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The potential use of simvastatin for cancer treatment: A review

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ABSTRACT

Statins, typically used to reduce lipid levels, have been rediscovered for exhibiting anticancer activities. Among them, especially simvastatin may influence the proliferation, migration, and survival of cancer cells. The concept of using statins to treat cancer has been adopted since the 1990s *In vitro* and in vivo experiments and cohort studies using statins have been carried out to demonstrate their antitumor effects (such as proliferation and migration impairment) by influencing inflammatory and oxidative stress-related tumorigenesis. Nevertheless, the biological mechanisms for these actions are not fully elucidated. In this review, we present an overview of the most important studies conducted from 2015 to date on the use of simvastatin in cancer therapy. This review brings the most recent perspectives and targets in epidemiological, in vitro, and in vivo studies, regarding the use of simvastatin alone or in combination with other drugs for the treatment of various types of cancer.

1. Mechanism of action of statins and cancer

Statins reduce circulating lipids, specifically the cholesterol present in low-density lipoprotein (LDL). This mechanism is due to the competitive inhibition of hydroxymethylglutaryl-coenzyme A reductase (HMGCR), which is a limiting enzyme of cholesterol synthesis. It is well-described that statins have an affinity for the enzyme thousands of times higher than that of the natural substrate, resulting in a lower formation of mevalonate (Fig. 1), which leads to a decrease in the concentration of intracellular cholesterol. Farnesyl pyrophosphate, which acts by stimulating protein activation, proliferation, and cell adhesion, might also be affected [1]. Under normal conditions, low intracellular cholesterol triggers a homeostatic feedback mechanism for transcribing the sterol regulatory element-binding protein (SREBP). Activation of SREBP results in a reduction in serum cholesterol levels. In some cancer cells, this feedback mechanism is impaired and makes them vulnerable to HMGCR inhibition [2,3].

Some findings suggest positive regulation of growth factor receptors in some tumor cells, such as breast cancer cells, are associated with cholesterol-dependent signaling events [4]. Thus, statins might be potential in the treatment and prevention of this disease [5]. These tumors frequently increase the expression of enzymes in the mevalonate biosynthesis pathway, and although statins inhibit the flow through this pathway, the mechanism of how they produce this therapeutic benefit in cancer remains unknown [6,7].

As previously described, statins are capable of inhibiting the HMG-CoA reductase enzyme leading to depletion of mevalonate and its downstream products, many of which are important mediators of the signaling pathway, integrity, and regulation of the cell cycle [8]. Studies on tumor cells revealed apoptosis as a linear and dose-dependent response to exposure to statins; however, this mechanism of induced apoptosis is not yet fully understood. Among products downstream of the mevalonate pathway, geranylgeranyl phosphates are responsible for inhibiting the apoptotic effect. Since statins induce depletion of geranylated proteins, it provokes cell apoptosis due to decreased mitochondrial transmembrane potential and increased activation of caspase-9 and caspase-3 [9].

Fujiwara and colleagues (2017) demonstrated that the induction of apoptosis by statins in hematopoietic tumor cells can occur by mitochondrial apoptotic signaling pathways. These are activated by suppressing mevalonate or geranylgeranyl pyrophosphate biosynthesis due to cell cycle arrest in the G1 phase due to suppressing the prenylation of the rapamycin (Ras) pathways [10].

Another possible mechanism already described is the involvement of statins in suppressing the growth of cancer cells, which induces the G1-phase arrest will also result in reduced cell migration [1]. It has been

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shown that simvastatin induces G1 cell cycle arrest by reducing CDK4/6 and cyclin D1 (Wang et al., 2016). Statins can also inhibit tumor angiogenesis since they may reduce the expression of matrix metalloproteinase-9 (MMP-9) in endothelial cells, which leads to reduced capacity invasive cells [1,9]. Other reports showed that statins decrease the expression of c-Myc, Ras and Rho protein and/or induce senescence in cancer cell lines causing suppression of cancer cell growth. Statins have also been shown to inhibit angiogenesis by increasing the inhibitory effect of TNF alpha on tumor growth and vascularization [11]. The schematic representation of the mevalonate pathway and some potential effects on tumor cells are shown in Fig. 1.

Hydrophilic statins, such as pravastatin and rosuvastatin, initially accumulate in the liver by hepatocyte-specific membrane transporters. Hydrophobic statins (such as lovastatin and simvastatin), unlike the hydrophilic ones, are distributed to various tissues. This diffuse distribution on extrahepatic tissues may explain their most frequent use [12].

The comparison of atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin demonstrated the best long-term results in lung cancer patients with heart failure after the use of lipophilic statins. Particularly simvastatin was the most important to reduce rates of cancer-specific mortality [13,14]. Studies have also shown that simvastatin exhibits lower hepatotoxicity and gastrointestinal effects than atorvastatin [15]. It is worth noting that, between the two most commonly prescribed statins (simvastatin and atorvastatin), the first one stands out in terms of the number of annual prescriptions for the treatment of hypercholesterolemia [16]. Thus, most of the data on the potential anticancer effect in preclinical and clinical studies using statins is attributed to simvastatin [17]. Beyond the inhibitory effect on cholesterol production, authors have described the pleiotropic effects of this drug (anti-proliferation, anti-apoptosis, antiangiogenesis, etc.), which are dependent on the activation of some proteins that interfere with important cell signaling pathways [18]. The antitumor effects of simvastatin involve different subcellular structures and overlapping molecular pathways. Antineoplastic drugs with pleiotropic effects are usually more effective in clinical practice, given that therapeutic resistance is more difficult to be developed [19].

2. Simvastatin in cancer research

2.1. Epidemiological studies

Although the correlation between simvastatin use and increase cancer survival remains unclear, several groups have investigated the epidemiology of this association [16,20–26]. The main results observed in such studies demonstrate a reduction in the progression and specific rate of cancer mortality in patients under simvastatin treatment.

Consistent evidence supports these findings in several studies with lung, breast, gastric, and pancreatic cancer patients [20,22,27]. Cardwell and collaborators (2015) demonstrated the association between the use of statins after the diagnosis of lung cancer and a reduction in specific mortality in more than 25% of patients.

Analyzing breast cancer patients, Borgquist et al. conducted a retrospective cohort study with 15,140 patients and related decrease in mortality rate after using simvastatin. Cardwell et al. also pointed out similar results in a cohort study in 17,880 patients with the same type of cancer [13]. These findings were also consistent with the results of a meta-analysis study, in which simvastatin significantly reduced (about 43%) specific mortality of breast cancer patients [24].

A retrospective cohort study of 2,142 patients with pancreatic ductal adenocarcinoma once again revealed a lower risk of mortality in

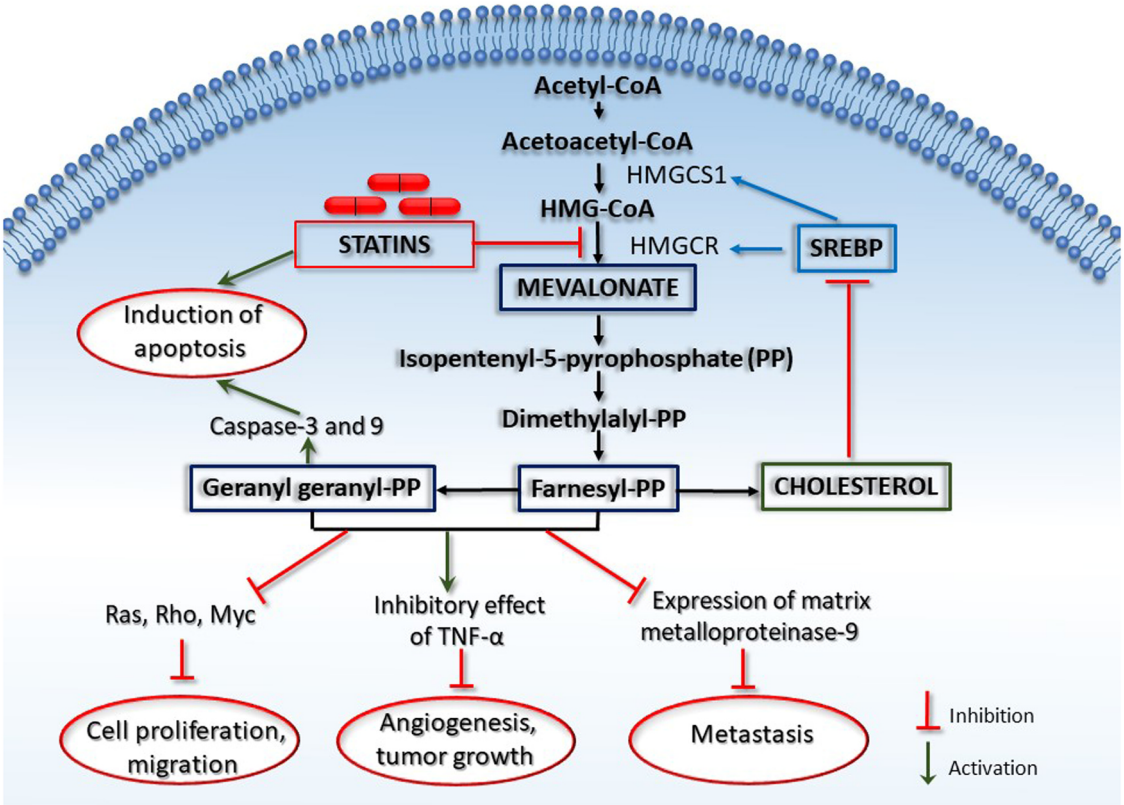

Fig. 1. Schematic representation of the mevalonate pathway and its potential effects on tumor cells. The mevalonate pathway converts acetyl-CoA to cholesterol and some nonsterol isoprenoids that play roles in cell growth and survival. Statins reduce mevalonate synthesis, and consequently, farnesylation and geranylgeranylation are decreased. This fact results in 1) decreasing of Ras, Rho, and c-Myc proteins expression, which decreases tumor cell proliferation and migration; 2) reduction of matrix metalloproteinase-9, a protein related to tumor cell metastasis; 3) Inhibition of angiogenesis by increasing the inhibitory effect of TNF alpha; 4) Activation of caspase-9 and caspase-3, which provokes cell apoptosis; 5. Statins also have been shown a direct effect on cell apoptosis.

patients taking simvastatin while the cholesterol level did not influence mortality. Based on these data, they suggested that the effects of simvastatin occur through a lipid-independent pathway [22]. Another investigation conducted in two large independent cohorts on population-based gastric cancer evidenced a 17% reduction in cancer-specific mortality by using statin after diagnosis [16].

There is still evidence that the use of simvastatin may reduce the risk of different kinds of cancer such as lung, hepatocellular, esophageal, endometrial, and prostate carcinoma [25]. Yang et al. reported an approximately 20% reduction in the risk of lung cancer in women using simvastatin from 17,329 patients diagnosed with lung cancer between 2005 and 2010 and 17,329 patients without lung cancer [21]. Simvastatin had a chemopreventive effect against lung cancer in patients with chronic obstructive pulmonary disease in a dose-dependent manner [23].

About hepatocellular carcinoma, Chen et al. showed that simvastatin decreased the comorbidities and the risk of this carcinoma in diabetic patients by about 63% [28]. Similar results were reported in patients with Barrett's esophagus. Besides decrease the risk of esophageal adenocarcinoma, the protective effect was strong at an advanced stage of the disease, particularly with the increased statin dose [29]. Another group concluded after a meta-analysis study that statins also decreased the risk of prostate cancer [25]. Matsuo and colleagues (2019) suggested after a retrospective multicenter study that statin might be associated with decreased risk of venous thromboembolism in women with endometrial cancer compared to non-statin users [26].

It has also been reported that patients receiving anthracycline-based chemotherapy associated with simvastatin for cancer treatment experienced less deterioration in declines in left ventricular ejection fraction (LVEF) compared to those who did not receive statins. This apparent attenuation in the anthracycline-related LVEF decline in statin users occurs even though they have more risk factors for future cardiovascular events than non-statin users [30]. This fact is another epidemiological evidence that reinforces the relevance of using simvastatin in antitumor therapies. In addition to the antiproliferative action, there are also indications of protective advantages against the potential side effect of anticancer chemotherapy.

2.2. In vitro studies

Numerous in vitro studies have demonstrated the antiproliferative effects of simvastatin on different cancer cell lines. Such in vitro studies suggest that simvastatin inhibits cancer cell growth by inducing apoptosis and inhibiting cell cycle progression through many cell signaling pathways [31,32]. Investigations to date reveal that the effects of this drug are dependent on the cell line, the concentration, and the duration of cell exposure to the drug [33]. Also, several studies explore simvastatin in multi-drug therapy [34,35].

A study using cancer cells from different epithelial origins, including breast (MCF7 and SKBr-3), prostate (LNCaP and PC-3), colon (Caco-2 and HCT-116), skin (SCC-M7 and SCC-P9), and the lung cancer cell lines (Calu-3 and Calu6) indicated that the prolonged exposure to simvastatin inhibited the cell growth more efficiently in less differentiated cells. Poorly differentiated tumors spread faster and may lack normal tissue structures [36].

Other studies confirm that the effects of simvastatin are more pronounced in highly metastatic malignant tumor cells compared to benign tumors of the same origin. Possibly it is because malignant tumors spread more quickly and require more isoprenoids from mevalonate to improve the signaling for survival in cells [35].

MDA-MB-231 cells were treated with simvastatin in different concentrations (1–5 μM) for 48 h, and simvastatin significantly caused the fragmentation of cell nuclei and induced cell death. Simvastatin significantly increased the levels of reactive oxygen species in a dose-dependent manner leading to oxidative stress and DNA damage in these cells [30].

Considering that in vitro studies in cell lines have shown an anticancer effect of simvastatin mainly based on the inhibition of proliferation and induction of apoptosis in cancer cells of different origins, we summarized some of these studies in Table 1.

2.3. In vivo studies

Published in vivo studies have also shown the antitumor activity of simvastatin against different subtype of tumors. In these studies, supratherapeutic doses of simvastatin compared to those used in patients with hypercholesterolemia have been employed. Due to the accentuated liver uptake and blood clearance of the statins, rodents

Table 1
In vitro response of simvastatin treatment against different types of cancer cells lines.

Target	Cell lines	Responses	Ref.
Tumor of Bone	G33, G53, G62	Inhibition of cell viability, suppression of proliferation, and induction of apoptosis	[37]
Pituitary tumors	AtT20, GH3	Reduction of cell viability and/or hormone secretion	[38]
Cervical cancer	SiHa, C-33A, HeLa, ViBo	Selective inhibition of cell proliferation and induction of apoptosis	[39]
Leukemia	Jurkat T	Inhibition of potassium channels, anti-proliferative and pro-apoptotic activity	[40]
Myeloid leukemia	U937, KG1, THP1, HL60	Induction of cell death	[41]
Colon cancer	HCT116, SW1116, HEK293A	Suppression of cell proliferation	[42]
Nasopharyngeal carcinoma	C666–1	Decrease of cell viability, induction of apoptosis, and G1-phase cell cycle arrest	[43]
Lipoma	LipPD	Reduction of cell viability and induction of apoptosis	[44]
Lung cancer	HLF-a, A549, H1299	Induction of pyroptosis, inhibition of cell proliferation and migration	[45]
Colorectal cancer	CP1 to CP5	Interruption of the cell cycle in the G1 phase	[4]
Pancreatic cancer	BxPC-3, MIA PaCa-2, PANC-1	Inhibition of cell proliferation	[46]
Osteossarcoma	AXT	Inhibition of cell proliferation and migration	[47]
Prostate cancer	PC-3, LNCaP, DU145	Inhibition of cell proliferation and migration	[19]
Bladder cancer	T24	Inhibition of proliferation and interruption of the cell cycle in the G1 phase	[48]
Colon cancer	Lovo, HT-29	Inhibition of cell proliferation	[22]
Breast cancer	MCF-7, T47D, MDA-MB-231, BT-549	Induction of apoptosis and inhibition of cell proliferation	[] (49, 50)
Ovarian cancer	Hey, SKOV3	Induction of apoptosis and inhibition of cell proliferation	[32]
Breast cancer	Radioresistant MDA-MB-231-RR, T47D-RR, Au565-RR	Eradicate radioresistant breast carcinoma cells and diminish migratory abilities	[51]
Breast cancer	SUM149, SUM159, MDA-MB-231	Inhibition of cell proliferation and interruption of the cell cycle	[52]
Leiomyoma	ELT-3	Induction of apoptosis and inhibition of cell proliferation	[53]

require higher doses of the drug to achieve the same therapeutic effects [54].

Vázquez-Borrego et al. demonstrated that simvastatin reduces the secretion of hormones by pituitary neuroendocrine tumors, leading to anti-secretory and antiproliferative effects [38]. Some studies using mouse xenograft models for lung cancer and leiomyoma described inhibition of tumor cell growth in a concentration-dependent manner [45, 54]. Miyazawa et al. in an analysis of nude mouse xenograft from PC-3 cells, again confirmed that simvastatin reduced the tumor size and inhibited the proliferation, migration, and invasion of prostate cancer cells [19].

Chen et al. also investigated the anticancer effects of simvastatin on colorectal cancer, and the results indicated potential antitumor activity of the drug [4]. In the same tumor model, Li et al. demonstrated that pretreatment with simvastatin reduced the microvessel density in vivo and markedly inhibited the angiogenesis process. Kamel et al., in turn, reported that simvastatin inhibited the growth of osteosarcoma in a dependent manner on the inhibition of mevalonate pathway [49,47].

Rennó et al. using female rats with 7,12-dimethyl-benz(a)anthracene (DMBA)–induced mammary cancer, observed that 40 mg/kg/day of simvastatin significantly reduced (around 80%) breast tumor growth, while stem cells in normal non-neoplastic breast tissues were not affected by simvastatin [55]. Karimi et al. also evaluated the therapeutic effect of simvastatin on mice-induced breast cancer [56]. They reported that simvastatin improved parameters of breast carcinogenesis, such as the average tumor volume and the percentage of mortality compared to mice with untreated breast tumors. In addition, it looks better in histopathological evaluation compared to animals treated with the therapeutic agent tamoxifen routinely prescribed [56].

3. Simvastatin-loaded nanosystems and/or in combination with other chemotherapeutic agents for tumor treatment

The nanocarriers loaded with antitumor drugs are strategies well-researched and promising to decrease toxicity to normal tissues and increase the effectiveness of chemotherapies in cancer treatment [57]. Due to the lipophilic character of simvastatin, intravenous administration would not be easy; however, it can be incorporated into nanocarriers reversing possible administration problems, which can improve efficiency and reduce toxicity [12].

Sedki and colleagues (2019) used superparamagnetic iron oxide nanoparticles for the tumor delivery of simvastatin. This nanocarrier significantly improved the anticancer activity of simvastatin against the prostate cancer cell line (PC-3) by activating the apoptosis process and delaying G2 phase of the cell cycle [58]. Although promising further in vivo studies must be performed to confirm the benefits of the formulation. Another group developed nanoparticles of poly D,L-lactide-co--glycolide (PLGA) and cholic acid nucleus for sustained and controlled administration of simvastatin for breast adenocarcinoma chemotherapy. Simvastatin-loaded nanoparticles showed a more efficient and sustainable tumor growth inhibition than non-encapsulated simvastatin at the same dose [59].

There are also studies of nanoparticles co-loaded with gemcitabine and simvastatin. In this study, the bioavailability of gemcitabine and simvastatin was increased by 1.4- and 1.3-times, respectively, compared to the free drug. The nanoparticles had greater intracellular uptake, a prolonged intracellular release of the drugs that resulted in high cytotoxicity for pancreatic cancer cells. By contrast, they showed adequate safety for normal cells [60]. Alpha-lipoic acid (ALA) nanoparticles have also been described as carriers for simvastatin. This study revealed that the cellular uptake of these nanoparticles was about 3-times greater than the free drug in breast carcinoma. In addition, data on cell viability showed that ALA nanoparticles enhance the cytotoxicity of simvastatin against MCF-7 cells [61].

Nanocapsules containing simvastatin were tested against breast cancer cells and showed greater cytotoxicity than the non-encapsulated drug [54]. The same group used lipid nanoparticles to transport simvastatin and showed an increase in antitumor effect and high cellular absorption on breast cancer [62]. The cytotoxic effect of simvastatin-loaded pH-sensitive polymeric nanocapsules was significantly increased, compared to the free form in colorectal cancer treatments. The findings showed that these nanocapsules could improve the distribution of simvastatin in the colon [63].

Simvastatin has also been incorporated into nanoemulsions in combination with doxorubicin [34]. This investigation reported that the nanosystem significantly improved efficiency and simultaneously reduced adverse effects of doxorubicin in an animal model of Ehrlich carcinoma. Histopathological changes in the liver revealed that hepatocytes were less affected by nanoemulsion treatments containing simvastatin and doxorubicin compared to nanoemulsions containing only doxorubicin. In addition, the investigation of biochemical parameters strengthened the histopathological findings. Serum alkaline phosphatase (ALP) levels were lower in the group treated with the nanoemulsion of doxorubicin and simvastatin, compared to the solution of these drugs [34].

There are some studies in which liposomal simvastatin has shown good results in the treatment of tumors. A liposomal system herceptin-conjugated simvastatin with doxorubicin revealed an excellent inhibition of prostate cancer in vitro and in vivo, with tumor volume inhibitory rates of up to 80.36% [64]. Another study showed that the liposomal form of simvastatin was more effective than the free drug for C26 colon carcinoma in vivo treatments [65].

Long-circulating liposomes have also been proposed as delivery systems for simvastatin in the treatment of C26 colon carcinoma. As a result, an increase of antitumor activity exerted via increased oxidative stress in the tumor environment was observed [66]. The antitumor activity of simvastatin encapsulated in a long-circulating liposome has been investigated in mice with B16.F10 melanoma as well. Again, higher inhibition of melanoma growth (about 85%) after liposomal treatment compared to free simvastatin could be observed [67].

Some publications also report the use of immunoliposomes to carry simvastatin. Matusewicz et al (2018) attached humanized anti-HER2 antibody to the lipid bilayer, and this immunoliposomal formulation of simvastatin was characterized as high selective for breast cancer cells with HER2 overexpression (antibody trastuzumab), low nonspecific cytotoxicity, and effective tumor growth inhibition [12]. Immunoliposomes containing simvastatin with an antibody to the epidermal growth factor receptor attached to their surface have also been developed. Basal-type breast cancers are strongly dependent on this signaling pathway. *In vitro* experiments conducted on MDA-MB-231 cells demonstrated that the formulation induced apoptosis. *In vivo* experiments indicated that the immunoliposomes were effectively delivered to the tumors and inhibited tumor growth by an average of 25% compared to the control [68].

Studies have shown that synergistic combinations of statins with other anticancer agents can benefit cancer treatment and might be an alternative treatment modality [69]. Combined therapies have been being investigated in cancer research since drug combinations have the potential to improve response to treatment and minimize the development of resistance [35].

A combination of low-cost, low-risk targeted drugs with chemotherapy to improve efficacy is a promising strategy that requires constant investigation. Simvastatin is less toxic than cytostatics, and consequently, a detailed study of its effects on different types of cancer cells can lead to progress in the treatment of cancer and result in fewer side effects, typically observed in anticancer therapies [12]. Several studies report gains in antitumor therapy when combining simvastatin with other therapeutic agents (Table 2).

The off-label use of simvastatin may also represent a promising pharmacological approach to obtain toxicity control. The use of simvastatin is promising in reducing chronic cardiotoxicity, interfering with the mechanisms of cardiomyocyte cell death induced by anthracyclines

Table 2
Studies using simvastatin in combined treatments with other therapeutic agents.

Target	Combination therapy	Responses	Ref.
Breast cancer (SK-BR-3 and MDA-MB-468)	Sim + Th1 cytokines	Enhanced cell death and significantly delayed tumor growth kinetics	[70]
Breast cancer (MCF-7)	Sim + Tamoxifen	Favorable antiangiogenic, and anti-metastatic activity	[71]
Breast cancer (MDA-MB-231, MDA-MB-468, MDA-MB-453, HS578T, MCF-10A, and HEK293)	Sim + Panobinostat (LBH589)	More efficient in preventing tumor growth and significant prolongation of the survival of tumor-bearing mice	[72]
Breast cancer (MDA-MB-231)	Sim + Pentoxifylline	Prevented growth of triple-negative breast cancer cells	[73]
Breast cancer (MDA-MB-231 and MCF-7)	Sim + Doxorubicin	Inhibited cell survival and increased apoptosis. Significant synergistic effects and antitumor activity, as evidenced by reduced tumor growth and tumor volume	[74]
Breast cancer (MDA-MB-231, MDA-MB-468, and MDA-MB-453)	Sim + Vorinostat (SAHA)	Potent synergistic apoptotic effect in triple-negative breast cancer cells and significantly decreased in tumor growth in xenografted mice	[72]
Breast cancer (MCF-7)	Sim + Doxorubicin	Enhanced the cytotoxicity of doxorubicin against MCF-7 cells in a dose-dependent manner	[53]
Breast cancer (MCF-7)	Sim + Exemestane	Decreased the viability of MCF-7 and reduced the required concentration of exemestane to inhibit cancer cell growth	[75]
Breast cancer (MCF7 and T47D)	Sim + Tamoxifen	Induced DNA damage in cells resistant to tamoxifen. Increased the apoptosis and inhibited xenograft growth	[76]
Colon carcinoma (C26)	Liposomal sim + liposomal 5–fluorouracil	Strong antitumor activity in C26 colon carcinoma in vivo. Antitumor actions of both combined treatments suggest that SIM acted as a sensitizer for tumor cells to 5-FU	[77]
Resistant colon cancer cells (LoVo)	Sim + Oxicam derivatives (PR17 and PR18)	Effective inhibited the growth of cancer cells even at low concentrations	[78]
Colon cancer (HT-29)	Sim + Irinotecan	Suppressed HT-29 cell proliferation and induced the apoptosis of colon cancer cells with or without irinotecan resistance	[79]
Colorectal cancer and melanoma (H1395, YUMAC, and YURIF)	Sim + Vemurafenib and Sim + Selumetinib	Synergism in inhibition of the MAPK pathway	[80]
Melanoma (B16BL6)	Sim + Dacarbazine	Significantly inhibited tumor growth and metastasis. Improved the survival rate in mice with metastases	[81]
Melanoma (B16. F10)	Sim + 5,6-dimethylxanthenone-4-acetic acid (DMXAA)	Reduced the proliferation and migration capacity of melanoma cells	[65]
Melanona (B16F10)	Sim + Paclitaxel nanoemulsions	High survival rates in vivo and negligible toxicity compared to free paclitaxel	[82]
Prostate cancer (LNCaP and VCaP)	Sim + Enzalutamide	Additive growth inhibition in cell accompanied with strong induction of autophagy	[83]
Prostate cancer (PC3)	Sim + NF-κB inhibitor (CAPE)	Reduced the cell viability and colony formation in a dose-dependent	[84]
Prostate cancer (LNCaP)	Sim + valproic acid + docetaxel	Reversed tumor cell resistance to docetaxel	[85]
Cervical cancer (SiHa, C-33A, HeLa and ViBo)	Sim + Paclitaxel	Increased the in vitro and in vivo efficacy compared to the drugs alone	[39]
Glioblastoma (U87, U251)	Sim + Temozolomide	Significantly increased in apoptotic cells	[86]
Mieloma múltiplo (U266)	Sim + Bortezomib	Simvastatin increased the effect of bortezomib at all concentrations while bortezomib alone was not active and caused a significant cytotoxic effect	[69]
Pancreatic cancer	Sim + Gemcitabine	Inhibited the cell viability, tumor growth, and metastasis	[87]
Head and neck squamous carcinoma (PJ-41 and HLaC78)	Sim + Celecoxib	Significantly reduced the tumor cell viability	[88]
Lung carcinoma (A549)	Sim + Ácido suberoilanilida hidroxâmico (SAHA)	Inhibited A549 cell proliferation and induced of tumor cell apoptosis	[39]
Mesothelioma (MSTO-211 H and A549)	Sim + Pemetrexed	Augmented apoptosis and autophagy in malignant mesothelioma	[89]

Sim: Simvastatin

[90]. Arroyo et al (2019) reported the potential effect, after oral administration, of simvastatin to prevent prostate cancer. In this particular study, simvastatin showed a chemopreventive effect on prostate cancer through antioxidant activity [91].

4. Clinical studies of simvastatin in cancer therapy

Clinical studies evaluating the use of simvastatin in the therapy of closed cancer patients are scarce, inconclusive, and still insufficient to demonstrate a clear effect [92]. But the number of ongoing clinical trials evaluating the clinical benefit of simvastatin in cancer is large since there are a variety of possible clinical scenarios. There are dozens of researches underway with human volunteers to increase knowledge about the use of simvastatin against cancer. Recent clinical trials are listed in Table 3.

5. Conclusion

The antineoplastic properties of statins, especially simvastatin, the

Table 3
Recent clinical trials investigating the relationship between simvastatin and cancer.

Status	Clinical Study	Phase	Intervention	ID
Completed	Chemotherapy plus simvastatin in advanced gastric cancer patients to assess antitumor activity	III	Sim 40 mg/day + Capecitabine/cisplatin	NCT01099085
Active	Evaluation of the survival benefits of statins in breast cancer patients	III	Sim 20 mg for 3 and 5 years	NCT03971019
Completed Conclusion: Clinical efficacy without increasing toxicity [93]	Study of simvastatin plus XELOX and Bevacizumab as first-line chemotherapy in metastatic colorectal cancer patients	II	Sim 80 mg	NCT02026583
Active	Evaluation of whether the addition of simvastatin to the dual anti-HER2 therapy regimen helps make the tumor responsive to the anti-HER2 therapy again	II	Sim 80 mg/day	NCT03324425
Active	Evaluation of the simvastatin effect in combination with neoadjuvant chemotherapy to clinical response and tumor-free margin in locally advanced breast cancer	II	Sim 40 mg/day	NCT04418089
Active	Study of neoadjuvant chemoradiotherapy with capecitabine plus simvastatin in advanced rectal cancer patients	II	80 mg/day for 5 weeks	NCT02161822
Active	Identification of the molecular and genetic mechanisms by which simvastatin influences breast cancer cell proliferation	II	Sim 40 mg daily for 2–4 weeks	NCT03454529
Active	Detection and prevention of anthracycline-related cardiac toxicity with concurrent simvastatin	II	Sim 40 mg once daily. Treatment will start 7 days prior to the planned doxorubicin chemotherapy initiation and will continue for weeks.	NCT02096588
Active	Comparison of the efficacy of Simvastatin and Irinotecan/Cisplatin chemotherapy with Irinotecan/Cisplatin chemotherapy alone in lung cancer	II	Sim 40 mg per day for21days	NCT01441349
Active	Comparison of simvastatin and placebo, before standard chemotherapy and radiation therapy, in the preoperative treatment of patients with rectal cancer	II	40 mg of Sim daily for 90 days, starting 1 week before standard radiation therapy	ACTRN12617001087347
Active	Study the effect of simvastatin on the size of uterine fibroids	II	Sim 40 mg daily for the 12 weeks	NCT03400826
Completed *No result posted	Examination of the safety and feasibility of aspirin with or without simvastatin in solid tumor patients	I	80 mg/day for 4 weeks	NCT02285738
Completed Conclusion: the first pediatric trial with statins as anticancer therapy. Therapy well-tolerated with predictable toxicity.	Simvastatin in combination with topotecan as a potential treatment alternative to recurrent or non-responsive tumors	I	Sim 140 mg/m^2 twice a day for 21 day. plistopotecan 0.75 mg/m^2 for 5 days	NCT02390843
Active	Dose escalation in subjects with pancreatic cancer and other advanced solid tumors	I	Sim 5 mg/day for 28 days	NCT03889795
Active	Evaluation of the safety, tolerability, and pharmacokinetics of high dose of simvastatin in patients with gastrointestinal cancers	I	Sim 5–10 mg/kg for 7 days and 14 days off treatment for 21 days	NCT03086291
Active	Evaluation of the feasibility of using simvastatin intervention, and its effects on ovarian cancer	I	40 mg/day by mouth for approximately 6 months during treatment with carboplatin and liposomal doxorubicin	NCT04457089

Sim: simvastatin

most used statin worldwide, have been under investigation for decades. In this review, we describe several studies in the last five years that sought to prove the antitumor potential of simvastatin. We observed in preclinical studies that simvastatin is involved in modulating cancer cell proliferation and apoptosis. Although some studies have shown simvastatin's antitumor efficacy, further research efforts are needed to discover the precise mechanisms of simvastatin that are still unknown.

In vitro and in vivo investigations also indicate interesting effects against various types of cancer, leading to the control of tumor growth. In addition, some studies reveal that simvastatin can enhance the response of conventional anticancer therapies when administered in combination with other drugs or even when associated with nanostructures.

On the other hand, the analysis of the clinical studies showed that there are still many questions to be answered. Several studies still need to be completed to ensure a relevant and a representative number of patients, while others reveal no conclusive outcomes. There is strong evidence that the use of simvastatin against tumors opens up the possibility of exploring a new tool to enrich the limited pharmacological arsenal available for cancer treatment. However, the involved mechanisms, the possible effective doses, and the combination of this statin with the antitumor drugs should be further investigated to confirm its feasibility as an alternative therapeutic strategy to cancer treatment.

Conflict of interest statement

The authors report no conflicts of interest in this work. The manuscript is the authors' review work. It has not been published previously and not under consideration for publication elsewhere, in whole or in part.

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