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Research Article

Natural bioactive compounds: An alternate strategy for *Glioblastoma multiforme* diagnosis and therapy

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Abstract
Over 10,000 cases of *Glioblastoma multiforme* are reported in the United States annually, making it one of the most dangerous malignant tumours. Numerous clinical evaluations and investigations demonstrate the interaction between pathogenesis and the increase of cell-reactive radicals in certain chronic diseases, such as cancer. Exogenous sources (xenobiotic interaction) and endogenous sources (physiological activities) are the two categories of sources of reactive nitrogen and reactive oxygen. When antioxidant regulatory mechanisms are circumvented, cellular oxidation/reduction transforms into oxidative stress, increasing the danger of cellular lipid, protein, and nucleic acid damage. Bioactive chemicals and their derivatives are used to treat *Glioblastoma multiforme*. As nanomedicine formulations for enhanced cancer theranostics relative to conventional approaches, these can be utilised independently, in conjunction with anticancer treatments, or all three. The paramount importance of phytochemicals in this context is the main topic of this review. In conclusion, the anti-inflammatory, anti-cancer, and antioxidant properties of bioactive molecules included in fruits, vegetables, and seeds may improve post-chemotherapy or post-treatment symptoms for cancer survivors. However, this could be a viable therapeutic approach for this tumour type if they are included in the drug delivery system based on nanocarriers for the treatment of GBMs. This target-specificity reduces off-target organ aggregation and improves medication internalisation into cells. Along with higher bioavailability and lower adverse effects, targeting effectiveness is also increased.

Keywords
Bioactive compounds, *Glioblastoma multiforme*, therapy..

Introduction

Glioblastoma multiforme (GBM) represents approximately 50% of the central nervous system's primary malignant tumours, making it one of the most common and dangerous brain tumours[1]. GBM is characterised by multinucleated, anaplastic, spherical, or pleomorphic cells that show poor cellular differentiation. GBM is classified into two groups: primary GBM, which arises from glial cells, and secondary GBM, which arises from a developed lower-grade astrocytoma.If treatment is not received, GBM is an extremely dangerous kind of brain cancer that has a six-month or less death rate[2]. Because this can have a major impact on overall survival, seeking specialised neurosurgical and neuro-oncological care at the earliest opportunity is crucial. Even with the development of cutting-edge targeted therapy and the immunotherapy procedure, the median survival rate following a diagnosis of GBM is reported to be between 12.5 and 18 months, with a 5-year survival rate of about 4-7%. The standard treatment for GBM consists of surgery followed by adjuvant chemoradiation therapy (CRT) using the DNA-alkylating chemical temozolomide (TMZ)[3].

Survival overall has increased, but progression-free survival (PFS) has decreased with

bevacizumab added to the usual treatment. Regarding the combination's cost-effectiveness as a first-line treatment, this conclusion has generated a great deal of discussion[5]. It has been discovered that, The MGMT (O6-methylguanine-DNA methyltransferase) promoter's methylation in newly diagnosed GBM predicts the patient's reaction to alkylating chemotherapy. Based on this information, selecting the best single-modal treatment for the frail elderly population may be highly dependent on this methylation status[4,6.] All of these therapies do, however, have their limitations. The most recent global cancer burden database, called "GLOBOCAN 2020," was just made public by International Agency for Cancer Research (IARC). 251,329 cancer-related fatalities (2.5%) and 308,102 new cases (1.6%) were reported by the IARC for 2020.Males are diagnosed with GBM 1.6 times more frequently than females, and the median age upon diagnosis is in the mid-60s. Cancer-initiating cells (CIS) and cancer stem cells (CSCs) are subsets of cells that are thought to be important for the development, maintenance, growth, response to treatment, recurrence, and multiplication of cancer cells[7]. The limitations in the treatment of Glioblastoma, however, stem from two main causes[13]. Initially, the many factors in *Glioblastoma* pathology reduce the efficacy of contemporary chemotherapy, rendering it less comfortable than the conventional kind. Medication delivery to the cancer site is frequently impeded by the blood-brain barrier (BBB), which can result in recurrence without full recovery8. Secondly, conventional chemotherapy for GBM is associated with side effects such as myelosuppression and cerebral edema and has limited efficacy. TMZ, in particular, has shown limited progress in extending longevity. Combined with radiation therapy and tumour removal, it only provided a two-month survival boost. Additionally, chemo-resistance contributes to low survival rates when patients experience recurring tumours. The development of refractory tumours, BBB impermeability, CRT tolerance, and systemic toxicity from larger doses of TMZ are some of the probable causes of this low survival rates[9].

To manage different forms of cancers, including brain tumours and gliomas, it is therefore imperative that novel approaches, such as the discovery of bioactive molecules, be developed[10]. Targeting vascular endothelial growth factor (VEGF), bevacizumab prevents the formation of new blood vessels in tumours, reducing their blood supply and delaying their growth. Treatment of various tumours has been demonstrated to benefit greatly from it. To maximise its efficiency, bevacizumab is frequently used with other chemotherapeutic medications. The capacity of this drug to shrink tumours makes it easier to remove them via radiation or surgery. This is one of its main advantages. Bevacizumab has significantly improved the overall prognosis of patients with specific cancer types[99]. These molecules can work as minimally- or non-toxic agents. These molecules possess the blood-brain barrier modulation capacity, hinder the formation of tumours, and hinder the recurrence of tumours, thereby enhancing the prognosis of overall patients. Analysing these bioactive substances' efficacy and in human subjects in particular, bioavailability is currently a topic of great interest. Developing nanocarriers has improved the targeted transport of bioactive materials into the brain, overcoming the restrictions imposed by the blood-brain barrier[11]. In the context of diagnosing and managing brain tumours, numerous polymeric nanoparticles that can penetrate the brain are commonly employed, with nanoparticles loaded with drugs or natural bioactive molecules exhibiting improved drug distribution to the brain. In particular, *Glioblastoma multiforme* (GBM) cancer stem cell growth inhibition with the use of phytoconstituent-loaded nanoparticles and other brain tumours may prove to be an effective strategy that combines the benefits of nanotechnologies with the use of bioactive materials that may not be toxic[12]. The application of phytochemical-loaded nanoparticles to combat GBM is highly unlikely, similar to treating GBM and glioma tumours using bioactive chemicals. Additionally, the strategies used so far to target the pool of GBM cancer stem cells directly with nanoparticles are also unlikely.

Targeting the growth of *Glioblastoma* can be achieved by focusing on cancer stem cells (CSCs). Stem cells are able to differentiate into many types of cells in the body and this distinct

characteristic is derived from their capacity to adapt and specialise[92]. The two main categories of stem cells that have received the most attention in the field of study are embryonic somatic neonatal stem cells and non-embryonic stem cells. Because stem cells live longer than other types of cells, there is a higher chance that they will acquire genetic mutations. In addition, stem cells have the capacity to self-renew and differentiate, as well as to migrate and have anticancer effects[14]. They can also be a good way to administer anticancer medicines to high-grade metastatic gliomas because they don't trigger an immune response. Stem cells can be classified into four types: Defective type CSCs, induced or programmed pluripotent stem cells (iPSCs), adult stem cells (ASCs), and embryonic stem cells (ESCs).Tumour recurrence is associated with several factors, including insufficient tumour margin for total excision, a high cell proliferation index, resistance to radiation and chemotherapy (especially in CSCs), and CSF fluid spreading[15,16]. The typical estimate for CSCs in the UK is between three and five percent. CSCs are usually dormant, but when they are activated by radiation, chemotherapy, or surgery, their number grows dramatically[93]. Patients typically die from tumour recurrence as a result of the fast expansion of CSCs. To increase the survival rate of Glioblastoma patients, targeting these stem cells as a therapeutic method shows significant potential. Neurospheres, particularly neural stem cells (NSCs), are widely employed in scientific studies[94]. These neurospheres consist of nerve cells stimulated by mitogens such as Non-conforming species proliferation can be promoted at lower cell densities by fibroblast growth component and epidermal growth factor (EPF)[17].

Cancer stem cells' (CSCs') capacity to undergo renewal results in the formation of a significant population of cells. Additionally, it gives rise to a quiescent stem cell and a committed progenitor[18]. Associated signalling pathways such as Polycomb (EZH2 and BMI-1) and Wnt, Notch, and Sonic Hedgehog are used to determine the regulation of self-renewal. Cell longevity is influenced by telomerase and resistance to certain growth-inhibiting medications is mediated through ATP-binding cassette (ABC) transporters[95]. These transporters also express cell surface receptors that have been linked to stem cells, such as CD133, CXCR4, LIF-R, c-met, and c-kit. p16INK4a, p53, and p19ARF are examples of tumour suppressors that inhibit the ability of cancer cells to proliferate and stem cells to regenerate themselves[19].Therefore, it can be inferred that CSCs and normal cells share common molecular factors that govern their essential roles, as evidenced by their similarity in sequence. Cancer cells and stem cells both use an array of signals. Both normal and natural stem cells possess unique characteristics, such as extensive self-regeneration and various differentiating abilities. Embryonic stem cells (ESCs), in particular, exhibit unlimited replicative potential due to the expression of telomerase[20].

CSC isolation can also be performed by identifying cell-surface markers that are indicative of stem cells21. Putative CSCs are identified in most tumours using the CD133 marker; carcinomas of the breasts, prostate, and neck are identified using CD44. Natural hematopoietic progenitor stem cells have been reported to be labelled by CD133 (prominin-1) in various organs. Five approaches, including Glioblastoma (GB)-specific ones, are available to target CSCs[96]. To help people suffering from this deadly illness, however, creative approaches are required to overcome resistance[22]. Significant interest has been shown in developing innovative drug delivery systems (DDSs) for treating GBM and diffuse brain tumours[98]. In comparison to conventional DDSs, SC-based DDSs have advantages such as lower immunogenicity and neurotoxicity, longer drug half-lives, sustained drug release, and improved drug delivery potency. Because of the substances they produce or because of the physical interactions they have with cancer cells, stem cells have antineoplastic qualities. Various modifications or payloads can enhance the anticancer effects of stem cells against GB. The tumour microenvironment has been recognized as a key determinant of aberrant tissue behaviour and plays a crucial role in malignant progression[23].The immune system, which includes natural killer cells, tumour-associated macrophages, T and B lymphocytes, pericytes, adipocytes, and mesenchymal stromal cells, as well as the extracellular matrix are the

components of the tumour microenvironment[97].

Therefore, the tumour microenvironment will consist of several elements in addition to tumour cells, the target of stem cell-based therapy. There are several ways to increase stem cell therapy's anticancer effectiveness[24]. One example of this is shown in **Figure 1**, where stem cells are administered intravenously and follow chemotactic gradients to the tumour location. In this procedure, nontoxic prodrugs are converted into cytotoxic drugs by an enzyme secreted by modified stem cells. As a result of the bystander effect, brain tumour cells experience apoptosis[25]. Oncolytic viruses (OVs) can also proliferate, lyse, or trigger immune system recognition in tumour cells, regardless of whether they are genetically engineered or naturally occurring. But the main issues that need to be discussed are the uneven distribution of OVs within a tumour, the restricted ability of malignant cells to spread, and the host's immune system's ability to quickly inactivate them. OVs can be delivered to tumour sites without triggering an immunological response from the host by using stem cells' tumour tropism. This will reduce these concerns. Animal models of gliomas have a higher survival rate when OVs are delivered to tumours using platforms such as neural and mesenchymal stem cells[26]. Additionally, nanoparticle-based drug delivery systems (DDSs) exhibit several drawbacks that require resolution. These are examples of low tissue distribution, fluctuation in the blood, low oral bioavailability, and possible toxicity. By employing stem cells as carriers for DDSs based on nanoparticles, several of these drawbacks can be minimised. Researchers aimed to show the feasibility of employing mesenchymal stem cells (MSCs) as carriers for administering nanoparticles to brain tumours in a study that concentrated on these cells[27].

Lipid nanocapsules (LNCs) and poly-lactic acid nanoparticles (PLA-NPs) are two types of coumarin-6-loaded nanoparticles studied in this study. The results show that these nanoparticles can serve the intended goal well. In a different work, co-assembling Paclitaxel (PTX), poly(-lactic-co-glycolic acid), and poly(-glutamic acid-co-distearyl-glutamate) resulted in the production of superparamagnetic iron oxide nanoparticles[28]. Adipose-derived stem cells (ADSCs) were used in this technique to deliver targeted nanotherapeutic payloads for thermo/chemotherapy to brain tumours. In their findings, they proposed an alternative approach

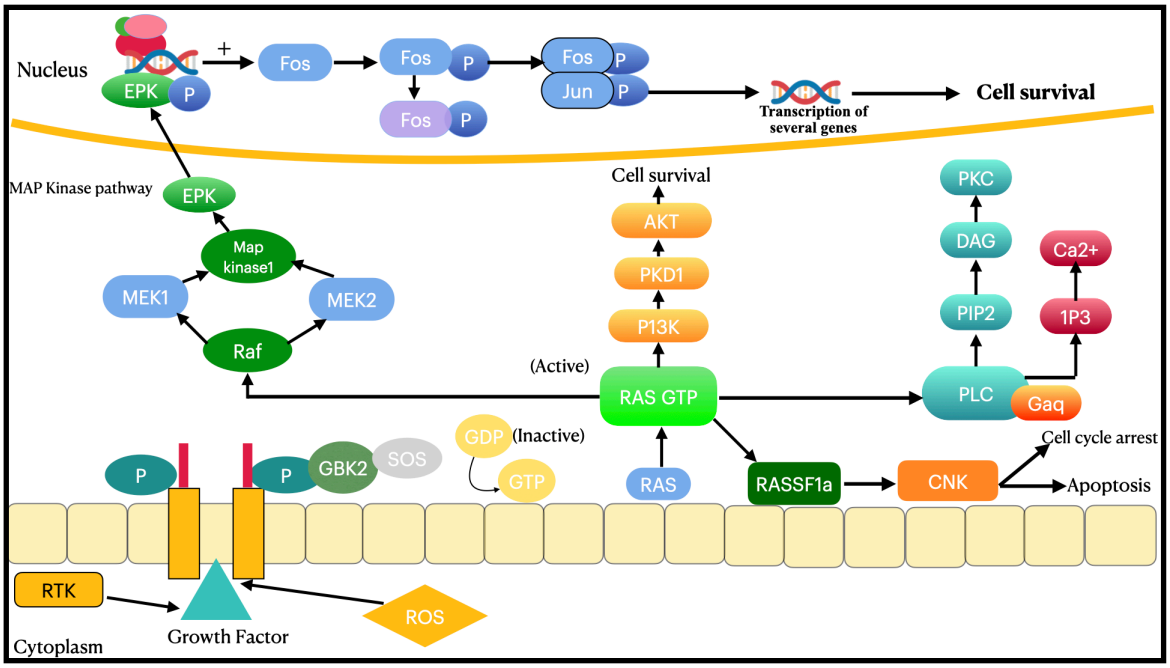

Figure 1. Various RAS signal pathways which regulates cell survival, calcium signalling and cell apoptosis

to immunotherapies[27,28]. According to their findings, PD-1 identifies regulatory T cells from malignant Glioma as exhausted, dysfunctional Tregs that release IFN-γ; higher PD-1 expression on human Tregs suggests something similar. These cells can be found in healthy individuals and are enriched in tumour infiltrates; they may become dysfunctional in their attempts to control the immune responses against tumours. Even with all of these developments, several issues still need to be resolved. Demographic factors, such as the possibility of particular types of stem cells developing into cancer and *in vivo* viability and survival, attenuating the antitumor immune response of stem cells, and choosing an appropriate therapeutic transgene are a few of these[29]. *Glioblastoma multiforme* (GBM) is a highly aggressive brain tumour characterised by poor cellular differentiation and a high mortality rate, even with advanced treatments[28]. Standard treatment includes surgery followed by chemo-radiation with temozolomide, although this has limited efficacy due to factors such as the blood-brain barrier and chemo-resistance. Bevacizumab, targeting VEGF, shows promise in improving prognosis when combined with other treatments[26]. Novel approaches, including bioactive molecules and nanocarrier technologies, are under investigation to enhance treatment efficacy by overcoming delivery barriers and targeting cancer stem cells[25]. Stem cell-based therapies offer potential for improving survival rates by delivering anticancer agents directly to tumours and leveraging their ability to home to cancer sites. However, challenges remain in optimizing these therapies for clinical use.

Oxidative stress (OS) and reactive oxygen species (ROS) distinguish reactive metabolites from free radicals and explain how defense mechanisms like antioxidants or organisms associated with reactive oxygen species get rid of them[30]. This disparity may impact the entire organism, which seriously damages cells and biomolecules. Residual oxygen species (ROS) are widely distributed and play a crucial role in starting signalling pathways in both plants and animals during harsh weather events that occur both within and outside of cells[31]. They have garnered attention as novel signal mediators involved in cell formation, differentiation, development, and death because of a variety of extracellular and intracellular functions. Aerobic cells generate reactive oxygen species (ROS) such as superoxide anion (O2−), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH•) as a result of the biological molecular reduction of oxygen in endogenous metabolic activities. The respiratory mitochondrial chain in cells is primarily responsible for producing ROS. As a result, reactive nitrogen species (RNS) may produce more peroxide, which can produce nitric oxide (NO)[30]. Reactive oxides like malondialdehyde and 4-hydroxynonenal aldehyde may also be produced. Important targets for oxidative damage are proteins and lipids, which can alter these molecules and increase the risk of mutagenesis. ROS can cause serious damage to cell structure and functions, somatic mutations, and neoplastic transformation since it is created over an extended period by continual environmental stress[32].

The initial development and progression of cancer have been related to DNA mutations that increase or cause DNA damage, genomic instability, and oxidative stress-induced cell proliferation. Strong functions can be performed and somatic alterations and transformations can occur when ROS is produced over an extended period of time under persistent environmental stress[33]. Carcinogenesis and its advancement have been associated with the emergence of genetic defects or damage to DNA, instability of the genome, and the proliferation of cells under oxidative stress. The intricate structure of anti-oxidative enzymes protects the body from these dangerous pro-oxidants. Any additional free radicals will undoubtedly result in oxidative strain, which will induce disease and tissue damage, given the pro- and anti-free-radical (antioxidant) balance. Furthermore, it is known that certain cytochrome 450 enzymes are produced by ROS. The biological functions of ROS and their potential role in the development of cancer and other diseases have been researched for many years[34]. There are intricate relationships between ROS, damage, signaling, and carcinogenesis. Regulatory tracks demonstrate the regulation of ROS in cells as well as a wide variety of signalling pathways caused by oxidative stress. Breaks and links in single- or double-stranded DNA may arise from

direct ROS production. It's important to keep in mind that the early development and proliferation of malignant cells require cells with higher ROS levels than normal cells[35].

Tumour radiation tolerance is typically associated with low ROS levels and strong ROS molecular expression. Moreover, the development of leukaemia from normal blood stem cells has been connected to the unchecked accumulation of ROS. According to the molecular characteristics of CSCs, this minority of cells could continue to produce stem cells and be able to create cancer at an acceptable level of cellular ROS. The highly developed antioxidant systems will also benefit the CSCs, enabling them to withstand medication and live longer[33,36]. The biological material that is crucial to the etiopathogenesis of various ailments, is destroyed due to a multitude of physiological and natural processes and the excessive production of free radicals. Therefore, it's unclear if pathological pathology develops as a result of unchecked ROS generation or as a cause of it[37]. Although free radicals (ROS) are species that largely cause DNA damage, their critical significance in many circumstances is debated, even though their involvement in the carcinogenesis mechanism is evident. The complex link between ROS levels and cancer depends on how well ROS processing and scavenging are tuned. ROS levels changed little, which helped cancer start and spread. Because of their improved antioxidant systems, cancer cells can therefore withstand slightly higher ROS levels than those found in their natural counterparts[38]. This characteristic enhances the production of ROS by making cancer cells more sensitive to external stimuli.

Response in the signalling pathway

Response in the signalling pathway mediated by ROS can enhance the signalling pathways mediated by platelet-derived growth factor (PDGF) and ROS EGF. These pathways are characterised by the stimulation of receptor tyrosine kinase activity, which leads to autophosphorylation [39]. AKT and PI3K-MAPK cascades of mitogen-activated protein kinase signalling are two downstream pathways that are triggered by this autophosphorylation. MAPK phosphatases inhibit a type of protein kinase called MAPK, which is involved in phosphorylation reactions that transfer external signal interacts with the nucleus via a cell membrane[40]. Thus, it is essential to comprehend how individuals react to oxidative stress from a biological and clinical standpoint. When oxygen radicals are present in excess, intracellular signals that prevent oxidative stress serve vital purposes. The Threonine/Serine kinases belonging to the MAPK family are involved in several physiological functions such as programmed cell death, energy metabolism, and genetic regulation[41]. The idea that disruption of the kinase cascade could potentially cause cancerous cells to change highlights the roles that MAPK pathways play in both cell division and apoptosis. Numerous signalling pathways, including MAPK cascades, have been demonstrated to be activated by oxidants.

MAPK p38, signals-regulated extracellular kinase (ERK) and extracellular signal-controlled c-Jun N-kinase (JNK) are three functionally similar MAPKs. The activation of JNK and p38 MAPK by inflammatory cytokines covers all the important pathways involved in cell survival, as seen in **Figure 1**[40,42]. The capacity to regenerate cells and sustain a lifetime blood supply is possessed by hematopoietic stem cells (HSCs). Hematopoietic maintenance depends on proper self-renewal control of HSCs, and researchers show that the lifespan of HSCs *in vivo* is limited by p38 MAPK activation in response to elevated reactive oxygen levels[43]. ROS increase results in silent maintenance defects and HSC-specific p38 MAPK phosphorylation. The stem cell population benefits from the ROS-p38 MAPK pathway as demonstrated by the restoration of ROS-induced deficiencies in the repopulating capacity of HSCs upon suppression of p38 MAPK. In addition, the prolonged administration of antioxidants or P38 MAPK inhibitors to HSCs derived from wild-type mice using sequential implantation techniques was prolonged. These data suggest that HSCs are shielded from the loss of self-renewal by p38 MAPK inactivation [44]. A recent finding indicates that epithelial cells in modern mammals may generate CSCs after the activation of Ras-MAPK-Path. The molecular processes limiting HSC lifespan may also provide guidance for effective human illness treatments.

Bioactive compounds and their mechanisms of action

The processes responsible for the development of these stem and tumorigenic identities include the epithelial-to-mesenchymal transition (EMT) activation. Bone marrow cell proliferation triggered by drugs may be mostly attributed to autocrine mechanisms from the SP side population that express VEGF/Flt1 and MAPK/ERK1/2 during the G0 phase[45]. Two autocrine loops and Flt1/VEGF are triggered, and Flt1/ERK1 decreases the inhibition of Nanosi-RNA. Expression of Oct 4 indicates an essential role in CSC development for the stress-inducing MAPK/ERK1.According to a different study, curcumin inhibits reactive oxygen species, downregulates the behaviour of the STAT3 signal transducer and activator, stimulates the activation of the MAPK pathway and produces reactive oxygen species[46]. These effects are reversed by the antioxidant N-acetylcysteine, suggesting a ROS-dependent mechanism. ROS-induced persistent JNK activation and JNK blocker deactivation, such as MAPK phosphatases, both increase apoptosis. Antioxidants suppress MAPK activation following a cellular stimulation, indicating that the MAPK pathway is activated in part by ROS. Simulating oxidative stress, exogenous H_2O_2 also activates MAPK pathways. Resveratrol (RSV) increased TMZ toxicity in SHG44 GBM cells by increasing ROS production, triggering the AMPK pathway, blocking mTOR signalling, and lowering the expression level of antiapoptotic proteins[46].

Glioblastoma (GBM) treatment and management are areas of interest for bioactive compounds' possible application. Plants contain active substances called phytoconstituents, or bioactive chemicals. These compounds have evolved and adapted alongside mammals and plants, making them suitable for consumption[47]. Fruits, berries, grains, and seed oils contain protective properties against cancer and oxidative stress (OS). Plant-based diets, high in flavonoids, carotenoids, and phenolic acids, offer dietary supplies of antioxidant phytochemicals that can shield cells from damage. These antioxidants have the power to rid the body of extra-active oxygen[48]. The ability of antioxidants to delay or impede the beginning of free radicals is a crucial factor in understanding their efficacy. By scavenging or inactivating free radicals, they stop their activation and subsequent reactions. Age-related oxidative stress in the brain increases the concentration of radical organisms, which upsets the antioxidant system and reduces the production of genes involved in DNA damage repair, stress response, and antioxidants[49]. The capacity of antioxidants to transfer hydrogen to free radicals determines how efficient they are. Even with the donation of free radical hydrogen, the transfer of hydrogen into a free radical still requires energy and occurs at a faster rate. The capacity of antioxidants to provide free hydrogen radicals can be predicted based on their standard one-electron reducing potential. Effective free radical scavengers (FRS) produce radicals that don't easily combine with oxygen to produce peroxides[47,48].

Carotenoids, which are commonly used as antioxidants, Have the capacity to neutralise free radicals and reactive oxygen species (ROS)[50]. They can prevent oxidation of both photosynthetic and non-photosynthetic species due to this characteristic. Numerous epidemiological and clinical studies have examined the potential of carotenoids to prevent ROS-mediated illnesses, including cancer, asthma, corneal ossification, and cognitive decline. This is due to the effects of carotenoids.

Several studies have demonstrated a link between carotenoids and a lower risk of some cancers. Moreover, several studies have shown that carotenoids may have insignificant or even harmful effects in terms of cancer prevention[51]. These carotenoids possess the capability to capture and confine single-species oxygen as well as lipid peroxyl radicals. The structural composition of carotenoids can also be correlated with their antioxidant capacity. More widely conjugated carotenoids, like astaxanthin, have higher levels of antioxidant activity. Antioxidants, including vitamins E and C, are also necessary for the defense against reactive oxygen species (ROS)[52]. However, the presence of vitamin C, E, or β-carotene is not the primary factor responsible for the antioxidant capacity of most herbal compounds. Rather, their antioxidant qualities are partially attributed to the mixture of flavonoids and phenolic acids.An essential component of cancer

treatment is the use of antioxidants as shown by several experimental and clinical experiments. Flavonoids, in particular, have garnered significant interest in their development due to their less harmful capacity to inhibit pro-survival activities mediated by autophagy[53].

Chrysin, the primary constituent of the pine needle extract, shows promise as an anticancer drug against *Glioblastoma* by efficiently blocking TMZ-induced autophagy and apoptosis. The connection between ROS-caused cancer and bioactive compounds, which are present in high concentrations of antioxidants and scavenge free radicals or chelate ions of metals[54].This connection inhibits the growth of normal cells and protects them from oxidative damage. Additionally, the Table 1 demonstrates the different bioactive compounds and their biological origins that function as chemosensitizers in *Glioblastoma* treatment. For *Glioblastoma*, cancer stem cells (CSCs) should also be targeted because they are found in the PVN (perivascular niche) containing pericytes, microglia, cancer cells, and endothelial cells[55].

Compounds such as tigogenin, iridin and triacetyl-resveratrol (TAR) specifically target the perivascular niche and prevent G144 and U87 murine glioma cells from growing intracerebrally in mice[56].This implies that directing therapeutic interventions towards the perivascular niche could enhance the survival of *Glioblastoma* patients. Moreover, other active substances have been discovered to stimulate cancer stem cells, as shown in several research studies.

Bittersweet

Rheumatoid arthritis is among the many disorders for which the Celastraceous community, to whom it is associated traditionally utilises it as a remedy. The many components of Celastrushave been shown to have anti-inflammatory, anti-cancer, and antioxidant qualities. Celastrus orbiculatus extract (COE) has been shown to inhibit U86 and U251 GBM cell invasion, adhesion, migration, and cellular survival[57]. Additionally, it has been demonstrated by the Akt/PI3K/mTOR signalling cell pathway modules that human-induced autophagy and apoptosis influence the adherence, migration, and proliferation of cells of stomach cancer have recently been found. Lipid peroxidation (LP) and xanthine oxidase were also inhibited by the COE, according to another research[58]. These results suggest that MnO_2 cytotoxicity is partially caused by oxidative stress. MnO_2-induced cytotoxicity was successfully reduced by the antioxidative characteristics of COE. In the end, naturally occurring substances such as COE may be useful in mitigating or amplifying the cytotoxicity of heavy metals linked to oxidative stress-related illnesses, including Parkinsonism-inducing MnO_2[58,59].

Resveratrol

Resveratrol (RESV) is a strong antioxidant in the domain of clusters, mulberries, and peanuts with demonstrated tumour action. It has been noted that downregulating MGMT expression,RESV therapy substantially decreases the TMZ resistance, especially the portion in T98G GBM cells that is dependent on NF-to-B signalling60.The cleavage of the amyloid receptor protein that is not amyloidogenic is greatly aided by RESV. It also lessens neuronal damage and improves the elimination of amyloid beta-peptides. The combination therapy of RESV and TMZ has been found to greatly diminish the development of GBM cell orthotopic xenografts[61]. X-linked apoptosis protein (XIAP) inhibitors and anti-apoptotic drugs were also utilised, and there were substantially fewer survivors. Additionally, it has been demonstrated that RESV increases the toxicity of TMZ by several different mechanisms, including the production of reactive oxygen species (ROS), the activation of the AMPK pathway, the inhibition of mTOR signalling, and the downregulation of the SHG44 GBM cells contain anti-apoptotic B-cell lymphoma 2 (Bcl-2) proteins. The growth of orthotopic GBM cell xenografts was also significantly suppressed by adding TMZ to the training regimen62. Redox-excited caspase-9, -8, and -3 expression in astrocytes has been shown to be considerably reduced by RESV, which also lowers the apoptotic level. Additionally, Bcl-2 and the Bax to Bcl-2 ratio in myoblasts are partially restored by RESV therapy. Moreover, a decrease in the quantity of Sirt1 protein was seen following H_2O_2 therapy applied to mouse

Table 1. This table summarizes several bioactive substances used in the treatment of Glioblastoma, detailing their effects and the specific molecules they target

Compounds	Source	Target molecule and action	Cell line	Reference
Gallic acid	In leaves of bear berry, in pomegranate root bark, gallnuts, witch hazel, teal leaves, oak bark etc.	Modulate the expression of microRNA, which targets the genes for some mitochondrial enzymatic antioxidants	T98G	78
Zerumbone	*Zingiber zerumbet*	Mediated apoptosis and induced cell cycle arrest in human GBM U-87 MG cells in the G2/M phase of the cell cycle.	U-87 MG	80
Chrysin	*Oroxylum indicum*, *Passiflora caerulea*, *Passiflora incarnate* (polyphenolics compounds that belongs to a class of flavonoid)	G1 phase through triggering either p38/MAPK signalling contributing to p21Waf1/Cip1 protein aggregation or by inhibiting proteasome activity. Administration of ethanolic extract of propolis (containing chrysin and CAPE) and TMZ results in growth inhibition of U87 MG GBM cells by reducing the translocation of NF-κB to the nucleus.	C6 glioma cells, U87 MG GBM	83
Mangostin	*Garcinia mangostana*	COX-2, NO	U87 MG, GBM 8401	91
Capsaicin	*Capsicum annuum*	Triggering apoptotic cell death glioma cells through the mitochondrial pathway mediated by ROS and Ca2+	U87 MG GBM	79
Shikonin	*Lithospermum erythrochizon*	Reduce the viability, migration and invasion of the GBM cell, decrease the expression of MMP-2 and MMP-9 through the inhibition of PI3K/Akt signalling	U87 and U251	87
Tagitinin C	*Tanacetum diversifolia*	Inhibit growth of U373 GBM cells by downregulating surviving expression in a dose dependent manner	U373 GBM	89
Tanacin	*Tanacetum huronense*	Highest inhibitory effect against the GBM cells	U87 GBM	88

table 1. (continued).

Compounds	Source	Target molecule and action	Cell line	Reference
Latex	*Ficus carica*	Upregulation of let-7 expression inhibits the growth of U87, U138MG and T98G cells. Reduced invasion and enhanced TMZ sensitivity	U87, U138MG &T98G	90
Auraptene 7-[(2E)-3, 7-dimethylocta-2, 6-dienoxy] chromen-2-one	Genus citrus	Apoptosis in U87 GBM cells at concentrations of 100 and 400 µg/mL through the increasing proportion of Bax/Bcl-2 gene expression.	U87 cells *in vitro*	81,82
Balanitin -6 Balanitin -7	*Balanites aegyptiaca*	The actin cytoskeleton	U373 GBM	84
Neferine	*Nelumbo nucifera*	Induces autophagy by PI3K/Akt/mTOR pathway inhibition and hyper-generation ROS	A549 cells	85
Homocysteine	*Brazilian propolis*	*In-vitro* amyloids aropolis formation intake made rats healed from cognitive decline caused by Hcy	SH-SY5Y, U251MG	86

skeletal muscle-derived muscle stem cells, a decrease that was counteracted by RESV. The location of nuclear p21 in myotubes and the enhanced activity of the p21 promoter are two factors that contribute to the decrease in brain cells. Myoblasts exhibit apoptotic sensitivity to ROS63,64.

In this work, the effects of combined therapy with PAX and RESV on Glioblastoma DBTRG cell activation of TRPM2 were assessed. Four treatment groups were created from DBTRG cells: Power supply for 24 hours, 50 µM PAX, 50 µM RESV, and PAX PLUS RESV. The transient receptor for melastatin 2 (TRPM2) potential channel is essential activated for the significant effect of this hybrid therapy on apoptosis and cell viability, as evidenced by the decrease in current density and Ca2+ fluorescence strength mediated by PAX and RESV in the presence of a TRPM2 inhibitor[65].

Plumbagin

Plumbago zeylanica L. roots provide plumbagin, a quinoid component also known as 5-hydroxy-2-methyl-1,4-naphthoquinone. This molecule is among the most common and varied kinds of metabolites found in plants[66].

Plumbagin shows anti-proliferative qualities against cancers of the breast, lungs, prostate, and melanoma, among other cancer types. Its other qualities include anti-inflammatory, anti-mutagenic, antidiabetic, and antioxidant. Act/mTOR, the nuclear factor kappa-light-chain enhancing agent of activated B cells (NF-kB), also known as c-Jun N-terminal kinase (JNK), and other signalling pathways are among those that plumbagin affects[67]. In apoptosis, DNA arrest, and cell cycle damage have all been observed in recent research that has investigated the plumbagin-induced inhibition of GBM cells. Moreover, Plumbagin has been shown to cause cytotoxicity and telomerase

activity inhibition in GBM cells with different mutational histories. Intracellular oxygen radicals have multiplied three- to five-fold over Plumbagin levels68. N-acetylcysteine neutralization has been demonstrated to inhibit reactive oxygen species apoptosis, indicating the critical involvement of oxidative stress in Plumbagin-induced cell death. Inhibiting mitochondrial electron transport and controlling Nrf-2-mediated antioxidative responses are how plubagin does this. Only caspase-3/7 activity was found to be increased when researchers looked into the regulation of the proteins Bcl2, MDM2, cycling B1, TNFRSF1A, and the genes E2F1 and PTEN. Plumbagin has proven to be beneficial in causing glioma cells to undergo apoptosis and G2/M arrest in addition to inhibiting cell migration, invasion, and replication. Remarkably, plumbagin has been found to upregulate the expression of p21CIP1 and p27KIP while downregulating the expression of cyclin D1, Cdc25B, survivin, and other downstream effectors of FOXM1.This suggests that plumbagin could act as a natural FOXM1 inhibitor, offering possible therapeutic agents for the treatment of gliomas[68,69]. To assess Plumbagin's effects *in vivo*, U87 cell implants were used to create gliomas in nude mice. These studies were conducted in great detail. The findings demonstrated that in this mouse model, plumbabin markedly suppressed the growth of tumours and gliomagenesis. Additionally, the suppression of *in vivo* FOXM1 expression coincided with the antitumor response triggered by plumbabin.

Withaferin

For thousands of years, the Ayurvedic medical system has employed withaferin, which is found in *Withania somnifera*, also known as ashwagandha. It contains a number of substances that are produced from various plant components, such as sitoindoside, 40 withanolides, 12 alkaloids, and many flavonoids[70]. Researchers investigated withaferin A (WA) and its effects on the U87 and U251 cell cycle. According to studies, WA causes intrinsic apoptosis in GBM cells via controlling the Bim and Worse forms, which considerably slows the growth of GBM *in vitro* and in vivo62. By dephosphorylating Thr161 on CDK1, In the G2/M stage of the cell cycle, WA inhibits GBM cells and increases p53-independent p21. Cell viability knockdown and cell cycle progression were preserved by downregulating not Bim's but Bad's expression. As WA triggers endoplasmic reticulum (ER) stress, we have shown that the ATF4-ATF3-CHOP axis results in G2/M arrest and apoptosis in GBM cells.Significantly reducing the development of GBM was the combination of TT Fields (4 V/cm) and WA (10–100 nM) per an additional investigation, surpassing the effect of WA and TTFields alone[70]. The combined therapies on GBM cells were found to have a synergistic correlation ($p < 0.01$, $n = 3$ trials) according to the Poisson-based regression significance analysis. The results demonstrate a novel strategy for treating GBM that is probably superior to any synergistic therapy by itself (WA or TT Fields)[71].

Diosquinone

The roots of Diospyros tricolour and Diospyros mespiliformis in the Ebenaceae family provide diosquinone, an epoxy of naphthoquinone. According to recent research, several cancer cells, including GBM, have been demonstrated to hinder the formation of diosquinone cells. Increased cytotoxicity of diosquinone against cancer cell lines from the breast, colon, prostate, and Glioblastoma has also been demonstrated. One of these cell lines is the U373 GBM p53 mutant cell line[41].

Curcumin

Curcuma longa (diferuloylmethane) contains curcumin, a member of the ginger family.Brain tumours have been the subject of research on this substance's anti-tumour effects, lung metastases, bowel cancer, and breast cancer[45,63]. Curcumin has shown a strong inhibitory effect on growth, both *in vivo* and *in vitro* specimens of different cancer types exhibit angiogenesis and apoptosis. It has also been shown to increase mice's overall survival rate and decrease brain tumour growth of U87 xenografts.Its anti-cancer activities have decreased despite its low human bioavailability, which causes limited absorption and quick elimination from the body. Researchers discovered

that when TF (tissue factor) was added to either etoposide or temozolomide (TMZ), the cytotoxicity increased in the U87 GBM (*Glioblastoma multiforme*) cell line.The triple-drug combination consists of TF, etoposide, and TMZ, on the other hand, were found to be significantly more cytotoxic to the U87 cell line62.It was convincingly shown that TF tuberoses frequently attacked the BBB. The second form of turmeric, called Curcuma amada extract, has also been shown to dramatically reduce the viability of rhabdomyosarcoma cells (RMS) in human embryonic (RD) and alveolar (SJRH30) cultures. Anti-apoptotic genes and AKT signalling in U87 cells be downregulated by CA treatment via the basic mechanism of antitumor immunity. Recall that the protein kinase B AKT, which is serine/threonine, regulates a number of biological processes, such as angiogenesis, apoptotic activation, and cell invasion and proliferation[38].

Curcumin effectively prevented glioma invasion by obstructing the JNK, p38, and ERK MAPK pathways. In U87 MG and U373 MG cells, this inhibited the MMP-1, -3, -9, and -14 mRNA synthesised in response to PMA. Matrix metalloproteinase overexpression promotes the migration and invasion of surrounding brain tissues by malignant brain tumour cells (MMPs)[70]. Specific MMPs are overexpressed in human malignant gliomas. The lungs, heart, liver, and kidney of the rats showed no signs of tissue harm from curcumin. Curcumin also increased PTEN expression, which inhibited the P13K/Akt pathway, resulting in a decrease in cell death via the production of p-Akt and p-mTOR. Additionally, curcumin inhibits the AKT/mTOR/p70S6K pathway in xenograft models and GBM cell lines, which promotes autophagy. In these assays, curcumin decreased mTOR, p-mTOR, gross Akt, phosphoP13Kp85, and p-AKT. mTOR is an essential regulator that governs the division and development of cells, and when it is active, it suppresses autophagy activities.In GBM cells, autophagy induces cell death can be effectively induced by inhibiting the expression of AKT and P13K, which regulates mTOR expression[52].

Boswellic acid

The gum extract of two different species of *Boswellia, Boswellia carteri* and *Boswellia serrat*a, is known as boswellic acid (BA) or 3-O-Acetyl-11-keto-β-boswellic acid (AKBA). Subcutaneous glioma and *Glioblastoma* cell proliferation have been observed to be inhibited. The anti-Glioblastoma qualities of AKBA were assessed in an orthotopic mouse model in order to look into the possible involvement of boswellic acid (BA) in cancer treatment and prevention[49]. The study also examined the molecular mechanisms behind the actions of boswellic acid, which give the substance its potent anti-cancer properties. The evidence that boswellic acid can be effectively synthesised and developed into a potentially successful cancer treatment is examined in this study's conclusion[51].

In an alternative investigation, the scientists examined how different glioma-initiating cell lines (T-325, S-24, T-269, ZH-161, and ZH-305) were clonogenic and viable. The BA derivatives also influenced their cell cycle progression and the process of inducing cell death.Examines were also made on the potential synergy between TMZ and radiation.Five glioma-initiating (LN-18, LN-319, A-172, T-98G, and ZH-161) and nine long-term (LN-308, LNT-229, D-247MG, LN-428, U87 MG, T-325, S-24, T-269) glioma cell lines were employed in the study.The proximate pharmacodynamics aim of BA needs to be defined even though radiation and TMZ have been established[53,54].

Epigallocatechin gallate

Polyphenolic green tea contains a type of catechin known as epigallocatechin-3-gallate (EGCG), which has several applications such as treating diabetes, reducing obesity, reducing inflammation, and preventing tumour surgery. The activity of angiogenesis, carcinogenesis, tumours, and cell death is inhibited by EGCG. These findings align with how the ROS has evolved in modulation[60]. Its anticancer action is thought to be caused via EGCG-mediated ROS growth regulation, despite the fact that it possesses both pro- and antioxidant qualities. Several investigations have shown that EGCG plays a pro-oxidant role in the effect of anticancer medicines, which contrasts with the previous review. According to researchers, the oxidative stress caused by EGCG is consistent

with both the DNA-induced repair process and the apoptotic response[63]. It has been demonstrated that EGCG's additive or synergistic action on chemo-preventive drugs increases anticancer efficacy and reduces toxicity by inhibiting the initiation, promotion, and development stages of the disease. This chemical was made worse by EGCG's fast metabolism, low bioavailability, and rapid excretion, all of which were impeded by health management. Nonetheless, the most promising method for increasing its bioavailability as a distribution tool is one based on nanotechnology[61,63].

Quercetin

Leafy green vegetables, citrus fruits, apples, honey, raspberries, tomatoes, red grapes, and many more foods naturally contain quercetin, a naturally occurring flavonoid. Among fruits and vegetables, onions have the greatest quercetin content[44]. Research has demonstrated the therapeutic significance of quercetin in the management and avoidance of several illnesses, such as neurological diseases, cardiovascular disease, and cancer.In various animal, cellular, and human system models, quercetin has been demonstrated to operate mechanistically via regulating gene expression and signalling pathways to exhibitanti-inflammatory, anti-oxidant, and anti-cancer properties. Another investigation reports that quercetin is involved in signal transduction pathways and the development of GBM cells, and numerous proteins, including IL-6, Bcl-2, Bax, VEGF, HSP, MMP-2/-9, and STAT3 are among those with which it interacts. Quercetin either triggered senescence-like growth arrest or induced apoptosis via the Caspase-3/-7 activation pathway in GL-261, U87, U138, C6, and other GBM cell lines, according to various investigations[48].

Celastrol

Celastrol, originating from Tripterygium wilfordii bark, is a potent anticancer medication that inhibits heat shock protein, inhibits it from interacting with Cdc37, and induces apoptosis in lung 95-D, prostate, colon, and the OVCAR-8 (ovarian caspase-3) enzyme in the treatment of ovarian cancer[69]. Apoptosis is triggered and oncoprotein production is inhibited by ceraserol with sudden myelogenous leukaemia1-ETO/C-KIT. Caspases-dependent pathways and the degradation of the Hsp90 client protein, it is also used to treat lung cancer cells.H1650 does not appear to have any records of Celastrol anticancer efficacy, although it does represent a subset of NSCLC patients who do not have a double EGFR mutation yet are gefitinib-resistant. The H1650 Cells were exposed to various celastrol concentrations for 6-24 hours, respectively, and were then labelled with Annexin V-FITC/PI to determine whether celastrol causes cytotoxicity and apoptosis in these cells. Caspases are essential for both intrinsic and extrinsic apoptotic pathways, and caspase 3/7 is considered to be the executor of apoptosis[70,71].

Cannabinoid

The plant *Cannabis sativa* contains a bioactive substance called a cannabinoid. Cannabidiol, or CBD, is a non-psychoactive cannabinoid derived from cannabis that has been demonstrated to possess anticancer properties against several types of cancer. Unlike THC (tetrahydrocannabinol), CBD does not produce a "high" and is considered non-toxic.Recent research indicates that GBM tumours include CB1 and CB2 receptors that are particular to cannabis. These receptors have been demonstrated to express themselves in GBM tissue biopsies, *in situ* in GBM cell lines as well as *ex vivo* primary tumour cells extracted from GBM patients. Researcher has reported on a number of pre-clinical trials examining the antineoplastic effects of cannabinoids and their combinations (specifically, THC:CBD)[71]. These studies have also found that when THC is combined with CBD, its antineoplastic effects are amplified.

Phase II clinical research, clinical trial NCT01812603, in patients with GBM, placebo-controlled research examining a THC: CBD mixture combined with dose-intense TMZ increased the beneficial effects of THC. CBD mixtures in models before clinical trials[72]. GW Pharmaceuticals has released these positive findings from a trial on the treatment of GBM

using an orphan medication designation. The main reasons of drug resistance were thought to be partial Nrf2-related pathway activation and increased SLC7A11 antioxidant response mechanism expression. Accordingly, these scientists postulated that glioma stems cell survival and tumour invasion may be decreased by combining system SLC7A11 control with CBD treatment by the use of particular ROS modulators[73,74].

Neurostatin

The brains of mammals contain the natural glycosphingolipid neurostatin, an O-acetylated ganglioside known as GD1b, which strongly prevents astrocyte and astrocytoma division[35]. However, it is cytostatic against grade III and IV human astrocytoma cells and C6 glioma cells now that it has been completely isolated from ganglioside extracts of rats, cows, and pigs. It has been demonstrated that neurostatin, in particular, inhibits the growth of glioma cells *in vivo* by increasing CD4+ and CD8+ lymphocytes, which in turn enhance the immune response associated with tumours have demonstrated that the mechanism behind neurostatin's anticancer activity in gliomas, both *in vivo* and *in vitro*, is disruption of the cell cycle as well as interference with angiogenic and invasive processes[34].

It has been shown that while upregulating p21 and p27, two cell cycle inhibitors, the expression of CDKs and cell cycle promoters (cyclins) suppresses neurostatin. There has been speculation that EGFR signalling has blocked the pro-mitogenic PI3K and MAPK pathways. Bioactive substances called neurostatin-like gangliosides found abundantly in nature that have been shown via preclinical research to be a promising therapeutic option for the treatment of gliomas[35,36].

Verubulin II (2S-abyssinone)

It has been established that verubulin, a strong bioactive substance extracted from the fruits, leaves, and bark of Broussonetia papyrifera (Moraceae), causes Glioblastoma and (*in vitro*) brain cancer. There have been reports of synthesising abyssinone II and related compounds as potential chemopreventive drugs. According to scientists, verubulin, a vascular disruptor and microtubule destabilizer, exhibits higher plasma-related brain concentrations in animals, and there are limited therapy choices for recurrent Glioblastoma. Both naive bevacizumab and chronic refractory GBM show modest effectiveness with single-agent verubulin at this dosage and regimen, while it is well-tolerated and consistent with mild but manageable toxicity[30].

Gingerol

Zingiber officinale, family Zingiberaceae, naturally contains a phenolic chemical called gingerol, which has anti-inflammatory and tumor-curing properties.Numerous research conducted on oleoresin, 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol, and 6-hydroshogaol have all been found through cell lines, *in vivo*, and *in vitro* systems as the intrinsic active chemicals responsible for its activity[48]. The focus of research has now switched to the health-promoting knowledge of naturally occurring bioactive substances to address illnesses connected to lifestyle choices. 6-USP14 was suppressed by gingerol-induced K63 beclin1 site deubiquitination and ferritin heavy chain 1 (FTH1) and changed the expression of other proteins *in vivo* and *in vitro*. It also caused U-118MG glioma cells to undergo angiogenesis[49].

In a p53-dependent way, gingerol increased the levels of death receptor (DR) 5. XIAP, Bcl-2, c-FLIP, survivin, and other anti-apoptotic proteins were more abundant due to the production of ROS, while decreased Bid and pro-apoptotic proteins like Bax were less abundant. Additionally, we found that the sensitising effects of gingerol scavenging reactive oxygen species (ROS) or overexpressing anti-apoptotic protein (Bcl-2) reduced TRAIL-induced cell death. Glioblastoma cell death caused by its function as a sensitising agent resistant to TRAIL has since been established[21].

Icariin

A flavonoid called Icariin has been isolated from the Herba epimedin, a Chinese medicinal herb. Its anti-inflammatory, low-toxicity, bone-healing, antidepressant, neuroprotective, and anti-cancer properties are also acknowledged[100]. Icarionin

levels in the brain are remarkably low, which indicates inadequate BBB transmission[31]. It makes sense that the metabolites of Icariin could be responsible for its neuroprotective properties. It is imperative to look into ways to better time the circulation of icariin and understand how metabolites of icariin affect the CNS or central nervous system.PG-liposome application has been shown to increase icariin's retention duration in tissues like the brain, suggesting that this delivery system may facilitate icariin's entry into the central nervous system[33,39]. More advanced techniques to improve a more comprehensive pharmacological assessment of icariin in the brain would be possible with its distribution, and this would enhance the drug's potential for treating neurological diseases[32]. TMZ and Icariin have been shown working together to inhibit the development of U87 MG cells. Apoptosis is another way that icariin enhances the cytotoxic effects of TMZ.

Tetrandrine

Stephania tetrandra is the source of the bisbenzylisoquinoline alkaloid tetrandrine (Tet). Its origin has been associated to anti-angiogenic effects, radiosensitizing qualities, and instances of cellular death[20]. Recently, Tet has been found to enhance the radiosensitivity of GBM cells U87 and U251, causing the G0/G1 cell cycle to halt, which severely hinders their growth. This is accomplished by reducing the expression of the vital genes for proliferation, cyclin D1 and PCNA, as well as reducing the radiation-induced ERK signalling cascade. Furthermore, we have also investigated various other bioactive compounds utilized in the management of GBM and their respective mechanisms of action[72].

Demand for bioactive substances

The effects on society and the increasing demand for bioactive substances to be delivered by nanotechnology for the treatment of Glioblastoma have attracted a lot of attention in recent years. This field has had profound socio-economic implications across various sectors. Additionally, it has been suggested that nanocarriers have the potential to minimize the dosage and frequency of drug administration while lowering side effects and preserving an identical pharmacological profile. This is due to the unique ability of nanocarriers to deliver drugs directly to specific tissues[71,73]. Patients with malignant brain tumors face significant challenges in terms of prognosis, and major improvements in therapeutic and surgical methods. For these patients, delivering medication over the largest obstacle to chemotherapy treatment is the blood-brain barrier (BBB). The creation of pharmacological drugs that can effectively transcend the blood-brain barrier and target cancerous cells is necessary to overcome this barrier.

Chemotherapeutic medications' failure to reach the targeted tumour cells frequently makes treating Glioblastoma more difficult, and this issue is exacerbated by a blood-brain barrier which exists. The flow of ions, nutrients, and cells into the brain is selectively regulated by adhesion junctions between endothelial cells in the brain and the tight junctions that form the brain-to-brain barrier (BBB)[50,52]. This prevents some cancer stem cells from being cytotoxic and from developing resistance to treatment by limiting the availability of medications to Glioblastoma cells. Large size, hydrophobicity, and efflux expressed by systems resistant to several drugs by tumour cells and the blood-brain barrier can also be responsible for the restricted distribution of chemotherapeutic drugs.Hence, there is a requirement for custom-made therapeutic approaches that can effectively penetrate the BBB and target the desired regions of the brain. Many strategies, including the use of drug-loaded nanocarriers, the passive penetration of lipidated products, and the generation of prodrugs that can take advantage of BBB transport processes, have been suggested. While some lipid-soluble small molecules can passively cross the BBB, most other molecules require specific transport mechanisms[51].Targeted medicines can therefore be developed by employing a more focused and selective strategy, like the use of nanoparticles. Designing nanocarriers with surfaces capable of overcoming pharmacological and biophysical obstacles is made possible by nanoparticles, especially those in colloidal form. Optimising

these characteristics can help medications cross the blood-brain barrier more easily.To maximise efficacy and minimize adverse effects, it is also possible to modify the surface characteristics of nanocarriers to permit pharmacological release that is monitored and focused[74].

Chemotherapeutic drugs based on nanomaterials that have been shown to penetrate the blood-brain barrier and reach the intended target include liposomes, dendrimers, carbon nanotubes, and polymeric micelles[72]. In cancer therapy, nanomedicine and synergistic medication formulations have gained importance because of their potential to yield greater therapeutic benefits than current practice's traditional drug combo therapy.Even though the medication can cross the blood-brain barrier and result in high local concentrations, a potentially useful strategy is to use a hydrogel-based Lauroyl-gemcitabine lipid nanocapsule-based local dispersion in the GBM tumour resection cavity (GemC12-LNC). Using a range of GBM cell lines, including U251, T98-G, 9L-LacZ, and U-87 MG, the cytotoxicity and internalisation processes of GemC12-LNC were examined. The hydrogel GemC12-LNC was successfully injected into the mouse brain. After intratumoral injection, GemC12-LNC significantly enhanced mice survival in an orthotopic xenograft model as compared to controls[71]. It was also shown to have the capacity to postpone tumour recurrence following perioperative injection in the GBM resection cavity. Researchers examined the impact of amide-conjugated biotin, which has the capacity to transport anticancer medicines, impacts how well the glucoheptoamidated poly(amidoamine) PAMAM G3 dendrimer is absorbed by the cells for up to 24 hours as they are incubated. As a result, highly susceptible U-118-MG cells were able to be taken up by the cells at a higher rate and normal cell cytotoxicity decreased[75].

`In order to determine whether traditional Chinese medicine's use of nanoscale drug synthesis is clinically viable, further extensive research is necessary. The bioactive chemical RESV-loaded nanoparticles have the potential to be a valuable chemotherapeutic agent for the treatment of malignant gliomas. The disease was evaluated using both *in vitro (*C6 glioma cell line) and in *vivo* (brain-implanted C6 cells) models[68,69].

On the survival of C6 glioma cells *in vitro*, it was discovered that trans-resveratrol- loaded lipid-core nanocapsules (RESV-LNC) had a higher anti-glioma effect than RESV in solution. An indication of the selectivity of cancer cells is the lack of negative effects of RESV-LNC therapy in organotypic cultures of the hippocampal regions, a safe cell model. According to the results, RESV's anti-glioma efficacy is enhanced by nanoencapsulation76. As a potential chemotherapeutic strategy for glioma treatment, this establishes the framework for future studies into the therapeutic suitability of RESV nanoformulations. In comparison to free resveratrol (3.45 ±0.3961 μg/g), an *in vivo* biodistribution study using Wistar rats revealed that SLN loaded with RESV is a potentially effective therapeutic system for evaluating brain tissue neoplastic diseases. A significant increase ($P < 0.001$) in brain concentration of RESV was observed with SLN, measuring 17.28 ± 0.6344 μg/g.The viability of glioma cells was reduced by RESV-LNC by apoptotic cell death and, in the S and G1 stages of the cell cycle, early arrest, as demonstrated by the Annexin-FITC/PI test[49].

Another bioactive substance called curcumin prevented U87 MG cells from proliferating while sparing healthy cells. Curcumin's water solubility and bioavailability were increased when it was encapsulated in a dendrosom[75]. Dendrimer-articulated curcumin has been developed by scientists as a possible therapeutic target for Glioblastoma in mice. Transfections with D-Cys-Cur and D-Cys on GL261 cells both had comparable anti-inflammatory effects. The mice lived longer when treated with both complexes in a similar way. Across all treatment groups, the tumour sizes in the mice remained constant[76]. Based on the aforementioned viewpoint, we have therefore included a few methods and attributes of cancer nanomedicine delivery[77].

Curcumin NP-encapsulated was therefore found to be advantageous in DAOY and D283Med medulloblastoma cell lines; HSR-GBM1 and JHH-GBM14 GBM neurosphere lines in terms of growth inhibition, affecting the CD133+stem-like population in particular[78].

Concluding remarks

Glioblastoma multiforme (GBM) poses significant challenges in oncology due to its aggressive nature and resistance to conventional therapies such as chemotherapy, radiation, immunotherapy, and surgery. The limitations of these treatments highlight the critical need for innovative therapeutic strategies. Nanotechnologies offer a promising avenue to overcome the barriers related to metabolism, chemoresistance, toxicity, stability, biodistribution, and solubility, particularly in the context of delivering bioactive compounds. These compounds are known for their ability to scavenge free radicals, reduce inflammation, and directly target cancer cells. Incorporating bioactive substances into nanocarrier drug delivery systems can potentially enhance the distribution and bioavailability of anticancer agents. This can lead to more effective eradication of malignant glioma cells, reduced adverse effects, and improved quality of life for survivors. This approach signifies a notable progress in combating GBM by enhancing the distribution and effectiveness of anticancer agents, reducing adverse effects, and improving the quality of life for survivors, thus warranting further exploration and development.

References

1. **Doan, P., Musa, A., Murugesan, A., Sipila, V., Candeias, N.R., Emmert-Streib, F., Ruusuvuori, P., Granberg, K., Yli-Harja, O., Kandhavelu, M. (2020).** *Glioblastoma multiforme* stem cell cycle arrest by alkylaminophenol through the modulation of EGFR and CSC signalling pathways. Cells. 9: 681.
2. **Mohtashami, E., Shafaei-Bajestani, N., Mollazadeh, H., Mousavi, S.H., Jalili-Nik, M., Sahebkar, A., Afshari, A.R. (2020).** The current state of potential therapeutic modalities for *Glioblastoma multiforme*: a clinical review. Current Drug Metabolism. 21: 564-578.
3. **Rajaratnam, V., Islam, M.M., Yang, M., Slaby, R., Ramirez, H.M., Mirza, S.P. (2020).** *Glioblastoma*: pathogenesis and current status of chemotherapy and other novel treatments. Cancers. 12(4): 937 (Basel).
4. **Mahmoudi, K., Bouras, A., Bozec, D., Ivkov, R., Hadjipanayis, C. (2018).** Magnetic hyperthermia therapy for the treatment of *Glioblastoma*: a review of the therapy's history, efficacy and application in humans. International Journal of Hyperthermia. 34(8): 1316-1328.
5. **Kim, J.S., Shin, D.H., Kim, J.-S. (2018).** Dual-targeting immunoliposomes using angiopep-2 and CD133 antibody for *Glioblastoma* stem cells. Journal of Controlled Release. 269: 245-257.
6. **Christodoulou, I., Goulielmaki, M., Devetzi, M., Panagiotidis, M., Koliakos, G., Zoumpourlis, V. (2018).** Mesenchymal stem cells in preclinical cancer cytotherapy: a systematic review. Stem Cell Research & Therapy. 9(1): 1-38.
7. **Najafi, M., Farhood, B., Mortezaee, K. (2019).** Cancer stem cells (CSCs) in cancer progression and therapy. Journal of Cellular Physiology. 234(6): 8381-8395.
8. **Islam, F., Gopalan, V., Law, S., Tang, J.C.-o., Lam, A.K.-y. (2019).** FAM134B promotes esophageal squamous cell carcinoma *in vitro* and its correlations with clinicopathologic features. Human Pathology. 87: 1-10.
9. **Dadwal, A., Baldi, A., Kumar, N.R. (2018).** Nanoparticles as carriers for drug delivery in cancer. Artificial Cells, Nanomedicine, and Biotechnology. 46: 295-305.
10. **Singh, A., Kukreti, R., Saso, L., Kukreti, S. (2019).** Oxidative stress: a key modulator in neurodegenerative diseases. Molecules. 24(8): 1583.
11. **Aggarwal, V., Tuli, H.S., Varol, A., Thakral, F., Yerer, M.B., Sak, K., Varol, M., Jain, A., Khan, M., Sethi, G. (2019).** Role of reactive oxygen species in cancer progression: molecular mechanisms and recent advancements. Biomolecules. 9(11): 735.
12. **Muñoz-Rugeles, L., Galano, A., Alvarez-Idaboy, J.R. (2018).** The other side of the superoxide radical anion: its ability to chemically repair DNA oxidized sites. Chemical Communications. 54(97): 13710-13713.
13. **Saikolappan, S., Kumar, B., Shishodia, G., Koul, S., Koul, H.K. (2019).** Reactive oxygen species and cancer: a complex interaction. Cancer Letters. 452: 132-143.
14. **Samii, A., Razmkhah, F. (2020).** Transformation of hematopoietic stem and progenitor cells by leukemia extracellular vesicles: a step toward leukemogenesis. Stem Cell Reviews and Reports. 16: 1081-1091.
15. **Thiagarajan, S., Arapoc, D.J., Husna Shafie, N., Keong, Y.Y., Bahari, H., Adam, Z., Ei, T. (2019).** *Momordica charantia* (Indian and Chinese bitter melon) extracts inducing apoptosis in

human lung cancer cell line A549 via ROS-mediated mitochondrial injury. Evidence-Based Complementary and Alternative Medicine. 2019.
16. **Golandaz, A., Pal, G., Uplanchiwar, A.K., Gautam, V., Butea, R.K. (2020).** *Butea monosperma* flower extract partially reduces high-fat diet-induced obesity in experimental rats. Obesity Medicine. 17: 100179.
17. **Louis, D.N., Perry, A., Reifenberger, G., Von Deimling, A., Figarella-Branger, D., Cavenee, W.K., Ohgaki, H., Wiestler, O.D., Kleihues, P., Ellison, D.W. (2016).** The 2016 World Health Organization classification of tumours of the central nervous system: a summary. Acta Neuropathologica. 131(6): 803-820.
18. **Dayem, A.A., Choi, H.-Y., Kim, J.-H., Cho, S.-G. (2010).** Role of oxidative stress in stem, cancer, and cancer stem cells. Cancers. 2(2): 859-884.
19. **McGranahan, T., Therkelsen, K.E., Ahmad, S., Nagpal, S. (2019).** Current state of immunotherapy for treatment of Glioblastoma. Current Treatment Options in Oncology. 20(3): 1-15.
20. **Jalili-Nik, M., Sadeghi, M.M., Mohtashami, E., Mollazadeh, H., Afshari, A.R., Sahebkar, A. (2020).** Zerumbone promotes cytotoxicity in human malignant Glioblastoma cells through reactive oxygen species (ROS) generation. Oxidative Medicine and Cellular Longevity. 2020: 3237983.
21. **Kanarek, N., Petrova, B., Sabatini, D.M. (2020).** Dietary modifications for enhanced cancer therapy. Nature. 579: 507-517.
22. **Akter, R., Chowdhury, M.A., Rahman, M.H. (2021).** Flavonoids and polyphenolic compounds as potential talented agents for the treatment of Alzheimer's disease and their antioxidant activities. Current Pharmaceutical Design. 27(3): 345-356.
23. **Kim, Y.S., Gong, X., Rubin, L.P., Choi, S.-W., Kim, Y. (2019).** β-Carotene 15, 15′-oxygenase inhibits cancer cell stemness and metastasis by regulating differentiation-related miRNAs in human neuroblastoma. Journal of Nutritional Biochemistry. 69: 31-43.
24. **Rehman, A., Tong, Q., Jafari, S.M., Assadpour, E., Shehzad, Q., Aadil, R.M., Iqbal, M.W., Rashed, M.M., Mushtaq, B.S., Ashraf, W. (2020).** Carotenoid-loaded nanocarriers: a comprehensive review. Advances in Colloid and Interface Science. 275: 102048.
25. **Pérez-Gálvez, A., Viera, I., Roca, M. (2020).** Carotenoids and chlorophylls as antioxidants. Antioxidants. 9(6): 505.
26. **Mordi, R.C., Ademosun, O.T., Ajanaku, C.O., Olanrewaju, I.O., Walton, J.C. (2020).** Free radical mediated oxidative degradation of carotenes and xanthophylls. Molecules. 25(5): 1038.
27. **Rodriguez-Amaya, D.B. (2019).** Update on natural food pigments – a mini-review on carotenoids, anthocyanins, and betalains. Food Research International. 124: 200-205.
28. **Akter, R., Rahman, M.H., Behl, T., Chowdhury, M.A.R., Manirujjaman, M., Bulbul, I.J., Elshenaw, S.E., Tit, D.M., Bungau, S. (2021).** Prospective role of polyphenolic compounds in the treatment of neurodegenerative diseases. CNS and Neurological Disorders - Drug Targets.
29. **Tagde, P., Kulkarni, G.T., Mishra, D.K., Kesharwani, P. (2020).** Recent advances in folic acid engineered nanocarriers for treatment of breast cancer. Journal of Drug Delivery Science and Technology. 56: 101613.
30. **Harmanci, D. (2018).** Targeting friend and foe: emerging therapeutics in the age of gut microbiome and disease. Journal of Microbiology. 56: 183-188.
31. **Rahman, M.H., Akter, R., Bhattacharya, T., Abdel-Daim, M.M., Alkahtani, S., Arafah, M.W., Al-Johani, N.S., Alhoshani, N.M., Alkeraishan, N., Alhenaky, A. (2020).** Resveratrol and neuroprotection: impact and its therapeutic potential in Alzheimer's disease. Frontiers in Pharmacology. 11.
32. **Oztürk, Y., Günaydın, C., Yalçın, F., Nazıroğlu, M., Braidy, N. (2019).** Resveratrol enhances apoptotic and oxidant effects of paclitaxel through TRPM2 channel activation in DBTRG Glioblastoma cells. Oxidative Medicine and Cellular Longevity. 2019.
33. **Hoosein, S., Robinson, G.R. (2018).** Dredge spoil deposits and distributions of invasive Celastrus orbiculatus Thunb. (Celastraceae, Oriental bittersweet) in a riparian ecosystem. Journal of the Torrey Botanical Society. 145(4): 321-331.
34. **Chu, Z., Shi, X., Chen, G., He, X., Qian, Y., Wang, H., Tao, L., Liu, Y., Jiang, W., Chen, J. (2021).** COE inhibits vasculogenic mimicry by targeting EphA2 in hepatocellular carcinoma, a research based on proteomics. Frontiers in Pharmacology. 12: 619732.
35. **Seo, Y.M. (2020).** Protective effect of Celastrus orbiculatus thunb extract on cultured neuroglial cells damaged by manganese dioxide, a Parkinsonism inducer. Korean Journal of Clinical Laboratory Science. 52(2): 150-157.

36. **Kapur, A., Beres, T., Rathi, K., Nayak, A.P., Czarnecki, A., Felder, M., Gillette, A., Ericksen, S.S., Sampene, E., Skala, M.C. (2018).** FIGO's response to the global challenge of hyperglycemia in pregnancy – toward a global consensus. Gynecological Endocrinology. 34(1): 1-3.
37. **Huang, H., Xie, H., Pan, Y., Zheng, K., Xia, Y., Chen, W. (2018).** Plumbagin triggers ER stress-mediated apoptosis in prostate cancer cells via induction of ROS. Journal of Neuro-Oncology. 45(1): 267-280.
38. **Tang, Q., Ren, L., Liu, J., Li, W., Zheng, X., Wang, J., Du, G. (2020).** Withaferin A triggers G2/M arrest and intrinsic apoptosis in Glioblastoma cells via ATF4-ATF3-CHOP axis. Cell Proliferation. 53(1): 12706.
39. **Chang, E., Patel, C., Pohling, C., Beygui, N., Ha, D.H., Gambhir, S.S. (2018).** Withaferin A and tumor treating fields synergistically inhibit glioma proliferation. AACR.
40. **Wong, S.C., Kamarudin, M.N.A., Naidu, R. (2021).** Anticancer mechanism of curcumin on human Glioblastoma. Nutrients. 13: 950.
41. **Munaut, C., Noël, A., Hougrand, O., Foidart, J.-M., Boniver, J., Deprez, M. (2021).** Vascular endothelial growth factor expression correlates with matrix metalloproteinases. Biomedicine & Pharmacotherapy. 141: 111928.
42. **Wang, Z., Liu, F., Liao, W., Yu, L., Hu, Z., Li, M. (2020).** Curcumin suppresses Glioblastoma cell proliferation by p-AKT/mTOR pathway and increases the PTEN expression. Archives of Biochemistry and Biophysics. 689: 108412.
43. **Maiti, P., Scott, J., Sengupta, D., Al-Gharaibeh, A., Dunbar, G.L. (2019).** Curcumin and solid lipid curcumin particles induce autophagy, but inhibit mitophagy and the PI3K-Akt/mTOR pathway in cultured Glioblastoma cells. International Journal of Molecular Sciences. 20: 399.
44. **Li, W., Ren, L., Zheng, X., Liu, J., Wang, J., Ji, T., Du, G. (2020).** 3-O-Acetyl-11-keto-β-boswellic acid ameliorated aberrant metabolic landscape and inhibited autophagy in Glioblastoma. Acta Pharmaceutica Sinica B. 10(2): 301-312.
45. **Adelusi, T.I., Du, L., Hao, M., Zhou, X., Xuan, Q., Apu, C., Sun, Y., Lu, Q., Yin, X. (2020).** Keap1/Nrf2/ARE signalling unfolds therapeutic targets for redox imbalanced-mediated diseases and diabetic nephropathy. Biomedicine & Pharmacotherapy. 123: 109732.
46. **Carrasco-Pozo, C., Cires, M.J., Gotteland, M. (2019).** Quercetin and epigallocatechin gallate in the prevention and treatment of obesity: from molecular to clinical studies. Journal of Medicinal Food. 22(8): 753-770.
47. **Chikara, S., Nagaprashantha, L.D., Singhal, J., Horne, D., Awasthi, S., Singhal, S.S. (2018).** Oxidative stress and dietary phytochemicals: role in cancer chemoprevention and treatment. Cancer Letters. 413: 122-134.
48. **Casanova, E., Salvadó, J., Crescenti, A., Gibert-Ramos, A. (2019).** Epigallocatechin gallate modulates muscle homeostasis in type 2 diabetes and obesity by targeting energetic and redox pathways: a narrative review. International Journal of Molecular Sciences. 20(3): 532.
49. **Almatroodi, S.A., Almatroudi, A., Khan, A.A., Alhumaydhi, F.A., Alsahli, M.A., Rahmani, A.H. (2020).** Potential therapeutic targets of epigallocatechin gallate (EGCG), the most abundant catechin in green tea, and its role in the therapy of various types of cancer. Molecules. 25(14): 3146.
50. **Rauf, A., Imran, M., Khan, I.A., ur-Rehman, M., Gilani, S.A., Mehmood, Z., Mubarak, M.S. (2018).** Anticancer potential of quercetin: a comprehensive review. Phytotherapy Research. 32(11): 2109-2130.
51. **Taylor, M.A., Khathayer, F., Ray, S.K. (2019).** Quercetin and sodium butyrate synergistically increase apoptosis in rat C6 and human T98G Glioblastoma cells through inhibition of autophagy. Neurochemical Research. 44(7): 1715-1725.
52. **Tavana, E., Mollazadeh, H., Mohtashami, E., Modaresi, S.M.S., Hosseini, A., Sabri, H., Soltani, A., Javid, H., Afshari, A.R., Sahebkar, A.J.B. (2020).** Quercetin: a promising phytochemical for the treatment of Glioblastoma multiforme. BioFactors. 46(3): 356-366.
53. **Alvarez-Arellano, L., Salazar-García, M., Corona, J.C. (2020).** Neuroprotective effects of quercetin in pediatric neurological diseases. Molecules. 25(23): 5597.
54. **Dumitru, C.A., Sandalcioglu, I.E., Karsak, M. (2018).** Cannabinoids in Glioblastoma therapy: new applications for old drugs. Frontiers in Molecular Neuroscience. 11: 159.
55. **Kosgodage, U.S., Uysal-Onganer, P., MacLatchy, A., Mould, R., Nunn, A.V., Guy, G.W., Kraev, I., Chatterton, N.P., Thomas, E.L., Inal, J.M. (2019).** Cannabidiol affects extracellular vesicle release, miR21 and miR126, and reduces prohibitin protein in *Glioblastoma multiforme* cells. Translational Oncology. 12(3): 513-522.
56. **Singh, D.B., Gupta, M.K., Pathak, R.K. (2020).**

Natural products in cancer chemoprevention and chemotherapy. Frontiers in Natural Product Chemistry. 6(6): 151-182.

57. **Singh, R., Singh, K. (2019).** *Zingiber officinale*: a spice with multiple roles. Research Journal of Life Sciences, Bioinformatics, Pharmaceuticals and Chemical Sciences. 125.
58. **Ma, R.-H., Ni, Z.-J., Zhu, Y.-Y., Thakur, K., Zhang, F., Zhang, Y.-Y., Hu, F., Zhang, J.-G., Wei, Z.-J. (2021).** A recent update on the multifaceted health benefits associated with ginger and its bioactive components. Food & Function. 12(2): 519-542.
59. **Czarnik-Kwaśniak, J., Kwaśniak, K., Kwasek, P., Świerzowska, E., Strojewska, A., Tabarkiewicz, J. (2020).** The influence of lycopene, [6]-gingerol, and silymarin on the apoptosis on U-118MG Glioblastoma cells *in vitro* model. Nutrients. 12(1): 96.
60. **Jin, J., Wang, H., Hua, X., Chen, D., Huang, C., Chen, Z. (2019).** An outline for the pharmacological effect of icariin in the nervous system. European Journal of Pharmacology. 842: 20–32.
61. **Chang, H.-F., Huang, W.-T., Chen, H.-J., Yang, L.-L. (2010).** Apoptotic effects of γ-mangostin from the fruit hull of *Garcinia mangostana* on human malignant glioma cells. Molecules. 15(12): 8953-8966.
62. **Jalili-Nik, M., Sadeghi, M.M., Mohtashami, E., Mollazadeh, H., Afshari, A.R., Sahebkar, A. (2020).** Zerumbone promotes cytotoxicity in human malignant Glioblastoma cells through reactive oxygen species (ROS) generation. Oxidative Medicine and Cellular Longevity. 2020.
63. **Afshari, A.R., Jalili-Nik, M., Soukhtanloo, M., Ghorbani, A., Sadeghnia, H.R., Mollazadeh, H., Roshan, M.K., Rahmani, F., Sabri, H., Vahedi, M.M. (2019).** Auraptene-induced cytotoxicity mechanisms in human malignant Glioblastoma (U87) cells: role of reactive oxygen species (ROS). EXCLI Journal. 18: 576-590.
64. **Bhattacharya, T., Maishu, S.P., Akter, R., Rahman, M.H., Akhtar, M.F., Saleem, A., Bin-Jumah, M., Kamel, M., Abdel-Latif, M.A., Abdel-Daim, M.M. (2021).** A review on natural sources derived protein nanoparticles as anticancer agents. Current Topics in Medicinal Chemistry.
65. **Teleanu, D.M., Chircov, C., Grumezescu, A.M., Volceanov, A., Teleanu, R.I. (2018).** Blood-brain delivery methods using nanotechnology. Pharmaceutics. 10(4): 269.
66. **Bhattacharya, T., Dey, P.S., Akter, R., Kabir, T., Rahman, H., Rauf, A. (2021).** Effect of natural leaf extracts as phytomedicine in curing geriatrics. Experimental Gerontology. 150: 111352.
67. **Ozdemir-Kaynak, E., Qutub, A.A., Yesil-Celiktas, O. (2018).** Advances in *Glioblastoma multiforme* treatment: new models for nanoparticle therapy. Frontiers in Physiology. 9: 170.
68. **Fana, M., Gallien, J., Srinageshwar, B., Dunbar, G.L., Rossignol, J. (2020).** PAMAM dendrimer nanomolecules utilized as drug delivery systems for potential treatment of Glioblastoma: a systematic review. International Journal of Nanomedicine, 15. 2789-2808.
69. **Aminabad, N.S., Farshbaf, M., Akbarzadeh, A. (2019).** Recent advances of gold nanoparticles in biomedical applications: state of the art. Cell Biochemistry and Biophysics. 77(2): 123-137.
70. **Kabir, M., Rahman, M., Akter, R., Behl, T., Kaushik, D., Mittal, V., Pandey, P., Akhtar, M.F., Saleem, A., Albadrani, G.M., Kamel, M. (2021).** Potential role of curcumin and its nanoformulations to treat various types of cancers. Biomolecules. 11(3): 392.
71. **Rossignol, J., Munro, N., Fana, M., Srinageshwar, B., Malkowski, C., Climie, S., Gallien, J., Swanson, D., Sharma, A., Dunbar, G. (2019).** Use of dendrimer nanoparticles encapsulated curcumin as a potential therapy for Glioblastoma in mice. Cell Transplantation, Sage Publications Inc., 2455 Teller Rd, Thousand Oaks, CA 91320 USA. 483-483.
72. **Akhtar, N., Mohammed, S.A., Singh, V., Abdellatif, A.A., Mohammad, H.A., Ahad, A., Yusuf, M., Khadri, H., Naz, M., Khan, O. (2020).** Liposome-based drug delivery of various anticancer agents of synthetic and natural product origin: a patent overview. Pharmaceutical Patent Analyst. 9(3): 87-116.
73. **Ashrafzadeh, M.S., Akbarzadeh, A., Heydarinasab, A., Ardjmand, M. (2020).** *In vivo* Glioblastoma therapy using targeted liposomal cisplatin. International Journal of Nanomedicine. 15: 7035-7049.
74. **Tao, X., Wang, K., Dong, J., Hou, Z., Wu, Z., Zhang, J., Liu, B. (2018).** Clinical features, surgical management, and prognostic factors of secretory meningiomas: a single-center case series of 149 patients. Journal of Neuro-Oncology. 136(3): 515-522.
75. **Li, M., Zhang, F., Su, Y., Zhou, J., Wang, W. (2018).** Nanoparticles designed to regulate tumor microenvironment for cancer therapy. Life Sci-

ences. 201, 37–44.
76. **Gao, C., Bhattarai, P., Chen, M., Zhang, N., Hameed, S., Yue, X., Dai, Z. (2018).** Amphiphilic drug conjugates as nanomedicines for combined cancer therapy. Bioconjugate Chemistry. 29(12): 3967-3981.
77. **Bhattacharya, T., Maishu, S.P., Akter, R., Rahman, M.H., Akhtar, M.F., Saleem, A., Bin-Jumah, M., Kamel, M., Abdel-Latif, M.A., Abdel-Daim, M.M. (2021).** A review on natural sources derived protein nanoparticles as anticancer agents. Current Topics in Medicinal Chemistry.
78. **Paolini, A., Curti, V., Pasi, F., Mazzini, G., Nano, R., Capelli, E. (2015).** Gallic acid exerts a protective or an anti-proliferative effect on glioma T98G cells via dose-dependent epigenetic regulation mediated by miRNAs. International Journal of Oncology. 46(4): 1491-1497.
79. **Xie, L., Xiang, G.H., Tang, T., Tang, Y., Zhao, L.Y., Liu, D., Zhang, Y.R., Tang, J.T., Zhou, S., Wu, D.H. (2016).** Capsaicin and dihydrocapsaicin induce apoptosis in human glioma cells via ROS and Ca2+-mediated mitochondrial pathway. Molecular Medicine Reports. 14(5): 4198-4208.
80. **Jalili-Nik, M., Sadeghi, M.M., Mohtashami, E., Mollazadeh, H., Afshari, A.R., Sahebkar, A. (2020).** Zerumbone promotes cytotoxicity in human malignant Glioblastoma cells through reactive oxygen species (ROS) generation. Oxidative Medicine and Cellular Longevity. 2020.
81. **Okuyama, S., Semba, T., Toyoda, N., Epifano, F., Genovese, S., Fiorito, S., Taddeo, V.A., Sawamoto, A., Nakajima, M., Furukawa, Y. (2016).** Auraptene and other prenyloxyphenylpropanoids suppress microglial activation and dopaminergic neuronal cell death in a lipopolysaccharide-induced model of Parkinson's disease. International Journal of Molecular Sciences. 17(10): 1716.
82. **Afshari, A.R., Jalili-Nik, M., Soukhtanloo, M., Ghorbani, A., Sadeghnia, H.R., Mollazadeh, H., Roshan, M.K., Rahmani, F., Sabri, H., Vahedi, M.M. (2019).** Auraptene-induced cytotoxicity mechanisms in human malignant Glioblastoma (U87) cells: role of reactive oxygen species (ROS). EXCLI Journal. 18: 576-590.
83. **Kasala, E.R., Bodduluru, L.N., Barua, C.C., Gogoi, R. (2015).** Chrysin and its emerging role in cancer drug resistance. Chemico-Biological Interactions. 236: 7-8.
84. **Gnoula, C., Mégalizzi, V., De Nève, N., Sauvage, S., Ribaucour, F., Guissou, P., Duez, P., Dubois, J., Ingrassia, L., Lefranc, F. (2008).** Balanitin-6 and -7: diosgenyl saponins isolated from Balanites aegyptiaca Del. display significant anti-tumor activity *in vitro* and *in vivo.* International Journal of Oncology. 32(1): 5-15.
85. **Poornima, P., Weng, C.F., Padma, V.V. (2013).** Neferine from Nelumbo nucifera induces autophagy through the inhibition of PI3K/Akt/mTOR pathway and ROS hyper generation in A549 cells. Food Chemistry. 141(4): 3598-3605.
86. **Hyun, K.H., Yoon, C.H., Kim, R.K., Lim, E.J., An, S., Park, M.J., Hyun, J.W., Suh, Y., Kim, M.J., Lee, S.J. (2011).** Eckol suppresses maintenance of stemness and malignancies in glioma stem-like cells. Toxicology and Applied Pharmacology. 254(1): 32-40.
87. **Zhang, F.Y., Hu, Y., Que, Z.Y., Wang, P., Liu, Y.H., Wang, Z.H., Xue, Y.X. (2015).** Shikonin inhibits the migration and invasion of human Glioblastoma cells by targeting phosphorylated β-catenin and phosphorylated PI3K/Akt: a potential mechanism for the anti-glioma efficacy of a traditional Chinese herbal medicine. International Journal of Molecular Sciences. 16(10): 23823-23848.
88. **Dissanayake, A.A., Bejcek, B.E., Zhang, C.R., Nair, M.G. (2016).** Sesquiterpenoid lactones in Tanacetum huronense inhibit human Glioblastoma cell proliferation. Natural Product Communications. 11(5): 579-582.
89. **Liao, M.H., Lin, W.C., Wen, H.C., Pu, H.F. (2011).** *Tithonia diversifolia* and its main active component tagitinin C induce survivin inhibition and G2/M arrest in human malignant Glioblastoma cells. Fitoterapia. 82(3): 331-341.
90. **Tezcan, G., Tunca, B., Bekar, A., Yalcin, M., Sahin, S., Budak, F., Cecener, G., Egeli, U., Demir, C., Guvenc, G., Yilmaz, G. (2015).** *Ficus carica* latex prevents invasion through induction of let-7d expression in GBM cell lines. Cellular and Molecular Neurobiology. 35: 175-187.
91. **Li, K., Wu, L., Chen, Y., Li, Y., Wang, Q., Li, M., Hao, K., Zhang, W., Jiang, S., Wang, Z. (2020).** Cytotoxic and antiproliferative effects of β-mangostin on Rat C6 glioma cells depend on oxidative stress induction via PI3K/AKT/mTOR pathway inhibition. Drug Design, Development and Therapy. 14: 5315-5324.
92. **Masoumi, J., Jafarzadeh, A., Abdolalizadeh, J., et al. (2021).** Cancer stem cell-targeted chimeric antigen receptor (CAR)-T cell therapy: challenges and prospects. Acta Pharmaceutica Sinica B. 11(7): 1721-1739.

93. **Nazio, F., Bordi, M., Cianfanelli, V., Locatelli, F., Cecconi, F. (2019).** Autophagy and cancer stem cells: molecular mechanisms and therapeutic applications. Cell Death & Differentiation. 26(4): 690-702.
94. **Annett, S., Robson, T. (2018).** Targeting cancer stem cells in the clinic: current status and perspectives. Pharmacology & Therapeutics. 187: 13-30.
95. **Seo, E. S., Shin, M., Lim, H., et al. (2022).** Clinical implication of residual MIBG-positive disease in the follow-up of high-risk neuroblastoma treated with tandem high-dose chemotherapy and autologous stem cell transplantation. Pediatric Blood Cancer. 69(7):
96. **Suh, J. K., Koh, K.-Nam, Min, S. Y., et al. (2020).** Feasibility and effectiveness of treatment strategy of tandem high-dose chemotherapy and autologous stem cell transplantation in combination with 131I-MIBG therapy for high-risk neuroblastoma. Pediatric Transplantation. 24(2):
97. **Emami Nejad, A., Najafgholian, S., Rostami, A., et al. (2021).** The role of hypoxia in the tumour microenvironment and development of cancer stem cell: a novel approach to developing treatment. Cancer Cell International. 21(1): 1-26.
98. **Boesch, M., Spizzo, G., Seeber, A. (2018).** Concise review: aggressive colorectal cancer: role of epithelial cell adhesion molecule in cancer stem cells and epithelial-to-mesenchymal transition. Stem Cells Translational Medicine. 7(6): 495-501.
99. **Jayson, G.C., Kerbel, R., Ellis, L.M., Harris, A.L. (2021).** Antiangiogenic therapy in oncology: current status and future directions. Lancet. 397(10280): 1111-1123.
100. **Gu, C.M., Zhan, Y.R., Chen, Y.F. (2020).** Analysis of icariin in herba epimedii drug-containing serum and study on its antitumor effect *in vitro*. Journal of Guangdong Pharmaceutical University. 36(4): 499-503.