

Hydroxybenzoic Acids as Bioactive Metabolites in Cancer Prevention: Emerging Mechanisms, Structure-Activity Relationships, and Future Perspectives

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ABSTRACT

Hydroxybenzoic Acids (HBAs) are naturally occurring phenolic compounds present in fruits, vegetables, and other plant-derived foods and can also be generated through metabolism or degradation of bioactive molecules, including aspirin-related compounds and dietary flavonoids. Increasing experimental evidence suggests that HBAs may contribute to some of the biological effects historically attributed to their parent compounds. Studies using HBAs have demonstrated antiproliferative activity against several cancer cell types with emerging evidence implicating Cyclin-Dependent Kinases (CDKs), CDK inhibitory proteins, and cellular transport mechanisms in these effects. Studies of salicylic acid metabolites and derivatives demonstrated that 2,3-Dihydroxybenzoic Acid (2,3-DHBA), 2,5-Dihydroxybenzoic Acid (2,5-DHBA), and related compounds can inhibit selected CDKs, while 2,4,6-Trihydroxybenzoic Acid (2,4,6-THBA), a flavonoid metabolite, exhibits particularly notable activity against multiple CDKs. Subsequent studies demonstrated that 2,4,6-THBA inhibits cancer-cell proliferation and that its cellular effects can depend upon the expression of monocarboxylate transporter SLC5A8. More recent evidence indicates that another naturally occurring metabolite, 2,3,4-Trihydroxybenzoic Acid (2,3,4-THBA), inhibits proliferation and colony formation in colon and breast cancer cells and increases expression of the CDK inhibitors p21 and p27. Collectively, these observations support a model in which HBAs may influence cancer-cell growth through multiple mechanisms determined partly by the number and positional arrangement of hydroxyl and carboxyl groups. However, mechanistic evidence remains preclinical and therefore, further biochemical, pharmacokinetic, microbiome, and *in vivo* investigations are therefore needed to determine whether physiologically achievable HBA concentrations can reproduce the effects observed experimentally. This review examines current evidence for the HBA metabolite hypothesis, evaluates emerging structure-activity relationships, and identifies critical questions that should be addressed to facilitate translation of these compounds from experimental models to clinical and preventive applications.

Keywords: Aspirin, Cancer prevention, Colorectal cancer, Cyclin-dependent kinases, Flavonoids, Gut microbiota, Hydroxybenzoic acids, Metabolites, p21, p27, SLC5A8.

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INTRODUCTION

Colorectal Cancer (CRC) represents a major global health burden, and considerable research has consequently focused on dietary and pharmacological approaches capable of reducing its development (Eng *et al.*, 2024; Hossain *et al.*, 2022). Among the compounds receiving substantial attention are aspirin and plant-derived flavonoids (Garcia-Albinez & Chan, 2011; Hasibaun *et al.*, 2024; Kopustinskiene *et al.*, 2020). Epidemiological, clinical,

and experimental observations have associated these compounds with reduced CRC risk, although their underlying mechanisms remain incompletely understood (Chan & Cook, 2012; Thun *et al.*, 2012; Pyo *et al.*, 2024).

A potentially important consideration is that the biological activities associated with aspirin and flavonoids may not depend exclusively upon parent molecules (Sankaranarayanan *et al.*, 2019; Sankaranarayanan *et al.*, 2020). Both undergo extensive metabolism and degradation in the Gastrointestinal (GI) tract to produce Hydroxybenzoic Acids (HBAs) (Sankaranarayanan *et al.*, 2020). Bioavailability of aspirin is 50-60%; the remaining aspirin is rapidly hydrolysed to salicylic acid both in the gastrointestinal tract and liver, which can subsequently undergo further metabolism, including formation of 2,3-Dihydroxybenzoic Acid (2,3-DHBA) and 2,5-Dihydroxybenzoic Acids (2,5-DHBA) (Bojić *et al.*, 2015,



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Kim *et al.*, 2016; Sankaranarayanan *et al.*, 2020). Flavonoids similarly undergo chemical and microbial degradation, generating simpler phenolic compounds including several HBAs such as 4-Hydroxybenzoic Acid (4-HBA), 2,4,6-Trihydroxybenzoic Acid (2,4,6-THBA), 3,4-Dihydroxybenzoic Acid (3,4-DHBA) and 3,4,5-Trihydroxybenzoic Acid (3,4,5-THBA) (Sankaranarayanan *et al.*, 2019).

This observation has led to the proposal of a “metabolite hypothesis”, according to which HBAs generated from aspirin and flavonoids through host metabolism, chemical degradation, and/or gut microbial activity could contribute to the biological effects conventionally attributed to the parent compounds (Sankaranarayanan *et al.*, 2019; Sankaranarayanan *et al.*, 2020). Importantly, HBAs are not exclusively degradation products: many occur naturally as secondary plant metabolites and are present in fruits, vegetables, and other foods (Sankaranarayanan *et al.*, 2020; Kalinowska *et al.*, 2021; Juurlink *et al.*, 2014).

Experimental findings provide support for investigating metabolite hypothesis. Several HBAs inhibit cancer-cell growth, but the effects differ substantially among structurally related compounds (Sankaranarayanan *et al.*, 2019; Sankaranarayanan *et al.*, 2020). The number and position of hydroxyl groups appear to influence biological activity, suggesting that HBAs should not be considered a functionally homogeneous class (Sankaranarayanan *et al.*, 2019; Sankaranarayanan *et al.*, 2020).

This review examines evidence linking HBAs with regulation of cancer-cell proliferation, with particular emphasis on CDKs and cell-cycle regulatory mechanisms. It further considers the possible importance of molecular structure, cellular transport, diet and intestinal microbial metabolism and discusses the experimental evidence still required to establish whether the observed cellular effects translate into meaningful cancer-preventive activity *in vivo*.

Sources and Formation of Hydroxybenzoic Acids

Hydroxybenzoic acids consist of a benzene ring containing a carboxylic acid group and one or more hydroxyl groups (Sankaranarayanan *et al.*, 2019). Variations in the number and position of hydroxyl substituents generate structurally related molecules with potentially distinct biological properties. Several HBAs are naturally present in plant-derived foods. Among those discussed in the current literature are 3-HBA, 4-HBA, 2,3-DHBA, 2,5-DHBA, 3,4-DHBA, 3,4,5-THBA, 2,4,6-THBA and 2,3,4-THBA (Figure 1) (Sankaranarayanan *et al.*, 2019; Sankaranarayanan *et al.*, 2020; Kalinowska *et al.*, 2021; Akter *et al.*, 2024; Wianowska & Olszowy-Tomczyk, 2023). Dietary sources described for different HBAs include berries, grapes, avocados, kiwi fruit, apples, tea, legumes and other plant products (Juurlink *et al.*, 2014). However, diet represents only one potential source. HBAs can also be generated through metabolism of pharmacological and

dietary precursor compounds (Sankaranarayanan *et al.*, 2019; Sankaranarayanan *et al.*, 2020).

Aspirin-derived HBAs

Following oral administration, aspirin is absorbed in the acidic environment of the stomach, and the remaining aspirin undergoes hydrolysis in the intestine by esterases to produce salicylic acid. Some absorbed aspirin is hydrolysed to salicylic acid by esterases in the plasma and liver (Williams *et al.*, 1989). Salicylic acid subsequently undergoes several metabolic processes, including conjugation and CYP450-mediated hydroxylation (Bojić *et al.*, 2015). Among the products generated through these pathways are 2,3-DHBA and 2,5-DHBA. Gastrointestinal gut microbial metabolism may provide an additional pathway for generating salicylic acid and hydroxylated salicylic acid derivatives (Kim *et al.*, 2016). These observations provided the rationale for investigating whether metabolites could interact with molecular targets involved in cell proliferation.

Flavonoid-derived HBAs

Flavonoids represent another potential source of HBAs. Their relatively low intestinal absorption and susceptibility to environmental and microbial degradation mean that substantial quantities of flavonoids and their metabolites can reach the Gastrointestinal (GI) tract (Stevens & Maier, 2016; Braune & Blaut, 2016; Hanske *et al.*, 2013). The structural organization of flavonoids is particularly relevant to their degradation. Different portions of the flavonoid molecule can generate different phenolic acids. The B-ring can produce compounds including 4-HBA, 3,4-DHBA and 3,4,5-THBA depending upon its hydroxylation pattern, whereas degradation associated with the A-ring can ultimately produce 2,4,6-THBA (Sankaranarayanan *et al.*, 2019; Seeram *et al.*, 2001; Fleschhut *et al.*, 2006). Recent studies have demonstrated that *B. glycinifermentans* isolated from human GI tract can degrade quercetin, a flavonoid compound to generate 2,4,6-THBA and 3,4-DHBA (Sankaranarayanan *et al.*, 2021). This provides a mechanistic connection among diet, intestinal microbiota, generation of HBAs and exposure of colonic epithelial cells to these metabolites (Sankaranarayanan *et al.*, 2019; Sankaranarayanan *et al.*, 2020).

Hydroxybenzoic Acids and Cyclin-Dependent Kinases

One of the most interesting mechanistic observations concerning HBAs involves regulation of the cell cycle. CDKs coordinate progression through different phases of the mammalian cell cycle (Milletti *et al.*, 2023; Ding *et al.*, 2020). CDK4 and CDK6 participate primarily in G1 progression, CDK2 contributes to the G1/S transition, and CDK1 plays an important role later in cell-cycle progression. Dysregulation of these pathways is common in cancer, making CDKs important targets for anticancer drug development.

Experiments examining salicylic acid metabolites and derivatives demonstrated differential inhibition of these enzymes. 2,3-DHBA and 2,5-DHBA inhibited CDK1, while the trihydroxy derivative 2,4,6-THBA showed broader CDK inhibitory activity (Sankaranarayanan *et al.*, 2020; Dachineni *et al.*, 2017). Molecular docking analyses additionally suggested potential interactions between these compounds and CDKs (Sankaranarayanan *et al.*, 2020). These observations introduced an important possibility: metabolism could transform relatively weakly active parent molecules into metabolites with distinct interactions with cell-cycle regulatory proteins.

2,4,6-THBA: Evidence for a CDK-Dependent Mechanism

Subsequent work investigated 2,4,6-THBA in greater mechanistic detail. *In vitro* kinase experiments demonstrated dose-dependent inhibition of CDK1, CDK2 and CDK4 by 2,4,6-THBA (Sankaranarayanan *et al.*, 2019). Structurally related compounds such as phloroglucinol or 3,4,5-THBA failed to inhibit or did not reproduce the same degree of inhibition on CDKs, suggesting that activity depends on specific structural characteristics rather than simply the presence of multiple hydroxyl groups. Comparison of 2,4,6-THBA with 3,4,5-THBA and phloroglucinol was particularly informative as the relative positions of the hydroxyl groups and the presence of the carboxyl group influenced CDK inhibition, providing evidence for a structure-activity relationship among these compounds (Sankaranarayanan *et al.*, 2019).

The study also identified SLC5A8 as an important component of the cellular response to 2,4,6-THBA (Sankaranarayanan *et al.*, 2019). Functional expression of this monocarboxylate transporter facilitated uptake of 2,4,6-THBA. In cells expressing functional SLC5A8, exposure to the metabolite was associated with increased expression of the CDK inhibitors p21 and p27 and reduced proliferation. These findings suggest a potentially dual mechanism by which 2,4,6-THBA may exert its inhibitory action on cancer cell growth: In the first mechanism, 2,4,6-THBA is taken by cells through the transporter protein SLC5A8, then it binds to CDKs to inhibit the enzyme activity. In the second mechanism, 2,4,6-THBA may induce the expression levels of CDK inhibitors p21 and p27 causing a cell cycle arrest and inhibition of cell proliferation. The proposed model is particularly interesting for CRC because SLC5A8 localization at the apical surface of colonic epithelial cells could potentially facilitate exposure to metabolites generated within the intestinal lumen. Nevertheless, the physiological concentration achieved *in vivo* remains a critical question and requires further study.

2,3,4-THBA: Emerging Evidence for Another Bioactive HBA

More recent experiments have extended the investigation to 2,3,4-trihydroxybenzoic acid (2,3,4-THBA), a naturally occurring plant metabolite (Aker *et al.*, 2024). In this study, the

authors examined its effects on HCT-116 human colon cancer cells and MDA-MB-231 breast cancer cells. Cell-proliferation and clonogenic assays demonstrated dose-dependent inhibition of growth and colony formation. The compound did not substantially alter the examined HER2 or FGF-R expression but increased expression of the CDK inhibitors p21 and p27. These observations again point toward cell-cycle regulation as a potential mechanism underlying the antiproliferative response.

Molecular docking further predicted interactions of 2,3,4-THBA with CDK1, CDK2, CDK4 and CDK6, with stronger predicted interactions reported for CDK1, CDK2 and CDK4. Importantly, however, molecular docking demonstrates predicted molecular interactions rather than actual enzyme inhibition. In this regard, it is important to perform biochemical CDK enzyme assays to validate the results obtained from docking studies.

Structure-Activity Relationships Among HBAs

Taking together, the studies suggest that one of the most important emerging questions is not simply whether HBAs are biologically active, but why some HBAs are active whereas structurally similar compounds show markedly different effects.

For example, previous comparisons found growth inhibition with several HBAs, including 2,3-DHBA, 2,5-DHBA, 3,4-DHBA, 3,4,5-THBA and 2,4,6-THBA, whereas other related compounds demonstrated weaker or absent growth-inhibitory effects (Sankaranarayanan *et al.*, 2019, Sankaranarayanan *et al.*, 2020). 4-hydroxybenzoic acid, 2,4-DHBA and 2,6-DHBA did not show any inhibition of cell proliferation over a range of concentrations (Sankaranarayanan *et al.*, 2019, Sankaranarayanan *et al.*, 2020). Likewise, 2,4,6-THBA inhibited several CDKs whereas 3,4,5-THBA displayed substantially weaker or no CDK inhibition despite having the same number of hydroxyl groups (Sankaranarayanan *et al.*, 2019). Thus, biological activity appears to depend upon at least three related structural variables: number of hydroxyl groups; positional arrangement of hydroxyl groups; presence and position of the carboxyl group. These differences could influence transporter recognition, membrane uptake, binding orientation within protein pockets and interactions with specific amino-acid residues. This structure-activity relationship deserves substantially greater attention because it could potentially explain why individual HBAs act through different mechanisms.

Plants as a Source of Hydroxybenzoic Acids: Biosynthesis in Plants

Hydroxybenzoic acids are widely distributed plant phenolic metabolites that occur either in free form or as components of more complex specialized metabolites. Their biosynthesis is closely associated with the shikimate pathway, which connects primary carbohydrate metabolism with the formation of aromatic amino acids and numerous phenolic compounds (Maeda &

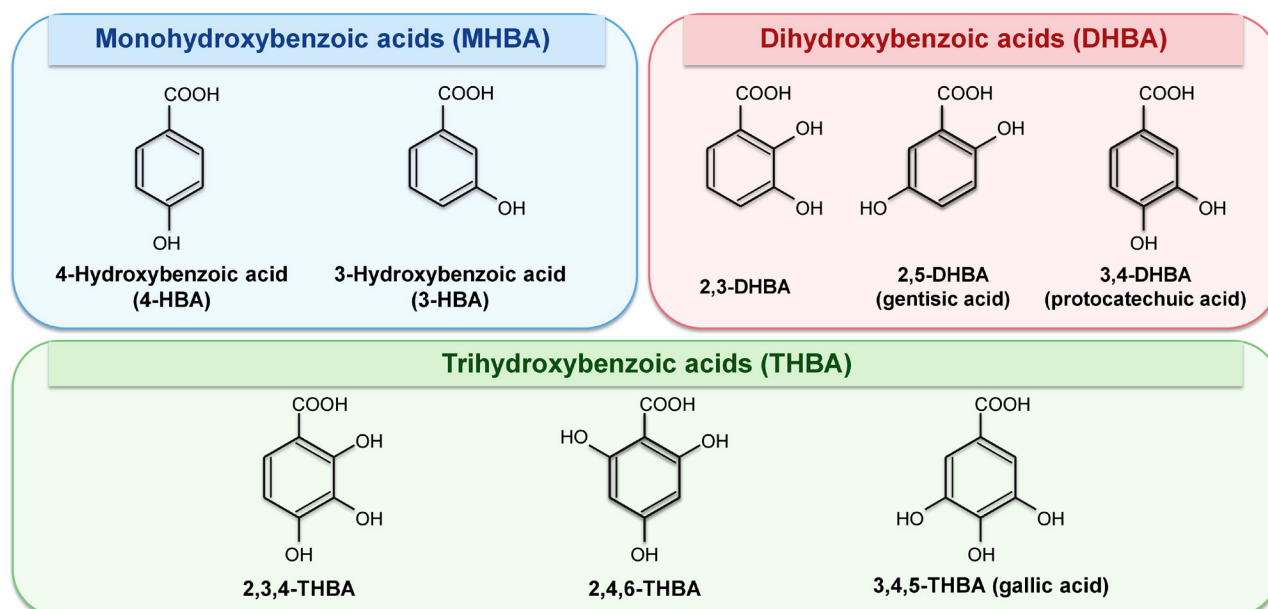


Figure 1: Structures of Monohydroxy Benzoic Acids (MHBA), Dihydroxy Benzoic Acids (DHBA) and Trihydroxy Benzoic Acids (THBA). The position of Carboxyl (COOH) and Hydroxyl (OH) groups in the benzene ring are indicated.

Dudareva, 2012). The pathway begins with condensation of Phosphoenolpyruvate (PEP), derived from glycolysis, and Erythrose-4-Phosphate (E4P), derived from the pentose phosphate pathway. Through a series of enzymatic reactions, these precursors generate 3-Dehydroquinate (3-DHQ), 3-Dehydroshikimate (3-DHS), shikimate and ultimately chorismate. Chorismate represents an important metabolic branch point leading to the aromatic amino acids phenylalanine, tyrosine and tryptophan. Phenylalanine generated through the shikimate pathway can be deaminated by Phenylalanine Ammonia-Lyase (PAL) to produce cinnamic acid. Cinnamate 4-Hydroxylase (C4H) subsequently generates p-coumaric acid, which then is converted to 4-HBA (Figure 2) (Maeda & Dudareva, 2012; Muir *et al.*, 2011; Bontpart *et al.*, 2016).

The biosynthesis of gallic acid (3,4,5-trihydroxybenzoic acid; 3,4,5-THBA) has been extensively investigated in plants (Muir *et al.*, 2011; Bontpart *et al.*, 2016). Earlier biochemical and isotope-labeling studies suggested several possible routes for 3,4,5-THBA (gallic acid) formation starting from 3-DHS via β -oxidation of a trihydroxycinnamic acid and hydroxylation of protocatechuic acid (3,4-DHBA) (Figure 2). Accumulating evidence now supports the early shikimate pathway, particularly 3-DHS, as an important precursor of gallic acid in several plant systems (Muir *et al.*, 2011; Bontpart *et al.*, 2016). Recognition of endogenous plant HBA biosynthesis and its presence in fruits and vegetables show that HBAs can also enter the body through diet (Kalinowska *et al.*, 2021; Juurlink *et al.*, 2014).

The Metabolite Hypothesis

The accumulated observations led to the proposal that HBAs may represent a mechanistic point of convergence between aspirin,

flavonoids and plant-based diets. According to this model (Figure 3), unabsorbed flavonoids and aspirin-related molecules reach the gastrointestinal environment, where host and microbial processes generate simpler HBAs. Degradation of aspirin/salicylic acid generates 2,3-DHBA and 2,5-DHBAs. Degradation of flavonoids can generate 4-HBA, 3,4-DHBA, 3,4,5-THBA and 2,4,6-THBA. Similar compounds are simultaneously introduced directly through foods as many fruits and vegetables contain free HBAs. These molecules can then enter epithelial cells and slow down the cell cycle progression via direct binding and inhibition of CDKs and or through upregulation of cell cycle regulatory proteins p21 and p27. A transient arrest in cell cycle may provide an opportunity for immune surveillance leading to destruction of cancer cells or DNA repair in cells containing damaged DNA, which are crucial steps for genomic stability and prevention of cancer (Sankaranarayanan *et al.*, 2020). This broader framework is especially relevant for colorectal cancer because compounds synthesized by plants can reach the colon both as free HBAs and as precursors that undergo further transformation in the gastrointestinal environment. The concept of metabolite hypothesis is diagrammatically represented in Figure 3. The hypothesis provides an attractive framework for integrating pharmacological, dietary and microbiome-associated observations. Nevertheless, the final step in this pathway—from experimentally demonstrated antiproliferative activity to actual prevention of cancer—requires considerably stronger evidence. It is to be noted that establishing a mechanistic link between plant HBA biosynthesis, dietary intake, intestinal concentrations and cancer prevention will require quantitative studies of HBA bioavailability and metabolism.

Critical Limitations of the Current Evidence and Future Research Directions

First, much of the experimental evidence has been generated using established cancer-cell lines. Such models are highly useful for identifying molecular mechanisms; however, it is to be noted that in these cells malignant transformation has already occurred. Therefore, it is important to validate these data in primary cultures of cells as well as in *in vivo* animal models. A second limitation concerns concentration. Demonstrating activity at micromolar or higher experimental concentrations does not by itself demonstrate that equivalent free concentrations occur in human colonic tissue after consumption of flavonoids, HBAs, or aspirin. A particularly informative experimental strategy would combine quantitative metabolomics with mechanistic and *in*

vivo approaches. HBA concentrations should be measured in intestinal contents, epithelial tissue, plasma and relevant biological specimens following controlled administration of defined precursor compounds or HBA-rich diets. Third, molecular docking studies indicate the potential of these HBAs to bind and interact with specific amino acid residues in CDKs; it does not conclusively prove their ability to inhibit CDK enzyme activity. While evidence has been provided for direct inhibition of CDKs by 2,4,6-THBA, 2,5-DHBA and 2,3-DHBA (Sankaranarayanan *et al.*, 2019, Sankaranarayanan *et al.*, 2020, Dachineni *et al.*, 2017), similar CDK assays have not been performed for 2,3,4-THBA (Akte *et al.*, 2024). For 2,3,4-THBA specifically, direct biochemical assays against CDK1, CDK2, CDK4 and CDK6 are needed to determine whether the interactions predicted by molecular modeling correspond to actual enzyme inhibition. A

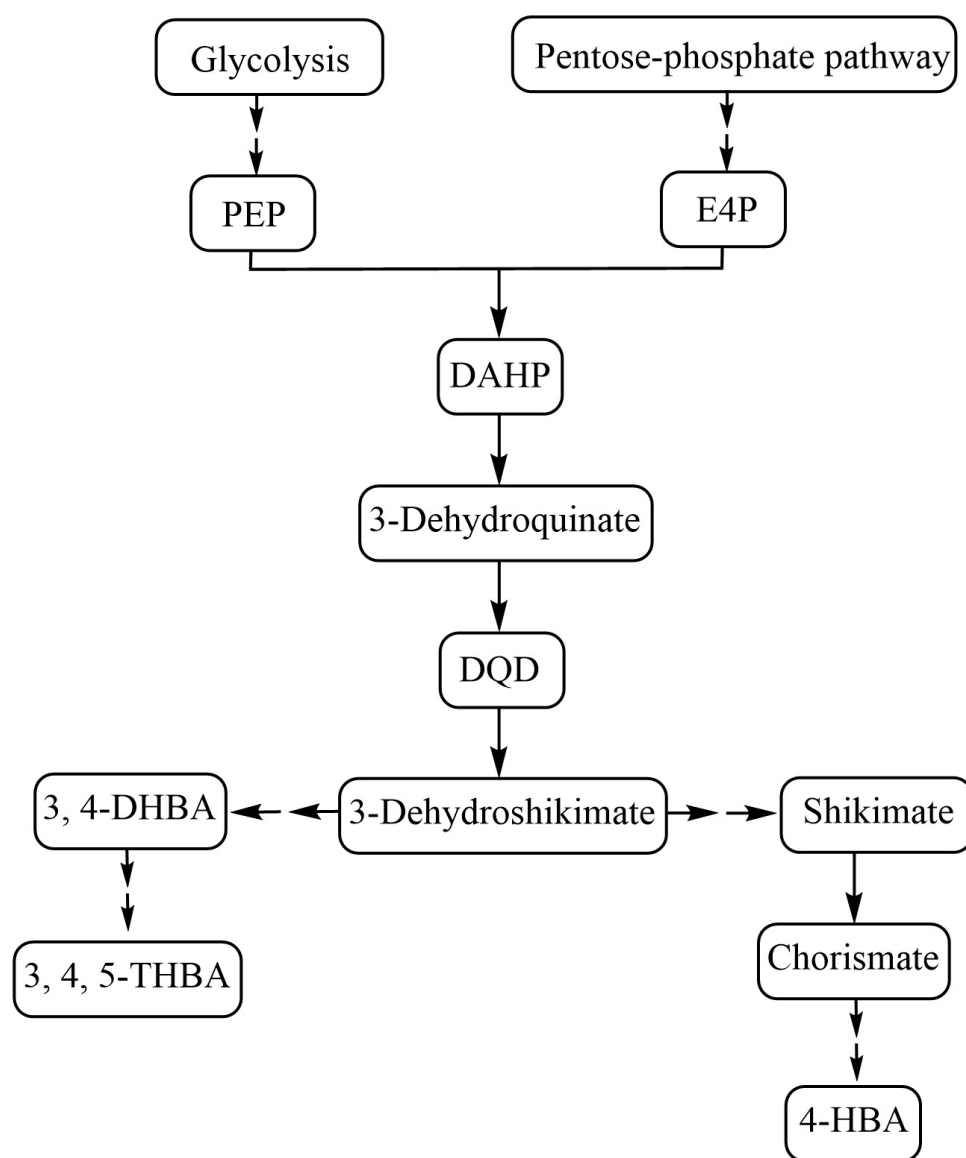


Figure 2: Schematic diagram showing the key intermediates of shikimate pathway diverted for the synthesis of HBAs (4-HBA, 3,4-DHBA and 3,4,5-THBA). Note that not all the sequential steps are shown in the diagram. PEP, phosphoenol pyruvate; E4P, erythrose-4-phosphate; DAHP, 3-deoxy-D-arabino-heptulosonate 7-phosphate; DQD, 3-dehydroquinate; 3,4-DHBA, 3,4-dihydroxybenzoic acid; 3,4,5-THBA, 3,4,5-trihydroxybenzoic acid; 4-HBA, 4-hydroxybenzoic acid.

Table 1: Summary of major Hydroxybenzoic Acids (HBAs), sources, experimental evidence and proposed mechanisms of actions. CDKs, cyclin-dependent kinases.

Compound	Major dietary source	Precursor / origin	Cancer models (studies)	Key biological effects	Proposed molecular targets / mechanism	Key limitations / future needs	References
2,3-DHBA	Berries, tea, some plant foods	Aspirin metabolite, dietary	Colon cancer cells (<i>in vitro</i>)	Inhibits CDK1 and CDK6; reduces proliferation	CDK1, CDK6	Physiological concentrations; <i>in vivo</i> validation	Hossain <i>et al.</i> , 2022; Stevens & Maier, 2016
2,5-DHBA	Leaves, legumes, some fruits	Aspirin metabolite, dietary	Colon cancer cells (<i>in vitro</i>)	Inhibits CDK1; reduces proliferation	CDK1	Limited <i>in vivo</i> data	Hossain <i>et al.</i> , 2022; Stevens & Maier, 2016
3,4-DHBA	Fruits, tea, vegetables	Dietary, flavonoid degradation	Colon cancer cells (<i>in vitro</i>)	Growth inhibition	Not fully defined	Mechanism unclear	Fleschhut <i>et al.</i> , 2006
3,4,5-THBA	Berries, grapes, tea, wine, nuts	Dietary, flavonoid degradation	Colon cancer cells (<i>in vitro</i>)	Inhibits proliferation weaker CDK inhibition than 2,4,6-THBA	Multiple (antioxidant, cell cycle)	Lower CDK activity; structure-dependent differences	Fleschhut <i>et al.</i> , 2006
2,4,6-THBA	Foods (limited), flavonoid degradation	Flavonoid metabolite	Colon cancer cells (<i>in vitro</i>)	Inhibits CDK1, CDK2, CDK4; increases p21/p27; reduces proliferation (SLC5A8-dependent)	CDKs, p21, p27, SLC5A8	Physiological concentrations; <i>in vivo</i> validation; microbial sources	Fleschhut <i>et al.</i> , 2006
2,3,4-THBA	Some fruits, plant metabolites	Dietary	Colon (HCT-116) and breast (MDA-MB-231) cancer cells (<i>in vitro</i>)	Inhibits proliferation and colony formation; increases p21/p27	Predicted interaction with CDK1, CDK2, CDK4, CDK6	Direct CDK inhibition not yet confirmed; <i>in vivo</i> studies needed	Kim <i>et al.</i> , 2016

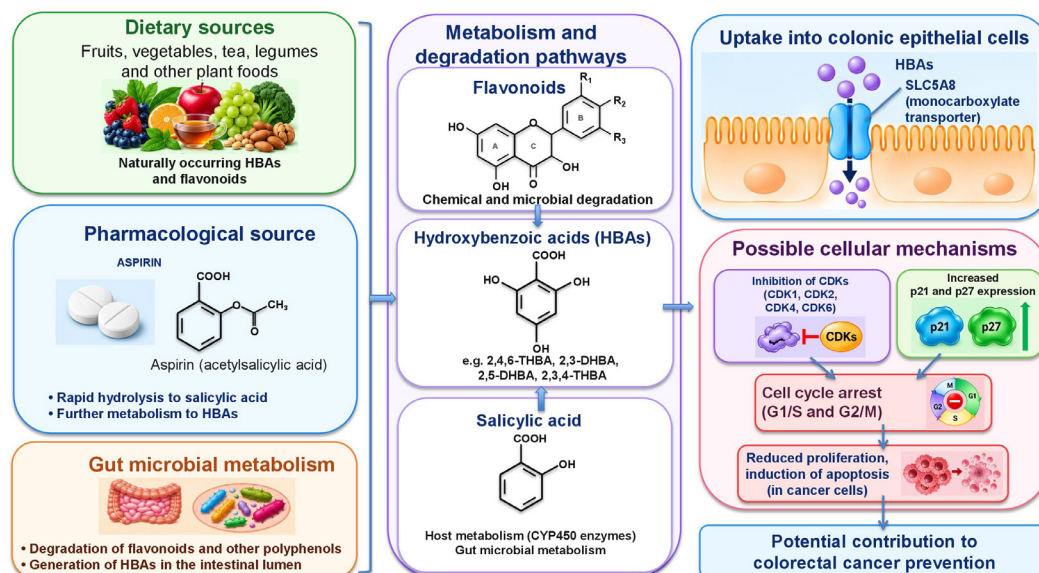


Figure 3: Metabolite hypothesis: Model depicting the convergence of pathways generating HBAs from flavonoids and aspirin through host/microbial enzymes. According to this hypothesis, flavonoids and aspirin/salicylic acids are degraded by host microbial enzymes to generate HBAs. Flavonoids differ in the number of hydroxyl group (OH) on the B ring (middle panel, top) and depending on the number of OH groups, degradation may produce 4-HBA, 3,4-DHBA or 3,4,5-THBA. The degradation of A ring of the flavonoid produces 2,4,6-THBA. HBAs are also obtained from dietary sources in free form. Degradation of aspirin and salicylic acid produces 2,3-DHBA and 2,5-DHBA. Some HBAs (e.g., 2,4,6-THBA) are taken up by SLC5A8, a monocarboxylic transporter into epithelial cells where they inhibit cancer cell proliferation by upregulation of cell cycle regulatory proteins p21 and p27, and by directly inhibiting CDKs. This may lead to cell cycle arrest and suppression of cancer cell growth (Sankaranarayanan *et al.*, 2020). R₁, R₂ and R₃ represent OH groups in the flavonoid rings. This figure was generated using AI (Microsoft Copilot software) but revised for clarity.

summary of major hydroxybenzoic acids (HBAs), their sources, experimental evidence and proposed mechanisms of actions is shown in Table 1.

The relationship between HBA structure and activity should also be investigated systematically using a panel of mono-, di-, and trihydroxybenzoic acids under identical experimental conditions. Such studies could establish quantitative structure-activity relationships and determine whether hydroxylation patterns favor CDK inhibition, transporter recognition or alternative molecular mechanisms. Finally, the microbiome component for a role in HBA-mediated cancer prevention requires additional investigations. If microbial degradation is central to HBA generation, individual variation in microbiome composition could substantially influence metabolite exposure and therefore biological response. A more detailed study with a set of human GI microbes with known flavonoids is necessary.

CONCLUSION

The available evidence supports HBAs as a biologically diverse class of phenolic metabolites capable of influencing cancer-cell proliferation. Studies of aspirin-derived metabolites, flavonoid-derived metabolites, and naturally occurring plant HBAs indicate that selected compounds interact with cell-cycle regulatory pathways, particularly CDKs and the CDK inhibitors p21 and p27. The collective evidence therefore supports continued investigation of metabolite hypothesis and additional studies are required to establish HBAs as clinically effective cancer-preventive agents. Establishing physiological exposure, identifying relevant microbial pathways, defining structure-activity relationships and demonstrating efficacy in appropriate *in vivo* prevention models represent important future studies.

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ABBREVIATIONS

CDKs: Cyclin-Dependent Kinases; **CRC:** Colorectal Cancer; **DHBA:** Dihydroxybenzoic Acid; **GI:** Gastrointestinal; **HBA(s):** Hydroxybenzoic Acid(s); **OH:** Hydroxyl Group; **THBA:** Trihydroxybenzoic Acid.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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