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Review Article

Pleiotropic Effect of Statins: Beyond Cholesterol Reduction

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ABSTRACT

Although statins are best known for their ability to decrease cholesterol, they are now known to be complex pharmacological agents with a variety of pleiotropic effects. This review looks at the strong evidence that statins have pleiotropic effects in addition to their well-known ability to decrease cholesterol levels in blood. We explore the molecular processes that underlie these pleiotropic effects, such as the regulation of oxidative stress and thrombosis, stabilization of atherosclerotic plaques, enhancement of endothelial function, and modulation of inflammatory pathways. We also investigate the possible therapeutic applications of statin pleiotropy in a range of disease states, such as cancer, autoimmune illnesses, neurodegenerative disorders, and cardiovascular disease. The present review provides a thorough overview of the complex and multifaceted character of statins, even though the precise therapeutic implications of several pleiotropic effects are still being investigated, demonstrating their potential to go beyond conventional methods for reducing cardiovascular diseases risk.

1. *Introduction*

Statins are essential for the treatment and prevention of cardiovascular disease (CVD), mainly because of their potent ability to decrease cholesterol. These drugs (**Fig. 1**) work by competitively inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an essential enzyme that is a catalyst in the liver's natural cholesterol production process[1]. Statins efficiently lower intracellular cholesterol levels by blocking HMG-CoA reductase by preventing it from converting to mevalonate (MA)(Fig. 2), which causes the hepatic low-density lipoprotein (LDL) receptors to upregulate in response[2, 3]. This adaptive reaction improves the bloodstream's ability to remove circulating low-density lipoprotein (LDL), commonly known as "bad" cholesterol. Statins have a significant effect on low-density lipoprotein (LDL) cholesterol levels; typically, these levels are reduced by 20% to 60%, depending on the statin in question and the dosage that is used[4]. There is little doubt that a substantial decrease in LDL cholesterol is associated with a decreased risk of major adverse cardiovascular events, such as myocardial infarction, stroke, and cardiovascular death. Numerous extensive RCTs (Randomized Controlled Trials) and meta-analyses have continually confirmed the therapeutic advantages of statins. People with increased cholesterol who had no prior history of heart disease had a stunning 31% lower chance of experiencing their first myocardial infarction, according to the groundbreaking West of Scotland Coronary Prevention Study (WOSCOPS)[5]. Similarly, the Collaborative Atorvastatin Diabetes Study (CARDS) demonstrated that statins are effective in this high-risk group of patients by reducing major cardiovascular events in patients with type 2 diabetes by 37%[6]. Statins are now considered an essential strategy for reducing cardiovascular risk due to the body of evidence gathered from these and other research. Their anti-inflammatory

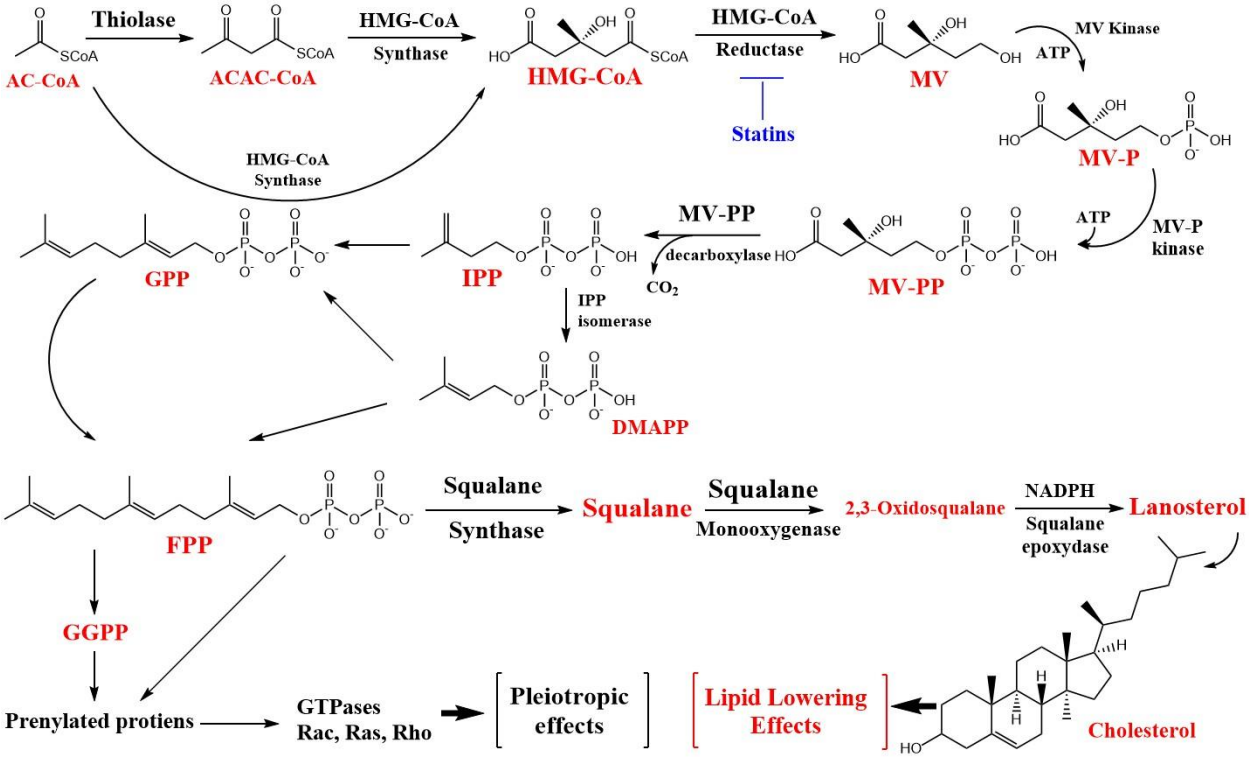

Figure 2: The mevalonate pathway [7]

and endothelial function-improving pleiotropic effects, which go beyond decreasing cholesterol, emphasize their therapeutic usefulness even more[8]. Although there is still work to be done on how best to utilize statins, there is no denying their critical role in cardiovascular therapy and their considerable contribution to the global drop in CVD morbidity and mortality. Pleiotropy, which comes from the Greek word for "more ways," describes the situation in which a single gene or, more specifically, a single medication, influences several phenotypic qualities or has a variety of consequences beyond its intended use. This idea is crucial to understanding how drugs work because it highlights the complex interactions between biological systems and increases the therapeutic potential of drugs. A prime example of pleiotropic medication activity are statins, which are well known for their potent ability to decrease cholesterol by inhibiting HMG-CoA reductase. In addition to their well-known lipid-modifying activities, statins have a variety of other pleiotropic effects (**Fig. 3**) that enhance their cardiovascular preventive qualities. Among these effects are:

Anti-inflammatory Actions:

Statins have been demonstrated to reduce inflammatory reactions by lowering adhesion molecule expression, preventing the synthesis of pro-inflammatory cytokines, and modifying immune cell activity[9]. Because plaque rupture is a major cause of acute coronary events, this anti-inflammatory activity may help stabilize atherosclerotic plaques and lower the risk of plaque rupture.

Enhancement of Endothelial Function:

Statins increase the production of endothelial nitric oxide synthase (eNOS), decrease oxidative stress, and improve nitric oxide bioavailability to support endothelial health[10]. These benefits enhance blood flow and vascular responsiveness, which helps to protect the heart.

Plaque Stabilization:

Atherosclerotic plaques are stabilized in part by the pleiotropic effects of statins on inflammation and endothelial function. Statins lessen the risk of thrombotic events by increasing endothelial integrity and decreasing inflammation, which makes plaques less prone to rupture[11].

Effects of Statins on Oxidative Stress:

Researches have demonstrated that Statins can reduce reactive oxygen species (ROS) and boost the production of antioxidant enzymes like superoxide dismutase (SOD)[12]. This antioxidant activity may aid the cardiovascular system and shield cells from oxidative harm. By preventing platelet activation, lowering thrombin production, and adjusting fibrinolytic activity, statins may have antithrombotic effects[13]. These effects might also help to enhance cardiovascular outcomes and reduce thrombotic events.

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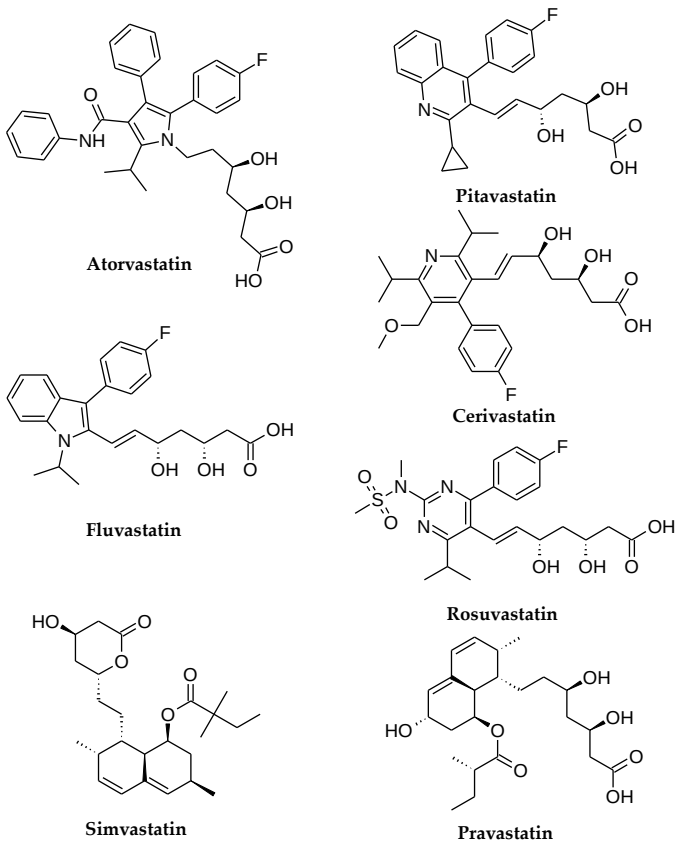

Figure 2. Chemical Structures of Statins

Antithrombotic Effects:

The therapeutic profile of statins includes the pleiotropic effects as a significant aspect. In addition to decreasing cholesterol, these varied effects also greatly add to statins' overall benefits in protecting the cardiovascular system. To maximize their therapeutic potential and optimize their clinical use, it is imperative to comprehend the entire range of pleiotropy associated with statins.

1. This review's goal is to provide a thorough summary and critical analysis of the available data on the pleiotropic effects of statins. Statins are well known for decreasing cholesterol, but they also have a variety of other biological effects in addition to lipid regulation. The purpose of this study is to compile the body of research on the various pleiotropic effects of statins, including how they affect thrombosis, oxidative stress, endothelial function, inflammation, and other pertinent pathways. We aim to assess the therapeutic implications of these pleiotropic effects and clarify the molecular mechanisms behind them by combining data from preclinical and clinical investigations. In the end, this review seeks to present a thorough and current summary of the complex nature of statins, emphasizing their potential therapeutic uses outside of the realm of conventional cardiovascular risk reduction.

2. Established Pleiotropic Effects of Statins

2.1. Statins and Endothelial Function:

The vascular endothelium is a crucial autocrine and paracrine organ that controls the cellular makeup and contractile state of the arterial wall. Endothelial dysfunction is one of the earliest signs of atherosclerosis and is exacerbated by hypercholesterolemia. It can occur even in the absence of angiographic evidence of the illness[14, 15]. The reduced production, release, and function of nitric oxide (NO) produced from endothelial cells is a crucial feature of endothelial dysfunction. It has been demonstrated that endothelial NO inhibits several atherogenic process components. For instance, vascular relaxation is mediated by NO produced by endothelium[16] and inhibits platelet aggregation[17], proliferation of vascular smooth muscle[18], and endothelial-leukocyte interactions[19, 20]. Superoxide anion ($O_2^{\cdot-}$) inactivates NO, reducing its bioavailability and causing vasoconstriction, hypertension, and nitrate tolerance[21, 22]. The complex mechanisms through which statins produce their endothelial-protective effects are explored in this review, with particular attention paid to increase NO production, enhanced vasodilation, and decreased oxidative stress, all of which contribute to improved blood flow, regulation of vascular tone, and overall cardiovascular health.

Molecular Mechanisms Underlying Statin-Induced Endothelial Function Improvement:

2.1.1. Nitric Oxide (NO) Production and Bioavailability

By increasing the synthesis and bioavailability of nitric oxide (NO), a powerful vasodilator and signaling molecule with anti-inflammatory and antithrombotic effects, statins have a significant impact on endothelial function[4]. The following mechanisms are used to accomplish this enhancement:

Elevated Expression of Endothelial Nitric Oxide Synthase (eNOS):

The enzyme that produces NO in endothelial cells, eNOS, is expressed more frequently in statin-treated cells. Many mechanisms, including the activation of protein kinase B (Akt) and the inhibition of Rho-kinase, contribute to this upregulation[1, 23, 24].

Enhanced eNOS Activity:

Statins not only raise the expression of eNOS but also enhance its phosphorylation and inhibit its uncoupling,

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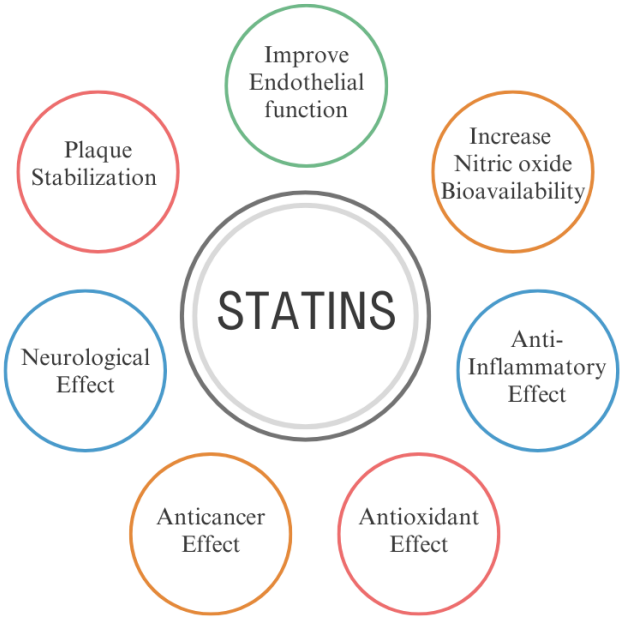

Figure 1: Pleotropic Effects of Statins.

which causes the production of reactive oxygen species (ROS) rather than NO[25, 26].

Decreased Levels of Asymmetric Dimethylarginine (ADMA):

ADMA is an endogenous eNOS inhibitor. By preventing ADMA synthesis and accelerating its breakdown, statins lower ADMA levels and increase the production of NO[9, 27].

Antioxidant Effects:

Statins ensure that eNOS functions at its best by scavenging reactive oxygen species (ROS) and upregulating antioxidant enzymes[28, 29].

2.1.2. Enhanced Vasodilation

Statins cause increased NO synthesis and bioavailability which improves vasodilation, a vital component of endothelial function. Cyclic guanosine monophosphate (cGMP) is produced by vascular smooth muscle cells when NO activates soluble guanylyl cyclase (sGC). This second messenger sets off a series of actions that relax smooth muscles and subsequently dilate blood vessels. Improved blood flow to tissues and decreased vascular resistance are two benefits of enhanced vasodilation, both of which lower blood pressure[30].

2.1.3. Reduced Oxidative Stress

Endothelial dysfunction is largely caused by oxidative stress, which is defined as an imbalance between the generation of reactive oxygen species (ROS) and antioxidant defenses. Statins reduce oxidative stress in several ways. Direct Antioxidant Effects: Statins scavenge reactive oxygen species (ROS) and prevent certain enzymes, including NADPH oxidase, from producing them[13, 31]. Superoxide dismutase (SOD), and glutathione peroxidase are examples of antioxidant enzymes that are upregulated by statins, strengthening the body's defenses against oxidative damage[32].

- Statins inhibit nuclear factor kappa B (NF-κB), a transcription factor that controls the expression of genes that promote inflammation and oxidation[33]. Statins shield endothelial cells from harm, maintain their functionality, and uphold vascular homeostasis by lowering oxidative stress.

2.1.4. Impact on Blood Flow, Vascular Tone, and Cardiovascular Health

The combined impact of statins on oxidative stress, vasodilation, and NO generation results in a marked enhancement in endothelial function. This improvement results in:

- Increased Blood Flow: Vasodilation makes it possible for more blood to reach tissues and organs, which guarantees that enough nutrients and oxygen are delivered. This is especially crucial in ischemia situations.
- Improved Vascular Tone: Statins help to maintain optimal vascular tone by regulating the contractility of vascular smooth muscle, which lowers the risk of hypertension and helps to regulate blood pressure[34].
- Reduced Inflammation: Better endothelial function lessens blood vessel inflammation, which prevents atherosclerosis from forming and advancing[35].
- Enhanced Vascular Repair: Statins support the regeneration and repair of endothelium, which enhances the resilience and health of the arteries[36].

2.1.5. Statins and Anti-Inflammatory Action: A Crucial Component of Cardio Protection

The presence of T cells and monocytes or macrophages in the atheroma is a characteristic of the intricate inflammatory process known as atherosclerosis[37, 38]. These macrophages' and T lymphocytes' release of inflammatory cytokines can alter thrombosis, collagen breakdown, SMC proliferation, and endothelial function[15]. Monocyte adherence to the endothelium and penetration into the subendothelial space are early stages of atherogenesis[38]. According to recent research, statins may have anti-inflammatory effects since they can lower the quantity of inflammatory cells in atherosclerotic plaques[39].

2.1.6. Inhibition of Inflammatory Cytokines

Pro-inflammatory cytokines are important mediators of inflammation in atherosclerosis, and statins efficiently reduce their production and release. These cytokines, which include interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), stimulate smooth muscle cell proliferation, leukocyte recruitment, and endothelial activation, all of which are involved in the development and propagation of plaque[25, 40].

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High-sensitivity C-reactive protein is a clinical indicator of inflammation (hs-CRP)[41]. Low-grade systemic inflammation is reflected by the acute phase reactant (hs-CRP), which is produced by the liver in response to proinflammatory cytokines like interleukin-6 (IL-6)[42]. In seemingly healthy men and women, elevated levels of hs-CRP have been demonstrated to be predictive of an increased risk for coronary artery disease (CAD)[43, 44]. When compared to normal persons, patients with CAD, coronary ischemia, and myocardial infarction have higher hs-CRP levels[45]. According to certain theories, CRP may also play a role in the development of atherosclerosis by attaching itself to modified LDL-C found in atherosclerotic plaques[46, 47]. Complement is activated once CRP binds, and this has been demonstrated to contribute to the advancement of atherosclerotic lesions[48]. Moreover, it has been demonstrated that CRP increases the expression of cellular adhesion molecules, inhibits the production of eNOS, and induces the expression of plasminogen activator inhibitor (PAI)-1 and complement activation, all of which raise the risk of thrombosis, inflammation, and endothelial dysfunction. In fact, after arterial damage, transgenic overexpression of human CRP in transgenic mice increases thrombosis and vascular inflammation[49]. Statins can lower circulating levels of pro-inflammatory cytokines in individuals with CVD and those at risk, according to several studies. Rosuvastatin dramatically lowered levels of high-sensitivity C-reactive protein (hsCRP) in the historic JUPITER study (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), was a landmark clinical study that investigated the efficacy of statin therapy in individuals with elevated high-sensitivity C-reactive protein (hsCRP) levels but normal LDL cholesterol levels[26, 27].

2.1.7. Modulation of Immune Cell Activity

Statins influence different immune cells implicated in atherosclerosis through immunomodulatory means. They prevent macrophages and T cells, which are important components of the inflammatory response, from proliferating and becoming activated[34, 50]. Additionally, statins encourage the development of regulatory T cells (Tregs) that are anti-inflammatory; these cells help maintain immunological homeostasis by stifling overreactions from the immune system[51].

2.1.8. Impact on Plaque Stabilization and Prevention of Cardiovascular Events

The anti-inflammatory actions of statins have profound implications for plaque stabilization and the prevention of acute cardiovascular events. By reducing inflammation within the arterial wall, statins stabilize atherosclerotic plaques by weakening the fibrous cap and raising the danger of rupture, inflammation encourages plaque instability. Statins reinforce the fibrous cap and lower the risk of plaque rupture, which is a main cause of acute coronary syndromes (ACS), by reducing inflammation[27]. Stimulating platelets and raising procoagulant factors, inflammation also contributes to thrombosis. Statins prevent acute events such as myocardial infarction and stroke by decreasing inflammation, which in turn reduces platelet activity and thrombus formation[31].

2.1.9. Statins and Antioxidant Effects: A Shield Against Oxidative Stress in Cardiovascular Disease

Reactive oxygen species (ROS) generation and antioxidant defense systems are out of balance under oxidative stress is essential to the pathophysiology of cardiovascular disease (CVD) and atherosclerosis[52]. ROS have the ability to harm endothelial cells, induce inflammation, and aid in the development and advancement of atherosclerotic plaques[53]. Beyond their ability to control cholesterol, statins have been demonstrated to have strong antioxidant properties that reduce oxidative stress and enhance their cardioprotective advantages[54].

Statins counteract oxidative stress by a variety of methods, including direct and indirect mechanisms:

Direct Scavenging of Free Radicals: Some statins, especially those with a lipophilic structure (atorvastatin), have built-in antioxidant capabilities and can scavenge free radicals directly, such as hydroxyl radicals and superoxide anions[28, 29]. By directly scavenging ROS, this method aids in their neutralization and stops their harmful effects on cellular constituents[55]. The expression and activity of natural antioxidant enzymes are upregulated by statins, which strengthens the body's defense against oxidative damage. Enzymes such as glutathione peroxidase (GPx), catalase, and superoxide dismutase (SOD) are among those that are upregulated. Superoxide anion is converted by SOD to hydrogen peroxide, which is subsequently further detoxified by GPx and catalase[54, 56]. NADPH oxidase inhibition: One of the main sources of ROS in vascular cells is NADPH oxidase. By blocking this enzyme's activity, statins lessen the generation of ROS and lessen oxidative stress[57, 58].

Implications for Vascular Health and Atherosclerosis Prevention

Statins' broad-ranging antioxidant effects extend to vascular health and atherosclerosis prevention[54]. Statins reduce oxidative stress by:

Preserving Endothelial Function:

Raising inflammation and decreasing NO bioavailability, oxidative stress damage's endothelial function. Statins

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protect endothelial integrity and function by lowering oxidative stress, which promotes vasodilation and prevents atherogenesis[25, 59].

Stopping LDL Oxidation:

One of the main causes of atherosclerosis is oxidized LDL (oxLDL). Statins function as antioxidants, which stop LDL oxidation and lessen macrophage absorption, two critical processes in the production of foam cells and plaque[60, 61].

Stabilizing Atherosclerotic Plaques:

Statins stabilize plaques and lessen the chance that they will burst by lowering oxidative stress[62]. Encouraging inflammation and matrix destruction, oxidative stress adds to the instability of plaque. One of the main causes of acute coronary syndromes is plaque rupture[15, 63, 64]. Highly thrombogenic substances are present in the lipid core of the atherosclerotic lesion, and a fibrous cap keeps them isolated from the circulatory[65]. Plaque rupture and subsequent thrombosis are finally caused by the fibrous cap fissuring, erosion, and ulceration[64]. Fibrous caps' primary constituent, collagen, gives them their tensile strength. Macrophages are crucial to the formation and eventual stability of atherosclerotic plaques because they could break down the fibrous cap, which contains collagen[66, 67]. Indeed, areas with high concentrations of macrophages seem to be where plaque matrix breakdown is most active[15, 63]. Activated macrophages may release proteolytic enzymes, such metalloproteinases (MMPs), which could weaken the fibrous cap, especially at the "vulnerable" shoulder area where the fibrous cap connects to the artery wall[68, 69]. Acute coronary syndromes are the result of plaque instability, rupture, and subsequent thrombosis caused by weakening fibrous caps[15, 64, 70]. Statins' cholesterol-lowering effects may increase the stability of plaque by lowering plaque size or altering the lipid core's physiochemical characteristics[71, 72]. On the other hand, angiography shows that lipid-lowering-induced changes in plaque size are generally small and take place overtime. Instead, the therapeutic advantages of decreasing lipids are most likely the result of decreased macrophage accumulation in atherosclerotic lesions and activated macrophages' suppression of MMP synthesis[73]. Statins use both independent and dependent pathways on cholesterol to suppress the expression of MMPs and tissue factor[71, 73, 74], with the direct or cholesterol-independent macrophage effects. Therefore, a combination decreases in lipids, macrophages, and MMPs mediates the plaque-stabilizing effects of statins[30]. By decreasing the tendency for plaque to rupture, these effects of statins may lower the incidence of acute coronary syndromes and potentially account for the rapid reduction in the time course of events in patients at high risk of recurrent myocardial ischemia in the MIRACL[75] and PROVE-IT trials[76].

2.2. Neurological Effects of Statins

Statins have gained more recognition for their possible pleiotropic effects in neurological diseases, despite being predominantly known for their benefits in decreasing cholesterol and improving cardiovascular health. This growing interest is a result of preclinical and epidemiological research indicating that statins may have neuroprotective effects by modulating different pathways related to oxidative stress, neuroinflammation, and vascular dysfunction, all of which are linked to the pathophysiology of several neurological disorders.

2.2.1. Alzheimer's Disease:

The most prevalent type of dementia, Alzheimer's disease (AD), is characterized by gradual cognitive decline, memory loss, and neurodegeneration. Studies using observational data have shown that statin users have a lower incidence of AD[77]. Investigations into the possible mechanisms behind this connection have been spurred by these findings.

Anti-inflammatory Effects:

Statins diminish neuroinflammation by suppressing pro-inflammatory cytokines and chemokines and modifying microglial activation[78]. Chronic neuroinflammation is an important contribution to Alzheimer's disease etiology, driving neuronal death and synaptic dysfunction[79].

Amyloid-β Clearance:

Statins may help remove amyloid-β (Aβ), a key protein in Alzheimer's disease, by increasing its breakdown and decreasing its formation, according to certain research[80]. The buildup of Aβ plaques is a key characteristic of AD pathogenesis.

Tau Phosphorylation:

Statins may also lower tau phosphorylation, which is linked to the production of neurofibrillary tangles, another clinical hallmark of Alzheimer's disease[81].

2.2.2. Parkinson's Disease:

Parkinson's disease (PD), a neurodegenerative condition marked by motor symptoms and cognitive impairment, is linked to the death of dopaminergic neurons in the substantia nigra. Epidemiological studies have revealed a potential preventive effect of statins against Parkinson's disease[82, 83].

Antioxidant Effects:

Statins diminish oxidative stress, a significant factor to dopaminergic neuronal loss in Parkinson's disease, by

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scavenging free radicals and upregulating antioxidant enzymes[84].

Mitochondrial Function:

- Statins may improve mitochondrial function that is reduced in Parkinson's disease by increasing mitochondrial biogenesis and enhancing mitochondrial respiratory chain activity[85].

2.3. Statins and Cancer

Statins, in addition to their well-established cardiovascular advantages, have emerged as promising cancer preventive and treatment possibilities due to their pleiotropic effects on different cellular pathways involved in carcinogenesis. While statins' primary mechanism of action is to reduce cholesterol manufacture, their impact goes beyond lipid metabolism to influence crucial processes in cancer formation and progression, including apoptosis induction, cell cycle arrest, and anti-angiogenesis[86-88].

2.3.1. Apoptosis Induction:

Apoptosis, or programmed cell death, is an important mechanism for maintaining tissue homeostasis and removing damaged or diseased cells[89]. Dysregulation of apoptosis plays a crucial role in cancer genesis and progression, allowing malignant cells to avoid cell death and proliferate uncontrollably[90]. Statins have been found to cause apoptosis in a range of cancer cell lines, including breast, prostate, lung, and colorectal cancer, using both intrinsic and extrinsic mechanisms[91].

Intrinsic Pathway:

Statins can activate the intrinsic apoptotic pathway by altering mitochondrial membrane potential, leading to the release of cytochrome c and activation of caspases[92]. This mechanism is frequently mediated via the suppression of geranylgeranylation, a post-translational modification required for the function of numerous proteins involved in cell survival and proliferation[93].

Extrinsic Pathway:

- Statins can also cause apoptosis through the extrinsic pathway by increasing the expression of death receptors and their ligands, such as Fas and TRAIL, on cancer cells[94]. This initiates a series of signaling processes, culminating in caspase activation and cell death.

2.3.2. Cell Cycle Arrest:

The cell cycle is a strictly controlled process that maintains normal cell division and proliferation. Cancer is characterized by the disruption of the cell cycle, which allows for uncontrolled proliferation[95]. Statins have been demonstrated to elicit cell cycle arrest in many cancer cells, particularly at the G1 phase, via modulating critical cell cycle regulators[96].

p21 and p27 Upregulation:

- Statins can increase the production of cyclin-dependent kinase inhibitors, p21 and p27, which block the activity of cyclin-CDK complexes and limit cell cycle progression from G1 to S phase[97].

Cyclin D1 Downregulation:

- Statins can also inhibit the production of cyclin D1, a major regulator of G1 phase progression, resulting in cell cycle arrest[98].

2.3.3. Anti-angiogenesis:

Angiogenesis, or the development of new blood vessels, is necessary for tumor growth and metastasis. Statins have been demonstrated to reduce angiogenesis by interrupting the signaling pathways involved in endothelial cell proliferation, migration, and tube formation.

VEGF Inhibition:

- Statins can reduce the expression of vascular endothelial growth factor (VEGF), an important pro-angiogenic factor, and its receptors on endothelial cells[99]. This inhibits endothelial cell growth and migration, limiting angiogenesis.

Rho GTPase Inhibition:

- Statins limit the function of Rho GTPases, tiny signaling proteins that control a variety of biological activities, including angiogenesis[100]. Inhibition of Rho GTPases affects endothelial cell movement and tube formation, resulting in diminished angiogenesis[101].

2.3.4.

3. Conclusion

In conclusion, beyond their primary role in lowering cholesterol, statins exhibit a range of pleiotropic effects that extend their benefits across various physiological and pathological processes. These include enhancing endothelial function, exerting anti-inflammatory and antioxidant actions, stabilizing atherosclerotic plaques, and potentially offering neuroprotective and anticancer benefits. By improving vascular health, reducing inflammation, and influencing cellular processes, statins provide therapeutic advantages beyond cardiovascular risk reduction. As ongoing research uncovers more about these multifaceted effects, the scope of statin therapy is likely to expand, paving the way for tailored applications that maximize patient outcomes across a broader spectrum of diseases.

Conflict of interest

The authors declare that no conflict of interest.

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