

The Medicinal Chemistry of Cyanidin and its Glycoside Derivatives: Focus on the Antiproliferative and Potential Anticancer Activity

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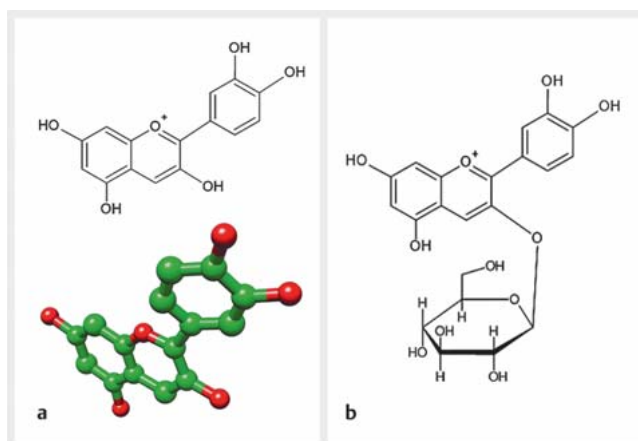
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ABSTRACT

Cyanidin and its glucosides are anthocyanins belonging to the class of flavonoid phytochemicals. These pigments give fruits and vegetables their typical reddish-purple nuance, and their peculiar chemical features result in a remarkable ability to neutralize reactive oxygen species and other mutagens. Thus, both cyanidin and its glycosides were proposed as candidates for chemoprevention, as anticancer agents, and as adjuvant therapies. Indeed, the compounds were investigated through various *in vitro* and *in vivo* models of colon, breast, kidney, prostate and liver cancer, and glioma. Cyanidin and its derivatives have been found to inhibit key signaling pathways, such as PI3K/Akt, MAPK, and NF- κ B, which can reduce cancer cell growth, induce apoptosis, and suppress metastasis. In the first part of the review, the chemical properties of cyanidin and its glycoside analogues will be discussed. Then, an overview of *in vitro* evidence on activity will be presented, followed by a report on preclinical and clinical data together with comments on the mechanisms involved. Eventually, the aspect of pharmacokinetic properties, bioavailability, and formulation will be dissected. Overall, the review indicates that cyanidin and its derivatives could be effective anticancer agents but also calls for a deeper understanding of the molecular mechanisms underlying their bioactivity. Despite promising results, resolving issues like stability, absorption, and targeted distribution is crucial to maximize their therapeutic potential. More research is needed to develop innovative cyanidin-based formulations for efficient cancer treatment.

Introduction

As described by the World Health Organization in its report, cancer is a major global cause of death, accounting for nearly 10 million fatalities annually (who.int/news-room/fact-sheets/detail/cancer, accessed May 2, 2025). Cancer, a widespread disease with 19 million diagnoses in 2020, poses a significant healthcare burden, with new cases predicted to exceed 29 million in 2024 [1, 2]. The increasing cancer incidence and drug resistance, which can occur through different molecular mechanisms [3], are driving the search for alternative disease management methods. Natural and nature-inspired compounds are gaining increasing attention [4]. Cyanidin belongs to the chemical class of anthocyanins, and it is found in nature as a glycosylated form in fruits, flowers, and vegetables. It contributes to giving flowers and fruits a distinctive reddish-purple (magenta) color. Natural glucosides are cyanidin-3-galactosides (galactose), cyanidin-3-glucosides (glucose), cyanidin-3-rutinosides (rutinose), cyanidin-3-sophorosides (sophorose), and cyanidin-3-sambubiosides (sambubiose). It must be noted that glycosides and aglycones have distinct properties from those found in bound form [5]. Some examples are red berries like blackberries, raspberries, blueberries, chokeberries, cranberries, elderberries, loganberries, acai berries, cherries, grapes, and hawthorn. More specifically, blackberries and bilberries are rich sources of cyanidins: 20% of the cyaniding content is present as cyaniding-3-rutinoside and 80% of the cyanidin content is present as cyaniding-3-glucoside [6], and after consumption cyanidins are often found as glucosides [7]. Plums, apples, crimson onions, black carrots, purple potatoes, and red cabbage represent sources of these compounds. In particular, seeds and skins generally have higher cyanidin concentrations. Other sources are elderberries, chokeberries, boysenberries, raspberries, and purple vegetables like yams and carrots [8–10]. Then, cyanidin is found in red cabbage [11]. Cyanidin has been studied in the context of several cancer models. It inhibits RAS and MAPK and activates caspases-3 and P-38, two novel molecular pathways. It may lead to cell differentiation, cell cycle arrest, and redox state changes, triggering harmful chemotherapeutic effects. However, it also enhances the effectiveness of chemotherapeutic targets, which are cancer cells that are less receptive to chemotherapy. Cyanidin plays a crucial role in treating cancer by addressing various mechanistic pathways [12]. Sea cucumber triterpene glycosides, when taken intraperitoneally, can significantly reduce tumor burden and metastasis in mice. These compounds also inhibit the proliferation of various human carcinoma cell lines *in vitro*. They induce tumor cell apoptosis through caspase cell death pathways, nuclear factors, NF- κ B, and specific cellular receptors and enzymes involved in carcinogenesis. These glycosides can be used as P-gp-mediated MDR reversal drugs [13]. A study investigated the antioxidant and antiproliferative properties of cyanidin-3-O-glucoside (C3G) and C3G liposomes in Caco-2 cells. The results showed that C3G liposomes decreased mitochondrial activity and reduced viabilities in Caco-2 cells. The antiproliferative effects of C3G liposomes were validated, showing that C3G liposomes were more effective than the standard compound C3G [14]. Glycosides have shown strong antiproliferative properties against various cancer cell types, with preliminary preclinical research



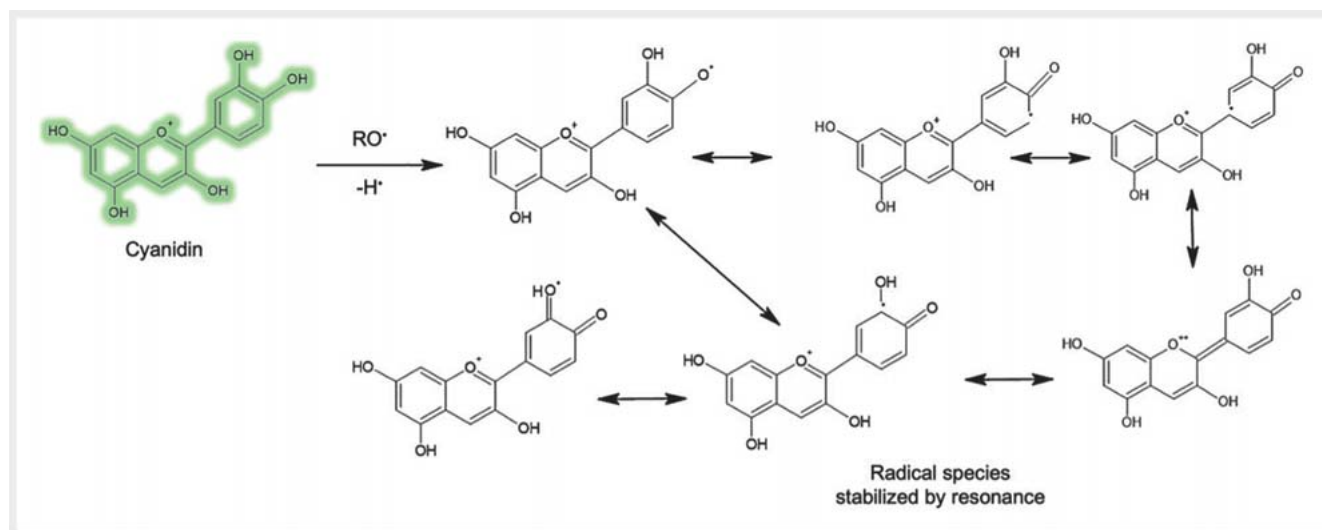
► **Fig. 1** Chemical structure and 3D representation of cyanidin (a) and chemical structure of its glucoside, cyanidin 3-glucoside (C3G).

showing cytotoxic effects [15]. This review article was prepared with the aim of providing a comprehensive and updated overview of the *in vitro* activity and *in vivo* evidence of the anticancer potential of cyanidin and its glycosides, with a critical discussion of the data retrieved from the literature, including the mechanistic aspects. More than 60 scientific papers were considered for the preparation of this review. The articles were retrieved following a literature search through scientific databases such as PubMed (pubmed.ncbi.nlm.nih.gov, accessed on Nov 9, 2024) and Scopus (scopus.com, accessed on Nov 9, 2024). A literature search was performed using the queries “cyanidin”, “glycoside”, “cancer”, “anticancer”, “antiproliferative”, and their combinations.

The Chemistry of Cyanidin

The chemical formula of cyanidin is $C_{15}H_{11}O_6^+$, and it has a molecular weight of 287.24. It occurs as an anthocyanin cation, and it is constituted by flavylium with hydroxy (-OH) groups replaced at positions 3, 3', 4', 5, and 7. Structurally, the molecule possesses a benzopyran ring (A and C) with a phenolic ring (B). As anticipated, it is often found in plants in its glycosylated form (► **Fig. 1**). It is a water-soluble solid with a melting point above 300 °C [16].

The presence of hydroxy groups in the structure is susceptible to oxidation. Cyanidin is a strong antioxidant and exhibits significant metabolic and neuroprotective effects. Its redox behavior determines the radical scavenging capacity (RSC) and binding potential of cyanidin-3-galactoside. However, whether there is glucose and/or a glycoside entity present determines how it will be metabolized and absorbed. Cyanidin-3-galactoside is particularly sensitive to deterioration. Temperature, light, pH, metal ions, solvents, and oxygen are only a few of the causes [17–19]. These elements have an impact on Cy3G's bioavailability and bioactivity [20,21]. A study explores Cy3G's intake and *in vivo* metabolism parameters once the protein's structural and physicochemical constraints are understood *in vitro*. The final destiny and bioactivity of Cy3G in target tissues are determined by the interaction of



► Fig. 2 Mechanism of radical scavenging by cyanidin.

these elements. The production of Cy3G in edible plants is crucial for understanding their high content [22].

The radical scavenging mechanism of phenolic compounds such as cyanidin is reported in ► Fig. 2, demonstrating the importance of hydroxy groups [23].

As seen in the above mechanism, cyanidins donate an electron to a free radical from -OH groups attached to the phenolic rings. This electron stabilizes and inactivates the free radical. In this process, the polyphenolic reducing agent changes to a stable aroxyl radical due to resonance rather than the free radical that it has reduced. The overall result is the termination of adverse oxidative chain reactions [23].

Therapeutic Potential of Cyanidin and its Glycoside Derivatives

Cyanidin and its corresponding glycosides have been studied through the years in several fields of medicinal chemistry, ranging from metabolic diseases to cardiovascular disorders and cancer. A particular focus was also set on the applications of such molecules against neurodegeneration. For instance, the inhibitory impact of C3G against GSK3 activity in neurons was investigated by Chen et al. in a mouse model. Their team determined how quickly C3G could reverse the neuronal damage caused by ethanol in the developing brain. In the cerebral cortex of 7-day-old mice, intraperitoneal injection of C3G inhibited ethanol-mediated caspase-3 activation, neurodegeneration, and microglial activation. The phosphorylation of serine 9 at GSK3 (a possible mediator of neurotoxicity) and the decrease in tyrosine 216 phosphorylation by ethanol were both observed to be blocked by C3G. Malondialdehyde (MDA) and p47phox expression were likewise suppressed by C3G when it was increased by ethanol. Thus, C3G was able to reduce the oxidative stress that ethanol had caused [24]. Additionally, C3G protection against ethanol-induced neuro-apoptosis makes

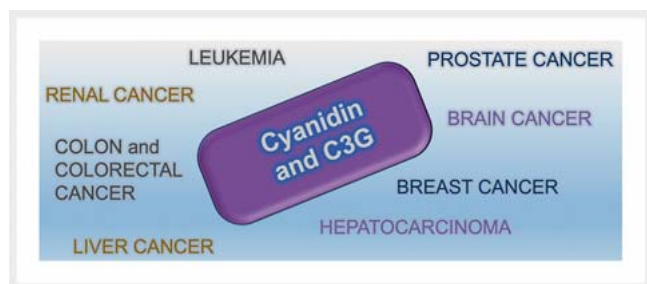
it feasible to reduce caspase-3 activation and the number of Fluoro-Jade C-positive cells [25].

Another relevant point is the one related to pharmacokinetic properties and biodistribution. Anthocyanins like C3G were described as crucial for memory, learning, and motor neuron activities in the brain because they are easy to locate and have potential to cross the blood-brain barrier (BBB), as testified by *in vivo* studies [26]. According to another study, mice fed a diet enriched with blackberries for 15 days exhibited C3G levels that were predominately greater in the brain homogenate than in the plasma, suggesting a preferential targeting [7]. Studies have shown that brain C3G concentration reaches about 3.5 nmol/g an hour after delivery because C3G rapidly distributes in the brain following intra-peritoneal injection [27]. The heart, liver, kidney, lungs, and prostate are the main organs for C3G accumulation 30 minutes after a tail vein injection (1 mg/kg) with 1–8 nmol/g concentration in animal models. This indicates a concentration of about 0.5 nmol/g in the plasma and about 1 nmol/g in the prostate and lungs [28]. The pharmacokinetic aspects will be discussed in more detail in the following section of the review.

In vitro activity of cyanidin and its glycoside analogues

Cyanidin has been demonstrated by several studies to be efficacious in the inhibition of different cancer cells. The relevant results have been organized in the following paragraphs.

In colon carcinoma cell lines, concerning the involved mechanism, cyanidin abrogated mitogen-stimulated metabolic function, decreased unbound intracellular calcium, and inhibited growth. Epidermal growth factor and neurotensin are linked with colon cancer, and cyanidin was found to inhibit the increase of calcium in cells caused by neurotensin. Epidermal growth factor interacts with receptors on cell surfaces and activates the intrinsic protein-tyrosine kinase, which then starts signaling pathways. This leads to biochemical alterations inside the cell, including an increase in the level of intracellular calcium, a rise in the synthesis



► **Fig. 3** Graphical representation of target organs/models for which *in vitro* activity of cyanidin and glycosides is reported. The artwork was prepared using Servier Medical Art (licensed under CC BY 4.0).

of protein and glycolysis that ultimately results in the proliferation of the cell. Cyanidin decreased this effect and thus reduced cell growth [29]. Cyanidin-3-rutinoside abrogates RKO human colon cancer cell motility as shown by a wound-healing study [30]. Additionally, Mazewski et al. showed that cyanidin-3-O-glucoside and another anthocyanin called delphinidin-3-O-glucoside were efficacious in arresting immune checkpoints in human colorectal cells. C3G and its analogue (delphinidin-3-O-glucoside) reduced the expression of PD-L1 protein in HCT-116 colon cancer cell lines. According to the authors, both C3G and its metabolite, which are in many foods, display the potential for interaction with and abrogating immune checkpoints (PD-L1 and PD-1) and can stimulate immune stimulus in the tumor microenvironment and cause the death of cancer cell [31]. The effect of a chloride form of the anthocyanidin, cyanidin chloride, was investigated on colorectal cancer cell lines. The treatment with cyanidin chloride (50 and 100 μM) elicited apoptosis and inhibited colony formation and cellular proliferation in three colon cancer (SW620, HT29, and HCT116) cells. Furthermore, the compound decreased the NF- κB signal [32].

Chen et al. stated that cyanidin-3-glucoside and derivatives such as peonidin-3-glucoside isolated from black rice inhibit breast cancer cell (HS578T) growth [33]. In particular, the compound (10, 20, or 40 μM) ameliorated the invasion/migration of breast cancer cell lines induced by ethanol and expressing high ErbB2 levels. C3G reduced ethanol-modulated cell adhesion to the extracellular matrix, as well as lamellipodial protrusion formation and the quantity of focal adhesions. More specifically, cyanidin-3-glucoside inhibited stimulation of the ErbB2/cSrc/FAK cascade, which is vital for the invasion/migration of cells. Thus, C3G could be important in blocking breast cancer metastasis caused by ethanol [34]. Also, C3G showed cytotoxic action on MCF-7 cells and reduced the expression of Bcl2 gene while it increased the expression of caspase 3, CYP2, CYP1, bax, and p53 genes [35]. Feng and co-workers stated that cyanidin-3-rutinoside obtained from black raspberries inhibited leukemia cells in a dose-dependent manner. Cyanidin glycoside caused apoptosis by elevating the levels of peroxides and stimulated mitogen-activated protein kinases, which then enhanced the mitochondrial cascade modulated by Bim. It did not show cytotoxicity on normal cells [36].

The anticancer therapeutic potential of cyanidin was also investigated in renal cancer. Anthocyanin at concentrations of 25 and 100 μM was observed to induce the arrest of the cell cycle, inhibit apoptosis, and inhibit carcinoma cell migration and invasion. In more detail, cyanidin at 100 μM concentration arrested renal cell carcinoma carcinogenesis via SEPW1 and EGR1, as the expression level of SEPW1 was higher and that of EGR1 was lower in the renal cell carcinoma tumor tissue. Also, the autophagy-associated gene, ATG4, and p62 were also regulated [37]. The anticancer efficacy was also in evidence against cancer usually affecting the adrenal glands. Cyanidin abrogated the NF- κB signal cascade by reducing the breakdown of I $\kappa\text{B}\alpha$ and NF- κB p65 subunit translocation from the cytosol to the nucleus, with subsequent suppressing of iNOS protein expression and nitric oxide production [38]. Cyanidin-3-glucoside found in rice bran abrogated PC3 prostate cancer cell line progression by epithelial-mesenchymal transition inhibition via a Smad signal transduction cascade regulating the expression of Snail/E-cadherin [39].

In another study, the effect of C3G was determined on the gluconeogenic pathway and cancer cell senescence induced by oxidative stress in the context of hepatocarcinoma cells. The compound (10 and 50 μM) stimulated adenosine monophosphate-activated protein kinase via adiponectin receptor signaling and decreased gluconeogenic cascade in the liver by suppressing the expression of gluconeogenic genes. C3G exerted significant antioxidant action and caused cellular senescence and apoptosis in hepatocarcinoma cells with senescence. Also, the cyanidin elevated the expression of senescence-linked β -galactosidase and expression levels of P53, P21, and P16, which are major biomarkers of senescence in cells [40]. In another recent study, C3G abrogated the β -catenin/MGMT cascade by increasing the mRNA levels of miR-214–5 p to alleviate chemotherapy resistance in glioma cells [41].

The main target organs for cyanidin and C3G highlighted by *in vitro* studies are resumed in ► **Fig. 3**.

The active anticancer form of cyanidin is a crucial factor to consider, and its formulation can enhance its biological activity. As anticipated, in Caco-2 cells, C3G liposome showed more remarkable antiproliferative activity than the free C3G via the inhibition of human tumor cell proliferation [14]. Liposomes and C3G treatment for THP-1 macrophages can reduce inflammatory mediators that include interleukin (IL)-1, tumor necrosis factor- α (TNF- α), IL-6, and IL-8 that are produced when lipopolysaccharide (LPS) is present. According to the results, LPS induction may raise levels of phosphorylated NF- κB and I $\kappa\text{B}\alpha$. This demonstrated that C3G and C3G liposomes might suppress phosphorylated protein expression. Consequently, macrophages might be protected from apoptosis. As a result, C3G delivered through liposome technology demonstrates anti-inflammatory activity with potential applications in the anticancer field [42].

***In vivo* activity of cyanidin and its glycoside analogues**

In addition to *in vitro* data, some reports also highlighted the potential anticancer role of cyanidin and its glycoside analogues *in vivo*.

In this connection, an *in vivo* investigation indicated that a higher concentration of C3G decreased intestinal adenoma for-

mation of human familial adenomatous polyposis by up to 45%. Adenomas are tumors that can result in cancer. Cyanidin and anthocyanins need further investigation as chemotherapeutic agents against colon cancer [43]. In some cases, *in vivo* results did not parallel *in vitro* studies. For example, a research work discovered that C3G confers protection against oxidative DNA injury in an *in vitro* model; however, it exhibited no antioxidant action at nutritionally relevant levels in an *in vivo* rat model [44]. On the other hand, C3G isolated from mulberry arrested cancer through the cleavage of caspase-3 and DNA fragmentation. In the same study, the compound abrogates tumor growth in nude mice inoculated with MDA-MB-453 breast cancer cells. Thus, in this case, the compound inhibited growth and proliferation in both *in vitro* and *in vivo* cancer models, showing the abrogation of tumor progression [45].

Ding and collaborators discovered that cyanidin glycosides abrogate lung carcinoma cell line proliferation and migration of epithelial carcinoma cell lines in mice [46]. Other studies investigated the potential of cyanidin derivatives in lung cancer in combination with traditional chemotherapy. More specifically, the effect of C3G in combination with 5-fluorouracil was studied on nude mice with lung large-cell carcinoma. The administration of C3G (5 mg/kg) alone or together with 5-fluorouracil (25 mg/kg) induced apoptosis, impaired growth of the tumor, and reduced levels of inflammatory proteins including IL-6, IL-1 β , C-reactive protein, and TNF- α . Moreover, it reduced inflammation-linked factors such as NF- κ B and COX-2. Additionally, also in combination with 5-fluorouracil, it influenced the expression of tumor microenvironment-linked factors CD54, CD73, Ki67, and PDL1 [47].

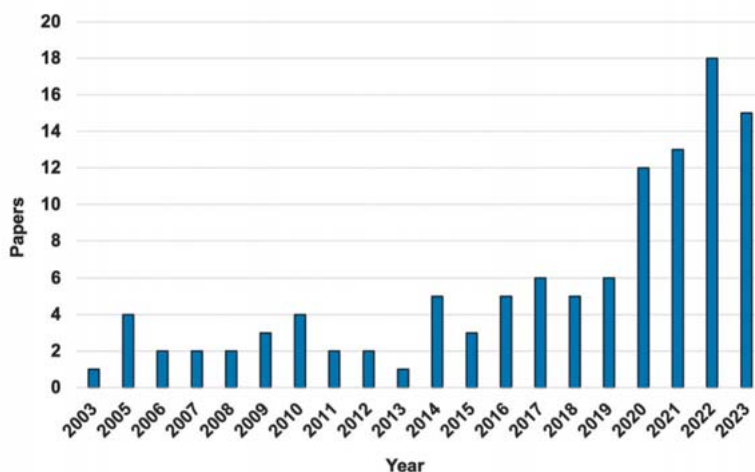
C3G topical application was proposed to decrease the level of COX-2 and stimulation of NF- κ B in the skin of mice exposed to UV-B in the context of cancer prevention [48]. Another study abrogated tumorigenesis in melanoma mice through estrogen receptor β . In this study, it was stated that the compound inhibited the G2/M phase of the cell cycle by acting on cyclin B1 and stimulated apoptosis through estrogen receptor β in both human melanoma cell lines and mouse models, thus arresting *in vivo* the growth of melanoma cells [49]. In a study, C3G was reported to exert anticancer activity against BALB/c nude mice with cervical cancer. The compound (40 mg/kg) abrogated the tumor and caused apoptosis in xenograft tumor nude mice, as well as a reduction in the level of Bcl-2 the expression of bax and cleaved caspase-3. C3G regulated the P13/AKT/mTOR signal transduction cascade [50]. C3G has chemopreventive properties against cancer in animal models. C3G was administered to C57BL/6 mice, and its anthocyanin metabolites were measured in various tissues. The study found that urine and gastrointestinal mucosa had the highest levels of C3G, with metabolites accounting for the majority of anthocyanins [27].

Pharmacokinetics and Bioavailability of Cyanidin and its Glycoside Derivatives

Pharmacokinetic studies of cyanidins and other anthocyanins pointed toward a better understanding of the absorption, bioavailability, distribution, metabolism, and elimination of such

compounds. These properties have a crucial impact on the biological action. Different indices can affect the pharmacokinetics of cyanidins and other anthocyanins from intake to elimination. More specifically, their biotransformations or interactions can occur even from the start, that is, through interaction with the buccal cavity [51]. Bioavailability is crucial as it indicates the percentage of cyanidin or its derivative that enters the systemic circulation from the GI tract, potentially reaching the target tissues. In humans, anthocyanins are absorbed when introduced via nasal intubation into the jejunum [52]. In rats, these compounds are well absorbed following *in situ* perfusion of ileum and jejunum [7]. The chemical structure of anthocyanins affects their absorption, and this varies with C3G, which shows a 22.4% absorption rate [53]. Overall, most of the cyanidin's were reported to be absorbed through the jejunum tissue (55.3%) of the small intestine [54], whereas in the duodenal tissue minor absorption was observed (10.4%), but no absorption was found in the colon or ileum. Cyanidins and their metabolites enter the systemic circulation and are transported to various organs in both health and disease states, where they perform their biological functions. In some cases, anthocyanins and cyanidin derivatives in particular are stored in some organs, once the plasma concentration is high. Low plasma concentrations of anthocyanins and cyanidins can be released from organs into the blood circulation [55].

Several studies were performed on animal models. Concerning biotransformation, approximately 7.5% of ingested anthocyanins are retrieved in their native state 2 h after administration of raspberries to experimental rats [56]. The plasma concentration of C3G rapidly decreases after intravenous administration due to reactions, with the methylated product detected 15 seconds after administration [57]. A study found that rats treated with anthocyanin-rich diets showed glucurono-conjugated and methylated derivatives of jejunum C3G [55]. Interestingly, C3G is not a substrate of lactase-phlorizin hydrolase or cytosolic β -glucosidase [58, 59]. Also, it was found that cyanidin's aglycones are metabolized to protocatechuic acid, which is again metabolized into three glucuronide conjugates [60]. Several other studies are focused on pharmacokinetics in humans, and differences between men and women were also considered. Following the administration of [13 C]-C3G to humans, 35 metabolites were discovered. In particular, B-ring and A-ring were labelled. Seventeen metabolites were observed in systemic circulation, 28 in feces, and 31 in urine [61]. Indeed, several studies indicated that methylated and/or glucuronidated conjugates are the main metabolites of anthocyanins in urines [62, 63], even if the anthocyanins and their metabolites excreted in urine after ingestion were reported to be 0.26 to 2.67%. Specifically, 721 mg of C3G orally administered to a human subject resulted in the detection of 1071.54 μ g total anthocyanins in urine after 24 h, but only 347.85 μ g (32.5%) of the parent anthocyanins were excreted unmodified in urine, whereas 723.69 μ g (67.5%) were seen as conjugated metabolites [64]. A similar behavior was observed in studies involving high doses administered orally to humans [65, 66]. Importantly, the pharmacokinetics of anthocyanins was also estimated in women. Cyanidin and other anthocyanins show better absorption when ingested via oral administration. Within 4 h of intake of total anthocyanins, C3G monoglucuronide, methylated derivatives, and other conju-



► **Fig. 4** The number of scientific publications per year reporting or discussing the anticancer activity of cyanidin according to PubMed (pubmed.ncbi.nlm.nih.gov, accessed on Nov 9, 2024). The query used was “cyanidin anticancer”.

gated metabolites were detected in urine [47]. A study demonstrated the bioavailability of anthocyanins from chokeberry juice at a dietarily relevant dose. Thirteen healthy volunteers consumed chokeberry juice containing 0.8 mg of anthocyanins/kg of body weight. After consumption, eight cyanidin compounds were detected in urine and blood. The renal pathway eliminated $0.25 \pm 0.02\%$ of the total anthocyanins consumed [67].

Overall, it can be deduced that intravenous administration is not optimal for cyanidins and their derivatives. However, cyanidin and its glycosides, such as C3g, administered through the oral route show better absorption through the intestinal wall and, in general, better bioavailability. This can result in high biological activity of the compounds. In addition, structural modifications of cyanidin glycosides also play a critical role in their absorption and bioavailability.

The Point of View of the Medicinal Chemist: Current Knowledge and Perspectives

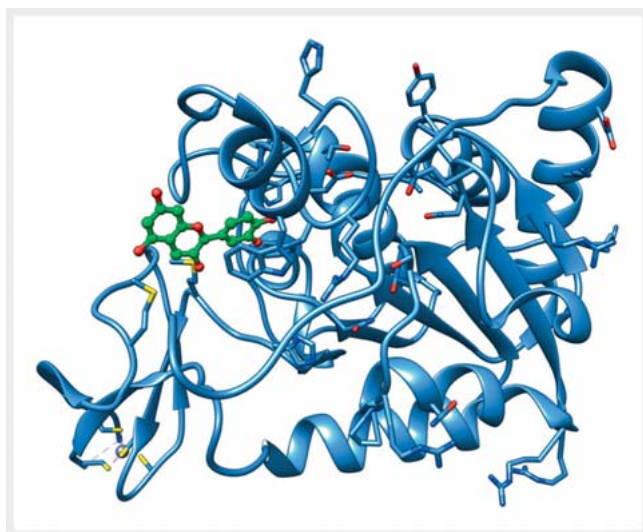
This review is an attempt to provide a concise account of the recent efforts undertaken to investigate the effects of cyanidin and its glycosides for cancer therapy. Being a strong scavenger and antioxidant, such compounds are used in a variety of ways to treat a wide range of illnesses and conditions. In particular, it may potentially serve as a direct anticancer agent but also in combination with conventional chemotherapy, as highlighted by the high number of *in vitro* and *in vivo* studies reviewed in the current paper.

The interest toward the anticancer activity of cyanidin is testified to by the growing number of scientific papers published yearly on this topic, as depicted in ► **Fig. 4**. In particular, as will be discussed in this paragraph, the literature flourished in the 2020 s.

The papers describing the *in vitro* and *in vivo* evidence concerning the anticancer activity, at different extents, of cyanidin and its

glycoside derivatives have been overviewed in this review article. Notably, in the 2020 to 2024 timeframe, some review articles also appeared in the literature, further testifying to the interest of the medicinal chemistry and natural products communities toward this topic, as briefly described in the following. Nevertheless, to the best of our knowledge, a comprehensive contribution like the current review was missing in the field. A brief overview of the available review articles in the literature is reported in the following.

In 2021, Liang and colleagues with their review entitled “Cyanidin 3-O-galactoside: a natural compound with multiple health benefits” provided a focused study on such glycoside, ranging from biosynthesis to antioxidant and bioactive properties. The authors overviewed *in vitro* data and *in vivo* anticancer evidence, highlighting chokeberry as a privileged source for this compound, but nevertheless reporting the lack of studies on humans [68]. In 2023, the research group of Safdar and colleagues published a review entitled “Cyanidin as potential anticancer agent targeting various proliferative pathways”. In this article, after discussing the main sources of cyanidin, the authors overviewed the evidence of the anticancer activity of the compound and glycosides (C3G) in breast, liver, prostate, and thyroid cancer. It is noteworthy that a functional description of such organs is also provided, together with the schematic representation of potentially involved molecular mechanisms [12]. In the same year, Posadino et al., in their review entitled “An updated overview of cyanidins for chemoprevention and cancer therapy”, approached this issue from a different perspective. The authors described sources and roles in traditional medicine and the classification of cyanidins and provided details on semi-synthetic derivatives. In this review, the anticancer activity is explored from the point of view of the mechanistic aspects. In particular, the effects on different development stages of tumorigenesis (early and late stages) were described. Additionally, the authors overviewed the reports concerning the reversion of chemotherapeutic drug resistance. In



► **Fig. 5** Cyanidin in complex with human Sirt6 (PDB ID 6QCH). The artwork was prepared using the UCSF Chimera [73].

the second part of the review, the authors reported current evidence of pharmacological mechanisms based on *in vitro* and *in vivo* studies, also highlighting the limitations in terms of drug-likeness and drug delivery challenges for such compounds [69].

In 2024, Zangade et al. published a review entitled “Flavonoid-metal ion complexes as potent anticancer metallodrugs: a comprehensive review”. The authors focused their overview on flavonoid-metal complexes that have been reported to have various biomedical and pharmacological activities. Flavonoids such as cyanidin can act as potent chelating agents for metal-chelate complex formation and can also be obtained synthetically. Notably, it has been noted that such complexes show enhanced anticancer activity [70]. Eventually, Purgatorio and colleagues, in a very recent review paper from 2024, published a very original review article entitled “A Critical Appraisal of the Protective Activity of Polyphenolic Antioxidants against Iatrogenic Effects of Anticancer Chemotherapeutics” in which they dissect the potential of polyphenols as auxiliary agents acting against oxidative stress toxicity induced by antitumor drugs. Cyanidin derivatives are mentioned in the review for their role in nitrosative stress, and the authors stressed how clinical studies are still required to assess adequate doses and delivery systems [71].

Despite the interest of the scientific community toward cyanidins as potential anticancer tools, some aspects still require further investigation.

First, it must be stressed that, despite cyanidin and C3G being effective in several cancer models, the studies often lack mechanistic details. Also, from the structural point of view, only a little information is available concerning the interaction of cyanidin with its macromolecular targets, an event that should trigger its bioactivity. In the Protein Data Bank (PDB), only one structure of cyanidin complex is present, consisting of mammalian Sirtuin 6 (Sirt6), a NAD⁺-dependent protein deacetylase involved in the regulation metabolism and chromatin homeostasis (► **Fig. 5**)

[72]. Thus, structural and functional details on the mechanisms through which cyanidin derivatives express their anticancer potential are still missing. Evidently, this limits the optimization of the compounds from a drug discovery perspective.

Then, the natural bioactive compounds such as cyanidin and its glucosides should be further investigated using *in vivo* models, and as highlighted by other review articles, very limited data on humans are available. Indeed, the overviewed papers highlighted discrepancies between *in vitro* and *in vivo* data in some of the cases. In general, using a single phytochemical for cancer therapy may not appear as a feasible strategy, and thus several of the current investigations are indeed directed toward their use in combination with other drugs.

Another aspect that should be considered is the need for an extensive investigation to determine the ideal and most efficient sources of cyanidin in different dietary routes. With phytochemical screening of a variety of foods, their metabolic pathway may provide a substantial basis for their consideration as anticancer compounds. Additionally, the optimal route of administration and delivery technologies still must be fully elucidated, while the production of prodrugs or semi-synthetic derivatives remains a mostly unexplored field.

Conclusion

In conclusion, the results presented in this review pave the way for the rational study of cyanidin and its analogues or metabolites as promising phytochemical candidates for cancer therapy based on *in vitro* and *in vivo* data. In the future, medicinal chemists should consider metabolic aspects related to chemical stability, pharmacokinetic profile, and effective dosage to confirm the potential of this class of molecules. Cyanidin and its glycoside derivatives have demonstrated promising anticancer potential in both *in vitro* and *in vivo* studies due to their ability to alter crucial molecular pathways linked to cancer development. Their modes of action include apoptosis induction, cell cycle arrest, antioxidant activity, metastasis suppression, and regulation of signaling pathways like PI3K/Akt, MAPK, and NF-κB. These substances have shown potential as safe and efficient therapeutic agents due to their specific cytotoxicity, targeting cancer cells while sparing healthy ones. Despite the promising preclinical evidence, several issues need to be resolved before clinical translation can proceed. The medicinal effectiveness of cyanidin and its derivatives is limited by their poor bioavailability and metabolic instability. Future research should focus on developing innovative drug delivery methods like nanoformulations and conjugation with biopolymers to enhance their stability and bioavailability. Furthermore, more thorough toxicological and pharmacokinetic research is needed to evaluate their safety and effectiveness in human models. Clinical trials are needed to assess the therapeutic potential of these compounds in cancer patients, despite their usefulness in *in vitro* and *in vivo* studies. Cyanidin derivatives may reduce medication resistance and adverse effects when combined with targeted therapies or traditional chemotherapeutics for synergistic effects. Cyanidin and its glycoside derivatives hold significant potential as anticancer drugs, but further research is needed to overcome their drawbacks and improve clinical use. Natural substances may be beneficial additions to

cancer treatment through bioavailability resolution, preclinical testing, and clinical trials.

Contributors' Statement

All authors contributed to the preparation of this review.

Conflict of Interest

The authors declare that they have no conflict of interest.

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