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Redox modulation by plant polyphenols targeting *vitagenes* for chemoprevention and therapy: Relevance to novel anti-cancer interventions and mini-brain organoid technology

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ABSTRACT

The scientific community, recently, has focused notable attention on the chemopreventive and therapeutic effects of dietary polyphenols for human health. Emerging evidence demonstrates that polyphenols, flavonoids and vitamins counteract and neutralize genetic and environmental stressors, particularly oxidative stress and inflammatory process closely connected to cancer initiation, promotion and progression. Interestingly, polyphenols can exert antioxidant or pro-oxidant cytotoxic effects depending on their endogenous concentration. Notably, polyphenols at high dose act as pro-oxidants in a wide type of cancer cells by inhibiting Nrf2 pathway and the expression of antioxidant vitagenes, such as NAD(P)H-quinone oxidoreductase (NQO1), glutathione transferase (GT), GPx, heme oxygenase-1 (HO-1), sirtuin-1 (Sirt1) and thioredoxin (Trx) system which play an essential role in the metabolism of reactive oxygen species (ROS), detoxification of xenobiotics and inhibition of cancer progression, by inducing apoptosis and cell cycle arrest according to the hormesis approach. Importantly, mutagenesis of Nrf2 pathway can exacerbate its "dark side" role, representing a crucial event in the initiation stage of carcinogenesis. Herein, we review the hormetic effects of polyphenols and nanoincapsulated-polyphenols in chemoprevention and treatment of brain tumors via activation or inhibition of Nrf2/vitagenes to suppress carcinogenesis in the early stages, and thus inhibit its progression. Lastly, we discuss innovative preclinical approaches through mini-brain tumor organoids to study human carcinogenesis, from basic cancer research to clinical practice, as promising tools to recapitulate the arrangement of structural neuronal tissues and biological functions of the human brain, as well as test drug toxicity and drive personalized and precision medicine in brain cancer.

1. Introduction

Over the last few decades, the incidence of brain cancer has markedly increased. In Europe, the incidence of primary central nervous system cancers ranges from 4.5 to 11.2 cases per 100,000 men and from 1.6 to 8.5 per 100,000 women [1]. Brain tumorigenesis is closely associated with oxidative stress and chronically altered microenvironment, but also with a reduced response of non-enzyme and enzyme antioxidant defense systems. Indeed, the imbalance between free-radical production and the efficiency of antioxidant defenses triggers the process, beeing brain very sensitive to free radical-induced damage. However, to counteract ROS production brain cells activate cytoprotective pathways involving the translocation of nuclear factor erythroid 2–related factor 2 (Nrf2) from cytosol into the nucleus and the up-regulation of antioxidant

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genes, termed *vitagenes*, including heat shock protein 70 (Hsp70) and heme oxygenase-1 (HO-1), as well as glutathione redox system to protect against brain cancer initiation and progression. Moreover, aberrant Nrf2 activation and mutations on keap-1 is reported in various types of malignancies. Currently, there is a growing interest in nutraceutical approaches through polyphenols, which have been investigated, both, in chemoprevention and therapeutic applications towards different types of tumors, including brain tumors [2]. Accordingly, increasing research efforts have been concentrated on the antioxidant and pro-oxidant effects of polyphenols, as pharmacological strategy against cancer [3,4]. Polyphenols have dual action regarding ROS homeostasis, acting as antioxidants under normal conditions and as potent pro-oxidants in cancer cells, triggering the apoptotic pathways and downregulating pro-inflammatory signaling *in vitro* and *in vivo* [5]. Intriguingly, polyphenols exert antioxidant or pro-oxidant activity depending on their dose, number and positions of hydroxyl groups, as well as on the ability to chelate redox metal ions (i.e., $Cu^{2+}$and Fe^{3+}) through Fenton and Fenton-like reactions. Indeed, the mobilization of endogenous metal ions, such as copper and iron, is an attractive hypothesis to explain the selective cytotoxicity of polyphenols targeting cancer cells. It has been established that the anticancer property of polyphenols is related to their prooxidant mechanism of action, rendering malignant cells more vulnerable towards natural drugs, such as flavonoids alone or their metal-(Cu-) flavonoid complexes interacting with DNA and inducing its degradation through ROS generation [6]. Conversely, at a mild concentration, polyphenols may activate antioxidant pathways, including intracellular antioxidant enzymes (e.g., superoxide dismutase, catalase, glutathione peroxidases, thioredoxins/thioredoxin reductases, peroxiredoxins), and non-enzymatic antioxidant molecules (e.g., glutathione, coenzyme Q, bilirubin), lastly acting as chemopreventive and therapeutic agents [7]. This postulates a promising target for anticancer therapies focused on the use of prooxidant polyphenols and/or on the inhibition of antioxidant systems in order to induce potent synergistic and specific anticancer effects of clinical relevance, as a potential alternative, orvasvan enhancement of classical chemotherapy [8]. Interestingly, selected inhibitors of antioxidant systems such as curcumin, piperlongumine, auranofin (AUR), Tri-1 (inhibitor of cytosolic TXNRD1), covalently bind to cytosolic selenocysteine-containing enzyme TXN reductase 1 (TXNRD1), converting it from an antioxidant to a prooxidant ROS-generating enzyme exhibiting a strong antitumor activity [9–11]. The cytotoxic, pro-oxidant, action of polyphenols, correlated to ROS-dependent induction of apoptosis and cell cycle arrest in cancer cells or activation of survival pathways is closely dependent on the dose. For instance, flavonoids such as anthocyanins at high concentration commonly present in black chokeberry (*Aronia melanocarpa, Rosaceae*) [12] and blueberry (*Vaccinium myrtillus, Ericaceae*) [13,14] cause apoptosis in cancer cells due to increased intracellular formation of ROS. However, moderate consumption of polyphenols induces healthy effects promoting activation of cellular stress response and *vitagenes* and inhibition of pro-inflammatory NF-kB-dependent pathway [15]. Likewise, green tea catechins, especially epigallocatechin-3-gallate (EGCG), at high doses seem to exert anti-cancer effects against multiple type of tumors attributed to a pro-oxidant activity induced by oxidative stress, leading to ROS-mediated cancer cell death, or alternatively at low doses they can scavenge ROS under conditions of high oxidative stress, preventing cellular damage [16]. On the other hand, high oral doses of EGCG (750–1500 mg/kg) showed hepatotoxic effects in CF-1 mice and humans. Notably, these hepatotoxic effects were associated with an increase in oxidative stress markers, such as lipid peroxidation, plasma 8-isoprostane, metallothionein, and γ-histone 2AX protein [17]. Therefore, dose is an important factor for the chemopreventive effects of polyphenols, and the role of pro-oxidant effects at higher doses, as anticancer therapy, must be carefully assessed.

2. The "dark side" of Nrf2 signaling pathway and *vitagenes* in cancer

In the past decades, Nrf2 was considered to prevent the occurrence and development of cancer. The antioxidant role of Nrf2 is to protect cells from the ROS induced damage by activating antioxidative enzymes. This activity neutralizes the cellular ROS to harmless molecules. The transcription factor Nrf2 is considered as a critical regulator of intracellular antioxidants and phase II detoxification enzymes by transcriptional upregulation of redox antioxidant response element (ARE)-containing genes termed *vitagenes*. The latter include heat shock protein 70, thioredoxin/thioredoxin reductases, peroxiredoxins, gamma glutamyl cysteine ligase, glutathione-S-transferases and sirtuin-1. All of which participate in neutralizing reactive oxygen species. Nrf2 and its related antioxidative enzymes prevents carcinogenesis by protecting normal cells from DNA mutations and it has been shown to act as a tumor suppressor [18]. On the other hand, the overexpression of Nrf2 and dependent *vitagenes* often induced in cancer cells protect cells from the ROS damage induced by radiation or chemotherapy. Interestingly, chemotherapeutic drugs such as resveratrol [19], sulforaphane [20], curcumin [21], carnosol [22] and lycopene [23] at low concentration can activate Nrf2 pathway and prevent tumorigenesis. Besides, some studies show that Nrf2 knockout mice increased cancer susceptibility to carcinogens and were refractory to the chemotherapeutic drugs [24,25]. However, recently, the cancer-promoting role of Nrf2 has been revealed. Surprisingly, Nrf2 was found to be constitutively upregulated in several types of human cancer tissues and cancer cell lines, and to protect tumor cells, particularly glioma cells enhancing tumor resistance to chemotherapeutic drugs and in ultimate promoting cancer initiation, proliferation, invasion and migration. All these events are referred as the "dark side" of Nrf2 (Fig. 1). In the report by Pan et al. the expression of Nrf2 in U251 glioma cells was manipulated using plasmid transfection. Upregulation of Nrf2 was associated to an increase of matrix metalloproteinase 9 (MMP9) and glioma cell migration, whereas downregulation of Nrf2 inhibited cell migration [26]. Heme oxygenase-1 (HO-1) is a critical enzyme of Nrf2-dependent vitagene pathway involved in antioxidant and anti-inflammatory responses [27]. An increasing body of evidence indicates that HO-1 also plays an important role in cancer. Especially, HO-1 was demonstrated to translocate into the nucleus regulating gene transcription, promoting tumor growth [28]. Therefore, high expression of HO-1 correlates with chemotherapy resistance in several type of cancer [29]. Furthermore, the constitutive expression of HO-1 and hemin (a by-product CO), exhibit cell-specific effects driving proliferation, survival and metastasis in glioblastoma cells [30]. Importantly, HO-1 protein overexpression was strongly correlated with worse prognosis in patients with grade II and III astrocytoma [31]. Moreover, in the C6 glioma cells HO-1 upregulated via Nrf2 mediated adaptive survival responses to 6-OHDA-nitrosative induced cell death [32]. Liu et al. reported that Nrf2 activation protected glioma cells against arsenic trioxide–induced oxidative stress, while Nrf2 knockdown reduced HO-1 induction by arsenic trioxide and enhanced oxidative damage in glioma cells [33]. In addition, the inhibition of Nrf2 in U251 cells decreased the expression of antioxidant enzymes, including HO-1, catalase, PRX, TRX and GSH by increasing ROS concentrations. These effects were mediated by the inhibition of the Ras/Raf/MEK signaling pathway. Therefore, the inhibition of Nrf2 expression could represent a new therapeutic anticancer strategy that enhances the effect of temozolomide treatment in glioma cells [34]. Ji et al. (2014) suggested that knockdown of Nrf2 control glioblastoma angiogenesis by inhibiting hypoxia-induced activation of HIF1α signaling in vitro and in vivo [35]. Recent evidence demonstrated cytoplasmic NRF2 expression was associated with a poor prognosis in grade II-IV tumors. Conversely, nuclear Nrf2, sulfiredoxin 1 (SRNX1) and DJ1 expressions in astrocytic gliomas of tumor tissue derived from patients with astrocytoma were associated with better patient survival. Thus, the nuclear Nrf2-SRNX1-DJ1 axis can be used in predicting patient

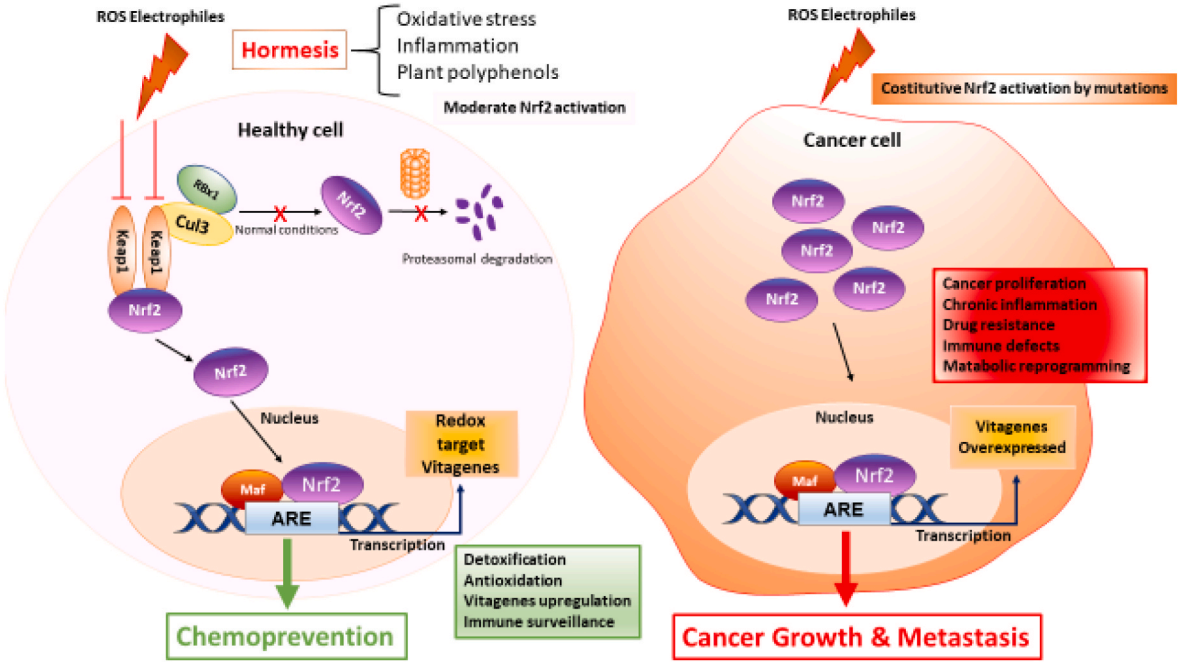

Fig. 1. Schematic representation of the dark side role of Nrf2 in cancer.

prognosis in gliomas [36]. Heat shock proteins (HSPs) are evolutionary conserved stress response proteins that act as molecular chaperones, preventing the formation of nonspecific protein aggregates and assisting proteins in the acquisition of their native protein folding. Furthermore, HSPs have anti-apoptotic activity and have been found to be increased in a wide range of human cancers; their overexpression has been associated with poor survival and response to therapy [37]. The heat shock protein 70 (HSP70) is a highly conserved protein in pro- and eukaryotes. In healthy cells, under physiological conditions, Hsp70 is expressed at low levels in nearly all intracellular compartments. Its expression is upregulated by a variety of cellular stimuli including heat, irradiation or chemical stress. In the context of cancer, Hsp70 translocates from the cytosol to the plasma membrane in malignant cells, whereas in non-malignant cells Hsp70 is selectively found in the cytosol [38]. In addition, cytosolic, membrane bound and extracellular Hsp70 is overexpressed in primary glioblastomas and should be considered as a monitoring parameter for clinical and therapeutic response in patients with glioblastomas [39]. It has been reported a parallel high expression of HSP27 (pSer82), HSP27 (pSer15), HSP40, HSP70 and HSP90 and total Akt and (phospho)Ak in both gliomas and meningiomas [40] as well as in medullablastoma [41]. Therefore, HSPs represent an attractive target for anticancer therapy. Additionally, Khalid et al. showed that HSP27 expression in gliomas correlated with histological grades of astrocytoma and with the Ki-67 index [42]. Moreover, Shen et al. studied low-grade gliomas and reported that the HSP27 expression was downregulated compared to autologous para-cancerous brain tissues [43]. The overexpression of HSPs in extracellular/surfaces of brain tumor cell lines (i.e., glioma, medulloblastoma, astrocytoma) induced exogenous immune responses using tumor-derived chaperone protein vaccines, which lead to antigen-specific immune responses and reduced tumor burden in treated mice [44]. Also, another member of *vitagenes*, the Sirtuin 1, a histone deacetylase protein plays an important role in glioma progression, invasion, and treatment response and is a potential therapeutic target in dose- and stage-dependently.

Redox homeostasis of cellular microenvironment is maintained by a controlled balance between antioxidant and pro-oxidant species. In healthy cells, under physiological conditions, keap1 protein inhibits the activation of the Nrf2 protein and induces its ubiquitination and proteosomal degradation. Nrf2 is upregulated in cancer cell lines and in some types of human cancer tissues and promotes cancer initiation, invasion, proliferation and migration. ROS and polyphenols at low concentration lead to oxidation of cysteine residues of Keap1 making Nrf2 to dissociate from the Keap1 protein, followed by stabilization of Nrf2 *via* phosphorylation. Consequently, Nrf2 translocates into the nucleus and binds to ARE along with the sMaf transcription factor leading to transcription and moderate expression of antioxidant target vitagenes. This induces cancer chemoprevention, immune surveillance, detoxification and antioxidation. In cancer cells, constitutive activation and dysregulation of Nrf2 pathway, due to mutations, promotes its excessive accumulation leading to drug chemoresistance, immune defects, metabolic reprogramming, cancer growth and metastasis.

Recent findings documented tumor promoting and tumor suppressing actions of Sirt1 [45]. In this scenario, upregulation of Sirt1 induces angiogenesis in conditions of oxidative and metabolic stress through dysregulation of apoptotic pathways [46]. The genetic or pharmacologic inhibition of Sirt1 activity arrests tumor growth and restores proper apoptotic signaling [47,48]. Consistent with this, accumulating studies observed that increased Sirt1/PGC-1α expression is strongly associated with increased chemo- and radio-resistance of glioblastoma stem cell clones [49]. On the other hand, the shRNA-induced knockdown of SIRT1 expression enhances the effectiveness of radiotherapy by inhibiting tumor growth in CD133+ GBM xenografts in mice [50]. Sirt1 is also highly expressed in glioma stem cells acting as tumor oncogene factor suppressing p53-dependent tumor surveillance [51]. In the context of tumor suppression, it has been reported that MicroRNAs (miRNAs), small non-coding RNAs, act as key regulators of gene expression. Their dysregulation is implicated in the development and progression of glioma. Especially, miR-133b modulates glioma growth and metastasis reducing Sirt1 expression [52]. The Thioredoxin (Trx)/Thioredoxin Reductase (TrxR) and Glutathione (GSH) systems are the most important cellular redox signaling to provide and maintain the intracellular environment in a reduced state, protecting against oxidative and nitrosative stress [53–56]. Overexpression of Trx/TrxR, GSH and Glutathione S-Transferases (GST) is often linked to increased malignancy rate of brain tumors, and higher expression is closely associated to therapy resistance [57]. It has been found a positive clinical correlation between the expression of Trx/TrxR and II-IV tumor but only high Trx expression was associated with poor prognosis in astrocytomas [58] and

oligodendrogliomas [59]. Consistently, recent studies suggested that high expression of cytoplasmic TrxR and Trx as well as nuclear Trx was associated with worse prognosis in adult and low-grade glioma and medulloblastoma patients [60]. Lastly, the ERK and PI3K pathways are hyperactivated and induce the expression of Nrf2. Importantly, MEK inhibitor PD08059 plus PI3K inhibitor LY292004 suppressed the protein expression of Nrf2 not only in the nucleus but also in the cytoplasm of human glioblastoma cells [61]. Overall, the data elicited the intrinsic "dark side" role of Nrf2 overexpression and vitagene pathway in promoting tumorigenic cascade as well as it was discussed of the potential therapeutic interventions through novel inhibitors that arrest the proliferation and chemoresistance by increasing apoptosis of brain cancer cells.

3. Antioxidant polyphenols and redox signaling for chemoprevention in brain tumors

In recent years, scientists focused their interest on plant-derived polyphenols as potential therapeutic agents in brain cancer management to minimize adverse drug reactions including oxidative stress, inflammation and drug toxicity. Growing evidence shed light on the pivotal role of antioxidant polyphenols in restoring redox homeostasis by modulating levels of cellular defense sensors such as glutathione (GSH), antioxidant enzymes and increasing expression of Nrf2 during the initiation and progression of cancer promoted by chronic inflammation, apoptosis and oxidative stress [62]. The latter is an intracellular excess of ROS relative to depletion of antioxidant capacity of the cell and induces carcinogenesis in cells with defective signaling factors. Nrf2 is a master regulator of redox cellular stress response pathways in various pathological states including cancer [63]. Under physiological conditions, Nrf2 is localized in the cytosol and regulated by its inhibitor Kelch-like ECH-associated protein 1 (Keap1). In this context, several investigations have shown that polyphenols act as potential antioxidant, anti-inflammatory and anti-carcinogenic mediators by modulating Nrf2 signaling pathways and molecular antioxidant biomarkers to suppress the incidence and progression of many human cancers in vitro and in vivo [64–68]. Recently, much evidence have demonstrated that polyphenols induce chemoprotective actions against oxidative stress and cancer by the stimulation of Nrf2, which accumulates and translocates into the nucleus where it binds to the antioxidant response element (ARE) inducing the transcription of multiple target genes, including phase II detoxification enzymes such as NAD(P)H: quinone oxidoreductase 1 (NQO1), heme oxygenase 1 (HO-1), thioredoxin, γ-glutamylcysteine synthetase and glutathione S-transferase (GST) [69]. In line with this observation, Nrf2 encodes vitagene antioxidant pathway to counteract different forms of stress (e.g., oxidative, environmental and mitochondrial stress). Vitagenes include Hsp 70, HO-1, γ-GCs, Trx and SIRTs [70–78] as biomarkers for stress adaptation, cross-tolerance and cellular resilience underlie of hormesis or preconditioning [79–84]. Nevertheless, deregulation of Nrf2 and/or Keap1 due to mutations and activated upstream oncogenes is associated with nuclear accumulation and constitutive activation of Nrf2 to protect cancer cells from apoptosis and induce proliferation, metastasis and chemoresistance. Emerging evidence reported that plant polyphenols (i.e., resveratrol, hydroxytyrosol, oleuropein, Hidrox®, saffron, sulforaphane, curcumin and moringa oleifera) may exert anticancer effects acting in a hormetic-like manner through the modulation of vitagenes, making the hormesis concept fully applicable to the field of chemoprevention and treatment by nutrition [80–84] and seems to be important in the personalization of treatment in brain cancer. Notably, polyphenols can act as antioxidants or pro-oxidants, depending on their concentration and cellular environment. Low activity of polyphenols at non-cytotoxic concentrations induces the activation of Nrf2 antioxidant pathways for chemoprevention of cancer (Fig. 2). On the other hand, at high concentration, phenolic compounds can act as pro-oxidants by inducing cytotoxic activity of cancer cells, and their potential role as chemotherapeutic compounds. The pro-oxidant mediated cytotoxicity of polyphenols in cancer cells depends on their chemical nature and concentration, and the

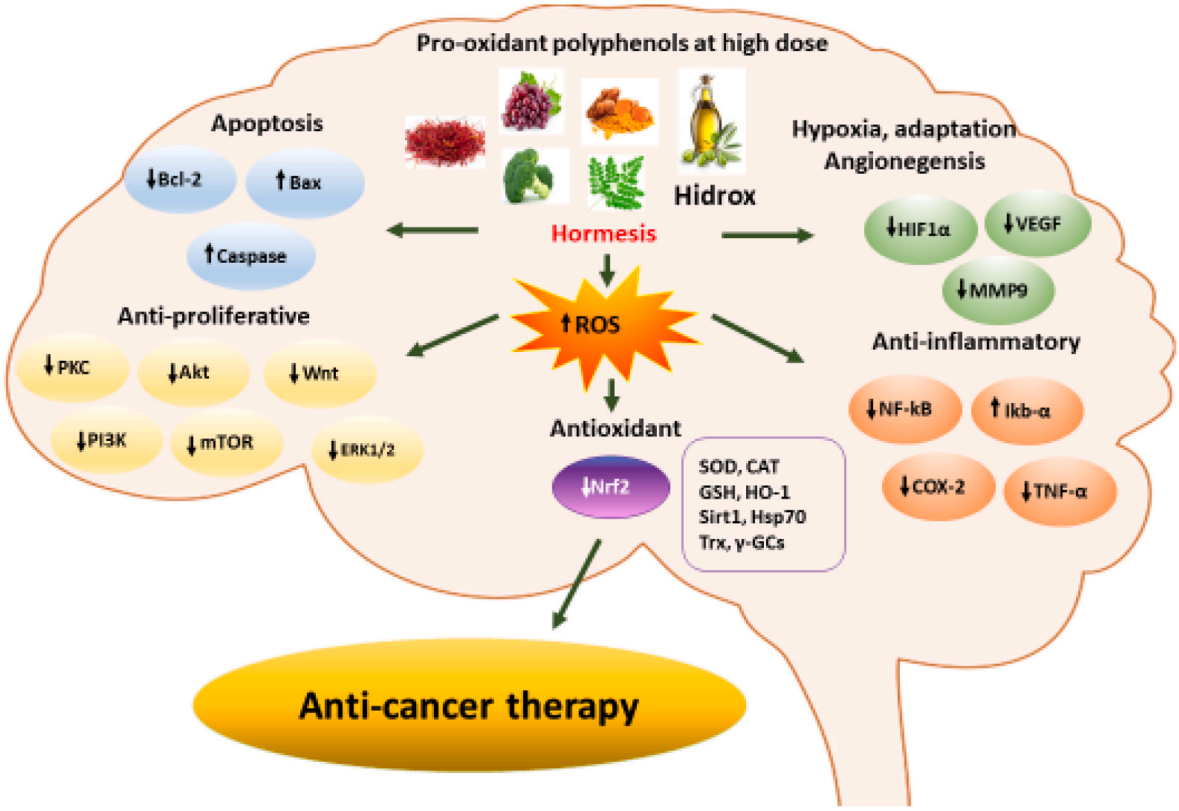

Fig. 2. Hormetic polyphenols and ROS generation involve many signaling pathways during brain cancer.

micro-environmental conditions, such as cell type, pH and redox stress [80]. Studies have demonstrated the anticancer role of a synthetic compound produced by modification of metabolite from Isaria sinclairii, the FTY720 in inhibiting the Nrf2 pathway and its downstream HO-1 and NQO-1 sensitizing human glioblastoma cells to chemotherapeutic drug such as temozolomide [85]. Moreover, FTY720 induced cell death, autophagy, apoptosis and necroptosis via suppression of Nrf2 and represent an attractive therapeutic agent for cancer therapy, especially for cancers with constitutive activation of Nrf2 such as glioblastoma [86]. The combination treatment with *Trifolium pretense* L extract and DOX synergistically downregulated Sirt1 expression and inhibited brain metastasis of 4T1 xenograft cells in a dose-dependent manner [87].

In brain cancer cells, polyphenols at high concentration can act as pro-oxidant inducers by increasing intracellular ROS which activates apoptosis in cancer cells and cell cycle arrest by downregulating Nrf2 expression and related genes. This is associated with an increase of anti-inflammatory factors, such as Ikb-α and with a decrease of pro-inflammatory mediators, such as NF-kB, COX-2 and TNF-α. Moreover, high concentration of polyphenols associated with ROS generation downregulate expression of proliferative factors, such as PKC, Akt, PI3K and mTOR, while upregulate pro-apoptotic Bax and caspase proteins, an effect associated to reduced expression of Bcl2 and HIF1α, VEGF and MMP9. The potential mechanism of actions of polyphenols at high dose, activating multiple molecular pathways, could be used as anticancer strategy in cancer patients.

Abbreviations: Bcl-2: B-cell lymphoma 2 protein; Bax: bcl-2-like protein 4; CAT: catalase; GSH: glutathione; γ-GCs: γ-glutammil sintetase; HIF-1: hypoxia inducible factor-1; HO-1: heme oxygenase-1; Hsp70: heat shock protein 70; MAPKs: mitogen-activated protein kinases; NF-kB: nuclear factor-kB; Ikb-α: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; COX-2: cyclooxygenase 2; TNF-α: tumor necrosis factor α; Nrf2: nuclear factor erythroid 2p45-related factor 2; PI3K: phosphatidylinositol-3-kinase; PKC: protein kinase C; Akt: protein-chinasi B; ERK1/2: extracellular signal-regulated kinase 1/2; mTOR: mechanistic target of rapamycin kinase; Wnt: Wingless-type; ROS: reactive oxygen species; SOD: superoxide dismutase; Trx: thioredoxin; VEGF: vascular endothelial growth factor; MMP9: matrix metalloproteinase 9; ↑ increase; ↓ decrease.

3.1. *Olive oil polyphenols and Hidrox®*

Polyphenolic compounds, mainly oleuropein (OLE), its major metabolite hydroxytyrosol (HT), hydroxytyrosol (HT)-rich aqueous olive pulp extract (Hidrox®), derived from olives and virgin olive oil exert potential antioxidant, anti-inflammatory and anti-tumor effects through the modulation of redox cellular defense systems in vitro and in vivo [88]. Extra virgin olive oil (EVOO), the principal source of fat in the Mediterranean diet, represents the topic of many studies because several epidemiological data suggest that it positively affects human health, reducing the incidence of cancer, hypertension, and cardiovascular diseases [89,90]. In support of this, emerging evidence demonstrated that oral administration of hydroxytyrosol, oleuropein and mixture of both phenolic compounds induce beneficial effects in rats with transplacental N-ethyl-N-nitrosourea (ENU)-induced brain tumors via redox control mechanisms involving endogenous enzymatic and non-enzymatic antioxidant defense are highly dependent on the gender of the animals [91]. Chronic inflammatory processes promote the initiation and development of cancer contributing to its recurrence by activation of inflammatory pro-angiogenic pathways [92]. Interesting studies reported that olive oil polyphenols such as hydroxytyrosol and oleuropein, inhibited inflammatory angiogenesis through the suppression of ROS-mediated NF-κB p65- dependent cyclooxygenase (COX)-2 and MMP-9 expression in human vascular endothelial cells [93]. In human glioblastoma cells, tyrosol, hydroxytyrosol, oleuropein and oleic acid significantly inhibit the effect of the chronic inflammatory cytokines such as (COX)-2, tumor necrosis factor (TNF)-α, NF-κB p65 expression and PGE2 secretion in a concentration-dependent manner. Also, oleic acid and tyrosol inhibited TNF-α-induced JNK and ERK phosphorylation, whereas only Tyrosol inhibited TNF-α-induced NF-κB phosphorylation [94]. Therefore, supplementation with olive oil polyphenols may represent an efficient dietary intervention in the prevention and/or management of glioblastoma. Moreover, oleuropein, inhibits LN-18 glioblastoma cell migration [95]. A recent our in vivo study demonstrated the protective effects of Hidrox® at a dose of 50 mg/kg in counteracting oxidative, inflammatory and apoptotic damage related to fertility induced by chemotherapeutic drug cyclophosphamide by the modulation of Nrf2-antioxidant defense pathway including, superoxide dismutase (SOD), GSH, HO-1 and catalase activity in a mouse model [96]. Also, Hidrox® exerts anti-inflammatory and antioxidant actions in animal models of endometriosis [97], chronic cystitis and pain [98] as well as in major neurodegenerative disorders [99] through a downregulation of interleukin (IL)-1β, IL2, IL6, TNF-α and vascular endothelial grow factor (VEGF) levels and an upregulation of Nrf2/vitagenes pathway. Demonstrated specific and rapid effects of oleic acid and HT on lipid synthesis in rat glioma cells. Particularly, the combination of 25 μM oleic acid and 25 μM HT induces a fast inhibition of radiolabeled acetate incorporation into both cholesterol and fatty acid fractions in glioma C6 cells [100]. Overall, most current therapies do not categorize between cancerous and normal cells, leading to unsolicited side effects and toxicity. In this sense, oleuropein and hydroxytyrosol olive oil derived polyphenols are excellent candidates in the anticancer therapy due to their promising therapeutic anti-inflammatory strategies described so much in vitro and in vivo experiments and the capability to cross the blood-brain barrier therefore, could represent an innovative nutritional tool to improve the quality of life of patients suffered from cancer.

3.2. *Resveratrol*

Resveratrol (3,4′,5-trihydroxystilbene) is a polyphenolic phytoalexin found in grapes, berries, peanuts, and red wine. Several in vitro and in vivo studies widely envisioned resveratrol as potentially useful for anticancer therapy when combined synergistically with other chemotherapeutic drugs, and it has received considerable attention for its potential as a chemopreventive agent against human cancers [101,102]. Jang et al., was the first author demonstrating the chemopreventive effects of resveratrol in inhibiting multistage carcinogenesis [103]. Brain cells are very sensitive to bioenergetic stress due to the high demand for adenosine triphosphate (ATP) in order to maintain neurotransmission. Recent evidence indicated that resveratrol modulates mitochondrial function and dynamics by several mechanisms, causing cytoprotective effects in both in vitro and in vivo experimental models involving brain cells [104]. Resveratrol can reach the brain parenchyma at sub-micromolar concentrations when administrated through conventional routes. In this way, resveratrol reduces cell invasion and increases the efficacy of radiotherapy (radiosensitizer effects) and chemotherapy (temozolomide) inducing both apoptosis and autophagy in human glioma cells through a reactive oxygen species (ROS) burst and extracellular signal-regulated kinase (ERK) activation. However, during these processes, autophagy protects glioma cells from apoptotic cell death. Resveratrol has been shown to augment the therapeutic efficacy of temozolomide by reducing ROS/ERK-mediated autophagy and subsequently increasing apoptosis both in vitro and in vivo [105].

Similarly, it has been demonstrated that resveratrol is a radiation sensitizer for highly radioresistant human SU-2 glioma stem cells. The synergistic effect of RES and radiation was seen in the inhibition of cell proliferation, induction of autophagy, promotion of apoptosis, prevention of DNA repair in the early stage, and induction of differentiation [106]. The molecular mechanism of the adjuvant action of resveratrol may depend upon the reduction of PI3K/AKT/NF-κB axis and downstream targets O-6-methylguanine-DNA methyltransferase (MGMT) and metalloproteinase-2 (MMP-2) [107]. Therefore, this recent study

confirmed a positive effect of resveratrol as an adjuvant agent in anti-glioblastoma therapy. In addition, resveratrol enhanced the sensitivity of highly resistant cells to temozolomide via activation of the DNA double strands/pATM/pATR/p53 pathway, leading to the activation of apoptosis. Additionally, RES promoted the differentiation of GIC involving p-STAT3 inactivation [108]. Also, it has been demonstrated that resveratrol sensitizes glioblastoma cells to the anticancer effects of other chemotherapeutic agents, including paclitaxel. Notably, the synergistic prooxidant effects of the combination of resveratrol and paclitaxel treatment increase intracellular steady-state ROS levels and mitochondrial dysfunction culminating in a decline in cell viability and increased cell death of glioblastoma cells via an apoptotic mechanism through the activation of transient receptor potential (TRP) melastatin 2 (TRPM2) [109]. Interestingly, Firouzi and coworkers recently evaluated the combined effect of resveratrol and methoxyamine on radiosensitivity of iododeoxyuridine in the spheroid culture of U87MG glioblastoma cell line by means of colony formation and alkaline comet assays. These researchers found that methoxyamine and resveratrol can significantly reduce colony number and induce DNA damage of glioblastoma spheroid cells treated with iododeoxyuridine in combination with gamma-rays. Therefore, resveratrol at a concentration of 20 μM shows promising anticancer effects when used in combination with radiation coupled with the radiosensitizer iododeoxyuridine (IUdR) [110]. In addition, Yang et al. discovered that resveratrol reduces the expression and activity of the POK erythroid ontogenic factor (Pokemon), a proto-oncoprotein that regulates the expression of many genes and plays a crucial role in tumorigenesis. In this study, it has been shown that resveratrol decreases Pokemon in glioma cells, inhibits the Sp1 DNA binding activity to the Pokemon promoter, enhances the recruitment of HDAC1, and lowers the p300 to the Pokemon promoter [111].

3.3. Saffron

Over the recent years, various authors illustrated antiproliferative action of saffron extract compounds named crocin and crocetin for cancer chemoprevention and treatment, especially in brain tumors [112, 113]. In line with this observation, emerging in vitro and in vivo evidence elucidated the antitumor properties of crocetin in glioma. Notably, crocetin treatment inhibited cell migration and induced apoptosis of glioblastoma cells and subcutaneously injected into xenograft model increasing the sensitivity of glioma cells to ionizing radiations dose-dependently [112]. Surprisingly, the treatment of glioblastoma cells with increasing doses of crocetin led to important decreases expression of cluster of differentiation CD44, CD90, CXCR4, and OCT3/4 mesenchymal markers, while increased the expression of βIII-Tubulin and neurofilaments (NFH) neuronal linage-related markers. This report is in accordance with the positive outcomes confirming that crocetin effectively overcame the BBB in animal models [114]. Multiple evidence indicated that histone deacetylase (HDAC) family including sirtuin 1-7 (SIRT 1–7) proteins could be suitable therapeutic targets for glioblastoma multiforme therapy due to their capacity to epigenetically modify the expression of genes (i.e., molecular chaperones) implicated in tumor progression and drug resistance [115]. Therefore, these protective molecules are promising alternative therapies for different human malignancies [116,117]. Conventional cancer therapies such as chemotherapy and radiotherapy essentially exert their cytotoxic effects by damaging the DNA of cancer cells. Consistent with this, natural antioxidant therapy with crocus extracts showed synergistic effects at a low dose of 3 mg/ml in combination treatment with temozolomide against C6 glioma rat cell line increasing the sensitivity of cancer cells and limiting the cytotoxic effects on healthy cells [113,118]. Current experimental in vitro studies revealed that crocetin owns cytotoxic and antiproliferative activities on multiple cancer cells as well as inhibitory roles for resistance to anti-cancer drugs in a concentration and time dependent manner [119]. In cervical cancer crocetin revealed an antiproliferative effect through the activation of p53 and p21 pathways increasing the sensitivity to vincristine [120]. Recent studies indicated that crocin and crocetin chemosensitize A2780 ovarian cancer cells to cisplatin which is mediated by the reduction of MRP1 and MRP2 resistance-related protein expression [121,122]. Therefore, extract saffron derived display a promising efficacy in combination with chemotherapeutic drugs in cancer therapy. Interestingly, a recent in vitro study observed that crocin inhibits proliferation and migration of metastasis-associated in colon cancer 1 (MACC1)-expressing colorectal cells in a concentration dependent manner [123]. It is noteworthy that crocetin (800 μM) also represses growth and migration by the upregulation of p38 mitogen-activated protein kinase (MAPK) and downregulation of vascular endothelial growth factor (VEGF) and matrix metalloproteinase 9 (MMP-9) signaling pathways in HCT-116 human colorectal cancer cells [124] as well as Wnt/b-catenin (Wingless-type/b-catenin) pathway in mouse breast carcinoma cells [125]. In addition, the combination of saffron aqueous extract and high-intensity interval training (HIIT) strategy suppress tumor growth through the upregulation of p53 and Sirtuin-1 in breast cancer cells [117]. Recent evidence reported the antioxidant activity of the crocin loaded nanoparticles on DPPH free radical scavenging and ferric reducing ability of plasma (FRAP) in chemoprevention and inhibition of tumorigenesis stages [126]. Moreover, the synergistic combination of trans sodium crocetinate (TSC) and temozolomide has also been under investigation in a clinical trial sponsored for potential use as a radiosensitizer, increasing the susceptibility of hypoxic cancer cells to radiation therapy, in patients with a form of brain cancer known as glioblastoma (ClinicalTrials.gov) [127]. Considering the observed effects of saffron extracts in the suppression of cancer cells, these bioactive compounds can be used in the prevention and treatment of cancer after confirmation in human clinical trials. Although, to date, in the literature there is a lack of clinical studies on saffron extracts as supplementation to therapeutic strategies in cancer. Overall, these outcomes elicited on the chemopreventive and pharmacological potential of saffron extracts alone or in combination that at low dose could be considered as a promising candidate for anticancer therapy in humans.

3.4. Curcumin

Curcumin is the most active natural polyphenol belonging to the ginger family Zingiberaceae present in the turmeric root of the herb, Curcuma longa [128]. For a long time, it has been known to function as a potent inhibitor of tumor growth, proliferation, invasion, angiogenesis, and metastasis. Curcumin has been applied for several cancer therapies, including brain tumors [129]. It can inhibit cancer proliferation by increasing oxidative stress, disrupting PI3k-Akt/mTOR signaling and induction of apoptosis, but it requires higher doses to be effective against cancer cells [130]. In addition, combined treatment with a low dosage of curcumin (7–14 μM) and low concentration (12–24 μM) of tyrphostin AG494 against EGFR significantly reduced proliferation and viability and increased genotoxicity of human brain cancer cells in glioblastoma multiforme [131]. A recent study reported that phytosomal curcumin exerts an immunotherapeutic action in cancer by mediating recruitment of tumoricidal M1 macrophages and activating natural killer (NK) cells causing destruction of the glioblastoma cells [132]. Moreover, it has been showed that artemisinin and curcumin are effective pro-oxidant agents able to generate ROS in cancer cells for brain tumor suppression and lifespan extension, as well as improving general health in *Drosophila melanogaster* [133]. In addition, curcumin decreased the constitutive activation of PI3K/Akt and NF-kB survival pathways, down-regulated the antiapoptotic protein bcl-xl and upregulating Bax as well as induced mitochondrial dysfunction at a dose of 30 μM in vitro (C6, U138MG, U87 and U373 cell lines), while had antiglioma effects decreasing gliobastoma tumor size at a dose of 50 mg/kg in vivo (C6 implants in rat brain). Most importantly, curcumin did not cause any tissue and metabolic toxicity in the liver, kidney, lungs, or heart of rats [134]. Other than that, recent experimental

evidence also shown that curcumin inhibited proliferation, migration and invasion by decreasing the p-Akt/p-mTOR pathway and promoted apoptosis by increasing PTEN and p53 expression in glioblastoma cells and in U87 xenograft model [135]. Additionally, curcumin induced autophagy by inhibiting the AKT/mTOR/p70S6K pathway in GBM cell lines and xenograft models [136]. In these studies, curcumin significantly decreased the levels of P13Kp85, phosphoP13Kp85, total Akt, p-AKT, mTOR, and p-mTOR. Interestingly, mTOR is not only a major effector of cell growth and proliferation, but it can also inhibit autophagy events in its active form [137]. Thus, inhibition of the expression of P13K and AKT, which regulate mTOR expression, could be a promising strategy to induce autophagy–cell death in glioblastoma cells.

3.5. Sulforaphane

Sulforaphane (SFN), is an isothiocyanate derived from cruciferous vegetables, particularly broccoli and broccoli sprouts, has been widely investigated due to its promising health-promoting properties in brain cancer and low toxicity in normal tissue in vitro and in vivo models. Recent findings demonstrated that SFN exhibited significant antiproliferative activity via the inhibition of histone deacetylase (HDAC) activity and the activation of ERK in vestibular schwannoma cells and mouse model with a murine schwannoma allograft. Moreover, SFN treatment induced apoptosis and cell cycle arrest at the G2/M phase in a concentration-dependent manner, particularly at a dose of 20 μM. Moreover, SFN can rapidly cross the BBB and accumulate in the CNS after i.p. administration [138–141]. Recently, a growing interest has also been directed towards application of SFN in GBM to induce apoptosis, and to inhibit both growth and invasion of GBM cells [142]. Furthermore, SFN can overcome the chemoresistance of tumor cells [143,144]. During tumor progression, the expression of matrix metalloproteinases (MMP), in particular MMP-9, significantly increases and it is associated with the alteration of BBB [145]. MMP-9 has already demonstrated to play a crucial role in the structural organization of endothelial cells [146]. Notably, Annabi et al. showed that the increased secretion of MMP-9 by human brain microvascular endothelial cells was decreased by SFN treatment. Moreover, SFN reduced cells migration, showing a potential role for this ITC to inhibit the functions mediated by MMP-9 in GBM [147]. There is no controversy about the significance of improving drug delivery across the BBB. In this view, the attractive modulation of BBB for therapeutic benefit might be an interesting mechanism behind the chemopreventive activity of SFN [148]. Induction of apoptosis associated with increased intracellular calcium concentration (Ca^{2+}) has been demonstrated in various in vitro models [149,150]. Karmakar et al. demonstrated in two different GBM cell lines that SFN caused endoplasmatic reticulum (ER) stress to raise Ca^{2+} and release caspase-12. Once activated by calpain, caspase-12 leads to caspase-9 activation. Moreover, SFN mediated both caspase-dependent apoptosis by increasing the Bax/Bcl-2 ratio and mitochondrial release of several pro-apoptotic molecules, such as cytochrome *c* and second mitochondria-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low pI (Smac/Diablo), and caspase-independent apoptosis by the apoptosis-inducing factor (AIF) [151,152]. These effects of SFN on GBM cells are further confirmed by Miao et al. (2017). They also demonstrated that L-SFN, a synthetic analogue of broccoli-derived isomer of SFN, induces apoptosis of GBM cells increasing ROS levels [153]. However, other reports revealed that SFN may protect normal cells against oxidative stress [154,155]. These paradoxical SFN activities are related to the intrinsic high level of ROS in cancer cells, which might contribute to amplify the death signal induced by anti-cancer agents. In contrast, this does not happen in normal cells, in which the same increase of the ROS level evokes a cytoprotective effect [156]. Accumulating evidence demonstrated that SFN can be considered a hormetic agent since is able to trigger biologically opposite effects depending on its concentration. Thus, at low concentrations it exerts chemopreventive, indirect antioxidant, and cytoprotective effects, instead at higher doses it triggers cytotoxic and antitumor properties [157]. Notably, it has been reported that SFN at a concentration of 10 μM generated ROS formed by mitochondrial respiratory chain and consequent apoptosis of glioblastoma cells. Moreover, SFN at a dose of 100 mg/kg inhibited tumor growth in ectopic xenograft mouse models [158]. Several studies have shown that the signal transducer and activator of transcription 3 (STAT3) mediates proliferative signals and it is constitutively activated in GBM [159,160]. Furthermore, SFN treatment induces the time- and dose-dependent down-regulation of Janus kinase 2 (JAK2) and Src tyrosine kinases phosphorylation in GBM cells via post-translational modification of cysteine residues, which potentially inhibit the STAT3 pathway in a ROS-dependent manner [153,161]. Even more interestingly, the activation and interaction between STAT3 and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) play crucial roles in controlling the dialog between cancer cells and their microenvironment, especially with immune cells that infiltrate tumors. NF-kB and STAT3 are strictly involved in the control of apoptosis-based tumor-surveillance, tumor angiogenesis and invasiveness [162]. In this context, SFN treatment caused down-regulation of NF-kB in human GBM cells [163]. In particular, the mechanisms of action of SFN to prevent GBM cell survival signals include both the inhibition of two inhibitor-of-apoptosis proteins (IAPs), and the up-regulation of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IkBα), an endogenous inhibitor of NF-kB [164]. In addition, SFN could inhibit migration and/or invasion in many kinds of cancer cells. Consistent with this, Zhang et al. investigated the effects of SFN on U251MG GBM cells to assess the potential effectiveness of this ITC to counteract the tumor growth and its infiltrative potential. To this aim, authors treated U251MG cells with SFN to investigate its anti-invasion activity. Moreover, Galectin-3 and E-cadherin, cell actors involved in cancer invasion, are highly expressed in GBM and are modulated by MMPs [165]. The outcomes obtained showed that SFN treatment reduced the invasive potential of GBM cells by increasing the protein levels of E-cadherin and by decreasing Galectin-3, MMP-2 and MMP-9 in a dose-dependent manner [166]. Furthermore, several studies have shown that SFN may be responsible for the activation of extracellular signal-regulated kinase 1/2 (ERK1/2) and the consequent induction of apoptosis in human brain glioma and neuroblastoma cells [163,167]. Li et al. (2013) demonstrated that transient activation of ERK1/2 can contribute to GBM migration and invasion [168]. Tumor cell invasion through the basement membrane is an essential step for the propagation of cells from the primary site to distal secondary sites. In this process, MMPs play a central role, because they might damage basement membrane to create space for GBM cells and promote the invasion cascade. The protein kinase ERK1/2 modulates the expression of CD44 glycoprotein, an adhesion molecule involved in tumor cell migration and invasion. A novel approach to GBM therapy is the combination of natural compounds with temozolomide (TMZ) [169]. In this view, Lan et al. evaluated the activity of SFN in sensitizing different malignant glioma cell lines resistant to TMZ treatment. The study showed that the synergistic combination of SFN with TMZ inhibited survival capability and increased the induction of apoptosis in TMZ-resistant GBM cells by the down-regulation of O6-methylguanine-DNA methyltransferase (MGMT) expression via NF-kB signaling pathway [170]. Most studies on the possible sensitizing efficacy of SFN have been focused on the interaction of this ITC with the tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL). TRAIL is the natural ligand for apoptotic receptors that contributes to TMZ resistance and triggers apoptosis in different in vitro and in vivo cancer models, without conferring significant toxicity to normal cells [171,172]. Although TRAIL exerts promising anticancer effects, several primary tumors, such as GBMs, present a phenotype quite resistant to apoptosis induced by TRAIL [173,174]. Interestingly, SFN is able to sensitize different TRAIL-resistant human cancer lines to TRAIL-induced apoptosis, mainly by triggering death receptors [175]. Recent evidence demonstrated that 20 μM SFN induces apoptosis via phosphorylated

ERK1/2-mediated upregulation of 26 S proteasome and Hsp70, and downregulation of βIII-tubulin, XIAP, Tau, Stathmin1 and α-tubulin, low-resistance and high-efficiency chemotherapy in combination with paclitaxel [176]. Moreover, sulforaphane-cysteine (SFN-Cys), an analog of SFN induced cell apoptosis via activation of ERK1/2 and the ERK1/2 signaling pathways increasing the ratio of Bax/Bcl-2 and upregulating cleaved caspase 3 in human glioblastoma U373MG and U87MG cells. Thus, indicating that SFN-Cys might be a more novel therapeutic agent versus SFN to glioblastoma chemoresistance, especially in Taxol-resistant cancer cells [177].

3.6. *Moringa oleifera*

Moringa oleifera (MO) is a traditional medicinal tree belonging to the Moringaceae family which has shown great potential as complementary and alternate medicine in cancer [178]. Emerging evidence highlighted the anti-inflammatory, antioxidant, antimicrobial, apoptotic and anti-proliferative effects of MO in vitro and in vivo [179–181]. Consistently, MO up-regulated some pro-apoptotic proteins such as Bax, p21, and p53 whereas modulated nuclear translocation of NF-κB in cancer cells in a concentration- and time-dependent manner [179]. It is well known that NF-κB is a central signaling factor involved in the development and progression of human cancers as well as in the acquisition of drug-resistant phenotype in highly aggressive malignancies [182]. However, recent studies documented that many natural compounds induce a functional crosstalk between PI3K/Akt/mTOR signaling pathway and NF-κB and potential biological implications with cancer therapy [183,184].

Accumulating evidence reported STAT5 (Signal Transducer and Activator of transcription 5) is commonly constitutively activated in cancer and causing cell proliferation [185]. Interestingly, the 4-(α-L-rhamnopyranosyloxy)-benzyl isothiocyanate of MO, also called moringin at low concentration of 0.4 μM showed to be a potent inhibitor of oncogenic STAT5, NF-κB and, to a lesser extent, STAT1/STAT2 signaling pathways [186]. Our recent work, evaluated antioxidant and bioenergetic role of MO in counteracting DEHP-induced mitochondrial dysfunction and oxidative stress as well as induce apoptosis in SH-SY5Y neuroblastoma cells [187]. Furthermore, other in vitro studies demonstrated the antitumor and anti-apoptotic effects of glucomoringin via oxidative stress mediated mechanisms in a dose-dependent manner. In this regard, it has been showed that glucomoringin at high dose (≥16 μM) significantly increased proapoptotic Bax and reduced Bcl-2 expression as well as enhanced the expression of Nrf2, CK2 alpha and p53 in astrocytoma cells. On the other hand, at 24 μM concentration, Nrf2 and CK2 alpha levels were reduced significantly while p53 level was partially reduced, suggesting a high degree of apoptosis and cell death regulated by p53 activation [188].

4. Hormesis and nanochemopreventive approach by polyphenols for brain cancer management

Hormesis is a phenomenon characterized by growth stimulation at low doses and growth inhibition at high doses and is involved in cell death signaling. In recent years, the knowledge concerning the hormetic dose–response induced by a novel nanomedicine approach through nutritional polyphenols is emerging with notable interest in cancer chemoprevention and therapy (Fig. 3). Nanoparticles have been rapidly growing and appeared relevant for the safe application of such innovative tools as well as to understand the brain health. Therefore, the concept of hormesis has generated considerable attention in the area of nano-toxicology and nano-risk assessment for brain anti-cancer therapy [189]. Emerging in vitro and in vivo evidence highlighted the importance of innovative therapeutic approaches based on nanoparticle technology in correlation with hormetic dose-response. Consistent with this, it has been recently demonstrated that silver nanoparticles (AgNPs) induce hormesis in astroglioma cells and the potential involvement of Mu-2-related death-inducing gene (MuD) in AgNP-induced hormesis. Therefore, AgNPs at low doses exhibited cytotoxic effects on astroglioma cell proliferation in a dose-dependent manner by increasing MuD expression resulting in anticancer effects of brain tumors [190]. Ferroptosis is a form of nonapoptotic cell death that is dependent on iron. The first author that described this process has been Dixon in 2012 [191]. Numerous studies interrogating the redox cellular signaling pathways (i.e., glutathione peroxidase 4, acyl-CoA synthetase long-chain family member 4 and phosphatidylethanolamines) regulating ferroptosis soon followed [192]. The mechanism of cell death is

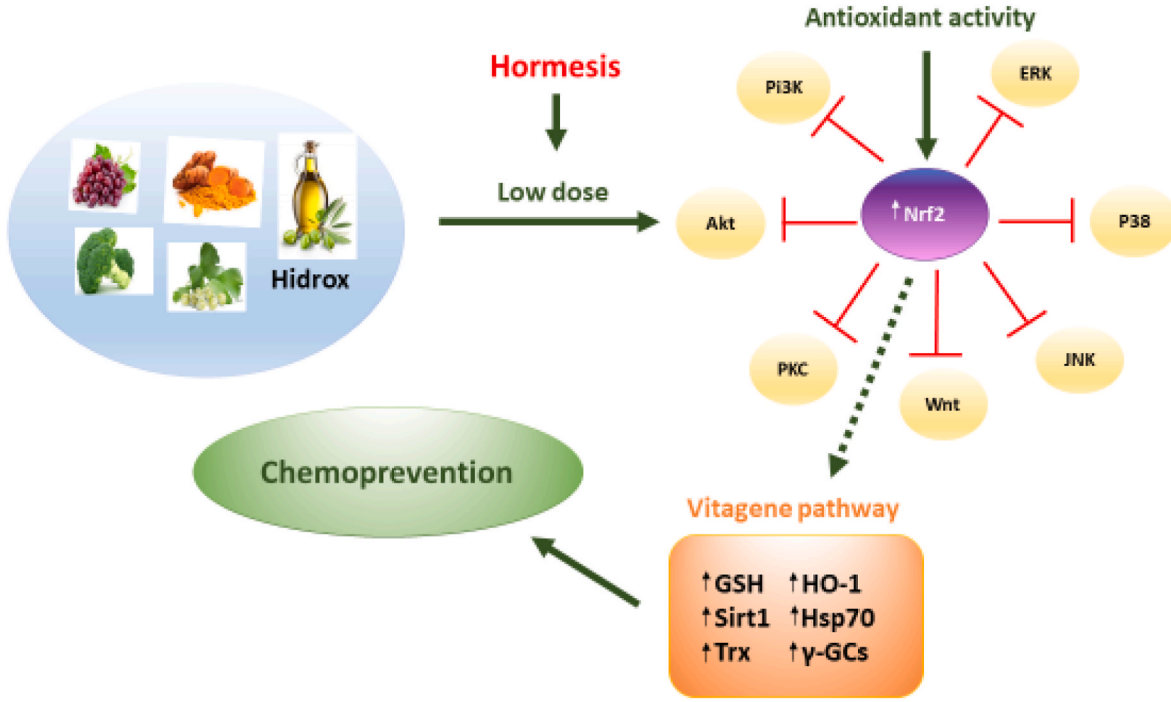

Fig. 3. Antioxidant activity of polyphenols by low expression of Nrf2 and vitagenes in cancer.

mediated by the production and accumulation of ROS induced by iron based on nanomaterials via Fenton reaction [193]. Specifically, the acceleration of Fenton reaction generates reactive oxygen species to induce cancer cell death. Recently, the ferroptosis therapy through nanoparticles is a novel form of cancer therapy that significantly improved the efficacy via accelerating the Fenton reaction by simultaneously increasing the local concentrations of all reactants (Fe^{2+}, Fe^{3+}, and H_2O_2) in glioblastoma cancer cells. Notably, the magnetic nanoparticles such as cisplatin (CDDP)-loaded Fe3O4/Gd2O3 hybrid nanoparticles with conjugation of lactoferrin (LF) and RGD dimer (RGD2) (FeGd-HN@Pt@LF/RGD2) are designed to cross the BBB and internalized into tumor site leading to significant inhibition of tumor growth. Moreover, these nanoparticles did not show toxic effects on animal models indicating good biocompatibility [194]. Interestingly, iron oxide nanoparticles-based system that efficiently delivers iron, cisplatin (Pt), and a glutathione peroxidase 4 (GPX4) small interfering RNA (si-GPX4) for the highly efficient synergistic induction of ferroptosis/apoptosis in GBM cells. The nanodrug FA/Pt + si-GPX4@IONPs has been projected to protect the loaded si-GPX4 from degradation. Furthermore, this nanodrug targeted selectively glioblastoma cells inducing apoptosis and was highly efficient and safe for cancer therapy in vitro and in vivo [195]. Emerging nanotechnology approaches have been proposed in the last decade for brain tumor therapy with several drugs and nanomaterials [196–198]. Siddiqui et al. introduced for first time the concept of "nanochemoprevention" through natural polyphenols for anticancer therapy [199]. Bioactive polyphenols contained inside nanoparticles increase in vivo bioavailability, chemical instability, extend a compound's blood circulation time, and allow for controlled and sustained drug release in specific cancer site minimizing normal cell damage, increasing anticancer effects and reducing systemic toxicity [200]. In this context, several studies investigated the antiglioma effects of *trans*-resveratrol-loaded lipid-core nanocapsules (RSV-LNC) based on in vitro (C6 glioma cell line) and in vivo (brain-implanted C6 cells) models. Interestingly, RSV-LNC treatment was not cytotoxic to hippocampal organotypic cultures, a model of healthy neural cells, suggesting selectivity for cancer cells. RSV-LNC induced losses in glioma cell viability through induction of apoptotic cell death, as assessed by annexin-FITC/PI assay, which was preceded by an early arrest in the S and G1 phases of the cell cycle. In brain-implanted C6 tumors, treatment with RSV-LNC (5 mg/kg/day, i.p.) for 10 days promoted a marked decrease in tumor size [201]. Moreover, other studies demonstrated the anti-oxidative properties of iron oxide NPs functionalized with caffeic acid (γFe_2O_3@CA) nanoparticles for ROS production in U87 glioblastoma and xenograft mice [202]. Recently, novel nanocurcumin strategies are emerging as promising anticarcinogenic natural polyphenol by inducing ROS and cell death markers, thereby inhibiting cell survival pathways in tumor microenvironment. Consistent with these anti-cancer therapies, Maiti et al. demonstrated that solid lipid curcumin particles (SLCPs) provided more bioavailability and higher anti-cancer effects in glioblastoma cells than to free natural curcumin. Accordingly, it has been showed that SLCPs increased cell death and DNA fragmentation [203] as well as induced autophagy, but inhibited mitophagy and the PI3K-AKT/mTOR pathway in glioblastoma cells [204]. In addition, combination treatments of SLCP and berberine increased ROS levels, induced cell-death and inhibited the PI3K/Akt/mTOR signaling pathway postulating a novel promising strategy to reduce or prevent glioblastoma growth in comparison to treatments alone [205]. In addition, in vitro and in vivo studies demonstrated that curcumin (CCM)-loaded chitosan-poly(lactic-co-glycolic acid) (PLGA) nanoparticles (NPs) modified with sialic acid (SA) to permeate the BBB and with anti-aldehyde dehydrogenase (anti-ALDH) targeting brain cancer stem cells and glioblastoma cells to inhibit tumor growth [206,207]. Lim and coworkers demonstrated that nanoparticle-encapsulated curcumin inhibits medulloblastoma and glioblastoma cells growth through the modulation of cell proliferation, survival and stem cell phenotype in a dose response manner [208]. Another novel nanoformulation consisting in AT101, the R-(−)-enantiomer of the cottonseed-derived polyphenol gossypol, is a promising drug in glioblastoma multiforme (GBM) therapy due to its ability to trigger autophagic cell death but also to facilitate apoptosis in tumor cells. This AT101 encapsulated in cubosomes revealed to have stronger in vitro cytotoxic effects evidenced by the induced rearrangement of cytoskeletal actin fibers in treated GBM cells, than against normal brain cells [209]. Recent evidence demonstrated a novel liposomal formulation of TriCurin (TrLp), that represent a synergistic combination of three polyphenols such as curcumin, epicatechin gallate and resveratrol as a potent anticancer strategy against Glioblastoma Multiforme (GBM) tumors. In particular TriCurin induced the repolarization of M2-like tumor (GBM)-associated microglia/macrophages to the tumoricidal M1-like phenotype and intra-GBM recruitment of activated natural killer cells to facilitate apoptosis of GBM and GBM stem cells [210]. Moreover, it has been tested the anticancer effects of the combination of temozolomide (50 μM) plus nanomicellar-curcumin (20 μM) treatments through inhibition of GBM growth via Wnt signaling, autophagy and apoptotic pathways [211]. Other recent evidence evaluated the synergistic effects of the combination of paclitaxel and curcumin via a T7-mediated, magnetic-guided dual-targeting mechanism. This study demonstrated that this dual-targeting brain co-delivery strategy efficiently penetrate the BBB and inhibits tumor growth in glioma cells and in orthotopic glioma mouse model [212]. The novel nanodrug delivery systems such as iron oxide nanoparticles (SPIONs) and curcumin (Cur) encapsulated into exosomes and then conjugated the exosome membrane with neuropilin-1-targeted peptide (RGERPPR, RGE), exhibited good stability, biocompatibility and potent anticancer effects when administrated in glioma cells and orthotopic glioma models. Thus, nanodrug delivery systems provided a potential anticancer approach to improve the diagnosis and treatment effects of intracranial tumors [213]. Furthermore, nanotheranostic studies integrating epigallocatechin-3-gallate (EGCG) and phenolic platinum (IV) prodrug (Pt-OH) by taking advantage of metal–polyphenol interactions have demonstrated a synergistic antitumor strategy for its high stability and excellent drug release as well as reduced systemic toxicity in vitro and in vivo [214]. In vitro and in vivo evidence conducted with human glioblastoma cells showed a higher uptake efficiency of temozolomide/Resveratrol-coloaded mPEG-PCL nanoparticles synergistically enhanced the cytotoxicity, apoptosis and chemosensitizer in U87 glioma cells as compared to cells treated by the combination of free drugs. Moreover, the co-delivery of both drugs also resulted in a stronger tumor growth inhibition than the combination of both free drugs, or each drug alone. The results proved that the dual-delivery of these drugs could be an excellent strategy for anti-glioma therapy [215]. In addition, in vivo studies using Wistar rats demonstrated that resveratrol-loaded glyceryl behenate-based solid lipid nanoparticles (SLN) significantly increase the brain concentration of resveratrol as compared to free resveratrol and higher efficiency in targeting and delivery contributing to decrease the adverse side effects. Thus, these lipid nanocarriers represent a promising potential as therapeutic agent to treat neoplastic diseases located in the brain tissue [216]. Jhaveri et al. (2018) developed liposome nanosystems using transferrin molecules and resveratrol encapsulated to enhance uptake from glioblastoma cells. Also, the developed liposomes exhibited physicochemical properties (size and charge) to allow their passage across the BBB. In vitro competitive binding experiments with glioblastoma cells from humans proved that modification with transferrin molecules enhanced the cellular uptake by taking advantage of the transferrin receptor-mediated endocytic pathway. This increased internalization justifies the observed higher efficiency in decreasing cellular viability of resveratrol when encapsulated in transferrin-modified liposomes, comparatively with non-modified nanosystems. The authors showed that encapsulated resveratrol displays a hormetic profile by increasing cellular ROS levels in a dose-dependent manner. At the higher concentrations of 200 and 400 μM resveratrol act as pro-oxidant enhancing selectively ROS levels in cancer cells compared to the normal cells.

Resveratrol-liposome showed a higher and apoptosis-inducing ability in the cancer cells by activation of caspase 3/7 as well as cell-cycle arrest forcing the cells from a quiescent state in G0/G1 phase into the S-phase resulting in their death at low concentrations (<100 μM). The prepared resveratrol-liposomes improved tumor growth inhibition and survival in glioblastoma tumor heterotopic xenograft-bearing mice, proving that the nanosystems are efficacy and safe drugs for glioblastoma therapy [217].

In normal cells, according to hormesis concept, low dose of polyphenols are protective by upregulating Nrf2 pathway and antioxidant vitagenes such as GSH, HO-1, Sirt1, Hsp70, Trx and γ-GCs and by downregulating proliferative pathways such as Pi3K, ERK, P38, Akt, PKC, JNK and Wnt for cancer chemoprevention.

5. Resilience and brain tumors

Resilience is an emerging concept consisting in a dynamic process to adapt to adverse life challenges and respond to homeostatic perturbations through the interaction of various risk and protective factors [218–220]. In the context of brain cancer, recent evidence focused their interest on the importance of resilience and coping strategies in patients, which are relevant to brain tumor treatment. Notably, the neurological deficits that often accompany brain tumors and their treatments result in psychological distress and social dysfunction that impact on adolescent survivors of brain tumors at various developmental stages [221]. It has been reported that adolescent survivors of brain tumors with emotional problems are at high risk of poor development of resilience. Therefore, is of crucial relevance to integrate healthcare approaches for survivorship when a brain tumor is newly diagnosed and expand as the child or adolescent progresses to each developmental stage. Nurses and teachers should design interdisciplinary school-based interventions to reduce the impact of emotional problems and enhance resilience in adolescent survivors of brain tumors [222]. Moreover, it has been explored the potential correlation between resilience and coping strategy in patients with brain tumors. In this regard, several studies documented that resilience enhances problem-focused coping strategy and total coping strategy of patients suffering from brain tumors [223]. In addition, other studies provided novel therapeutic insights to improve cellular resilience targeting glioblastoma stem cells to adapt to heterogeneity of tumor microenvironment [224]. Interestingly, mouse modeling studies have demonstrated that specific mutational events such as NF1 loss or PDGFB overexpression shift the tumor ecosystem towards macrophage infiltration or vascular dysfunction, respectively [225]. Consistent with human studies demonstrating NF1 loss following temozolomide treatment in recurrent tumors [226], NF1 silencing correlated with temozolomide resistance [225]. A cross-selection study on data from 56 caregivers of patients with brain metastases have revealed coping strategies to increase resilience to cognitive impairment and provide personalized and precision medicine in cancer [227]. Another cross-selection study of 250 patients with brain tumors highlighted the function of familial/household role and working status in mediating resilience, and demonstrates the well-known protective effect of resilience for mental health in brain tumor patients in Pakistan [228]. These promising findings are of clinical importance with regards to the development of culture-specific evidence-based resilience-building interventions that may help patients with brain tumors to cope with the psychological distress of cancer. A randomized trial enrolled 100 patients undergoing surgical treatment for pituitary adenoma evaluated the cognitive bias modification for attention and interpretation. It has been observed that cognitive bias modification effectively improves psychological resilience and reduces symptoms of anxiety and depression, thus ameliorating quality of life (QoL) following surgery [229]. Dietary polyphenols modulate carcinogenic processes through the alteration of different molecular targets, such as Wnt/β-catenin, PI3K/Akt/mTOR, MAPK (p38, JNK and Erk1/2), NF-κB and Nrf2 to induce resilience and cancer chemoprevention [230]. Increasing evidence highlighted the crucial role of polyphenols in increasing resilience of Nrf2 and antioxidant target genes in several chronic inflammatory diseases including cancer [231–233]. Chronic stress and ROS are considered the primary determinants of resilience induction (health) or human pathologies which depend from their hormetic cellular concentration. Indeed, in normal conditions, high levels of ROS are known to function as harmful products and an important cause of mitochondrial dysfunction [234]. On the other hand, low levels of polyphenols have been discovered to be beneficial to health by modulating Nrf2 transcription factor activation and increasing cellular stress response and related target genes to block and neutralize oxidative stress and ROS [235,236]. Importantly, it has been reported a functional crosstalk between resilience Nrf2/HO-1/wnt/β-catenin axis in promoting protection in chronic inflammatory pathologies such as neurodegeneration and cancer [237]. Conversely, the aberrant activation of Nrf2 and Wnt/β-catenin signaling cascades is a genetic predisposition to carcinogenesis [238]. However, recent evidence demonstrated a variety of ROS-based and quinone-based pharmacological approaches to generate new diagnostic and prognostic drugs targeting overexpression of Nrf2 and genes to provide a strong rationale for effective therapeutic strategies to overcome drug chemoresistance [239]. Taken together, low stress resilience may contribute to increased mortality among cancer patients by upregulation of several inflammatory pathways and downregulation of antioxidant cellular pathways. Polyphenols at high concentrations enhance cellular resilience and induce oxidative stress and ROS to block proliferative cascade in cancer cells.

6. Mini-brain tumor organoid technology

The introduction of novel in vitro three-dimensional culture platforms paved the way to innovative possibilities for cancer research and offers valuable tools for studying brain cancer. Spheroids, organoids and organ-on-a-chip technologies are 3D microscopic organotypic structures with different level of complexity, grown from stem cells or organ progenitors, and consist of different cell types that self-organize to establish appropriate cell-cell contacts and microenvironment, thus recapitulating the histoarchitecture and cellular composition, as well as the physiological aspects of the tissue of origin [240–243]. Organoids can be genetically modified to study tumor initiation: recent technological advances in human organoid technology and CRISPR genome engineering generated a genetically defined model of human glioblastoma by introducing oncogenic mutations in cerebral organoids of glioblastoma-like and central nervous system primitive neuroectodermal tumor via transposon- and CRISPR/Cas9-mediated mutagenesis [244,245]. These brain cancer organoids provided a valuable complement to current basic and preclinical models to achieve better knowledge concerning brain tumor biology as well as to test potential drugs in a personalized setting [245].

These organotypic models better mimic the in vivo scenario of brain tumor growth and invasion compared to previous models [246,247,250,255]. For instance, in cancer organoid, tumors are surrounded by other cells recapitulating their interactions, which is not the case of models based on tumors stem cells. Organoids derived from patient biopsies provide the tumor microenvironment (TME), which is crucial for studying glioblastoma cells mechanisms to infiltrate healthy brain tissue [246,248]. Novel 3D-bioprinted mini-brains consisting of glioblastoma cells and macrophages were employed to study the interactions between these two cell types and to test treatments targeting this interaction. It was demonstrated that in organoids, glioblastoma cells actively recruit macrophages and polarize them into a GAM-specific phenotype, showing clinical relevance to transcriptomic and patient survival data. Furthermore, it has been shown that macrophages induce glioblastoma cell progression and invasiveness in the mini-brains. Carmustine, a chemotherapeutic drug, and two immunomodulatory drugs, AS1517499, - Stat6 inhibitor-, and BLZ945, - colony stimulating factor 1 receptor (Csf-1r) inhibitor- can inhibit the interaction between

glioblastoma-associated macrophages and tumor cells resulting in reduced tumor growth and more sensitivity to chemotherapy [249].

Considering the individual genetic heterogeneity and the heterogeneous response to anti-cancer treatment, organoids derived from patients stem cells represent a valuable tool for drug screening and precision medicine. Brain cancer organoid allow to test several treatments and predict drug response in short time and allow to identify the one with the best chance of fighting brain cancer in a specific individual [248]. Intriguingly, glioblastoma patients derived-brain organoids are utilized to generate biobank for basic and translational research and for testing personalized therapies [80,247]. Several in vitro and in vivo evidence shed light on the chemopreventive and therapeutic applications through brain cancer organoids. The chimeric antigen receptor (CAR)-T cells represent a potent new approach to treat GBM [251]. Recent studies investigating patient-specific responses to immunotherapies by co-culturing GBOs with chimeric antigen receptor (CAR) T cells. These cells genetically engineered to express surface proteins that recognize specific antigens on tumor cells, is a useful technique to access CAR T cell antigen specificity and tumor-killing efficacy [252]. Cerebral organoids and patient-derived glioma stem cells represent a powerful tool for investigating glioblastoma multiforme biology in a primitive human brain environment and for modeling diverse therapeutic interventions in ex-vivo models [253]. The combination of human induced pluripotent stem cell (iPSC), glioblastoma brain spheres 3D culture by a novel high throughput histology (microTMA) platform provides an interesting support for testing anti-cancer drugs (i.e., temozolomide and doxorubicin) and personalized medicine, as well as offering an alternative to animal in vivo studies. Notably, temozolomide (100 μM) and doxorubicin (0.3 μM) treatments caused ~30% and ~80% decreases in the size of the tumors, respectively without alteration on normal neuronal cells [254]. Goranci-Buzhala and coworkers demonstrated that inhibitor of ADAM10 prevent glioma stem cells integration into brain organoids, as similarly shown in mouse orthotopic xenograft assays [255]. Krieger et al. (2020) confirmed the biological relevance of organoid-based model systems and the interactions between GBM and organoid cells. This study also provides the basis for high-content drug screens to assess patient-specific drug action on tumor and healthy brain cells, thus helping to identify the most effective drug at clinically relevant time scales [250]. Moreover, recent data observed the effects of tazemetostat treatment in vitro in medulloblastoma organoids and in vivo in postnatal transfection of mouse cerebella to provide a more personalized drug therapy in medulloblastoma patients with high OTX2/c-MYC levels and low levels of SMARCA4 or *SMARCA4* mutations [256]. Choe et al. (2021), developed a 3D in vitro metastatic brain cancer organoids (MBCCO) elucidating on cell proliferation, specific gene functions, cell-microenvironment interactions occurring during metastasis and drug screening by measuring the effects of anticancer agents such as gefitinib. The authors demonstrated the astrocyte accumulation around and their interaction with cancer cells through connexin 43 in the MBCCO model [257].

Taken together the data shed more light on novel mini-brain cancer organoids. These models offer a promising preclinical model to assess drug efficacy and allow deeper mechanistic insights on cancer biology and generate biobanks of patient-derived tumor organoids for drug development research, as well as personalized and regenerative medicine for brain cancer therapy.

7. Conclusions

In conclusion, in the present review we have provided evidence on the chemoprotective and therapeutic effects of hormetic polyphenols, which, at low concentration, inhibit oxidative stress, inflammation and induce apoptosis of brain cancer cells by activation of Nrf2 pathway and *vitagenes*. Interestingly, recent reports have documented a "dark side" role of Nrf2 in cancer. Notably, the constitutive upregulation of Nrf2/vitagene pathway by mutations can promote cancer cell growth, resulting in drug resistance. Therefore, novel potential chemopreventive strategies, using Nrf2 inhibitors to increase efficacy of chemotherapeutic agents, could be a promising tool for anticancer therapy in patients with advanced brain cancer. In addition, we have discussed emerging nanomedicine approaches with polyphenol incapsulated in synthetic constructs alone or in combination to chemotherapeutic drugs, which enhance brain delivery efficiency, reduce the dose and inhibit cell proliferation by inducing ROS cytotoxicity in cancer cells. This occurs in a dose response manner, as demonstrated, both, *in vitro* and *in vivo*. Recently, the mini-brain organoid technology represent an excellent preclinical platform for cancer research with the aim of developing novel personalized therapies and asses drug efficacy that allows deeper mechanistic insights on brain cancer biology and therapy. Further studies are, however, required to determine the precise role of mini-brain cancer organoids in clinical setting and development of new therapeutic interventions by combining nutritional low dose polyphenols with chemotherapy tested as supplementation in cancer patients to reduce inflammation and chemoresistance. Thus, targeting of antioxidant Nrf2/vitagene axis to increase apoptotic cancer cell death represent a promising diagnostic and prognostic approach to enhance brain anticancer therapy in humans.

Declaration of competing interest

The authors declare no conflicts of interest.

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