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Review Article

Statins as a Combatant for Treatment of Glioblastoma

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Abstract

The competitive HMG-CoA reductase (HMGCR) inhibitors, commonly referred to as "statins," have been shown in preclinical tests to have promise anticancer characteristics in addition to beingpotent medications that lower cholesterol and lower cardiovascular risk. When combined with other cancer treatment strategies, statins seem to improve the treatment outcome for a variety of malignancies. After surgical resection followed by concomitant radiation and chemotherapy, the median overall survival (OS) for glioblastoma multiforme (GBM), a particularly lethal cerebral tumour, is only about one year. Due to their capacity to inhibit cell growth, survival, migration, metastasis, inflammation, and angiogenesis in both in vitro and in vivo investigations, statins have recently come to light as prospective adjuvant medications for the treatment of GBM. Statins' therapeutic effects on the survival of GBM patients are still debatable, though. When just focusingon the treatment of cancer, specifically GBM, this study intends to analyse and address some of the known effects of statin medicines, including concurrent statin therapy with chemotherapeutic agents.

Keywords: statin, glioblastoma, brain tumor, antitumor, cholesterol, apoptosis.

Introduction

Despite different treatment modalities, such as the maximum safe surgical resection, radiation therapy, and chemotherapy with temozolomide (TMZ), patients of glioblastoma multiforme (GBM), one of the most aggressive cerebrum tumours, have an estimated survival of 12 to 18 months after diagnosis.[1] The competitive HMG-CoA reductase (HMGCR) inhibitors, commonly referred to as "statins," have been shown in preclinical tests to have promise anticancer characteristics in addition to being potent medications that lower cholesterol and lower cardiovascular risk.[2] In addition to finally allowing cholesterol to form, the mevalonate process may also produce important chemicals, such as non-sterol isoprenoids like dolichol, ubiquinol, farnesol, and geranylgeraniol.[3] The lipid-lowering drugs known as statins are very popular and frequently prescribed. They can be divided into two groups based on their source: natural or fungus-derived (simvastatin, pravastatin, and lovastatin) and synthetic (atorvastatin, rosuvastatin, fluvastatin, cerivastatin, and pitavastatin). The capacity of statins to block the extremely rate- limiting enzyme of the mevalonate pathway, 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase, is determined at the molecular level (HMGCR). They subsequently prevent the formation of geranylgeranyl diphosphate (GGPP) and farnesyl diphosphate (FPP), which are required to prenylate numerous proteins, including Rho, Rac1, and Ras (small G proteins).[4,5] Via the downstream signalling pathways, statins' alteration of Ras' prenylation controls cell growth, survival, migration, invasion, metastasis, and death. Several investigations have demonstrated thatboth in vitro and in vivo.[6,7] statins like atorvastatin have anticancer action by blocking the mevalonate system. Using statins for at least five years was linked to a relatively low risk of colorectal cancer, according to a case control analysis.[8] Another case-control study discovered thatmen who use statins may have a lower chance of developing prostate cancer.[9] Several investigations have revealed that statins cause a portion of tumor-derived cell lines' cells to undergo programmed death, indicating a susceptibility to statin-specific apoptosis in vivo.[10]

Only a few clinical trials have proven a link between statins and GBM survival, despite preclinical data supporting statin antitumor activity in GBM. Long-term statin medication may be advantageous for GBM patients, according to one clinical research.[11] Statins have been shown to block the invasion, migration, and differentiation of GBM cells in preclinical GBM investigations through Ras/Rho-prenylation.[12] A crucial and insidious function in the emergence of GBM is played by the mevalonate pathway, and more especially by HMGCR. HMGCR was found to be upregulated in a clinical GBM sample.[13] Statins may potentially cause apoptosis in GBMs by downregulating the antiapoptotic protein Bcl-2 and inhibiting extracellular signal- regulated kinase (ERK) 1/2 and protein kinase B (Akt).[14,15] This paper critically analyses evidence on the use of statins in the treatment of GBM and explores the effects of statins and their potential molecular anticancer pathways in preclinical investigations.

2. Possible cancer-fighting properties of statins

Increased endothelium and/or atherosclerotic plaque stability, anti-inflammatory, immunomodulatory, neuroprotective, and anticancer characteristics are among these advantages.

[16] Statins frequently suppress the synthesis of a number of different metabolites, such as isoprenoids, which are utilised to modify a number of proteins (Ras, Rac1, and RhoA) following transcription. This illustrates the cytoprotective effects of statins.[5] These molecules can explain the pharmacological anticancer effects of non-cholesterol-based statins because they are necessary fora number of vital cellular processes.[6] Statins may inhibit the small Rho GTPase protein family members' post-translational prenylation in cancer, preventing their translocation to the plasma membrane. This inhibits cell growth and triggers apoptosis. However, a research by Matzno et al. found that farnesylated Ras protein depletion rather than geranylated Rho protein was responsiblefor statin-induced apoptosis in muscle tissue.[7] The statin-mediated suppression of isoprenoids formation also aids in the induction of apoptosis and halts the progression of the cell cycle in certain cancer cell types.[17] Systematic reviews and meta-analyses, two types of large-scale reviews, have not consistently demonstrated a protective effect of statins against cancer.[13,14] A recent large cohort research including almost 200,000 people found that long-term statin treatment improved the survival rates of patients with various cancers.[11] Although statins as a class of medication mayreduce mortality in 6 breast cancer patients, a meta-analysis in 2017 revealed that the antitumor impact varies by statin type and is also modified by time to follow up.

[18] Lipophilic statins, such as simvastatin, atorvastatin, and fluvastatin, have demonstrated a significant protective role in patients with breast cancer. At the same time, all-cause mortality was slightly increased by hydrophilic statins, like rosuvastatin and pravastatin.[19] Statin users, however, demonstrated longer medium relapse-free survival and maintained a lower risk of recurrence in young breast cancer patients, according to numerous studies.[20,21] Promising outcomes have been obtained from in vivo studies as well. Simvastatin treatment has been shown to reduce the tumor size of xenografts made from breast cancer and prostate cancer cells in mice.[22]

2.1.Beginning of apoptosis

The transformation of a normal cell into a malignant cell can be seen as the result of a series of genetic alterations; for this reason, inducing programmed cell death, also known as apoptosis, is one of the crucial mechanisms used in the treatment of malignancies.[23] One study found that statinscause different cancer cells to undergo apoptosis via the mitochondrial pathway.[24] Pharmacologically, altered Ras or RhoA prenylation, the release of the second mitochondria-derived activator of caspases (Smac/DIABLO), and a decrease in mitochondrial membrane potential (m) are likely to control the pathways that statin-7 induces apoptosis.24 According to numerous studies, statins lower levels of the anti-apoptotic protein Bcl-2 expression, which increases Bax and Bim levels, caspases-2/-3/-8/-9 activation, poly (ADP ribose) polymerase (PARP) cleavage, and DNA laddering.[25] Simvastatin and lovastatin effectively decrease the viability of prostate cancer cells (PC3, DU145, and LnCap) by inducing apoptosis through the activation of caspases-3/-8/-9, according to data from the study by Hoque et al.[26] The effects of statins on myeloma tumor cells through caspase-dependent apoptosis have also been demonstrated by Cafforio et al.[24] According to these results, Fujiwara et al. suggested that statins increase caspase-3/-9 activation, induce the expression of Bim, stop the cell cycle at the G1 phase, and decrease m by inhibiting the Ras/ERK and Ras/mTOR pathways, all of which promote cell death.[27] This finding supports the idea that statins may be effective antitumor medications. The tumor necrosis factor (TNF) and Fas-L molecules play a role in mediating prostate cancer cell apoptosis, and simvastatin treatment causes increased mRNA and protein expression of these molecules.[28]

2.2. Statins' cytostatic effects

Statins prevent the synthesis of mevalonate, a precursor to cholesterol that is catalysed by HMGCR, as was mentioned in the preceding section.[15] Mevalonate overexpression has been linked to tumour development and cell survival. Statins that block the mevalonate pathway prevent the synthesis of GGPP and FPP and, as a result, a number of useful proteins, including RhoA, which is necessary for the post-translation of particular cell cycle regulatory proteins.[29] By controlling the cell cycle, statins have an antiproliferative and pro-apoptotic effect on cancer cells.[30] Statins have been shown to disrupt the G1 or S phases, which causes numerous cancer cells to undergo invitro apoptosis.[31,32]

Simvastatin has been discovered to cause breast cancer cells to die and disable the PI3K/Akt and mitogen-activated protein kinase (MAPK)/ERK signalling pathways.[33] Simvastatin, on the other hand, inhibited proliferation and caused cell cycle arrest in the G0/G1 phase (CDK4, CDK6, and cyclin D1) through PPAR- activation in bladder cancer cells by decreasing the abundance of the protein involved in the phase regulation of the G0- and G1-phase.[34] Simvastatin had no discernibleeffect on apoptosis and cleaved caspase-3/-9, however. This demonstrates how simvastatin affects the TP53, CDKN1A, and CDK1 genes that control the cell cycle. Higher 9 cell percentages in theG0/G1 phases and lower cell percentages in the S-phase are indicators that it suppresses cell growth.[35]

The ability of new simvastatin compounds to stop the S phase and induce apoptosis in prostate cancer has been demonstrated.[36] Recent research has shown that rosuvastatin polymeric nanocapsules have superior anticancer activity on human liver (HepG2) cancer cells through enhanced apoptosis and cell cycle arrest at the G2/M-phase, further highlighting their therapeuticpotential for hepatic cancer.

2.3. Potentiation of chemotherapeutic action

Adjuvant statin use has the potential to increase biological activity and reduce the resistance to conventional anticancer therapy, according to preclinical research.[37] This highlights a potentiating effect of statins against rectal cancer as they are linked to greater downstaging of rectal tumours and may play a role as adjuncts to neoadjuvant treatment, along with aspirin and metformin.[38]

An aminopeptidase inhibitor medication called tosedostat has demonstrated positive efficacy in treating acute myeloid leukemia (AML). Cloos et al. demonstrated that CHR2863, a structurally similar compound to tosedostat, potentiates the anticancer activity of various statins (fluvastatin, pravastatin, lovastatin, and simvastatin) in U937 AML cells. The synergy of CHR2863 with statins, which increases the sub-G1 percentage, was further supported by an increase in apoptotic induction and cell cycle arrest in 10 of the studies.[39] Retrospective analysis of persistent and refractory AML cases treated with tosedostat-containing combination therapy revealed a therapeutic benefit for statin-using individuals. In contrast to patients not taking statins, AML patients who were taking both statins and tosedostat had a 50% chance of surviving for six months.[40]

Statins upregulate proprotein convertase subtilisin/kexin type 9 (PCSK9) in addition to increasingthe expression of the low-density lipoprotein receptor (LDLR), which creates a

significant source for LDLR degradation.[41] The design of PCSK9 inhibitors can therefore improve the cholesterol-reducing capabilities of statins since this creates a negative feedback reaction that lessens the influence of statins on lipid reduction.[42] The potential link between PCSK9 inhibitors and cancer risk has been investigated in numerous clinical studies to date.[43] By decreasing the activity of the PCSK9 promoter, silibinin A, the main active component of silymarin, has been shown to reduce PCSK9 expression in HepG2 cells. Silibinin A may be discovered as a new PCSK9 inhibitor that can increase the efficacy of statin therapy since it particularly inhibits the statin-induced phosphorylation pathway of p38 MAPK.[44] Simvastatin, fluphenazine, and its two derivatives also increase the cytotoxicity of doxorubicin (0-35 M) when used in combination with doxorubicin-resistant colon cancer cells as compared to phenothiazine derivatives. Simvastatin treatment of colon cancer cells has been shown to enhance the anti-multidrug resistance (MDR), anti-inflammatory, and pro-apoptotic actions of phenothiazines, as shown by Roda-Pomianekthe et al.[45] Table 1 displays a few statin-based combination tactics for fighting different cancer forms.

2.4. Statin's antimetastatic effects

About 90% of all cancer-related deaths are caused by cancer metastasis,[46] which is also the main source of cancer mortality rates. Statins might be thought of as long-term adjuvant treatments to delay clinical crises and lower mortality in afflicted people since they can prevent the formation of metastatic tumours.[47] For the lipid moiety required for cell proliferation, adhesion, cell cycle progression, and signalling, transformed malignant cells predominantly rely on the mevalonate pathway.[48] The mevalonate pathway has been shown to be more active in a variety of tumours; as a result, inhibiting the mevalonate route using HMGCR inhibitors will result in a decrease in mevalonate and its products, which will have a strong inhibitory effect on cancer cell metastasis. [49] Rho serves a purpose, thus inhibiting its manufacture will reduce cell proliferation and thereby prevent the development of the tumour.[50] Rho activity may also be connected to the activity of cancer stem cells since tumours contain a population of cancer stem cells that can cause metastatic dissemination.[51] For instance, atorvastatin (0-250 M) demonstrates antitumorigenic and antimetastatic effects in ovarian cancer cells in vitro,[52] and simvastatin and atorvastatin both resultin a concentration-dependent reduction in the ability of human cholangiocarcinoma cells to form colonies and migrate.[53] Simvastatin also greatly increases DNA damage in ovarian cancer cells through the Akt/MAPK signalling cascade and decreases cell adherence and invasion.[54]

Epithelial-to-mesenchymal transformation (EMT), a dynamic multi-gene programming cycle, is apowerful cancer metastasis mechanism.[55] By blocking the mevalonate route, lipophilic statins have been demonstrated to adversely alter the EMT pathways of signalling stem-like cells in breast cancer.[56] In non-small cell lung cancer cells, atorvastatin attenuates the overexpression of SphK1, inhibits cell migration, and prevents actin filament remodelling, which all contribute to the partial inhibition of the EMT process brought on by transforming growth factor (TGF)-1.[57] Additionally, phosphatase and tensin homolog (PTEN)/Akt pathway downregulation and the activation of RhoBare two additional aspects of atorvastatin's carcinostatic effects on breast cancer, both in vitro and in vivo.[58]

3. Statins and GBM

GBM exhibits great invasiveness, rapid development, and apoptosis resistance.[59] Alternative therapeutic modalities should target to decrease proliferation and cause cell apoptosis as a drug repositioning strategy. In several tumoral cell lines, inhibiting HMGCR results in the induction of apoptosis and the decrease of tumour growth; however, the precise molecular mechanisms of statins, which are potential HMGCR inhibitors, are not well understood in GBM.[60] We have outlined the probable mechanisms and anticancer effects of statins in GBM from both preclinical and clinical research in the subsections that follow.

3.1 Preclinical research

The biosynthesis of cholesterol and the production of the intermediate metabolites GGPP and FPP, which are used in the prenylation of proteins, are both carried out by the mevalonate pathway, as was previously mentioned.[61] Notably, mevalonate and GGPP pretreatment significantly inhibit statin-induced apoptosis[62] and simvastatin induces cell death in a variety of human tumor cell lines, including astrocytoma, neuroblastoma, and GBM,[63] via the intrinsic apoptotic pathway. For instance, by inhibiting Ras-signaling in a prenylation-dependent manner, atorvastatin increases the effectiveness of TMZ in GBM.[64,65] The mevalonate pathway, which encourages apoptosis inhibition and cellular proliferation, is suppressed by cholesterol-lowering statins in this instance, which has been shown to improve the clinical outcomes of several malignancies.[66]

According to laboratory data, statins are showing promise as potential antitumor treatments for

14 GBM due to their pro-apoptotic, anti-proliferative, anti-invasive, radiosensitive, and radioprotective effects.[67,68] However, compared to the clinical plasma concentration used as a lipid-lowering agent, these preclinical studies have used high concentrations of statins.[69,70] For example, statins have been demonstrated by Weiss et al. to have proangiogenic effects at low therapeutic doses (nanomolar) but antiangiogenic effects at high doses (micromolar), which are reversible by GGPP.[69] The emergence of TMZ resistance in GBM following ongoing TMZ therapy is one of the fundamental issues with clinical GBM therapy. However, the study used a high dose of statins compared to clinically therapeutic concentrations.[71] As a result, the antitumor activities of statins against GBM are different from the anti-lipid effects and may depend on its concentration for efficacy.[72,73] Recently, statin therapy has shown an improved anti-GBM effect of TMZ in vitro.

Pharmacologically, lovastatin may cause autophagy induction through inhibition of the Akt/mTOR signaling cascade. The autophagosome-lysosome fusion machinery may also be impacted by lovastatin's suppression of lysosomal associated membrane protein-2 and dynein. These findings suggest that lovastatin has the potential to significantly increase the efficacy of TMZ chemotherapy in GBM cells. Combining TMZ and lovastatin may be a promising GBM therapy intervention because the mechanism may be related to impaired autophagic flux, which enhances apoptosis of the malignant cells.[74] For the treatment of GBM, the combination of statins and TMZ has demonstrated promise. Simvastatin, a blood-brain barrier permeable statin, also reduces theamount of autophagy induced by TMZ by preventing the development of autophagolysosomes.[75,76] The presence of acidic vesicular organelles (AVO), a sign of autophagy, is increased in A172 GBM cells after treatment with atorvastatin and TMZ, as demonstrated by Oliveira et al.[77] Simvastatin (0–50 M) was also found to induce the development of intracytoplasmic acidic vesicles that resemble autophagolysosomes in U251 and C6 GBM cells. Simvastatin-induced autophagy in vitro is confirmed mechanistically by the upregulation of the autophagosome-associated LC3-II, pro- autophagic beclin-1, and the downregulation of the selective autophagic target p62. Simvastatin is a central negative regulator for autophagy and

Akt activation, and it is interesting to note that it induces the activation of AMP- activated protein kinase (AMPK) and inhibits mTOR. These noteworthy results led Misirkic et al. to hypothesize that AMPK-dependent autophagic response inhibition might make GBM cells more susceptible to statin-induced apoptotic cell death.[78]

Statins have also been demonstrated to accelerate apoptosis and inhibit tumor growth in GBM.[78] In this regard, it has been suggested that lovastatin may make GBM cells more susceptible to apoptosis caused by TRAIL.[79] Lovastatin significantly increases the expression of DR5 in GBM cell lines and tumor-bearing mice, triggering the extrinsic apoptosis pathway.[80] Lovastatin has been shown to increase the short- and long-term cytotoxicity of TMZ and to induce GBM cell death in a dose-dependent manner. Additionally, concurrent lovastatin and TMZ exhibit synergistic behavior in cell apoptosis, suggesting lovastatin's potential role as a synthetic booster in the treatment of GBM.[81] When it comes to the intrinsic pathway of apoptosis, atorvastatin (10 M) causes GBM spheroids to undergo apoptosis by activating caspase-8/-3 and suppressing the expression of Bcl-2, TRAF3IP2, and interleukin (IL)-17RA.[82,83]

Histone acetylation levels are frequently significantly lower in human tumors, which is thought to be a global epigenetic indicator of malignancy. Human cancer cells from the colon, stomach, kidney, breast, and brain all exhibit increased histone deacetylase (HDAC) activity.[84,85] Recent research has shown that statins reduce HDAC activity and, as a result, raise the expression of p21 in a variety of cancer cells, including GBM. Interestingly, it has been demonstrated that fluvastatin effectively induces H2A histone family member X (-H2AX) and apoptosis in GBM8401 cells, which is followed by increased histone H3 and H4 acetylation. Additionally, this combination causes an upregulation of the gene p21, which is important for the cell cycle and apoptosis.[86]

According to several research, statins' ability to induce apoptosis is mediated via the HMGCR pathway suppression through the downregulation of the PI3K/Akt pathway, the activation of JNK1/2, an increase in the expression of Bax and Bim, and the activation of caspases on GBM. [87,88] Accordingly, Yanae et al. examined the cytotoxicity of statins (mevastatin, fluvastatin, or simvastatin, 1-20 M) towards the C6 GBM cells. Through the activation of caspase-3 and inhibition of ERK1/2/Akt, statins have been demonstrated to reduce cell growth and induce apoptosis in these cells.[62] Simvastatin's antitumor action in U251 and U87 MG GBM cells is also mediated by manipulation of lipid rafts, Fas translocation, downregulation of PI3K/Akt, and caspase-3 activation, according to Wu et al.'s analysis.[89]

Numerous studies have shown that MMP production by microglia stimulated by GBM cells can facilitate cell proliferation, migration, and invasion. Additionally, forced HMGCR expression encourages GBM cell growth and migration, whereas forced HMGCR expression inhibits GBM cell growth, migration, and metastasis.[90] Simvastatin (0.2-30 M) has been demonstrated by Gliemroth et al. 18 to decrease tumour cell growth and migration, but it does not appear to have any effect on the remaining U87 MG cells' invasiveness.[91] According to certain research, atorvastatin can diminish MMP-2/-14/-9 expression levels and considerably lessen cancer cell invasion when used in conjunction with the RhoA-JNK-c-Jun-MMP-2 signalling pathway.[92,93] Fluvastatin's effects on p-JNK1/2 upregulation, p-ERK1/2 expression reduction, and a decline in MMP-9 activity in C6 rat malignant GBM cells seem to be connected to its antiproliferative and anti-invasiveness properties.[94] Additionally, GBM alters the expression of membrane type (MT)- 1-MMP in tumor-associated microglial cells, facilitating GBM invasion and growth via the toll-like receptor (TLR) signalling pathway. According to research by Yongjun et al., atorvastatin inhibits GBM invasion and migration via lowering microglial MT1-MMP expression, which in turn inhibits MMP-2 activity. [95]

Integrins cluster as a result of RhoA activation, which makes it easier for FAK to be activated by tyrosine phosphorylation at position 397.[96] By controlling MMP expression, focused complex formation at the leading edge of the cell, and FA deconstruction at the trailing edge, FAK signalling cascades control the invasion and metastasis of cancer cells.[97,98] Cerivastatin was utilised to inactivate FAK by disrupting the cytoskeleton in a study on GBM cells, which prevented migration.[99] This finding suggests that cerivastatin may be useful in combination therapy with traditional anticancer medications by preventing the invasion of GBM.

Recently, a possible connection between statins and TGF- in different cancer cells has been discovered. TGF- expression is decreased when the Ras/MEK/ERK and Ras/PI3K/Akt pathways are blocked by statins via mevalonate [100]. Simvastatin (0–50 M) impacts human GBM cells (U87 MG, U251 MG, and T98G cells) via TGF- inhibition, causing angiogenesis suppression, according to Xiao et al. Simvastatin decreases GBM migration and invasion, promotes apoptosis and autophagy, and does so both in vitro and in vivo, according to other investigations in this work.[101] According to these studies, statins are extremely important for GBM patients receiving angiogenesis target therapy. In a three-dimensional in vitro model, it was found that atorvastatin has a strong anti-angiogenic effect against GBM spheroids by suppressing the expression of CD31 and vascular endothelial growth factor (VEGF).[102] Simvastatin has also been shown to increase necrosis and apoptosis in vivo when used at low doses as opposed to control and high- dose groups. Simvastatin has a dual role in GBM, as shown by the fact that high-dose simvastatin increases vessel caliber by decreasing pericytic cells along the tumor vessel wall in comparison to both control and low-dose simvastatin groups.[103] According to research on HMGCR inhibitors, statins lessen ERK signaling, FPP and GGPP levels, and cancer cell migration and proliferation.[104] In U343 and U87 MG GBM cells, lovastatin has been shown to affect H-Ras and Rac1 post- translational modifications as well as the regulation of mevalonate and Ras-Raf-MEK-ERK.[105]

4. Findings from clinical research

Statins may have potent antitumor effects, according to a growing body of preclinical data, but it is unclear how they interact with conventional therapy and affect cancer patients' clinical outcomes.[106] Iarrobino et al. have recently shown the effect of statin use on outcomes in a study involving 303 patients with advanced pancreatic adenocarcinoma. It was discovered that statin (simvastatin and atorvastatin) usage is correlated with increased OS in affected patients. Additionally, statin use has been linked to a significant reduction in all-cause mortality, primarily by reducing the risk of distant metastases prior to or during diagnosis.[107] Additionally, statin use is associated with a 2-year increase in OS in patients receiving radiation therapy, surgery, and chemotherapy, indicating that statins may help to improve the results of interventions for advanced-stage pancreatic cancer.[108] The effectiveness of statin use in a sizable cohort of patients with stage IV non-small-cell lung cancer has been demonstrated by Lin et al. in another study. The median survival time for the statin group was seven months as opposed to four months for the non- statin group of patients. Additionally, statin use was linked to increased OS and survival only for lung cancer.[109] However, they did demonstrate that statins improve OS in patients who had previously received nivolumab treatment for advanced non-small cell lung cancer.[110] In contrast, Omori et al. discovered that OS was not improved.

In a phase I/II trial involving 18 patients with malignant GBM, lovastatin with and without radiation therapy was well tolerated, and so far, a negligible impact on tumor growth has been noted.[111] According to a case-control study, simvastatin therapy for longer than six months was inversely associated with the risk of glioma.[112] This study demonstrated the risk of GBM among statin users.

Statin use may have a chemical-preventive effect on the treatment of cancer, according to some research, but the impact of statins on the prognosis of GBM has not yet been investigated. Long- term prediagnostic statin use may increase the 21 survival of GBM patients and lower the risk of brain cancer, according to research by Chen et al. and Gaist et al.[113] Additionally, a statistically significant improvement in OS was seen in GBM patients who had been taking a statin for more than a year. The probable chemoprevention impact was only seen in lipophilic statin users, despite the limited statistical precision. The biochemical characteristics of lipophilic statins, which have ahigher ability than hydrophilic statins to cross the blood-brain barrier, may help to explain this[114] On the other hand, mortality was comparable between both groups of GBM patients and the use of perioperative statins is not associated with an improvement in progression-free survival (PFS).[66] In agreement with this finding, a secondary analysis of two significant GBM trials failed to find any proof that statin use was related to outcomes in patients with newly diagnosed GBM.[115] According to a study by Seliger et al., taking statins had no effect on the OS or PFS of GBM patients[116] or the risk of developing GBM.[117] Additionally, Cote et al. discovered a marginally elevated risk of GBM with statin use.[118] In a phase II study being conducted (NCT02029573) on patients with GBM, atorvastatin is being combined with radiotherapy and TMZ.

Table 1. Combinational strategies with statins in various cancer models.

S.N.	Combination Regimens	TYPE of Study	Main Effect (S)	Ref
1.	Simvastatin +tamoxifen	*In vitro* and *in vivo*	A rise in necrotic and apoptoticcell death A decline in MMP-2/-9 and VEGF	119
2.	Simvastatin + oxicam derivates	*In vitro*	Caspase-3-dependent apoptosisinduction increased Bax expression, decreased Bcl-2 expression, and decreased COX2 expression and activity.	120
3.	Simvastatin + receptor-interacting protein 140	*In vitro*	suppression of cell survival and proliferation via the Wnt/catenin signaling pathway	121
4.	Fluvastatin + ALA andEA in an NLC1 formula	*In vitro*	vitro Pre-G1 phase significantlyincreased, resulting in cell death	122
5.	Atorvastatin+cyanidin-3-glucoside	*In vitro*	Enhancing cell cycle arrest to have a synergistic effect on inhibiting proliferation and migration A reduction in MAPK activity by downregulating p-p38, p-ERK1/2, and p-JNK expression Increasing p21Cip1 and alteringthe PI3K/Akt pathway	123
6.	Atorvastatin+nobiletin	*In vitro In vivo*	Coaxing extensive cell cyclearrest and apoptosis together A reduction in the incidence andprevalence of colonic tumors	124
7.	Simvastatin+herceptin-conjugated liposomes co-loadedwith	*In vitro In vivo*	Strong cancer cell proliferationinhibition Synergistic effects againstangiogenesis	125
	Atorvastatin + caffeine	*In vitro*	Induction of apoptosis andinhibition of cell growth Preventing tumor sphere formation,migration, and invasion Reducing the levels of the proteinsphospho-ERK1/2, phospho-Akt, Bcl-2, and Survivin	126
	Simvastatin+metformin	In vitro	Induction of apoptosis Blocking the mTOR pathway	127
	Atorvastatinmetformin	*In vitro*	Induction of apoptosis and inhibition of cell growth Preventing tumor sphere formationand cell migration Survivin's expression was significantly reduced as a result of the substance's potent inhibitory effect on NF-B activity. 4) Decreasing phospho-Akt and phosphor-ERK1/2 levels	128
	Statins + metformin	Clinical study	Dual users did not experience any positive effects	129
	Simvastatin+celecoxib	*In vitro*	Significantly decreased tumor cell viability, growth, and IL-6 and IL-8secretion	130

	Simvastatin+doxorubicin	*In vitro*	A decrease in the capacity of cells to form colonies A rise in ROSconcentrations A decrease in theexpression of the CDK2, CDK4, and CDK6 cell cycle regulatory proteins Upregulating the expression of the cyclin dependent kinase inhibitor p21, upregulating the expression of cytochrome c a n d c a s p a s e -3, a n d downregulating the expression of cyclin D1	131
	Pravastatin + sorafenib	*Phase III, multicenter study*	OS in the affected population did notimprove.	132

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