Resveratrol in Brain Cancer

Subjects: Oncology

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A brain tumor (BT) is a condition in which there is growth or uncontrolled development of the brain cells, which usually goes unrecognized or is diagnosed at the later stages. Since the mechanism behind BT is not clear, and the various physiological conditions are difficult to diagnose, the success rate of BT is not very high. This is the central issue faced during drug development and clinical trials with almost all types of neurodegenerative disorders. Resveratrol (RES) is a polyphenol extracted from mulberries (*Morus species*), grapes (*Vitis vinifera*), and peanuts (*Arachis hypogaea*). It is a phytoalexin that spermatophytic plants make in reaction to stress, damage, or UV radiation, as well as fungus (e.g., Botrytis cinerea) and/or another pathogen. RES has been proven to have antioxidant, anti-inflammatory, cardioprotective, and analgesic properties, as well as a function in diabetes and obesity. Because of its growing importance in neurological illnesses such as Parkinson's, Alzheimer's, and other neurodegenerative disorders, as well as BT, RES has received a lot of attention.

brain tumor blood–brain barrier P-glycoprotein

1. A Basic Outline on Resveratrol

Resveratrol (RES) is a polyphenol extracted from mulberries (*Morus species*), grapes (*Vitis vinifera*), and peanuts (*Arachis hypogaea*). It is a phytoalexin that spermatophytic plants make in reaction to stress, damage, or UV radiation, as well as fungus (e.g., Botrytis cinerea) and/or another pathogen [1]. Several biotic and abiotic factors have been investigated in the context of induced RES production in a variety of plants. Plants synthesize RES via the phenylalanine route [2]. Resveratrol 3-O-beta-glycosyltransferases convert the end product to trans form, which can subsequently isomerize to cis form or trans and cis-priced. Furthermore, the stilbene route is a branch of the phenylpropanoid system, which is an extension of the flavonoid pathway [3]. Michio Takaoka isolated RES from the root of *Veratrum grandiflorum O*. Loes in 1939. In 1963, RES was determined to be a chemical component of *Polygonum cuspidatum* (Ko-jo-kon). The first known detection technique for trans-resveratrol was published in 1976. Renaud and de Lorgeril first published the "French paradox" in 1992, after which RES faded into oblivion [4]. The French paradox is based on epidemiological evidence from French people who had a high-fat, high-cholesterol diet while having a low incidence of coronary heart disease. In reality, as compared to the United Kingdom, the United States, or Sweden, France continues to have a low incidence and mortality rate from coronary heart disease. The concentration of RES in various wines was examined the same year [5]. A 2001 study discovered a link between moderate-to-low wine consumption and a decreased risk of mortality from cardiovascular and cerebrovascular disorders. Following these discoveries, the French paradox sparked widespread interest, with

hundreds of research projects conducted on various parts of it [6]. RES has been proven to have antioxidant, anti-inflammatory, cardioprotective, and analgesic properties, as well as a function in diabetes and obesity. Because of its growing importance in neurological illnesses such as Parkinson's, Alzheimer's, and other neurodegenerative disorders, as well as BT, RES has received a lot of attention [7]. RES has also been shown to have anticancer characteristics in a variety of different malignancies, including prostate cancer, liver cancer, breast cancer, lung cancer, skin cancer, and colorectal cancer [8].

2. A Background Search on Brain Cancer

A brain tumor (BT) is an unconditional development of cells in the brain [9]. The symptoms of BT are difficult to diagnose, and the symptoms worsen during the progression of this disease. BT can originate in the brain (known as primary BT) or spread from other parts of the body (known as secondary or metastatic BT). The growth and location in the brain determine the response of cancer to nervous functioning [10]. The symptoms and mitigation options are also contingent on the size and location. The condition or state in which a tumor cannot be detected in human body is called remission. Another problem that causes treatment failure is the recurrence of cancer after treatment [11]. The risk of reoccurrence can be in the original location or other parts of the body. If the tumor spreads, that is, when metastasis occurs, then the success rate of the treatment is reduced to 15% [12]. It is not always possible to recover from BT. If the tumor cannot be controlled or cured, then the disease may be called terminal or advanced. When diagnosed with advanced BT, the expected life span is calculated to be less than 6 months [13].

Primary BTs generally initiate in the brain or the tissues closer to the brain, such as the pituitary gland, cranial nerves, pineal gland, or meninges-brain covering membrane. The origin of BT is generally a mutation in the DNA, which results in the uncontrollable division of the brain cells and the death of the healthy cells [14]. In adults, primary BT is more prevalent than secondary BT.

Cancer growth can reduce blood flow even in perineural regions by compressing blood vessels due to the limited space in the brain. Furthermore, the neurovascular unit develops differently in the cancer core compared to the cancer periphery and neuroparenchyma, the latter of which has an intact blood–brain barrier (BBB) as BT lesions grow [15].

The cancer vasculature becomes increasingly heterogeneous as the primary BT progresses and brain metastasis develops. Neuronal viability and vascular function are directly affected by local and distal changes caused by an expanding neoplastic lesion [16]. Because the vasculature changes during cancer growth, existing vessels must be co-opted, and/or new ones must be created through angiogenesis to meet the nutritional needs of proliferating cancer cells. Postnatal vasculogenesis, vascular mimicry, intussusception, and transdifferentiation are some of the other mechanisms by which cancers increase blood vessel supply [17]. Cancer progression is accompanied by vascular dysfunction and an acidic microenvironment, which are fueled in part by hypoxia-inducible factor 1 (HIF1) transcriptional programs. Studies reported that when vascular endothelial growth factor (VEGF) signaling is

blocked in mice, BTs are lopped into their immature and leaky vessels, and the remaining vasculature is actively remodeled to look like normal vasculature [18].

Surgery, chemotherapy, radiotherapy, and targeted therapy are some of the treatment options for BT. The option used for low-grade cancer is mostly surgical removal of the tumor [19]. Medications are used as a treatment option to destroy cancer cells, categorized as chemotherapy and targeted therapy. A chemotherapeutic regimen is used to inhibit cancer cell division and the growth of the cancer cells, which can destroy the cancer cells and reduce the symptoms. Sometimes, chemotherapy is suggested after radiotherapy or surgery. Drugs that can bypass the BBB are commonly used as BT drugs, such as canmustine, temozolomide, and combinations of vincristine, lomustine, and procarbazine [20]. If the growth of the cancer cells is not retarded, then other treatment options are taken into consideration. In addition to standard chemotherapy, an alternative is targeted therapy, such as anti-angiogenesis therapy or therapy that focuses on genetic changes.

The chemical-based treatment strategy has various side effects and toxic effects, which include hair loss, nausea, vomiting, fatigue, diarrhea, loss of appetite, etc. [21]. Some drugs may even cause hair loss, kidney damage, and increase the risk of infection [22]. Current research focusing on natural remedies for mitigating BT lags behind, partially because there is no clear-cut idea about the BT mechanism itself. However, herbal and natural remedies may help to reduce the risk of BT, ease some of its symptoms, and even inhibit cell growth [23]. Herbal remedies are generally recommended as safe, even under long use and in larger doses. Hence, the combination of a drug or a natural compound and a chemotherapeutic drug could be a possible effective therapeutic modality for the mitigation of BT.

3. RES—A General Concept and a Basic Outline

RES is a plant-derived polyphenol found in berries, grapes, nuts, and red wine [1]. RES crosses the BBB, which may have an impact on the nervous system [24]. It also affects the enzyme isocitrate dehydrogenase and, more importantly, resistance to standard mitigation through a variety of mechanisms, including O6-methylguanine methyltransferase. For example, RES was shown to inhibit resistance to standard alkylating agents such as temozolomide by inhibiting O6-methylguanine methyltransferase activity [25].

RES is a low-toxicity molecule that targets specific potential biological signaling pathways and affects several carcinogenesis-related genes [26]. The important antiproliferative capability of RES was already indicated in a diverse array of cancer forms when administrated alone or in addition to various anticancer agents and targeted therapies. Its ability to prevent BT includes the inhibition of oxidative stress and inflammation and also the regulation of cell proliferation through the signaling of apoptosis pathways. It may influence the activity of cancer cells by affecting various signaling mechanisms such as PI3K/AKT/mTOR, nuclear factor-kB (NF-kB), p53, Wnt, or even signal transducer and activator of transcription-3 (STAT3).

3.1. Resveratrol and Its Pharmacological Action in the General Aspect

3.1.1. Resveratrol's Pharmacological Influence on Immunity

The first research of RES on immunomodulatory effects revealed that it suppressed interleukin-2-induced (IL-2) and spleen cell proliferation. It has a greater impact on lymphocyte and macrophage production of IL-2, IFN-β, and TNF/IL-12 [27]. RES is either directly or indirectly involved in the establishment and modulation of innate and adaptive immunity [28]. The immune system is affected by RES in a dose-dependent manner. At low dosages, it activates the immune system for an immunological response, while at higher levels, it suppresses the immune system [29]. Another research discovered that it promoted chicken growth by increasing immune responses and decreasing immunocyte mortality. RES inhibited the Toll/IL-1 receptor, reducing the activity of the respiratory syncytial virus [30]. RES suppressed enterovirus replication and reduced the virus's generation of IL-6 and TNF-α [31]. RES increased CD4+ cell proliferation, splenic lymphocyte proliferation, and peritoneal macrophage activity in mice [32]. Intravenous RES therapy decreases ischemia-induced inflammation and oxidants produced by HX/XO, but not leukotriene B4 [33].

3.1.2. Resveratrol's Effect on Cancer

Jang et al. discovered that RES could suppress carcinogenesis in mouse skin cancer models, and further research has confirmed this conclusion [34]. Later, it was shown that RES inhibited cancer cell growth in the ovary, stomach, intestine, prostate, colon, liver, pancreas, brain, and thyroid. In HL-60 leukemic cells, RES decreased free radical production caused by 12-O-tetradecanoylphorbol-13-acetate [35]. By scavenging OH and superoxide generated by cells, as well as lipid peroxidation occurring inside cell membranes, RES protects against DNA damage caused by ROS production. The antimutagenicity of N-methyl-N-nitro-N-nitrosoguanidine in *S. Typhimurium strain* TA100 was shown using RES. A recent study in colorectal cancer has revealed that RES is a multifunctional factor with anti-inflammatory and anticancer properties [36]. They have also been shown to block the NF-kB signaling pathway. RES has also been demonstrated to inhibit TNF-α stimulated colorectal cell invasion and viability. RES also suppressed the activation of NF-kB and carcinogenic gene products in colorectal cells, as well as other signaling molecules such as vimentin, slug, and E-cadherin [37].

3.1.3. Toxicity Effects of Resveratrol

Several researchers have found that RES has harmful impacts. After 24 h, no adverse effects were seen in 15 healthy volunteers who received a single high dose (500 mg) of RES while fasting. Long-term therapy with RES at a dosage of 2.5 g per day, however, produced vomiting, diarrhea, and nausea in healthy patients [38]. Surprisingly, long-term (up to one year) intake of grape RES at levels as high as 16 mg exhibited no discernible negative effects. After a dose of 5 g RES in the form of SRT501 (developed by Sirtris, a GSK company) was administered in two cycles during multiple myeloma, renal toxicity was observed in healthy controls, type 2 diabetics, and patients with lactic acidosis, mitochondrial encephalomyopathy, and stroke-like episodes (MELAS) syndrome. The researchers concluded that the appropriate amount of RES is required to treat a range of disorders [7].

4. RES Brain Delivery

RES use has been linked to several health benefits, including anti-inflammatory, anti-carcinogenic, and brain inhibitory responses [39]. The neuroprotective responses of RES in neurological diseases like Alzheimer's (AD) [40] and Parkinson's (PD) [41] are signified by the establishment of neurons that are protected from oxidative damage and toxicity, as well as the prevention of apoptotic neuronal death [42]. In BTs, RES induces cell apoptosis while inhibiting angiogenesis and cancer invasion. Despite its enormous potential as a therapeutic agent for a wide range of diseases, RES has some barriers [4]. It is chemically unbalanced and is degraded by isomerization when unprotected from high temperatures, pH changes, UV light, low water solubility, or specific enzymes [43]. As a result, RES has limited biological, low bioavailability, and pharmacological benefits. To get around these restrictions, RES can be carried via nanocarriers [2]. This subfield of nanomedicine studies how the use of nanoscale materials affects pharmacokinetics, drug administration, and pharmacodynamics [44]. The use of nanotechnology in the mitigation and prevention of neurological diseases also conceals the physicochemical assets of therapeutic drugs to enhance their half-life and cross the BBB. This is essentially achieved by encapsulating the drug in a nanoparticle (NP) composed of an array of substances [45]. There is a rising trend to encapsulate and deliver RES to the brain. RES encapsulated liposomes, lipid nanoparticles, and polymeric nanoparticles are being used to encapsulate RES. Furthermore, the majority of these nanocarriers have been obtained by targeting molecules that can recognize brain regions [3]. In both in vitro and in vivo experimental models, RES has been shown to regulate redox biology, mitochondrial function, and dynamics [46]. RES also mitigates the mitochondrial dysfunction caused by oxidative stress. RES regulates the release of mitochondrial antioxidant enzymes, limiting reactive species stimulation by these organelles [47]. RES also promotes mitochondrial biogenesis, which enhances mitochondrial bioenergetics in mammalian cells. The researchers discussed the responses of RES to brain mitochondria. Brain cells (both neuronal and glial) are vulnerable to mitochondrial dysfunction due to their high demand for ATP [48]. Moreover, brain cells produce a lot of oxygen, which causes the mitochondria to generate a lot of reactive species. As a result, strategies focusing on mitochondrial function restoration in these types of cells are of therapeutic interest in neurodegenerative diseases requiring mitochondrial impairment and enhancing reactive species capacity, resulting in neuroinflammation and cell death [49]. The mechanism by which RES protects mitochondrial function and dynamics is unknown, and more research is needed to determine how RES affects mitochondrial-related factors. Moreover, it is critical since RES, depending on the dosage, can cause cytotoxicity [1].

5. Combination, Synergistic Response, and the Response to Conventional Therapy

A combination strategy is proposed to produce a synergistic response. In this concept, two herbal ingredients or an herbal and a synthetic agent could be combined either by physical or chemical conjugation [50]. The combination of the herbal and synthetic agents is found to be best for the mitigation of BT as it could reduce the toxic response of the synthetic agent, which is achieved by reducing the dose [51].

The synergistic activity of the combination can be confirmed by using in vitro cell line studies. In addition, analytical methods are being used to confirm the compatibility of the drugs [52]. Focus on the combination strategy when used

with a synthetic chemotherapeutic agent can help in dose reduction and, hence, the toxic response can also be reduced. The use of herbal remedies mainly acts as a P-gp inhibitor; hence the efflux mechanism can be altered [39]. The combination of the herbal and the synthetic remedy can be conjugated using a chemical conjugation as well as a physical combination method. The addition of the lipids will help to cross the BBB as well as act as a P-gp inhibitor [53].

Many techniques, including prodrugs and nanotechnology-based technologies, have been attempted and employed to increase the bioavailability and cellular absorption of RES. The RES is entrapped and transported to the target location by a lipoidal layer and interior hydrophilic layers. Distinct encapsulating methods have varied advantages and disadvantages, as well as different impact qualities [54]. As a result, a nanocarrier system capable of extending molecule life while preserving biological and physical features is required. This focuses on unique RES management and execution strategies for increased treatment effectiveness [55].

Several techniques for delivering RES to the brain have been researched in recent years. Several materials have been utilized to encapsulate RES and increase its activity. Various drug delivery systems have been reported to have advantageous qualities such as increased stability, bioavailability, and biocompatibility. Several methods of extending the duration that NPs are in circulation may be employed. One of the most common approaches is the attachment or adsorption of many molecules to the surface of the NPs [7]. PEG and polysorbates, which are hydrophilic stabilizers, can be utilized. These molecules also provide steric stability to the NP surface, making it simpler to bind other ligand moieties such as antibodies, aptamers, and proteins recognized by BBB receptors [56]. These ligand molecules can aid the immune system in recognizing and eliminating NPs. PEG molecules on the surfaces of the NPs, on the other hand, prevent this behavior.

Targeted molecules might be added to the surface of the NP to increase the bioavailability of the encapsulated RES [57]. Because these ligand moieties connect to the BBB's existing receptors, NPs may be actively transported across the barrier, enabling brain tissue targeting. Electrostatic forces contribute to the binding of positively charged ligands to the luminal surface of BBB cells. Because the receptor for the ligand must be overexpressed at the BBB, it must be carefully targeted to brain tissue to prevent negative effects on healthy tissues while increasing RES accumulation. To avoid competitive binding of the natural ligand, the saturation of the receptor must also be carefully regulated [58].

Temozolomide is the standard treatment for glioblastoma, although it fails owing to numerous resistance mechanisms and biological obstacles [59]. The O (6)-Methylguanine DNA-methyltransferase (MGMT) protein is associated with temozolomide resistance because it repairs DNA damage caused by temozolomide-induced methylation. Huang and colleagues observed that RES prevented the activation of the NF-kB transcription factor in glioma cells, which is essential for MGMT activation [60]. As a result, RES enhances temozolomide effectiveness by reversing therapeutic resistance. According to previous research, RES improved the chemosensitization of glioma cells to temozolomide activity by altering many signaling pathways and producing apoptosis and cell cycle arrest [61].

6. Possible Route of Administration

Nowadays, most antineoplastic drugs for BT are administered either systemically, intravenously, or orally based on the drug's absorption. Although certain drugs have features that allow them to enter BTs, the constraints discussed above prevent most chemotherapies from being delivered [62].

The delivery of a drug intra-arterially (IA) is intended to increase the quantity of a drug delivered to a vascular region by bypassing first passage metabolism [63]. Nevertheless, for medications that travel efficiently through the CNS, reside time may be reduced, resulting in reduced effectiveness. So far, IA delivery alone has not resulted in a better prognosis for BT patients. Iatrogenic disruption of the BBB (BBBD) before standard chemotherapy has proven to have better outcomes. In preclinical models, IA chemotherapy combined with BBBD enhances the concentration of drugs in the brain parenchyma [64]. The most typical method is osmotic BBBD using drugs like mannitol, supplemented by IA chemotherapy [65]. However, MRI-guided ultrasound-induced BBBD has recently been studied. This provides for more concentrated BBBD and is well tolerated. However, the results of BBBD and IA chemotherapy have varied among tumor types, and the research has been unclear because of small sample sizes. Yet, there were some encouraging outcomes, especially in cancers that have historically been considered difficult to treat, such as brain stem gliomas. For anticancer medicines that are likely to link to tumor tissue (and so not be promptly effluxed) and for chemosensitive malignancies, including primary CNS lymphoma and germ cell tumors, BBBD and focused chemotherapy techniques show the most promise [66]. The negative effects of BBB disruption and IA drug delivery are often ischemic and are most possibly due to catheterization of the vessel for distribution as well as the irritative effects of the medication. It could also be significant neurotoxicity from therapy. BBBD with IA is mainly confined to a small number of skilled institutions since the operations are invasive, complicated, and accompanied by infrequent but possibly harmful comorbidities [67].

In preclinical models, standard radiation treatment used to treat primary and metastatic BT promotes BBB permeability. This is an especially noteworthy finding considering the shown effectiveness of temozolomide in individuals with freshly diagnosed glioblastoma multiforme (GBM) against the low usage of temozolomide alone for recurrent GBM [68]. Therapies that restore the BBB, on the other hand, may, in turn, reduce the drug's access to the tumor. Others suggest that normalization of the vasculature increases medication delivery by normalizing pressure gradients. If these theories are correct, a series of treatments that differently break but then repair the BBB may enhance drug transport (across a disrupted BBB) while maintaining drug concentrations within the tumor (by mending the BBB), permitting for optimal medication exposure of the tumor. Since 1996, when the US Food and Drug Administration licensed Gliadel (MGI Pharma, Bloomington, MN) for recurrent high-grade gliomas, patients suffering from malignant gliomas have had access to polymer-based drug delivery. Gliadel is a polyanhydride biodegradable polymer wafer impregnated with BCNU (carmustine) that is inserted into the surgical cavity during tumor debulking and has resulted in a 2-month improvement in outcomes in patients with both diagnosed and recurring malignant gliomas [69]. It is generally tolerated, and side effects such as increasing edema, cerebrospinal fluid leakage, and delayed wound healing are uncommon. This method provides local disease management but is hampered by the limited release of BCNU distant from the resection cavity. It is also limited to individuals with restricted cancer who can endure a complete gross resection. Despite these limitations, Gliadel can be quite

successful when utilized as a part of a multimodal strategy [70]. Gliadel in conjunction with systemic medicines, such as temozolomide and O6-benzylguanine, is also being studied. Finally, new research indicates that the highest tolerable dose of BCNU in polymers in patients with recurrent gliomas may be 40 mg, rather than the 7.7 mg presently allowed and utilized in clinical practice. Efficacy trials at a higher dosage may yield even better survival outcomes. Gliadel is being used to treat brain metastases. Patients with single brain metastases from distinct solid tumors received resection, Gliadel wafer insertion, or whole irradiation. There were no local herpes outbreaks in 25 patients, and overall survival was 25% after 2 years. Gliadel appeared to manage local illness, and it was well tolerated [71].

Several alternative devices for local distribution have already been developed after Gliadel's certification. Phase II studies with paclitaxel employing gel technology (ReGel; Protherics, London, UK) in adults with chronic gliomas are now underway. The gel fits the contour of the resection cavity and gradually releases paclitaxel for 4 to 6 weeks [72]. Placing cisplatin-infused plates inside a tumor is another local delivery approach that has shown early potential. According to preliminary findings, they are well tolerated in individuals with newly diagnosed GBM undergoing radiation treatment. The median survival time was 14 months versus 7 months for the control group. All of these techniques are constrained by the necessity for surgical resection and result in a restricted distribution area; hence, they cannot control the full range of infiltrative BT. Furthermore, the regulatory process for such devices is time-consuming, necessitating a fresh testing and approval process for each combination of delivery method and medicine [73]. Local delivery systems, however, provide a direct, well-tolerated, and effective therapy in certain individuals and may serve as the cornerstone of a successful multimodal strategy. Convection-enhanced delivery (CED) uses catheters implanted into and around a tumor to administer anticancer medicines with hydrostatic pressure. It is an appealing strategy for drugs that are too big to penetrate the BBB or too toxic for systemic delivery. That is a very appealing strategy for conjugated, targeted toxin therapy, antibodies, and sometimes even entire cells [12]. The Phase III Randomized Analysis of Convection-Enhanced Delivery of IL13-PE38QQR to Survival Endpoint (PRECISE) trial, which investigated interleukin-13 conjugated to cintredekin besudotox (PE38QQR), and also the TransMID (transferrin-CRM107) trial, which investigated a modified diphtheria toxin (CRM107) conjugated to transferrin in patients with relapsed malignant gliomas. The median survival in the PRECISE trial was 36.4 weeks (compared with 35.3 weeks with Gliadel). The TransMID trial was recently halted at the interval analysis stage to determine the probability of improved overall survival compared with standard second-line glioma therapies, and final results are still pending [74]. CED delivery has been used to test several other antibody-mediated therapies and immunotherapies. All had tolerable toxicity but highly variable efficacy.

CED has many of the same limitations as polymer-based therapies, such as a constrained distribution area and the need for surgery [75]. Furthermore, because drug delivery is dependent on high infusion rates, there may be a higher risk of neurotoxicity from enhanced intracranial pressure. Innately, more catheters installed throughout heterogeneous tumors should result in more delivery; even so, this may be technically complex, and it has not been demonstrated in clinical practice. The most likely case is that other factors, including the rate of efflux from the CNS, proximity to white matter tracks, and bulk flow patterns, influence the delivery, and hence the efficacy, of the infused agent [76]. Because drug distribution is a major limitation of CED, imaging techniques such as fluorodeoxyglucose–positron emission tomography (FDG-PET), diffusion-weighted imaging (DWI), MRI, and single

photo emission computed tomography (SPECT) are progressively used to image agents inside the brain after CED [77].

A blood–CSF (B-CSF) barrier exists in addition to the BBB. The barrier is made up of fenestrated endothelial cells on the luminal side as well as tightly joined epithelial cells without fenestration on the basolateral side (the ependyma). Multidrug resistance transporters are expressed all along the B-CSF barrier, limiting drug entry from systemic circulation to the CSF and clearing drugs attempting to enter the CSF from the brain [78]. Given that leptomeningeal disease affects up to 5% to 15% of patients with solid tumors, there have been concerted attempts to improve drug delivery to CSF spaces. There are three methods for delivering drugs into the CSF spaces: intrathecal, intraventricular, and intracavitary. Multiple processes are needed for this procedure, and drugs may have limited numbers all across CSF pathways [79]. Intraventricular administration of drugs necessitates the use of hardware (i.e., implanted reservoirs), and it is likely to lead to increased drug volume distribution throughout CSF pathways. Even though it is well tolerated, there are a few side effects, such as arachnoiditis, meningitis, and focal neurologic injury. Besides this, if there are CSF flow abnormalities, each of these methods will result in a reduced volume of distribution (and potentially increased toxicity). Because these abnormalities are frequent in people with leptomeningeal disease, CSF flow research must be ordered before starting any CSF drug transfusion [80].

Anticancer therapies can be delivered directly to tumor cysts or cavities via implanted reservoirs. In patients with recurrent malignant glioma, for example, a phase II trial of chlorotoxin combined with the radioisotope 131I (131I-TM-601) infuses radioactive therapy into the tumor resection cavity via an Ommaya reservoir. This method allows for repeat dosing but is limited due to the limited volume of distribution [81].

The anticancer activity of RES can be influenced by different administration techniques. Bioavailability improves when RES is protected from considerable metabolization in the gastrointestinal tract and liver, which is especially essential in intracranial cancers [82]. Following RES mitigation, there is a wide range of apoptotic foci with reduced Cyclin D1 staining, as well as increased autophagy with increased autophagy-related proteins LC3 as well as Beclin 1, and improved autophagy with increased autophagy-related proteins LC3 and Beclin 1. As a result, novel therapeutic approaches are desperately needed [83]. The breakdown of the BBB is an important step in the development of therapies for central nervous system (CNS) syndromes. In this situation, the intranasal route of drug administration has also been projected as a non-invasive alternate route for straight targeting of the CNS [84]. This method of drug administration avoids the BBB, reducing systemic toxicity. Some formulations, primarily based on the use of nano-sized and nanostructured therapeutic agents, have recently been developed to improve nose-to-brain transport [85]. The purpose is to deliver a summary of the approaches advanced for delivering anticancer compounds via nasal administration to mitigate GBM. Particular attention will be paid to the properties of nanomedicines proposed for nose-to-brain delivery [85]. Preclinical and clinical data suggest that nasal delivery of anticancer drugs could be a game-changer in the fight against GBM. The BBB keeps potential mitigation moieties from entering the brain. Directly targeting the brain via olfactory and trigeminal neural pathways, even while passing through the BBB, has grown in importance for the delivery of a wide range of therapeutics to the brain. The intranasal route of administration delivers drugs to the brain without causing systemic absorption, avoiding side responses, and increasing neurotherapeutic potency [86]. Various drug delivery systems (DDSs) for targeting the

brain via the nasal route have been researched in the last several decades. For example, liposomes, nanoparticles (NPs), and polymeric micelles are examples of novel DDSs that can be responsive tools for targeting the brain without causing toxicity in the nasal mucosa and CNS [87]. Mayuri and Shilpa, in 2017, found out that cubosomal in situ nasal gel containing RES was found to be effective for brain targeting [88]. Valentina et al. developed lipid microparticles (LMs) that were untreated or coated with chitosan and contained the neuroprotective polyphenol resveratrol for nasal delivery [89].

References

1. Shaito, A.; Posadino, A.M.; Younes, N.; Hasan, H.; Halabi, S.; Alhababi, D.; Al-Mohannadi, A.; Abdel-Rahman, W.M.; Eid, A.H.; Nasrallah, G.K.; et al. Potential Adverse Effects of Resveratrol: A Literature Review. Int. J. Mol. Sci. 2020, 21, 2084.
2. Santos, A.C.; Pereira, I.; Pereira-Silva, M.; Ferreira, L.; Caldas, M.; Magalhães, M.; Figueiras, A.; Ribeiro, A.J.; Veiga, F. Nanocarriers for Resveratrol Delivery: Impact on Stability and Solubility Concerns. Trends Food Sci. Technol. 2019, 91, 483–497.
3. Annaji, M.; Poudel, I.; Boddu, S.H.S.; Arnold, R.D.; Tiwari, A.K.; Babu, R.J. Resveratrol-loaded Nanomedicines for Cancer Applications. Cancer Rep. 2021, 4, e1353.
4. Kaur, A.; Tiwari, R.; Tiwari, G.; Ramachandran, V. Resveratrol: A Vital Therapeutic Agent with Multiple Health Benefits. Drug Res. 2022, 72, 5–17.
5. Chen, L.-G.; Wang, C.-C.; Lee, Y.-S.; Sie, Y.-Y.; Chang, C.-I.; Hou, W.-C. Vitisin A, a Resveratrol Tetramer, Improves Scopolamine-Induced Impaired Learning and Memory Functions in Amnesiac ICR Mice. Biomedicines 2022, 10, 273.
6. Liu, Y.; Song, X.; Wu, M.; Wu, J.; Liu, J. Synergistic Effects of Resveratrol and Temozolomide against Glioblastoma Cells: Underlying Mechanism and Therapeutic Implications. Cancer Manag. Res. 2020, 12, 8341.
7. Chopra, H.; Bibi, S.; Islam, F.; Ahmad, S.U.; Olawale, O.A.; Alhumaydhi, F.A.; Marzouki, R.; Baig, A.A.; Emran, T. Bin Emerging Trends in the Delivery of Resveratrol by Nanostructures: Applications of Nanotechnology in Life Sciences. J. Nanomater. 2022, 2022, 3083728.
8. Jøraholmen, M.W.; Johannessen, M.; Gravningen, K.; Puolakkainen, M.; Acharya, G.; Basnet, P.; Škalko-Basnet, N. Liposomes-in-Hydrogel Delivery System Enhances the Potential of Resveratrol in Combating Vaginal Chlamydia Infection. Pharmaceutics 2020, 12, 1203.
9. Bagchi, S.; Chhibber, T.; Lahooti, B.; Verma, A.; Borse, V.; Jayant, R.D. In-Vitro Blood-Brain Barrier Models for Drug Screening and Permeation Studies: An Overview. Drug Des. Devel. Ther. 2019, 13, 3591.

10. Sevenich, L. Brain-Resident Microglia and Blood-Borne Macrophages Orchestrate Central Nervous System Inflammation in Neurodegenerative Disorders and Brain Cancer. Front. Immunol. 2018, 9, 697.
11. Hays, P. Trends in Precision Oncology and Precision Medicine 2.0. In Advancing Healthcare through Personalized Medicine; Springer: Berlin/Heidelberg, Germany, 2021; pp. 419–480.
12. Lim, J.X.; Karlsson, B.; Pang, A.; Vellayappan, B.A.; Nga, V. Stereotactic Radiosurgery in Alveolar Soft Part Sarcoma Brain Metastases: Case Series and Literature Review. J. Clin. Neurosci. 2021, 93, 227–230.
13. Ardern-Holmes, S.; White, C.; Bahure, S.; So, S.; McCowage, G.; Hovey, E.; Troon, S.; De Souza, P.; Simes, J.; Slancar, M. The Effect of Bevacizumab on Vestibular Schwannoma Related to Neurofibromatosis Type 2. Australas. J. Neurosci. 2021, 31, 5–14.
14. Uddin, M.; Mamun, A.A.; Rahman, M.; Kabir, M.; Alkahtani, S.; Alanazi, I.S.; Perveen, A.; Ashraf, G.M.; Bin-Jumah, M.N.; Abdel-Daim, M.M. Exploring the Promise of Flavonoids to Combat Neuropathic Pain: From Molecular Mechanisms to Therapeutic Implications. Front. Neurosci. 2020, 14, 478.
15. Kadry, H.; Noorani, B.; Cucullo, L. A Blood–Brain Barrier Overview on Structure, Function, Impairment, and Biomarkers of Integrity. Fluids Barriers CNS 2020, 17, 69.
16. Patel, D.K.; Gwathmey, K.G. Neoplastic Nerve Lesions. Neurol. Sci. 2022, 43, 3019–3038.
17. Zuazo-Gaztelu, I.; Casanovas, O. Unraveling the Role of Angiogenesis in Cancer Ecosystems. Front. Oncol. 2018, 8, 248.
18. Yang, L.; Xie, X.; Tu, Z.; Fu, J.; Xu, D.; Zhou, Y. The Signal Pathways and Treatment of Cytokine Storm in COVID-19. Signal Transduct. Target. Ther. 2021, 6, 255.
19. Kumar, M.; Noronha, S.; Rangaraj, N.; Moiyadi, A.; Shetty, P.; Singh, V.K. Choice of Intraoperative Ultrasound Adjuncts for Brain Tumor Surgery. medRxiv 2022.
20. Elfadadny, A.; El-Husseiny, H.M.; Abugomaa, A.; Ragab, R.F.; Mady, E.A.; Aboubakr, M.; Samir, H.; Mandour, A.S.; El-Mleeh, A.; El-Far, A.H.; et al. Role of Multidrug Resistance-Associated Proteins in Cancer Therapeutics: Past, Present, and Future Perspectives. Environ. Sci. Pollut. Res. 2021, 28, 49447–49466.
21. Quiñones, S. Sea Moss for Hair: Discover How You Can Solve Hair Loss, Hair Damage, Hair Breakage, Frizz, Split-Ends, Scalp Irritation, and Much More Using Dr. Sebi’s Guide on How to Use Sea Moss on Hair; 2021.
22. Ozsahin, D.U.; Meck, K.; Halimani, S.T.; Uzun, B.; Ozsahin, I. Fuzzy PROMETHEE-Based Evaluation of Brain Cancer Treatment Techniques. In Applications of Multi-Criteria Decision-

Making Theories in Healthcare and Biomedical Engineering; Elsevier: Amsterdam, The Netherlands, 2021; pp. 41–58.

23. Silva dos Santos, J.; Goncalves Cirino, J.P.; de Oliveira Carvalho, P.; Ortega, M.M. The Pharmacological Action of Kaempferol in Central Nervous System Diseases: A Review. Front. Pharmacol. 2021, 11, 565700.
24. Rahman, M.; Akter, R.; Bhattacharya, T.; Abdel-Daim, M.M.; Alkahtani, S.; Arafah, M.W.; Al-Johani, N.S.; Alhoshani, N.M.; Alkeraishan, N.; Alhenaky, A.; et al. Resveratrol and Neuroprotection: Impact and Its Therapeutic Potential in Alzheimer's Disease. Front. Pharmacol. 2020, 11, 2272.
25. Kiskova, T.; Kubatka, P.; Büsselberg, D.; Kassayova, M. The Plant-Derived Compound Resveratrol in Brain Cancer: A Review. Biomolecules 2020, 10, 161.
26. Chen, H.; Liu, R.H. Potential Mechanisms of Action of Dietary Phytochemicals for Cancer Prevention by Targeting Cellular Signaling Transduction Pathways. J. Agric. Food Chem. 2018, 66, 3260–3276.
27. Ntolkeras, G.; Barba, C.; Mavropoulos, A.; Vasileiadis, G.K.; Dardiotis, E.; Sakkas, L.I.; Hadjigeorgiou, G.; Bogdanos, D.P. On the Immunoregulatory Role of Statins in Multiple Sclerosis: The Effects on Th17 Cells. Immunol. Res. 2019, 67, 310–324.
28. Corogeanu, D.; Diebold, S.S. Direct and Indirect Engagement of Dendritic Cell Function by Antibodies Developed for Cancer Therapy. Clin. Exp. Immunol. 2022, uxac026.
29. Mukherjee, S.; Hussaini, R.; White, R.; Atwi, D.; Fried, A.; Sampat, S.; Piao, L.; Pan, Q.; Banerjee, P. TriCurin, a Synergistic Formulation of Curcumin, Resveratrol, and Epicatechin Gallate, Repolarizes Tumor-Associated Macrophages and Triggers an Immune Response to Cause Suppression of HPV+ Tumors. Cancer Immunol. Immunother. 2018, 67, 761–774.
30. Ascough, S.; Paterson, S.; Chiu, C. Induction and Subversion of Human Protective Immunity: Contrasting Influenza and Respiratory Syncytial Virus. Front. Immunol. 2018, 9, 323.
31. Bai, Z.; Zhao, X.; Li, C.; Sheng, C.; Li, H. EV71 Virus Reduces Nrf2 Activation to Promote Production of Reactive Oxygen Species in Infected Cells. Gut Pathog. 2020, 12, 22.
32. Liu, Z.; Ni, H.; Yu, L.; Xu, S.; Bo, R.; Qiu, T.; Gu, P.; Zhu, T.; He, J.; Wusiman, A.; et al. Adjuvant Activities of CTAB-Modified Polygonatum Sibiricum Polysaccharide Cubosomes on Immune Responses to Ovalbumin in Mice. Int. J. Biol. Macromol. 2020, 148, 793–801.
33. Gozin, A.; Sellak, H.; Franzini, E.; Pasquier, C. Reactive Oxygen Species Increase Neutrophil Adherence to Endothelial Cells and Activate Tyrosine Phosphorylation of Cytoskeleton Proteins. In Antioxidant Food Supplements in Human Health; Elsevier: Amsterdam, The Netherlands, 1999; pp. 371–384.

34. Kapadia, G.J.; Azuine, M.A.; Tokuda, H.; Takasaki, M.; Mukainaka, T.; Konoshima, T.; Nishino, H. Chemopreventive Effect of Resveratrol, Sesamol, Sesame Oil and Sunflower Oil in the Epstein–Barr Virus Early Antigen Activation Assay and the Mouse Skin Two-Stage Carcinogenesis. Pharmacol. Res. 2002, 45, 499–505.
35. Chang, S.N.; Khan, I.; Dey, D.K.; Cho, K.-H.; Hwang, B.S.; Bae, K.B.; Kang, S.C.; Park, J.G. Decursinol Angelate Ameliorates 12-O-Tetradecanoyl Phorbol-13-Acetate (TPA)-Induced NF-KB Activation on Mice Ears by Inhibiting Exaggerated Inflammatory Cell Infiltration, Oxidative Stress and pro-Inflammatory Cytokine Production. Food Chem. Toxicol. 2019, 132, 110699.
36. Zhang, Q.; Zhang, F.; Li, S.; Liu, R.; Jin, T.; Dou, Y.; Zhou, Z.; Zhang, J. A Multifunctional Nanotherapy for Targeted Treatment of Colon Cancer by Simultaneously Regulating Tumor Microenvironment. Theranostics 2019, 9, 3732.
37. Honari, M.; Shafabakhsh, R.; Reiter, R.J.; Mirzaei, H.; Asemi, Z. Resveratrol Is a Promising Agent for Colorectal Cancer Prevention and Treatment: Focus on Molecular Mechanisms. Cancer Cell Int. 2019, 19, 180.
38. Salem, H.F.; Kharshoum, R.M.; Abou-Taleb, H.A.; Naguib, D.M. Brain Targeting of Resveratrol through Intranasal Lipid Vesicles Labelled with Gold Nanoparticles: In Vivo Evaluation and Bioaccumulation Investigation Using Computed Tomography and Histopathological Examination. J. Drug Target. 2019, 27, 1127–1134.
39. Meng, T.; Xiao, D.; Muhammed, A.; Deng, J.; Chen, L.; He, J. Anti-Inflammatory Action and Mechanisms of Resveratrol. Molecules 2021, 26, 229.
40. Karthika, C.; Appu, A.P.; Akter, R.; Rahman, M.H.; Tagde, P.; Ashraf, G.M.; Abdel-Daim, M.M.; ul Hassan, S.S.; Abid, A.; Bungau, S. Potential Innovation against Alzheimer's Disorder: A Tricomponent Combination of Natural Antioxidants (Vitamin E, Quercetin, and Basil Oil) and the Development of Its Intranasal Delivery. Environ. Sci. Pollut. Res. 2022, 29, 10950–10965.
41. Tagde, P.; Tagde, S.; Tagde, P.; Bhattacharya, T.; Monzur, S.M.; Rahman, M.; Otrisal, P.; Behl, T.; Abdel-Daim, M.M.; Aleya, L. Nutraceuticals and Herbs in Reducing the Risk and Improving the Treatment of COVID-19 by Targeting SARS-CoV-2. Biomedicines 2021, 9, 1266.
42. Means, J.C.; Lopez, A.A.; Koulen, P. Resveratrol Protects Optic Nerve Head Astrocytes from Oxidative Stress-Induced Cell Death by Preventing Caspase-3 Activation, Tau Dephosphorylation at Ser422 and Formation of Misfolded Protein Aggregates. Cell. Mol. Neurobiol. 2020, 40, 911–926.
43. Assadpour, E.; Mahdi Jafari, S. A Systematic Review on Nanoencapsulation of Food Bioactive Ingredients and Nutraceuticals by Various Nanocarriers. Crit. Rev. Food Sci. Nutr. 2019, 59, 3129–3151.

44. Serov, N.; Vinogradov, V. Artificial Intelligence to Bring Nanomedicine to Life. Adv. Drug Deliv. Rev. 2022, 184, 114194.
45. Küjüktürkmen, B.; Bozkır, A. A New Approach for Drug Targeting to the Central Nervous System: Lipid Nanoparticles. Nanoarchitecton. Biomed. 2019, 335–369.
46. Böhmdorfer, M.; Szakmary, A.; Schiestl, R.H.; Vaquero, J.; Riha, J.; Brenner, S.; Thalhammer, T.; Szekeres, T.; Jäger, W. Involvement of UDP-Glucuronosyltransferases and Sulfotransferases in the Excretion and Tissue Distribution of Resveratrol in Mice. Nutrients 2017, 9, 1347.
47. Cao, G.; Yang, S.; Cao, J.; Tan, Z.; Wu, L.; Dong, F.; Ding, W.; Zhang, F. The Role of Oxidative Stress in Intervertebral Disc Degeneration. Oxid. Med. Cell. Longev. 2022, 2022, 2166817.
48. Castelli, V.; Grassi, D.; Bocale, R.; d'Angelo, M.; Antonosante, A.; Cimini, A.; Ferri, C.; Desideri, G. Diet and Brain Health: Which Role for Polyphenols? Curr. Pharm. Des. 2018, 24, 227–238.
49. Lin, M.; Liu, N.; Qin, Z.; Wang, Y. Mitochondrial-Derived Damage-Associated Molecular Patterns Amplify Neuroinflammation in Neurodegenerative Diseases. Acta Pharmacol. Sin. 2022, 1–9.
50. Karthika, C.; Hari, B.; Rahman, M.H.; Akter, R.; Najda, A.; Albadrani, G.M.; Sayed, A.A.; Akhtar, M.F.; Abdel-Daim, M.M. Multiple Strategies with the Synergistic Approach for Addressing Colorectal Cancer. Biomed. Pharmacother. 2021, 140, 111704.
51. Karthika, C.; Sureshkumar, R. Incorporation of Natural Assumption to Deal with Cancer. Environ. Sci. Pollut. Res. 2021, 28, 4902–4917.
52. Karthika, C.; Sureshkumar, R. Can Curcumin along with Chemotherapeutic Drug and Lipid Provide an Effective Treatment of Metastatic Colon Cancer and Alter Multidrug Resistance? Med. Hypotheses 2019, 132, 109325.
53. Zhu, M.; Wang, S. Functional Nucleic-Acid-Decorated Spherical Nanoparticles: Preparation Strategies and Current Applications in Cancer Therapy. Small Sci. 2021, 1, 2000056.
54. Koshani, R.; Jafari, S.M. Ultrasound-Assisted Preparation of Different Nanocarriers Loaded with Food Bioactive Ingredients. Adv. Colloid Interface Sci. 2019, 270, 123–146.
55. Cayero-Otero, M.D.; Espinosa-Oliva, A.M.; Herrera, A.J.; Garcia-Dominguez, I.; Fernandez-Arevalo, M.; Martin-Banderas, L.; de Pablos, R.M. Potential Use of Nanomedicine for the Anti-Inflammatory Treatment of Neurodegenerative Diseases. Curr. Pharm. Des. 2018, 24, 1589–1616.
56. Saraf, S.; Jain, A.; Tiwari, A.; Verma, A.; Panda, P.K.; Jain, S.K. Advances in Liposomal Drug Delivery to Cancer: An Overview. J. Drug Deliv. Sci. Technol. 2020, 56, 101549.
57. Botti, G.; Dalpiaz, A.; Pavan, B. Targeting Systems to the Brain Obtained by Merging Prodrugs, Nanoparticles, and Nasal Administration. Pharmaceutics 2021, 13, 1144.

58. Moura, R.P.; Martins, C.; Pinto, S.; Sousa, F.; Sarmento, B. Blood-Brain Barrier Receptors and Transporters: An Insight on Their Function and How to Exploit Them through Nanotechnology. Expert Opin. Drug Deliv. 2019, 16, 271–285.
59. Rock, C.L.; Thomson, C.; Gansler, T.; Gapstur, S.M.; McCullough, M.L.; Patel, A.V.; Andrews, K.S.; Bandera, E.V.; Spees, C.K.; Robien, K. American Cancer Society Guideline for Diet and Physical Activity for Cancer Prevention. CA Cancer J. Clin. 2020, 70, 245–271.
60. Du, H.-Y.; Olivo, M.; Mahendran, R.; Huang, Q.; Shen, H.-M.; Ong, C.-N.; Bay, B.-H. Hypericin Photoactivation Triggers Down-Regulation of Matrix Metalloproteinase-9 Expression in Well-Differentiated Human Nasopharyngeal Cancer Cells. Cell. Mol. life Sci. 2007, 64, 979–988.
61. Shahcheraghi, S.H.; Salemi, F.; Peirovi, N.; Ayatollahi, J.; Alam, W.; Khan, H.; Saso, L. Nrf2 Regulation by Curcumin: Molecular Aspects for Therapeutic Prospects. Molecules 2021, 27, 167.
62. Abbott, N.J.; Romero, I.A. Transporting Therapeutics across the Blood-Brain Barrier. Mol. Med. Today 1996, 2, 106–113.
63. Blakeley, J. Drug Delivery to Brain Tumors. Curr. Neurol. Neurosci. Rep. 2008, 8, 235–241.
64. D'Amico, R.S.; Khatri, D.; Reichman, N.; Patel, N.V.; Wong, T.; Fralin, S.R.; Li, M.; Ellis, J.A.; Ortiz, R.; Langer, D.J. Super Selective Intra-Arterial Cerebral Infusion of Modern Chemotherapeutics after Blood–Brain Barrier Disruption: Where Are We Now, and Where We Are Going. J. Neurooncol. 2020, 147, 261–278.
65. Chen, W.; Wu, Q.; Mo, L.; Nassi, M. Intra-Arterial Chemotherapy Is Not Superior to Intravenous Chemotherapy for Malignant Gliomas: A Systematic Review and Meta-Analysis. Eur. Neurol. 2013, 70, 124–132.
66. Joshi, S.; Ellis, J.A.; Ornstein, E.; Bruce, J.N. Intraarterial Drug Delivery for Glioblastoma Mutiforme. J. Neurooncol. 2015, 124, 333–343.
67. Donovan, M.D. Effect of Route of Administration and Distribution on Drug Action. In Modern Pharmaceutics Volume 1 Basic Principles and Systems; CRC Press: Boca Raton, FL, USA, 2009; p. 155.
68. Pająk, B. Looking for the Holy Grail—Drug Candidates for Glioblastoma Multiforme Chemotherapy. Biomedicines 2022, 10, 1001.
69. Ohnishi, T.; Yamashita, D.; Inoue, A.; Suehiro, S.; Ohue, S.; Kunieda, T. Is Interstitial Chemotherapy with Carmustine (BCNU) Wafers Effective against Local Recurrence of Glioblastoma? A Pharmacokinetic Study by Measurement of BCNU in the Tumor Resection Cavity. Brain Sci. 2022, 12, 567.
70. Parodi, A.; Rudzińska, M.; Deviatkin, A.A.; Soond, S.M.; Baldin, A.V.; Zamyatnin, A.A. Established and Emerging Strategies for Drug Delivery across the Blood-Brain Barrier in Brain Cancer.

Pharmaceutics 2019, 11, 245.

71. Liu, C.-A.; Harn, H.-J.; Chen, K.-P.; Lee, J.-H.; Lin, S.-Z.; Chiu, T.-L. Targeting the Axl and MTOR Pathway Synergizes Immunotherapy and Chemotherapy to Butylidenephthalide in a Recurrent GBM. J. Oncol. 2022, 2022, 3236058.
72. Stawicki, B.; Schacher, T.; Cho, H. Nanogels as a Versatile Drug Delivery System for Brain Cancer. Gels 2021, 7, 63.
73. Rahman, H.S.; Tan, B.L.; Othman, H.H.; Chartrand, M.S.; Pathak, Y.; Mohan, S.; Abdullah, R.; Alitheen, N.B. An Overview of In Vitro, In Vivo, and Computational Techniques for Cancer-Associated Angiogenesis Studies. Biomed Res. Int. 2020, 2020, 8857428.
74. Gatto, L.; Di Nunno, V.; Franceschi, E.; Tosoni, A.; Bartolini, S.; Brandes, A.A. Pharmacotherapeutic Treatment of Glioblastoma: Where Are We to Date? Drugs 2022, 82, 491–510.
75. Jaramillo-Botero, A.; Abrol, R.; van Duin, A.; Goddard III, W.A. Multiscale-Multiparadigm Modeling and Simulation of Nanometer Scale Systems and Processes for Nanomedical Applications. In Nanomedicine; Jenny Stanford Publishing: Dubai, United Arab Emirates, 2019; pp. 245–300. ISBN 0429065760.
76. Warren, K.E. Beyond the Blood: Brain Barrier: The Importance of Central Nervous System (CNS) Pharmacokinetics for the Treatment of CNS Tumors, Including Diffuse Intrinsic Pontine Glioma. Front. Oncol. 2018, 8, 239.
77. Novak, D.; Hüser, L.; Elton, J.J.; Umansky, V.; Altevogt, P.; Utikal, J. SOX2 in Development and Cancer Biology. In Seminars in Cancer Biology; Elsevier: Amsterdam, The Netherlands, 2020; Volume 67, pp. 74–82.
78. Gosselet, F.; Loiola, R.A.; Roig, A.; Rosell, A.; Culot, M. Central Nervous System Delivery of Molecules across the Blood-Brain Barrier. Neurochem. Int. 2021, 144, 104952.
79. Nzou, G.; Seeds, M.C.; Wicks, R.T.; Atala, A.J. Fundamental Neurovascular Components for the Development of Complex and Dynamic in Vitro Brain Equivalent Models. J. Alzheimers Neurodegener. Dis. 2019, 5, 21.
80. Schiopu, S.R.I.; Habl, G.; Haefner, M.; Katayama, S.; Herfarth, K.; Debus, J.; Sterzing, F. Helical Tomotherapy in Patients with Leptomeningeal Metastases. Cancer Manag. Res. 2019, 11, 401.
81. Feldman, L.; Chen, M. Delivery of Antineoplastic Therapeutics to the Central Nervous System. In Cancer Regional Therapy; Springer: Cham, Switzerland, 2019; pp. 427–438.
82. Gheorghiu, M.L.; Negreanu, F.; Fleseriu, M. Updates in the Medical Treatment of Pituitary Adenomas. Horm. Metab. Res. 2020, 52, 8–24.

83. Hecker, A.; Schellnegger, M.; Hofmann, E.; Luze, H.; Nischwitz, S.P.; Kamolz, L.; Kotzbeck, P. The Impact of Resveratrol on Skin Wound Healing, Scarring, and Aging. Int. Wound J. 2022, 19, 9–28.
84. Nath, R.; Roy, R.; Barai, G.; Bairagi, S.; Manna, S.; Chakraborty, R. Modern Developments of Nano Based Drug Delivery System by Combined with Phytochemicals-Presenting New Aspects. Int. J. Sci. Res. Sci. Technol. 2021, 8, 107–129.
85. Bonferoni, M.C.; Rossi, S.; Sandri, G.; Ferrari, F.; Gavini, E.; Rassu, G.; Giunchedi, P. Nanoemulsions for “Nose-to-Brain” Drug Delivery. Pharmaceutics 2019, 11, 84.
86. Hirlekar, R.S.; Momin, A.M. Advances in Drug Delivery from Nose to Brain: An Overview. Curr. Drug ther. 2018, 13, 4–24.
87. Fan, Y.; Chen, M.; Zhang, J.; Maincent, P.; Xia, X.; Wu, W. Updated Progress of Nanocarrier-Based Intranasal Drug Delivery Systems for Treatment of Brain Diseases. Crit. Rev. Ther. Drug Carr. Syst. 2018, 35, 433–467.
88. Ahirrao, M.; Shrotriya, S. In Vitro and in Vivo Evaluation of Cubosomal in Situ Nasal Gel Containing Resveratrol for Brain Targeting. Drug Dev. Ind. Pharm. 2017, 43, 1686–1693.
89. Trotta, V.; Pavan, B.; Ferraro, L.; Beggiato, S.; Traini, D.; Des Reis, L.G.; Scalia, S.; Dalpiaz, A. Brain Targeting of Resveratrol by Nasal Administration of Chitosan-Coated Lipid Microparticles. Eur. J. Pharm. Biopharm. 2018, 127, 250–259.