

REVIEW ARTICLE

Updated evidence on raspberries as functional foods: Anticancer bioactivity and therapeutic implications

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Abstract

Raspberries (RBs) (*Rubus idaeus*) are rich in bioactive compounds with promising anticancer properties. This review provides a comprehensive analysis of the anticancer effects of RBs, highlighting their potential as natural agents in cancer prevention and therapy. Bioactive compounds in RBs induce apoptosis, arrest the cell cycle, inhibit angiogenesis, and suppress metastasis. Preclinical studies demonstrate significant anticancer effects against colon, breast, lung, prostate, and cervical cancers, with clinical studies also supporting their therapeutic potential. Although preclinical findings are encouraging, further large-scale clinical trials are needed to confirm their efficacy and safety in humans. Optimizing formulations to enhance bioavailability and therapeutic effectiveness is crucial. This review emphasizes the potential of dietary interventions involving RBs as a complementary approach to conventional cancer therapies, paving the way for future research and clinical innovations.

KEYWORDS

angiogenesis inhibition, apoptosis, bioactive compounds, cancer, cell cycle arrest, chemoprevention, molecular mechanisms, raspberries

1 | INTRODUCTION

The American Cancer Society reports the rising rates of global cancer burden as the second cause of death worldwide (10 million deaths in 2020). As reported, by 2040 the future burden will probably be even larger until there are 27.5 million new cancer cases and 16.3 million reported cancer deaths, due to the increasing prevalence of modifiable risk factors, including smoking, unhealthy diet, and physical

inactivity (Bray et al., 2018). Furthermore, for the WCRF (World Cancer Research Fund International), understanding the role of so-called modifiable factors, such as diet, nutrition, physical activity, and body weight, is important to prevent cancer incidence and to support people living with and after cancer with appropriate recommendations. Consumption of at least 30 g of fiber and 400 g of fruit and vegetables every day can counteract some types of cancer, as well as prevent overweight and obesity. In fact, plant bioactives, fruits, and vegetables

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are the most important sources of phytochemicals, lead molecules for their properties, and bioactive actions (Azzini et al., 2024; Sharma et al., 2019; Tuli et al., 2021). Several plant products have demonstrated therapeutic and preventive effects toward cancer with few side effects, as well as reducing the adverse effects of treatments such as chemo- and radiotherapy. Only a few natural products, including podophyllotoxin, taxanes, and vinca alkaloids, are commercially available and used as anticancer agents (Motyka et al., 2023; Sousa-Pimenta et al., 2023). Berries and their related nutritional activities in humans and animals against different diseases have drawn the interest in the research field. Due to their broad spectrum of functions, including anti-inflammatory, antidiabetic, cardioprotective, anticancer, and therapeutic, berries are considered safe functional foods (UI Ain et al., 2022). Belonging to the Rosaceae family, different species of raspberries (RBs) are grown worldwide, including black, purple, and golden, but in Europe, the most common is the red one (*Rubus idaeus*) (Zhuo, 2008). RBs can be eaten as fresh, dried, frozen, or processed fruit, although many phytochemicals tend to be lower than in fresh fruit (Zhang et al., 2021). Its regular consumption, about a portion of 150 g, in the context of a balanced diet, can in fact help maintain good health and prevent various diseases. RBs contain few carbohydrates, a fair amount of dietary fiber, vitamin C, essential minerals, and several vitamins. The red coloring of the berry is due to the content of anthocyanins such as cyanidin, pelargonidin, and delphinidin (Giampieri et al., 2023). Other substances of phenolic nature include hydroxycinnamic acids, hydroxybenzoic acids, flavonols in free and conjugated form, and condensed tannins (Burton-Freeman et al., 2016). This review presents a thorough and current examination of the anticancer effects of RBs. It focuses on recent findings regarding their bioactive components, clarifies the molecular mechanisms involved, and evaluates how these laboratory research results can be translated into clinical settings.

2 | REVIEW METHODOLOGY

A comprehensive literature search was conducted using the National Library of Medicine (PubMed), ScienceDirect, and Google Scholar databases. The search terms included “raspberries,” “cancer,” “bioactive compounds,” and “anticancer mechanisms.” The search focused on English-language manuscripts published between 2004 and 2023. To ensure a thorough and systematic search, Medical Subject Headings terms, such as “Raspberries,” “*R. idaeus*,” “Cancer,” “Neoplasms,” “Bioactive Compounds,” “Phytochemicals,” “Polyphenols,” “Flavonoids,” “Anthocyanins,” “Ellagic Acid,” “Antineoplastic Agents,” “Apoptosis,” “Cell Cycle Arrest,” “Angiogenesis Inhibitors,” “Metastasis Suppression,” “Clinical Trials as Topic,” “In Vitro Techniques,” and “In Vivo Techniques,” were used. Boolean operators were employed to combine these terms and refine the search to include relevant studies. The inclusion criteria were as follows: (1) studies that investigated the anticancer properties of RBs or their bioactive compounds, (2) experimental studies conducted in vitro, in vivo, or clinical trials, and (3) studies that provided detailed information on the chemical composition and molecular mechanisms of action. Exclusion criteria

were as follows: (1) studies not related to cancer, (2) articles without full-text access, and (3) studies lacking detailed methodological information. The taxonomy of the RB species included in this review was validated using the World Flora Online database to ensure accurate classification (World Flora Online, 2023). The chemical structures of the identified bioactive compounds were verified using the PubChem database to confirm their molecular identities and properties (PubChem).

Relevant articles were meticulously reviewed, and data were extracted on the chemical composition, molecular mechanisms, pre-clinical and clinical evidence, and bioavailability of RB bioactive compounds. The extracted data were categorized on the basis of the type of study (in vitro, in vivo, and clinical), type of cancer, and the specific bioactive compounds investigated. The most representative and significant data were summarized in tables and figures for clarity and ease of interpretation.

3 | SOURCES, PHYTOCHEMISTRY, AND CHEMICAL STRUCTURE-ANTICANCER ACTIVITY RELATIONSHIP

3.1 | Natural sources

Rubus L. is one of the most varied and largest genera belonging to Rosaceae family; it comprises over 740 species, which are classified into 15 subgenera, with a great distribution in the world (Lopez-Corona et al., 2022; Rocabado et al., 2008) that includes several fruit species rich in nutrient and bioactive compounds (Aguilera & Toledo, 2022; Baby et al., 2018; Golovinskaia & Wang, 2021; Meng et al., 2022; Skrovankova et al., 2015). The over 250 heterozygous species within the *Rubus* genus comprise many economically important domesticated subgenera (Bobinaite, Viskelis, & Venskutonis, 2016), such as blackberry (*R. fruticosus* L.), red RB (RRB, *R. idaeus* L.), black RB (BRB, *R. occidentalis* L.), and yellow RB (YRB, *Rubus chingii* Hu), which are largely used as fresh products in the food industry, but also in the medicinal one (Meng et al., 2022). Different cultivars and varieties of RBs are widely distributed across the globe, primarily in Europe, North America, and the North and West of Asia (Zhuo, 2008) generally in regions with mild winters and long, moderate summers. Within the same species, there are several wild and native species and various cultivars, which have different colors, produced in Alaska, Scandinavia, but also in India, China, and Japan, which occupy a small niche in the world market (“Temperate fruit crop breeding: germplasm to genomics,” 2009). The Himalayan YRB (*Rubus ellipticus* Smith) and the Hill RB or Mysore RB (*Rubus niveus*), for example, are spread in the region mountain of India and Sri Lanka, respectively, as well as in wild throughout the temperate Himalayan region, in India, China, Thailand, and the Philippine Islands (Chen et al., 2020; Saini et al., 2014; Schulz & Chim, 2019). In Europe, the most common cultivars are the “RRB” (*R. idaeus* L. subsp. *Idaeus*), whereas in North America, the RRB (*R. idaeus* subsp., *strigosus* Michx) and the BRB (*R. occidentalis* L., *Rubus* subgen) are widespread (Bobinaite, Viskelis, & Venskutonis, 2016), the latter also established

locally in some European regions (Czech Republic, Slovakia, Russia, and Poland) (Schulz & Chim, 2019).

RRBs are the fourth most significant fruit product in the world (Skrovankova et al., 2015). These berries are commercially and economically important and more consumed than BRBs, which are less commonly diffuse and grown. RB fruits are a variety of small fleshy berries, an aggregate composite of individual drupelets, originating from the pistil of each flower, held together by almost invisible hairs with brilliant color (i.e., red, purple, orange, yellow, or black) as well as a flavor and taste own. RBs, with respect to other berries, are more susceptible to postharvest losses due to their high respiration rate, high ethylene production, and thin skin. By having a greater moisture loss, they are more vulnerable to fungal infections of the absence of an outer cuticle and to the presence of a cavity in the center of the fruit once picked. These "soft" fruits are very appreciated for culinary versatility and employment to making recipes and food products and for use of their constituent and/or extracts as an ingredient in functional food, nutraceutical, and dietary supplement productions (Guzmán et al., 2023; Imran Sheikh et al., 2021).

RBs are consumed majorly freshly but do not having a long shelf life, and once picked, they are often frozen or processed into purees, jams, juice (Diaconeasa et al., 2019; Zhang et al., 2019) and/or used as ingredients in ice cream, yogurt, desserts, wines, and brandy. Beyond the fruit, also other parts of plant such as stem, roots, leaves, seeds, and various by-products of their making can be utilized for nutraceutical, pharmaceutical and cosmetic application, and preparation (Baenas et al., 2020; Ispiryan et al., 2021; Li et al., 2022; Maric et al., 2020; Pavlovic et al., 2016; Teng et al., 2017; Vazquez-Gonzalez et al., 2020). By considering the product's sustainability, many RB residues of manufacture may be used as ingredients, because they are rich in dietary fiber, essential fatty acids, and phenolic compounds with a high added value or used for innovative and healthy food formulation as functional constituents, prebiotic, and technological components (Baenas et al., 2020; Bederska-Lojewska et al., 2021; Ispiryan et al., 2021; Li et al., 2022; Mannino et al., 2022; Schulz & Chim, 2019; Vazquez-Gonzalez et al., 2020; Zhang et al., 2019).

3.2 | Chemical composition

Table 1 reports a comparison of nutrient composition of RRB collected from different databases (Italian food composition tables AlimentiNU-Trizione, USDA database FoodData Central) and some studies express on fresh weight basis (FW). As showed in Table 1, these berries have a high-water content (ranging from 84.1 to 87.3 g/100 g), low protein (from 0.05 to 1.56 g/100 g), and lipid (from 0.0 to 0.65 g/100 g) resulting low in calorie (on average 51 kcal/100 g FW). RBs are rich in carbohydrates (2.68–12.5 g/100 g), mainly fructose and sucrose (>60% total sugars) (Ponder & Hallmann, 2020), and total dietary fiber (TDF, 6.1–7.4 g/100 g FW) compared to other berries (Baby et al., 2018) typically with 71% for the insoluble fraction (insoluble dietary fiber) (Baenas et al., 2020). Other beneficial compounds, including mineral such as Ca (ranged from 14.0 to 49.0 mg/100 g), Mg (ranged

from 16.5 to 24.2 mg/100 g), P (ranged from 20.0 to 52.0 mg/100 g), K (ranged from 134.0 to 225 mg/100 g), Mn (ranged from 0.12 to 2.0 mg/100 g), Zn (ranged from 0.17 to 0.61 mg/100 g), Cu (ranged from 13.0 to 155.0 µg/100 g), as well as Fe (ranged from 0.23 to 1.0 mg/100 g). Essential vitamins and fatty acids, mainly in seeds (Baby et al., 2018; Golovinskaia & Wang, 2021; Nile & Park, 2014; Rao & Snyder, 2010) (FoodData Central; AlimentiNUTrizione—Lamponi, Freschi), are also contained. In RBs, oleic acid and alpha-linolenic acid amounts (g/100 g total fatty acid) have been discovered most abundant respect to other berries (Zorzi et al., 2020). Moreover, chemical and phytochemical composition of RBs can be affected by various factors, including species, variety, and interaction among genotypes (Chen et al., 2013, 2020; Garcia et al., 2020; Kula et al., 2016; Mazur et al., 2014; Ponder & Hallmann, 2019; Saini et al., 2014; Yang & Choi, 2017), agricultural practices (Anjos et al., 2020; Evdokimenko et al., 2021; Ponder & Hallmann, 2019, 2020), production system, that is, organic versus conventional (Anjos et al., 2020; Frias-Moreno et al., 2021; Ponder & Hallmann, 2019), environmental factors (season, climate, weather condition, and timing of light exposure) geographic and location grown, stage of ripening (Anttonen & Karjalainen, 2005; Frias-Moreno et al., 2021; Ponder & Hallmann, 2019), harvest time (Shin et al., 2018), and postharvest storage conditions and manufacture (Giovannelli et al., 2014; Zhang et al., 2021). Therefore, it is very difficult to define a clear chemical profile of the various RB cultivars. Mazur et al. (2014) evaluating the RB genotype variations during three different picking times, found significant difference for both genotype (year-to-year variation) and harvest season (timing exposure of light), proving that the phenolic content, color (red), and overall features were significantly affected. In RRB fruits, growing technology seems to determine a different synthesis of primary and secondary metabolites. In a study conducted by Evdokimenko et al. (2021), the RBs grown with conventional technology showed a different mineral content, a superior phytonutrient content and higher antioxidant activity than RBs grown on nutrient media (by cultivating RB plants in pots filled with a nutritive substrate based on coconut fibers). Agricultural practices (Anjos et al., 2020; Ponder & Hallmann, 2019, 2020) have a potential to determine from low to a moderate increment of most nutrient relate to different levels of fertilization (such as nitrogen) applied to crops, as well the quality and composition of nutrients in the soil. As this regard, to comparing the RBs conventionally grown with those cultivated using nutrient substrate based on coconut fibers, Evdokimenko et al. (2021) did not found differences on total mineral amounts but have observed significant differences for individual element (e.g., the RBs grown on nutrient substrate contained 1.5 times more K and Na, 3 times more Se than conventionally RBs). Moreover, literature data about chemical composition are often contrasting (Arnold et al., 2022). By assessing the effect of fertilization systems (organic vs. conventional) on the physicochemical characteristics, bioactive compounds (polyphenolic profile and vitamin C content), and antioxidant capacity of RBs at three maturity stages (pink, ripe, and overripe), Frias-Moreno et al. (2021) did not found differences for their physicochemical characteristic, but they have found variation for bioactive compound synthesis, which was been influenced by fertilization system and

TABLE 1 Nutrient composition of raspberries (RBs) (*Rubus* spp.): Value expressed per 100 g of fresh weight (FW).

References	1	2	3	4	5	6
Macronutrients						
Water (g)	84.6	85.75	85.6 (84.1–87.3)	87.0 ± 11.0		
Energy (kcal)	49	52.0	51	–		
Protein (g)	1.0	1.2	1.01 (0.75–1.56)	0.05 ± 0.01		
Lipid (g)	0.6	0.65	0.19 (0.0–0.43)	0.02 ± 0.02		
Ash (g)			0.35 (0.25–0.45)	0.80 ± 0.10		
Carbohydrate (g)		11.94 ^a	12.9 ^a	12.0 ± 0.3		
Sugars (g) total	6.5	4.42	2.68	5.8 ± 0.1		(9.7–12.5) vs. (9.2–11.4)
Sucrose		0.2	<0.25	–		(2.3–5.8) vs. (1.9–5.8)
Glucose		1.86	0.99 (0.0–3.04)	–		(1.4–2.4) vs. (1.6–2.4)
Fructose		2.35	1.68 (0.0–3.58)	–		(4.7–6.7) vs. (4.0–5.7)
Dietary fiber (g)	7.4	6.5		6.1 ± 0.6		
Soluble dietary fiber (SDF)		–		1.9 ± 0.1		
Insoluble dietary fiber (IDF)		–		4.3 ± 0.2		
Total organic acids						
						(1430–1790) vs. (1430–1880)
Citric acid (mg)		–	1740 (1460–2190)			1380–1740) vs. (1370–1830)
Malic acid (mg)		–	54 (0.0–87.0)			(39.4–51.7) vs. (46.1–55.4)
Minerals						
Calcium (mg)	49	25.0	16 (14.0–23.0)		15–30	
Iron (mg)	1.0	0.69	0.45 (0.23–0.76)		0.4–0.6	
Magnesium (mg)		22.0	19.2 (16.5–24.2)			
Phosphorous (mg)	52	29.0	27 (22.0–35.0)		20.0–22.0	
Potassium (mg)	220	151.0	156 (134.0–206.0)		200.0–225.0	
Sodium (mg)	3	1.0	<2.5		0.5–1.0	
Zinc (mg)		0.42	0.22 (0.17–0.45)		0.32–0.61	
Copper (mg)		0.09	0.053 (0.013–0.155)		trace	
Manganese (mg)		0.67	0.494 (0.12–1.01)		1.5–2.0	
Selenium (µg)		0.2	–		–	
Vitamins						
Thiamin (vitamin B1) (mg)	0.05	0.032	0.03			
Riboflavin (vitamin B2) (mg)	0.02	0.038	0.04			
Niacin (vitamin B3) (mg)	0.50	0.598	0.6			
Pantothenic acid (vitamin B5) (mg)		0.329	0.329			
Pyridoxine (vitamin B6) (mg)		0.06	0.06			
Folate (vitamin B9) (mg)		21.0	21.0			
choline (mg)		12.3				
Ascorbic acid (vitamin C) (mg)	25	26.2 (18.6–34.2)	23.0			25.0–33.8) vs. (30.5–40.5)
Vitamin E (alpha-tocopherol) (mg)		0.87	0.87			
tocopherol, beta (mg)		0.06				
tocopherol, gamma (mg)		1.42				
tocopherol, delta (mg)		1.04				
Vitamin K, phyloquinone (µg)		7.38	19.3			
Carotene, beta (µg)		12.0	12			

(Continues)

TABLE 1 (Continued)

References	1	2	3	4	5	6
Carotene, alpha (μg)			–			
Biotina (μg)		3.43 (0–7.1)	3.43			
Vitamina A, RAE (μg)	13	2				
Luteina + zeaxanthin (μg)		136				

^aCalculate by difference 1—Italian food composition data fresh RBs (<https://www.alimentinutrizione.it/tabelle-nutrizionali/007740>); 2—(Baby et al., 2018; Golovinskaja & Wang, 2021; Rao & Snyder, 2010; data adapted from USDA reference) generic RB; 3—RB, fresh, raw; from FoodData Central ([usda.gov; https://fdc.nal.usda.gov/fdc-app.html#/food-details/2346410/nutrients](https://fdc.nal.usda.gov/fdc-app.html#/food-details/2346410/nutrients)); 4—Baenas et al. (2020); 5—Nile and Park (2014); 6—(Ponder & Hallmann, 2020) (n = 4 RB; cv. collected in summer and n = 1 Polka cv. collected in autumn) organic versus conventional (org vs. conv.) average of 2-year production.

ripening stage. In RBs, the organic fertilization may induce oxidative stress causing an increase in antioxidant defense mechanisms and so, an enhance the bioactive compound production, thus improving their antioxidant capacity (Frias-Moreno et al., 2021). In contrast, conventionally grown RBs showed a significantly higher vitamin C and organic acids (majorly malic acid) contents (Table 1) when have been compared to organic RBs (Ponder & Hallmann, 2020). Anyway, RB fruit from summer harvest contained more ascorbic acid than RB fruit from the autumn harvest, probably due to a major sun radiation exposition (more sun hours per day) and due to the enhanced availability of sugars as precursors of ascorbate synthesis in the summer (Ponder & Hallmann, 2019; Schulz & Chim, 2019).

RRBs are a great source of both vitamin C (ranged from 18.6 to 40.5 mg of ascorbic acid/100 g FW) and vitamin K (ranged from 7.8 to 19.3 μg phyloquinone/100 g FW).

3.3 | Phytochemistry

RBs have a high level of a wide range of bioactive molecules potentially able to perform beneficial effects. Figure 1 displays some well-known and previously reported chemopreventive compounds, including vitamins A, C, and E, and folic acid; calcium and selenium; carotene and lutein; phytosterols such as sitosterol and stigmasterol; triterpene esters; and phenolic molecules such as anthocyanins, flavonols, flavanols, proanthocyanidins, ellagitannins, and phenolic acids. In RB, anthocyanins contribute 84.2% by dry weight of the phenolics, the ellagitannins are 11.5%, ellagic acid and derivatives are 0.7%, and flavonols are 3.6%, which counts about 15.8% of non-anthocyanin phenolics (Shi & Chen, 2022).

In plant, the phenolic compounds (polyphenols) are generated through various chemical pathways to self-protection (Lopez-Corona et al., 2022), which is known that their concentration may increase as a response to abiotic and biotic stresses increases (Nejat & Mantri, 2017). As well described by Mohd (2021), the biosynthesis of the phenolic compound family begins into vacuoles of plant cells through the production of dehydroshikimate precursor (shikimate pathway) that by action of enzyme shikimate dehydrogenase can lead to the production of ellagitannins, gallotannins, or phenylalanine. Into phenylpropanoid pathway, the phenylalanine is involved into production of *p*-coumaroyl CoA; the last also represents the precursor of the flavonoid path-

way because through reaction with three molecules of malonyl CoA it brings to phenolic compound productions (i.e., anthocyanins and stilbenes). As Table 2 shows, phenolic compound family of RB includes four main flavonoid groups, with anthocyanins, flavonols, flavan-3-ols, tannins (in free and condensed form) and proanthocyanidins, and non-flavonoid compounds. Similarly, to other berries, the antioxidant activity is correlated to type and amount of bioactive compounds as well as their additively or synergistically interaction, that is, it was demonstrated that RBs more rich of phytochemicals showed a higher antioxidant capacity (Chen et al., 2013; Lopez-Corona et al., 2022; Toshima et al., 2021). Briefly, from a chemical point of view, flavonoids are divided in six sub-classes (anthocyanidins, flavonols, flavanones, flavanols, flavones, and isoflavones), and they are characterized for the presence of two phenyl rings linked by a pyran ring that may not have (i.e., aglycones) or may have a molecule of sugar bonded (glycoside or glucoside), and they can exhibited in various fruits a specific profile due to the absence or presence of characteristic groups. Flavanols can occur in a glycosylated or acetylated form; flavan-3-ols, predominantly as (+)-catechin, (–)-epicatechin, gallocatechin, and epigallocatechin, are anthocyanins when anthocyanidins bound the sugars to their chemical structures, while depending on the number and position of the interflavanic bonds, proanthocyanidins are type A and B polymers. The non-flavonoid group includes four subclasses: stilbenes, tannins, coumarins, and phenolic acids. Tannin class includes hydrolysable and condense tannins (in accordance with chemical bonds that link their monomers) and when conjugation also in complex tannins. Phenolic acids are seldom found as free acids, usually are present in the conjugated forms of esters and glycosides, and are categorized into three groups: hydroxybenzoic, hydroxyphenylacetic, and hydroxycinnamic acids (Bouyahya et al., 2022; Lopez-Corona et al., 2022).

3.3.1 | Flavonols and flavan-3-ols

Flavonols and flavan-3-ols are two flavonoids' subgroups, poorly soluble substances, detected in lower content in RB than other berries. They can act by antioxidant, antibacterial, and anticancer activities and can exert protection in cardiovascular illnesses. In red, RBs are detected only in small quantities of flavonols in free and conjugated form (majorly quercetin, rutin, and kaempferol) as presented in Table 2. The hydroxyl group at position 3 of the C-ring in their chemical

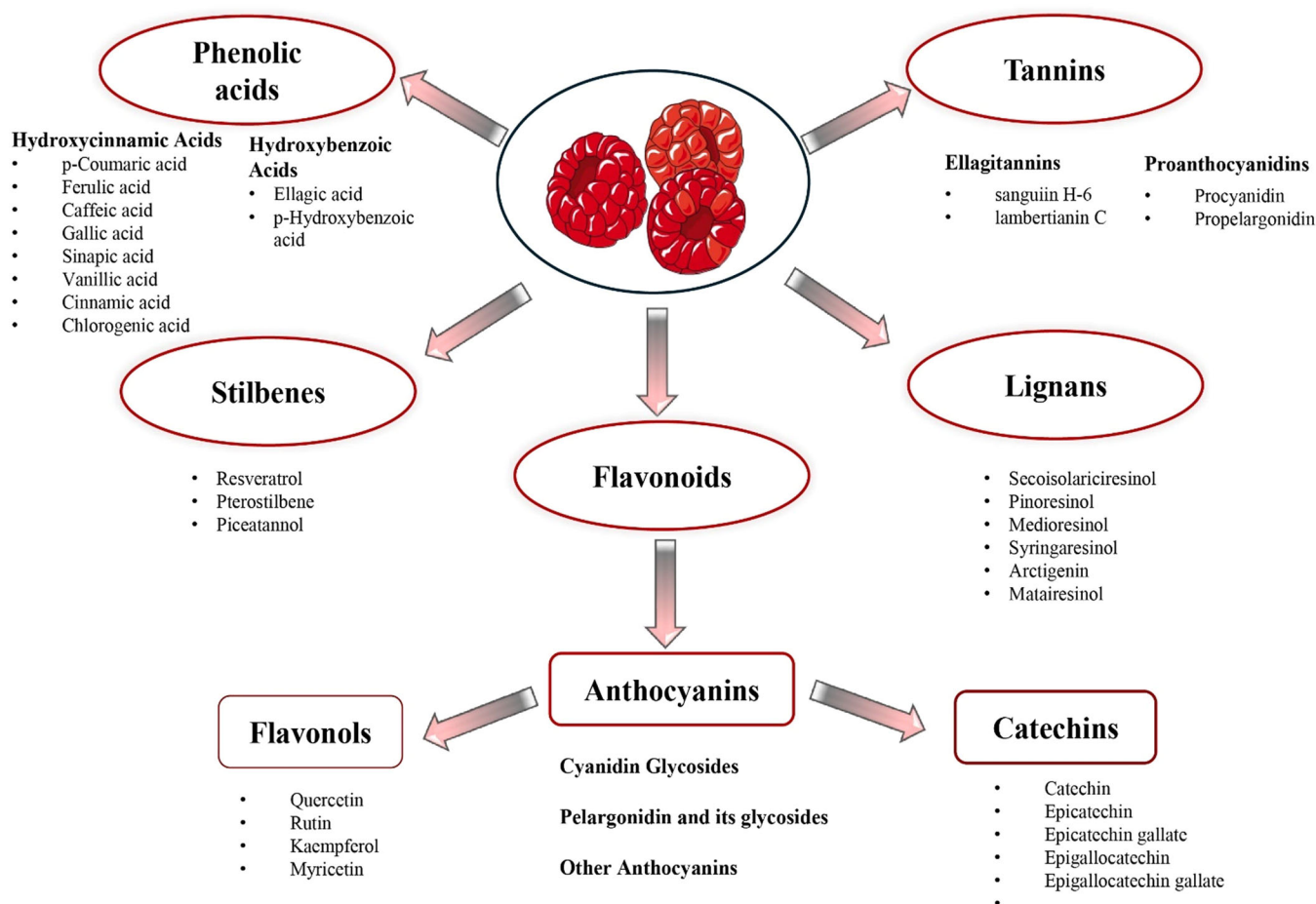


FIGURE 1 Diagram with bioactive components in raspberries.

structures may be substituted with several sugars, usually by galactose, glucose, and rutinose (Borges et al., 2010; Cervantes et al., 2020; Hao et al., 2021). BRB has significantly higher total flavonoid contents (ranging from 127.4 to 250.5 mg catechin equivalents [CE]/100 g FW) than red (ranging from 22.2 to 192.1 mg CE/100 g FW) and yellow RBs (120.7–179.0 mg CE/100 g FW: methanolic extract), and generally, they were more abundant in organic fruits and harvests at summertime. Similarly, by comparing the chemical composition of Korean BRB Bokbunja (*Rubus coreanus*, Miquel) with other berries, Yang and Choi (2017) found the highest total flavonoid contents than cultivated and wild types (127.4 > 47.9 > 22.6 mg (±)–CE/100 g FW, respectively). Basu and Maier (2016) reported that BRB extract had the highest flavonoid content (expressed as quercetin equivalent [QE]) with respect to RRB (Table 3): 186.4:114.5 mg QE/g of fruit extracts, respectively. Table 3 shows the total flavonoid content, expressed as mg CE/100 g FW determined in various RB cultivars.

The presence of flavonol glycosides in various RBs was not confirmed in different studies (Borges et al., 2010; Liu et al., 2020; Marhuenda et al., 2016; Mazur et al., 2014; Mikulic-Petkovsek et al., 2012) due to both species variety and cultivation type (wild vs. cultivated; conventional vs. organic) as well as variation in their concentration with season, time, and temperature storage were recorded

(Anjos et al., 2020; Marhuenda et al., 2016; Ponder & Hallmann, 2019). The concentration of total phenolic compounds is, in fact, affected by maturity stage, by increasing to increase stage of maturity (Frias-Moreno et al., 2021). As this regards, there has been reported variation, due to an increase of concentration of anthocyanins during stage of maturation (Rodriguez-Pulido et al., 2017), storage time, and temperature used (Borges et al., 2010; Marhuenda et al., 2016; Mikulic-Petkovsek et al., 2012; Ponder & Hallmann, 2019), on the contrary during maturing have been reported in BRB (*R. occidentalis*) a decreasing of many phenolic compound contents, including majorly ferulic acid and rutin, as well as gallic acid, caffeic acid, p-coumaric acid, myricetin, luteolin, and kaempferol (Shin et al., 2018). Several literature data reported RBs as a small source of quercetin-3-glucoside and quercetin-3-glucuronide representing a major flavonols in RB fruits (Kula et al., 2016; Mazur et al., 2014). Anyway, quercetin-3-glucoside, quercetin-3-rutinoside, quercetin-3-glucuronide, and kaempferol glucuronide have been identified in both red and BRBs (Kassim et al., 2009; Maatta-Riihinen et al., 2004; Mikulic-Petkovsek et al., 2012; Sariburun et al., 2010), but BRB significantly showed a higher quercetin value than red ones (Basu & Maier, 2016; Schulz & Chim, 2019; Yang & Choi, 2017). Similarly, in Korean BRB (*R. coreanus*), quercetin (450 mg/kg FW) and kaempferol (25.0 mg/kg FW) are most

TABLE 2 Phenolic compound family of raspberry (RB).

Principal flavan-3-ols and flavonols	Anthocyanins	Principal phenolic acids and hydrolysable tannins	Condensed tannins
Kaempferol glycosides: • Kaempferol-3-rutinoside • Kaempferol-3-glucoside • Kaempferol-glucuronide Quercetin glycosides: • Quercetin-3-glucuronide • Quercetin-3-rutinoside = rutin • Quercetin-3,4'-diglucoside • Quercetin-3-O-galactoside = hyperoside • Quercetin-3-O-glucoside = isoquercitrin • Quercetin-3-rhamnoside = quercitrin • Isorhamnetin = 3-methylquercetin CatechinEpicatechinMyricetinLuteolin	Cyanidin glycosides: • Cyanidin-3,5-O-di glucoside • Cyanidin-3-rutinoside • Cyanidin-3-sophoroside • Cyanidin-3-glucosyl rutinoside • Cyanidin-3-sambubioside • Cyanidin-3-sophoroside-5-rhamnoside • Cyanidin-3-(2-glucosylrutinoside) Pelargonidin and its glycosides: • Pelargonidin-3-glicoside • Pelargonidin-3-sophoroside • Pelargonidin-3-rutinoside Peonidin-3-rutinosidePetunidin-3-glucosideDelphinidin-3,5-di-O-glucosideMalvidin glycosides	Gallic acid:p-Hydroxybenzoic acidp-Coumaric acidChlorogenic acidCaffeic acidFerulic acid (cinnamic acid derivate)Ellagic acid and its glycosidesEllagitannins: • Sanguin H-6 • Lambertianin C	Proanthocyanidins: • Procyanidin • Propelargonidin
References	References	References	References
Borges et al. (2010), Bouyahya et al. (2022), Cervantes et al. (2020), Hao et al. (2021), Mikulic-Petkovsek et al. (2012), Ponder and Hallmann (2019), Schulz and Chim (2019), Shin et al. (2018), Skrovankova et al. (2015)	Borges et al. (2010), Bouyahya et al. (2022), Cervantes et al. (2020), Hao et al. (2021), Kula et al. (2016), Marhuenda et al. (2016), Ponder and Hallmann (2019), Schulz and Chim (2019), Veberic et al. (2015)	Borges et al. (2010), Bouyahya et al. (2022), Cervantes et al. (2020), Hao et al. (2021), Jakobek et al. (2007), Kula et al. (2016), Schulz and Chim (2019), Shin et al. (2018), Smeriglio et al. (2017)	Rao and Snyder (2010), Smeriglio et al. (2017)

concentrated respect to red and wild RB cultivars (Schulz & Chim, 2019; Yang & Choi, 2017). (+)-catechin was reported as a major flavan-3-ol at a concentration of 2.4 mg/100 g FW (Rao & Snyder, 2010). Moreover, the most abundant flavan-3-ols present in RRB (*R. idaeus*) are catechin (range from 14.9 to 730 mg/kg FW) and epicatechin (range

from 18.1 to 450 mg/kg FW), with lesser amount of quercetin (ranged from 0.3 to 0.7 mg/kg FW), that in *R. coreanus* was more represented (450 mg/kg FW) (Schulz & Chim, 2019). The contents in total phenolics, anthocyanins, and ellagic acid of various cultivars of RBs (*Rubus* spp.) are presented in Table 4. As reported, the values have been col-

TABLE 3 Total flavonoid contents of raspberries (RBs) (*Rubus* spp.) expressed as mg catechin equivalents (CE)/100 g fresh weight (FW).

mg catechin equivalents (CE)/100 g fresh weight		Rubus species	References
RRB (<i>Rubus idaeus</i> and other cultivars)			
RRB (variety Encore)		43.8 ± 4.2	Gansch et al. (2009)
RB (<i>Rubus idaeus</i> L., diamond jubilee)		22.2	Cervantes et al. (2020)
RRB (<i>Rubus idaeus</i>)		47.9	Yang and Choi (2017)
Wild RB (<i>Rubus crataegifolius</i> , Bunge—Korea)		22.6	Yang and Choi (2017)
RRB: 3 cultivars “Laszka,” “Glen Ample,” and “Glen Fine” of organic vs. conventional RB at summer time harvest		93.5–111.1 vs. 82.6–103.1	Ponder and Hallmann (2019)
RRB (<i>Rubus idaeus</i>)		114.5 (mg quercetin equivalents)/g	Basu and Maier (2016)
Organic vs. conventional RB (cv. Polka): at autumn time harvest		71.4–108.5 vs. 74.8–108.5	Ponder and Hallmann (2019)
Chinese wild RB (<i>Rubus hirsutus</i> Thunb.)		192.1 (small fruits) to 68.23 (large fruits)	Fu et al. (2015)
BRB: <i>Rubus occidentalis</i> and other cultivars			
BRB—10 cultivars: “Allen,” “Black Hawk,” “Black Knight,” “Hanover,” “Huron,” “Jewel,” “Mac Black,” “Munger,” “New Logan,” and “Plum Farmer”		150.3–250.5	Gansch et al. (2009)
Korean BRB Bokbunja (<i>Rubus coreanus</i> , Miquel)		127.4	Yang and Choi (2017)
BRB		186.4 (mg quercetin equivalents)/g	Basu and Maier (2016)
YRB various cultivars			
One yellow-fruited BRB (PI 618560, USDA-ARS National Clonal Germplasm Repository, Corvallis, OR)		120.7 ± 5.3	Gansch et al. (2009)
Yellow Himalayan RB (<i>Rubus ellipticus</i>): (a) methanol extract; (b) acetone extract		a. 179.0 b. 307.4	Saini et al. (2014)

TABLE 4 Total phenolics, anthocyanins, and ellagic acid composition of RBs (*Rubus* spp.): Values are expressed per 100 g of fresh weight (FW).

RRB (<i>Rubus idaeus</i> and other species)				
	Total phenolics (mg gallic acid/100 g FW)	Anthocyanin contents (mg/100 g FW)	Total ellagic acid contents (mg/100 g FW)	References
RRB (<i>Rubus</i> spp.) different cultivars (n = 12)	192.0–359.0	19.0–51.0 (as mg cyanidin-3-glucoside)	38.0–118.0	Anttonen and Karjalainen (2005)
Red RBs (<i>Rubus idaeus</i>)	517.0	65.0	47.0	Wada and Ou (2002)
RRB (variety Encore)	342.0 ± 36.5	36.2 ± 0.5 (as mg cyanidin equivalent)		Gansch et al. (2009)
RRB various cultivars (n = 17): "Sputnica," "Norna," "Novokitaevskaja," "Aborigen," "Mirazh," "Lashka," "Glen Moy," "Meeker," "Zorinka," "Siveli," "Benefis," "Ottawa," "Husar," "Polesie," "Polana," "Polka," "Pokusa"	278.6–503.9	29.2–130.6 (as mg cyanidin-3-glucoside)	119.8–310.3	Bobinaite et al. (2012)
RB (<i>Rubus idaeus</i> L., diamond jubilee)	140.0 ± 4 (mg gallic acid equivalents/100 g FW)	74.0 ± 6 (as sum of total anthocyanins identified) or 23.0 ± 1 (as mg cyanidin-3-glucoside equivalent)	–	Cervantes et al. (2020)
RRB: fruits extract	434.3 ± 6.3 (mg gallic acid equivalents/g FW)		–	Basu and Maier (2016)
RRB different cultivars (n = 5)		92.1 ± 19.7 (as sum anthocyanin glycosides identified)	–	Wu et al. (2006)
Red RBs (<i>Rubus idaeus</i>)		133.9 ± 8.4 (as sum anthocyanins identified)	–	Marhuenda et al. (2016)
RRB (<i>Rubus idaeus</i>)		39.4–53.9 (as sum anthocyanins identified)	263.7–330.9 (majorly ellagitannins: 260.0–326.2 mg/100 g FW)	Koponen et al. (2007)
RRB (<i>Rubus idaeus</i> L., var. Heritage): RB extract with high antocyanins and low sugar		130.1	377.1	Hao et al. (2021)
RB <i>Rubus</i> species: 2 cv. (1) <i>R. inominatus</i> S. Moore; (2) <i>R. niveus</i> Thunb (Hill RB)	(1) 126.0 ± 0.3 (2) 402.0 ± 0.7	(1) 52.0 ± 0.6 (2) 230.0 ± 2.2 (as mg cyanidin-3-glucoside)	–	Moyer et al. (2002)
RB (Glen Lyon) during stage of maturation from very early (1 stage) to overripe (7 stages)	From 894.0 to 298.0 (mg gallic acid/100 g FW)	From 7.5 to 60.8 (as mg malvidin-3-glucoside/100 g FW)	–	Rodriguez-Pulido et al. (2017)
Different genotypes of <i>Rubus chingii</i> Hu: variation of phenological phases		From 12.7 to 58.6 (as mg total monomeric anthocyanins/100 g FW)	5.32–10.98 (red fruits); 9.47–30.71 (green-to-yellow fruits)	Chen et al. (2021)

(Continues)

TABLE 4 (Continued)

RRB (<i>Rubus idaeus</i> and other species)				
	Total phenolics (mg gallic acid/100 g FW)	Anthocyanin contents (mg/100 g FW)	Total ellagic acid contents (mg/100 g FW)	References
RRB (<i>Rubus idaeus</i>)	142.1 (mg gallic acid equivalents/100 g FW)	43.3 (as mg cyanidin-3-glucoside equivalents/100 g FW)	-	Yang and Choi (2017)
Wild RRB (<i>Rubus crataegifolius</i> , Bunge—Korea)	92.2 (mg gallic acid equivalents/100 g FW)	18.0 (as mg cyanidin-3-glucoside equivalents/100 g FW)	-	Yang and Choi (2017)
RRB: 3 cv. "Laszka," "Glen Ample," "Glen Fine" of organic vs. conventional RRB at summer time harvest (range of 2 years)	156.4–160.0 vs. 127.0–148.0	82.5–104.0 vs. 73.8–98.1	-	Ponder and Hallmann (2019)
RRB (cv. Polka) of organic vs. conventional at autumn time harvest (average or range of 2 years)	152.2 vs. 146.05	67.7–96.6 vs. 69.5–94.9	-	Ponder and Hallmann (2019)
Chinese wild RRB (<i>Rubus hirsutus</i> Thunb.): variation of contents in fruits with different sizes	269.0 (small fruits)–108.23 (large fruits)	Total anthocyanins 12.43 (small fruits) 16.71 (large fruits)	-	Fu et al. (2015)
BRB (<i>Rubus occidentalis</i> and other cultivars)				
	Phenolics (mg/100 g FW)	Anthocyanin contents (mg/100 g FW)	Total ellagic acid contents (mg/100 g FW)	References
BRB (<i>Rubus occidentalis</i>)	980.0	589.0	90.0	Wada and Ou (2002)
BRB 10 cultivars: "Allen," "Black Hawk," "Black Knight," "Hanover," "Huron," "Jewel," "Mac Black," "Munger," "New Logan," and "Plum Farmer"	489.3–875.3	259.7–396.4 (as mg cyanidin equivalent)	-	Gansch et al. (2009)
BRB (<i>Rubus occidentalis</i> L., Bristol)	714.7 ± 15.5	325.5 ± 6.9 (as mg cyanidin-3-glucoside)	323.5 ± 17.0	Bobinaite et al. (2012)
BRB	965.6 ± 2.9 (mg gallic acid equivalents/g FW)	-	-	Basu and Maier (2016)
BRB cultivar (n = 1)	687.0 (as sum anthocyanin glycosides identified)	-	-	Wu et al. (2006)
<i>Rubus occidentalis</i> L. and hybrid black RBs, cultivar (n = 3): "Earlsweet," "Jewel," "Munger"	890.0–1079.0	464.0–627.0 (as mg cyanidin-3-glucoside)	-	Moyer et al. (2002)
Korean BRB (<i>Rubus coreanus</i> , Miquel, Bokbunja)	291.1 (mg gallic acid equivalents/100 g FW)	274.2 (as mg cyanidin-3-glucoside equivalents/100 g FW)	-	Yang and Choi (2017)
One yellow-fruited BRB (PI 618560, USDA-ARS National Clonal Germplasm Repository, Corvallis, OR)	425.6 ± 24.9	6.9 ± 2.3 (as mg cyanidin equivalent)	-	Gansch et al. (2009)
(Continues)				

TABLE 4 (Continued)

RRB (<i>Rubus idaeus</i> and other species)		Total phenolics (mg gallic acid/100 g FW)	Anthocyanin contents (mg/100 g FW)	Total ellagic acid contents (mg/100 g FW)	References
YRB (various cultivars)					
YRB (cv. Beglianka)		391.1 ± 13.0	2.1 ± 0.1 (as mg cyanidin-3-glucoside)	229.0 ± 10.9	Bobinaite et al. (2012)
YRB, cultivar (n = 2)		241.0–265.0	120.7 ± 5.3 (mg cyanidin equivalent)	58.0	Anttonen and Karjalainen (2005)
Himalayan YRB (<i>Rubus ellipticus</i>): (a) methanol extract; (b) acetone extract		a. 550.0 b. 782.7 (mg of gallic acid equivalent/100 g of frozen fruits)			Saini et al. (2014)

lected from different studies and are expressed per 100 g of fresh fruit.

Considerable variation in the phenolic compounds among red, black, and YRB cultivars (Table 4) is shown. Total phenolics quantified from literature data for RRBs varied from 92.2 to 894.0 (mg of gallic acid/100 g FW) as well as were observed differences due to stage maturation (decrease: very early > overripe), agricultural practices (organic > conventional), and size fruits (small > large). A higher level of total phenolic compounds has been reported in BRBs (ranging from 291.0 to 1079.0 mg of gallic acid equivalent/100 g FW), than red and yellow RBs. In RBs, the main phenolic compounds are anthocyanins and ellagitannins, both of which are reported to be the main promoters of RBs' antioxidant activity (Nile & Park, 2014; Rao & Snyder, 2010; Teng et al., 2017).

3.3.2 | Anthocyanins

Anthocyanins exhibit a basic skeleton of C6-C3-C6 and derive from binding sugars to anthocyanidins. They are the natural pigments responsible for the color of many fruits and vegetables and are very unstable and susceptible to degradation. Indeed, the chemistry of anthocyanins and their stability can be influenced by several factors, such as oxygen, enzymes, temperature, light, and pH (Khoo et al., 2017; McGhie & Walton, 2007). The anthocyanins profile of RBs is highly variable among different species, and their prevalence form is glycosides of their respective anthocyanidins (also called aglycone). The prevailing anthocyanins in RBs are cyanidin, cyanidin-3-O-sophorose, cyanidin-3-O-glucosylrutinoside, cyanidin-3-O-glucoside, cyanidin-3-O-rutinoside, and cyanidin-3-O-sambubioside, as well as presence in trace of pelargonidin derivatives (Borges et al., 2010; Kula et al., 2016; Ludwig et al., 2015; Rocabado et al., 2008). The profile is characteristic, and because the cyanidins were typically glycosylated with 3-sophorose (56%) in cultivated RRB, with 3-sophorose (30%) and 3-glucose (27%) in wild RRB, and with 3-rutinoside (80%) in Arctic bramble, the composition of the predominant anthocyanins was used to distinguish the *Rubus rosso* species from each other. Only in BRBs cultivars (*R. occidentalis* L.; "Blackcap" and "Black Jewel") was found cyanidin-3-xylosyl-rutinoside as a typical *Rubus* species' anthocyanin in [48]. Table 4 reports the anthocyanin levels among different berries. Their levels in BRBs, vary from 259.7 to 627.0 mg of anthocyanin/100 g of fresh fruit, by showing higher concentrations than in red (from 19.0 to 230.0 mg of anthocyanin/100 g of fresh fruit) and yellow RBs (from 2.1 to 120.7 mg of anthocyanin/100 g of fresh fruit). Marhuenda et al. (2016) reported a slightly higher total anthocyanin content in RB (133.9 ± 8.4 mg/100 g) than other berries (blueberries), as well as the cyanidin-3-glucoside (57.5 ± 3.4 mg/100 g) and cyanidin-3-glucosylrutinoside (56.4 ± 3.8 mg/100 g) were recognized as the main anthocyanins in RB, subsequently cyanidin-3-rutinoside (19.6 ± 1.2 mg/100 g) and cyanidin-3-sophorose at very low concentration (0.4 ± 0.1 mg/100 g). In fresh RBs (*R. idaeus* L., Diamond Jubilee), peonidin-3-glucoside, cyanidin-3-O-glucoside, and pelargonidin-3-O-rutinoside were also found, which represented 39%, 26%, and 13% of

the anthocyanins analyzed (Cervantes et al., 2020). Anyway, the presence of peonidin-3-glucoside in RB has not been reported in other studies (Veberic et al., 2015). RBs grown with organic fertilization improved their total phenolic compound content at all stages of ripening, and ripe RBs were characterized by a higher ellagic acid and gallic acid content and showed higher values of antioxidant capacity (Frias-Moreno et al., 2021), just as a high positive correlation was found between the total anthocyanin or total polyphenol content and antioxidant capacity in ripe RB fruits (Iqbal et al., 2022; Toshima et al., 2021).

3.3.3 | Ellagitannins

Ellagitannins are hydrolysable tannins widely distributed in berries, located within the vacuoles of the plant cell and responsible for most health benefits. Their acidic or basic hydrolysis releases hexahydroxydiphenyl units, which spontaneously form ellagic acid, and this reaction is commonly used for the detection and quantification of dietary ellagitannins (Bobinaite, Viskelis, Bobinas, et al., 2016; Koponen et al., 2007). Koponen et al. (2007) reported in RRB a content of ellagitannins ranged from 260.0 to 326.2 mg/100 g FW. Anyway, the amount of dietary ellagitannin as well as the determination of the precise structure is difficult to evaluate for their molecular complexity (Bobinaite, Viskelis, Bobinas, et al., 2016). Sanguin H-6 dimer represents the principal ellagitannins in RBs, followed by the tetramer C lambertianin, a lower amount of sanguin H-10, and small quantities of ellagic acid, which is product of their hydrolysis (Borges et al., 2010; Kula et al., 2016; Liu et al., 2020; Ludwig et al., 2015; Veberic et al., 2015). In RRBs (*R. idaeus*), there has been reported a high content of Lambertianin C (376 mg/kg FW), whereas in BRB (*R. occidentalis*), there has been found a major content of sanguin H-6 that ranged from 14.8 to 15.4 mg/kg FW (Schulz & Chim, 2019).

3.3.4 | Phenolic acids

RB contains a higher concentration of phenolic acids and hydrolyzable tannins in comparison to flavonol contents. RRBs contain several hydroxycinnamic acids (*p*-coumaric, ferulic, caffeic, gallic, sinapic, vanillic, and cinnamic acids), hydroxybenzoic acids (ellagic and *p*-hydroxybenzoic acids), and their conjugates (Golovinskaia & Wang, 2021; Gulcin et al., 2011; Lee et al., 2012; Maatta-Riihinen et al., 2004; Rao & Snyder, 2010). As shown in Table 4, RRB found a higher concentration the total ellagic acid (varied from 38.0 to 377.1 mg/100 g FW) than in black (90.0–323.5 mg/100 g FW) and yellow ones (58.0–229.0 mg/100 g FW). Moreover, Schulz and Chim (2019) have reported among phenolic acids, usually found in their conjugated forms as esters and glycosides a higher level of *p*-hydroxybenzoic acid (ranged from 233 to 534 mg/kg FW) in RRBs (*R. idaeus*), as well as for gallic acid (622 mg/kg FW) in yellow ones (*R. ellipticus*). About hydroxycinnamic acids, it was found a great variability in the amount of caffeic acid (ranged from 22.5 to 754 mg/kg FW), ferulic acid (ranged from 0.9 to 820 mg/kg FW), and *p*-coumaric acid (ranged from 0.5 to

361 mg/kg FW) in RRB, whereas chlorogenic acid was more represented in hill RB (*R. niveus*) and YRB (*R. ellipticus*) cultivars. The volatile compounds of RBs also play a key role in imparting their flavor and aroma, along with the other nutraceutical compounds. In this berry, the main volatile compounds include monoterpenes, acids, alcohols, esters, aldehydes, ketones, hydrocarbons, C-13 norisoprenoids, lactones, sesquiterpenes, furans, sulfur, and phenols (Aprea et al., 2015).

4 | BIOAVAILABILITY AND PHARMACOKINETICS OF RBS

Many studies have shown that the protective effect of so-called bioactive substances, almost all of which are of plant origin and, for this reason, also referred to as phytochemicals, is carried out by virtue of the regular consumption of plant foods such as fruit, vegetables, whole grains, seeds, nuts, legumes, and certain spices. Eating phytochemicals through food consume, such as RBs and/or their integration in diet, could provide us the protection and positive biological effect that they provide to the plants, for example, the capacity to neutralize free radicals in the body, mitigating the damaging effects of oxidative stresses on cells, thus reducing the risk of chronic diseases in animal and human. Their preventive action is carried out by influencing various cellular activities and preventing the risk of chronic degenerative diseases, including certain forms of cancer and cardiovascular disease. Many positive effects are attributed to bioactive compounds, such as antioxidant and anti-inflammatory activities; modulation of enzymes with detoxifying action; stimulation of the immune system; regulation of hormone metabolism; and antibacterial and antiviral activities (Tuli et al., 2021). Therefore, their consume has been related to the prevention of many human pathologies like degenerative, metabolic, cardiovascular, or ocular illnesses and certain types of cancer (Battino et al., 2009; Battino et al., 2019; Burton-Freeman et al., 2016; Golovinskaia & Wang, 2021; Lopez-Corona et al., 2022; Nile & Park, 2014; Rao & Snyder, 2010; Shi & Chen, 2022). In vitro and in vivo studies report that they can act as potent antioxidants to prevention oxidative stress and certain types of cancer (Guttenplan et al., 2016; Lopez-Corona et al., 2022; Mace et al., 2014), cardiovascular diseases (Battino et al., 2019; Burton-Freeman et al., 2016; Lim et al., 2023), type II diabetes, obesity (Guo et al., 2012), neurodegenerative diseases associated with aging (as Alzheimer's and Parkinson's diseases) (Burton-Freeman et al., 2016; Hussain et al., 2018), help to regulate gut microbial composition and metabolite profile (Lim et al., 2023) and fight various infections (Battino et al., 2009; Jimenez-Garcia et al., 2013; Lim et al., 2023; Nile & Park, 2014; Rao & Snyder, 2010; Singh et al., 2020). To exert their beneficial activities, phytochemicals must be bioavailable, after release from the food matrix blood absorption and transportation to the tissues. Numerous investigations have demonstrated that *R. idaeus* exhibits many pharmacological activities, but several factors can affect bioavailability depending on the nature of the food and on who consumes it, including bioaccessibility, food matrix effect, transporters, molecular structures, and metabolizing enzymes. On the other hand,

the different structural phytochemicals present in RBs may give rise to different chemical characteristics, physiologic benefits, and pharmacokinetic behaviors, and approximately 194 compounds have been isolated from *R. idaeus*, which is rich in phenols, terpenoids, alkaloids, steroids, and fatty acids. Ludwig et al. studied 10 volunteers upon 300 g of homogenized RBs consumption showing an extensive degradation of RB anthocyanins and ellagitannins in a great variety of metabolites, including methyl-, glycine-, glucuronide-, and sulfate derivatives of phenolic acids, phenylpropanoids, ellagic acid, and urolithins. Anthocyanins' metabolism gets underway in the upper GIT probably due to pH with 4'-hydroxy hippuric acid and ferulic acid derivatives circulating in plasma with a maximum (or peak) serum concentration (C_{max}) at 1–1.5 h after consumption of RBs. Compounds originating from it had plasma C_{max} times of 424 h and were still being excreted in urine 32–48 h after the ingestion of RBs. High interindividual variability was found in the amounts and type of urolithin conjugates probably due to different colonic microflora composition (Ludwig et al., 2015). Several factors, including absorption, metabolism, distribution, and excretion after drug administration, could impact the bioavailability before its transport to the site for its effect. As well described by Lopez-Corona et al. (2022), RB's anthocyanins are absorbed and metabolized into the colon; only a few glycosidic forms of dietary anthocyanins are absorbed into the stomach and small intestine, and their metabolites are glucuronide, sulfate, glycine, and methyl derivatives. On the contrary, the metabolism of ellagitannins, stable molecules in the stomach, because they have high molecular weight and are too large to be absorbed, starts in the colon by transformation into ellagic acid prior to interacting with gut the microbiota, to followed by transformation into urolithins for action microflora: Their final concentrations will vary between individuals, because the microbiota of the host may also differ. The final derivatives from ellagitannins are urolithin-A, isourolithin-A, and urolithin-B, which can be quantified in both plasma and urine, whereas sulfate, glucuronide, glycine, and methyl derivatives represent the final metabolites of anthocyanins. Until reaching the small and large intestines where interact with the intestinal microbiota of the host, ellagitannins and anthocyanins are stable, and only low amounts of anthocyanins are directly absorbed into the small intestine. After ingestion of RB extracts, the metabolic behavior of phenolic compounds seems to be mainly influenced by pH and intestinal microbiota; therefore, in vitro digestion could indirectly reflect the metabolic behavior of the main active phenolics and so to optimize the understanding of the potential benefits for the human body (Lopez-Corona et al., 2022).

5 | PRECLINICAL ANTICANCER STUDIES

Several studies have been conducted in the past, using tissue culture techniques and animal models, supporting the beneficial properties of these individual phytochemicals in RBs (Rao & Snyder, 2010; Ravoori et al., 2012).

5.1 | In vitro studies

The following Table 5 summarized some promising candidates for future preclinical studies (in vitro) and food-based chemoprevention strategies for several types of cancer. Significant cytotoxicity at IC₅₀ value of $8.6 \pm 1.9 \mu\text{M}$ was observed in the HCT116 cell line due to a flavonoid with a 2-(phenanthren-9-yl)-4H-chromen-4-one structure from *Rubus rosifolius* S.Vidal (Rosaceae) (Yin et al., 2024). Seeram et al. (2006) found an inhibition of two colon cancer cell proliferation by increasing concentration of different RB extracts, and the proapoptotic effects were probable stimulated by cyclooxygenase-2 (COX-2) expression. A different degree of potency was reported between cell line with an IC₅₀ 187.60 ± 0.01 for RB IC₅₀ 89.11 ± 0.02 BRB in HT-29, whereas in HCT116 IC₅₀ of 188.00 ± 0.01 and 89.00 ± 0.02 , respectively, for RB and BRB. Compared to untreated controls, cells treated with BRB extracts showed a 3-fold higher induction to apoptosis than untreated controls, while those with RB extracts 1.7-fold. RB extract showed proapoptotic effects to stimulate apoptosis of the COX-2 expressing colon cancer cell line, HT-29. Guo et al. (2020) reported the chemoprevention role of anthocyanins from BRB in colorectal cancer (CRC) (SW480 and Caco2 cell line). Thus, BRB anthocyanins could impact on the expression of specific miRNAs that abnormal expression is usually associated with CRC development. In their study, exploring the ability of BRB anthocyanins in affects the expression of these mRNAs in human CRC cell lines (LoVo and SW480), the authors found a significant cell proliferation inhibition with respect to the control (no BRB supplement). Later, to provide a new treatment strategy for CRC, the same authors [2020] used BRB anthocyanins in addition to chemotherapeutic drugs. In fact, the authors found that BRB anthocyanins enhanced the antiproliferative effects of 5-fluorouracil and celecoxib in CRC cells by regulating miR-483-3p/DKK3/Wnt/ β -catenin and miR-338-5p/SIRT1-related pathways, thus influencing CRC progression. Medium cytotoxicity IC₅₀ value of $24.1 \pm 0.8 \mu\text{M}$ from 5-phenylthiophene-2-carbaldehyde a flavonoid derivative from *R. rosifolius* S.Vidal (Rosaceae) was highlighted against human breast cancer (MDA-MB-435) by Yin et al. (2024). George et al. (2022) described the capability of a root extract of *Rubus fairholmianus* (10 $\mu\text{g/mL}$) to activate apoptosis in breast cancer cells (MCF-7 cells). The proposed mechanism is the decreased cellular proliferation and apoptosis by increasing cytoplasmic cytochrome c and caspase 3/7 p53 and Bax and by decreasing (Bcl-2). Cancer breast cells (MCF-7) exposed to RB and BRB extracts at 25–200 $\mu\text{g/mL}$ for 48 h, displayed a cell proliferation inhibition with an IC₅₀ for RB 190.80 ± 0.05 and BRB 145.40 ± 0.04 , respectively (Seeram et al., 2006). Antioxidant and antiproliferative constituents from fruits of *R. chingii* Hu extract were screened in MCF-7 cancer breast cell. Among these constituents, tormentic acid demonstrated the greatest cytotoxicity against cancer breast cell. The observed cytotoxicity against MCF-7 was 91.84% at the concentration of 100 $\mu\text{g/mL}$ with IC₅₀ of tormentic acid MCF-7 = 24.23 $\mu\text{g/mL}$ (Zhang et al., 2017). A BRB volatile extract significantly suppresses the proliferation of A549 lung cancer cells (ATCC CCL-185) at IC₅₀ 1.5 mg/L at 48 h showing a

TABLE 5 Anticancer activities of *Rubus* extracts and bioactive compounds in various pharmacological experimental models.

Study type	Cancer type	Cell line (in vitro)/model (in vivo)	Extract/compound concentration/dosage	Results/mechanism of action	References
In vitro studies	Oral leukoplakia	MSK-Leuk1	BRB extract (70% anthocyanins) IC50 = 160 µg/mL	↑GSH, ↓DBP-induced DNA damage ↓DBPDE-dA levels from 360.7 ± 114.9 to 92.1 ± 34.0	Chen et al. (2022)
			Flavonoid (2-(phenanthren-9-yl)-4H-chromen-4-one) IC50 = 8.6 ± 1.9 µM	Cytotoxicity ↑Apoptosis	Yin et al. (2024)
			RB extract IC50 = 187.60 ± 0.01 µg/mL	↑COX-2 expression ↑Apoptosis	Seeram et al. (2006)
	Colon cancer	HCT116	BRB extract IC50 = 89.11 ± 0.02 µg/mL	↑COX-2 expression ↑Apoptosis	
			RB extract IC50 = 188.00 ± 0.01 µg/mL	↑Apoptosis	
			BRB extract IC50 = 89.00 ± 0.02 µg/mL	↑Apoptosis	
	Breast cancer	SW480	BRB anthocyanins	↓miR-483-3p; ↓CRC cell proliferation and migration	Guo et al. (2020)
			Flavonoid (5-phenylthiophene-2-carbaldehyde) IC50 = 24.1 ± 0.8 µM	Medium cytotoxicity; ↑Apoptosis	Yin et al. (2024)
			Rubus <i>fairholmianus</i> root extract IC50 = 10 µg/mL	↑Cytochrome c, ↑Caspase 3/7, ↑p53, ↑Bax, ↓Bcl-2; ↑Apoptosis	George et al. (2022)
	Lung carcinoma	A549 (ATCC CCL-185)	RB extract IC50 = 190.80 ± 0.05 µg/mL	↑Apoptosis	Seeram et al. (2006)
			BRB extract IC50 = 145.40 ± 0.04 µg/mL	↑G0/G1 phase; ↓G2/M phase; ↓Procaspase-3/9; ↓PARP ↑Apoptosis	Gu et al. (2022)
			RB seed extract IC50 = 14.07 ± 0.96 µg/mL	↑Apoptosis	Simonovic et al. (2021)
		A549	Tormentoric acid IC50 = 62.36 µg/mL	↑Apoptosis	Zhang et al. (2017)

(Continues)

TABLE 5 (Continued)

Study type	Cancer type	Cell line (in vitro)/model (in vivo)	Extract/compound concentration/dosage	Results/mechanism of action	References
	Oral cancer	KB	RB extract IC50 = 95.40 ± 0.02 µg/mL	↑Apoptosis	Seeram et al. (2006)
			BRB extract IC50 = 80.80 ± 0.11 µg/mL	↑Apoptosis	
		CAL-27	RB extract IC50 = 164.50 ± 0.08 µg/mL	↑Apoptosis	
		CAL-27	BRB extract IC50 = 92.58 ± 0.08 µg/mL	↑Apoptosis	
Prostate cancer	LNCaP	LNCaP	RB extract IC50 = 100.00 ± 0.06 µg/mL	↑Apoptosis	
			BRB extract IC50 = 66.75 ± 0.06 µg/mL	↑Apoptosis	
		HeLa	RB extract -	↑p53, ↑FAS, ↑caspase-anti-proliferative ↑Apoptosis	
	Cervical cancer	C33A	YRB extract (acetone and methanol) EC50 = 5.04 and 4.9 mg/mL	↓Proliferation; viability reduced to 40%, ~60% inhibition; Acidic extracts reduced viability to 60%, ~40% inhibition	Saini et al. (2014)
		HeLa	BRB ethanol extract 25, 100, 200 µg/mL	-54% proliferation; +210% apoptosis; Maximum decrease in HeLa growth of 54% compared to control	Sham et al. (2021)
		SiHa	BRB ethanol extract 25, 100, 200 µg/mL	-45% proliferation; +180% apoptosis; maximum decrease in SiHa growth 52% compared to control	
		C-33A	BRB ethanol extract 25, 100, 200 µg/mL	-38% proliferation; +70% apoptosis; maximum decrease in C-33A growth of 67% compared to control	
Vulvar squamous cell carcinoma	VSCC	VSCC	BRB extract 200, 400, 800 µg/mL	↑Caspase-14 ↑Apoptosis	Joehlin-Price et al. (2014)
			Tormentic acid IC50 = 40.57 (HepG2), 54.22 (Bel-7402) µg/mL	↑Apoptosis HepG-2 = 82.81%, Bel-7402 = 80.18% at 100 µg/mL	
	Liver cancer	HepG2, Bel-7402			Zhang et al. (2017)
		Huh7	RRB extract 49.20 mg/mL	↑Apoptosis; ↑S phase; PTEN/AKT pathway regulation; Increased apoptosis from 38.43% ± 2.13% to 56.43% ± 3.12%	

(Continues)

TABLE 5 (Continued)

Study type	Cancer type	Cell line (in vitro)/model (in vivo)	Extract/compound concentration/dosage	Results/mechanism of action	References
In vivo studies	Colitis-associated CRC	Mouse model of colitis-associated CRC	BRB 10% (w/w)	↑Fecal microbiome health	Rodriguez et al. (2022)
				↑Colon length	
				↓Tumor multiplicity	
				No apparent effect on colitis signs, colon inflammation, or mucosal damage	
Melanoma		A375 xenograft immunodeficient BALB/C nude mice	Total saponins from <i>Rubus parvifolius</i> L. (TSRP)	↓Tumor growth	Cao et al. (2021)
				↓Lung metastasis	
Ehrlich's ascites carcinoma and Dalton's lymphoma ascites		Murine tumor-bearing model	Raspberry pulp polysaccharides (RPPs)	↑Cellular immune response	Yang et al. (2015)
				Antitumor activity	
Hepatocellular carcinoma		Mouse model	Methanol extract of <i>Rubus ellipticus</i> leaves (RELM) 250 mg/kg	↑Life span by 46.76%; ↓Volume of DLA solid tumors by 2.5 cm	George et al. (2015)
Hepatocellular carcinoma		Mouse model	Total alkaloids of <i>Rubus alceifolius</i> Poir (TARAP) –	↓Notch signaling pathway (Notch1, delta-like ligand 4, jagged 1); ↓VEGF A; ↓VEGF receptor-2;	Zhao et al. (2015)
				↓tumor angiogenesis	

Note: ↑—Increase; ↓—decrease.
Abbreviations: ATCC CCL-185, A549 cell line from American Type Culture Collection; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; BRB, Black Raspberry; BRBDE-dA, Benzol[a]pyrene-7,8-dihydrodiol-9,10-epoxide-deoxyadenosine; COX-2, cyclooxygenase-2; CRC, colorectal cancer; DBP, dibenzo[a,h]pyrene; DBPDE, dibenzo[a,h]pyrene-11,12-dihydrodiol-13,14-epoxide; DLA, Dalton's lymphoma ascites; EC50, Half maximal effective concentration; G0/G1 phase, Gap 0/Gap 1 phase of the cell cycle; G2/M phase, Gap 2/Mitosis phase of the cell cycle; GSH, glutathione; IC50, half maximal inhibitory concentration; LNCaP, lymph node carcinoma of the prostate; miR-483-3p, MicroRNA-483-3p; PARP, poly (ADP-ribose) polymerase; PTEN/AKT, phosphatase and tensin homolog; RB, red raspberry; RELM, methanol extract of *Rubus ellipticus* leaves; RRB, red raspberry bush; TSRP, total saponins from *Rubus parvifolius* L.; VEGF, vascular endothelial growth factor; VSCC, vulvar squamous cell carcinoma; w/w, weight/weight ratio; YRB, yellow raspberry bush.

strong suppression in A549 viability by suppressing the expression of procaspase-3 and 9 and PARP. BRB volatile extracts overturn the cell cycle progression at G0/G1 phase cell population slightly increased ($69.6\% \pm 2.8\%$) compared to the control ($63.8\% \pm 6.1\%$) and cell population in G2/M phase slightly decreased ($14.3\% \pm 4.4\%$) compared to the control ($22.3\% \pm 3.5\%$) (Gu et al., 2022). In addition, an RB seed extract selectively inhibits the growth of human lung cancer cells in vitro (Simonovic et al., 2021). Authors found RB seeds extract antiproliferative versus A-549 cells at $IC_{50} = 14.07 \pm 0.96 \mu\text{g/mL}$ but inactive ($IC_{50} > 300 \mu\text{g/mL}$) in MRC-5 cells as well as non-mutagenic toward normal MRC-5 lung cells. Tormentic acid, extracted from *R. chingii*, exhibited excellent cytotoxicity activities against A549 with an IC_{50} of tormentic acid A549 = $62.36 \mu\text{g/mL}$. The observed inhibition rate was 83.6% and 72.41% at the concentration of 200 and 100 $\mu\text{g/mL}$, respectively (Zhang et al., 2017). *R. idaeus* L. extracts exhibited almost fulfilled inhibition on the invasion ($p < .001$) of highly metastatic A549 cells by reducing activities of matrix metalloproteinase-2 (MMP-2) and urokinase-type plasminogen activator (u-PA) by Yih Shou Hsieh et al [2013]. On human oral leukoplakia cell model (MSK-Leuk1) powder BRB extract containing approximately 70% anthocyanins at a concentration of 160 $\mu\text{g/mL}$ in culture media enhances the synthesis of glutathione (GSH) increasing its conjugation of the fjord-region dibenzo[a,l]pyrene (DBP) diol epoxide (DBPDE) derived from DBP leading to inhibition of DBP-induced DNA damage. Chen et al. (2022) found that BRBE decreased DBPDE-dA levels from 360.7 ± 114.9 DBPDEdA/106 dA to 92.1 ± 34.0 DBPDE-dA. BRB and RRB extracts inhibit growth and stimulate apoptosis of oral cancer cells in KB with IC_{50} for RB 95.40 ± 0.02 and black rasp 80.80 ± 0.11 as well as in CAL-27 with IC_{50} 164.50 ± 0.08 and IC_{50} 92.58 ± 0.08 for RB and black rasp, respectively (Seeram et al., 2006). Same authors exposed to berry extracts LNCaP (prostate cancer model) and found an inhibition of cell proliferation by RB of $IC_{50} = 100.00 \pm 0.06$ and black rasp $IC_{50} = 66.75 \pm 0.06$, respectively. RB extract showed possible anticancer activity against cervical cancer. Sham and colleagues [2021] treated HeLa cells with RB extract producing a decrease in cells in comparison to controls. The antitumor effect was demonstrated by increasing expression of antiproliferative molecule P53 and rising expression of proapoptotic molecule tumor necrosis factor receptor superfamily member 6 (FAS). Antioxidant and antiproliferative activities of phenolics isolated from fruits of Himalayan YRB (*R. ellipticus*) were tested on human cervical cancer cells by Saini et al. (2014). Although no inhibition activity was exposed against HeLa cells, the extracts showed potent antiproliferative activity against C33A cells (40%–60%). The inhibition of C33A cell proliferation was dose-dependent and the same degree of inhibition was observed with the different extracts (EC_{50} 5.04 and 4.9 mg/mL acetone and methanol extracts fruit concentration, respectively). BRB ethanol extract prevents cell growth and controls apoptosis in different cervical cancer cells. A 5-day continuous exposure to BRB ethanol extract displayed a decrease proliferation of 43% (HeLa), 53% (SiHa), and 45% (C-33A), respectively. When exposed to BRB ethanol extract for 3 days, HeLa cells displayed -54% proliferation $\pm 210\%$ apoptosis, SiHa cells showed -45% proliferation $\pm 180\%$ apoptosis, and C-33A cells revealed -38% proliferation $\pm 70\%$ apop-

tosis. Joehlin-Price et al. (2014) examined in vitro effects of a BRB extract on a vulvar squamous cell carcinoma (VSCC) cell line. Caspase-14 is a key protein in malignant and premalignant vulvar squamous lesions, predominantly absent or markedly reduced in VSCC cell lines. After BRB extract treatment with 200, 400, and 800 $\mu\text{g/mL}$, VSCC cell cultures showed a significant increase in caspase-14 (p values .024, .021, and .014, respectively) in comparison to untreated cells (control).

RRB extract was able to inhibit, also, the growth of hepatocellular carcinoma (HCC) cells (Zhang et al., 2018). RRB extract prevented cell cycle process and induced the apoptosis in HepG2 and Huh7 cells by IC_{50} 49.20 mg/mL. The treatment with 10, 25, and 50 mg/mL of RRB extract significantly increased the percentage of HepG2 cells in S-phase from $35.29\% \pm 3.23\%$ to $42.32\% \pm 3.08\%$, to $45.65\% \pm 2.72\%$, and to $52.78\% \pm 3.84\%$, respectively, in comparison to the control group by suppressing HCC cell proliferation through controlling the phosphatase and tensin homolog (PTEN)/AKT signaling pathway. The expression levels of P27 were significantly increased in and authors concluded that RRB induced S phase arrest through the changes of cyclin-CDK proteins. Antioxidant activity and cytotoxicity was exerted by tormentic acid extract from extracted from *R. chingii* Hu showed an $IC_{50} = 40.57 \mu\text{g/mL}$ and $IC_{50} = 54.22 \mu\text{g/mL}$, respectively, for in HepG-2 and Bel-7402. High inhibition rates above 80% against HepG-2 and Bel-7402 (82.81% and 80.18%, respectively) at the concentration of 100 $\mu\text{g/mL}$ were reported by Zhang et al. (2017). Moreover, neuroprotective effects of phenylpropanoid enantiomers from RRB in human neuroblastoma SH-SY5Y cells were also provided by Zhou et al. (2018). As can be seen from the table of in vitro studies, the antitumor activities are attributable to different phytochemical compounds found in RBs as well as the metabolic processes through which they exert their cytotoxicity by inhibiting cell proliferation, inhibiting migration, and inducing apoptosis. Different cell models as well as different types and concentrations of the extracts are used in the different studies. To be able to deduce an unambiguous result for each cell of the different cancer types is difficult, although anticancer activities are well established.

5.2 | In vivo studies

In a recent study (Rodriguez et al., 2022), the supplementation with BRB 10% (w/w) conducted on a mouse model of colitis-associated CRC reduced tumor multiplicity and increased colon length, whereas it did not apparently affect colitis signs, colon inflammation, or mucosal damage. The composition of the fecal microbiome also improved in favor of taxa with presumed health benefits. Cao et al. (2021) measured a remarkable anti malignant melanoma effect of total saponins from *Rubus parvifolius* L. (TSRP) in A375 xenograft immunodeficient BALB/C nude mice. The TSRP treatment effectively blocked the tumor growth in immunodeficient nude mice as well as significantly inhibited the lung metastasis of melanoma. In addition, the RB pulp polysaccharides (RPPs) showed antitumor activity in vivo against malignant melanoma, using a murine tumor-bearing model, partly by enhancing the cellu-

lar immune response of the host organism. These properties of RPP are indicated by the Yang et al. (2015) as a potential immunostimulant and/or adjuvant agent of chemotherapy for the treatment of malignant melanoma. A treatment of 250 mg/kg with methanol extract of *R. ellipticus* leaves (RELM) was found to prolong the life span of mice with Ehrlich's ascites carcinoma by 46.76% and reduce the volume of Dalton's lymphoma ascites solid tumors by 2.5 cm. George et al. (2015) indicated *R. ellipticus* as a valuable natural antioxidant effective for the treatment of skin diseases, wounds, and tumors, indicating a safety of RELM up to a dose of 2 g/kg. Tumor angiogenesis inhibition of total alkaloids of *Rubus alceifolius* Poir (TARAP), by suppression of the Notch signaling pathway (including Notch1, delta-like ligand 4, and jagged 1 mediators) was highlighted in a mouse model of hepatocellular carcinoma. In fact, TARAP led to effective cancer treatment by inhibiting the expression of vascular endothelial growth factor (VEGF) A and VEGF receptor-2 in tumor tissues (Zhao et al., 2015). Table 5 summarized anticancer activities of *Rubus* extracts and bioactive compounds in various pharmacological experimental models.

6 | MECHANISM OF ANTITUMOR ACTION OF RASPBERRIES

Cancer is a multifactorial disease, and several preclinical, in vitro, and animal studies showed that several plant foods due to their composition in phytochemicals are able to counteract it (Herrera-Bravo et al., 2024; Rahman et al.). The diverse RB's chemopreventive functions have attracted great interest in cancer prevention attributed to a wide range of phytochemicals by several harmonizing and overlapping mechanisms of action, including induction of metabolizing enzymes, gene expression modulation and effects on cell proliferation, apoptosis, and subcellular signaling pathways (Kristo et al., 2016; Qi et al., 2024; Shi & Chen, 2022; Wang et al., 2024).

6.1 | Chemopreventive effects

The intricate balance between intracellular reactive oxygen species (ROS) production and the antioxidant system is fundamental for cellular homeostasis and the prevention of oxidative stress-related diseases (Azzini et al., 2024; Gaikwad & Srivastava, 2021). Oxidative stress, a pivotal factor in carcinogenesis, occurs when the body encounters external biological, physical, or chemical stimuli, leading to an imbalance between the generation and neutralization of free radicals (Afzal et al., 2023; Iqbal et al., 2024). This imbalance results in elevated levels of ROS, including nitric oxide radicals, hydroxyl radicals, superoxide anions, and hydrogen peroxide, which can cause extensive damage to intracellular biomolecules, such as proteins, lipids, and DNA. Such damage can lead to chromosome instability and activation of signaling pathways like phosphatidylinositol-3-kinase/Akt (PI3K/Akt), thereby promoting uncontrolled cell proliferation and malignancy (Afzal et al., 2023).

RBs (*R. idaeus*), rich in a variety of bioactive compounds, have demonstrated significant chemopreventive potential due to their antioxidant properties. These berries are abundant in phenolic acids, flavonoids, anthocyanins, and vitamins, which collectively contribute to their antioxidant capacity (Shi & Chen, 2022). Phenolic compounds, such as ellagitannins, ellagic acid, quercetin, and catechins, are effective free radical scavengers, directly neutralizing ROS and preventing oxidative stress (Rathod et al., 2023; Sharifi-Rad et al., 2023). Anthocyanins, particularly cyanidin-3-glucoside, not only inhibit lipid peroxidation but also protect against DNA damage caused by oxidative stress. Vitamins C and E, present in RBs, enhance this antioxidant defense by neutralizing ROS in both aqueous and lipid cellular compartments, respectively (Gonçalves et al., 2021). The antioxidant properties of RBs are intricately linked to their anticancer mechanisms through several pathways:

(i) Neutralization of reactive oxygen species (ROS)

Antioxidants in RBs help neutralize ROS, which are known to cause oxidative stress and damage cellular components, including DNA, proteins, and lipids; this oxidative damage can lead to mutations and promote cancer development. By scavenging ROS, RB antioxidants help protect cellular integrity and prevent the initiation of cancer (Dhalaria et al., 2020) (Figure 2).

(ii) Enhancement of endogenous antioxidant defenses

RBs promote the activity and biosynthesis of endogenous antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) (Lim & Choi, 2021). These enzymes play an important role in detoxifying ROS, thus enhancing the cell's overall antioxidant capacity. The promotion of GSH synthesis further augments this detoxification process (Townsend et al., 2003). Moreover, RB antioxidants enhance the activity of detoxification enzymes such as glutathione S-transferase (GST) and quinone reductase. These enzymes help in detoxifying carcinogens, thereby reducing the overall carcinogenic burden on the body.

(iii) Modulation of cellular signaling pathways

RBs influence cellular signaling pathways involved in oxidative stress responses. For instance, the activation of the Nrf2 pathway by RB compounds leads to the upregulation of genes associated with antioxidant defense and detoxification (Song et al., 2020). Moreover, RB antioxidants modulate various cell signaling pathways that are critical in cancer development and progression. For example, they can inhibit the NF- κ B pathway, which is involved in inflammation and cancer. By downregulating this pathway, RB antioxidants reduce inflammation and tumor promotion.

(iv) Inhibition of pro-oxidant enzymes

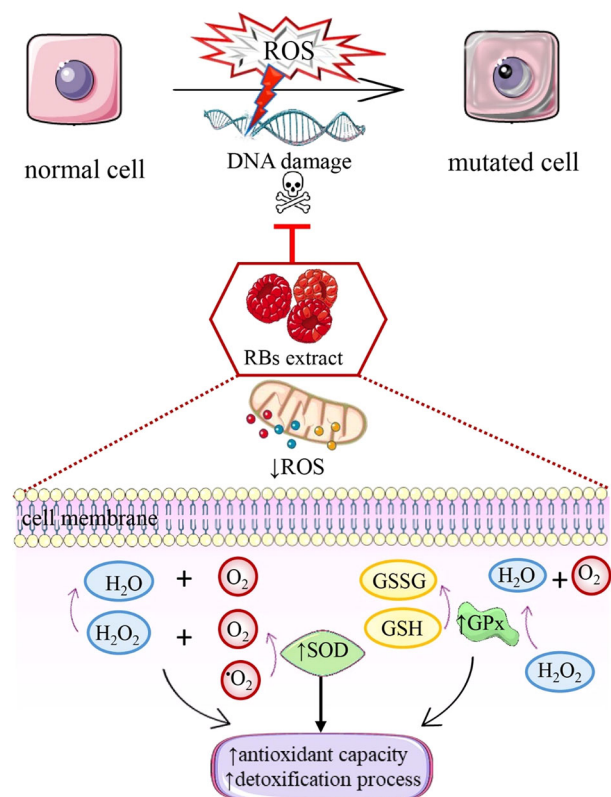


FIGURE 2 Protective mechanism of raspberry extracts against reactive oxygen species-induced DNA damage. The schematic representation illustrates the protective effects of raspberry (RB) extract on normal cells exposed to reactive oxygen species (ROS), highlighting its role in preventing DNA damage and subsequent cell mutation. A normal cell exposed to ROS leads to DNA damage, resulting in a mutated cell. The introduction of RB extract, symbolized by raspberries, inhibits this ROS-induced DNA damage. RB extract mitigates ROS levels within the cell, decreasing oxidative stress on cellular components. The antioxidant mechanism of RB extract involves the enhancement of superoxide dismutase (SOD) activity, which converts superoxide radicals ($O_2^{\bullet -}$) into hydrogen peroxide (H_2O_2). Glutathione peroxidase (GPx) subsequently catalyzes the conversion of hydrogen peroxide into water. During this process, reduced glutathione (GSH) is oxidized to form glutathione disulfide (GSSG), contributing to cellular detoxification and enhancing the antioxidant capacity of the cell. DNA, deoxyribonucleic acid; GPx, glutathione peroxidase; GSH, reduced glutathione; GSSG, oxidized glutathione; H_2O_2 , hydrogen peroxide; $O_2^{\bullet -}$, superoxide radical; RB, raspberry; ROS, reactive oxygen species; SOD, superoxide dismutase.

RBs inhibit pro-oxidant enzymes such as NADPH oxidase and xanthine oxidase, thereby decreasing the overall ROS burden within cells. This inhibition helps to mitigate DNA damage and modulate pathways associated with cell proliferation (Song et al., 2020). The regulation of intracellular ROS levels and the antioxidant system by RBs highlights their potential as chemopreventive agents. Through their multifaceted antioxidant mechanisms, RBs not only mitigate oxidative stress but also enhance cellular defenses, contributing to the prevention of oxidative stress-related diseases, including cancer. Further research is essential to elucidate the precise molecular interactions and path-

ways underlying the antioxidant activities of RBs, which could guide dietary strategies for cancer prevention and broader public health applications.

6.2 | Epigenetic modulation

RRB phytochemicals can regulate gene expression through epigenetic modifications (Shankar et al., 2013) (Figure 3). For instance, these compounds can inhibit DNA methyltransferases (DNMTs) and histone deacetylases, leading to the reactivation of tumor suppressor genes and suppression of oncogenes. This regulation can impede cancer cell growth and proliferation (Huang et al., 2016). In the animal model, *N*-nitrosomethylbenzylamine (NMBA) is used to induce the tumor through metabolic activation with the formation of O6-methylguanines, by single base mispairing in DNA and thus carcinogenesis. In a study among more than 1000 genes induced by NMBA treatment, results exhibited that RB modulates more than 400 genes, including pro-inflammatory cytokines such as chemokine, ligand 2, S100A8 (also known as MRP8), and interleukin (IL)-19; furthermore, modulated genes involved inflammation cell differentiation, cell cycle, angiogenesis, and carbohydrate and lipid metabolism. In another study (Huang et al., 2016), the inhibition of esophageal SCC by BRB was associated with DNMTs 1, DNMT 3b, and methylation of secreted frizzled-related protein 4 (Sfrp4).

In a study by Wang et al. (2013), BRBs were found to prevent the progression of ulcerative colitis to colon cancer in an IL-10 knockout mouse model through epigenetic mechanisms. Mice fed with 5% BRBs had significantly less colonic ulceration and reduced nuclear translocation of β -catenin, a key component in the Wnt signaling pathway. BRBs exerted their protective effects by reversing the hypermethylation of Wnt pathway antagonist genes such as *wif1*, *sox17*, and *qki*. These genes, usually silenced in the knockout mice, were reexpressed due to BRB-induced hypomethylation. This hypomethylation was associated with decreased levels of DNA methylation and histone modification enzymes, including *dnmt3b*, *hdac1*, *hdac2*, and *mbd2*, which are typically elevated in the knockout mice (Wang et al., 2013). The study highlights that BRBs modulate epigenetic mechanisms, specifically by reducing promoter methylation and downregulating methylation-promoting proteins, thereby restoring the expression of key genes that inhibit aberrant Wnt signaling. These findings suggest BRBs as a potential dietary intervention to prevent colon cancer by correcting epigenetic dysregulation in ulcerative colitis (Wang et al., 2013).

The study by Sales et al. (2022) explores how BRB extracts (BRBE) enhance DNA repair in human HeLa cells. The research shows that BRBE treatment boosts nucleotide excision repair (NER) efficiency for both bulky and non-bulky DNA lesions, such as those induced by the carcinogen benzo[a]pyrene and oxidatively-derived guanidinohydantoin. This enhancement is linked to an increased expression of key NER proteins, including xeroderma pigmentosum group A protein and XPB (xeroderma pigmentosum group B protein), fundamental for DNA damage recognition and unwinding, while having a lesser effect on xeroderma pigmentosum group D protein. These

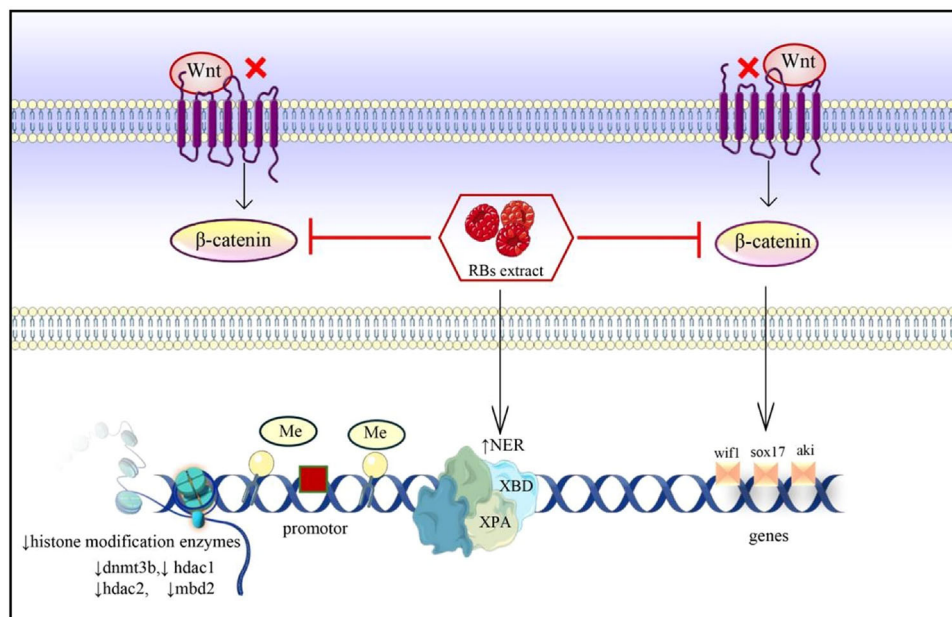


FIGURE 3 Epigenetic changes induced by raspberry extracts. The diagram illustrates the epigenetic changes and molecular mechanisms by which red raspberry (RB) extracts modulate the Wnt signaling pathway and enhance DNA repair. RB extracts inhibit the Wnt pathway by preventing the nuclear translocation of β -catenin, thereby reducing its ability to activate Wnt target genes involved in cell proliferation. Additionally, RB extracts decrease the expression of histone modification enzymes such as dnmt3b, hdac1, hdac2, and mbd2, leading to hypomethylation of promoter regions and reactivation of genes wif1, sox17, and qki. This demethylation facilitates the nucleotide excision repair (NER) process, marked by increased activity of key NER proteins xeroderma pigmentosum group A protein (XPA) and xeroderma pigmentosum group D protein (XPD), thereby enhancing DNA repair mechanisms. β -catenin, beta-catenin; BRBs, black raspberries; dnmt3b, DNA (cytosine-5)-methyltransferase 3 beta; hdac1, histone deacetylase 1; hdac2, histone deacetylase 2; mbd2, methyl-CpG-binding domain protein 2; NER, nucleotide excision repair; RBs, red raspberries; sox17, SRY-box transcription factor 17; wif1, Wnt inhibitory factor 1; XPA, xeroderma pigmentosum group A protein; XPD, xeroderma pigmentosum group D protein.

findings suggest that BRBE improves the repair capacity of HeLa cells, potentially reducing DNA damage and cancer risk (Sales et al., 2022).

6.3 | Anti-inflammatory effects

RB bioactives exhibit anti-inflammatory properties by modulating pro-inflammatory cytokines and enzymes (Kristo et al., 2016). For example, they can downregulate the expression of inducible nitric oxide synthase (iNOS) and COX-2, both of which are overexpressed in tumors. This reduces the production of inflammatory mediators such as prostaglandin E2 (PGE2) and nitrite (Chen, Rose, et al., 2006). Moreover, RB extracts have been shown to reduce macrophage and neutrophil infiltration into esophageal tissues, enhancing immune defenses, and eliminating tumor cells (Shi et al., 2017). Another study (Stoner & Aziz, 2007) showed that supplementation with BRB increased the length of life of NMBA-treated rats in a dose-dependent but not significantly, and the NMBA dosage, BRB concentration, and treatment time are important factors in accurately measuring tumor outcome and survival. In addition to the mechanisms already described, BRB may inhibit the development of esophageal SCC through down-regulation of the expression of iNOS and COX-2 (overexpressed in the presence of tumors), production of PGE2, and nitrite in rats treated with NMBA plus BRB in contrast to treated with NMBA alone (Chen, Hwang, et al., 2006). BRB affects not only the expression and activity of

COX-2 and iNOS but also their upstream regulatory pathways, including mitogen-activated protein kinases (MAPK), nuclear factor kappa B, and AKT (Shi et al., 2016). BRB supplementation efficiently prevents esophageal cancer through the synergistic of the phytochemicals, their medium, and final metabolites. Recently, Huang et al. (2020) have pointed out as the benzoate metabolites of BRBs, such as hippurate, upregulated Smad4 (tumor suppressor in human CRC in epithelium), and Gzmb (target of a transcriptional complex formed by Smad4) expression, that might enhance the cytotoxicity of primary human natural killer (NK) cells, thereby delaying CRC progression. BRB is able to reduce the expression of the pro-inflammatory cytokines pentraxin-3, IL-1, and soluble epoxide hydrolase and increase the anti-inflammatory ones, IL-10 and IL-12.

6.4 | Inhibition of angiogenesis

Angiogenesis, the formation of new blood vessels, is essential for tumor growth and metastasis (Lugano et al., 2020). RB bioactives can inhibit angiogenesis by downregulating angiogenic factors such as VEGF and its receptor (VEGFR). This prevents the formation of new blood vessels necessary for tumor survival and expansion. The results of a study emphasized the RBs ability in impairing angiogenesis by significantly suppressing VEGF and microvessel density (MVD) in rats feeding the experimental diet compared to those on the

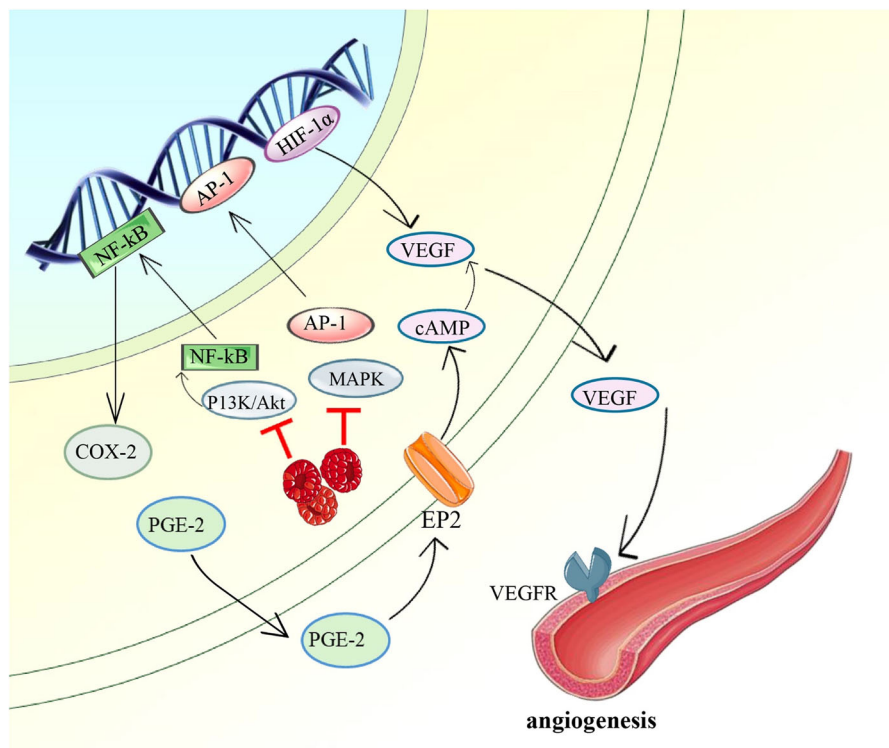


FIGURE 4 Inhibition of angiogenesis by raspberry extracts. The figure delineates the molecular mechanisms through which red raspberry (RB) extracts exert anti-angiogenic effects via epigenetic modulation and inhibition of key signaling pathways. RB extracts suppress the PI3K/Akt and MAPK pathways, leading to reduced activation of the transcription factor AP-1, which subsequently downregulates the expression of vascular endothelial growth factor (VEGF). This reduction in VEGF expression inhibits angiogenesis. Additionally, RB extracts inhibit the expression of cyclooxygenase-2 (COX-2) through the PI3K/Akt/NF- κ B pathway, resulting in decreased production of prostaglandin E2 (PGE-2). PGE-2 typically binds to the EP2 receptor, which elevates cyclic adenosine monophosphate (cAMP) levels and further stimulates VEGF expression. By disrupting these pathways, RB extracts significantly reduce VEGF-mediated angiogenesis. AP-1, activator protein 1; cAMP, cyclic adenosine monophosphate; COX-2, cyclooxygenase-2; EP2, prostaglandin E2 receptor 2; HIF-1 α , hypoxia-inducible factor 1-alpha; MAPK, mitogen-activated protein kinase; NF- κ B, nuclear factor kappa B; PGE-2, prostaglandin E2; PI3K/Akt, phosphoinositide 3-kinase/protein kinase B; RB, red raspberry; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

control diet (Figure 4) (Chen, Rose, et al., 2006). The anti-angiogenic effects of BRB extracts are mediated through the suppression of the PI3K/Akt and MAPK signaling pathways. This suppression results in reduced activation of the transcription factor AP-1, which in turn leads to the downregulation of VEGF expression (Lu et al., 2006). RRB extracts can suppress the PI3K/Akt/mTOR signaling pathway, leading to decreased levels of hypoxia-inducible factor 1 α (HIF-1 α), a key transcription factor that enhances VEGF expression (Dharmawansa et al., 2020; Fakhri et al., 2020). Additionally, PGE₂, produced via COX-2, can elevate VEGF expression by binding to the prostanoid receptor 2 (EP2), increasing cAMP levels. BRB extracts inhibit COX-2 expression through the PI3K/Akt/NF- κ B pathway, ultimately resulting in reduced VEGF expression (Fakhri et al., 2020). BRB reduces macrophage and neutrophil infiltration into esophageal tissues, thereby enhancing immune defenses and eliminating tumor cells. Finally, BRB increases the antioxidant activity of GPx and SOD2 and reduces the production of 8-oxoguanine, hydrogen peroxide (H₂O₂), and lipid hydroperoxide (Figure 4) (Shi et al., 2017). A recent study highlighted that the topical application of gels containing 10% freeze-dried BRB on oral precancerous lesions was shown to decrease MVD and reduce the risk of malignant transformation (Mallery et al., 2008). Moreover, in mouse

models of esophageal cancer, a 30-week regimen of whole BRB powder led to the downregulation of VEGF, HIF-1 α , and CD34.

6.5 | Modulation of immune response

RB bioactives can modulate the immune response, enhancing the body's ability to recognize and destroy cancer cells (Pan et al., 2018). This involves the activation of various immune cells, such as T cells and natural killer (NK) cells, and the production of cytokines that promote an antitumor immune response (Kristo et al., 2016). The anti-inflammatory and immune action modulation is carried out by the anthocyanins present in BRB, which have a more effective action when compared to a diet enriched with anthocyanins or protocatechuic acid (Peiffer et al., 2014). In rats treated with NMBA and then fed a residual fraction of BRB, strawberries, or blueberries, Wang et al. (2010) found a reduction in tumor development with all three experimental diets, although the berries had a different composition in ellagitannins. Therefore, the authors concluded that ellagitannins might not be the key bioactive component of berries in reducing tumor development. At the same time, Aqil et al. (2016) investigated which part of the

polyphenols from blueberry and BRB was most effective in reducing lung tumor growth. The results show that anthocyanidins exhibit a higher degree of efficacy than anthocyanins. The combination of blueberry and BRB rendered a higher degree of lung tumor growth inhibition than the individual entities, highlighting their synergistic effect. Recently, a study highlighted the role antitumor via e PD-1/PD-L1 blockade of ellagic acid, the main component of the unripe BRB and use as a potent immunotherapeutic agent against cancer (Kim et al., 2020).

6.6 | Induction of apoptosis

RB phytochemicals induce apoptosis in cancer cells through intrinsic and extrinsic pathways (Gaikwad & Srivastava, 2021). Ellagic acid and quercetin, prominent RB constituents, increase mitochondrial membrane permeability, leading to cytochrome c release and activation of caspase-9 and -3, which are key executors of the intrinsic apoptotic pathway (Salimi et al., 2015). Furthermore, these compounds upregulate the expression of proapoptotic proteins, such as Bax, while downregulating anti-apoptotic proteins like Bcl-2 (Salimi et al., 2015). In the extrinsic pathway, ellagic acid enhances the expression of death receptors such as Fas and TNF-related apoptosis-inducing ligand and receptors, promoting the activation of caspase-8 (Mahmoudi et al., 2024). This leads to the cleavage of downstream substrates, ultimately resulting in apoptotic cell death.

6.7 | Inhibition of cell proliferation

The anti-proliferative effects of RBs are primarily mediated through cell cycle arrest (Kristo et al., 2016). RB extracts have been shown to cause cell cycle arrest at both the G1/S and G2/M phases. This arrest is often associated with the upregulation of cyclin-dependent kinase inhibitors (e.g., p21/Cip1/Waf1 and p27/Kip1) and downregulation of cyclins (e.g., cyclin D1 and cyclin E) and cyclin-dependent kinases (CDKs), which are essential for cell cycle progression (Zhang et al., 2018). Mechanistically, ellagic acid induces the expression of p21 via the p53-dependent pathway, contributing to G1 arrest, whereas quercetin impacts the ATM/ATR signaling pathways to enforce G2/M arrest (Li et al., 2005).

6.8 | Modulation of cell signaling pathways

The bioactive compounds in RBs modulate several cell signaling pathways critical for cancer development and progression. Notably, ellagic acid inhibits the NF- κ B pathway, which is important for inflammation, cell survival, and proliferation. Ellagic acid achieves this by preventing the phosphorylation and degradation of I κ B α , an inhibitor of NF- κ B, thereby reducing NF- κ B nuclear translocation and subsequent transcriptional activation of pro-inflammatory and pro-survival genes (Kim et al., 2020). RB extracts also suppress the PI3K/Akt/mTOR pathway, a key regulator of cell growth and survival. Inhibition of this pathway by

RB polyphenols leads to decreased phosphorylation of Akt and mTOR, which in turn reduces protein synthesis and cell proliferation. Additionally, studies have shown that RB extracts activate AMP-activated protein kinase (AMPK), further inhibiting mTOR signaling and promoting autophagy (Zhang et al., 2021). Another recent study investigated the antitumor effects of RRB (*R. idaeus* L.) extract on HCC cells, focusing on the underlying molecular mechanisms. RRB extract (RRE), rich in bioactive phytochemicals, had previously been noted for its ability to inhibit tumor growth. Researchers employed CCK8, colony formation, and flow cytometry assays to assess the impact of RRE on HCC cell proliferation and cell cycle distribution. The results indicated that RRE significantly suppressed cell proliferation and induced cell cycle arrest at the S phase in HCC cells. This effect was mediated through the upregulation of PTEN deleted on chromosome 10 by reducing PTEN gene promoter methylation and inhibiting DNMT1 expression, thereby modulating the AKT signaling pathway. These findings suggested that RRE might serve as a potential supplementary therapy for HCC patients by targeting the PTEN/AKT pathway (Zhang et al., 2018).

7 | HUMAN CLINICAL STUDIES

Several studies show that making healthy and appropriate food choices over time can reduce the risk of contracting cancer and support possible courses of treatment. However, it cannot be guaranteed with absolute certainty that food reduces the risk of developing cancer to zero.

In the human model, 30 patients with Barrett's esophagus were treated with 32 g/day for women and 45 g/day for men of BRB supplementation for 6 months without finding changes in the histopathology of Barrett's but only reduced oxidative stress with a significant reduction in levels of the lipid peroxidation markers 8-epi PG F2 (8-Iso-PGF2) and 8-hydroxy-2-deoxyguanosine (8-OHdG) in patients who completed the 26-week treatment. Moreover, after 12 and 26 weeks of LBR (Lyophilized Black Raspberries) consumption, urinary levels of the ellagitannin metabolites, urolithin A-glucuronide, urolithin A-sulphate, and dimethylelagic acid glucuronide, increased significantly, indicating, according to the authors, their usefulness as indicators of compliance for planning clinical studies (Kresty et al., 2006; Kresty et al., 2018). Wang et al. evaluated the effects of oral consumption of BRB powder (60 g/d) for 1–9 weeks on biomarkers of tumor development in the human colon and rectum in 20 patients by taking biopsies of adjacent normal tissues and colorectal adenocarcinomas before and after supplementation. The berries seem to modulate expression of genes associated with Wnt pathway, proliferation, apoptosis, and angiogenesis through demethylation tumor suppressor genes (SFRP2, PAX6a, p16, SFRP5, and WIF1) upstream, and protectively modulate the expression of genes (β -catenin, E cadherin) downstream, of the Wnt pathway. In conclusion, BRBs beneficially influence both genetic and epigenetic biomarkers in tissues from CRC patients, promoting increased apoptosis and epigenetic regulation (Wang et al., 2011). Mallery et al. (2014) conducted a clinical trial involving 32 subjects with premalignant oral intraepithelial lesions. Participants were treated with bioadhesive gels containing 10% w/w freeze-dried BRBs,

administered at a dose of 2 g/day (0.5 g four times daily) for 6 weeks. The study observed significant reductions in histologic grades, COX-2 expression, and MVDs, indicating a potential chemopreventive effect of BRBs on oral intraepithelial neoplasia (Mallery et al., 2014). Shumway et al. evaluated 29 subjects with similar oral lesions, utilizing the same BRB bioadhesive gel regimen. Over 6 weeks, the intervention led to reductions in histologic grades and loss of heterozygosity events, further supporting the chemopreventive properties of BRBs (Shumway et al., 2008).

Knobloch et al. investigated the impact of BRBs on oral SCC in 62 subjects. Participants were given oral troches containing freeze-dried BRB powder at a dose of 4.3 g/day for an average of 13.9 days. The study demonstrated significant downregulation of pro-survival genes (AURKA, BIRC5, and EGFR) and pro-inflammatory genes (NFKB1, PTGS2), suggesting BRBs' potential in reducing tumorigenic and inflammatory processes in oral cancer (Knobloch et al., 2016).

Another clinical study was conducted on 20 subjects diagnosed with Barrett's esophagus, who consumed lyophilized BRBs at doses of 32 g/day for females and 45 g/day for males, once daily for 6 months. The results indicated significant reductions in oxidative stress markers, specifically 8-PGF2 α and 8-OHdG levels (Knobloch et al., 2016). Kresty et al. (2018) expanded this research with another group of 20 subjects over 26 weeks, using the same BRB dosage. The intervention resulted in decreased levels of 8-PGF2 α , increased GST-pi expression, and significant changes in biomarkers such as urolithin A-glucuronide and components of the antioxidant panel, indicating enhanced antioxidant defense mechanisms (Kresty et al., 2018). In a Phase Ib clinical study, Wang et al. (2014) investigated the effects of BRBs on rectal polyps in patients with familial adenomatous polyposis (FAP). Fourteen patients were treated with BRBs daily for 9 months. Seven patients received BRB powder orally plus two BRB suppositories inserted into the rectum at bedtime, whereas the other seven received an oral placebo plus the suppositories. Rectal polyp counts and sizes were assessed at baseline and after 9 months of treatment. The study found that BRBs significantly decreased the burden ($p = .036$) but not the number ($p = .069$) of rectal polyps. No additional benefit was observed with the oral BRBs. Responders to the treatment showed significant decreases in cellular proliferation, DNMT 1 protein expression, and p16 promoter methylation. The MBD-seq assay revealed more demethylated transcription start sites, including those for miRNAs, in BRB-treated adenomas from responders. These findings suggest that BRB suppositories alone are sufficient for regressing rectal polyps in FAP patients (Wang et al., 2014). Pan et al. conducted a study to assess the metabolic changes induced by BRBs in patients with CRC. Twenty-eight CRC patients were administered 60 g/day of freeze-dried BRB powder for 1–9 weeks. Urine and plasma specimens were collected before and after the intervention, and a mass spectrometry-based nontargeted metabolomic analysis was performed on each specimen. The analysis identified over 400 metabolites, with 34 metabolites in urine and 6 in plasma showing significant changes post-intervention. Notably, increased levels of 4-methylcatechol sulfate in both urine and plasma were signifi-

cantly correlated with higher levels of the apoptotic marker TUNEL (Terminal deoxynucleotidyl transferase dUTP Nick-End Labeling) in post-BRB tumors. Additionally, the tricarboxylic acid cycle metabolite cis-aconitate was increased in post-BRB urine. BRB-derived polyphenols were metabolized into various benzoate species, which were significantly elevated in post-intervention specimens and positively correlated with enhanced levels of amino acid metabolites. These findings suggest that BRBs induce substantial metabolic changes, impacting amino acid, energy, carbohydrate, and lipid metabolism, and support their potential benefits in CRC patients through the regulation of multiple metabolic pathways (Pan et al., 2015). In a pilot clinical study, Dong et al. investigated the hypomethylating properties of freeze-dried BRBs in patients with low-risk myelodysplastic syndrome (MDS) or MDS/myeloproliferative neoplasm (MDS/MPN). These bone marrow disorders, characterized by cytopenias and progression to acute myeloid leukemia, currently rely on hypomethylating agents (HMAs) for treatment, which, despite their efficacy, are associated with significant toxicities. The study included 20 subjects (12 with MDS and 3 with MPN) who consumed 16 ounces of BRB powder daily for 3 months. Peripheral blood mononuclear cells were isolated before and after the intervention, with CD45+ cells undergoing methylation analysis via reduced-representation bisulfite sequencing. Each patient served as their own control, with pre-intervention measurements as baselines. Results indicated that BRBs were well tolerated with no side effects. Methylation analysis showed significant changes in 477 promoter regions, suggesting that BRBs induced hypomethylation, which may promote leukocyte differentiation. This supports the potential of BRBs as a natural, safer alternative to conventional HMAs for managing MDS and MDS/MPN, warranting further investigation through larger, randomized, placebo-controlled trials (Dong et al., 2022). These clinical studies collectively demonstrate the promising anticancer effects of BRBs, particularly through the modulation of gene expression, reduction of oxidative stress, and regulation of epigenetic markers across various cancer types and precancerous conditions. The findings suggest that BRBs may serve as a valuable adjunct in cancer prevention and treatment strategies.

8 | TOXICITY, SIDE EFFECTS, AND SAFETY

Although several clinical and experimental studies have been made to look at the bioactivity, bioavailability, and metabolism of BRBs in human study, several key areas remain to be explored, to establish optimum intake levels consistent with safety, tolerance, and various disease prevention. Conversely, collateral effects have been reported too, when high doses of polyphenols are consumed, mainly by supplement use that have been produced by isolating these compounds from their food matrix. To date, our need increased regulation and guidelines about consumption and supplementation intake to ensure consumers' safety and a good informed (Cory et al., 2018). RB is often used as a supplement as it shows a wide range of health benefits. However, its use has raised some criticism regarding potential toxicity, threshold levels, and adverse effects. The RB can be consumed in different formulas, for

example, fresh, in leaves, or through supplementation with molecules specific to the berry. RB ketone (4-(4-hydroxyphenyl)-2-butanone) is a food supplement, and the recommended intake is between 100 and 1400 mg/day. This naturally occurring substance is often misinterpreted as inherently safe; it is not extracted directly from RBs and, according to the recommendations, would be gained by a daily intake of 23–326 kg fresh RBs. Table 6 summarizes the clinical studies on the anticancer effects of BRBs. These levels exceed the estimated dietary exposure level used to evaluate RB ketone as a flavoring substance (3.8 mg/day). Both threshold of toxicological concern and margin of safety values show that concern cannot be excluded when RB ketone is consumed in these high amounts. However, no studies are identifying a toxic effect at high doses, and further investigations will have to be made in this direction to ensure the safety of this supplement (Bredsdorff et al., 2015). Other studies have investigated the potential toxicity of RB leaves used by pregnant women, a widespread practice to facilitating birth. The results do not show a significant effect, and toxicity is only observed in animal models where a large amount of RB leaf extract can be administered intravenously (Cheang et al., 2016; Johnson et al., 2009; Makaji et al., 2011; Nordeng et al., 2011). The supplementary use of RB is also common for pre-diabetic patients or type 2 diabetes mellitus. Studies show that consumption of 1–1.5 cups of fresh or frozen RB as part of a healthy diet has beneficial effects and no toxicity levels are observed even at higher concentrations (Derrick et al., 2021). Finally, a study by Lozowicka et al. (2012) investigated the presence of almost 150 pesticides in RBs from the 3 Polish areas: Lubelskie, Podlaskie, and Warminsko-Mazurskie. Among the 128 samples, 66 (51.6%) were found to detect residues: 14.1% contained one pesticide and around 38% multiple pesticide residues. Furthermore, the results show as 27 (21.1%) RB samples exceeded the maximum residue limits. However, it represents a low risk of exposure to consumers' health, and the authors concluded that it is not a cause for concern.

9 | LIMITATIONS AND CLINICAL GAPS

Despite the promising preclinical evidence supporting the anticancer properties of RBs and their bioactive compounds, several limitations must be addressed before these findings can be effectively translated into clinical practice. First, the majority of the studies to date have been conducted in vitro using cancer cell lines or in animal models, primarily murine models. These models provide valuable mechanistic insights but may not accurately replicate the complexities of human cancer, which limits the direct applicability of these findings to human patients. Additionally, the bioavailability and metabolism of RB-derived compounds in humans are not fully understood, with significant interindividual variability in the absorption and efficacy of these bioactives. The chemical composition of RBs can also vary significantly depending on factors such as cultivar, growing conditions, and processing methods, affecting the consistency and potency of their anticancer effects. Currently, there is a paucity of large scale, randomized clinical trials evaluating the efficacy of RB bioactives in cancer prevention or treatment. Most clinical evidence is limited to small pilot studies

or observational data, which often involve dietary interventions with whole RBs or extracts and focus on biomarkers of oxidative stress and inflammation rather than direct cancer outcomes. These types of studies are insufficient to establish causal relationships or clinical guidelines. Furthermore, the optimal dosage, formulation, and delivery method of RB bioactives for cancer therapy remain unclear. There is also a need to explore the potential interactions of these compounds with conventional cancer therapies, as well as their long-term safety and potential side effects in cancer patients.

To bridge the gap between laboratory research and clinical application, several translational approaches should be considered. Developing standardized extracts of RB bioactives with consistent potency and composition is crucial for clinical studies. This includes identifying and quantifying key bioactive compounds and ensuring reproducibility in their preparation. Comprehensive studies on the pharmacokinetics and bioavailability of RB bioactives in humans are needed to understand how these compounds are absorbed, distributed, metabolized, and excreted. This information is essential for determining effective dosing regimens. Conducting well designed, large-scale randomized controlled trials is imperative to evaluate the efficacy and safety of RB bioactives in cancer prevention and therapy. These trials should include diverse patient populations and cancer types to assess the generalizability of the findings. Investigating the synergistic effects of RB bioactives with conventional cancer treatments, such as chemotherapy, radiotherapy, and immunotherapy, could enhance therapeutic outcomes. Preclinical studies should focus on elucidating the mechanisms of these interactions. Considering the variability in individual responses to RB bioactives, personalized approaches that take into account genetic, metabolic, and microbiome profiles could optimize their therapeutic potential. Integrating RB bioactives into dietary interventions for cancer patients could provide a complementary approach to conventional therapies. Clinical nutrition studies should explore the impact of regular RB consumption on cancer progression and patient quality of life. Engaging with regulatory bodies to establish guidelines for the use of RB bioactives in clinical settings is essential for their acceptance and integration into standard cancer care. By addressing these limitations and clinical gaps through targeted translational approaches, the therapeutic potential of RBs and their bioactive compounds in cancer prevention and treatment can be more fully realized. This will pave the way for innovative dietary and pharmacological strategies that leverage the natural anticancer properties of these functional foods.

10 | CONCLUSION AND FUTURE PROSPECTS

To summarize, RBs are a source of many phytochemicals, including various flavonoids, phenolic acids, and vitamins. Numerous in vitro studies have demonstrated the activity of various extracts from RB against different aspects of the tumorigenic process, providing evidence of its beneficial potential. Although the antiproliferative and anti-inflammatory activities, the reduction of oxidative stress, and tumor suppressive activity have been demonstrated in different human

TABLE 6 Summary of clinical studies on the anticancer properties of black raspberries (BRBs).

Cancer type/condition	Type of study and participants	Intervention	Duration	Outcomes	References
Barrett's esophagus	Clinical trial, 30 patients	32 g/day for women, 45 g/day for men of BRB supplementation	26 weeks	No changes in histopathology, ↓ oxidative stress (↓ 8-Iso-PGF2 and 8-OHdG), ↑ urinary ellagitannin metabolites	Kresty et al. (2006)
Barrett's esophagus	Clinical trial, 20 subjects	Same BRB dosage as previous study	26 weeks	↓ 8-PGF2α levels, ↑ GST-π expression, changes in biomarkers (uroolithin A-glucuronide, antioxidant panel)	Kresty et al. (2018)
CRC	Clinical trial, 20 patients	60 g BRB powder daily	1–9 weeks	Modulation of Wnt pathway, demethylation of tumor suppressor genes (SFRP2, WIF1) protective modulation of genes (b-catenin, E-cadherin) ↑ apoptosis, ↓ DNMT1 and β-catenin levels ↑ TUNEL	Wang et al. (2011)
Premalignant oral intraepithelial lesions	Clinical trial, 32 subjects	10% BRB bioadhesive gel (2 g/day, 0.5 g four times daily)	6 weeks	Significant ↓ in histologic grades, ↓ COX-2, ↓ MVD	Mallery et al. (2014).
Premalignant oral lesions	Clinical trial, 29 subjects	10% BRB bioadhesive gel (2 g/day, 0.5 g four times daily)	6 weeks	↓ In histologic grades and loss of heterozygosity events	Shumway et al. (2008)
Oral squamous cell carcinomas	Clinical trial, 62 subjects	4.3 g/day BRB powder oral troches	13.9 days	↓ Pro-survival genes (AURKA, BIRC5 EGFR) and pro-inflammatory genes (NFKB1, PTGS2)	Knobloch et al. (2016)
Familial adenomatous polyposis (FAP)	Phase Ib study, 14 patients	BRB powder and suppositories vs. placebo	9 months	↓ Rectal polyp burden, significant ↓ in cellular proliferation, DNA methyltransferase 1 protein expression, p16 promoter methylation	Wang et al. (2014)
CRC	Clinical trial, 28 patients	60 g/day BRB powder	1–9 weeks	Substantial metabolic changes, ↑ 4-methylcatechol sulfate, correlated with higher TUNEL levels, ↑ cis-aconitate, elevated benzoate species and amino acid metabolites	Pan et al. (2015)
Myelodysplastic syndrome (MDS) or Myelodysplastic/myeloproliferative neoplasm (MDS/MPN)	Pilot study, 20 subjects	16 ounces of BRB powder daily	3 months	Well-tolerated, significant hypomethylation in 477 promoter regions, potential for promoting leukocyte differentiation	Dong et al. (2022)

Note: ↓, decreased; ↑, increased.
Abbreviations: 8-Iso-PGF2, 8-epi prostaglandin F2; 8-OHdG, 8-hydroxy-2-deoxyguanosine; 8-PGF2α, 8-prostaglandin F2α; AURKA, aurora kinase A; b-catenin, beta-catenin; BIRC5, baculoviral IAP repeat containing 5 (survivin); BRB, black raspberry; COX-2, cyclooxygenase-2; CRC, colorectal cancer; DNMT1, DNA methyltransferase 1; EGFR, epidermal growth factor receptor; FAP, familial adenomatous polyposis; GST-π, glutathione S-transferase Pi; MDS, myelodysplastic syndrome; MDS/MPN, myelodysplastic/myeloproliferative neoplasm; MVD, microvessel densities; NFKB1, nuclear factor kappa B subunit 1; PTGS2, prostaglandin-endoperoxide synthase 2 (cyclooxygenase-2); SFRP2, secreted frizzled-related protein 2; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; urolithin A-glucuronide, Metabolite of ellagitannins; WIF1, Wnt inhibitory factor 1.

cancer cell lines and animal models, more additional standardized research is needed. Future research should focus on several key areas. First, large-scale, randomized clinical trials are essential to evaluate the efficacy and safety of RB bioactives in cancer prevention and therapy. These studies should include diverse patient populations and cancer types to assess the generalizability of the findings. Second, comprehensive studies on the bioavailability and metabolism of RB-derived compounds in humans are crucial. Understanding how these compounds are absorbed, distributed, metabolized, and excreted will help determine effective dosing regimens and optimize therapeutic efficacy. Additionally, the potential interactions of RB bioactives with conventional cancer therapies should be explored. Investigating these synergistic effects could enhance therapeutic outcomes and provide insights into how these natural compounds can be integrated into standard cancer care. Finally, personalized approaches that consider genetic, metabolic, and microbiome profiles could optimize the therapeutic potential of RB bioactives. Integrating these compounds into dietary interventions for cancer patients could provide a complementary approach to conventional therapies. By addressing these limitations and focusing on targeted translational approaches, the therapeutic potential of RBs and their bioactive compounds in cancer prevention and treatment can be more fully realized. This will pave the way for innovative dietary and pharmacological strategies that leverage the natural anticancer properties of these functional foods.

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