

Review

Natural Compounds in Glioblastoma Therapy: Preclinical Insights, Mechanistic Pathways, and Outlook

Kevin Zhai ¹, Manaal Siddiqui ¹, Basma Abdellatif ¹, Alena Liskova ², Peter Kubatka ³
and Dietrich Büsselberg ^{1,*}

¹ Department of Physiology and Biophysics, Weill Cornell Medicine-Qatar, Education City, Qatar Foundation, Doha P.O. Box 24144, Qatar; kez4003@qatar-med.cornell.edu (K.Z.); mas4002@qatar-med.cornell.edu (M.S.); bwa4001@qatar-med.cornell.edu (B.A.)

² Department of Obstetrics and Gynecology, Jessenius Faculty of Medicine, Comenius University in Bratislava, 036 01 Martin, Slovakia; alenka.liskova@gmail.com

³ Department of Medical Biology, Jessenius Faculty of Medicine, Comenius University in Bratislava, 036 01 Martin, Slovakia; peter.kubatka@uniba.sk

* Correspondence: dib2015@qatar-med.cornell.edu; Tel.: +974-4492-8334

Simple Summary: Glioblastoma (GBM) is a tumor of the brain or spinal cord with poor clinical prognosis. Current interventions, such as chemotherapy and surgical tumor resection, are constrained by tumor invasion and cancer drug resistance. Dietary natural substances are therefore evaluated for their potential as agents in GBM treatment. Various substances found in fruits, vegetables, and other natural products restrict tumor growth and induce GBM cell death. These preclinical effects are promising but remain constrained by natural substances' varying pharmacological properties. While many of the reviewed substances are available as over-the-counter supplements, their anti-GBM efficacy should be corroborated by clinical trials moving forward.

Abstract: Glioblastoma (GBM) is an aggressive, often fatal astrocyte-derived tumor of the central nervous system. Conventional medical and surgical interventions have greatly improved survival rates; however, tumor heterogeneity, invasiveness, and chemotherapeutic resistance continue to pose clinical challenges. As such, dietary natural substances—an integral component of the lifestyle medicine approach to chronic diseases—are examined as potential chemotherapeutic agents. These heterogenous substances exert anti-GBM effects by upregulating apoptosis and autophagy, inducing cell cycle arrest, interfering with tumor metabolism, and inhibiting proliferation, neuroinflammation, chemoresistance, angiogenesis, and metastasis. Although these beneficial effects are promising, natural substances' efficacy in GBM is constrained by their bioavailability and blood–brain barrier permeability; various chemical formulations are proposed to improve their pharmacological properties. Many of the reviewed substances are available as over-the-counter dietary supplements, underscoring their viability as lifestyle interventions. However, clinical trials remain necessary to substantiate the *in vitro* and *in vivo* properties of natural substances.

Keywords: glioblastoma; brain cancer; natural compounds; flavonoids; polyphenols; carotenoids; lignans; coumarins; steroids; tannins; terpenes; lifestyle medicine



Citation: Zhai, K.; Siddiqui, M.; Abdellatif, B.; Liskova, A.; Kubatka, P.; Büsselberg, D. Natural Compounds in Glioblastoma Therapy: Preclinical Insights, Mechanistic Pathways, and Outlook. *Cancers* **2021**, *13*, 2317. <https://doi.org/10.3390/cancers13102317>

Academic Editors: Raffaele Capasso, Barbara Romano and Carmela Fimognari

Received: 24 February 2021

Accepted: 7 May 2021

Published: 12 May 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Glioblastoma: Occurrence, Mechanisms, Treatments, and Challenges

Glioblastoma (GBM) is a malignant tumor of the central nervous system (brain or spinal cord) that arises from astrocytes. It is the most common type of primary brain tumor, with occurrence rates of 3.19 cases per 100,000 patients in the United States, and 2.05 per 100,000 in the United Kingdom [1]. While the prognosis of GBM is often poor, two-year survival rates have improved in recent years, rising from 7% for cases diagnosed from 1993–1995 to 17% for cases diagnosed from 2005–2007 in the USA. Survival rates are

also age-related: 39% of patients diagnosed between ages 20 and 44 survive, compared to only 1% of those diagnosed past age 80 [2].

While the efficacy of GBM treatment has improved, numerous challenges remain—especially concerning conventional therapeutic modalities. For instance, surgical tumor resection improves survival rates but is hindered by the extensive invasion and ill-defined tumor boundaries of GBM [3,4]. The efficacy of chemotherapeutic drugs may be reduced by the development of (multi-)drug resistance [5]. Moreover, extracranial metastasis—though rare—can greatly complicate treatment [6].

The challenges posed by GBM stem mainly from the genetic and molecular signaling pathways through which this type of tumor occurs. Genetic alterations in GBM include the amplification of the epidermal growth factor receptor (EGFR) and cyclin-dependent kinase (e.g., CDK4) genes, the deletion of the genes for cyclin-dependent kinase inhibitors (e.g., CDK2NA), and the silencing of the O-6-methylguanine-DNA methyltransferase (MGMT) gene [7]. These and other genetic changes upregulate cellular mechanisms that favor proliferation (e.g., through Akt/mTOR signaling), cell cycle progression, excessive and self-perpetuating inflammation, tumor metastasis, angiogenesis, metabolic changes (known as the Warburg effect), and chemoresistance. Simultaneously, the effectors of apoptosis and autophagy are largely downregulated or inhibited (Figure 1). As such, conventional oncologic therapies mostly aim to reverse this imbalance between growth and death by inhibiting proliferation and upregulating apoptosis.

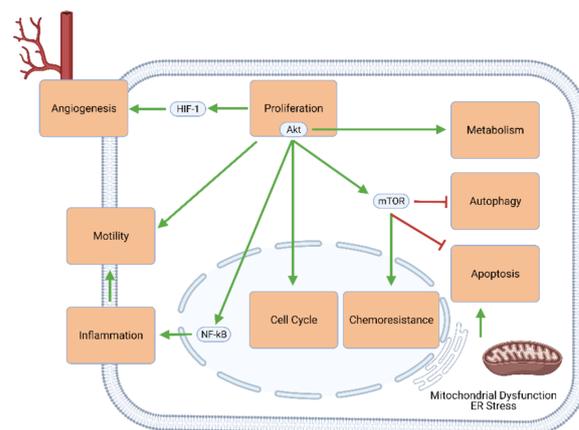


Figure 1. Intracellular signaling mechanisms involved in GBM development and progression. Elements of proliferative signaling pathways—especially Akt and mTOR—promote angiogenesis, motility and migratory potential, neuroinflammation, cell cycle progression, chemoresistance, and tumor metabolism, and concurrently inhibit GBM cell death through apoptosis and autophagy.

The molecular complexity and difficulties posed by chronic diseases such as brain cancers have encouraged some clinicians to take a holistic approach to their treatment. Lifestyle medicine focuses on lifestyle factors (e.g., diet, physical activity, and the environment) and overall health maintenance to minimize risk factors associated with chronic diseases [8]. Dietary natural substances are an essential component of lifestyle medicine and can suppress cancer or overcome challenges associated with conventional therapies. Intake of these compounds may occur through the daily diet or over-the-counter supplements. While in vitro studies are promising, they are yet to be tangibly replicated in clinical trials.

2. Natural Compounds Modulating Glioblastoma

Numerous natural substances—with established biological benefits—exert oncologic effects on GBM in vitro and/or in vivo. These include alkaloids, carboxylic acid derivatives, carotenoids, flavonoids, coumarins, curcuminoids, terpenes, lignans, natural steroids, tannins, and plant extracts (Figures 2 and 3; Table 1).

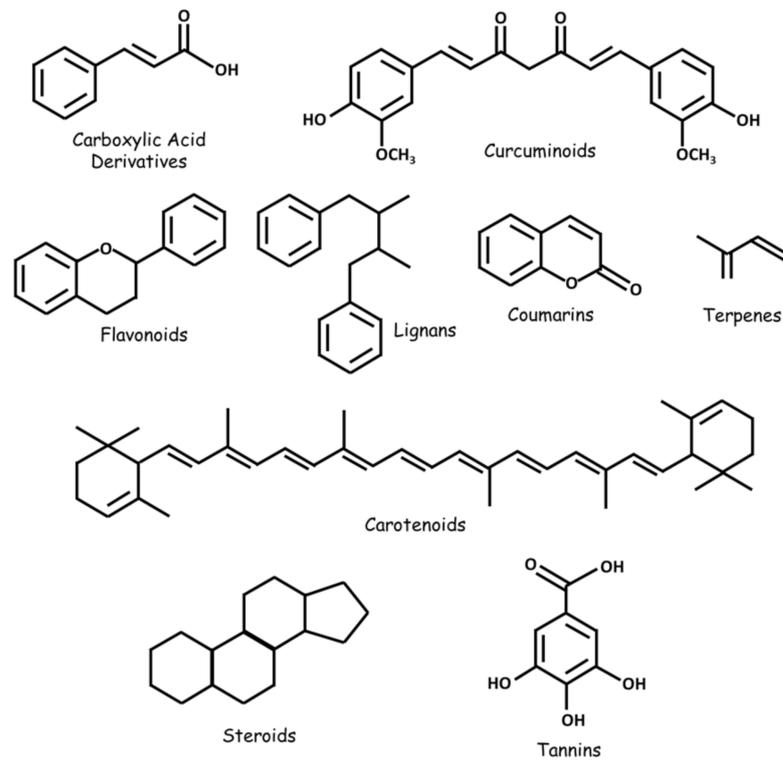


Figure 2. Some classes of natural substances with therapeutic potential in GBM.

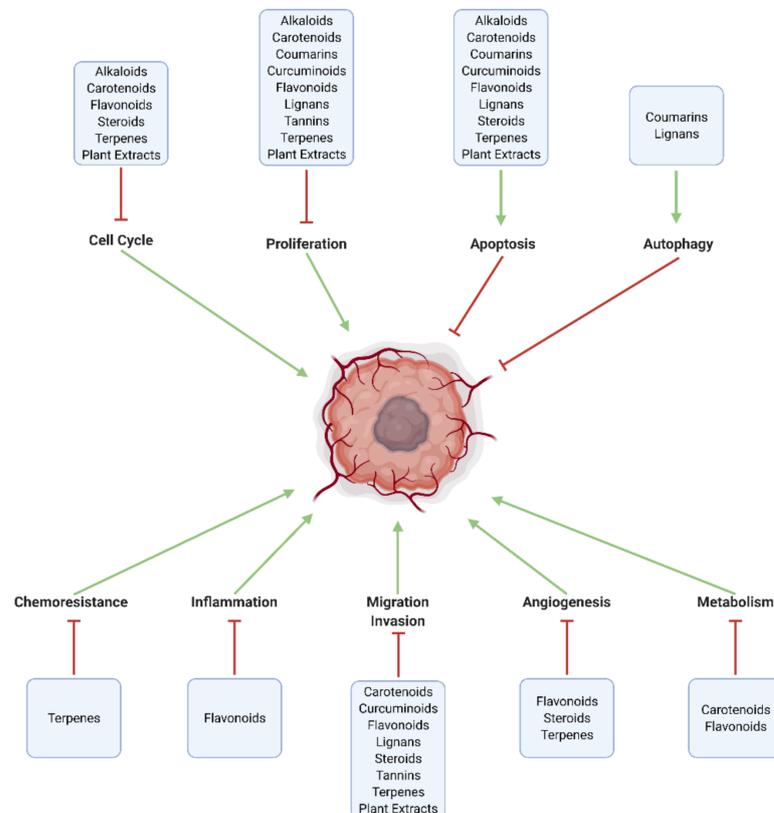


Figure 3. Major pathways modulated by natural substances in GBM. Effective chemotherapeutic substances increase cell death through apoptosis and autophagy, and inhibit intracellular mechanisms related to proliferation, cell cycle progression, tumor metabolism (Warburg effect), angiogenesis, invasion and metastasis, neuroinflammation, and chemoresistance.

Table 1. Classes and sources of natural substances with anti-GBM efficacy demonstrated in recent preclinical studies. Many of the listed compounds occur in multiple natural sources.

Substance	Class/Type	Primary Source(s)
Alkaloids		
Berberine	Quaternary Ammonium Salt	Barberry (<i>Berberis</i>)
Carboxylic Acid Derivatives		
Cinnamic Acid	Monocarboxylic Acid	Cinnamon (<i>Cinnamomum</i>)
Ferulic Acid	Hydroxycinnamic Acid	Giant fennel (<i>Ferula communis</i>)
Carotenoids		
Adonixanthin	Carotenone	Derivative of astaxanthin
Astaxanthin	Xanthophyll	Chlorophyte (<i>Haematococcus pluvialis</i>)
Crocin	Apocarotenoid	Saffron (<i>Crocus sativus</i>)
Coumarins		
Galbanic Acid	Sesquiterpene Coumarin	Celery/carrot/parsley family (<i>Umbelliferae</i>)
Osthole	Coumarin	Monnier's snowparsley (<i>Cnidium monnieri</i>)
Curcuminoids		
Curcumin	Curcumin	Turmeric (<i>Curcuma longa</i>)
Flavonoids		
Chrysin	Dihydroxyflavone	Blue passion flower (<i>Passiflora caerulea</i>)
Diosmin	Flavone Glycoside	Germander (<i>Teucrium gnaphalodes</i>)
EGCG	Catechin	Green tea (<i>Camellia sinensis</i>)
Galangin	Trihydroxyflavone	Galangal (<i>Alpinia officinarum</i>)
Matteucinol	Dihydroxyflavone	Naudin (<i>Miconia chamissois</i>)
Naringin	Flavanone Glycoside	Grapefruit (<i>Citrus × paradisi</i>)
Quercetin	Flavonol	Oak (<i>Quercetus</i>)
Resveratrol	Stilbenoid	Grape (<i>Vitis</i>)
Rutin	Flavonol Glycoside	Rue (<i>Ruta graveolens</i>)
Silymarin (Silibinin)	Flavonolignan	Milk thistle (<i>Silybum marianum</i>)
Tectorigenin	Methylated Isoflavone	Leopard lily (<i>Iris domestica</i>)
Xanthohumol	Prenylated Chalconoid	Hops (<i>Humulus lupulus</i>)
Lignans		
Arctigenin	Lignan/Polyphenol	Greater burdock (<i>Arctium lappa</i>)
Magnolol	Biphenyl	Houpu magnolia (<i>Magnolia officinalis</i>)
Steroids		
Diosgenin	Phytosteroid Sapogenin	Fenugreek (<i>Trigonella foenum-graecum</i>)
Gamabufotalin	Steroid Lactone	Toad (<i>Bufo</i>)
N45	Steroid Saponin	Nan chong lou (<i>Paris vietnamensis</i>)
Withaferin A	Steroid Lactone	Ashwa-gandha (<i>Withania somnifera</i>)
Tannins		
Tannic Acid	Hydrolysable Tannin	Oak (<i>Quercetus</i>)

Table 1. Cont.

Substance	Class/Type	Primary Source(s)
Terpenes		
AM01-06	Sesquiterpene Lactone	Sunflower (<i>Eremanthus</i> spp.)
Betulinic Acid	Triterpenoid	White birch (<i>Betula pubescens</i>)
Cedrol	Sesquiterpene Alcohol	Cypress (<i>Cupressus</i>); Juniper (<i>Juniperus</i>)
Coronarlin D	Diterpene	White ginger lily (<i>Hedychium coronarium</i>)
Eucalyptal A	Monoterpenoid	Southern blue gum (<i>Eucalyptus globulus</i>)
Gossypol	Terpenoid Aldehyde	Cotton (<i>Gossypium</i>)
Paeoniflorin	Terpene Glycoside	Chinese peony (<i>Paeonia lactiflora</i>)
Paris saponin H	Triterpenoid Saponin	Chong Lou (<i>Rhizoma paridis</i>)
Pisosterol	Triterpene	Dead man's foot (<i>Pisolithus tinctorius</i>)
Rupesin E	Iridoid (Monoterpenoid)	Indian valerian (<i>Valeriana jatamansi</i>)
Tubeimoside-1	Triterpenoid Saponin	Tu bei mu (<i>Rhizoma bolbostemmae</i>)
Crude/Purified Plant Extracts		
BcH, BcS	Extract-Food Supplement	Water hyssop (<i>Bacopa monnieri</i>)
CE70, CE95	Ethanol Extract	Shaggy ink cap (<i>Coprinus comatus</i>)
CP	Chloroform Partition	Johnnyberry (<i>Miconia chamissois</i>)
CW	Aqueous Extract	Shaggy ink cap (<i>Coprinus comatus</i>)
KE70, KE95	Ethanol Extract	Golden chanterelle (<i>Cantherellus cibarius</i>)
KW	Aqueous Extract	Golden chanterelle (<i>Cantherellus cibarius</i>)
PE70, PE95	Ethanol Extract	Puffball (<i>Lycoperdon perlatum</i>)
PPE	Ethanol Extract	Polish propolis (bee glue)
PW	Aqueous Extract	Puffball (<i>Lycoperdon perlatum</i>)
RE70, RE95	Ethanol Extract	Saffron milk cap (<i>Lactarius deliciosus</i>)
RW	Aqueous Extract	Saffron milk cap (<i>Lactarius deliciosus</i>)
Other		
Carnosine	Dipeptide	Liebig's meat extract
CrataBL	Protein: Lectin + Serine Protease Inhibitor	Beach block (<i>Crataeva tapia</i>)
GL-PP	Polysaccharide Peptide	Lingzhi (<i>Ganoderma lucidum</i>)

2.1. Alkaloids

Alkaloids are structurally diverse, often basic natural compounds that contain at least one nitrogen atom. They also commonly contain oxygen atoms in organic rings. These compounds induce DNA damage, cell cycle arrest, ER stress, apoptosis, and autophagy, and concurrently inhibit angiogenesis and proliferation in tumor cells [9,10]. Moreover, alkaloids can overcome cancer drug resistance, as they inhibit cellular drug resistance pumps [10]. An alkaloid of interest in GBM therapy is berberine (BBR), a quaternary ammonium salt from barberry.

2.2. Carboxylic Acid Derivatives

Carboxylic acid derivatives are organic compounds with one or more carboxylic acid (COOH) functional groups. These organic acids have oncologic potential by modulating intracellular second messengers and suppressing DNA synthesis, transcriptional activity, and proliferation in tumor cells [11]. In recent years, cinnamic acid, a monocarboxylic acid

from cinnamon, and ferulic acid, a cinnamic acid derivative from the giant fennel, have demonstrated anti-GBM efficacy *in vitro*.

2.3. Carotenoids

Carotenoids are red, orange, and yellow natural (often phytochemical) pigments. Two major classes exist within this family: (1) carotenes, which contain exclusively hydrogen and carbon atoms, and (2) xanthophylls, which contain oxygen atoms in addition to the hydrocarbon structure. Chemically, carotenoids are cyclic or acyclic tetraterpenoids with 40 carbon atoms—some of which are in conjugated double bond systems [12]. These pigments exert oncologic effects by upregulating the extrinsic and intrinsic apoptotic pathways in tumor cells [13]. They also disrupt tumor cell migration and invasion and thereby hinder metastasis [14]. Carotenoids discussed in this review include astaxanthin, a xanthophyll derived from chlorophyte; adonixanthin, a carotenone and derivative of astaxanthin; and crocetin, an apocarotenoid from saffron.

2.4. Flavonoids

Flavonoids are polyphenolic secondary metabolites of plants and occur in seven classes: anthocyanidins, flavones, flavanones, flavonols, flavan-3-ols, isoflavones, and chalcones. The flavonoid structural backbone is polyphenolic, with fifteen carbon atoms arranged in a three-ring structure. These compounds have well-characterized antitumor effects through the upregulation of apoptosis and disruption of migration, invasion, and metastasis [15,16]. Moreover, flavonoids modulate tumor cell glucose metabolism and downregulate the Warburg effect [17–19]. Flavonoids with anti-GBM potential include diosmin, a flavone glycoside from germander; epigallocatechin-3-gallate (EGCG), a catechin found mainly in green tea; mattheucinol, a dihydroxyflavone from *naudin*; naringin, a flavonone glycoside found in grapefruit and other citrus fruits; quercetin, a flavonol found in oak, onions, and kale; resveratrol, a stilbenoid found in grapes and red wine; rutin, a flavonol glycoside found in rue and citrus fruits; silymarin, an extract from milk thistle of which silibinin (a flavonolignan) is the major constituent; tectorigenin, a methylated isoflavone found in the leopard lily; chrysin, a dihydroxyflavone found in honey and propolis; galangin, a trihydroxyflavone that occurs in galangal; and xanthohumol, a chalcone (prenylated chalconoid) found in hops.

2.5. Coumarins

Coumarins are phenylpropanoid phytochemicals with one benzene ring and one heterocycle. These plant-derived compounds upregulate proapoptotic pathways, induce terminal differentiation, and reduce multi-drug resistance in cancerous cells [20]. Osthole, a coumarin found in Monnier's snowparsley, and galbanic acid, a sesquiterpene coumarin abundant in *Ferula* species (*Apiaceae*), are coumarins of interest in GBM treatment.

2.6. Curcuminoids

Curcumin and its derivatives are (poly)phenolic plant secondary metabolites that comprise the curcuminoid family. Chemically, curcuminoids are diarylheptanoids, which have a seven carbon chain connecting two substituted aromatic rings. These polyphenols decrease proliferation and induce apoptosis, cell cycle arrest, and mitochondrial dysfunction in cancers of the nervous system [21]. They also notably modulate tumor angiogenesis and inflammation [22]. Curcumin, derived from the south Asian turmeric plant, exhibits inhibitory effects on GBM.

2.7. Terpenes

Unsaturated plant-derived hydrocarbons with the general chemical formula $(C_5H_8)_n$ comprise the terpene family. These compounds are classified by the number of carbon atoms they contain; classes include monoterpenes (with 10 carbon atoms), sesquiterpenes (with 15), and diterpenes (with 20). Natural terpenes exert anticancer properties by in-

ducing apoptosis and cell cycle arrest and suppressing tumor angiogenesis and metastasis [23,24]. Terpenes discussed in this review include AM01-06, sesquiterpene lactones from sunflower; betulinic acid, a triterpenoid from the white birch tree; cedrol, a sesquiterpene alcohol from the cypress and juniper trees; coronarin D, a diterpene from white ginger lily; eucalyptal A, a monoterpenoid from the southern blue gum tree; gossypol, a terpenoid aldehyde from cotton; paeoniflorin, a terpene glycoside from the Chinese peony; pisosterol, a triterpene from a fungus known as dead man's foot; rupesin E, a monoterpenoid from Indian valerian; *Paris* saponin H, a triterpenoid saponin found in the Chong Lou plant; and tubeimoside-1, a triterpenoid saponin from the Chinese plant tu bei mu.

2.8. Lignans

Lignans are polyphenolic plant secondary metabolites that contain two benzene rings linked by carbon–carbon bonds. These natural polyphenols inhibit topoisomerases in tumor cells and thus interfere with DNA synthesis and proliferation [25]. Clinically, lignans decrease the risk of breast cancer [26]. Arctigenin, a lignan found in greater burdock, and magnolol, a biphenyl from the Houpu magnolia, have therapeutic potential in GBM.

2.9. Natural Steroids

Natural compounds containing the four-ring steroid nucleus—with 17 carbon atoms forming 3 cyclohexane (A, B, C) and 1 cyclopentane (D) rings—are classified as steroids. These biomolecules exert cytotoxic effects by inducing apoptosis and cell cycle arrest in tumor cells. Natural steroids can also target hormones, and as such may have anti-estrogen and anti-progestin properties [27]. Steroids of interest include withaferin A, a steroidal lactone from the Ashwa-gandha plant; N45, a steroidal saponin isolated from the Chinese medicinal plant nan chong lou; gamabufotalin, a steroidal lactone in the traditional Chinese medicine “ChanSu,” or toad skin extract; and diosgenin, a phytosteroid saponin found in Mediterranean fenugreek.

2.10. Tannins

Tannins are large, heavily hydroxylated polyphenols that can bind to (bio)macromolecules. They are classified by their base units: hydrolysable tannins (with gallic acid as the base unit), phlorotannins (phloroglucinol), and condensed tannins (flavan-3-ol). Tannins induce apoptosis and autophagy, inhibit proliferation, metastasis, and angiogenesis, and act synergistically with chemotherapeutics in cancerous cells [28]. Tannic acid, a hydrolysable tannin from oak, will be discussed in this review.

2.11. Crude and Purified Plant Extracts

Crude and purified plant extracts contain numerous chemical compounds with potential biological activities. Members of this highly heterogeneous family with anti-GBM potential include BcH and BcS, water hyssop extracts sold as dietary supplements; aqueous and ethanol extracts from the shaggy ink cap (CW, CE70, and CE95), golden chanterelle (KW, KE70, and KE95), puffball (PW, PE70, and PE95), and saffron milk cap (RW, RE70, and RE95) mushrooms; CP, a chloroform partition from the johnnyberry plant; and PPE, an ethanol extract from Polish propolis.

3. Mechanistic Effects of Natural Compounds on Glioblastoma

3.1. Generalized Anti-Cancer Markers

Several generalizable effects can demonstrate the anti-GBM potential of natural compounds and highlight promising substances for further mechanistic studies (Table 2). Nearly all the substances discussed in this review decrease GBM cell viability in vitro. Cell viability assays are useful in (1) differentiating cytotoxic from biologically inert compounds and (2) identifying effective treatment concentrations to be used in further experiments. For example, decreased intracellular ATP is a marker of cell death; this effect was observed in GBM cells after treatment with curcumin, BBR, gossypol, and carnosine [29–31]. Several

other substances, including xanthohumol and rupesin E, decreased cloning and colony formation—further indicators of cancer cell viability and malignancy—in GBM cultures.

Table 2. Generalized downstream effects of natural compounds on GBM. Many of the reviewed substances exert measurable cytotoxic effects in vitro. Moreover, several substances reduce tumor size and improve survival in-animal models of GBM.

Effect	Substance	Cell Line	Source
Increases survival	Eucalyptal A	U87MG orthotopic implants, nude mice	[32]
	Cedrol	DBTRG-05MG subcutaneous xenografts, nude mice	[33]
	Crocetin	Luc-U251MG orthotopic implants, CD1 mice	[34]
Decreases tumor area/perimeter	Astaxanthin	GL261 orthotopic implants, C57BL/6J mice	[35]
	Adonixanthin	GL261 orthotopic implants, C57BL/6J mice	[35]
	McC1	U251 heterotopic xenograft, fertilized chicken eggs	[36]
Decreases tumor volume	Astaxanthin	GL261 orthotopic implants, C57BL/6J mice	[35]
	Adonixanthin	GL261 orthotopic implants, C57BL/6J mice	[35]
	Naringin	U87 subcutaneous xenograft, athymic mice	[37]
	Xanthohumol	U87, LN229	[38]
	Tannic Acid	C6 orthotopic implants, Wistar rats	[39]
	Withaferin A	U87 subcutaneous xenografts, nude mice	[40]
	TBMS1	U87 subcutaneous xenografts, NOD/SCID mice	[41]
Decreases tumor weight	Xanthohumol	U87, LN229	[38]
	TBMS1	U87 subcutaneous xenografts, nude mice	[41]
Increases cell death/ dec. viability	EGCG	U251, MO59J	[42]
	Cinnamic Acid	LN-229	[43]
	Ferulic Acid	LN-229	[43]
	Astaxanthin	GL261, U251MG	[35]
	Adonixanthin	GL261, U251MG	[35]
	Cedrol	DBTRG-05MG, RG2	[33]
	AM02	U87MG, T98G	[44]
	AM04	U87MG, T98G	[44]
	AM05	U87MG, T98G	[44]
	AM06	U87MG, T98G	[44]
	Naringin	U87	[37]
	Xanthohumol	U87, T98G, LN229	[38]
	Rupesin E	GSC-3#, GSC-12#, GSC-18#	[45]
	Diosmin	U87, GBM02, GBM95	[46]
	Coronarlin D	U251	[47]
	CP	GAMG, U251	[36]
	McC1	GAMG, U251	[36]
	SLCP	U87, U251	[29]
	BBR	U87, U251	[29]
	Tannic Acid	C6	[39]
Withaferin A	U87, U251	[40]	

Table 2. Cont.

Effect	Substance	Cell Line	Source
Increases cell death/ dec. viability	Betulinic Acid	U251, LN229	[48]
	TBMS1	U87, LN229	[41]
	Carnosine	U87, T98G	[31]
	CrataBL	U87	[49]
	Tectorigenin	GBM-8401, GBM-8901	[50]
	Resveratrol	U87	[51]
	Quercetin	U87	[51]
	Curcumin	U87	[52]
	Paeoniflorin	U251, T98G	[53]
	Diosgenin	C6, T98G	[54]
	CW	LN-18	[55]
	CE70	U87, LN-18	[55]
	CE95	U87, LN-18	[55]
	KW	U87, LN-18	[55]
	KE70	U87, LN-18	[55]
	KE95	U87, LN-18	[55]
	RW	U87, LN-18	[55]
	RE70	U87, LN-18	[55]
	RE95	U87, LN-18	[55]
	PW	U87, LN-18	[55]
	PE70	U87, LN-18	[55]
	PE95	U87, LN-18	[55]
	Silymarin	U118	[56]
	BcS	U87, T98G, LN-18	[57]
	BcH	U87, T98G, LN-19	[57]
	BBR	U87	[58]
	GL-PP	U251	[59]
Pisosterol	U87, U343, AHOL1, 1231N1	[60]	
Decreases colony formation	Xanthohumol	U87, T98G, LN229	[38]
	Rupesin E	GSC-3#, GSC-18#	[45]
	CP	GAMG, U251	[36]
	McC1	U251, GAMG	[36]
	Tannic Acid	C6	[39]
Decreases cloning	Arctigenin	U87MG, T98G	[61]
	AM01	U87MG, T98G	[44]
	AM02	U87MG, T98G	[44]
	AM03	U87MG, T98G	[44]
	AM04	U87MG, T98G	[44]
	AM05	U87MG, T98G	[44]
	AM06	U87MG, T98G	[44]
TBMS1	U87, LN229	[41]	

Table 2. Cont.

Effect	Substance	Cell Line	Source
Decreases sphere formation	Gossypol	TS13-20, TS13-18	[30]
	SLCP	U87, U251	[29]
Decreases intracellular ATP	BBR	U87, U251	[29]
	Gossypol	Diff13-20	[30]
	Carnosine	U87, T98G	[31]
Upregulates p53 (mRNA)	Pisosterol	U87, U343, AHOL1, 1231N1	[60]
	BBR	U87, U251	[29]
Upregulates p53 (protein)	SLCP	U251	[29]
	Pisosterol	U87, U343, AHOL1, 1231N1	[60]

The effects of some natural substances on GBM cells in culture are replicable in vivo, underscoring their therapeutic potential. Specific terpenes, carotenoids, flavonoids, and steroids inhibit tumor growth (measured through tumor area, perimeter, weight, and volume) in murine and rat xenograft models. Interestingly, the flavonoid mattecucinol also reduces the area of GBM implants in fertilized chicken eggs. These effects may improve survival rates and times in tumor-bearing animals, as is the case for eucalyptal A, cedrol, and crocetin (see Table 2).

3.2. Proliferation, Apoptosis, and Autophagy

Cell fate is regulated by a delicate balance between proliferation and death. In GBM and other tumor cells, growth factors, chemokine ligands, and other upstream signals mediate a shift towards excessive growth and proliferation (Figure 4; Table 3) [62]. Growth factors, including tumor growth factor β (TGF- β), insulin-like growth factor (IGF), hepatoma-derived growth factor (HDGF), and glial cell-derived neurotrophic factor (GDNF), are upregulated in GBM and contribute to downstream Ras/Raf/MEK/ERK and PI3K/Akt signaling. The upregulated chemokine (C-C motif) ligands 2 (CCL2) and 5 (CCL5) further contribute to the PI3K/Akt pathway. However, the flavonoids rutin and quercetin downregulate these proliferative signals in vitro and in vivo [63]. In the absence of natural inhibitory substances, the described growth factors and ligands bind to cell membrane receptors and activate Ras-GTP to begin the proliferative Ras/Raf/MEK/ERK pathway. In the first step, Ras-GTP activates Raf (a third degree MAPK, or MAP3K). Raf consequently activates the MAPK/ERK kinase (MEK; a second degree MAPK, or MAP2K)—an enzyme also activated by the MET proto-oncogene. MEK activates extracellular signal-regulated kinases (ERK) and their associated MAPKs in the third mechanistic step. Finally, ERK MAPKs upregulate hypoxia-inducible factor 1 α (HIF-1 α), whose downstream target is the epidermal growth factor receptor (EGFR). Osthole, a coumarin, may inhibit MEK activation in the second step through the downregulation of Raf [64]. TBMS1 may have a similar inhibitory function, as it downregulates MET [41]. Moreover, TBMS1, astaxanthin, and adonixanthin downregulate ERK/p-ERK to inhibit the final step of HIF-1 α upregulation [35,41].

In addition to the Ras-GTP pathway, proliferation is also critically induced through Akt/mTOR and NF- κ B signaling. Upstream of these targets, serine/arginine-rich splicing factor 1 (SRSF1) activates myosin 1B (MYO1B), which in turn upregulates the phosphoinositide-3-kinase (PI3K). PI3K, along with MET, adenosine monophosphate-activated protein kinase (AMPK), and reactive oxygen species (ROS), upregulates Akt, a central mediator of tumor cell proliferation. This step may be hindered by TBMS1, as it downregulates MET. Superoxide dismutase (SOD) and catalase (CAT) downregulate ROS levels and could therefore also inhibit Akt activation when upregulated by tannic acid and berberine [39,58]. Finally, Akt activity can be reduced through the downregulation of PI3K. Eucalyptal A

downregulates PI3K by inhibiting SRSF1 and MYO1B, while curcumin, osthole, diosgenin, and berberine downregulate PI3K directly [29,32,54,64].

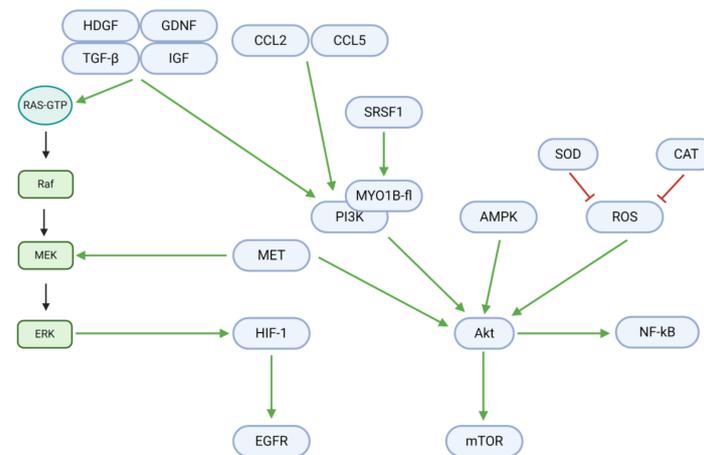


Figure 4. Intracellular mechanisms promoting proliferation in GBM. Growth factors, chemokine ligands, and other upstream signals upregulate the Ras/Raf/MEK/ERK and PI3K/Akt pathways. Downstream effectors, including HIF-1, EGFR, NF-κB, and mTOR, promote DNA synthesis, transcription, and tumor cell proliferation. Proliferative effectors notably engage in crosstalk with other signals in GBM, including those for angiogenesis (HIF-1), cell cycle progression (Akt), metabolism (Akt), motility (PI3K), apoptosis (Akt/mTOR), and autophagy (Akt/mTOR/Beclin-1).

Table 3. Natural substances decrease proliferation in GBM by downregulating upstream growth factors and chemokine ligands, components of the Ras/Raf/MEK/ERK and PI3K/Akt pathways, and downstream effectors.

Effect	Substance	Cell Line	Source
Decreases proliferation/growth	Rutin	C6	[63]
	Quercetin	C6	[63]
	Eucalyptal A	U87MG, LN229	[32]
	Rupetin E	GSC-3#, GSC-18#	[45]
	Crocetin	U87, U138, U251, U373	[34]
	Coronarlin D	U251	[47]
	SLCP	U87, U251	[29]
	BBR	U87, U251	[29]
	Tannic Acid	C6	[39]
	Gossypol	Diff13-20, Diff13-18	[30]
	Betulinic Acid	U251, LN229	[48]
	CrataBL	U87	[49]
	Galbanic Acid	U87	[65]
	N45	U87	[66]
Decreases DNA synthesis	Pisosterol	U87, U343, AHOL1, 1231N1	[60]
	CE95	U87	[55]
	CE70	U87, LN-18	[55]
	KW	U87, LN-18	[55]
	KE95	U87, LN-18	[55]
	KE70	U87, LN-18	[55]

Table 3. Cont.

Effect	Substance	Cell Line	Source
Decreases DNA synthesis	PW	U87	[55]
	PE70	U87	[55]
	RW	U87, LN-18	[55]
	PPE	U87, T98G, LN-18	[57]
	BcH	U87, T98G, LN-18	[57]
Downregulates SRSF1 (mRNA)	Eucalyptal A	U87MG, LN229	[32]
Downregulates SRSF1 (protein)	Eucalyptal A	U87MG, LN229	[32]
Downregulates MYO1B-fl (protein)	Eucalyptal A	U87MG, LN229	[32]
Downregulates p-PDK1 (protein)	Eucalyptal A	U87MG, LN229	[32]
Downregulates TGF (mRNA)	Rutin	U251 orthotopic implants, WR	[63]
	Quercetin	U251 orthotopic implants, WR	[63]
Downregulates TGF- β (mRNA)	Rutin	C6	[63]
	Quercetin	C6	[63]
Downregulates IGF (mRNA)	Rutin	C6, WR-U251 orthotopic implants	[63]
	Quercetin	C6, WR-U251 orthotopic implants	[63]
Downregulates CCL2 (mRNA)	Rutin	U251 orthotopic implants, WR	[63]
	Quercetin	U251 orthotopic implants, WR	[63]
Upregulates CCL5 (mRNA)	Rutin	C6, WR-U251 orthotopic implants	[63]
	Quercetin	C6, WR-U251 orthotopic implants	[63]
Downregulates HDGF (mRNA)	Rutin	C6, WR-U251 orthotopic implants	[63]
	Quercetin	C6, WR-U251 orthotopic implants	[63]
Downregulates GDNF (mRNA)	Rutin	C6, WR-U251 orthotopic implants	[63]
	Quercetin	U251 orthotopic implants, WR	[63]
Downregulates PI3K (protein)	SLCP	U87	[29]
	BBR	U87	[29]
	Diosgenin	C6	[54]
Downregulates (p-)PI3K (protein)	Osthole	MOGGCCM, T98	[64]
	SLCP	U87, U251	[29]
	BBR	U87, U251	[29]
	Metformin	U87	[67]
Downregulates Akt (mRNA)	Arctigenin	U87MG	[61]
Downregulates Akt (protein)	Cedrol	RG2	[33]
	Metformin	U87, U251	[68]
	SLCP	U87	[29]
	BBR	U87	[29]
Downregulates p-Akt (mRNA)	Arctigenin	U87MG, T98G	[61]
Downregulates p-Akt (protein)	Eucalyptal A	U87MG, LN229	[32]
	Astaxanthin	GL261	[35]
	Adonixanthin	GL261	[35]
	Cedrol	DBTRG-05MG, RG2	[33]

Table 3. Cont.

Effect	Substance	Cell Line	Source
Downregulates p-Akt (protein)	Arctigenin	U87MG, T98G	[61]
	Xanthohumol	U87	[38]
	CP	GAMG	[36]
	McC1	GAMG, U251	[36]
	SLCP	U87, U251	[29]
	BBR	U87, U251	[29]
Downregulates mTOR (protein)	Diosgenin	C6	[54]
	Metformin	U87	[67]
	SLCP	U87	[29]
Downregulates p-mTOR (mRNA)	BBR	U87, U251	[29]
	Arctigenin	U87MG, T98G	[61]
	Arctigenin	U87MG, T98G	[61]
Downregulates p-mTOR (protein)	SLCP	U87	[29]
	BBR	U87, U251	[29]
	Diosgenin	T98G	[54]
Downregulates Raf (protein)	Osthole	MOGGCCM, T98	[64]
Downregulates c-Myc	Eucalyptal A	U87MG, LN229	[32]
	Xanthohumol	U87, T98G, LN229	[38]
	SLCP	U87	[29]
	BBR	U87	[29]
Downregulates ROS	Astaxanthin	GL261	[35]
	Adonixanthin	GL261	[35]
	Tannic Acid	C6	[39]
Upregulates CAT activity	Tannic Acid	C6	[39]
	BBR	U87	[58]
Upregulates SOD activity	Tannic Acid	C6	[39]
	BBR	U87	[58]
Downregulates JNK (protein)	Cedrol	DBTRG-05MG, RG2	[33]
Downregulates p-JNK (protein)	Cedrol	RG2	[33]
Downregulates p-MEK (protein)	TBMS1	U87, LN229	[41]
Downregulates p-ERK (protein)	Astaxanthin	GL261	[35]
	Adonixanthin	GL261	[35]
	TBMS1	LN229	[41]
Downregulates p38 (protein)	Diosgenin	T98G	[54]
Upregulates p-p38 MAPK (protein)	Astaxanthin	GL261	[35]
	Adonixanthin	GL261	[35]
Downregulates HIF-1 α activity	Metformin	U251	[68]
Downregulates NF- κ B	Diosgenin	C6, T98G	[54]
Downregulates MET (protein)	TBMS1	U87, LN229	[41]

Downstream, Akt upregulates the mammalian target of rapamycin (mTOR) and nuclear factor kappa of activated B cells (NF- κ B), which induce proliferation. However, arctigenin, curcumin, diosgenin, and berberine downregulate (p-)mTOR, while diosgenin downregulates NF- κ B [29,54,61]. Moreover, galbanic acid exerts antiproliferative, anti-metastatic, and pro-apoptotic effects via PI3K/Akt/mTOR signaling, while N45, a natural steroidal saponin, upregulates apoptosis through ROS/PI3K/Akt signaling in TMZ-resistant GBM cells [65,66].

Many natural substances' anti-cancer properties arise from the activation of cell death through apoptosis and/or autophagy. Endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and downstream caspase activity mediate the apoptotic death of GBM cells (Figure 5, Table 4). Withaferin A and EGCG upregulate activating transcription factor 4 (ATF4), an upstream effector of ER stress [40,42]. ATF4 targets ATF3, which consequently activates the C-homologous protein (CHOP). CHOP, which is also activated by withaferin A, upregulates p21 and the apoptotic proteins Bad and Bim [40].

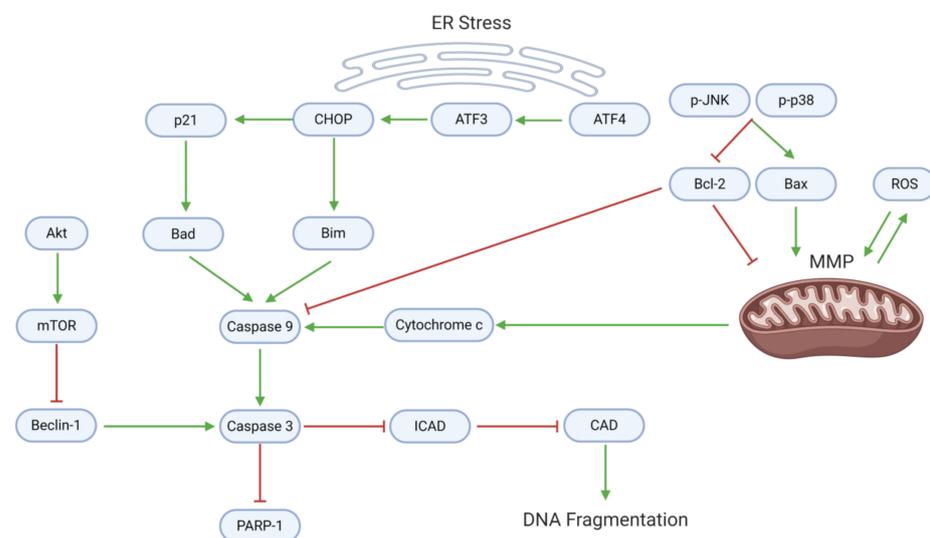


Figure 5. Proapoptotic mechanisms, which involve mitochondrial dysfunction, ER stress, and caspase activation, are suppressed in GBM. Dysregulation of mitochondrial homeostasis (often through oxidative imbalance) leads to the release of cytochrome c, a caspase activator. ER stress upregulates activating transcription factors; in turn, ATFs activate CHOP, p21, and proapoptotic proteins that enhance caspase activation. Active caspase 9 (along with Beclin-1) cleaves caspase 3, which enforces apoptosis and DNA fragmentation. In proliferating GBM cells, however, the anti-apoptotic protein Bcl-2 directly inhibits caspase 9, while mTOR inhibits Beclin-1.

In conjunction with ER stress, several mitochondrial mechanisms promote GBM cell apoptosis. Astaxanthin and adonixanthin upregulate (p-)p38 and associated MAPKs, which upregulate the proapoptotic Bax and downregulate the antiapoptotic Bcl-2 [35]. Alterations in the Bax:Bcl-2 ratio, mediated also by curcumin, berberine, pisosterol, and diosgenin, contribute to the depolarization of the mitochondrial membrane potential (MMP) [29,54]. Moreover, coronarin D, curcumin, and berberine upregulate intracellular ROS, further contributing to MMP depolarization [29,47,58]. MMP depolarization leads to cytochrome c release, as seen after treatment with curcumin or berberine [29].

Downstream, cytochrome c, Bad, and Bim promote the activation of caspase 9, which in turn activates caspase 3. A blockade of Akt/mTOR signaling mediated by arctigenin or osthole enhances the activity of Beclin-1, which supports caspase 3 activation [61,64]. Caspase 3 specifically blocks the inhibitor of caspase-activated DNase (ICAD), allowing CAD to cause DNA fragmentation—an effect observed after diosgenin application [54]. Consequently, caspase 3 cleaves poly-ADP ribose polymerase 1 (PARP-1), activating apoptosis.

Table 4. Natural substances increase apoptotic cell death in GBM by downregulating apoptotic inhibitors and upregulating active caspases, which cleave PARP-1 and induce DNA fragmentation.

Effect	Substance	Cell Line	Source
Causes apoptosis	Arctigenin	U87MG, T98G	[61]
	Osthole	MOGGCCM, T98	[64]
	Xanthohumol	U87	[38]
	Rupesin E	GSC-3#, GSC-18#	[45]
	Diosmin	GBM02, GBM95	[46]
	SLCP	U87, U251	[29]
	BBR	U87, U251	[29]
	Gossypol	TS13-20, Diff13-20	[30]
	Withaferin A	U87, U251	[40]
	Tectorigenin	GBM-8401, GBM-8901	[50]
	Diosgenin	C6, T98G	[54]
	Pisosterol	U87, U343, AHOL1, 1231N1	[60]
	Causes DNA fragmentation	SLCP	U87, U251
BBR		U87, U251	[29]
Upregulates (c)-caspase 9 (protein)	Cedrol	RG2	[33]
	Coronarin D	U251	[47]
	CP	GAMG	[36]
	McC1	GAMG	[36]
	Withaferin A	U87, U251	[40]
Upregulates caspase 3 (mRNA)	Pisosterol	U87, U343, AHOL1, 1231N1	[60]
Upregulates (c)-caspase 3 (protein)	EGCG	MO59J, U251	[42]
	Cedrol	DBTRG-05MG, RG2	[33]
	Osthole	T98	[64]
	Xanthohumol	U87, T98G, LN229	[38]
	Rupesin E	GSC-3#, GSC-18#	[45]
	Crocetin	U87, U138, U251, U373	[34]
	Diosmin	GBM02, GBM95	[46]
	Coronarin D	U251	[47]
	CP	GAMG	[36]
	McC1	GAMG, U251	[36]
	SLCP	U87, U251	[29]
	BBR	U87, U251	[29]
	Withaferin A	U87, U251	[40]
	Betulinic Acid	U251, LN229	[48]
	Resveratrol	U87	[51]
	Quercetin	U87	[51]
	GL-PP	U251	[59]
Pisosterol	U87, U343, AHOL1, 1231N1	[60]	

Table 4. Cont.

Effect	Substance	Cell Line	Source
Upregulates (c-)PARP (protein)	Cedrol	RG2	[33]
	Xanthohumol	U87	[38]
	Coronarin D	U251	[47]
	CP	U251	[36]
	McC1	GAMG, U251	[36]
	Gossypol	TS13-20, Diff13-20	[30]
	Withaferin A	U87, U251	[40]
Downregulates PARP-1 (protein)	Diosgenin	C6, T98G	[54]
Downregulates ICAD (protein)	Diosgenin	C6, T98G	[54]
Upregulates Bax (protein)	SLCP	U87, U251	[29]
	BBR	U87, U251	[29]
	Diosgenin	C6, T98G	[54]
Downregulates Bcl-2 (mRNA)	Pisosterol	U87, U343, AHOL1, 1231N1	[60]
Downregulates Bcl-2 (protein)	Diosgenin	C6, T98G	[54]
	Pisosterol	U87, U343, AHOL1, 1231N1	[60]
Upregulates Bad (protein)	Withaferin A	U87, U251	[40]
Upregulates Bim (protein)	Withaferin A	U87, U251	[40]
Depolarizes MMP	Coronarin D	U251	[47]
	CP	U251	[36]
	McC1	U251	[36]
	Gossypol	TS13-20	[30]
	Withaferin A	U87, U251	[40]
Upregulates ROS	Coronarin D	U251	[47]
	SLCP	U87, U251	[29]
	BBR	U87, U251	[29]
Upregulates cytochrome c (protein)	SLCP	U87, U251	[29]
	BBR	U87, U251	[29]
Upregulates GRP78 (mRNA)	Withaferin A	U87, U251	[40]
Upregulates GRP78 (protein)	EGCG	MO59J	[42]
Upregulates ATF4 (mRNA)	Withaferin A	U87, U251	[40]
Upregulates ATF4 (protein)	Withaferin A	U87, U251	[40]
	EGCG	U251	[42]
Upregulates ATF6 (mRNA)	Withaferin A	U251	[40]
Upregulates XBP1 (mRNA)	Withaferin A	U87, U251	[40]
Upregulates XBP1 (protein)	Withaferin A	U87, U251	[40]
Upregulates CHOP (mRNA)	Withaferin A	U87, U251	[40]
Upregulates CHOP (protein)	Withaferin A	U87, U251	[40]
Upregulates Bax (protein)	Cedrol	DBTRG-05MG	[33]

Autophagy is blocked in proliferating GBM cells by Akt/mTOR signaling (Figure 6, Table 5). However, arctigenin and osthole upregulate Beclin-1 mRNA and protein levels. Beclin-1 interestingly has dual roles in apoptosis and autophagy, and upregulates light

chain 3B (LC3B), which promotes autophagosome formation [61,64]. Moreover, arctigenin may increase autophagy through the upregulation of phosphorylated P62 (p-P62) [61].

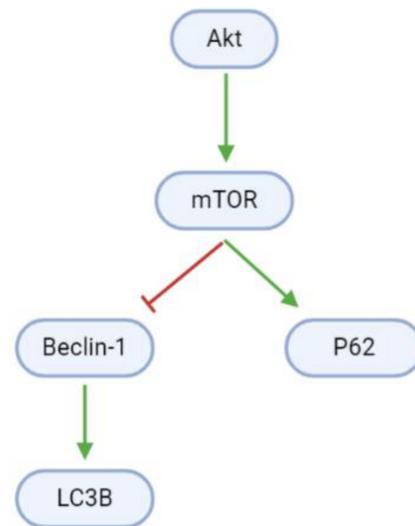


Figure 6. Pathways promoting cell death through autophagy are inhibited in GBM cells. mTOR inactivates the pro-autophagy Beclin-1 and upregulates the anti-autophagy P62.

Table 5. Arctigenin and osthole promote autophagy by upregulating Beclin-1 and LC3B-II and downregulating P62.

Effect	Substance	Cell Line	Source
Causes autophagy	Osthole	MOGGCCM	[64]
Upregulates Beclin-1 (mRNA)	Arctigenin	U87MG, T98G	[61]
Upregulates Beclin-1 (protein)	Arctigenin	U87MG, T98G	[61]
	Osthole	MOGGCCM	[64]
Upregulates LC3B-II (mRNA)	Arctigenin	U87MG, T98G	[61]
Upregulates LC3B-II (protein)	Arctigenin	U87MG	[61]
Downregulates P62 (mRNA)	Arctigenin	U87MG, T98G	[61]
Downregulates P62 (protein)	Arctigenin	U87MG, T98G	[61]

3.3. Cell Cycle

In addition to modulating cell proliferation and death, natural substances may also affect tumorigenesis through the induction of cell cycle arrest (Figure 7, Table 6). Uncontrolled cell cycle progression due to the Akt-mediated inhibition of cyclin-dependent kinase (CDK) inhibitors (CDKNs) causes rapid GBM cell division. However, a blockade of Akt activates (1) forkhead homeobox O (FOXO), which in turn activates the CDKN p27; and (2) the p53 tumor suppressor, which activates the CDKN p21. Elevated intracellular ROS levels mediate further upregulation of p21. ROS damages DNA, upregulating H2A family member X (H2AX) and consequently p21, as evidenced after Coronarin D, CP, and Mcc1 treatment [36,47].

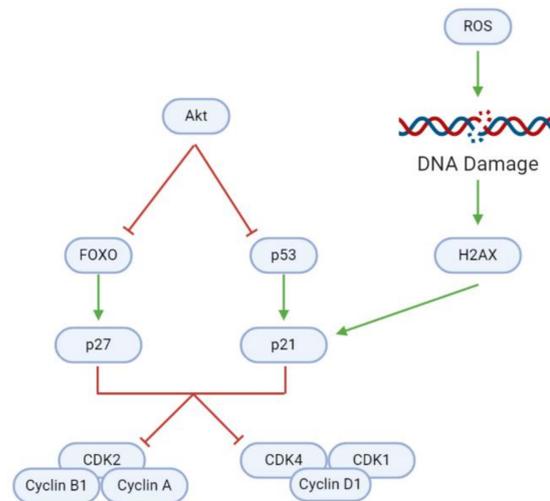


Figure 7. Inhibition of regulatory proteins allows for continuous cyclin/CDK activity and cell cycle progression in GBM cells. In healthy cells, FOXO and p53 can activate p27 and p21, respectively, and consequently induce cell cycle arrest to maintain homeostasis. DNA damage as a result of ROS accumulation is a key trigger for p21 activation. However, overactive Akt inhibits FOXO and p53, and therefore facilitates uncontrolled tumor cell growth and division.

Table 6. Natural substances induce cell cycle arrest in GBM by upregulating p53, p21, and p27, and inhibiting several cyclins and their associated CDKs.

Effect	Substance	Cell Line	Source
Causes G0/G1 phase cell cycle arrest	Cedrol	DBTRG-05MG, RG2	[33]
	Coronarin D	U251	[47]
	Tannic Acid	C6	[39]
	Tectorigenin	GBM-8401	[50]
	BBR	U87	[58]
	GL-PP	U251	[59]
Causes G2/M phase cell cycle arrest	Eucalyptal A	U87MG, LN229	[32]
	Withaferin A	U87, U251	[40]
	TBMS1	U87, LN229	[41]
	Pisosterol	U87, U343, AHOL1, 1231N1	[60]
Downregulates Cyclin D1 (protein)	Astaxanthin	GL261	[35]
	Adonixanthin	GL261	[35]
Downregulates CDK1 (protein)	Cedrol	DBTRG-05MG	[33]
	Withaferin A	U87, U251	[40]
Downregulates CDK2 (protein)	TBMS1	U87	[41]
	Cedrol	DBTRG-05MG, RG2	[33]
Downregulates CDK4 (protein)	Tectorigenin	GBM-8401	[50]
Downregulates Cyclin A (protein)	Cedrol	DBTRG-05MG, RG2	[33]
	TBMS1	U87, LN229	[41]
Downregulates Cyclin B1 (protein)	Cedrol	DBTRG-05MG, RG2	[33]
	TBMS1	U87, LN229	[41]

Table 6. Cont.

Effect	Substance	Cell Line	Source
Upregulates (p-)H2AX (protein)	Coronarin D	U251	[47]
	CP	U251	[36]
	McC1	GAMG, U251	[36]
Downregulates (p-)RB (protein)	Tectorigenin	GBM-8401	[50]
Upregulates p21 (protein)	Coronarin D	U251	[47]
	<i>Paris saponin H</i>	U251	[69]
	Withaferin A	U87, U251	[40]
	Tectorigenin	GBM-8401	[50]
Upregulates p27 (protein)	Astaxanthin	GL261	[35]
	<i>Paris saponin H</i>	U251	[69]
	Adonixanthin	GL261	[35]
	AM05	T98G	[44]

As CDKNs, p21 and p27 inhibit specific cyclin-CDK complexes that are necessary for cell cycle progression. Inhibition of CDK2, Cyclin A, and Cyclin B1, as seen after treatment with cedrol or TBMS1, leads to G2/M phase cell cycle arrest [33,41]. In contrast, *Paris saponin H* upregulates p21 and p27 and downregulates Cyclin D1, eventually causing G1 phase cell cycle arrest [69]. Likewise, the inhibition of CDK1, CDK4, and Cyclin D1 by Withaferin A, TBMS1, astaxanthin, adonixanthin, and cedrol prompts G0/G1 phase arrest [33,35,40,41].

3.4. Inflammation and Immune Cell Modulation

Neuroinflammation is an essential component of GBM tumorigenesis and interacts with various pro- and anticancer mechanisms (Table 7). Bispo da Silva et al. characterized rutin and quercetin's pleiotropic effects on GBM-associated inflammation [63]. These flavonoids induce the chemotaxis and activation of microglia—resident macrophages in the nervous system—as evidenced by the immune cells' adoption of amoeboid and multipolar morphologies. Moreover, rutin and quercetin promote microglial proliferation and migration to tumor sites, where they modulate cytokine levels and thereby affect the tumor inflammatory profile. For instance, rutin and quercetin treatment upregulates interleukins 1 (IL-1), 1- β (IL-1 β), and 18 (IL-18)—pro-inflammatory cytokines of the IL-1 family. Chemokine (C-X3-C motif) ligand 1 (CX3CL1), which promotes microglial migration, is also activated. Concurrently, interleukins 4 (IL-4), 8 (IL-8), and 10 (IL-10), which have tumorigenic properties under certain circumstances, are downregulated.

Interestingly, the effects of natural compounds on interleukin 6 (IL-6) and tumor necrosis factor (TNF) vary between cell lines (see Table 7). Rutin and quercetin upregulate IL-6 at the mRNA level in C6 and TG1 (quercetin only) cells. However, along with CrataBL, they downregulate IL-6 at the mRNA level in U251 and TG1 (rutin only) cells and U251 xenografts in Wistar rats. They also downregulate IL-6 at the protein level in C6 and U87 cells. Similar pleiotropic effects are observed with TNF, which is upregulated at the mRNA and protein levels in U251, C6, and TG1 cells, but downregulated at the mRNA level in U251-Wistar rat xenograft models. These varying data underscore the need for further investigation into the immuno-modulatory properties of natural substances in GBM.

Table 7. Rutin, quercetin, and CrataBL exert pleiotropic and sometimes cell line-dependent effects on neuroinflammation.

Effect	Substance	Cell Line	Source
Activates microglia	Rutin	C6	[63]
	Quercetin	C6	[63]
Upregulates IL-1 (mRNA)	Rutin	U251 orthotopic implants, WR	[63]
	Quercetin	U251 orthotopic implants, WR	[63]
Upregulates IL-1 β (mRNA)	Rutin	C6	[63]
	Quercetin	C6	[63]
Downregulates IL-4 (mRNA)	Rutin	U251 orthotopic implants, WR	[63]
	Quercetin	U251 orthotopic implants, WR	[63]
Upregulates IL-6 (mRNA)	Rutin	C6	[63]
	Quercetin	C6, TG1	[63]
Downregulates IL-6 (mRNA)	Rutin	U251, TG1, WR-U251 orthotopic implants	[63]
	Quercetin	U251, WR-U251 orthotopic implants	[63]
Downregulates IL-6 (protein)	Rutin	C6	[63]
	CrataBL	U87	[49]
Downregulates IL-8 (protein)	CrataBL	U87	[49]
Downregulates IL-10 (mRNA)	Rutin	C6, U251, TG1, WR-U251 orthotopic implants	[63]
	Quercetin	C6, U251, TG1, WR-U251 orthotopic implants	[63]
Downregulates IL-10 (protein)	Rutin	C6	[63]
Upregulates IL-18 (mRNA)	Rutin	U251 orthotopic implants, WR	[63]
	Quercetin	U251 orthotopic implants, WR	[63]
Upregulates TNF (mRNA)	Rutin	U251, TG1	[63]
	Quercetin	U251	[63]
Downregulates TNF (mRNA)	Rutin	U251 orthotopic implants, WR	[63]
	Quercetin	U251 orthotopic implants, WR	[63]
Upregulates TNF (protein)	Rutin	C6	[63]
Upregulates TNF- α (mRNA)	Rutin	C6	[63]
	Quercetin	C6	[63]
Upregulates CX3CL1 (mRNA)	Rutin	C6, WR-U251 orthotopic implants	[63]
	Quercetin	C6	[63]
Downregulates (p-)STAT3 (protein)	Curcumin	U87	[52]

3.5. Migration, Invasion, and Metastasis

GBM cell migration, invasion, and metastasis are mainly mediated through the epithelial-mesenchymal transition (EMT) and modulation of the cytoskeletal actin framework (Figure 8; Table 8). To promote cell motility through actin, RhoA, a small GTPase, activates the Rho-associated protein kinase (ROCK); ROCK, in turn, activates the Lim kinase (Limk) through phosphorylation. Concurrently with RhoA/ROCK/Limk signaling, PI3K activates protein kinase A (PKA). Both Limk and PKA inhibit the activity of Cofilin (actin depolymerization factor), which ordinarily destabilizes cytoskeletal actin filaments and thereby impairs cell motility. Cofilin is active in the dephosphorylated form; as such, Limk and PKA may inhibit its activity through phosphorylation to produce p-Cofilin. Cofilin activity may be restored by paeoniflorin, which downregulates all components of the RhoA/ROCK/Limk pathway [53]. Eucalyptal A may also promote Cofilin activity, as

it downregulates PKA [32]. Finally, the signal transducer and activator of transcription 3 (STAT3), a transcription factor commonly associated with inflammation, activates the actin bundling protein Fascin. Fascin acts antagonistically to Cofilin to stabilize the cytoskeleton and enhance cell motility; however, curcumin suppresses (p-)STAT3 and thereby downregulates Fascin activity [52].

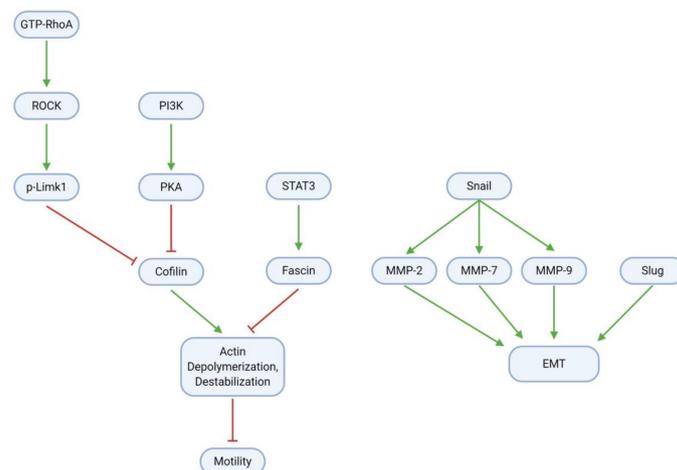


Figure 8. GBM cells gain migration and invasion abilities through EMT and modulation of the cytoskeletal actin framework. Regularization of actin filaments by STAT3/Fascin enhances cell motility; this process is reversible by Cofilin, which in tumor cells is inhibited by RhoA/ROCK/Limk and PI3K/PKA signaling. Upregulation of Snail, Slug, and MMPs further increases motility through EMT induction.

Tumor cell adhesion and motility are further influenced by EMT, a process in which tumor cells become less adhesive and more migratory, and therefore more invasive. The Snail protein is upregulated in glioblastoma and activates the matrix metalloproteinases (MMP) 2, 7, and 9, which together with Slug contribute to the EMT. Several natural compounds have anti-EMT properties in GBM. These include TBMS1 and galangin, which directly downregulate Snail (and therefore the MMPs) and Slug [41,70]. Astaxanthin, adonixanthin, and diosgenin also downregulate MMPs; however, it remains unclear whether these effects are Snail-dependent [35]. Moreover, magnolol suppresses GBM cell migration by regulating focal adhesions and N-cadherin, while gamabufotalin demonstrates antimetastatic effects by downregulating urokinase plasminogen activator (uPA) and carbonic anhydrase 9 (CA9) and upregulating tissue inhibitor of metalloproteinases 3 (TIMP-3) [71,72].

Table 8. Natural substances decrease GBM cell migration and invasion by downregulating EMT modulators (Snail, Slug, and MMPs), Cofilin inhibitors (RhoA/ROCK/Limk and PKA), and actin polymerizers (STAT3/Fascin).

Effect	Substance	Cell Line	Source
Reduces cell migration	Eucalyptal A	U87MG, LN229	[32]
	Astaxanthin	GL261, U251MG	[35]
	Adonixanthin	GL261, U251MG	[35]
	Arctigenin	U87MG, T98G	[61]
	Crocetin	U87, U251	[34]
	CP	GAMG	[36]
	McC1	U251, GAMG	[36]
	Tannic Acid	C6	[39]
	TBMS1	U87, LN229	[41]

Table 8. Cont.

Effect	Substance	Cell Line	Source
Reduces cell migration	Curcumin	U87	[52]
	Paeoniflorin	U251, T98G	[53]
	Diosgenin	C6, T98G	[54]
	Rutin	C6	[63]
	Magnolol	LN229, U87MG	[71]
	Gamabufotalin	U87	[72]
	Quercetin	C6	[63]
Reduces cell invasion	Eucalyptal A	U87MG, LN229	[32]
	Arctigenin	U87MG, T98G	[61]
	McC1	GAMG, U251	[36]
	CrataBL	U87	[49]
	Curcumin	U87	[52]
	Paeoniflorin	U251, T98G	[53]
	Diosgenin	C6, T98G	[54]
Downregulates MMP-2 (protein)	Astaxanthin	GL261	[35]
	Adonixanthin	GL261	[35]
	Arctigenin	U87MG	[61]
	TBMS1	U87, LN229	[41]
	Diosgenin	T98G	[54]
Downregulates MMP-7 (protein)	TBMS1	U87, LN229	[41]
Downregulates MMP-9 (protein)	Arctigenin	U87MG	[61]
	Diosgenin	C6	[54]
Downregulates p-PKA 1/2/3 (prot.)	Eucalyptal A	U87MG, LN229	[32]
Downregulates p-Cofilin (protein)	Eucalyptal A	U87MG, LN229	[32]
Downregulates fibronectin (protein)	Adonixanthin	GL261	[35]
Downregulates laminin (protein)	CrataBL	U87	[49]
Downregulates Snail (protein)	TBMS1	U87, LN229	[41]
	Galangin	U87, U251	[70]
Downregulates Snail (mRNA)	Galangin	U87, U251	[70]
Downregulates Slug (protein)	TBMS1	U87, LN229	[41]
Downregulates Fascin (protein)	Curcumin	U87	[52]
Reduces actin filament number	Paeoniflorin	T98G, U251	[53]
Downregulates GTP-RhoA (protein)	Paeoniflorin	T98G, U251	[53]
Downregulates ROCK (protein)	Paeoniflorin	T98G, U251	[53]
Downregulates (p-)Limk1 (protein)	Paeoniflorin	T98G, U251	[53]

3.6. Angiogenesis

Angiogenesis—the development of active blood vessels in and around tumor sites—is a key element of GBM progression (Table 9). Vascular endothelial growth factor (VEGF) mediates this process; it is upregulated by HIF-1 and downregulated by A disintegrin and metalloproteinase with thrombospondin motifs 1 (ADAMTS1). As such, substances such as *Paris* saponin H that inhibit HIF-1 will consequently downregulate VEGF [69]. The

sesquiterpene lactone AM04 upregulates ADAMTS1 and thereby downregulates VEGF in U87 and T98G cells [44].

Table 9. Natural substances reduce angiogenesis and neovascularization primarily by downregulating VEGF.

Effect	Substance	Cell Line	Source
Decreases angiogenesis area	McC1	U251 heterotopic xenograft, fertilized chicken eggs	[36]
Decreases blood vessel junctions	McC1	U251 heterotopic xenograft, fertilized chicken eggs	[36]
Decreases tube formation	Diosgenin	C6, T98G	[54]
Upregulates ADAMTS1 (protein)	AM04	U87MG, T98G	[44]
Downregulates CD31 (mRNA)	Naringin	U87 subcutaneous xenograft, athymic mice	[37]
Downregulates CD105 (mRNA)	Naringin	U87 subcutaneous xenograft, athymic mice	[37]
Downregulates tumor hemoglobin	Naringin	U87 subcutaneous xenograft, athymic mice	[37]
Downregulates VEGF (protein)	Metformin	U251	[68]
	Paris saponin H	U251	[69]
	CrataBL	U87	[49]
	Diosgenin	C6	[54]

Reduced VEGF activity decreases tumor neovascularization; importantly, this is observable in vivo. Treatment of U87 xenografts in athymic mice with the flavonoid naringin downregulates tumor hemoglobin and the angiogenic markers cluster of differentiation 31 (CD31) and 105 (CD105) [37]. Moreover, mattecucinol decreases the angiogenic area and the number of blood vessel junctions in a U251 xenograft-fertilized chicken egg model [36]. These in vivo effects demonstrate the potential applicability of specific natural substances as angiogenic modulators that inhibit GBM.

3.7. Metabolism

Cancer cells exhibit modified metabolic processes that meet the extensive energy demands of growth, proliferation, and metastasis—a phenomenon known as the Warburg effect [73]. In GBM cells, Akt promotes glucose metabolism through the upregulation of glycogen synthase kinase 3 β (GSK3 β). GSK3 β , in turn, upregulates F-box and WD-40 domain-containing protein 7 (FBW7) and c-Myc, leading to the activation of hexokinase 2 (HK2). HK2 is a major metabolic enzyme that contributes to the aerobic glycolysis observed in tumor cells by increasing glucose uptake and lactate production (Figure 9, Table 10). Xanthohumol downregulates GSK3 β , and as such decreases downstream HK2 activity, glucose consumption, and lactate production [38]. In contrast, carnosine upregulates pyruvate dehydrogenase kinase 4 (PDK4), which downregulates metabolism, while crocetin downregulates fatty acid synthase (FASN), which catalyzes metabolically relevant fatty acid synthesis [31,34].

3.8. Chemoresistance

The effects of natural substances on GBM chemoresistance remain largely uncharacterized in the recent literature. Chang et al. reported that cedrol downregulates O6-alkylguanine DNA alkyltransferase (MGMT) at the protein level in DBTRG-05MG and RG2 cells [33]. MGMT, a DNA repair protein, confers resistance to alkylating agents (e.g., temozolomide) by reversing guanine alkylation [74]. Studies from 2014 moreover indicate that pine needle extract, chrysin, and quercetin sensitize GBM cells to TMZ [75,76]. At

any rate, further data are necessary to substantiate the potential of natural substances in overcoming GBM drug resistance.

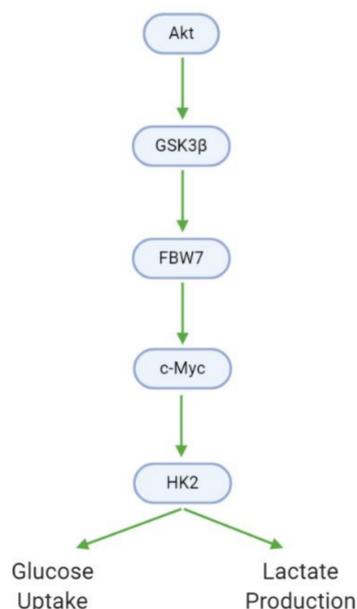


Figure 9. GBM cells utilize altered metabolic processes (Warburg effect) characterized by increased glucose uptake and lactate generation. Akt, via GSK3 β , mediates the transition between the healthy and Warburg phenotypes.

Table 10. Xanthohumol, carnosine, and crocetin interfere with key enzymes in GBM cell metabolism.

Effect	Substance	Cell Line(s)	Source
Downregulates HK2 (protein)	Xanthohumol	U87, T98G, LN229	[38]
Decreases glucose consumption	Xanthohumol	U87, T98G, LN229	[38]
Decreases lactate production	Xanthohumol	U87, T98G, LN229	[38]
Downregulates (p-)GSK3 β (protein)	Xanthohumol	U87	[38]
Upregulates PDK4 (mRNA)	Carnosine	U87, T98G	[31]
Downregulates FASN (protein)	Crocetin	U87, U138, U251, U373	[34]

4. Synergistic and Combinatory Effects (Multiple Natural Compounds)

While the actions of natural substances in conjunction with anticancer drugs are widely investigated, few studies have demonstrated the synergistic effects of concurrently applied natural substances in GBM (Table 11). One such study by Moskwa and colleagues demonstrates that Polish propolis (PPE) and BcH together decrease viability and DNA synthesis (a marker of proliferation) in T98G, LN-18, and U87 cells [57]. These findings demonstrate synergistic cytotoxic and anti-proliferative activities.

Another study by Maiti et al. shows that a combinatory treatment of solid lipid curcumin particles (SLCP) and BBR induces apoptosis and decreases proliferation and viability in U87 and U251 cells [29]. Synergistic apoptotic effects are mediated through the upregulation of ROS, Bax, cytochrome c, and caspases, while a blockade of PI3K/Akt/mTOR signaling decreases proliferation.

Table 11. Synergistic effects of natural substances on GBM. Concurrent administration of PPE and BcH enhances GBM cytotoxicity and reduces DNA synthesis, while curcumin and BBR together reduce proliferation and increase apoptotic cell death.

Effect	Cell Line	Subs. 1	Subs. 1 Conc.	Subs. 2	Subs. 2 Conc.	Source
Increases cell death/dec viability	U87	SLCP	20 μ M	BBR	100 μ M	[29]
	U251	SLCP	20 μ M	BBR	100 μ M	[29]
	T98G	PPE	30 μ g/mL	BcH	5, 10, 25, 50, 100 μ g/mL	[57]
	LN-18	PPE	30 μ g/mL	BcH	50, 100 μ g/mL	[57]
	U87	PPE	30 μ g/mL	BcH	50, 100 μ g/mL	[57]
Decreases proliferation	U87	SLCP	20 μ M	BBR	100 μ M	[29]
	U251	SLCP	20 μ M	BBR	100 μ M	[29]
Causes apoptosis	U87	SLCP	20 μ M	BBR	100 μ M	[29]
	U251	SLCP	20 μ M	BBR	100 μ M	[29]
Causes DNA fragmentation	U87	SLCP	20 μ M	BBR	100 μ M	[29]
	U251	SLCP	20 μ M	BBR	100 μ M	[29]
Decreases DNA synthesis	T98G	PPE	30 μ g/mL	BcH	25, 50 μ g/mL	[57]
	LN-18	PPE	30 μ g/mL	BcH	25, 50 μ g/mL	[57]
	U87	PPE	30 μ g/mL	BcH	25, 50 μ g/mL	[57]
Decreases intracellular ATP	U87	SLCP	20 μ M	BBR	100 μ M	[29]
	U251	SLCP	20 μ M	BBR	100 μ M	[29]
Upregulates ROS	U87	SLCP	20 μ M	BBR	100 μ M	[29]
	U251	SLCP	20 μ M	BBR	100 μ M	[29]
Upregulates Bax (protein)	U87	SLCP	20 μ M	BBR	100 μ M	[29]
	U251	SLCP	20 μ M	BBR	100 μ M	[29]
Upregulates cytochrome c (protein)	U87	SLCP	20 μ M	BBR	100 μ M	[29]
	U251	SLCP	20 μ M	BBR	100 μ M	[29]
Upregulates (c-)caspase 3	U87	SLCP	20 μ M	BBR	100 μ M	[29]
	U251	SLCP	20 μ M	BBR	100 μ M	[29]
Downregulates c-Myc (protein)	U87	SLCP	20 μ M	BBR	100 μ M	[29]
	U251	SLCP	20 μ M	BBR	100 μ M	[29]
Upregulates p53 (protein)	U87	SLCP	20 μ M	BBR	100 μ M	[29]
	U251	SLCP	20 μ M	BBR	100 μ M	[29]
Downregulates Akt (protein)	U87	SLCP	20 μ M	BBR	100 μ M	[29]
Downregulates (p-)Akt (protein)	U87	SLCP	20 μ M	BBR	100 μ M	[29]
	U251	SLCP	20 μ M	BBR	100 μ M	[29]
Downregulates PI3K (protein)	U87	SLCP	20 μ M	BBR	100 μ M	[29]
Downregulates (p-)PI3K (protein)	U87	SLCP	20 μ M	BBR	100 μ M	[29]
	U251	SLCP	20 μ M	BBR	100 μ M	[29]
Downregulates mTOR (protein)	U87	SLCP	20 μ M	BBR	100 μ M	[29]
	U251	SLCP	20 μ M	BBR	100 μ M	[29]
Downregulates (p-)mTOR (protein)	U87	SLCP	20 μ M	BBR	100 μ M	[29]
	U251	SLCP	20 μ M	BBR	100 μ M	[29]

5. Challenges and Considerations in the Use of Natural Substances for GBM Treatment

5.1. Bioavailability and BBB Permeability

Bioavailability, metabolism, and blood–brain barrier (BBB) permeability are key factors in assessing natural substances' clinical viability in GBM treatment. These properties vary widely between substances, and in many cases must be overcome to achieve sufficient *in vivo* and clinical concentrations. Oral bioavailability, a measure of a compound's ability to reach the systemic circulation after ingestion, is lacking in several substances discussed in this review. BBR, for instance, has low oral bioavailability due to its poor absorption and rapid first-pass metabolism [77]. Osthole and curcumin are similarly constrained [21,78,79]. Furthermore, the flavonoids quercetin, naringin, and EGCG exhibit low oral bioavailability due to metabolic alterations and their high molecular weights [80]. Finally, the bioavailability of carotenoids varies with their structures; xanthophylls (which are more lipid-soluble) exhibit greater absorption than carotenes (which are purely hydrocarbon) [81]. In this light, the oral dosages necessary to replicate *in vitro* concentrations may be high and vary widely between substances.

Beyond bioavailability, BBB permeability is another consideration in designing brain-targeting therapies. Effective anti-GBM drugs must cross the BBB—a specialized endothelial cell layer that largely prevents passive diffusion between the brain and cranial blood vessels. Interestingly, BBR and coumarins, which have low oral bioavailability, are well absorbed through the BBB [82,83]. The BBB is furthermore permeable to xanthophylls (as evidenced by their cranial and retinal distribution), lipophilic flavonoids such as naringin and quercetin, and arctigenin [84–86]. In contrast, the flavonoid diosgenin does not appreciably cross the rat BBB after the administration of general yam extract [87]. Similarly, orally administered paeoniflorin cannot pass through the murine BBB [88].

While the bioavailability and BBB permeability of some natural compounds are independently corroborated, current preclinical research on GBM remains limited by poor modeling of physiological conditions and the BBB. Assessment of GBM cells in culture with high concentrations of natural products provides valuable mechanistic insights but does not reflect physiological realities. Several reviewed trials included animal models; however, some of these studies utilized heterotopic rather than orthotopic xenografts. Heterotopic—including subcutaneous—xenografts have limited utility, as they do not model the BBB. Orthotopic implants, in contrast, accurately model both the BBB and the *in situ* heterogeneity of brain tumors. Trials on orthotopic animal models therefore constitute an initial step in assessing natural compounds' clinical viability. Of the reviewed substances, astaxanthin, adonixanthin, crocetin, eucalyptal A, tannic acid, rutin, and quercetin exerted appreciable anti-GBM effects in murine orthotopic models [32,34,35,39,63]. As such, these compounds are promising with regard to *in situ* bioavailability and BBB permeability.

5.2. Selectivity of Natural Compounds for GBM

In addition to favorable chemical and pharmacological properties, the selectivity of natural compounds for GBM cells is a key consideration for current preclinical and future clinical research. Effective chemotherapeutic agents should target cancerous cells while minimizing damage to healthy cells such as astrocytes. To this end, withaferin A, tannic acid, mattecucinol, diosmin, cedrol, and rupesin E have been evaluated for GBM selectivity *in vitro*.

Recent preclinical studies reveal varying levels of GBM selectivity between compounds and cell lines. Tannic acid did not alter the viability of normal rat astrocytes at concentrations up to 75 μM , while diosmin at up to 150 μM remained minimally cytotoxic toward human astrocytes [39,46]. In contrast, withaferin A, cedrol, and rupesin E exhibited dose-dependent cytotoxicity; these compounds inhibited only GBM cells at lower concentrations, but both GBM cells and astrocytes at higher concentrations. Withaferin A was nontoxic toward HA1800 astrocytes at concentrations of 1 and 3 μM , but displayed significant cytotoxicity at 10 μM [40]. Cedrol also demonstrated this pattern of selectivity,

with an IC_{50} for CTX TNA2 rat astrocytes more than two-fold higher than its IC_{50} values for DBTRG-05MG and RG2 GBM cell lines [33]. Similarly, the IC_{50} values of rupesin E were significantly greater for human cerebellar astrocytes than glioma stem cells [45]. Finally, matteucinol's selectivity was cell line-dependent, with seemingly paradoxical selectivity indices of 1.60 and 0.36 for GAMG and U251 cells, respectively, compared to human astrocytes [36]. In this light, tannic acid and diosmin in particular are promising compounds; nevertheless, the *in vivo* selectivity of natural compounds and the variables that affect it must be clarified prior to the commencement of clinical trials.

5.3. Delivery Mechanisms to Enhance Natural Compounds' Anti-GBM Properties

It is important to note that bioavailability, BBB permeability, and GBM selectivity are necessary for effective therapeutic design; high bioavailability alone without BBB permeability (or vice versa) is insufficient, and non-selective compounds could cause detrimental side effects. As such, numerous formulations were developed to enhance these properties of natural substances. For instance, protein complexes, microemulsions, nanosuspensions, and nanoparticles increase the bioavailability, absorption, and brain uptake of curcumin [21]. In particular, dodecamer peptide-functionalized polydopamine-coated curcumin-loaded zein nanoparticles effectively cross the BBB and deliver curcumin to GBM cells, with high penetration into 3D tumor spheroids. Although this delivery platform has great potential, it requires further *in vivo* evaluation [89]. Diosgenin-olive oil suspensions, quercetin polylactide-co-glycolide nanoencapsulations, and transferrin-modified osthole liposomes exhibit improved BBB permeability over the natural substances alone [87,90,91]. Chitosan-coated lipid microparticles and ApoE3-conjugated solid lipid nanoparticles improve resveratrol's brain delivery [92]. Moreover, BBB-permeable theranostic photonic nanoparticles constitute an option for optically tracked drug delivery and release. Indeed, encapsulated visible and/or near-infrared photonic molecules in ultrasmall micellar structures with curcumin as a therapeutic and photonic component crossed the BBB and accumulated near orthotopic GBM xenografts. The intracranial delivery and release of curcumin is furthermore traceable through fluorescent imaging [93]. Indeed, phototheranostic nanoplatfroms represent a promising approach for brain tumor imaging and therapy [94,95]. In conclusion, *in vivo* examination of these formulations represents a significant step forward; however, further standardization and experimentation are necessary prior to the commencement of clinical trials.

6. Implications for Lifestyle Medicine

6.1. Lifestyle Approaches to (Brain) Cancer

Lifestyle medicine focuses on changes in everyday habits, such as nutritional intake, physical activity levels, and risky behaviors (e.g., smoking). Clinical studies notably revealed that diet is a key factor modulating brain cancer risk and progression. For instance, Hu and colleagues correlated increased consumption of fresh vegetables and fruits with reduced risks of brain cancer development [96,97]. Moreover, the high fat, low carbohydrate ketogenic diet interferes with GBM cell glucose metabolism and demonstrates clinical efficacy [98,99].

Intake of some of the natural substances discussed in this review may be increased through simple dietary adjustments. In particular, grapefruit (naringin), grapes (rutin), green tea (EGCG), and cinnamon (cinnamic acid) are routinely consumed in various regions of the world. Other substances, however, may have non-dietary sources and/or be hampered by low intrinsic bioavailability, absorption, and BBB permeability; dietary supplements may be appropriate in these cases.

6.2. Availability of Natural Substances as Supplements

Over-the-counter (OTC) supplements may be utilized in various cases according to practical constraints and patient preferences. The Dietary Supplement Label Database (DSLDB; <https://dslid.od.nih.gov/dslid/> accessed on 2 February 2021), maintained by the

US National Institutes of Health, provides insights into the availability of various natural compounds as supplements. Based on DSLD data, a number of the reviewed compounds are available in OTC supplements: the alkaloid BBR; the carboxylic acid derivatives cinnamic acid and ferulic acid; the carotenoids astaxanthin and crocetin; the coumarin osthole; curcumin; the flavonoids diosmin, EGCG, naringin, quercetin, resveratrol, chrysin, and rutin; the lignan magnolol; the natural steroids withaferin A and diosgenin; and the terpenes betulinic acid and paeoniflorin. Many of these supplements exert positive physiological effects; in particular, astaxanthin and curcumin positively influence the central nervous system [100–112].

6.3. Promising Natural Compounds and the Path to Clinical Trials

While a wide variety of natural compounds exhibit anti-GBM effects *in vitro* and *in vivo*, clinical trials are required to demonstrate their safety and efficacy. Candidate substances should be available on the market as OTC supplements, and demonstrate appreciable bioavailability, BBB permeability, and *in situ* selectivity for GBM. In this regard, rutin and quercetin hold promise as neuroinflammatory modulators in GBM: both flavonoids are available as OTC supplements, and their efficacy in murine orthotopic models demonstrates their bioavailability and BBB permeability [63]. The carotenoids astaxanthin and crocetin meet the same criteria [34,35]. Tannic acid is also promising, as it exhibits efficacy in orthotopic models as well as selectivity for GBM cells and minimal toxicity to astrocytes [39].

As these (and other) promising compounds progress toward clinical trials, the heterogeneity of brain tumors necessitates the cross-validation of such compounds' mechanistic effects and selectivity between GBM cell lines. Physiological properties, such as bioavailability and BBB permeability, should be further clarified through preclinical studies with orthotopic tumor models and oral administration. If necessary, novel drug delivery systems can be designed to enhance these properties; however, formulations such as nanoparticles require standardization and safety evaluation prior to the commencement of clinical trials.

Finally, the potential for toxicity or adverse interactions between natural compounds and conventional drugs must be assessed and minimized. With regard to toxicity, four of the five promising compounds highlighted earlier in this section—rutin, quercetin, astaxanthin, and crocetin—are clinically safe [113–116]. Fewer studies concerning the fifth compound, tannic acid, are available; however, some of these trials reveal possible hepatotoxic and mutagenic effects [117]. Beyond toxicological studies, candidate natural compounds should be extensively trialed *in vitro* and *in vivo* with contemporary anti-GBM chemotherapeutics, such as TMZ, vincristine, carboplatin, etoposide, and irinotecan. Some recent studies revealed potentially detrimental drug–drug interactions. One pleiotropic flavonoid, quercetin, interacts dose-dependently with etoposide *in vitro* and modulates its efflux and metabolism *in vivo*, increasing the chemotherapeutic's bioavailability and plasma concentration and decreasing its clearance [118,119]. In contrast, St. John's Wort (which contains quercetin) decreases plasma irinotecan levels [120]. Moreover, low-dose quercetin reduces brain concentrations of vincristine—an important consideration in GBM therapy [121]. However, the same flavonoid exerts protective effects against vincristine-induced peripheral neurotoxicity [122]. Quercetin's glycoside, rutin, is also a promising flavonoid; however, minimal data are available on its interactions with anti-GBM drugs. Data on astaxanthin, crocetin, and tannic acid are likewise limited; however, astaxanthin demonstrated protective effects against toxicity induced by cyclophosphamide, a salvage chemotherapeutic sometimes used in GBM. Notably, astaxanthin alleviated DNA damage—at the molecular and chromosomal levels—as well as oxidative stress *in vivo* [123]. These varying results underscore the need for further studies to elucidate the nature and implications of interactions between natural compounds and anti-GBM drugs.

7. Conclusions and Outlook

Natural compounds are an integral component of lifestyle medicine approaches to chronic diseases such as GBM. Members of the alkaloid, carboxylic acid derivative, carotenoid, coumarin, curcuminoid, flavonoid, lignan, steroid, tannin, and terpene families exert chemotherapeutic effects on GBM in vitro and in vivo. As such, they increase tumor cell death by upregulating pathways for autophagy and apoptosis and inhibiting those for proliferation. The reviewed substances concurrently induce cell cycle arrest, stabilize the neuroinflammatory profile, interfere with the Warburg effect, and inhibit angiogenesis and metastasis.

Although the results of in vitro and animal studies are promising, they remain uncorroborated by clinical trials. Importantly, natural substances' clinical and lifestyle medical viability remain constrained by their pharmacokinetic and pharmacodynamic properties. Effective GBM therapies require appreciable oral bioavailability, BBB permeability, and GBM selectivity; however, the reviewed substances are highly heterogeneous in this regard. Various formulations are proposed to improve their pharmacological properties but are not yet clinically validated.

Finally, in evaluating natural compounds as chemotherapeutic agents in lifestyle medicine, their OTC availability must be considered. Many alkaloids, carboxylic acid derivatives, carotenoids, coumarins, curcuminoids, flavonoids, and natural steroids with in vitro anti-GBM efficacy are available in dietary supplements, while some of the discussed lignans, tannins, and terpenes are not. Caution is necessary in regular supplementation with natural substances, as the potential for adverse effects and/or drug–drug interactions exists.

In closing, recent preclinical studies underscore the viability of natural substances as candidate agents in GBM therapy. Innovative biochemical formulations could improve their physiological properties, and clinical trials could substantiate their beneficial effects.

Author Contributions: Conceptualization, K.Z. and D.B.; literature review and resources, K.Z.; writing—original draft preparation, K.Z.; writing—review and editing, K.Z., B.A., M.S., A.L., P.K. and D.B.; figure preparation and editing, K.Z. and D.B.; visualization, K.Z. and D.B.; supervision, D.B. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by a National Priorities Research Program grant (NPRP 115-1214-170101; awarded to Dietrich Büsselberg, June 2019–Current) from the Qatar National Research Fund (QNRF, a member of Qatar Foundation). The statements made herein are solely the responsibility of the authors. The publication costs of this article was partially funded by the Weill Cornell Medicine-Qatar Distributed eLibrary and partially by Qatar Foundation through the Weill Cornell Medicine-Qatar Biomedical Research Program-Mamtani Lab.

Acknowledgments: Figures 1 and 3–9 were produced using BioRender ([biorender.com](https://www.biorender.com), accessed on 10 December 2020).

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

ADAMTS1	A Disintegrin And Metalloproteinase with Thrombospondin motifs 1
Akt	serine-threonine kinase Akt
AM01	4 β ,5-dihydro-15-deoxy-eremantholide
AM02	4 β ,5-dihydro-2',3'-epoxy-15-deoxy-goyazensolide
AM03	4 β ,5-dihydro-1',2'-epoxy-15-deoxy-eremantholide
AM04	goyazensolide
AM05	lychnofolide
AM06	15-deoxy-goyazensolide

AMPK	5' Adenosine Monophosphate-activated Protein Kinase
APC	κ N',N'-3-acetyloxy-BA-28-[2-(2-aminoethyl)aminoethyl]amide dichlorido platinum(II)
ATF4	Activating Transcription Factor 4
ATF6	Activating Transcription Factor 6
Bad	Bcl-2 associated death promoter
Bax	Bcl-2 associated x protein
BBR	BerBeRine
Bcl-2	B-cell lymphoma 2
c-Myc	MYC proto-oncogene
CA9	Carbonic Anhydrase 9
CAD	Caspase-Activated DNase
CAT	CATalase
CCL2	C-C motif chemokine Ligand 2
CCL5	C-C motif chemokine Ligand 5
CD105	Cluster of Differentiation 105
CD31	Cluster of Differentiation 31
CDK2	Cyclin-Dependent Kinase 2
CDK4	Cyclin-Dependent Kinase 4
CHOP	C/EBP HOMologous Protein
CX3CL1	chemokine (C-X3-C motif) Ligand 1
DE9B	3-acetyloxy-BA-28-[2-(2-aminoethyl)aminoethyl]amide
DSLID	Dietary Supplement Label Database
ECAR	ExtraCellular Acidification Rate
EGFR	Epidermal Growth Factor Receptor
EMT	Epithelial-Mesenchymal Transition
ERK	Extracellular signal-Regulated Kinase
FASN	Fatty Acid SyNthase
FBW7	F-Box and WD repeat domain-containing 7
FPR1	Formyl Peptide Receptor 1
GBM	GlioBlastoMa
GDNF	Glial cell-Derived Neurotrophic Factor
GSC	Glioma Stem Cell
GSK3 β	Glycogen Synthase Kinase 3 β
GTP-RhoA	Guanosine TriPhosphate-RhoA
H2AX	H2A histone family member X
HDAC1	Histone DeACetylase 1
HDAC3	Histone DeACetylase 3
HDGF	Hepatoma-Derived Growth Factor
HIF-1 α	Hypoxia Inducible Factor-1 α
HK2	HexoKinase 2
ICAD	Inhibitor of Caspase-Activated DNase
IGF	Insulin-like Growth Factor
IL-1(β)	InterLeukin 1(β)
IL-18	InterLeukin 18
IL-4	InterLeukin 4
IL-6	InterLeukin 6
IL-10	InterLeukin 10
JNK	c-Jun N-terminal Kinase
LC3B-II	microtubule-associated proteins 1A/1B Light Chain 3B
MAPK	Mitogen Activated Protein Kinase
Mcl-1	Myeloid cell leukemia 1
MDR1	MultiDrug Resistance protein 1
MGMT	O ⁶ -MethyGuanine-DNA-MethylTransferase
MMP-2	Matrix MetalloProteinase-2
MMP-9	Matrix MetalloProteinase-9
mTOR	mammalian Target Of Rapamycin
MYO1B	MYOsin 1B
NOS2	Nitric Oxide Synthase 2

Nox-4	NADPH oxidase 4
OCR	Oxygen Consumption Rate
OS	Overall Survival
OTC	Over-The-Counter
PAK 1/2/3	p21/Cdc42/Rac1-Activated Kinase 1/2/3
PARP	Poly (ADP-Ribose) Polymerase
PDK1	Pyruvate Dehydrogenase Kinase 1
PDK4	Pyruvate Dehydrogenase Kinase 4
PFS	Progression Free Survival
PI3K	PhosphoInositide 3-Kinase
PTGS2	ProstaGlandin-endoperoxide Synthase 2
PTPN1	Protein Tyrosine Phosphatase Non-receptor type 1
Raf	Rapidly accelerated fibrosarcoma
ROCK	RhO-assoCiated protein Kinase
ROS	Reactive Oxygen Species
SLCP	Solid Lipid Curcumin Particles
SOD	SuperOxide Dismutase
SRSF1	Serine/arginine-Rich Splicing Factor 1
TBMS1	TuBeiMoSide-1
TGF(- β)	Tumor Growth Factor (β eta)
TIMP-3	Tissue Inhibitor of MetalloProteinases 3
TMZ	TeMoZolomide
TNF(- α)	Tumor Necrosis Factor (α lpha)
uPA	urokinase Plasminogen Activator
VEGF	Vascular Endothelial Growth Factor
XBP1	X-box Binding Protein 1

References

- Tamimi, A.F.; Juweid, M. Epidemiology and Outcome of Glioblastoma. In *Glioblastoma*; de Vleeschouwer, S., Ed.; Exon Publications: Brisbane, QLD, Australia, 2017. [\[CrossRef\]](#)
- Darefsky, A.S.; King, J.T., Jr.; Dubrow, R. Adult glioblastoma multiforme survival in the temozolomide era: A population-based analysis of Surveillance, Epidemiology, and End Results registries. *Cancer* **2012**, *118*, 2163–2172. [\[CrossRef\]](#) [\[PubMed\]](#)
- Lima, F.R.; Kahn, S.A.; Soletti, R.C.; Biasoli, D.; Alves, T.; da Fonseca, A.C.; Garcia, C.; Romao, L.; Brito, J.; Holanda-Afonso, R.; et al. Glioblastoma: Therapeutic challenges, what lies ahead. *Biochim. Biophys. Acta* **2012**, *1826*, 338–349. [\[CrossRef\]](#)
- Ringel, F.; Pape, H.; Sabel, M.; Krex, D.; Bock, H.C.; Misch, M.; Weyerbrock, A.; Westermaier, T.; Senft, C.; Schucht, P.; et al. Clinical benefit from resection of recurrent glioblastomas: Results of a multicenter study including 503 patients with recurrent glioblastomas undergoing surgical resection. *Neuro Oncol.* **2016**, *18*, 96–104. [\[CrossRef\]](#) [\[PubMed\]](#)
- Haar, C.P.; Hebbbar, P.; Wallace, G.C.t.; Das, A.; Vandergrift, W.A., 3rd; Smith, J.A.; Giglio, P.; Patel, S.J.; Ray, S.K.; Banik, N.L. Drug resistance in glioblastoma: A mini review. *Neurochem. Res.* **2012**, *37*, 1192–1200. [\[CrossRef\]](#) [\[PubMed\]](#)
- Kalokhe, G.; Grimm, S.A.; Chandler, J.P.; Helenowski, I.; Rademaker, A.; Raizer, J.J. Metastatic glioblastoma: Case presentations and a review of the literature. *J. Neurooncol.* **2012**, *107*, 21–27. [\[CrossRef\]](#)
- Balca-Silva, J.; Matias, D.; Carmo, A.D.; Sarmiento-Ribeiro, A.B.; Lopes, M.C.; Moura-Neto, V. Cellular and molecular mechanisms of glioblastoma malignancy: Implications in resistance and therapeutic strategies. *Semin. Cancer Biol.* **2019**, *58*, 130–141. [\[CrossRef\]](#)
- Bodai, B.I.; Nakata, T.E.; Wong, W.T.; Clark, D.R.; Lawenda, S.; Tsou, C.; Liu, R.; Shiue, L.; Cooper, N.; Rehbein, M.; et al. Lifestyle Medicine: A Brief Review of Its Dramatic Impact on Health and Survival. *Perm. J.* **2018**, *22*, 17–25. [\[CrossRef\]](#)
- Lu, J.J.; Bao, J.L.; Chen, X.P.; Huang, M.; Wang, Y.T. Alkaloids isolated from natural herbs as the anticancer agents. *Evid. Based Complement. Alternat. Med.* **2012**, *2012*, 485042. [\[CrossRef\]](#)
- Isah, T. Anticancer Alkaloids from Trees: Development into Drugs. *Pharmacogn. Rev.* **2016**, *10*, 90–99. [\[CrossRef\]](#)
- De, P.; Baltas, M.; Bedos-Belval, F. Cinnamic acid derivatives as anticancer agents—A review. *Curr. Med. Chem.* **2011**, *18*, 1672–1703. [\[CrossRef\]](#) [\[PubMed\]](#)
- Meléndez-Martínez, A.J.; Mapelli-Brahm, P.; Hornero-Méndez, D.; Vicario, I.M. Chapter 1. Structures, Nomenclature and General Chemistry of Carotenoids and Their Esters. In *Carotenoid Esters in Foods*; Royal Society of Chemistry: London, UK, 2019; pp. 1–50. [\[CrossRef\]](#)
- Koklesova, L.; Liskova, A.; Samec, M.; Buhrmann, C.; Samuel, S.M.; Varghese, E.; Ashrafzadeh, M.; Najafi, M.; Shakibaei, M.; Busselberg, D.; et al. Carotenoids in Cancer Apoptosis-The Road from Bench to Bedside and Back. *Cancers* **2020**, *12*, 2425. [\[CrossRef\]](#)

14. Koklesova, L.; Liskova, A.; Samec, M.; Zhai, K.; Abotaleb, M.; Ashrafizadeh, M.; Brockmueller, A.; Shakibaei, M.; Biringer, K.; Bugos, O.; et al. Carotenoids in Cancer Metastasis-Status Quo and Outlook. *Biomolecules* **2020**, *10*, 1653. [[CrossRef](#)]
15. Abotaleb, M.; Samuel, S.M.; Varghese, E.; Varghese, S.; Kubatka, P.; Liskova, A.; Busselberg, D. Flavonoids in Cancer and Apoptosis. *Cancers* **2018**, *11*, 28. [[CrossRef](#)]
16. Liskova, A.; Koklesova, L.; Samec, M.; Smejkal, K.; Samuel, S.M.; Varghese, E.; Abotaleb, M.; Biringer, K.; Kudela, E.; Danko, J.; et al. Flavonoids in Cancer Metastasis. *Cancers* **2020**, *12*, 1498. [[CrossRef](#)]
17. Samec, M.; Liskova, A.; Koklesova, L.; Samuel, S.M.; Zhai, K.; Buhmann, C.; Varghese, E.; Abotaleb, M.; Qaradakh, T.; Zulli, A.; et al. Flavonoids against the Warburg phenotype-concepts of predictive, preventive and personalised medicine to cut the Gordian knot of cancer cell metabolism. *EPMA J.* **2020**, *11*, 377–398. [[CrossRef](#)] [[PubMed](#)]
18. Samec, M.; Liskova, A.; Koklesova, L.; Mersakova, S.; Strnadel, J.; Kajo, K.; Pec, M.; Zhai, K.; Smejkal, K.; Mirzaei, S.; et al. Flavonoids Targeting HIF-1: Implications on Cancer Metabolism. *Cancers* **2021**, *13*, 130. [[CrossRef](#)] [[PubMed](#)]
19. Brockmueller, A.; Sameri, S.; Liskova, A.; Zhai, K.; Varghese, E.; Samuel, S.M.; Büsselberg, D.; Kubatka, P.; Shakibaei, M. Resveratrol's Anti-Cancer Effects through the Modulation of Tumor Glucose Metabolism. *Cancers* **2021**, *13*, 188. [[CrossRef](#)]
20. Riveiro, M.E.; de Kimpe, N.; Moglioni, A.; Vazquez, R.; Monczor, F.; Shayo, C.; Davio, C. Coumarins: Old compounds with novel promising therapeutic perspectives. *Curr. Med. Chem.* **2010**, *17*, 1325–1338. [[CrossRef](#)] [[PubMed](#)]
21. Zhai, K.; Brockmuller, A.; Kubatka, P.; Shakibaei, M.; Busselberg, D. Curcumin's Beneficial Effects on Neuroblastoma: Mechanisms, Challenges, and Potential Solutions. *Biomolecules* **2020**, *10*, 1469. [[CrossRef](#)] [[PubMed](#)]
22. Agrawal, D.K.; Mishra, P.K. Curcumin and its analogues: Potential anticancer agents. *Med. Res. Rev.* **2010**, *30*, 818–860. [[CrossRef](#)]
23. Thoppil, R.J.; Bishayee, A. Terpenoids as potential chemopreventive and therapeutic agents in liver cancer. *World J. Hepatol.* **2011**, *3*, 228–249. [[CrossRef](#)] [[PubMed](#)]
24. Kuttan, G.; Pratheeshkumar, P.; Manu, K.A.; Kuttan, R. Inhibition of tumor progression by naturally occurring terpenoids. *Pharm. Biol.* **2011**, *49*, 995–1007. [[CrossRef](#)]
25. Lee, K.-H.; Xiao, Z. Lignans in treatment of cancer and other diseases. *Phytochem. Rev.* **2003**, *2*, 341–362. [[CrossRef](#)]
26. Rodriguez-Garcia, C.; Sanchez-Quesada, C.; Toledo, E.; Delgado-Rodriguez, M.; Gaforio, J.J. Naturally Lignan-Rich Foods: A Dietary Tool for Health Promotion? *Molecules* **2019**, *24*, 917. [[CrossRef](#)]
27. Gupta, A.; Kumar, B.S.; Negi, A.S. Current status on development of steroids as anticancer agents. *J. Steroid Biochem. Mol. Biol.* **2013**, *137*, 242–270. [[CrossRef](#)] [[PubMed](#)]
28. Cai, Y.; Zhang, J.; Chen, N.G.; Shi, Z.; Qiu, J.; He, C.; Chen, M. Recent Advances in Anticancer Activities and Drug Delivery Systems of Tannins. *Med. Res. Rev.* **2017**, *37*, 665–701. [[CrossRef](#)]
29. Maiti, P.; Plemmons, A.; Dunbar, G.L. Combination treatment of berberine and solid lipid curcumin particles increased cell death and inhibited PI3K/Akt/mTOR pathway of human cultured glioblastoma cells more effectively than did individual treatments. *PLoS ONE* **2019**, *14*, e0225660. [[CrossRef](#)]
30. Kim, H.Y.; Lee, B.I.; Jeon, J.H.; Kim, D.K.; Kang, S.G.; Shim, J.K.; Kim, S.Y.; Kang, S.W.; Jang, H. Gossypol Suppresses Growth of Temozolomide-Resistant Glioblastoma Tumor Spheres. *Biomolecules* **2019**, *9*, 595. [[CrossRef](#)]
31. Oppermann, H.; Faust, H.; Yamanishi, U.; Meixensberger, J.; Gaunitz, F. Carnosine inhibits glioblastoma growth independent from PI3K/Akt/mTOR signaling. *PLoS ONE* **2019**, *14*, e0218972. [[CrossRef](#)]
32. Hua, D.; Zhao, Q.; Yu, Y.; Yu, H.; Yu, L.; Zhou, X.; Wang, Q.; Sun, C.; Shi, C.; Luo, W.; et al. Eucalyptal A inhibits glioma by rectifying oncogenic splicing of MYO1B mRNA via suppressing SRSF1 expression. *Eur. J. Pharmacol.* **2020**, 173669. [[CrossRef](#)]
33. Chang, K.F.; Huang, X.F.; Chang, J.T.; Huang, Y.C.; Lo, W.S.; Hsiao, C.Y.; Tsai, N.M. Cedrol, a Sesquiterpene Alcohol, Enhances the Anticancer Efficacy of Temozolomide in Attenuating Drug Resistance via Regulation of the DNA Damage Response and MGMT Expression. *J. Nat. Prod.* **2020**, *83*, 3021–3029. [[CrossRef](#)] [[PubMed](#)]
34. Colapietro, A.; Mancini, A.; Vitale, F.; Martellucci, S.; Angelucci, A.; Llorens, S.; Mattei, V.; Gravina, G.L.; Alonso, G.L.; Festuccia, C. Crocetin Extracted from Saffron Shows Antitumor Effects in Models of Human Glioblastoma. *Int. J. Mol. Sci.* **2020**, *21*, 423. [[CrossRef](#)]
35. Tsuji, S.; Nakamura, S.; Maoka, T.; Yamada, T.; Imai, T.; Ohba, T.; Yako, T.; Hayashi, M.; Endo, K.; Saio, M.; et al. Antitumour Effects of Astaxanthin and Adonixanthin on Glioblastoma. *Mar. Drugs* **2020**, *18*, 474. [[CrossRef](#)] [[PubMed](#)]
36. Silva, A.G.; Silva, V.A.O.; Oliveira, R.J.S.; de Rezende, A.R.; Chagas, R.C.R.; Pimenta, L.P.S.; Romão, W.; Santos, H.B.; Thome, R.G.; Reis, R.M.; et al. Mattheucinol, isolated from *Miconia chamissois*, induces apoptosis in human glioblastoma lines via the intrinsic pathway and inhibits angiogenesis and tumor growth in vivo. *Investig. New Drugs* **2020**, *38*, 1044–1055. [[CrossRef](#)]
37. Aroui, S.; Fetoui, H.; Kenani, A. Natural dietary compound naringin inhibits glioblastoma cancer neoangiogenesis. *BMC Pharmacol. Toxicol.* **2020**, *21*, 46. [[CrossRef](#)] [[PubMed](#)]
38. Yuan, J.; Peng, G.; Xiao, G.; Yang, Z.; Huang, J.; Liu, Q.; Yang, Z.; Liu, D. Xanthohumol suppresses glioblastoma via modulation of Hexokinase 2-mediated glycolysis. *J. Cancer* **2020**, *11*, 4047–4058. [[CrossRef](#)]
39. Bona, N.P.; Pedra, N.S.; Azambuja, J.H.; Soares, M.S.P.; Spohr, L.; Gelsleichter, N.E.; de, M.M.B.; Sekine, F.G.; Mendonca, L.T.; de Oliveira, F.H.; et al. Tannic acid elicits selective antitumoral activity in vitro and inhibits cancer cell growth in a preclinical model of glioblastoma multiforme. *Metab. Brain Dis.* **2020**, *35*, 283–293. [[CrossRef](#)] [[PubMed](#)]
40. Tang, Q.; Ren, L.; Liu, J.; Li, W.; Zheng, X.; Wang, J.; Du, G. Withaferin A triggers G2/M arrest and intrinsic apoptosis in glioblastoma cells via ATF4-ATF3-CHOP axis. *Cell Prolif.* **2020**, *53*, e12706. [[CrossRef](#)]

41. Cao, J.; Zhao, E.; Zhu, Q.; Ji, J.; Wei, Z.; Xu, B.; Cui, H. Tubeimoside-1 Inhibits Glioblastoma Growth, Migration, and Invasion via Inducing Ubiquitylation of MET. *Cells* **2019**, *8*, 774. [[CrossRef](#)]
42. Martin, S.; Lamb, H.K.; Brady, C.; Lefkove, B.; Bonner, M.Y.; Thompson, P.; Lovat, P.E.; Arbiser, J.L.; Hawkins, A.R.; Redfern, C.P. Inducing apoptosis of cancer cells using small-molecule plant compounds that bind to GRP78. *Br. J. Cancer* **2013**, *109*, 433–443. [[CrossRef](#)]
43. Naumowicz, M.; Kusaczuk, M.; Zajac, M.; Gal, M.; Kotynska, J. Monitoring of the Surface Charge Density Changes of Human Glioblastoma Cell Membranes upon Cinnamic and Ferulic Acids Treatment. *Int. J. Mol. Sci.* **2020**, *21*, 6972. [[CrossRef](#)]
44. Izumi, C.; Laure, H.J.; Barbosa, N.G.; Thome, C.H.; Ferreira, G.A.; Sousa, J.P.B.; Lopes, N.P.; Rosa, J.C. Sequesterpene Lactones Isolated from a Brazilian Cerrado Plant (*Eremanthus* spp.) as Anti-Proliferative Compounds, Characterized by Functional and Proteomic Analysis, are Candidates for New Therapeutics in Glioblastoma. *Int. J. Mol. Sci.* **2020**, *21*, 4713. [[CrossRef](#)] [[PubMed](#)]
45. Qi, S.G.; Quan, L.Q.; Cui, X.Y.; Li, H.M.; Zhao, X.D.; Li, R.T. A natural compound obtained from *Valeriana jatamansi* selectively inhibits glioma stem cells. *Oncol. Lett.* **2020**, *19*, 1384–1392. [[CrossRef](#)]
46. Soares, J.M.; Faria, B.M.; Ascari, L.M.; Souza, J.M.; Soares, A.G.; Cordeiro, Y.; Romao, L.F. Diosmin induces caspase-dependent apoptosis in human glioblastoma cells. *An. Acad. Bras. Cienc.* **2019**, *91*, e20191031. [[CrossRef](#)] [[PubMed](#)]
47. Franco, Y.E.M.; Okubo, M.Y.; Torre, A.D.; Paiva, P.P.; Rosa, M.N.; Silva, V.A.O.; Reis, R.M.; Ruiz, A.L.T.G.; Imamura, P.M.; de Carvalho, J.E.; et al. Coronarin D Induces Apoptotic Cell Death and Cell Cycle Arrest in Human Glioblastoma Cell Line. *Molecules* **2019**, *24*, 4498. [[CrossRef](#)]
48. Bache, M.; Hein, A.; Petrenko, M.; Guttler, A.; Kessler, J.; Wichmann, H.; Kappler, M.; Emmerich, D.; Paschke, R.; Vordermark, D. Evaluation of the Betulinic Acid-Cisplatin conjugate APC and its precursor DE9B for the treatment of human malignant glioma. *Chem. Biol. Interact.* **2019**, *314*, 108841. [[CrossRef](#)] [[PubMed](#)]
49. Bonturi, C.R.; Silva, M.C.C.; Motaln, H.; Salu, B.R.; Ferreira, R.D.S.; Batista, F.P.; Correia, M.; Paiva, P.M.G.; Turnsek, T.L.; Oliva, M.L.V. A Bifunctional Molecule with Lectin and Protease Inhibitor Activities Isolated from *Crataeva tapia* Bark Significantly Affects Cocultures of Mesenchymal Stem Cells and Glioblastoma Cells. *Molecules* **2019**, *24*, 2109. [[CrossRef](#)] [[PubMed](#)]
50. Yeh, L.T.; Hsu, L.S.; Chung, Y.H.; Chen, C.J. Tectorigenin Inhibits Glioblastoma Proliferation by G0/G1 Cell Cycle Arrest. *Medicina* **2020**, *56*, 681. [[CrossRef](#)]
51. Onay Ucar, E.; Sengelen, A. Resveratrol and siRNA in combination reduces Hsp27 expression and induces caspase-3 activity in human glioblastoma cells. *Cell Stress Chaperones* **2019**, *24*, 763–775. [[CrossRef](#)]
52. Park, K.S.; Yoon, S.Y.; Park, S.H.; Hwang, J.H. Anti-Migration and Anti-Invasion Effects of Curcumin via Suppression of Fascin Expression in Glioblastoma Cells. *Brain Tumor Res. Treat.* **2019**, *7*, 16–24. [[CrossRef](#)] [[PubMed](#)]
53. Yu, G.; Wang, Z.; Zeng, S.; Liu, S.; Zhu, C.; Xu, R.; Liu, R.E. Paeoniflorin Inhibits Hepatocyte Growth Factor- (HGF-) Induced Migration and Invasion and Actin Rearrangement via Suppression of c-Met-Mediated RhoA/ROCK Signaling in Glioblastoma. *Biomed. Res. Int.* **2019**, *2019*, 9053295. [[CrossRef](#)]
54. Khathayer, F.; Ray, S.K. Diosgenin as a Novel Alternative Therapy for Inhibition of Growth, Invasion, and Angiogenesis Abilities of Different Glioblastoma Cell Lines. *Neurochem. Res.* **2020**, *45*, 2336–2351. [[CrossRef](#)] [[PubMed](#)]
55. Nowakowski, P.; Markiewicz-Żukowska, R.; Gromkowska-Kępką, K.; Naliwajko, S.K.; Moskwa, J.; Bielecka, J.; Grabia, M.; Borawska, M.; Socha, K. Mushrooms as potential therapeutic agents in the treatment of cancer: Evaluation of anti-glioma effects of *Coprinus comatus*, *Cantharellus cibarius*, *Lycoperdon perlatum* and *Lactarius deliciosus* extracts. *Biomed. Pharmacother.* **2021**, *133*. [[CrossRef](#)]
56. Czarnik-Kwasniak, J.; Kwasniak, K.; Kwasek, P.; Swierzowska, E.; Strojewska, A.; Tabarkiewicz, J. The Influence of Lycopene, [6]-Gingerol, and Silymarin on the Apoptosis on U-118MG Glioblastoma Cells In Vitro Model. *Nutrients* **2019**, *12*, 96. [[CrossRef](#)]
57. Moskwa, J.; Naliwajko, S.K.; Markiewicz-Zukowska, R.; Gromkowska-Kępką, K.J.; Nowakowski, P.; Strawa, J.W.; Borawska, M.H.; Tomczyk, M.; Socha, K. Chemical composition of Polish propolis and its antiproliferative effect in combination with *Bacopa monnieri* on glioblastoma cell lines. *Sci. Rep.* **2020**, *10*, 21127. [[CrossRef](#)] [[PubMed](#)]
58. Palma, T.V.; Lenz, L.S.; Bottari, N.B.; Pereira, A.; Schetinger, M.R.C.; Morsch, V.M.; Ulrich, H.; Pillat, M.M.; de Andrade, C.M. Berberine induces apoptosis in glioblastoma multiforme U87MG cells via oxidative stress and independent of AMPK activity. *Mol. Biol. Rep.* **2020**, *47*, 4393–4400. [[CrossRef](#)] [[PubMed](#)]
59. Wang, C.; Lin, D.; Chen, Q.; Lin, S.; Shi, S.; Chen, C. Polysaccharide peptide isolated from grass-cultured *Ganoderma lucidum* induces anti-proliferative and pro-apoptotic effects in the human U251 glioma cell line. *Oncol. Lett.* **2018**, *15*, 4330–4336. [[CrossRef](#)]
60. Ferreira, W.A.S.; Burbano, R.R.; Pessoa, C.D.O.; Harada, M.L.; Borges, B.D.N.; de Oliveira, E.H.C. Pisosterol Induces G2/M Cell Cycle Arrest and Apoptosis via the ATM/ATR Signaling Pathway in Human Glioma Cells. *Anticancer Agents Med. Chem.* **2020**, *20*, 734–750. [[CrossRef](#)]
61. Jiang, Y.; Liu, J.; Hong, W.; Fei, X.; Liu, R. Arctigenin Inhibits Glioblastoma Proliferation through the AKT/mTOR Pathway and Induces Autophagy. *Biomed. Res. Int.* **2020**, *2020*, 3542613. [[CrossRef](#)] [[PubMed](#)]
62. Zhai, K.; Liskova, A.; Kubatka, P.; Busselberg, D. Calcium Entry through TRPV1: A Potential Target for the Regulation of Proliferation and Apoptosis in Cancerous and Healthy Cells. *Int. J. Mol. Sci.* **2020**, *21*, 4177. [[CrossRef](#)] [[PubMed](#)]
63. Da Silva, A.B.; Coelho, P.L.C.; Oliveira, M.D.N.; Oliveira, J.L.; Amparo, J.A.O.; da Silva, K.C.; Soares, J.R.P.; Pitanga, B.P.S.; Souza, C.D.S.; de Faria Lopes, G.P.; et al. The flavonoid rutin and its aglycone quercetin modulate the microglia inflammatory profile improving anti-glioma activity. *Brain Behav. Immun.* **2020**, *85*, 170–185. [[CrossRef](#)]

64. Sumorek-Wiadro, J.; Zajac, A.; Langner, E.; Skalicka-Wozniak, K.; Maciejczyk, A.; Rzeski, W.; Jakubowicz-Gil, J. Antiglioma Potential of Coumarins Combined with Sorafenib. *Molecules* **2020**, *25*, 5192. [[CrossRef](#)] [[PubMed](#)]
65. Shahcheraghi, S.H.; Lotfi, M.; Soukhtanloo, M.; Ghayour Mobarhan, M.; Jaliani, H.Z.; Sadeghnia, H.R.; Ghorbani, A. Effects of Galbanic Acid on Proliferation, Migration, and Apoptosis of Glioblastoma Cells Through the PI3K/Akt/MTOR Signaling Pathway. *Curr. Mol. Pharmacol.* **2021**, *14*, 79–87. [[CrossRef](#)] [[PubMed](#)]
66. Zhang, S.; Lu, Y.; Li, H.; Ji, Y.; Fang, F.; Tang, H.; Qiu, P. A steroidal saponin from *Paris vietnamensis* (Takht.) reverses temozolomide resistance in glioblastoma cells via inducing apoptosis through ROS/PI3K/Akt pathway. *Biosci. Trends* **2020**, *14*, 123–133. [[CrossRef](#)]
67. Lee, J.E.; Lim, J.H.; Hong, Y.K.; Yang, S.H. High-Dose Metformin Plus Temozolomide Shows Increased Anti-tumor Effects in Glioblastoma In Vitro and In Vivo Compared with Monotherapy. *Cancer Res. Treat.* **2018**, *50*, 1331–1342. [[CrossRef](#)]
68. Lo Dico, A.; Valtorta, S.; Ottobrini, L.; Moresco, R.M. Role of Metformin and AKT Axis Modulation in the Reversion of Hypoxia Induced TMZ-Resistance in Glioma Cells. *Front. Oncol.* **2019**, *9*, 463. [[CrossRef](#)] [[PubMed](#)]
69. Bi, L.; Liu, Y.; Yang, Q.; Zhou, X.; Li, H.; Liu, Y.; Li, J.; Lu, Y.; Tang, H. Paris saponin H inhibits the proliferation of glioma cells through the A1 and A3 adenosine receptor-mediated pathway. *Int. J. Mol. Med.* **2021**, *47*. [[CrossRef](#)]
70. Chen, D.; Li, D.; Xu, X.B.; Qiu, S.; Luo, S.; Qiu, E.; Rong, Z.; Zhang, J.; Zheng, D. Galangin inhibits epithelial-mesenchymal transition and angiogenesis by downregulating CD44 in glioma. *J. Cancer* **2019**, *10*, 4499–4508. [[CrossRef](#)] [[PubMed](#)]
71. Cheng, Y.C.; Tsao, M.J.; Chiu, C.Y.; Kan, P.C.; Chen, Y. Magnolol Inhibits Human Glioblastoma Cell Migration by Regulating N-Cadherin. *J. Neuropathol. Exp. Neurol.* **2018**, *77*, 426–436. [[CrossRef](#)]
72. Yuan, B.; Shimada, R.; Xu, K.; Han, L.; Si, N.; Zhao, H.; Bian, B.; Hayashi, H.; Okazaki, M.; Takagi, N. Multiple cytotoxic effects of gamabufotalin against human glioblastoma cell line U-87. *Chem. Biol. Interact.* **2019**, *314*, 108849. [[CrossRef](#)]
73. Liberti, M.V.; Locasale, J.W. The Warburg Effect: How Does it Benefit Cancer Cells? *Trends Biochem. Sci.* **2016**, *41*, 211–218. [[CrossRef](#)] [[PubMed](#)]
74. Sarkaria, J.N.; Kitange, G.J.; James, C.D.; Plummer, R.; Calvert, H.; Weller, M.; Wick, W. Mechanisms of chemoresistance to alkylating agents in malignant glioma. *Clin. Cancer Res.* **2008**, *14*, 2900–2908. [[CrossRef](#)] [[PubMed](#)]
75. Liao, C.L.; Chen, C.M.; Chang, Y.Z.; Liu, G.Y.; Hung, H.C.; Hsieh, T.Y.; Lin, C.L. Pine (*Pinus morrisonicola* Hayata) needle extracts sensitize GBM8901 human glioblastoma cells to temozolomide by downregulating autophagy and O(6)-methylguanine-DNA methyltransferase expression. *J. Agric. Food Chem.* **2014**, *62*, 10458–10467. [[CrossRef](#)]
76. Sang, D.P.; Li, R.J.; Lan, Q. Quercetin sensitizes human glioblastoma cells to temozolomide in vitro via inhibition of Hsp27. *Acta Pharmacol. Sin.* **2014**, *35*, 832–838. [[CrossRef](#)] [[PubMed](#)]
77. Liu, C.S.; Zheng, Y.R.; Zhang, Y.F.; Long, X.Y. Research progress on berberine with a special focus on its oral bioavailability. *Fitoterapia* **2016**, *109*, 274–282. [[CrossRef](#)]
78. You, L.; Feng, S.; An, R.; Wang, X. Osthole: A Promising Lead Compound for Drug Discovery from a Traditional Chinese Medicine (TCM). *Nat. Prod. Commun.* **2009**, *4*. [[CrossRef](#)]
79. Rehman, S.U.; Kim, I.S.; Kang, K.S.; Yoo, H.H. HPLC Determination of Esculin and Esculetin in Rat Plasma for Pharmacokinetic Studies. *J. Chromatogr. Sci.* **2015**, *53*, 1322–1327. [[CrossRef](#)] [[PubMed](#)]
80. Thilakarathna, S.H.; Rupasinghe, H.P. Flavonoid bioavailability and attempts for bioavailability enhancement. *Nutrients* **2013**, *5*, 3367–3387. [[CrossRef](#)]
81. Fernández-García, E.; Carvajal-Lérída, I.; Jarén-Galán, M.; Garrido-Fernández, J.; Pérez-Gálvez, A.; Hornero-Méndez, D. Carotenoids bioavailability from foods: From plant pigments to efficient biological activities. *Food Res. Int.* **2012**, *46*, 438–450. [[CrossRef](#)]
82. Wang, X.; Wang, R.; Xing, D.; Su, H.; Ma, C.; Ding, Y.; Du, L. Kinetic difference of berberine between hippocampus and plasma in rat after intravenous administration of *Coptidis rhizoma* extract. *Life Sci.* **2005**, *77*, 3058–3067. [[CrossRef](#)] [[PubMed](#)]
83. Yang, Y.F.; Xu, W.; Song, W.; Ye, M.; Yang, X.W. Transport of Twelve Coumarins from *Angelicae Pubescentis Radix* across a MDCK-pHaMDR Cell Monolayer—An In Vitro Model for Blood-Brain Barrier Permeability. *Molecules* **2015**, *20*, 11719–11732. [[CrossRef](#)] [[PubMed](#)]
84. Widomska, J.; Zareba, M.; Subczynski, W.K. Can Xanthophyll-Membrane Interactions Explain Their Selective Presence in the Retina and Brain? *Foods* **2016**, *5*, 7. [[CrossRef](#)]
85. Youdim, K.A.; Qaiser, M.Z.; Begley, D.J.; Rice-Evans, C.A.; Abbott, N.J. Flavonoid permeability across an in situ model of the blood-brain barrier. *Free Radic. Biol. Med.* **2004**, *36*, 592–604. [[CrossRef](#)] [[PubMed](#)]
86. Li, J.; Li, X.; Ren, Y.S.; Lv, Y.Y.; Zhang, J.S.; Xu, X.L.; Wang, X.Z.; Yao, J.C.; Zhang, G.M.; Liu, Z. Elucidation of Arctigenin Pharmacokinetics and Tissue Distribution after Intravenous, Oral, Hypodermic and Sublingual Administration in Rats and Beagle Dogs: Integration of In Vitro and In Vivo Findings. *Front. Pharmacol.* **2017**, *8*, 376. [[CrossRef](#)] [[PubMed](#)]
87. Yang, X.; Nomoto, K.; Tohda, C. Diosgenin content is a novel criterion to assess memory enhancement effect of yam extracts. *J. Nat. Med.* **2021**, *75*, 207–216. [[CrossRef](#)] [[PubMed](#)]
88. Yu, J.B.; Zhao, Z.X.; Peng, R.; Pan, L.B.; Fu, J.; Ma, S.R.; Han, P.; Cong, L.; Zhang, Z.W.; Sun, L.X.; et al. Gut Microbiota-Based Pharmacokinetics and the Antidepressant Mechanism of Paeoniflorin. *Front. Pharmacol.* **2019**, *10*, 268. [[CrossRef](#)]
89. Zhang, H.; van Os, W.L.; Tian, X.; Zu, G.; Ribovski, L.; Bron, R.; Bussmann, J.; Kros, A.; Liu, Y.; Zuhorn, I.S. Development of curcumin-loaded zein nanoparticles for transport across the blood-brain barrier and inhibition of glioblastoma cell growth. *Biomater. Sci.* **2021**. [[CrossRef](#)]

90. Ghosh, S.; Dungdung, S.R.; Chowdhury, S.T.; Mandal, A.K.; Sarkar, S.; Ghosh, D.; Das, N. Encapsulation of the flavonoid quercetin with an arsenic chelator into nanocapsules enables the simultaneous delivery of hydrophobic and hydrophilic drugs with a synergistic effect against chronic arsenic accumulation and oxidative stress. *Free Radic. Biol. Med.* **2011**, *51*, 1893–1902. [[CrossRef](#)]
91. Kong, L.; Li, X.T.; Ni, Y.N.; Xiao, H.H.; Yao, Y.J.; Wang, Y.Y.; Ju, R.J.; Li, H.Y.; Liu, J.J.; Fu, M.; et al. Transferrin-Modified Osthole PEGylated Liposomes Travel the Blood-Brain Barrier and Mitigate Alzheimer's Disease-Related Pathology in APP/PS-1 Mice. *Int. J. Nanomed.* **2020**, *15*, 2841–2858. [[CrossRef](#)]
92. Ahmadi, Z.; Mohammadinejad, R.; Ashrafzadeh, M. Drug delivery systems for resveratrol, a non-flavonoid polyphenol: Emerging evidence in last decades. *J. Drug Deliv. Sci. Technol.* **2019**, *51*, 591–604. [[CrossRef](#)]
93. Singh, A.; Kim, W.; Kim, Y.; Jeong, K.; Kang, C.S.; Kim, Y.; Koh, J.; Mahajan, S.D.; Prasad, P.N.; Kim, S. Multifunctional Photonic Nanoparticles for Crossing the Blood-Brain Barrier and Effecting Optically Trackable Brain Theranostics. *Adv. Funct. Mater.* **2016**, *26*, 7057–7066. [[CrossRef](#)]
94. Jia, Y.; Wang, X.; Hu, D.; Wang, P.; Liu, Q.; Zhang, X.; Jiang, J.; Liu, X.; Sheng, Z.; Liu, B.; et al. Phototheranostics: Active Targeting of Orthotopic Glioma Using Biomimetic Proteolipid Nanoparticles. *ACS Nano* **2019**, *13*, 386–398. [[CrossRef](#)]
95. Tang, W.; Fan, W.; Lau, J.; Deng, L.; Shen, Z.; Chen, X. Emerging blood-brain-barrier-crossing nanotechnology for brain cancer theranostics. *Chem. Soc. Rev.* **2019**, *48*, 2967–3014. [[CrossRef](#)] [[PubMed](#)]
96. Hu, J.; La Vecchia, C.; Negri, E.; Chatenoud, L.; Bosetti, C.; Jia, X.; Liu, R.; Huang, G.; Bi, D.; Wang, C. Diet and brain cancer in adults: A case-control study in Northeast China. *Int. J. Cancer* **1999**, *81*, 20–23. [[CrossRef](#)]
97. Hu, J.; Johnson, K.C.; Mao, Y.; Guo, L.; Zhao, X.; Jia, X.; Bi, D.; Huang, G.; Liu, R. Risk factors for glioma in adults: A case-control study in northeast China. *Cancer Detect. Prev.* **1998**, *22*, 100–108. [[CrossRef](#)]
98. Zhou, W.; Mukherjee, P.; Kiebish, M.A.; Markis, W.T.; Mantis, J.G.; Seyfried, T.N. The calorically restricted ketogenic diet, an effective alternative therapy for malignant brain cancer. *Nutr. Metab.* **2007**, *4*, 5. [[CrossRef](#)]
99. Artzi, M.; Liberman, G.; Vaisman, N.; Bokstein, F.; Vitinshtein, F.; Aizenstein, O.; Ben Bashat, D. Changes in cerebral metabolism during ketogenic diet in patients with primary brain tumors: (1)H-MRS study. *J. Neurooncol.* **2017**, *132*, 267–275. [[CrossRef](#)] [[PubMed](#)]
100. Danwilai, K.; Konmun, J.; Sripanidkulchai, B.; Subongkot, S. Antioxidant activity of ginger extract as a daily supplement in cancer patients receiving adjuvant chemotherapy: A pilot study. *Cancer Manag. Res.* **2017**, *9*, 11–18. [[CrossRef](#)]
101. D'Addato, S.; Scandiani, L.; Mombelli, G.; Focanti, F.; Pelacchi, F.; Salvatori, E.; di Loreto, G.; Comandini, A.; Maffioli, P.; Derosa, G. Effect of a food supplement containing berberine, monacolin K, hydroxytyrosol and coenzyme Q10 on lipid levels: A randomized, double-blind, placebo controlled study. *Drug Des. Dev. Ther.* **2017**, *11*, 1585–1592. [[CrossRef](#)]
102. Bumrungpert, A.; Lilitchan, S.; Tuntipopipat, S.; Tirawanchai, N.; Komindr, S. Ferulic Acid Supplementation Improves Lipid Profiles, Oxidative Stress, and Inflammatory Status in Hyperlipidemic Subjects: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Nutrients* **2018**, *10*, 713. [[CrossRef](#)]
103. Zanotta, D.; Puricelli, S.; Bonoldi, G. Cognitive effects of a dietary supplement made from extract of *Bacopa monnieri*, astaxanthin, phosphatidylserine, and vitamin E in subjects with mild cognitive impairment: A noncomparative, exploratory clinical study. *Neuropsychiatr. Dis. Treat.* **2014**, *10*, 225–230. [[CrossRef](#)]
104. Hitoe, S.; Shimoda, H. Seaweed Fucoxanthin Supplementation Improves Obesity Parameters in Mild Obese Japanese Subjects. *Funct. Foods Health Dis.* **2017**, *7*. [[CrossRef](#)]
105. Ilic, D.; Forbes, K.M.; Hammad, C. Lycopene for the prevention of prostate cancer. *Cochrane Database Syst. Rev.* **2011**, CD008007. [[CrossRef](#)] [[PubMed](#)]
106. DiSilvestro, R.A.; Joseph, E.; Zhao, S.; Bomser, J. Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people. *Nutr. J.* **2012**, *11*, 79. [[CrossRef](#)]
107. Tabira, T.; Kawamura, N. A Study of a Supplement Containing Huperzine A and Curcumin in Dementia Patients and Individuals with Mild Cognitive Impairment. *J. Alzheimers Dis.* **2018**, *63*, 75–78. [[CrossRef](#)] [[PubMed](#)]
108. Duranti, G.; Ceci, R.; Patrizio, F.; Sgro, P.; di Luigi, L.; Sabatini, S.; Felici, F.; Bazzucchi, I. Chronic consumption of quercetin reduces erythrocytes oxidative damage: Evaluation at resting and after eccentric exercise in humans. *Nutr. Res.* **2018**, *50*, 73–81. [[CrossRef](#)] [[PubMed](#)]
109. Batista-Jorge, G.C.; Barcala-Jorge, A.S.; Silveira, M.F.; Lelis, D.F.; Andrade, J.M.O.; de Paula, A.M.B.; Guimaraes, A.L.S.; Santos, S.H.S. Oral resveratrol supplementation improves Metabolic Syndrome features in obese patients submitted to a lifestyle-changing program. *Life Sci.* **2020**, *256*, 117962. [[CrossRef](#)]
110. Hoseini, A.; Namazi, G.; Farrokhian, A.; Reiner, Z.; Aghadavod, E.; Bahmani, F.; Asemi, Z. The effects of resveratrol on metabolic status in patients with type 2 diabetes mellitus and coronary heart disease. *Food Funct.* **2019**, *10*, 6042–6051. [[CrossRef](#)]
111. Kumar, R.M.; van Gompel, J.J.; Bower, R.; Rabinstein, A.A. Spontaneous intraventricular hemorrhage associated with prolonged diosmin therapy. *Neurocrit. Care* **2011**, *14*, 438–440. [[CrossRef](#)]
112. Nouri, K.; Walch, K.; Weghofer, A.; Imhof, M.; Egarter, C.; Ott, J. The Impact of a Standardized Oral Multinutrient Supplementation on Embryo Quality in in vitro Fertilization/Intracytoplasmic Sperm Injection: A Prospective Randomized Trial. *Gynecol. Obstet. Investig.* **2017**, *82*, 8–14. [[CrossRef](#)]
113. Sharma, S.; Ali, A.; Ali, J.; Sahni, J.K.; Baboota, S. Rutin: Therapeutic potential and recent advances in drug delivery. *Expert Opin. Investig. Drugs* **2013**, *22*, 1063–1079. [[CrossRef](#)] [[PubMed](#)]

114. Harwood, M.; Danielewska-Nikiel, B.; Borzelleca, J.F.; Flamm, G.W.; Williams, G.M.; Lines, T.C. A critical review of the data related to the safety of quercetin and lack of evidence of in vivo toxicity, including lack of genotoxic/carcinogenic properties. *Food Chem. Toxicol.* **2007**, *45*, 2179–2205. [[CrossRef](#)]
115. Brendler, T.; Williamson, E.M. Astaxanthin: How much is too much? A safety review. *Phytother. Res.* **2019**, *33*, 3090–3111. [[CrossRef](#)] [[PubMed](#)]
116. Hashemi, M.; Hosseinzadeh, H. A comprehensive review on biological activities and toxicology of crocetin. *Food Chem. Toxicol.* **2019**, *130*, 44–60. [[CrossRef](#)] [[PubMed](#)]
117. Sharma, K.; Kumar, V.; Kaur, J.; Tanwar, B.; Goyal, A.; Sharma, R.; Gat, Y.; Kumar, A. Health effects, sources, utilization and safety of tannins: A critical review. *Toxin Rev.* **2019**, 1–13. [[CrossRef](#)]
118. Li, X.; Choi, J.S. Effects of quercetin on the pharmacokinetics of Etoposide after oral or intravenous administration of etoposide in rats. *Anticancer Res.* **2009**, *29*, 1411–1415.
119. Samuel, T.; Fadlalla, K.; Mosley, L.; Katkoori, V.; Turner, T.; Manne, U. Dual-mode Interaction Between Quercetin and DNA-damaging Drugs in Cancer Cells. *Anticancer Res.* **2012**, *32*, 61–71. [[PubMed](#)]
120. Pal, D.; Mitra, A.K. MDR- and CYP3A4-mediated drug-herbal interactions. *Life Sci.* **2006**, *78*, 2131–2145. [[CrossRef](#)]
121. Mitsunaga, Y.; Takanaga, H.; Matsuo, H.; Naito, M.; Tsuruo, T.; Ohtani, H.; Sawada, Y. Effect of bioflavonoids on vincristine transport across blood–brain barrier. *Eur. J. Pharmacol.* **2000**, *395*, 193–201. [[CrossRef](#)]
122. Yardim, A.; Kandemir, F.M.; Ozdemir, S.; Kucukler, S.; Comakli, S.; Gur, C.; Celik, H. Quercetin provides protection against the peripheral nerve damage caused by vincristine in rats by suppressing caspase 3, NF-kappaB, ATF-6 pathways and activating Nrf2, Akt pathways. *Neurotoxicology* **2020**, *81*, 137–146. [[CrossRef](#)]
123. Tripathi, D.N.; Jena, G.B. Intervention of astaxanthin against cyclophosphamide-induced oxidative stress and DNA damage: A study in mice. *Chem. Biol. Interact.* **2009**, *180*, 398–406. [[CrossRef](#)] [[PubMed](#)]