanillic acid, 3-methoxy-4-hydroxyphenylacetic acid; HPP, 3-(4-hydroxyphenyl)-propionic acid; HSL, hormone sensitive lipase; HUVECs, human umbilical vein endothelial cells; IBMX, isobutylmethylxanthine; ICAM-1, intercellular adhesion molecule-1; IgE, immunoglobulin E; IGF-1, insulin-like growth factor 1; IL-1-3β, interleukin-1β; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinases; LC3, light chain 3; LDL, low-density lipoprotein; LLC, Lewis lung carcinoma; LPL, lipoprotein lipase; LDLr, low density lipoprotein receptor; LPO, lipid peroxidation; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MDR, multidrug resistance; MIP-2, macrophage inflammatory protein 2; MKK4, mitogen-activated protein kinase kinase 4; MMP, matrix metalloproteinase; mPHAA, 3-hydroxyphenylacetic acid; mTOR, mammalian target of rapamycin; NADPH, nicotinamide adenine dinucleotide; NASH, non-alcoholic steatohepatitis; NF-κB, nuclear factor-kappa B; NGF, nerve growth factor; NIK, NF-κB-inducible kinase; NO, nitric oxide; Nrf2, nuclear factor (erythroid-derived 2)-like 2; NSAIDs, non-steroidal anti-inflammatory drugs; *O*-DMA, *O*-desmethylangolensin; OX-LDL, oxidized low-density lipoprotein; OVA, ovalbumin; PCA, passive cutaneous anaphylaxis; PCNA, proliferating cell nuclear antigen; PD, Parkinson's disease; $PGE_2$, prostaglandin $E_2$; PI3K, phosphatidylinositol 3-kinase; PKA, cyclic AMP-dependent protein kinase; PMN, polymorphonuclear leukocyte; p75NTR, p75 neurotrophin receptor; PPAR-γ, peroxisome proliferator-activated receptor γ; PR, progesterone receptor; p70S6K, p70 ribosomal protein S6 kinase; PTEN, phosphatase and tensin homolog deleted on chromosome ten; PUD, peptic ulcer disease; Q-3G, quercetin 3-*O*-glucoside; RANTES, regulated on activation, normal T cell expressed and secreted; RASSF1, Ras association (RalGDS/AF-6) domain family members; Rb, retinoblastoma protein; RES, resveratrol; ROS, reactive oxygen species; 6S, 6-shogaol; SIRT-1, sirtuin-1; SOD, superoxide dismutase; SR-A, scavenger receptors-A; SRC-3, steroid receptor coactivator-3; SREBP-2, sterol regulatory element-binding protein-2; STZ, streptozotocin; SULT, sulfotransferases; TBARS, thiobarbituric acid reactive substances; *t*-BHP, *tert*-butylhydroperoxide; *t*-BOOH, *tert*-butyl hydroperoxide; TF(s), theaflavin(s); TFDG, theaflavin-3,3′-digallate; TF3G, theaflavin-3′-gallate; Th1, T-helper 1; THC, tetrahydrocurcumin; 6,7,4′-THI, 6,7,4′-trihydroxyisoflavone; 7,3′,4′-THI, 7,3′,4′-trihydroxyisoflavone; 7,8,4′-THI, 7,8,4′-trihydroxyisoflavone; 5,6,7′,4′-TEHI, 5,6,7,4′-tetrahydroxyisoflavone; 6,7,3′,4′-TEHI, 6,7,3′,4′-tetrahydroxyisoflavone; 6,7,8′,4′-TEHI, 6,7,8,4′-tetrahydroxyisoflavone; 7,8,3′,4′-TEHI, 7,8,3′,4′-tetrahydroxyisoflavone; TIMPs, tissue inhibitor of metalloproteinases; TNF-α, tumor necrosis factor-α; TNF-κB, tumor necrosis factor-κB; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; TrkA, tyrosine receptor kinase A; *t*-R-3,4′DS, *trans*-resveratrol-3,4′-disulfate; *t*-R-3,5DS, *trans*-resveratrol-3,5-disulfate; *t*-R-3G, *trans*-resveratrol-3-*O*-glucuronide; *t*-R-4′G, *trans*-resveratrol-4′-*O*-glucuronide; TXA2, thromboxane A2; TXB2, thromboxane B2; TYR, tyrosinase; UGT, UDP-glucuronosyltransferases; VCAM-1, vascular CAM-1; VEGF, vascular endothelial growth factor; VLDL, very low-density lipoprotein; VMAT2, vesicular monoamine transporter 2.

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