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Statins: Adverse reactions, oxidative stress and metabolic interactions

Aimei Liu [b], Qinghua Wu [c,d], Jingchao Guo [b], Irma Ares [a], José-Luis Rodríguez [a], María-Rosa Martínez-Larrañaga [a], Zonghui Yuan [b,e,f], Arturo Anadón [a,*], Xu Wang [a,b,**], María-Aránzazu Martínez [a]

[a] Department of Pharmacology and Toxicology, Faculty of Veterinary Medicine, Universidad Complutense de Madrid, Madrid 28040, Spain
[b] National Reference Laboratory of Veterinary Drug Residues (HZAU) and MAO Key Laboratory for Detection of Veterinary Drug Residues, Huazhong Agricultural University, Wuhan, Hubei 430070, China
[c] College of Life Science, Yangtze University, Jingzhou, China
[d] Center for Basic and Applied Research, Faculty of Informatics and Management, University of Hradec Kralove, Hradec Kralove, Czech Republic
[e] MAO Laboratory for Risk Assessment of Quality and Safety of Livestock and Poultry Products, Huazhong Agricultural University, Wuhan, Hubei 430070, China
[f] Hubei Collaborative Innovation Center for Animal Nutrition and Feed Safety, Wuhan, Hubei, China

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ABSTRACT

Statins, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, are currently the most effective lipid-lowering drugs, effectively reducing the plasma total cholesterol and low-density lipoprotein, while also decreasing three triacylglycerols and increasing plasma high-density lipoprotein to a certain extent. However, the excessive or long-term use of statins can cause *in vitro* cytotoxicity, *in vivo* liver injury, liver necrosis, kidney damage, and myopathy in both human beings and animals. Many studies indicate that oxidative stress is involved in the various toxicities associated with statins, and various antioxidants have been evaluated to investigate their protective roles against statin-induced liver, kidney, and muscle toxicities. Widespread attention has been given to statin-induced oxidative stress, with and without the use of other drugs. Much of the information about the mechanism for this reduction comes from cell culture and in experimental animal studies. The primary focus of this article is to summarize the research progress associated with oxidative stress as a plausible mechanism for statin-induced toxicity, as well as its metabolic interactions. This review summarizes the research conducted over the past five years into the production of reactive oxygen species, oxidative stress as a result of statin treatments, and their correlation with statin-induced toxicity and metabolism. Statin-induced metabolism involves various CYP450 enzymes, which provide potential sites for statin-induced oxidative stress, and these metabolic factors are also reviewed. The therapeutics of a variety of compounds against statin-induced organ damage based on their anti-oxidative effects is also discussed to further understand the role of oxidative stress in statin-induced toxicity. This review sheds new light on the critical roles of oxidative stress in statin-induced toxicity and prevention of this oxidative damage, as well as on the contradictions and unknowns that still exist regarding statin toxicity and the cellular effects in terms of organ injury and cell signaling pathways.

Abbreviations: ALP, alkaline phosphatase; AKI, acute kidney injury; ALT, alanine aminotransferase; ATP, adenosine triphosphate; AUC, area under concentration curve; AUClast, the last measurable concentration; ALD, aldosterone; ATSV, atorvastatin; ABT-335, the choline salt of fenofibric acid; AT1, angiotensin II type 1; BDL, BUNDLE; BUN, blood urea nitrogen; BCRP, breast cancer suppressor protein; BW, body weight; CAT, catalase; CK, creatine kinase; CoQ10, coenzyme Q10; CT26, mouse colon cancer cells; CYP, cytochrome P450; Cmax, maximum concentration; CQ, chloroquine; DDIs, drug-drug interactions; DPP-4, dipeptidyl peptidase IV; ERK, extracellular regulated protein kinase; ER, endoplasmic reticulum; FSE, *Fructus schisandrae*; EF-G, elongation factor gene; GSH, glutathione; GPx, glutathione peroxidase; GR, glutathione reductase; GST, glutathione S-transferase; GSSG, oxidized glutathione; GPx1, glutathione peroxidase 1; GGT, gamma glutamyl transpeptidase; GTE, green tea extract; GR, glutathione reductase; $HO^{\bullet}$, hydroxyl radical; HOO^{-}, perhydroxy radical; H_2O_2, hydrogen peroxide; HO-1, heme oxygenase 1; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; HIV-1, human immunodeficiency virus 1; IL-6, interleukin 6; JNK, c-Jun N-terminal kinase; LDH, lactate dehydrogenase; MAPKs, mitogen-activated protein kinase; MCF-7, breast cancer cells; MDA, malondialdehyde; MMP, mitochondrial membrane potential; MPT, mitochondrial permeability transition; MPTP, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; MDA-LDL, malondialdehyde-modified LDL; NQO1, NADPH quinone oxidoreductase 1; Nrf2, nuclear factor erythroid 2-related factor 2; NRG, naringenin; NAC, *N*-AcetylCysteine; O_2^{-}, superoxide anion; 8-OH-dG, 8-hydroxydeoxyguanosine; OATP1B1, anion transport polypeptide; OATP, organic anion transporting polypeptide; OLM, olmesartan; PGC-1α, peroxisome proliferator activated receptor-γ coactivator-1α; PGC-1β, peroxisome proliferator activated receptor-γ coactivator-1β; p38, mitogen activated protein kinase; PIP, piperine; ROS, reactive oxygen species; RA, rheumatoid arthritis; SAMS, statin-associated muscle symptoms; SOD, superoxide dismutase; SCH, human gastric cancer cell line; SNPs, single nucleotide polymorphisms; TBARS, thiobarbituric acid reacting substances; TNF-α, tumor necrosis factor alpha; TAS, total antioxidant status.

* Corresponding author.
** Corresponding author at: National Reference Laboratory of Veterinary Drug Residues (HZAU) and MAO Key Laboratory for Detection of Veterinary Drug Residues, Wuhan, Hubei 430070, China.
E-mail addresses: aanadon@ucm.es (A. Anadón), wangxu@mail.hzau.edu.cn (X. Wang).

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Contents

1. Introduction

Statins, also known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are the most important class of lipid-lowering drugs, which reduce cholesterol synthesis in patients with hypercholesterolemia by regulating the production of plasma lipoproteins (Fig. 1) (Fuhrmeister, Tews, Kromer, & Moosmann, 2012; Zhang et al., 2017). HMG-CoA reductase inhibitors block the synthesis of cholesterol in the liver, thus triggering the compensatory reactions that lead to a reduction of low-density lipoprotein (LDL)-cholesterol in plasma. However, our understanding of this reduction mechanism primarily comes from cell culture and laboratory animal studies. Statins are well established in the treatment of hypercholesterolemia and have attained a central place in cardiovascular medicine because of their proven benefits in both the primary and secondary prevention of cardiovascular events. Statins include lipophilic and hydrophilic types: simvastatin, lovastatin, cerivastatin, fluvastatin, pitavastatin and atorvastatin are lipophilic statins, whereas pravastatin is hydrophilic statins (Davignon, 2012; Kubota et al., 2004; Viola et al., 2012). Compared with most other statins, rosuvastatin is relatively hydrophilic, similar in this respect to pravastatin (Li et al., 2012). The structural differences of statins may determine their differences in function and side effects. The common names, chemical name and normal route with doses of statins are shown into Fig. 1.

Statins are extensively used to reduce the morbidity and mortality associated with cardiovascular disease, such as in the prevention of unstable angina and myocardial infarction, and decrease the need for surgical coronary revascularization (Tobert, 2003); simvastatin is also potentially effective in reducing the risk of developing Alzheimer's disease in patients (Abrahamson, Ikonomovic, Dixon, & DeKosky, 2009; Ostrowski et al., 2016; Robin et al., 2014). Recent studies have shown the relationship between statin use and cancer risk reduction (Afzali, Vatankhah, & Ostad, 2016; Atil, Berger-Sieczkowski, Bardy, Werner, & Hohenegger, 2016). Statins usually have a reasonable safety profile in therapeutic doses, even if cerivastatin was withdrawn from the market in 2001 because of its serious side-effects (Tobert, 2003), and the application of atorvastatin is now restricted due to several acute and chronic side effects, including liver, kidney, and neurotoxicity, but atorvastatin is a highly effective drug used for the treatment of hypercholesterolemia (Pal, Ghosh, Ghosh, Bhattacharyya, & Sil, 2015; Sakaeda, Kadoyama, & Okuno, 2011). One of the adverse effects of statin treatment is myotoxicity (Bouitbir et al., 2011; Bouitbir, Charles, et al., 2012; Bouitbir, Daussin, et al., 2012; Bouitbir et al., 2016; Bonifacio, Sanvee, Bouitbir, & Krahenbuhl, 2015; Bonifacio, Mullen, et al., 2016; Bonifacio, Sanvee, et al., 2016; Fuhrmeister et al., 2012; Singh et al., 2015), with a 1–7% incidence of myotoxic reactions in patients treated with HMG-CoA reductase inhibitors (Goli, Goli, Byrd, & Roy, 2002). Myotoxicity is regarded as a dose-dependent adverse reaction, resulting in a wide spectrum of conditions that range from mild myalgia to potentially lethal rhabdomyolysis or fulminant rhabdomyolysis with acute renal failure as a result of myoglobinuria (Echaniz-Laguna, Mohr, & Tranchant, 2010; Joy & Hegele, 2009). The risk of myositis and rhabdomyolysis that can result in renal failure increases when the statins are combined with cyclosporine, gemfibrozil, clofibrate, or niacin, with care required in these situations. In recent years, hepatotoxicity, such as the elevation of serum enzyme activities of alkaline phosphatase (ALP), aspartate aminotransferase, and alanine aminotransferase (Farag, Mohamed, & Youssef, 2015; Motawi, Teleb, El-Boghdady, & Ibrahim, 2014; Pal, Ghosh, et al., 2015; Pal, Sarkar, Pal, & Sil, 2015), and nephrotoxicity, such as the administration of atorvastatin, caused acute kidney injury (Annigeri & Mani, 2015; Pal, Sarkar, et al., 2015). Statins appear to possess similar side effect profiles, differing only in their maximum potency.

Statins, which are primarily used to reduce the concentration of low-density lipoprotein cholesterol, have also been shown to reduce oxidative stress by modulating redox systems. For instance, statins have been found to play an antioxidant role in some cardiovascular (Tissier et al., 2018) and atherosclerotic diseases (Mason, Dawoud, Jacob, Sherratt, & Malinski, 2018). Study also demonstrated that the antiatherogenic effects of statins are related to their pleiotropic activities, particularly to their antioxidant effects (Profumo, Buttari, Saso, & Rigano, 2014). A number of pleiotropic effects of statins have been described over the past decade, and their ability to suppress global oxidative stress is probably one of the most important mechanisms by which they exert their beneficial effects on the cardiovascular system (Antoniades & Channon, 2014). Studies conducted both *in vitro* and *in vivo* support the role of oxidative stress in the development of atherosclerosis and cardiovascular diseases. Statins reduce oxidative stress by blocking the generation of ROS and reducing the NAD+/NADH ratio (Lim & Barter, 2014). These drugs also have effects on nitric oxide synthase, lipid peroxidation and the adiponectin levels (Lim & Barter, 2014). It is possible that the antioxidant properties of statins contribute to their protective cardiovascular effects, independent of the lipid-lowering actions of these agents (Lim & Barter, 2014).

However, oxidative stress may also be responsible for statin-induced-possible adverse effects such as various diabetic complications (Park, Kwon, Cho, Paick, & Kim, 2017), myopathy (Du Souich, Roederer, & Dufour, 2017) and the development of fatty liver (Hadzi-Petrushev, Dimovska, Jankulovski, Mitrov, & Mladenov, 2018). For instance, possible adverse effects of statins on glucose homeostasis may be related to the redox system. In atherosclerotic tissues, statins play an antioxidant role, however, in hepatic, kidney and muscle cells, statins cause hepatotoxicity, nephrotoxicity and muscle toxicity by oxidative stress. Therefore, the effects of statins on oxidative stress are different in different organs or tissues (Jiao et al., 2017).

There is increasing evidence statin toxicity is closely linked to oxidative stress. It is well known that deficient antioxidant defense or the overproduction of free radicals usually leads to oxidative stress, which may be initiated by reactive oxygen species (ROS), such as the superoxide anion ($O_2^{\bullet -}$), hydroxyl radical ($HO^{\bullet}$), and perhydroxy radical (HOO^{-}) (Wang et al., 2017).

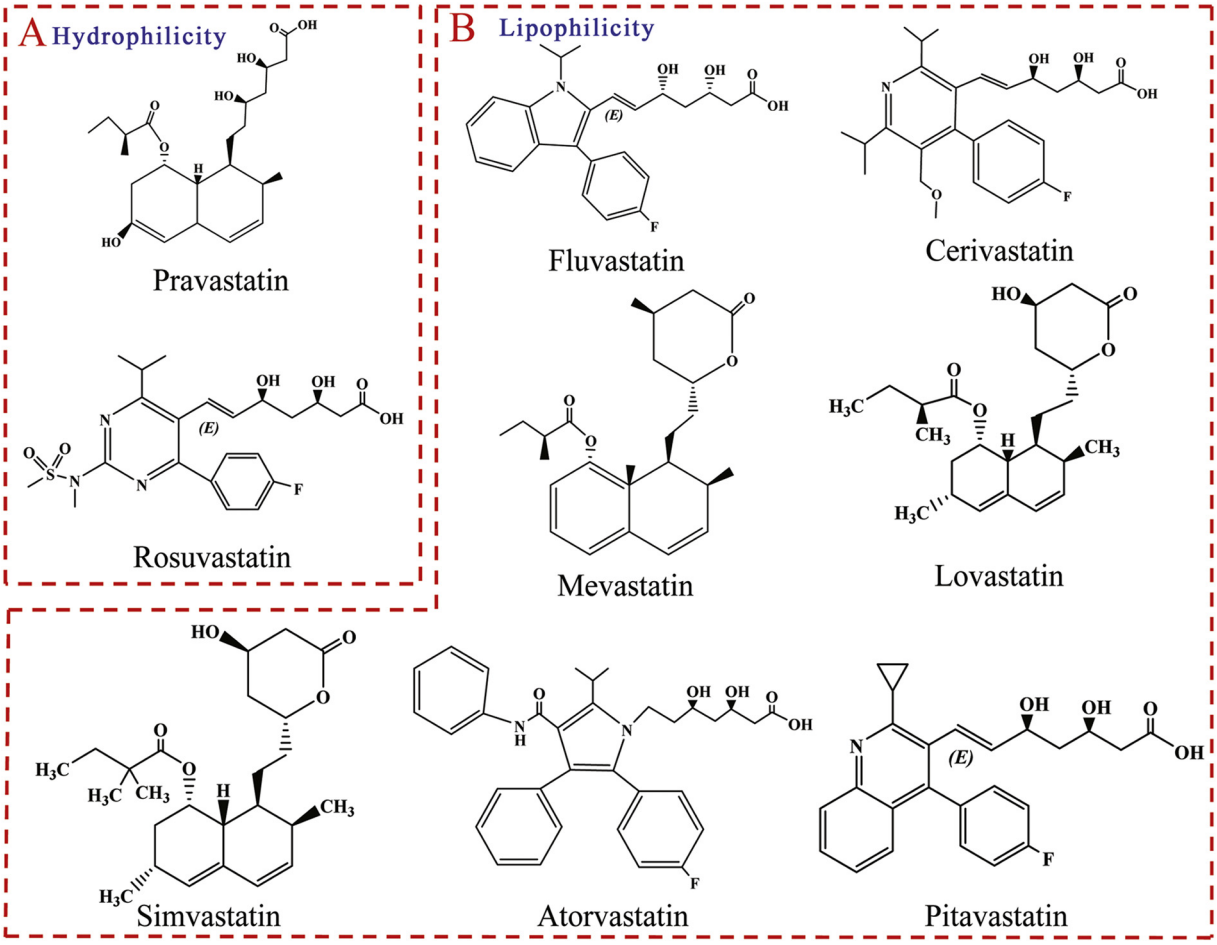

Fig. 1. Chemical structures of the main statins: A) hydrophilic statins and B) lipophilic statins.

Note:	Common names	Chemical name	Oral route and doses
	Simvastatin	1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxooxan-2-yl]ethyl}-3,7-dimethyl- 1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate	5–80 mg/day
	Lovastatin	1S,3R,7S,8S,8aR)-8-[2-[(2R,4R)-4-hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl] (2S)-2-methyl-butanoate	10–80 mg/day
	Cerivastatin	3R,5S,6E)-7-[4-(4-fluorophenyl)-5-(methoxymethyl)-2,6-bis(propan-2-yl)pyridin-3-yl]-3,5-dihydroxy-hept-6-enoic acid	0.3 mg/day
	Fluvastatin	3S,5R,6E)-7-[3-(4-fluorophenyl)-1-(propan-2-yl)-1H-indol-2-yl]-3,5-dihydroxyhept-6-enoic acid	10–80 mg/day
	Pitavastatin	(+)-monocalciumbis(3R,5S,6E)-7-(2-cyclopropyl-4-[4-fluorophenyl]-3-quinolyl-3,5-dihydroxy-6-heptenoate	2–4 mg/day
	Atorvastatin	3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid	10–20 mg/day
	Pravastatin	3R,5R)-7-[(1S,2S,6S,8S,8aR)-6-hydroxy-2-methyl-8-{[(2S)-2-methylbutanoyl] oxy}-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-dihydroxy heptanoic acid	40 mg/day
	Rosuvastatin	3R,5S,6E)-7-[4-(4-fluorophenyl)-2-(N-methyl-methanesulfonamido)-6-(propan-2-yl) pyrimidin-5-yl] -3,5-dihydroxyhept-6-enoic acid	2.5-40 mg/day

It has been revealed that ROS is generated during the metabolism of statins, thus resulting in oxidative stress and various levels of toxicity, including skeletal muscle toxicity and hepatic and renal damage (Bouitbir, Charles, et al., 2012; Pal, Ghosh, et al., 2015; Pal, Sarkar, et al., 2015). Given the prolific use of statins around the world, a comprehensive analysis of their side effects warrants more attention. The influence of a number of side effects, including oxidative stress, ROS on statin-associated myotoxicity, photosensitivity disorders, hepatotoxicity, and nephrotoxicity have recently been investigated (Bouitbir, Charles, et al., 2012; Motawi et al., 2014; Pal, Ghosh, et al., 2015; Pal, Sarkar, et al., 2015). Various *in vitro* studies in primary and passage cells or mitochondria and *in vivo* studies, such as human beings, guinea-pig, rats, and mice, have identified that oxidative stress plays a critical role in statin-induced toxic effects. Several reviews on statins have been published to date, including a systematic review and meta-analysis of statins and primary prevention of venous thromboembolism (Kunutsor, Seidu, & Khunti, 2017), current evidence and challenges of statin therapy (Elnaem, Mohamed, Huri, Azarisman, & Elkalmi, 2017), the efficacy and safety of statins and exercise combination therapy (Gui et al., 2017), the mechanisms of myotoxicity induced by statins (Du Souich et al., 2017), the unintended effects of statins from observational studies in the general population (Macedo et al., 2014), reports of idiosyncratic post-marketing liver injuries (Bjornsson, Jacobsen, & Kalaitzakis, 2012), the safety of statins (Bays, 2006), and the pathophysiologic and clinical perspectives of statins (Baker & Tarnopolsky, 2001). The toxicity, toxic mechanisms, and antagonistic effects of statins on myotoxicity, photosensitivity disorders, neurotoxicity, hepatotoxicity, and renal toxicity have recently gained increasing attention, with the publication of new articles on the important role of oxidative stress and the antioxidants used as antagonists in the toxicities of statins.

Statins are widely used as anti-hyperlipidemic agents worldwide, and are also potent drugs used as lipid-lowering agents in cardiovascular diseases. However, a number of recent studies have shown that statins may protect against cardiovascular-related mortality but also induce skeletal muscle toxicity. Furthermore, statins can induce photosensitivity disorders, neurotoxicity, hepatotoxicity, and renal toxicity in some patients. Although the side effects of statins have been widely reported in recent years, the mechanism of their toxicity-oxidative stress needs further elaboration. In addition, statins combined with other drugs may cause organ toxicity, but the mechanism of combined toxicity is not in-depth. The role of other drugs in the metabolism of statins is also unclear.

Therefore, it is appropriate at this point to review the recent research progress focused on the toxic mechanisms of statins or combined toxicity. The scope of this review is primarily intended to summarize the evidence associated with statin-induced toxicity related to oxidative stress, and also to identify considerable potential therapeutics for statin-induced toxicity. We summarized the possible mechanisms of oxidative stress induced by statins in Table 1. The studies related to the toxicity of statins and oxidative stress under both *in vitro* and *in vivo* conditions are summarized in Tables 2 and 3, respectively. The metabolic pathways, metabolizing enzymes, the influential factors in the metabolism of statins, and the toxicity of its metabolites are also reviewed. Furthermore, various antioxidants used as antagonists are summarized to potentially identify effective strategies for the application of antioxidants to inhibit statin-induced toxicity. This will provide some reference for the treatment or prevention of side effects of statins.

2. Adverse reactions by overdoses or prolonged administration of statins

2.1. Myopathy and hepatotoxicity

The most adverse side effects associated with statins are myopathy and an asymptomatic increase in hepatic transaminases (Fig. 3), which can lead to hepatotoxicity. In a widely reported case, known as the "lipobay incident", there were 31 documented cases where patients taking Lipobay (cerivastatin) had died of severe myopathy due to striated muscle dissolution, which have since brought widespread attention to the risks of statin use (Zeman, Zak, Vecka, & Romaniv, 2003). Statin-associated muscle symptoms are reported by 10–29% of patients in clinical practices, which are a major determinant of statin nonadherence, discontinuation, and switching (Jacobson, Khan, Maki, Brinton, & Cohen, 2017). Of the respondents, 60% of former statin users reported experiencing new or worsened muscle pain while taking statin, in contrast to only 25% of current users, where reducing the statin dose brought some relief to muscle-related symptoms (Jacobson et al., 2017). Although statins are the most widely prescribed class of drugs for coronary artery disease (CAD) patients, a recent cross-sectional study conducted among 300 adult CAD patients visiting the outpatient department of a tertiary care hospital in northern India, who were receiving statins for their diagnosis, revealed that myopathy and muscle-related ailments, such as muscle pain, cramps, and muscle weakness, were the most prevalent side effects (32, 34, and 47%, respectively), followed by numbness, tingling, and burning in the extremities (31%) (Mulchandani, Lyngdoh, Chakraborty, & Kakkar, 2017). Furthermore, joint pain and cognitive impairments were seen in nearly 20% of the patients (Mulchandani et al., 2017).

More important evidence is that a recent international survey regarding statin-associated symptoms indicated that 72% of overall adverse events were muscle related. Although rates of statin-associated muscle symptoms in randomized controlled trials are relatively low and similar to placebo, the prevalence in clinical practice is markedly higher, with observational data estimating rates of 11% to 29% (Backes, Ruisinger, Gibson, & Moriarty, 2017). Notable findings include the inconsistency with reproducing muscle complaints, as approximately 40% of subjects report statin-associated muscle symptoms (SAMS) when taking a statin but not while receiving placebo, but a substantial cohort reports intolerable muscle symptoms with placebo but none when on a statin. Therefore, managing the highly intolerant requires candid patient counseling, shared decision-making, eliminating contributing factors, careful clinical assessment and the use of a myalgia index score, and isolating potential muscle-related adverse events by gradually reintroducing drug therapy with the utilization of intermittent dosing of lipid altering agents (Backes et al., 2017). While statins are widely used drugs for cardiovascular prevention, their utilization may cause various grades of muscle toxicity. Statin discontinuation alone is not always sufficient to restore muscle to its pre-injury state, which can potentially evolve into serious inflammatory muscle disease, with severe myopathy cases reported in aged patients who were treated with high statin doses (Canzonieri et al., 2017). However, more research is needed to develop patient-centric and evidence-based approaches for managing statin-associated muscle symptoms, which is especially important in light of recent data that have shown increased cardiovascular risk among patients who discontinue statin therapy.

Studies have clearly shown that statins can cause idiosyncratic hepatotoxicity. Limiting “hepatotoxicity” to the dose-dependent reaction leaves the reader with the impression that statins are not hepatotoxic due to the lack of dose dependency; on the contrary, statin metabolism is reduced in patients with preexisting liver conditions. Statins are also known to increase alanine aminotransferase (ALT), with a slight dose dependency, as ALT increases for higher statin doses (Schulze & Glass, 2012). Although statins can be given to liver patients, this may cause a certain degree of liver toxicity.

Altogether, increasing reports have shown that satins can lead to myopathy and hepatotoxicity. A recent international survey of statin-related symptoms showed that 72% of the overall adverse events were muscle-related. Statins increase ALT in the liver. However, certain data indicate that these symptoms often present in populations with underlying musculoskeletal complaints and are not likely statin related. Therefore, in clinical practice, it is necessary to determine more accurately whether myopathy is caused by statins to treat the myopathy.

2.2. Other adverse reactions

In addition to myopathy, commonly used statin drugs also increase the risk of hyperkalemia (Deska & Nowicki, 2017). Treatment options for hypercholesterolemia in patients with statin intolerance and myotonic dystrophy are currently limited, with some patients developing severe myalgias in the proximal lower and upper extremities shortly after simvastatin treatment, along with an increase in serum creatine kinase (CK) to 317 U/L (Shakir, Shin, Hoang, & Mai, 2017). Patients treated with various statins, including rosuvastatin, have subsequently experienced similar outcomes (Shakir et al., 2017). Because statins are prescribed on a long-term basis, their possible interactions with other drugs deserve particular attention, as many patients will typically receive pharmacological therapy for concomitant conditions during the course of statin treatment (Bellosta & Corsini, 2012). The meta-analysis suggests that SLCO1B1-521T>C polymorphism may be a risk factor for statin-induced adverse drug reactions, especially in simvastatin therapy (Jiang et al., 2016).

Although statins are generally safe, both minor and severe adverse reactions occasionally arise, and the toxicity (adverse reactions) caused by overdoses or the prolonged administration of statins still requires more attention, especially when given to patients taking concomitant medications that inhibit the statin clearance and lead to increased statin plasma concentrations. Furthermore, recent studies have shown that oxidative stress may be an important mechanism for statin-induced toxicity (adverse reactions) (Bouitbir et al., 2011; Bouitbir, Charles, Echaniz-Laguna, et al., 2012).

Table 1
The potential mechanisms of statins-inducing oxidative stress.

Statins	Models	Mechanism of induced oxidative stress	Reference
Simvastatin	In muscle biopsies of patients	Altered mitochondrial function with diminished production of ATP, excess production of ROS, and apoptosis. Altered Ca^{2+} homeostasis, down-regulated the expression of PGC-1α/β and SOD1/2 and MAFbx.	Bouitbir et al. (2016); Schirris et al. (2015); Bouitbir, Charles, et al., 2012
	In human rhabdomyosarcoma cells	Reduced mitochondrial oxidative function and ATP production.	Vaughan, Garci-Smith, Bisoffi, Conn, and Trujillo (2013)
	In cardiac fibroblasts and myofibroblasts	Impeded geranylgeranyl prenylation and activation of small GTPases and activated caspase3 and thus enhanced apoptosis.	Copaja et al. (2011)
	Human muscle fibers from the *Vastus lateralis*	Impaired mitochondrial respiratory chain with accumulation of reduced NADH.	Sirvent, Mercier, Vassort, and Lacampagne (2005)
	In C2C12 myotubes	Impaired mitochondrial respiration at complex I and/or III. Increased mitochondrial production of $O_2^{\bullet-}$ by inhibiting complex III.	Kwak et al. (2012)
	In human skeletal muscle fibers	Enhanced $[Ca^{2+}]$s, result of an early release of Ca^{2+} from the mitochondria through mPTP and Na^{+}-Ca^{2+} exchanger channels, and a late efflux associated to the uptake of $[Ca^{2+}]$s by SERCA and release by the SR Ca^{2+} channel RyR.	Sirvent et al. (2005)
	In vivo in rats In hepatocytes	Affected RhoA/AKT/PGC-1α pathway: reduced phosphorylated AKT, FoxO1 and FoxO3 in the sarcoplasma, and increases FoxO1 and FoxO3 in nuclear fractions; in parallel, the expression of MAFbx and MuRF-1 mRNA is elevated, with muscle fiber necrosis and elevated serum CK.	Sirvent et al. (2005)
Atorvastatin	In bovine aortic endothelial cells	Increased ROS and activates PKCζ-$Thr^{410/403}$, liver kinase B1-Ser^{428}, and AMPK Thr^{172}.	Choi et al. (2008)
	In muscles of mice	Reduced ubiquinone by almost 50%.	Muraki et al. (2012)
	In male Sprague-Dawley rats	Decreased in muscle ATP.	El-Ganainy et al. (2016)
	In male Wistar rats	Regulated ROS/PGC-1 signalling pathway in mitochondrial function in cardiac as well as skeletal muscles.	Hoppeler (2016)
	In *plantaris* muscle of male Wistar rats	Reduced mitochondrial DNA, cytochrome oxidase 1, nuclear respiratory factor 1, and maximal mitochondrial respiration. Increased the production of ROS.	Bouitbir, Charles, et al., 2012
	In C2C12 myotubes	Regulated RhoA/AKT/PGC-1α pathway.	Du Souich et al. (2017)
Lovastatin	Male Sprague-Dawley rat vascular smooth muscle cells	Promoted apoptosis, secondary to the inhibition of the prenylation of small GTPases of the Rho family, effect reverted by the addition of mevalonate, FPP or GGPP.	Guijarro et al. (1998)
	In cultured myotubes	Enhanced MAFbx, with reduction of myotube diameter.	Cao et al. (2009)
	In C2C12 myotubes	Affected RhoA/AKT/PGC-1α pathway: decrease AKT and FoxO3 Ser^{253} phosphorylation, and therefore enhance nuclear translocation of FoxO3 and its binding to MAFbx promoter, with the subsequent increase of MAFbx mRNA and muscle atrophy.	Du Souich et al. (2017)
Cerivastatin	In myocytes and L6 skeletal muscle myoblasts from male Sprague Dawley rats	Decreased mitochondrial respiration, fatty acid oxidation and membrane potential. Increase mitochondrial swelling, as well as the release of cytochrome c into the sarcoplasma. Depressed mitochondrial respiration due to the inhibition of the electron transport chain, and uncoupling of oxidative phosphorylation.	Kaufmann et al. (2006)
	In C2C12 myotubes	Decreased basal oxygen consumption rate, as well as maximal respiration of complex I, II, and glycerol-3-phosphate dehydrogenase driven respiration, with reduction of ATP production. Inhibit cytochrome c oxidoreductase activity, and complex III driven respiration.	Schirris et al. (2015)
Fluvastatin	Single skeletal myofibers of rat flexor digitorium	Led to a dose-dependent formation of craters along the sarcolemma, swelling of the SR and mitochondria, and intracellular vacuoles.	Sakamoto, Honda, Yokoya, Waguri, and Kimura (2007)
	In myocytes and L6 skeletal. In muscle myoblasts from male Sprague-Dawley rats	Decreased mitochondrial respiration, fatty acid oxidation and membrane potential; Increased mitochondrial swelling, as well as the release of cytochrome c into the sarcoplasma. Depressed mitochondrial respiration due to the inhibition of the electron transport chain, and uncoupling of oxidative phosphorylation.	Kaufmann et al. (2006)
	In male Wistar rats	Elevated $[Ca^{2+}]$ s in fibers of the fast-twitch extensor digitorum longus muscle, increase not associated to enhanced sarcolemmal cationic permeability.	Liantonio et al. (2007)
	Mitochondria isolated from hearts in male mice (C57BL/6J)	Increased the release of Ca^{2+} from the mitochondria through the mPTP and the increase in $[Ca^{2+}]$s activates an additional release of Ca^{2+} from the SR through the RyR channel.	Madungwe, Zilberstein, Feng, and Bopassa (2016)
	In male Wistar rats	Reduced resting chloride conductance by blocking ClC-1 channels, effects that can produce muscular fatigue and cramps.	Liantonio et al. (2007)
Pitavastatin Rosuvastatin Pravastain	In C2C12 myoblasts	Caused mitochondrial damage. Inhibited the RhoA/AKT cascade, thus promoting apoptosis.	Schirris et al. (2015); Kaufmann et al. (2006)

Note: AKT, protein kinase B; AMPK, AMP-activated protein kinase; CK, creatine kinase; ClC-1, chloride channel; FoxO1, forkhead box O1; FoxO3, forkhead box O3; FPP, farnesyl pyrophosphate; GGPP, geranylgeranyl pyrophosphate; HMG-CoAR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; MAFbx or atrogin-1, muscle atrophy F-box; mPTP, mitochondrial permeability transition pore; MuRF-1, muscle RING-finger protein-1; NADH, reduced β-nicotinamide adenine dinucleotide; O•2−, superoxide; OR, odds ratio; PGC, transcription factors peroxisome-proliferator-activated receptor coactivator; PKCζ, protein kinase C; RhoA, Ras homolog gene family member A; ROS, reactive oxygen species; RYR3, ryanodine receptor 3; SERCA3, sarco-endoplasmic reticulum transporting Ca2+, ATPase 3; SOD, superoxide dismutase; SR, sarcoplasmic reticulum.

3. Oxidative stress

3.1. Generation of oxidative stress, ROS

Statin-induced ROS generation plays critical roles in myotoxicity and phototoxicity. In a study to investigate mitochondrial function and ROS production in skeletal muscle after exhaustive exercise in atorvastatin-treated rats (10 mg/kg BW) for two weeks, it was revealed that exhaustive exercise exacerbated metabolic perturbations and ROS production in skeletal muscle, suggesting that ROS generation can reduce the exercise capacity and promote muscular symptoms in sedentary atorvastatin-treated animals (Bouitbir et al., 2011). Interestingly,

Table 2
In vitro statins related oxidative stress studies.

Cell type	Time of incubation/assay	Dose	Aim	Result/conclusion	Reference
Hepatocytes from male Sprague-Dawley rats	ROS, GSH, GSSG, MMP tests: 1, 2, 3 h.	Statins induced cytotoxicity: statins (simvastatin, lovastatin and atorvastatin, 200 μM). Oxidative stress: simvastatin (200 μM) or + L-carnitine (100 μM).	To evaluate the effect of L-carnitine on the cytotoxic effects of statins on the freshly isolated rat hepatocytes.	Statins: increased ROS formation, cellular GSSG and TBARS, and decreased cellular GSH level and MMP.	Abdoli, Azarmi, and Eghbal (2015)
	TBARS: 2 and 3 h.	Lovastatin (200 μM) or + L-carnitine (100 μM). Atorvastatin (450 μM) or + L-carnitine (100 μM).		L-carnitine: co-administration decreased ROS generation, cellular TBARS and GSSG, increased cellular GSH level and MMP.	
Hepatocytes from male Sprague-Dawley rats	Cell viability: 1, 2, 3 h. ROS generation: 1, 2, 3 h.	NAC (200 μM) (no difference before or co-adding of statins) + atorvastatin (450 μM), or simvastatin (200 μM), or	To reveal the mechanism of hepatotoxicity induced by statins.	Statins: resulted in cytotoxicity characterized by an elevation in cell death, increasing ROS generation and TBARS level and decreased MMP level.	Abdoli, Azarmi, and Eghbal (2014)
	Lipid peroxidation: 2, 3 h. MMP assay: 1, 2, 3 h.	lovastatin (200 μM)		NAC: caused reduction in amount of ROS formation, TBARS levels and improved cell viability and MMP.	
Hepatocytes from male Sprague-Dawley rats.	Cell viability: 1, 2, 3 h.	Pretreatment coenzyme Q_{10} (CoQ_{10}) (200 μM).	To establish the protective effect of CoQ_{10} against cytotoxicity induced by statins.	Statins: depleted cellular GSH, increased the levels of GSSG, TBARS, and ROS formation, and decreased MMP.	Eghbal, Abdoli, and Azarmi (2014)
	ROS generation.	Atorvastatin (450 μM) + CoQ_{10}		Pretreatment with CoQ10: lowered GSSG, LPO level, ROS generation and increased GSH and MMP levels.	
	Lipid peroxidation-MMP assay.	Simvastatin (200 μM) + CoQ_{10}			
	Cellular GSH/GSSG	Lovastatin (200 μM) + CoQ_{10}			
Satellite cells from the *Musculus obliquus internus abdominis* of healthy human	Cell Viability: 24 h. Uptake and oxidation of glucose. Cysteine protease activity.	Simvastatin (10, 20, 30, 40 μM)	To study the effects of simvastatin on glucose metabolism and the activity of legumain (asparaginyl endopeptidase)	Simvastatin: induced myotoxicity by impaired mitochondrial dysfunction, resulted in the dose-dependent decrease in both glucose uptake and oxidation in mature myotubes, and led to decrease in maturation and activity of legumain.	Smith et al. (2014)
Hepatocytes from male Sprague-Dawley rats	Statins-induced cytotoxicity. ROS, GSH, GSSG and MMP tests: 1, 2, and 3 h.	Statins-induced cytotoxicity: atorvastatin (250, 450, 500 μM), simvastatin (150, 200, 250 μM), lovastatin (150, 200, 250 μM); GSH, GSSG, ROS, and MMP tests: atorvastatin (450 μM), simvastatin (200 μM), lovastatin (200 μM)	To reveal the cytotoxic effects of statins toward isolated rat hepatocytes	Statins: caused cytotoxicity toward rat hepatocytes dose dependently, increased ROS and GSSG formation, accompanied by a significant increase of TBARS and a decrease in MMP, and decreased cellular GSH level.	Abdoli, Heidari, Azarmi, and Eghbal (2013)
Hepatocytes from male Sprague-Dawley rats	Cell viability: 24 h. Proteomic and transcriptomic analysis.	Hepatocytes exposed to simvastatin (16.54 μM).	To reveal the mechanisms of hepatotoxicity induced by simvastatin.	Simvastatin: increased 61 and decreased 29 proteins among a total of 607 differentially expressed proteins, increased 206 and decreased 41 gene expressions, and increased NRF2- mediated oxidative stress response and CYP2D1, CYP2D3, CYP2D10, CYP2D26, CYP1A2, CYP51.	Cho et al. (2013)
The PC3 human prostate cancer cell line	Cell death and superoxide generation: 2 h	Simvastatin (60 μM), or + L-carnitine (6 μM), or + piracetam (6 μM); Simvastatin (60 μM), + L-carnitine (4 μM), + piracetam (4 μM)	To investigate the pathways leading to simvastatin induced cell death and the protection of L-carnitine or piracetam.	Simvastatin: induced MPT and cell necrosis. L-carnitine and piracetam: combination with statins increased MPT, and decreased the rate of mitochondrial superoxide generation.	Costa, Fernandes, de Souza-Pinto, and Vercesi (2013)
H_9C_2 cardiomyocytes, L_6 myotubes	ROS in cardiac muscle. Mitochondrial biogenesis. 48 and 72 h	Atorvastatin (1 μM); NAC (1 mM);	To reveal the effects of statin treatment on ROS, production-induced mitochondrial biogenesis in cardiac and skeletal muscles in humans, animals and cell culture models.	Atorvastatin: increased ROS production at 48 h, and increased PGC-1α, NRF1, TFAm, and citrate synthase mRNA expression in H_9C_2 cells while decreased PGC-1α gene expression in L_6 cells. NAC: decreased ROS generation, PGC-1α, NRF1, TFAm, SOD2 mRNA expression, and decreased SOD2 concentration in H_9C_2 cells while increased PGC-1α gene expression in L_6 cells.	Bouitbir, Daussin, et al. (2012)
H9c22-1 and C2C12 cells	Cell viability: 24h.	H9c22-1cells Treated with: cerivastatin	To study molecular origin of serious myotoxic potential induced by	Cerivastatin: decreased selenoprotein synthesis and reduced the steady	Fuhrmeister et al. (2012)

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Table 2 (*continued*)

Cell type	Time of incubation/assay	Dose	Aim	Result/conclusion	Reference
		(0.001, 0.001, 0.01, 0.1, 1, 10 μM).	statins.	state -levels of GPx1 and selenoprotein N.	
	Cerivastatin and myoblast selenoprotein expression.	Cells cultivated with: selenite (500 pM for 10 days) + cerivastatin (0, 5, 10, 50, 100 nM). Atorvastatin on myoblast survival. Mevalonic acid: entirely prevented the statin-induced decrease in peroxide resistance.		Selenite, ebselen, and ubiquinone: unable to prevent the devitalizing effect of statin treatment. Toxicity for 3 days: cerivastatin (0.01, 0.1, 1, 10 μM).	
Reversibility of atorvastatin--induced antioxidative impairment.		Toxicity for 3 days: atorvastatin (1, 10, 100 μM).	These results indicate: muscle cells may be particularly susceptible to a statin-induced suppression of essential antioxidant selenoproteins.		
Human keratinocytes cell line NCTC-2544	Cell viability: 72 h. Detection of DNA fragmentation. Intracellular calcium measurement. ATP assay. Caspase-3 assay. TBARS assay.	Pitavastatin (20 and 100 μM). Phenanthridine (PP4) (10, 20 μM)	To study photo- toxicity mechanism induced by pitavastatin and its photoproducts.	Pitavastatin and the photoproduct PP4 principally induced necrosis and exert their phototoxic effect mainly in the cellular membranes. The present results suggest that the phototoxicity of pitavastatin may be mediated by the formation of benzophenanthridine-like, photoproducts that appear to have high potential as photosensitizers.	Viola et al. (2012)
Yeast cells	Cell morphology and viability: 5 days.	Cell morphology and viability: Atorvastatin (3.5 to 110 mM).	To gain further insight into the molecular mechanisms of atorvastatin toxicity.	Atorvastatin: displayed marked morphological deformities, reduced cell viability and led to mitochondrial dysfunction.	Callegari, McKinnon, Andrews, and de Barros Lopes (2010)
	Mitochondrial function: 3 days.	Mitochondrial function: atorvastatin (3.44 to 880 mM).		Ergosterol, coenzyme Q and a heme precursor: ineffective in the prevention of statin-induced mitochondrial disruption and cell death. Geranyl pyrophosphate and farnesyl pyrophosphate: significantly restored cell viability.	
CT26 and B16BL6 cells	Cell viability: 24 h.	MTT assay: CT26 and B16BL6 cells treated with simvastatin (0, 0.2, 1, 5, 10, 20 μM for 24 h).	To elucidate the role of oxidative stress in the cytotoxicity of simvastatin in murine CT26 colon carcinoma cells and B16BL6 melanoma cells.	CT26 cells: more sensitive to simvastatin than B16BL16 cells; Simvastatin resulted in significant apoptotic cell death and perturbations in parameters indicative of oxidative stress in CT26 cells, decreased Mn-SOD, CAT, GPx1, and SESN 3 level.	Qi et al. (2010)
	Glutathione content assay. Oxidative stress. Caspase activity. Real-time PCR analysis.	CT26 cells incubated with simvastatin (5 μM for 0, 6, 16, 24 h).		Isoprenoids decreased oxidative stress parameters and cell death. L-buthionine-sulfoximine: increased oxidative stress induced by simvastatin.	
NCTC-2544 cells	Cell viability: 72 h.	Fluvastatin (5, 10, 15, 20, 25 μM).	To investigate the mechanism of phototoxicity of fluvastatin.	Fluvastatin: and its main photoproduct induced principally necrosis and induced a rapid increase of intracellular calcium followed by an extensive cell lipid membrane peroxidation and a significant oxidation of model proteins, suggesting that these compounds exerted their toxic effect mainly in the cellular membranes.	Viola et al. (2010)
	Detection of DNA fragmentation. Intracellular calcium measurement. ATP assay. Oxidative stress. TBARS assay. Protein oxidation.			On the basis of our results, the phototoxicity of fluvastatin may be mediated by the formation of benzocarbazole-like photoproduct that acts as strong photosensitizer.	
HepG2 cells	GPx4 expression: 4 days.	GPx expression: atorvastatin (10, 100, and 1000 nM), or cerivastatin (10, 50, and 100 nM), or lovastatin (10, 100, and	To reveal the elevation effects of statins on liver enzymes	Atorvastatin, cerivastatin, and lovastatin: clinically common concentrations induce a selective, differential loss of selenoprotein expression in cells.	Kromer and Moosmann (2009)

Table 2 (*continued*)

Cell type	Time of incubation/assay	Dose	Aim	Result/conclusion	Reference
	GPx activity: 4 days.	1000 nM); Glutathione assay, or GPx activity, or ROS production: statins (10, 100, and 1000 nM)		Statins: reduced biosynthesis, steady-state expression level, and catalytic activity of GPx, whereas did not affect the mRNA levels of GPx1 and GPx4.	
	Glutathione assay: 4 days. ROS production: 4 days.			Statins: induced a significantly increased sensitivity of the cells to peroxides, an effect that was largely reversible by supraphysiological concentrations of selenite.	
Skeletal muscle cell from human beings	Fatty acid oxidation assay: 48 h	Lovastatin (0-20 μM)	To test the hypothesis that myotubes from patients intolerant of lipid-lowering therapies have abnormal fatty acid oxidation responses	Lovastatin: stimulated greater palmitate oxidation in cells from statin intolerance than control, no difference in muscle biopsy myopathy scores between the groups, greater basal octanoate oxidation in cells from statin intolerance than in cells from statin-naive volunteers undergoing knee arthroplasty.	Phillips et al. (2009)
Human peripheral blood lymphocytes	Cell viability: 6, 24, and 48 h. Alkaline comet assay.	Atorvastatin (30.21 ng/mL)	To investigate the genotoxic potential of atorvastatin	Atorvastatin: a significantly greater tail length, tail intensity, and tail moment in all treated lymphocytes than control, and a significantly higher total number of micronuclei, nucleoplasmic bridges and nuclear buds in the exposed than in controlled lymphocytes.	Gajski, Garaj-Vrhovac, and Orescanin (2008)
Breast cancer cells (MCF-7 cells)	Cell proliferation: 48h.	Cell proliferation: statins (1.25, 2.5, 5, 10, 20, and 40 μM).	To reveal the mechanism of antiproliferative and antitumoral effects of statins	Fluvastatin, simvastatin and atorvastatin: induced increase in ROS production that was associated with cell death, inhibited cell proliferation by resulting in a decrease in the DNA synthesis and a cell cycle arrest in the G_1 and G_2/M phases.	Sanchez et al. (2008)
	DNA synthesis and cell cycle: 48 h.	DNA synthesis, cell cycle and ROS: fluvastatin (1.25 μM), simvastatin (2.5 μM), and atorvastatin (40 μM).		Fluvastatin: led to a loss in the mitochondrial membrane potential.	
	Cell membrane damage. ROS production: 2 h.	ROS production: statins (1.25, 2.5, 5, 10, 20, and 40 μM) + NAC (20 mM)		NAC: abrogated the ROS generation by statins.	
Liver mitochondria from male Sprague-Dawley rats	Mitochondrial oxygen consumption: 20 min. Oxidative phosphorylation assay.	Statins (150 μM).	To reveal the mitochondrial impairment of thiazolidinediones, fibrates, and statins.	All statins: no inhibition effect on complex II activity. Simvastatin: inhibited complex I, II +III, IV, and V. Fluvastatin and cerivastatin: caused 40-45% inhibition of complex V. Atorvastatin and pravastatin: no inhibition on complex activity. The inhibition of the oxidative phosphorylation complexes: simvastatin ˃ lovastatin ˃ fluvastatin = cerivastatin ˃ atorvastatin = pravastatin. Lovastatin, simvastatin, and cerivastatin: impaired mitochondrial respiration the most. Simvastatin and lovastatin: impaired multiple oxidative phosphorylation complexes.	Nadanaciva, Dykens, Bernal, Capaldi, and Will (2007)
HepG2 cells	Assay of mitochodrial CoQ10	HepG2 cells treated with simvastatin (0, 1, 3, 5 and 10 μM).	To study if simvastatin reduced mitochondrial CoQ_{10} levels, and the hepatic damage and oxidative stress markers.	Simvastatin: decreased HMG CoA reductase activity, mitochondrial CoQ_{10} levels, and higher doses of the drug resulted in a moderately higher degree of cell death, increased 8-OHdG level and a reduction in ATP synthesis.	Tavintharan et al. (2007)
	18 h. Assay of HMG CoA reductase activity. Oxidative damage to DNA. ATP assay.	CoQ_{10} (5 and 10 μg/mL).		CoQ_{10}: reduced cell death and 8-OHdG level, and increased ATP synthesis.	

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Table 2 (*continued*)

Cell type	Time of incubation/assay	Dose	Aim	Result/conclusion	Reference
L6 cells (rat skeletal muscle myoblasts) and skeletal muscle mitochondria from male Sprague-Dawley rats	Lactate dehydrogenase LDH) assay: 24 h.	LDH: 0.1-1000 μM.	To investigate mitochondrial toxicity of four lipophilic stains cerivastatin, fluvastatin, atorvastatin, simvastatin and one hydrophilic statin pravastatin	Four lipophilic statins (100 μM): induced death in 27-49% of the cells, β-oxidation was decreased by 88-96%.	Kaufmann et al. (2006)
	Mitochondrial membrane potential assay: 10 min.	MMP test: 0.1-1000 μM.		Four lipophilic statins: resulted in mitochondrial swelling, cytochrome c release and DNA fragmentation decreased glutamate-driven state 3 respirations and respiratory control ratio in mitochondria.	
	Cytochrome c immune-cytochemistry assay: 24 h.	Uncoupling effects: 100 μM.		Pravastatin: no toxicity up to 1 mM.	
	Cellular ATP content assay: 24 h.	Oxidative metabolism of L-glutamate: 2- 400 μM.		Cerivastatin, fluvastatin and atorvastatin (100 μM): decreased the mitochondrial membrane potential by 49-65%, whereas simvastatin and pravastatin were less toxic. Lipophilic statins: impair the function of skeletal muscle mitochondria, whereas the hydrophilic pravastatin is significantly less toxic.	
Human hepatocytes	Cell viability: 24 h.	Cell viability: Stains 1-30 μM.	To reveal the hepatotoxicity of statins	Lipophilic statins: reduced the viability of hepatocytes whereas the hydrophilic statin pravastatin) did not cause cell injury.	Kubota et al. (2004)
	Reversal test: 24 h.	Reversal test: mevalonate 10-100 μM or GGPP 1-10 μM.		Mevalonate or geranylgeranyl pyrophosphate GGPP): attenuated the simvastatin-induced loss of cell viability.	
	Apoptotic test: 24 h.	Apoptotic test: statins 30 μM.		Simvastatin: induced DNA fragmentation and increased the number of apoptotic cells, whereas caspase inhibitors zDEVD-fmk, zLEHD-fmk and zIETD-fmk) can attenuate DNA fragmentation and cell apoptosis.	
	Expression of Bcl-2 and Bax: 12 h.	Expression of Bcl-2 and Bax: simvastatin 30 μM or mevalonate 30 μM.		Simvastatin: increased the activities of caspase-3, caspase-9 and caspase-8, and reduced the protein content and mRNA expression for Bcl-2 without affecting Bax mRNA expression. Both lipophilic and hydrophilic statins: significantly reduced the content of endogenous cholesterol.	

Note: GPx1, glutathione peroxidase 1; GSH, reduced glutathione; GSSG, oxidized glutathione; HMG-CoA, 3-hydroxy-3-methylgutaryl CoA; LPO, lipid peroxidation; MMP, mitochondrial membrane potential; MPT, membrane permeability transition; ROS, reactive oxygen species; Bax, Bcl-2-associated X protein; Bcl-2, B-cell CLL/lymphoma 2.

another study suggested ROS triggered atorvastatin-induced activation of the mitochondrial biogenesis pathway, with an improvement in the antioxidant capacities of the heart, whereas the effects of ROS on muscle were the opposite, indicating that ROS generation played different roles in the protection of cardiovascular-related mortality and skeletal myotoxicity (Bouitbir, Charles, et al., 2012). Research on statin-induced (150 μmol/L dose) mitochondrial impairment in rat liver mitochondria revealed that lovastatin, simvastatin, and cerivastatin impaired mitochondrial respiration the most, with simvastatin and lovastatin impairing multiple oxidative phosphorylation complexes; the inhibition of the oxidative phosphorylation complexes showed that simvastatin > lovastatin > fluvastatin = cerivastatin > atorvastatin = pravastatin (Nadanaciva et al., 2007). However, the relationship between statin-induced ROS generation and the subsequent change in mitochondrial respiration is still unknown, highlighting the need for further investigations in muscle and liver cells. Additionally, it has been revealed that the phototoxicity of atorvastatin can be attributed to singlet oxygen formation, with the phenanthrene-like photoproduct as a photosensitizer (Montanaro, Lhiaubet-Vallet, Iesce, Previtera, & Miranda, 2009).

Similarly, statin-induced ROS formation has also been regarded as a potent liver and kidney damage mechanism due to statins. A recent study revealed that statins (200 μM of simvastatin, 200 μM of lovastatin, and 450 μM of atorvastatin) resulted in a very significant elevation in ROS formation at 1, 2, and 3 h, compared with the controls, when freshly-isolated rat hepatocytes were exposed to statins (Abdoli et al., 2015). Another study found that atorvastatin led to an increase in the liver mitochondrial ROS after rats were treated with a high-fat diet containing atorvastatin (0.3% diet) for eight weeks (Wat et al., 2016). A recent study identified that atorvastatin increased ROS production in hepatic (Fig. 3) and renal tissues, along with significant renal tubular damage and liver damage, after the administration of atorvastatin at a daily dose 30 mg/kg BW for 8 weeks (Pal, Sarkar, et al., 2015). Pal, Ghosh, et al. (2015) recently reported that high doses of atorvastatin (10, 30, and 50 mg/kg BW) increased ROS production, along with the enhancing ALP and ALT levels and causing hepatic tissue damage, after mice were treated with atorvastatin (Fig. 3). In a study to evaluate the cytotoxic effects of the most commonly used statins, atorvastatin (250, 450, and 500 μM), lovastatin (150, 200, and 250 μM), and simvastatin (150, 200, and 250 μM) exposure to isolated rat hepatocytes for 1, 2, and 3 h, respectively, revealed that a significant elevation in ROS formation was accompanied by a significant amount of lipid peroxidation and mitochondrial depolarization, indicating that the adverse effect of

Table 3
In vivo statins related oxidative stress studies.

Species	Time of exposure/assay	Dose	Aim	Result/conclusion	Reference
Human					
Male healthy volunteers	8 weeks Measurements of mitochondrial respiration. Measurements of Ca^{2+} sparks. Biochemical parameters.	Simvastatin (80 mg per day)	To evaluate the impact of high-dose statin administration on muscle mitochondrial respiration and Ca^{2+} homeostasis and systemic markers of oxidative stress	Simvastatin: increased ALP, CK and isoprostanes with no global change in mitochondrial respiration, lactate/pyruvate ratio or Ca^{2+} sparks. Statin-treated ones with the highest CK increase: resulted in a significantly lower Vmax rotenone succinate and an increase in Ca^{2+} spark amplitude.	Galtier et al. (2012)
Patient (biopsies from deltoid muscles)	-	-	To investigate the statin-induced myopathy	Statins to atrial muscle: reduced ROS generation, increased maximal oxidative capacities, PGC-1α, PGC-1β, SOD1 and SOD2 gene expressions. Statins to deltoid muscle: increased ROS generation, decreased maximal oxidative capacities, PGC-1α, PGC-1β, SOD1 and SOD2 gene expressions.	Bouitbir, Charles, et al., 2012
Patient	3 years Serum CoQ_{10}, sodium, chloride, bicarbonate and lactate levels.	Simvastatin (40 mg per day)	To investigate the role of mitochondrial respiratory chain in simvastatin- induced toxicity.	Simvastatin: decreased serum concentrations of CoQ10, and therefore resulted in CoQ10 deficiency in the tissue mitochondria.	Goli et al. (2002)
Guinea-pig					
Male guinea-pigs	18 days Serum biochemistry. Histopathology. Cytochrome P450 content.	Simvastatin (125 and 30 mg/kg BW per day)	To investigate the hepatotoxicity of simvastatin.	High dose of simvastatin: led to hepatotoxic effect hepatocellular necrosis accompanied in some animals by a biliary duct proliferation, significantly decreased the microsomal CYP 450 content, daily food intake and body weight, and had 10-fold elevation in serum aspartate and alanine aminotransferase activities.	Horsmans, Desager, and Harvengt (1990)
Rat					
Male Sprague-Dawley rats	8 weeks Biochemical analyses. CD68 staining and quantification.	Atorvastatin (300 mg/kg BW) and FSE (450 mg/kg BW) per day	To evaluate the combination effects of atorvastatin and FSE.	FSE: reduced liver ALT, AST, CD68, MPT, and ROS levels, increased liver GPx, led to a trend to reduce calcium-induced MPT within the liver.	Wat et al. (2016)
Sprague-Dawley rats	Liver glutathione peroxidase assay. Oxidative stress biomarkers. MPT.			Atorvastatin: significantly decreased liver GPx levels, increased liver CD68 level, and led to a increase in the liver MPT and liver mitochondrial ROS.	
Male albino rats	21 days	Atorvastatin (2, 5 and 10 mg/kg BW)	To evaluate the effects of treatment of rats with atorvastatin on liver function, oxidative stress, and histology and on the severity of acetaminophen hepatotoxicity.	Atorvastatin: resulted in a dose-dependent significant rise in serum activities of ALP, AST, and ALT, high dose of atorvastatin decreased GSH levels and SOD activity, increased MDA levels, and elicited histopathological changes in the liver.	Farag et al. (2015)
	Tissue biochemical assays, TBARS, MDA and SOD. Histological examination.	Acetaminophen (500 mg/kg BW) per day		Atorvastatin: low doses of atorvastatin (2 or 5 mg/kg BW) showed significantly lower activities of serum enzymes, higher hepatic GSH levels and SOD activities, lower MDA levels and milder histopathological changes compared with rats challenged with acetaminophen after pretreatment with or without atorvastatin 10 mg/kg BW	
Female Wistar rats	28 days	Simvastatin (20 and 40 mg/kg BW, orally).	To assess the effect of naringenin on simvastatin-induced hepatic damage in rat and to investigate the effects of these drugs on cytochrome P450 CYP2E1 and 3A1/2 isoforms.	Simvastatin: resulted in hepatotoxicity, increased serum AST, ALT, LDH, CK, decreased SOD activity, increased liver MDA level and GST activity together with the reduction of liver GSH content and CAT activity.	Motawi et al. (2014)
	Biochemical analysis.			Naringenin: combination with simvastatin significantly reduced serum AST, LDH, CK, ALT, liver MDA level and GST activity, increased blood SOD activity and hepatic GSH content and CAT activity, protein profile, DNA fragmentation, and the histopathological changes.	
	DNA gel electrophoresis.	Naringenin (50 mg/kg BW, orally) per day.		Simvastatin and/or naringenin: potential to inhibit CYP3A1/2 and CYP2E1.	

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Table 3 (*continued*)

Species	Time of exposure/assay	Dose	Aim	Result/conclusion	Reference
	Histopathological examination.				
Male Wistar rats	Atorvastain: 2 weeks, orally. Quercetin: 5 days before atorvastatin.	Atorvastatin (10 mg/kg BW) + quercetin (25 mg/kg BW) per day	To investigate whether statins optimized cardiac mitochondrial function but impaired vulnerable skeletal muscle by inducing different ROS levels.	Atorvastatin to *plantaris*: increased ROS production decreased GSH level, relative amount of mtDNA, PGC-1α, PGC-1β, Cox1, and SOD2 gene expressions. Atorvastatin to cardiac muscle: decreased ROS production, GSH level and SOD2 gene expression, and increased Cox1, PGC-1β gene expressions and the relative amount of mtDNA. Quercetin to *plantaris* and cardiac muscle: decreased ROS production, increased GSH level and SOD2 gene expression, increased PGC-1α, PGC-1β, Cox1 gene expressions in *plantaris* while decreased Cox1 and PGC-1β in cardiac muscle.	Bouitbir, Charles, et al., 2012
Male Wistar rats	2 weeks Total cholesterol assay. Muscle mitochondrial respiration. Oxidative stress biomarkers. qPCR assay.	Atorvastatin (10 mg/kg BW) per day	To characterize mitochondrial function and ROS production in skeletal muscle after exhaustive exercise in atorvastatin- treated rats.	Atorvastatin: increased ROS level in the *plantaris* muscle and the exhaustive exercise rats, decreased the maximal mitochondrial respiration in atorvastatin-treated rats or the combination of exhaustive exercise and atorvastatin-treated rats, and decreased the glycogen content.	Bouitbir et al. (2011)
Male Wistar rats	7 days Biochemical analysis. Glutathione assay. Measurement of oxygen uptake by isolated mitochondria. Liver histology qPCR assay.	Fluvastatin (1 or 5 mg/kg BW) per day	To verify the effect of fluvastatin on cholestatic liver injury.	Fluvastatin: high dose led to the deterioration of hepatocellular injury, increased serum ALT, AST, GGT, ALP, total and conjugated bilirubin level in BDL rats compared to sham-operated rats treated with fluvastatin while increased ALT, AST and GGT and decreased glutathione content compared to BDL rats without treatment. Fluvastatin: significant decrease in the liver IL-6, Mdr1b, Mrp3, and Ugt1a1 mRNA expression levels, the activity of complex I in the liver mitochondria in BDL rats compared to BDL control, increase in TGF-β production.	Lotkova et al. (2011)
Male Wistar rats	60 days Cytosolic Ca^{2+} levels	Fluvastatin (5 and 20 mg/kg BW), atorvastatin (5 and 10 mg/kg BW) per day	To investigate the toxic mechanism of statins induce skeletal muscle.	Fluvastatin and atorvastatin: a significant increase of resting cytosolic calcium.	Liantonio et al. (2007)
Female Wistar rats	Simvastatin preliminary study days 1-7, and days 15-42. Cerivastatin preliminary study days 1-16. Simvastatin time-course study days 1-16. Cerivastatin time-course study days 1-16.	Simvastatin preliminary study 80 mg/kg BW for days 1-7, and 60 mg/kg BW for days 15-42), orally. Cerivastatin preliminary study 0.5, 1, 2, and 3 mg/kg BW for days 1-16), orally. Simvastatin time-course study 80 mg/kg BW for days 1-16), orally. Cerivastatin time-course study 0.5 mg/kg BW for days 1-16), orally.	To investigate the development of statin-induced muscle necrosis	Simvastatin and cerivastatin: Muscle necrosis occurring after 10 days even if the dose was increased, and still occurring after this time when dosing was terminated earlier as a result of morbidity. Necrotic response of fibres to statins: Matched their oxidative/glycolytic metabolic nature. Mitochondrial: Notable increase in mitochondrial myelinoid bodies in some nonnecrotic glycolytic fibres from muscles showing early multifocal single fibre necrosis.	Westwood, Bigley, Randall, Marsden, & Scott (2005)
Mice					
Male Swiss mice	8 weeks Biochemical analysis.	Atorvastatin (1, 5, 10, 30, and 50 mg/kg BW) per day	To investigate the dose-dependent hepatic tissue toxicity in atorvastatin induced oxidative impairment and cell death in mice.	Atorvastatin: enhanced ALT, ALP level, increased ROS production, reduced liver GSH, SOD, CAT, GST, GR and GPX levels, and increased liver MDA and GSSG level. Atorvastatin: markedly decreased MMP, disturbed the Bcl-2 family protein balance, enhanced cytochrome c release in the	Pal, Ghosh, et al., 2015

Table 3 (*continued*)

Species	Time of exposure/assay	Dose	Aim	Result/conclusion	Reference
				cytosol, increased the levels of Apaf1, caspase-9, -3, cleaved PARP protein and ultimately led to apoptotic cell death. Atorvastatin: distinctly increased the phosphorylation of p38, JNK, and ERK MAPKs, enhanced caspase12 and calpain level.	
	Oxidative stress biomarkers. Histological studies. TUNEL staining.				
Male Swiss mice	Atorvastatin: 8 weeks.	Atorvastatin (30 mg/kg BW), orally.	To investigate the protective role of arjunolic acid against atorvastatin induced oxidative impairment and cell death in hepatic and renal tissue in mice.	Atorvastatin: enhanced serum ALT, ALP, LDH, creatinine, and BUN levels, increased ROS production, MDA, protein carbonyl, GSSG level in liver and kidney tissues, reduced SOD, CAT, GST, GR, GPx, and GSH in liver and kidney tissues, and led to liver and kidney damage.	Pal, Sarkar, et al., 2015
	Arjunolic acid: 4 days.	Arjunolic acid (20 mg/kg BW), orally.		Atorvastatin: activated caspase-3 and reciprocal regulation of Bcl-2/Bax with the concomitant reduction of MMP and increased level of cytosolic cytochrome c, Apaf1, caspase-9, markedly increased the phosphorylation of MAPKs, enhanced caspase-12 and calpain level.	
	Vitamin C: 4 days	Vitamin C (20 mg/kg BW), intraperitoneally.		Post-treatment with arjunolic acid or vitamin C: decreased MDA and PCs, increased GSH, SOD, CAT, GR, GPx, and GSSG levels in liver and kidney tissues, and suppressed apoptotic events.	
Hyper-cholesterolemic LDL receptor knockout mice	15 days	Lovastatin (100 mg/kg BW, orally) per day	To investigate whether the treatment of LDL receptor knockout mice with lovastatin influences the susceptibility to develop MPT and whether statins could exert direct effects on isolated mitochondria.	Lovastatin: presented a higher susceptibility to develop MPT, and lovastatin-induced MPT in a dose-dependent manner.	Velho et al. (2006)
	Measurements of mitochondrial transmembrane electrical potential ($\Delta\Psi$).			Lovastatin and simvastatin: decreased the content of total mitochondrial membrane protein thiol groups. Pravastatin: had a weaker effect in inducing MPT.	

Note: ALT, alanine aminotransferase, ALP, aspartate aminotransferase; AST, gamma-glutamyl transferase; BDL, bile duct ligation; CK, creatine kinase; CYP450, cytochrome P450; FSE, *Fructus schisandrae* aqueous extract; GGT, alkaline phosphatase; GSH, reduced glutatione; GSSG, oxidized glutatione; IL-6, interleukin 6; MDA, malondialdehyde; Mdr, multidrug resistence protein; MMP, mitochondrial membrane potential; MPT, mitochondrial permeability transition; Mrp, multidrug resistence associated protein; PGC-1, peroxisome proliferator-activated receptor gamma co-activator; SOD, superoxide dismutase; TGF-β, transforming growth factor ß; Ugt1a1, uridine diphosphate-glucuronosyltransferase 1a1; qPCR, quantitative real-time polymerase chain reaction.

statins toward hepatocytes is mediated through oxidative stress, and that the hepatocyte mitochondria play an important role in the statin-induced toxicity (Abdoli et al., 2013). After the human HepG2 hepatocytes were treated with statins (10, 100, and 1000 nM) for four days, the increase in ROS generation induced by atorvastatin and cerivastatin was noted, indicating that a low dose of statins could also result in ROS production (Kromer & Moosmann, 2009). In a study to reveal the mechanism of statin-induced hepatotoxicity, ROS generation was observed along with impairment of mitochondrial function during the treatment of rat hepatocytes with atorvastatin (450 μM), or simvastatin (200 μM), or lovastatin (200 μM) for 1, 2, and 3 h, respectively (Abdoli et al., 2014; Eghbal et al., 2014).

Additionally, statin-induced ROS production also resulted in cell death in other cell lines (Fig. 3). When breast cancer cells (MCF-7) were treated with fluvastatin (1.25 μM), simvastatin (2.5 μM), and atorvastatin (40 μM) for 2 h, respectively, it was revealed that the statin-induced increase in ROS production was associated with cell death, inhibited cell proliferation that resulted in a decrease in DNA synthesis, and a cell cycle arrest in the G_1 and G_2/M phases, suggesting that the statin-induced cytotoxic effect is mediated by ROS production (Sanchez et al., 2008).

Taken together, the results of these studies suggested that ROS formation plays critical roles in statin-induced oxidative stress and related toxicities. ROS generation can promote muscular symptoms by mitochondrial biogenesis pathway and atered the antioxidant state of the organ. However, the reason behind differential ROS generation in heart or other cells, such as muscle, liver, and kidney cells, which is the trigger for their following pharmacology or toxic effect of these cells is thus worthy of further investigation.

3.2. Statin-mediated oxidative damage

Statin-induced ROS generation can lead to oxidative stress and change the antioxidant defense system, which may result in damage to cellular macromolecules, such as lipids, DNA, and proteins (Abdoli et al., 2013; Abdoli et al., 2014; Costa et al., 2013; Eghbal et al., 2014; Motawi et al., 2014). Following oxidative stress, cell death can occur via apoptotic cell death or necrotic mechanisms (Costa et al., 2013). During this process, enhanced lipid peroxidation, DNA damage, and protein oxidative damage may appear, along with other statin-induced toxicities (Tables 2 and 3). Increasing the production of ROS and the imbalance of antioxidant status may induce lipid, protein and DNA oxidation, leading to toxicity and apoptosis through various signaling and intrinsic mitochondrial pathways (Fig. 2). The changes of statin-induced oxidative stress and some downstream toxic effects will be described below, as shown in Fig. 2.

3.2.1. Damage to lipids

Lipid peroxidation is one of the main results of the chemically-induced oxidative damage to cell membrane lipids. Malondialdehyde (MDA) and thiobarbituric acid reacting substances (TBARS) are the main parameters that reflect the changes in lipid peroxidation. MDA, as one part of TBARS, is the most abundant individual aldehyde resulting

from lipid peroxidation, with its level serving as a marker of lipid oxidation (Wang et al., 2017).

Atorvastatin caused a significant increase in MDA levels in both liver and kidney tissues in mice after 8 weeks of treatment at 30 mg/kg BW (Pal, Sarkar, et al., 2015). Another study confirmed the atorvastatin-induced increase in MDA levels in mouse livers, and also revealed that a much lower dose of atorvastatin (1 mg/kg BW) for eight weeks could still result in a significant increase in MDA levels in mouse livers, along with significant increases in ALP and ALT levels in the serum of experimental mice, suggesting that lipid peroxidation might be a sensitive parameter for statin-induced liver damage, as well as ALT and ALP levels in the liver (Pal, Ghosh, et al., 2015).

It has been reported that when rats were treated with simvastatin at 20 and 40 mg/kg BW for 30 days, there was a marked increase in liver MDA levels combined with increases in AST, ALT, LDH, and CK serum enzymes (Motawi et al., 2014). Similarly, high doses of atorvastatin (10 mg/kg BW) resulted in increased liver MDA levels, whereas low doses of atorvastatin (2 and 5 mg/kg BW) decreased liver MDA levels after 21 days of treatments in rats, indicating that the effect of atorvastatin on the liver is dose-dependent, and that hepatic lipid peroxidation, as well as oxidative stress, plays a role in atorvastatin-induced hepatotoxicity (Farag et al., 2015). Abdoli et al. (2014) revealed that three kinds of statins, atorvastatin (450 μM), simvastatin (200 μM), and lovastatin (200 μM), led to a significant cytotoxicity characterized by an elevation in cell death, increasing ROS generation and consequently lipid peroxidation and impairment of mitochondrial function. Similarly, it was revealed that cellular TBARS was significantly increased when freshly-isolated rat hepatocytes were treated with the same three kinds of statins for 1–3 h, suggesting that lipid peroxidation might be an important marker for monitoring the oxidative stress-related adverse effect of statins toward hepatocytes (Abdoli et al., 2013; Abdoli et al., 2015; Eghbal et al., 2014).

In summary, it has been documented that lipid peroxidation is generally a universal and significant phenomenon in the oxidative stress-related toxicity of statins *in vivo* and *in vitro*. Furthermore, various studies have indicated that statin-induced lipid peroxidation seems to be dose- or time-dependent. However, various studies have been carried out to better understand the toxic mechanism of statin-induced liver damage, whereas few have focused on other statin-induced toxicities. Therefore, it seemed to be necessary to reveal the role of oxidative stress-related lipid peroxidation in more statin-induced toxicities.

3.2.2. Damage to DNA

DNA is sensitive to oxidative stress, with the formation of the major oxidative DNA damage product 8-hydroxydeoxyguanosine (8-OH-dG) generally used as an indicator of oxidative DNA damage (Ihsan et al., 2011; Shaukat, Liu, Hussain, Khan, & Gregory, 2016). It has been documented that higher doses of simvastatin (5 and 10 μM) can lead to a significant increase in the degree of oxidative stress to nuclear DNA in HepG2 cells, as well as increased 8-OH-dG levels, suggesting that high statin doses could induce DNA damage through oxidative stress (Tavintharan et al., 2007). Compared with lipid peroxidation, there are few reports on oxidative stress-related DNA damage due to statin-induced toxicities. However, it seems that high doses of statins can lead to DNA oxidative damage, suggesting that this statin-induced toxic effect is worthy of further investigation.

3.2.3. Damage to proteins

Protein is also the major target of oxidative stress, which can be transformed into protein carbonyls upon oxidation (Pal, Sarkar, et al., 2015). Protein carbonyls have been documented as a marker of global protein oxidation that can be generated by multiple different ROS in blood, tissues, and cells (Bolton & Dunlap, 2017; Wang, Martinez, Dai, et al., 2016; Wang, Martinez, Wu, et al., 2016). Although a large number of studies on statin-induced oxidative stress have been investigated, protein peroxidation has rarely been reported in their toxicities. It has been revealed that atorvastatin can significantly increase protein carbonyl levels in mouse liver and kidney tissues after 8 weeks of treatment at 30 mg/kg BW by gavage, along with significant ROS production from the mitochondria to the cytosol and nucleus that may lead to hepatic and renal damage, indicating that protein carbonyl caused by statins might result from the ROS generation by mitochondria and therefore serve as an oxidative marker for the oxidative impairment in statin-induced toxicities (Pal, Sarkar, et al., 2015).

Pal, Sarkar, et al. (2015) suggested that protein peroxidation was an additional indicator of statin-induced hepatic and renal oxidative injury. However, few studies have investigated other statins, such as simvastatin, lovastatin, and fluvastatin, even though these statins have also been documented to generate excessive ROS in their toxicities.

3.3. Alterations in antioxidant status

The induction of ROS by oxygen free radicals, including $O_2^{\bullet-}$, $HO^{\bullet}$, and hydrogen peroxide (H_2O_2), usually causes the alteration of the enzymatic antioxidant defense systems in *in vitro* and *in vivo* models (Yang & Lee, 2015) . Catalase (CAT), superoxide dismutase (SOD), glutathione (GSH), glutathione peroxidase (GPx), glutathione reductase (GR), and glutathione S-transferases (GST) are the primary antioxidant enzymes, and they serve as good redox biomarkers, since they are the first-line indicators of the antioxidant state through oxidation/reduction processes (Yang & Lee, 2015). GSH, the most abundant intracellular antioxidant, is involved in the protection of cells against oxidative damage and in various detoxification mechanisms (Shi et al., 2015). GSH also acts as a substrate and co-substrate in many essential enzymatic reactions involving GPx, GR, and GST, where a decrease in the GSH level usually impairs the cells' response to oxidants (Aydin, 2011) (Fig. 2).

Statins can lead to significant alterations in the antioxidant status in *in vitro* models. Atorvastatin (1 μM) increased ROS production after 48 h in H9C2 cells (Bouitbir et al., 2016). Higher doses of simvastatin (10 μM) increased the 8-OH-dG level, resulting in a moderately higher degree of cell death and DNA damage (Tavintharan et al., 2007). Four days of atorvastatin (450 μM), simvastatin (200 μM), or lovastatin (200 μM) usage resulted in cytotoxicity characterized by an elevation in cell death, thus increasing ROS generation in rat hepatocytes (Abdoli et al., 2014).

Fluvastatin (1.25 μM), simvastatin (2.5 μM), and atorvastatin (40 μM) increased ROS production that was associated with cell death by inhibiting cell proliferation, thus resulting in a decrease in DNA synthesis and a cell cycle arrest in the G_1 and G_2/M phases (Sanchez et al., 2008). Statins (simvastatin, lovastatin, and atorvastatin: 200 μM) increased ROS formation and cellular GSSG levels, and decreased cellular GSH levels, leading to cytotoxicity (Abdoli et al., 2013). Atorvastatin (450 μmol/L), simvastatin (200 μmol/L), and lovastatin (200 μmol/L) significantly depleted cellular GSH, increased the levels of GSSG and ROS formation, and decreased mitochondrial membrane potential (MMP) (Eghbal et al., 2014). Simvastatin (5 μM at 0, 6, 16, and 24 h) resulted in significant apoptotic cell death and perturbations in the parameters indicative of oxidative stress in CT26 cells, including decreased Mn-SOD, CAT, and GPx1 levels (Qi et al., 2010).

Statins could also lead to significant alterations in antioxidant status in *in vivo* models. Administration of atorvastatin (30 mg/kg BW/day) (Pal, Ghosh, et al., 2015) or (1, 5, 10, 30, and 50 mg/kg BW) (Pal, Sarkar, et al., 2015) for eight weeks enhanced the ALT and ALP levels in serum enzymes, increased ROS production, and altered the prooxidant-antioxidant status of mouse livers by reducing their GSH, SOD, CAT, GST, GR, and GPx levels, and increasing their MDA and GSSG levels. Simvastatin, taken at an oral dose of 20 and 40 mg/kg BW/day for 30 days, increased AST, ALT, LDH, and CK serum enzymes, decreased SOD activity, and increased liver MDA levels and GST activity, together with a reduction in liver GSH concentration and CAT activity, exerting an oxidative stress which may contribute to hepatotoxicity in rats (Motawi et al., 2014). Fluvastatin, taken at a dose of 5 mg/kg BW for 7 days, led to the deterioration of hepatocellular injury, increased

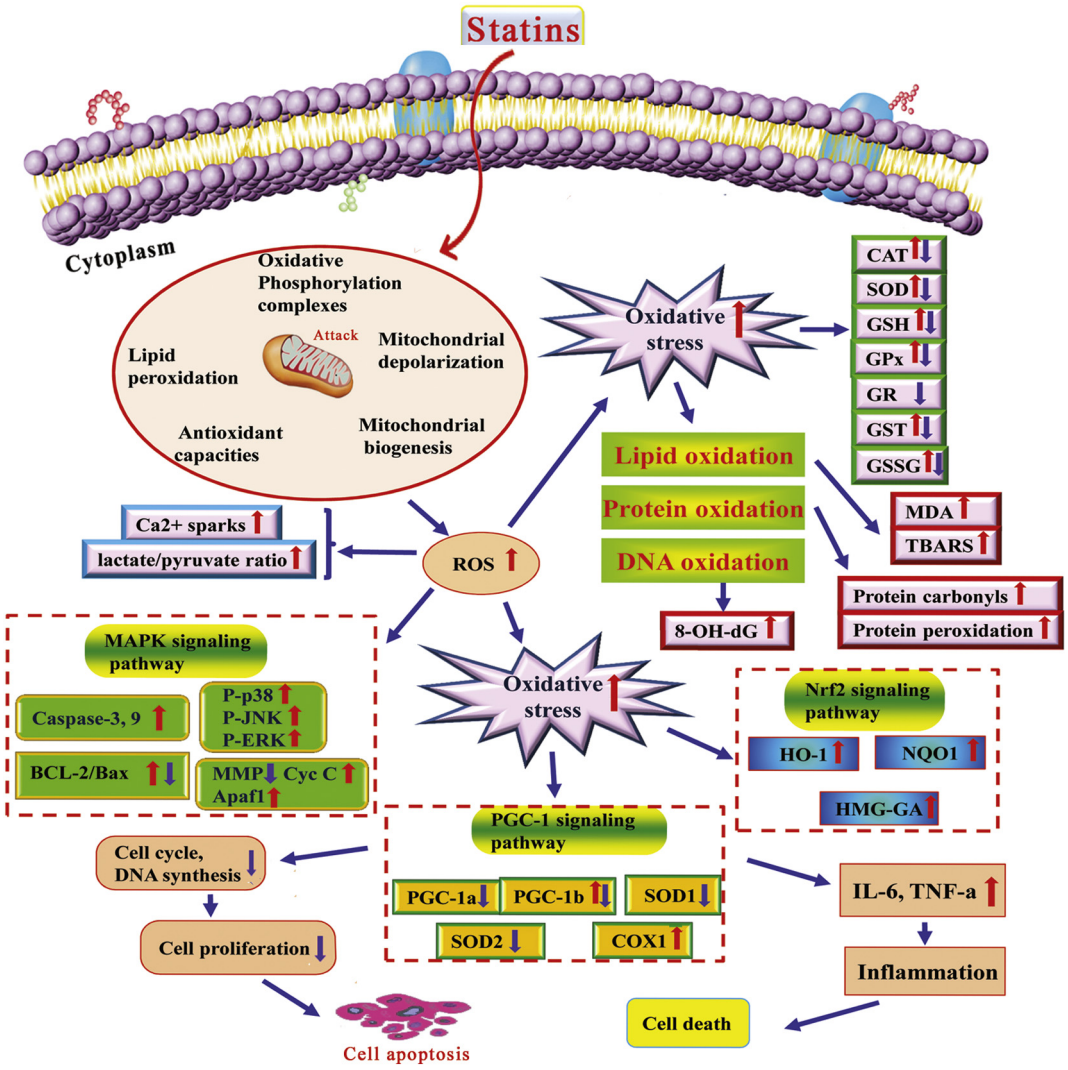

Fig. 2. Oxidative stress-mediated mode of action proposed for statins. Increased ROS generation, as well as the imbalance in antioxidant status, may induce lipid, protein, and DNA oxidations, leading to toxicity and apoptosis via various signaling and intrinsic mitochondrial pathways.

ALT, AST and GGT levels (Fig. 3), and decreased glutathione concentration compared to BDL rats, indicating the change in antioxidative status (Lotkova et al., 2011). Atorvastatin (10 mg/kg BW) decreased GSH levels and SOD activity, increased MDA levels, and elicited histopathological changes in the liver; however, lower doses of atorvastatin (2 or 5 mg/kg BW) showed significantly higher hepatic GSH levels and SOD activities, lower MDA levels, and milder histopathological changes, suggesting that the degree of statin-induced oxidative stress is dose-dependent (Farag et al., 2015). Statins reduced ROS generation and increased maximal oxidative capacities, PGC-1α, PGC-1β, SOD1, and SOD2 gene expressions in atrial muscle; however, statins increased ROS generation and decreased maximal oxidative capacities, PGC-1α, PGC-1β, SOD1, and SOD2 gene expressions in deltoid muscle (Fig. 3) (Bouitbir, Charles, et al., 2012). However, the mechanism of the difference in the antioxidant system of statins in different parts of the muscle needs further study. Perhaps, this may be due to the different mechanisms of statins inducing oxidative stress in different muscles. Atorvastatin (0.3% of diet) significantly decreased liver GPx levels, which led to an increase in liver mitochondrial ROS (Wat et al., 2016). Statins (atorvastatin (10, 100, and 1000 nM), cerivastatin (10, 50, and 100 nM), or lovastatin (10, 100, and 1000 nM)) induced the gene expression of heme oxygenase 1 (HO-1) and NADPH quinone oxidoreductase 1, HMG-CoA reductase, and reduced biosynthesis, steady-state expression level, and catalytic activity of GPx, whereas they did not affect the mRNA levels of GPx1 and GPx4 (Kromer & Moosmann, 2009) (Fig. 2).

A misbalance of antioxidant status can be involved in the toxicities induced by *in vivo* and *in vitro* statin overdose. Furthermore, studies have suggested that the antioxidant system, especially where GSH levels are used as redox biomarkers, are sensitive to the toxic effects of statin overdoses.

Taken together, statins can lead to significant alterations in the antioxidant status in *in vitro* and *in vivo* models including the primary antioxidant enzymes such as CAT, SOD, GSH, GPx, GR, and GST, antioxidant signaling pathways such as PGC-1 and expression of related genes. The antioxidant system has abnormal changes in the side effects of statins, but if specific antioxidant markers can be screened for a statin, it will be a major challenge in the future to diagnose the side effects of such statins.

4. Stress-mediated biological response and the mechanism of statin-inducing oxidative stress

Oxidative stress plays an important role in a large number of biological responses and cell signaling pathways. Thus, significant changes in the gene expression and subsequent stimulation or inhibition of signal transduction usually result in many toxicological effects. Potential mechanisms of statin-inducing oxidative stress in muscle and liver are

summarized (Table 1). Additionally, the role of statin-induced oxidative stress and the resultant cell damage and alteration of cell signaling pathways has been widely studied, both *in vitro* (Table 2) and *in vivo* (Table 3).

4.1. Impact on mitochondrial respiration

As an important nonsterile compound and an essential carrier in the mitochondrial respiratory chain that participates in oxidative phosphorylation, a previous study has suggested that the Q_{10} coenzyme (CoQ_{10}) might be responsible for simvastatin-induced myopathy in one patient with lactic acidosis, indicating that interference of the mitochondrial respiratory chain may play a role in statin toxicity (Goli et al., 2002; Tavintharan et al., 2007).

Patients who suffered from a chronic disease and were long-term statin users commonly experienced impairment of mitochondrial respiration described on the permeabilized skeletal muscle fibers, mainly within complex I of the respiratory chain, indicating that statins may induce muscle breakdown by damaging the mitochondrial respiratory chain (Galtier et al., 2012). Simvastatin (150 μmol/L) inhibited complexes I, II+III, IV, and V, while fluvastatin and cerivastatin (each at 150 μmol/L) caused 40–45% inhibition of complex V, thus impairing mitochondrial respiration (Nadanaciva et al., 2007). However, simvastatin at 80 mg daily for 8 weeks increased ALP, CK, and isoprostanes, with no global change in mitochondrial respiration, the lactate/pyruvate ratio, or Ca^{2+} sparks in the muscle of healthy male Caucasians (Galtier et al., 2012). Conversely, atorvastatin at 3.44–880 mM for 3 days led to mitochondrial dysfunction in yeast cells, disturbing normal mitochondrial respiration (Callegari et al., 2010), and fluvastatin at 1 or 5 mg/kg BW for 7 days led to a significant decrease in the activity of complex I in the liver mitochondria of BDL rats compared to the BDL control (Lotkova et al., 2011).

Interestingly, studies have shown that statins directly inhibit complexes I and III to alter mitochondrial electron transport chains, reduce the availability of ATP and mitochondrial membrane potential, and enhance ROS.

In addition, statins increase [Ca^{2+}] mainly by opening MPTP and NCE channels, followed by releasing Ca^{2+} from SR via RyR channels. The opening of MPTP and NCE channels may be due to the decrease of mitochondrial membrane potential, not to the increase of ROS or the decrease of GGPP, FPP or mevalonate. It is speculated that the decrease of ATP in cardiomyocytes may affect the activity of EF-UX transporters of MDR1 and BCRP of ATP binding cassette family, and facilitate the accumulation of statins into cardiomyocytes (Guijarro et al., 1998; Sirvent et al., 2005).

4.2. Signal pathway of PGC-1α activity regulation

Peroxisome proliferator activated receptor-like factor (PGC-1α) plays a central role in mitochondrial transcription. Atorvastatin increased ROS production, and decreased GSH levels and the relative amounts of the mtDNA, PGC-1α, PGC-1β, Cox1, and SOD2 gene expressions in *plantaris* muscle, whereas atorvastatin decreased ROS production, GSH levels, and SOD2 gene expressions, and increased Cox1 and PGC-1β gene expressions and the relative amount of mtDNA in cardiac muscle (Fig. 3) (Bouitbir, Charles, et al., 2012). Statins increased ROS generation, and decreased maximal oxidative capacities, PGC-1α, PGC-1β, SOD1, and SOD2 gene expressions in patient deltoid muscle (Bouitbir, Daussin, et al., 2012) (Fig. 2).

4.3. Caspase/Bcl-2/Bax/MAPKs pathway

Atorvastatin (1, 5, 10, 30, and 50 mg/kg BW) (Pal, Ghosh, et al., 2015; Pal, Sarkar, et al., 2015) increased ROS production, and then activated caspase-9, -3, and reciprocal regulation of Bcl-2/Bax, with the concomitant reduction of MMP and increased levels of cytosolic cytochrome c, Apaf1, caspase-9, as well as the distinct increase in the phosphorylation of p38, Jun kinase (JNK), and extracellular signal-regulated kinase (ERK) mitogen-activated protein kinases (MAPKs) (Fig. 2).

4.4. Inflammatory cytokines

The production of inflammatory cytokines is a susceptibility factor for drug-induced organ injury. An eight-week oral treatment of atorvastatin (10 mg/kg BW/day) exacerbated hepatic steatosis, inflammation (IL-6 and TNF-α), and fibrosis, as well as increased hepatic ROS and MDA in casein injection mice, and increased the protein expression of liver nuclear factor erythroid 2-related factor 2 (Nrf2) which is a key regulator of the antioxidant defense and involved in negative regulation of oxidative stress (Wu et al., 2016). Simvastatin induces the activation and nuclear translocation of Nrf2 and the expression of various antioxidant enzymes including HO-1, peroxidase-1, SOD, GSH-Px and gamma-GCS via ERK and PI3K/Akt pathway in colon cancer cells (Jang et al., 2016). Fluvastatin (1 or 5 mg/kg BW) for seven days showed a significant decrease in the liver IL-6 mRNA expression levels, and increases in TGF-β production and the activity of complex I in the liver mitochondria in BDL rats compared to BDL control (Lotkova et al., 2011).

4.5. Calcium ions

Histological studies also support the dose-dependent toxic effect of atorvastatin in organ pathophysiology. These results reveal that atorvastatin induces hepatic tissue toxicity via MAPKs, mitochondria, and the endoplasmic reticulum (ER)-dependent signaling pathway, in which calcium ions and ROS act as the pivotal mediators of the apoptotic signaling (Pal, Ghosh, et al., 2015).

Fluvastatin (5 and 20 mg/kg BW) and atorvastatin (5 and 10 mg/kg BW) could significantly increase resting cytosolic calcium, which plays a role in statin-inducing skeletal muscle toxicity (Liantonio et al., 2007). Simvastatin (80 mg daily) for eight weeks increased aspartate amine transferase, CK, and isoprostanes, with no global change in mitochondrial respiration, the lactate/pyruvate ratio, or Ca^{2+} sparks (Fig. 2) (Galtier et al., 2012). Guillaume, Lethier, and Andre (2015) demonstrated that magnesium (Mg^{2+} concentration range 0.00–2.60 mm) or calcium supplementation (Ca^{2+} concentration range 0.00–3.25 mm) increased the passive diffusion of statins, and thus played a role in their potential toxicity by increasing the statin passive diffusion, with H_2O_2 and the oxidative stress playing a role in the statin passive diffusion.

In conclusion, the signaling pathways, including the Nrf2/HO-1, PGC-1α, P38/JNK, MAPKs, and calcium ion pathways, have been shown to be involved in statin-induced toxicity and apoptosis (Fig. 2). These pathways have been suggested to be closely correlated with statin-induced oxidative stress, suggesting that more attention needs to be paid to other signaling pathways related to oxidative stress due to statin-induced toxicity. Furthermore, during the liver damage induced by long-term statin use, the poisoning effect manifests itself as liver damage, occurring as a result of inflammation and oxidative stress.

Additionally, a few studies have revealed that statin could induce oxidative stress by metabolism (this will be mentioned below.). It was believed that there is close relationship between them, thus warranting the need for future investigations. Importantly, myotoxin is a common side effect of statins, but the relationship between muscular handling of statins and oxidative stress remains unclear. If we can reveal or prevent the statin-induced myotoxicity statins from the metabolic point of view, it will be a major breakthrough in the future.

5. Prevention of statin-mediated oxidative stress

ROS generation and oxidative stress have been documented to play crucial roles in the development of statin-induced liver damage and nephrotoxicity (Wat et al., 2016). Various compounds have been investigated to combat statin-induced toxicity. While most of these

compounds are antioxidants, some are natural plant extracts with antioxidant effects (Fig. 3).

5.1. In vivo studies

The mechanism and protective potential of chemicals in *in vivo* studies against statin-induced toxic effects has been performed in rats (Bouitbir, Charles, et al., 2012; Motawi et al., 2014; Wat et al., 2016) and mice (Pal, Sarkar, et al., 2015). It has been documented that a diet containing 0.45% *Fructus -schisandrae* (FSE) aqueous extract, a traditionally used liver-toning Chinese herb, could decrease ROS production, as well as liver ALT, AST, CD68, and calcium-induced mitochondrial permeability transition (MPT), and significantly increase liver GPx level after rats were exposed to atorvastatin (0.3% of diet) for eight weeks, suggesting that FSE could significantly prevent liver toxicity and antioxidative statins induced by atorvastatin alone (Wat et al., 2016). As a natural flavonoid, aglycone of naringin, or NRG with antioxidant effects, is widely distributed in citrus fruits, tomatoes (*Solanum lycopersicum*), cherries (*Prunus avium*), grapefruit (*Citrus x paradisi*), and cocoa (*Theobroma cacao*) (Santos, Oliveira, Nagem, Pinto, & Oliveira, 1999). After rats were administered with simvastatin at 20 and 40 mg/kg BW for 28 days, NRG was given at 50 mg/kg BW, which significantly reduced the oxidative stress caused by simvastatin and improved rat liver function, along with decreases in AST, LDH, CK, and ALT serum enzyme activity and reduced liver histopathological changes (Motawi et al., 2014). However, when rats were treated with atorvastatin at 10 mg/kg BW for two weeks, it played different roles in cardiac and *plantaris* muscle, as there was a decrease in ROS generation in cardiac muscle, but an increase in ROS production in *plantaris* muscle. When administered in combination with quercetin (25 mg/kg BW), a member of the flavonoids family that is one of the most prominent dietary antioxidants in plants (Moon, Wang, & Morris, 2006), similar effects on the cardiac and *plantaris* muscles were observed, as quercetin decreased ROS generation and increased GSH levels and SOD2 gene expressions in both *plantaris* and cardiac muscle, while also increasing the PGC-1α, PGC-1β, and Cox1 gene expressions in *plantaris* and decreasing Cox1 and PGC-1β gene expressions in cardiac muscle, thus suggesting that the role of quercetin might be different in different tissues (Bouitbir, Charles, et al., 2012). Another study revealed that a post-treatment regimen of either arjunolic acid (20 mg/kg BW) or vitamin C (20 mg/kg BW) could reduce atorvastatin-induced ROS production after an 8-week treatment at 30 mg/kg BW by altering the oxidative stress parameters (decrease in MDA and PCs, and increase in GSH, SOD, CAT, GR, GPx, and GSSG levels) in both mouse liver and kidney tissues, and suppressing all the apoptotic events, combined with the significant decrease in the renal dysfunction-related specific markers, such as BUN and creatinine, as well as decreases in ALT, ALP, and LDH levels in liver tissue injury (Pal, Sarkar, et al., 2015).

5.2. In vitro studies

A few *in vitro* studies have revealed the protective effects of various chemicals on statin-induced toxicity.

5.2.1. N-acetyl cysteine (NAC)

It was documented that the ROS scavenger, NAC (1 mmol/L), could decrease ROS generation, and negate both the increase in PGC-1α, NRF1, TFAm, and SOD2 mRNA expressions in H_9C_2 cells and the decrease in PGC-1α gene expressions in L_6 cells caused by atorvastatin (1 μM), indicating that NAC can decrease the statin-induced toxicities by altering the ROS/PGC-1 signaling pathway (Bouitbir, Charles, et al., 2012). Similarly, NAC also demonstrated hepatoprotective effects, with reductions in ROS formation and lipid peroxidation, as well as increases in cell viability and MMP, when rat hepatocytes were administered the combination of NAC (200 μM) and atorvastatin (450 μM) simvastatin (200 μM), or lovastatin (200 μM) (Abdoli et al., 2014). Additionally, after MCF-7 breast cancer cells were treated with three kinds of statins (fluvastatin, simvastatin, and atorvastatin: 1.25–40 μM) for 2 h, NAC (20 mM) abrogated the statin-induced ROS generation (Sanchez et al., 2008). Qi et al. (2010) reported that NAC suppressed both ROS generation related to the Akt signaling pathway and simvastatin-induced Foxo3a phosphorylation, while simvastatin-induced cell death and apoptosis were blocked when CT26 cells were incubated with simvastatin (5 μM) in the presence of NAC (5 mM) for 12 or 24 h, suggesting that NAC might show protective effects by decreasing the activation of signaling pathways related to ROS generation and oxidative stress (Qi et al., 2010). Furthermore, GSH also significantly inhibited cytotoxicity caused by exposure to simvastatin (5 μM) for 24 h, either alone (5 mM GSH) or in combination (2.5 mM GSH) with NAC (2.5 mM). Similar protective effects on the simvastatin-induced inhibition of CT26 cell survival were noted when cells were treated with the combination of SOD (50 units/ml) and CAT (50 units/ml) during a 24-h treatment with simvastatin (5 μM), along with a decrease in ROS production, whereas SOD (100 units/ml) or CAT (100 units/ml) alone had no significant protective effects, suggesting that the combination of SOD and CAT decreased the cytotoxicity of simvastatin by decreasing simvastatin-induced ROS generation (Qi et al., 2010). However, it is unclear why the combination of SOD and CAT showed significant protective effects when no such effects were observed from SOD or CAT alone.

5.2.2. Coenzyme Q_{10} (CoQ_{10})

CoQ_{10}, also known as ubiquinone, is a potent antioxidant and an integral cofactor in the mitochondrial respiratory chain that helps to generate adenosine triphosphate (ATP) (Deichmann, Lavie, & Andrews, 2010). In a study to investigate the hepatic damage and markers of oxidative stress induced by simvastatin, it was documented that CoQ_{10} could reduce cell death and 8-OH-dG levels and increase ATP synthesis when HepG2 cells were treated with simvastatin (0, 1, 3, 5, and 10 μM) and CoQ_{10} (5 and 10 μg/ml) for 18 h, suggesting that CoQ_{10} deficiency plays an important role in statin-induced hepatopathy, and that CoQ_{10} supplementation protects HepG2 cells from this complication (Tavintharan et al., 2007). A recent study reported that pretreatment with CoQ_{10} could protect hepatocytes from statin-induced injuries by decreasing GSSG and TBARS levels and ROS generation and increasing GSH and MMP levels after rat hepatocytes were exposed to a combination of CoQ_{10} (200 μmol/L) and different statins (atorvastatin, 450 μmol/L; simvastatin, 200 μmol/L; or lovastatin, 200 μmol/L) (Eghbal et al., 2014). However, it has been reported in several clinical studies that CoQ_{10} has no protective effect regarding statin-induced myotoxicity (Caso, Kelly, McNurlan, & Lawson, 2007; Vaughan et al., 2013; Young et al., 2007). However, it has been suggested that CoQ_{10} might play different roles for different statin-induced toxicities, thus making it worthy of further investigations.

5.2.3. Selenium

It has been demonstrated that selenium (25 and 250 nM) supplementation results in the significantly increased capacity of the cells to survive the peroxide challenge induced by atorvastatin (1 μM) or cerivastatin (100 nM) in HepG2 hepatocytes, indicating that selenoprotein suppression is causally involved in statin-induced hepatocyte impairment (Kromer & Moosmann, 2009). However, a study of the molecular origin of serious cerivastatin-induced myotoxicity in muscle cells documented that the devitalizing effect of cerivastatin treatment (50 nM) could not be prevented by the tested selenite concentrations (0.2, 0.5, and 25 nM), indicating that statin-induced antioxidative impairment cannot be competitively overridden by simple selenium supplementation, but rather involves a non-competitive epistatic mechanism (Fuhrmeister et al., 2012).

5.2.4. L-carnitine and piracetam

L-carnitine, an essential cofactor in mitochondrial respiration, has been shown to improve the antioxidant status, exhibiting a protective

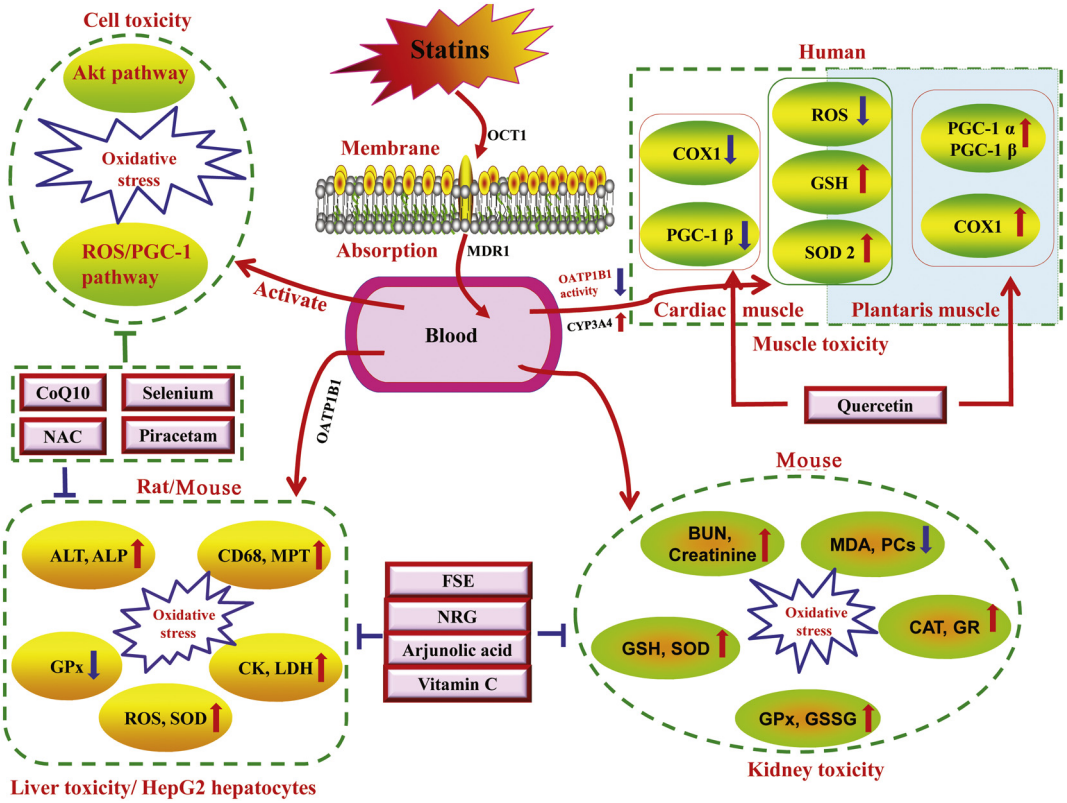

Fig. 3. Schematic illustration of the preventive effect of different compounds, including antioxidants and free radical scavengers, on statin-induced oxidative stress. The use of different antioxidants, such as quercetin, selenium, piracetam, CoQ_{10}, arjunolic acid, vitamin C, NRG, extract from *Fructus Schisandrae* (FSE), and NAC, can suppress statin-induced oxidative stress levels, which improves the total antioxidant status, and thus leads to the prevention of apoptosis.

effect on lipid peroxidation by reducing the formation of hydrogen peroxide (Rani & Panneerselvam, 2002). As revealed, during the co-administration of L-carnitine (100 μM) and three kinds of statins (simvastatin, 200 μM; lovastatin, 200 μM; atorvastatin, 450 μM) for 1–3 h, L-carnitine caused a significant decrease in cell death, along with significant reductions in ROS production and cellular TBARS and GSSG levels, and increased cellular GSH and MMP levels (Abdoli et al., 2015).

Piracetam, a derivative of gamma-aminobutyric acid, has been reported to ameliorate oxygen and glucose deprivation-induced injuries in rat cortical neurons via inhibition of oxidative stress (He et al., 2014). Cell necrosis was significantly reduced when either L-carnitine (4 μM) or piracetam (4 μM) were administered in combination with simvastatin (60 μM) in human PC3 cells, along with an increase in MPT and a decrease in the rate of mitochondrial superoxide generation (Costa et al., 2013).

Various compounds have been tested to decrease statin-induced toxicity (Fig. 3). Many studies have focused on inhibiting ROS generation and increasing the antioxidant ability against mitochondria damage. Some employed antioxidants extracted from various plants, which reduced statin-induced ROS generation and oxidative stress. However, the detoxification effects of these compounds on statin-induced myotoxicity or hepatotoxicity were not the same, indicating that they may require different detoxification mechanisms. A better understanding of the detoxification mechanism of statins will enable the discovery of new efficient antidotes for the clinical use of statins, particularly the implementation of antioxidants from the natural plants.

However, previous studies have shown that an antioxidant agent may be used in combination with a variety of statins, such as N-acetyl cysteine with simvastatin, atorvastatin, lovastatin, fluvastatin co-application. A statin may also be used in combination with various antioxidant agents, such as simvastatin with N-acetyl cysteine, Coenzyme Q10, L-carnitine and piracetam. It is worth noting that the dosage of statins may also affect the use of antioxidants, because the dosage of statins affects the mechanism by which oxidative stress is triggered. Constructively, according to the mechanism of oxidative stress induced by each statin, antioxidant agents can be selected and used in combination with statins to achieve the purpose of prevention. In addition, natural and low toxic antioxidants should be selected for use in combination with statins.

6. Metabolism of statins

6.1. Metabolic pathways

Both simvastatin and lovastatin undergo extensive phase I metabolism to several oxidative products and some of the hydroxy acid forms of these phase I metabolites, such as 3′α, 5′β-dihydrodiol SV, 3′α-hydroxy SV, 6′β-hydroxy SV, and 6′β-hydroxy lovastatin, are also HMG-CoA reductase inhibitors, whereas dihydrodiol SV, 3′α-hydroxy SV, 3′α, 5′β-dihydrodiol simvastatin, and 3′α-hydroxy LV have been previously reported to be inactive metabolites (Khera & Hu, 2013). The metabolizing enzymes and corresponding metabolites of simvastatin, lovastatin, cerivastatin, fluvastatin, pitavastatin, atorvastatin, pravastatin and rosuvastatin have been mentioned (Figs. 4, 5, 6).

6.2. Metabolizing enzymes

Previous studies documented that CYP450 enzymes were mainly responsible for the metabolism of statins. A study by Prueksaritanont et al. (1997) indicated that CYP3A1/2 was the major enzyme subfamily involved in simvastatin metabolism. Simvastatin is hydrolyzed by esterase in the liver to yield an active metabolite simvastatin acid (Vickers et al., 1990), and both simvastatin and simvastatin acid are further metabolized to several inactive metabolites, including the 6'-hydroxy and 3',5'-dihydrodiol forms, by CYP3A in humans and rats (Ishigami et al., 2001; Prueksaritanont et al., 1997; Prueksaritanont, Ma, & Yu, 2003).

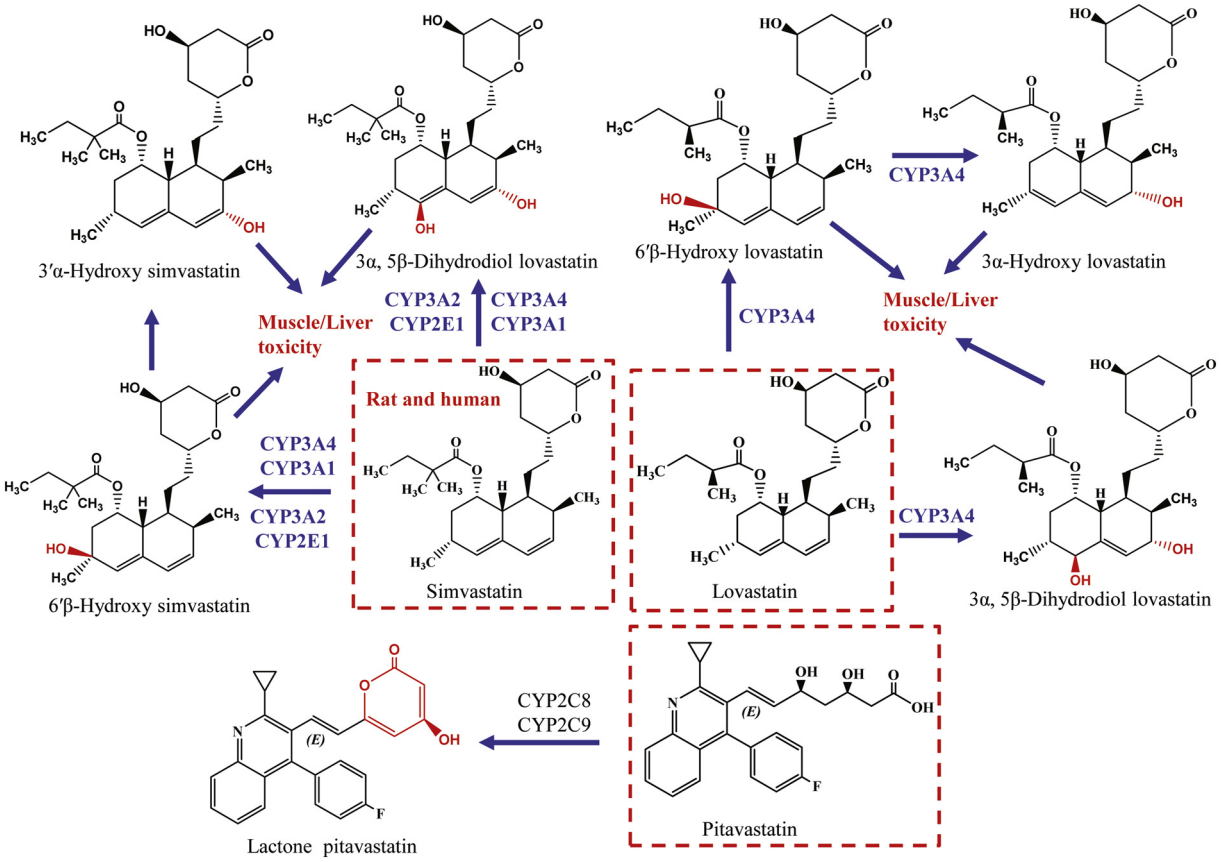

Fig. 4. Metabolic pathways of simvastatin, lovastatin, and pitavastatin, metabolizing enzymes and their associated metabolites.

Three statins, pitavastatin, rosuvastatin, and pravastatin, are minimally metabolized through CYP 450 enzymes (Baker & Datta, 2011; Jacobsen et al., 1999; Olsson, McTaggart, & Raza, 2002). CYP2C8 has been documented to metabolize cerivastatin (Backman, Filppula, Niemi, & Neuvonen, 2016). CYP3A4 metabolizes lovastatin in the liver to yield three major metabolites, 6β-hydroxy lovastatin, β-hydroxyacid lovastatin, and 6'-exomethylene lovastatin (Liu, Zeng, Shang, Cen, & Wei, 2008). After oral administration, an inactive lactone is hydrolyzed by carboxyesterases to its corresponding β-hydroxy acid, and the hydrolyzate is regarded as the main metabolite and active pharmaceutical ingredient of lovastatin (Li, Fan, Zhang, & Cao, 2007).

6.3. Statins cause oxidative stress through metabolism

There are several points to prove that abnormal drug metabolism can lead to oxidative stress. Firstly, as known, excessive free radicals in cells can lead to oxidative stress. In the process of abnormal drug metabolism, a large number of free radicals are produced, resulting in oxidative stress and damage to cells. For example, CoQ_{10}, as the only antioxidant synthesized exogenously, it can protect biological membranes from free radicals and the lipid peroxidation process. However, the use of statins in reducing serum lipids and cholesterol in the body can cause a deficiency of CoQ_{10} in the body. These results suggest that statins can reduce CoQ_{10} *in vivo*, which leads to the damage of free radicals and lipid peroxidation to biological membranes. It is worth exploring that free radical accumulation and lipid peroxidation may be related to the metabolism and handing of statins.

Secondly, statin-induced myotoxicity has been associated with the loss/decrease of function of these transporters such as ABCB1, ABCG2 and SLCO1B1 which are associated with muscular handling or metabolism of statins (Becker et al., 2013). If statins and/or metabolites are accumulate in the myocyte, which may cause myotoxicity. Statins accumulate in muscles needs a lot of excretion and thus requires a lot of energy, resulting in accelerated mitochondrial respiration, mitochondrial fuctional dysfunction, producing a large number of free radicals and causing cell oxidative stress (Lou et al., 2014). For instance, muscular fatigue and myalgia induced by statins are marily associated with low ATP concentrations, presence of ROS, altered [Ca^{2+}]s metabolism, and accumulation of lactate healthy individuals (Horscroft & Murray, 2014).

Importantly, there are also some studies to prove this point. Simvastatin induced oxidative stress and contributed to hepatotoxicity in rats by affecting the activities of two microsomal CYP isoenzymes, including CYP2E1 and CYP3A1/2. At the same time, the inhibition of simvastatin to CYP3A1/2 will increase the formation of SVA (active hydroxyl acid form of simvastatin) which also considered as CYP 3A1/2 inhibitor which increases simvastatin toxicity. Therefore, statins may inhibit their metabolic enzymes, thereby inducing oxidative stress and leading to toxicity. On the contrary, naringenin (NRG) is capable to decrease hepatic MDA lever and GST activity in simvastatin-treated rats, and the inhibitory effect of NRG on CYP2E1 activity is likely to be one of the mechanisms by which NRG produce its hepatoprotective effect (Motawi et al., 2014). This proves negatively that statins cause oxidative stress through metabolism, resulting in hepatotoxicity.

7. Metabolism drug interactions

7.1. Drugs that affect the metabolism of statins

There is concern that the drugs that affect statin metabolism may also trigger adverse statin effects, such as myopathy. The plasma concentrations of the active forms of statins, such as simvastatin, lovastatin, atorvastatin, and fluvastatin, might be significantly increased by the

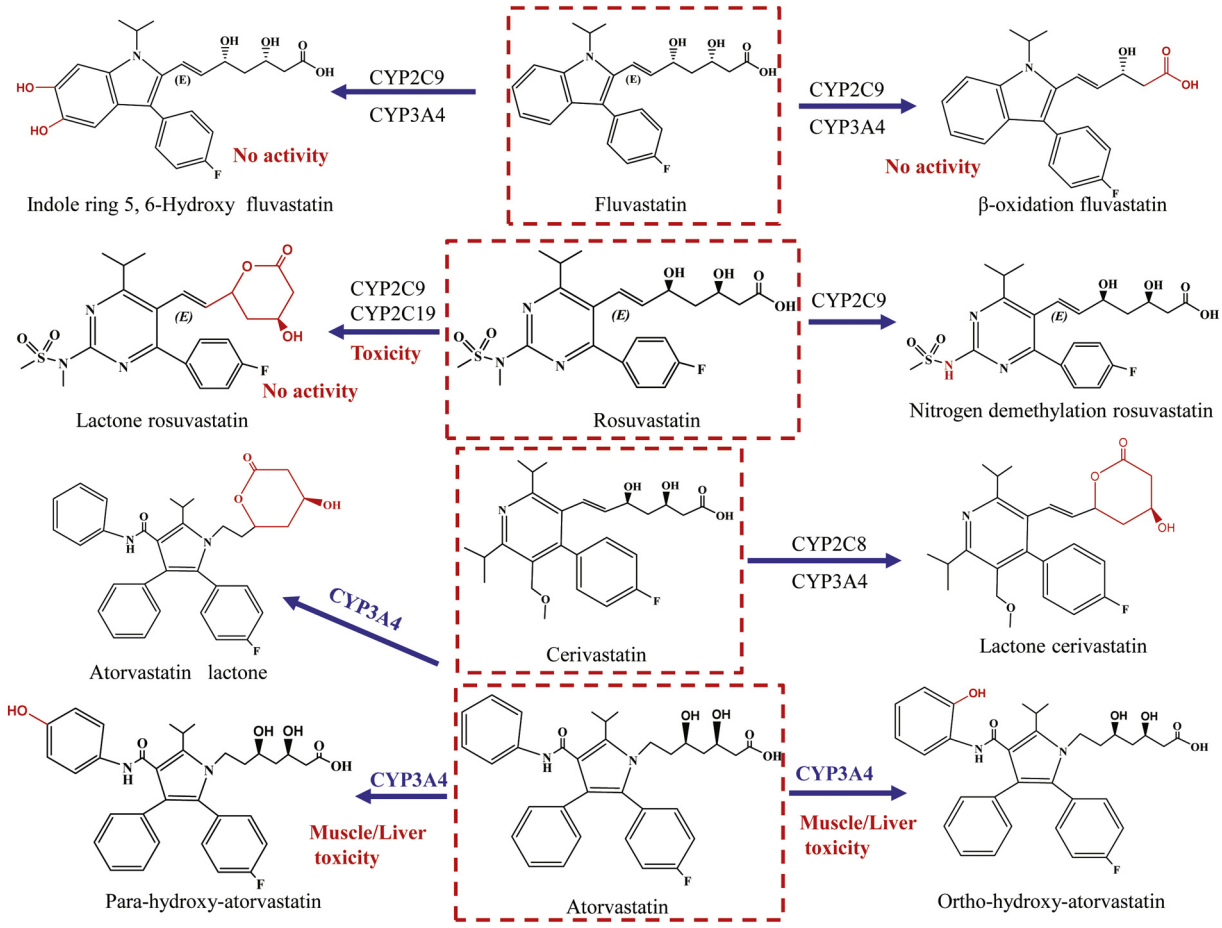

Fig. 5. Metabolic pathways of fluvastatin, rosuvastatin, cerivastatin, and atorvastatin, metabolizing enzymes and their associated metabolites.

potent inhibitors, CYP3A4 and CYP2C9. However, other statins, such as pravastatin, rosuvastatin, and pitavastatin, are not susceptible to inhibition by any CYP (Hirota & Ieiri, 2015). Other drugs may accelerate or inhibit this metabolism through the statin metabolizing enzymes, thereby affecting the toxic effects of statins (Table 3).

7.1.1. Drugs that accelerate the metabolism of statins

Previous studies have suggested that mAbs anti IL-6, IL-1β, or TNF-α could increase the hepatic levels of CYP3A4, 2B6, and 2C8, and thus accelerate the clearance of drugs metabolized by this pathway. A pharmacokinetic study conducted in 12 patients with rheumatoid arthritis taking tocilizumab (an anti-IL-6 receptor antibody) and simvastatin (a CYP3A4 substrate) reported that maximum plasma drug concentration (Cmax) and the plasma concentration-time curve (AUC) of simvastatin and its main metabolite (β-hydroxy-simvastatin acid) were significantly reduced after tocilizumab infusion (Ferri et al., 2016; Schmitt, Kuhn, Zhang, Kivitz, & Grange, 2011). Similarly, simvastatin levels were significantly reduced by the co-administration of alitretinoin (or 9-cis-retinoic acid, which is a form of vitamin A) (Schmitt-Hoffmann et al., 2011). Therefore, it was suggested that the monitored patients receiving tocilizumab should be treated concomitantly with drugs metabolized by CYP3A4, 2C9, or 1A2, such as atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporine, or benzodiazepines (Schmitt et al., 2011).

In vitro and *in vivo* studies suggested green tea extract (*Camellia sinensis*) and/or (-)-epigallocatechin-3-gallate may significantly increase the bioavailability of simvastatin by inhibiting the activity of CYP1A1, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A4 (Albassam & Markowitz, 2017). Tocilizumab was shown to desuppress CYP3A4 activity, and also decrease the elimination half-life and area under the curve up to the last measurable concentration (AUC_{last}) of the small molecule CYP3A4 substrate simvastatin hydroxy acid, measured before and after tocilizumab treatment (Long et al., 2016). The interactions of rifampin, a potent inducer of cytochrome P-450 oxidative enzymes, with atorvastatin may decrease the therapeutic response, therapeutic failure, or toxic reactions (Baciewicz, Chrisman, Finch, & Self, 2008). A recent *in vivo* pharmacokinetics study revealed that berberine (5,6-dihydro-9,10-dimethoxybenzo-1,3-benzodioxolo, quinolizinium) could induce the metabolism of lovastatin, while significantly decreasing the AUC and Cmax of lovastatin, suggesting that berberine possesses induction effects through the CYP450 3A4 enzyme (Cui et al., 2016). The co-administration of atorvastatin with different medications, such as itraconazole, clarithromycin, cimetidine, rifampin and phenytoin, may thus affect the pharmacokinetic profiles of atorvastatin and the form of its metabolites (Zhang, 2015).

Altogether, abnormal metabolism of statins may be an important mechanism of their toxicity, so other drugs to accelerate the metabolism of statins may lead to the accumulation of their metabolites in the organs, leading to organ toxicity.

7.1.2. Drugs that inhibit the metabolism of statins

Cerivastatin is a CYP2C8 substrate drug, and many drugs, such as gemfibrozil and inducers, have been identified as CYP2C8 inhibitors, which affect the metabolism of cerivastatin, and thus promote a strong potential for drug interactions (Backman et al., 2016). Evacetrapib may impact the metabolism of simvastatin by inhibiting all of the major CYPs, including CYP2C9, CYP2C19, and CYP3A (Cannady et al., 2015). Amiodarone has been reported to increase the exposure of simvastatin by 1.2- to 2-fold by inhibiting CYP3A (Chen, Mao, & Hop, 2015). A clinically significant interaction between warfarin and simvastatin is

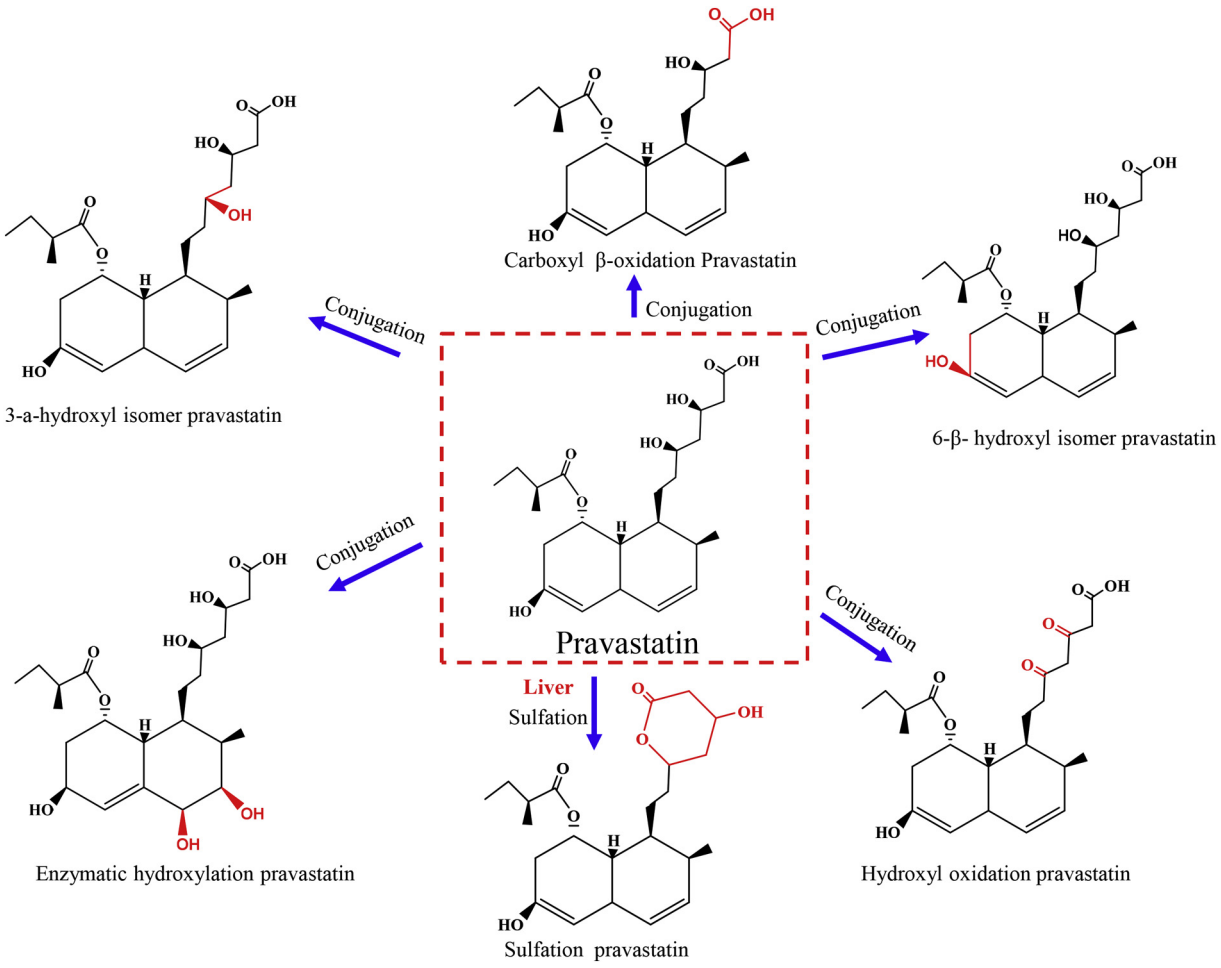

Fig. 6. Pravastatin hydroxy-metabolites that should be excreted by conjugation.

unique to carriers of the CYP2C9*3 allele, thus affecting the metabolism of simvastatin (Botton, Hutz, & Suarez-Kurtz, 2012). An *in vitro* investigation has shown that the interaction between simvastatin and desloratadine is unlikely to result from the inhibition of drug metabolism by CYP450 enzymes; however, *in vitro* synergistic myotoxicity of simvastatin and desloratadine was observed, suggesting a role in loratadine-simvastatin interaction (Han et al., 2015). Furthermore, a drug interaction between the cytochrome P450 3A4 inhibitor ticagrelor (a platelet aggregation inhibitor) and substrate atorvastatin (80 mg) may have precipitated the development of rhabdomyolysis in patients (Kido, Wheeler, Seratnahaei, Bailey, & Bain, 2015).

The amiodarone drug interactions predicted from the reversible inhibition of the four P450 activities were found to be in good agreement with the magnitude of reported clinical drug-drug interactions (DDIs) with lidocaine, warfarin, metoprolol, and simvastatin (McDonald, Au, & Rettie, 2015). Clarithromycin, which is known as a potent inhibitor of the cytochrome P450 isoenzyme CYP3A, may increase the plasma concentration of metabolized statins, therefore increasing the risk of interaction with statins, as noted in pharmacokinetic studies (Mesgarpour, Gouya, Herkner, Reichardt, & Wolzt, 2015). Clopidogrel, a drug that inhibits the aggregation of blood platelets, is reported to be associated with cerivastatin-induced rhabdomyolysis, where clopidogrel and its metabolites are capable of inhibiting CYP2C8 *in vitro*, with a single 300 mg dose of clopidogrel being able to inhibit CYP2C8-mediated metabolism by clopidogrel acyl-beta-glucuronide (Kim et al., 2016). Piperine, the major alkaloid component from *Piper longum* L. and *Piper nigrum* L., could enhance the bioavailability of rosuvastatin via inhibition of CYP3A and P-glycoprotein activity (Li et al., 2016). A case report suggested that the combination of high-dose simvastatin with the antifungal agent itraconazole might result in muscle pain and highly elevated levels of CK and myoglobin, compatible with statin-associated rhabdomyolysis, suggesting that the potent inhibitors of liver enzyme CYP3A4, such as itraconazole and posaconazole, should be avoided when taking statins or using non-CYP3A4-inhibiting antifungal drugs, such as terbinafine (Dybro, Damkier, Rasmussen, & Hellfritzsch, 2016).

Another case report suggested that once-daily ticagrelor and atorvastatin (80 mg) might result in rhabdomyolysis, indicating that more attention should be given to the possible drug interaction via CYP3A4 and its potential complications (Kido et al., 2015). Therefore, the disposition of statins is highly variable, which makes both the metabolization of enzymes predictions of statin DDIs challenging tasks. It is thus necessary to investigate DDIs in greater detail and also avoid the interaction between various drugs and statins.

7.2. Statin metabolism-related gene polymorphism

Gene polymorphism affects the pharmacokinetics and pharmacodynamics of statins, which thus affects the efficacy of statins. Gene polymorphisms and DDI will affect the plasma and liver concentrations of statins by the anion transport polypeptide (OATP1B1) and breast cancer suppressor protein (BCRP), resulting in myopathy. The drug interactions known to increase the risk of statin-induced myopathy, including macrolide antibiotics, calcium channel antagonists, and amiodarone, which were associated with pharmacokinetic alterations of the DDI with statins and genetic polymorphisms in CYPs involved in the metabolism of statins (Hill, McCloskey, & Sheerin, 2015; Hirota & Ieiri, 2015). Changes in either the LDL-C lowering of statins or myopathy risk can shift the risk-to-benefit

ratio for their clinical use, which thus has implications for statin management in clinical trials during the development of novel therapeutics.

7.3. Drug effects on the metabolism of statins by OATP1B1 and BCRP

The key transporters of statin-induced liver metabolism, such as OATP1B1 and BCRP, can affect the plasma and liver concentrations of statins, thereby affecting the efficacy and safety of statins (Hirota & Ieiri, 2015).

Alam et al. (2016) indicated that pre-incubation with the lysosomotropic drug CQ downregulates OATP1B1 transport activity, which then causes the interaction of OATP1B1 and statins, and thus increases the risk of myopathy more than when using statins alone in HEK293-OATP1B1 cells or human SCH. The statin models reasonably predicted the observed exposure change due to Organic Anion Transporting Polypeptide (OATP) 1B1 polymorphism or clinical DDIs with itraconazole, erythromycin, and gemfibrozil, but they under-predicted the observed DDIs caused by rifampin and cyclosporine (Duan, Zhao, & Zhang, 2016). Further analysis demonstrated that OATP1B1 inhibition by rifampin or cyclosporine in the existing inhibitor models needs to be approximately tenfold stronger to recapitulate the observed DDI with these two inhibitors. A study confirmed the importance of OATP1B1 in the disposition of these two statins, and explored potential causes for the underprediction of the inhibitory effect of rifampin and cyclosporine (Duan et al., 2016). Co-administration of spironolactone with pravastatin in rats showed a significant increase in the systemic exposures of pravastatin (2.5-fold increase in AUC) due to transport-mediated DDIs (Badolo, Bundgaard, Garmer, & Jensen, 2013). As revealed in cynomolgus monkeys, rifampin, a potent inhibitor for OATP1B, significantly decreased plasma clearance and increased the AUC of intravenously administered rosuvastatin by 2.8- and 2.7-fold, respectively, and increased the AUC and Cmax of orally administered rosuvastatin by 6- and 10.3-fold, respectively (Chu et al., 2015). However, rifampin was reported to show a significant increase plasma exposure of either intravenous or orally administered atorvastatin in human beings, whereas rifampin increased them in cynomolgus monkeys, suggesting species differences in the rate-limiting elimination pathways of atorvastatin (Chu et al., 2015).

As a major pungent substance in hot pepper (*Capsicum pubescens*), capsaicin (CAP, trans-8-methyl-*N*-vanillyl-6-nonenamide) has been reported to interact with the metabolism of simvastatin. It was reviewed that the chronic ingestion of capsaicin (3 or 7 mg/kg for the first seven days, orally) and the combination of simvastatin (8 mg/kg, on the first and seventh days, intravenously) significantly reduced the $AUC_{0-\infty}$ of simvastatin, while increasing the liver Ugt1a1 expression level, which suggests that a patient treated with statins should not eat peppers to avoid the food-drug interaction (Zhu et al., 2016).

BCRP is the main hepatic transporter of rosuvastatin, and a decrease of rosuvastatin transfer leads to an increase of liver rosuvastatin concentration, which may be the main mechanism for the difference in the efficacy of LDL-C in different genotypes (Kasuya et al., 2012). A clinical interaction study between fostamatinib and rosuvastatin confirmed the critical role of BCRP in statin absorption, as the inhibition by fostamatinib resulted in significant 1.96- and 1.88-fold increases in the rosuvastatin area under the AUC and Cmax, respectively (Elsby, Martin, Surry, Sharma, & Fenner, 2016). Co-administration with isavuconazole increased the mean area under the plasma concentration-time curves (90% confidence interval) of atorvastatin (Yamazaki et al., 2017).

7.4. Drug effects on the metabolism of statins by intestinal metabolic enzymes

Statins are partly absorbed after intestinal metabolism. Antibiotics suppress the activities of the drug-metabolizing enzymes by inhibiting the proliferation of gut microbiota; however, it is not clear whether other drugs can inhibit the metabolism of statins by affecting the proliferation of intestinal microflora (Kim, 2015). Another study reported that when female rats were administrated a single dose of green tea extract (GTE) (400 mg/kg BW) and simvastatin (20 mg/kg BW, orally), GTE significantly increased the bioavailability of simvastatin with 3.4-fold and 3.3-fold increases in AUC_{0-6h} and Cmax respectively, compared to the control condition, suggesting that the change in the simvastatin pharmacokinetics may result from the GTE inhibition of intestinal CYP3A activity (Misaka et al., 2013).

8. Co-administration of statins and other drugs leads to toxicity

8.1. Simvastatin

A DDI between high-dose simvastatin and itraconazole for several years may lead to muscle pain and highly elevated levels of CK and myoglobin (Dybro et al., 2016). The interaction between statins and ciprofloxacin can have potentially serious outcomes, potentially resulting in decreased CK levels, unstable liver and renal functions, and muscle weakness (Goldie, Brogan, & Boyle, 2016). Another case reported that a 62-year-old woman who took simvastatin (40 mg *nocte*) for 13 years and then only several days of ciprofloxacin presented slowly progressive muscle weakness, deranged liver function, and a significant increase in CK levels, whose symptoms then improved after discontinuation of simvastatin, suggesting that cipropfloxacin might significantly increase the toxicity of simvastatin (Goldie et al., 2016). The interaction between amlodipine and simvastatin resulted in muscle pain, weakness of the muscles, dizziness, and confusion in the patient (Kennedy-Dixon, Gossell-Williams, Hall, & Anglin-Brown, 2015; Schetz, Foerster, & Sein Anand, 2015). Rhabdomyolysis could have been caused by a drug interaction between simvastatin with azithromycin (Alreja, Inayatullah, Goel, & Braden, 2012). The combination of simvastatin with antiretroviral drugs for the treatment of an HIV-infected patient resulted in rhabdomyolysis; however, the substitution of simvastatin with atorvastatin led to rhabdomyolysis-induced renal failure and liver toxicity (Bastida et al., 2014). Another case reported that a 68-year-old man taking a combination of clarithromycin and simvastatin sustained a severe acute kidney injury, in addition to statin-induced rhabdomyolysis (Hill et al., 2015).

8.2. Other statins

Pravastatin lactone yielded detectable inhibition of HIV-1 integrase strand transfer activity (31.65% at 100 μM), and a correlation between lipophilicity and increased statin-induced cellular toxicity was observed (Harrison et al., 2015). Atorvastatin and HMG-CoA reductase inhibitors are the most frequently used medications in the world due to their very limited adverse toxic side effects (Nandy & Gaini, 2016). However, one potentially life-threatening adverse effect is statin-induced rhabdomyolysis, either independently or in combination with fusidic acid, which can happen either in atorvastatin monotherapy or as a complication of the pharmacokinetic interaction between atorvastatin and fusidic acid (Nandy & Gaini, 2016).

A study suggested that herb-drug interactions may occur when nutraceuticals containing rooibos extracts are co-administered with hypoglycemic drugs, such as atorvastatin (Patel, 2016). The co-administration of sofosbuvir/ledipasvir with rosuvastatin showed significantly increased drug effects, which is associated with an increased risk of rhabdomyolysis (Patel, Andres, & Qureshi, 2016). A study revealed levels of aldosterone (ALD), a hormone responsible for blood pressure in human plasma, were significantly higher in atorvastatin (ATSV) and olmesartan (OLM) treatment conditions, when compared to OLM as single treatment condition (Das, Dan, & Pal, 2014).

Settergren, Eiermann, and Mannheimer (2013) reported that calcium blockers and fibrates (fenofibrate or bezafibrate) may increase

Table 4
Drugs interactions with statins in the past five years.

Drugs involved in drug-drug interactions (DDIs)	Models/dose	Statins	Aim	Results	Reference
LCZ696 (sacubitril/valsartan), a novel angiotensin receptor neprilysin inhibitor	Healthy human male subjects: administered with LCZ696 (a novel angiotensin receptor neprilysin inhibitor) 200 mg twice daily, 5 days (period 1), administered with atorvastatin 80 mg once daily, 4 days (period 2) and subsequently co-administered with LCZ696200 mg, 5 days (period 3).	Atorvastatin	To evaluate potential pharmacokinetics drug--drug interaction between atorvastatin and LCZ696	Co-administration with LCZ696: increased Cmax of atorvastatin, *ortho*-hydroxy-atorvastatin,and *para*-hydroxy-atorvastatin by 74, 68, and 108 %, respectively, increased AUC of corresponding analytes by 34, 22, and 26 %, respectively.Cmax of atorvastatin and its metabolites increased two-fold, with a marginal increase in the AUC (<1.3-fold).	Ayalasomayajula et al. (2017)
Diazepam	Wistar Han rat treated with simvastatin (2.5, 5, 10, 20 mg/kg BW) for 4-6 weeks, and/or diazepam (2.5, 5, 10 mg/kg BW) administered once on the day of the study.	Simvastatin	To examine the effect of chronic oral administration of simvastatin on the anxiolytic activity and pharmacokinetics of diazepam in rats. To evaluate potential pharmacodynamics interaction by behavioral tests [the elevated plus maze (EPM) test and the Vogel conflict test (VCT)]. To evaluate potential pharmacokinetics interaction measuring plasma concentrations of diazepam and its metabolites.	Diazepam, 5 and 10 mg/kg BW given together with simvastatin 10 and 20 mg/kg BW, showed no anxiolytic effect in the EPM test. VCT diazepam combinations with simvastatin did not produce any anxiolytic effect either, with an exception of the co-administration of diazepam 10 mg/kg and simvastatin10 mg/kg BW. Simvastatin (20 mg/kg BW) significantly reduced the AUC of diazepam by 56% and temazepam by 54.6%.	Slupski, Trocha, & Rutkowska (2017)
Organic anion transporting polypeptide OATP1B1, mediates the hepatic uptake of many drugs. Antimalarial drug chloroquine (CQ) used for rheumatoid arthritis	HEK293-OATP1B1cells without and with pre-incubation, CQ (100 μM). Human Sandwich-Cultured Hepatocytes (SCH) with pre-incubation with CQ at clinically relevant concentration.	Pitavastatin Rosuvastatin Pravastatin	To determine: the effects of CQ on OATP1B1 protein degradation, OATP1B1-mediated transport, -OATP1B1-over expressing cell line, and statin uptake in human sandwich cultured hepatocytes (SCH).	Treatment with CQ increased OATP1B1total protein levels in HEK293-OATP1B1cells and in human SCH. The *in vitro* data obtained in combination with pharmaco- epidemiologic studies support that CQ has potential to cause OATP-mediated drug-drug interactions. CQ plus statins (pitavastatin, rosuvastatin and pravastatin) leads to higher risk for myopathy than these statins alone	Alam et al. (2016)
LCZ696 (sacubitril/valsartan)	*In vitro* evaluation of OATP inhibitory effect in human embryonic kidney HEK Flp-In and in HEK293 cells in the presence and absence of sacubitril, LBQ657 (an active metabolite of sacubitril) and rifampicin. Clinical study, healthy human subjects treated with simvastatin 40 mg alone or in combination with LCZ696 or after 1 or 2 h of LCZ696 dosing	Simvastatin	To evaluate *in vitro* potential of LCZ696 analytes to inhibit the OATP1B1 and OATP1B3 transporters. To investigate the effect of LCZ696 on the pharmacokinetics of simvastatin and simvastatin acid following co-administration	*In vitro* studies indicated that sacubitril, a LCZ696 analyte, inhibits OATP1B1- and OATP1B3-mediated transport. LCZ696 (co-administration of simvastatin): decreased the Cmax of simvastatin and simvastatin acid by 7% and 13%, respectively. When administered 1 h after LCZ696 dosing, the corresponding Cmax of simvastatin and simvastatin acid decreased by 16% and 4%, respectively. When administered 2 h after LCZ696 dosing, the Cmax of simvastatin decreased by 33% and that of simvastatin acid increased by 16%.	Ayalasomayajula et al. (2016)
Co-administered drug: Amiodarone, Acenocoumarol, Amlodipine, Diltiazem, Valsartan, Spironolactone, Fenofibrate, Digoxin, Budesonide	Human subjects (125 patients, age range 39 to 93 years)	Atorvastatin (15 cases) Simvastatin (13 cases) Rosuvastatin (9 cases)	To identify, characterize and quantify the prevalence of the pDDIs of statins in reimbursed prescriptions from a community pharmacy in Bucharest.	A quarter of patients included in the study were at risk of developing severe adverse effects. 132 prescriptions pertaining to 125 patients were included in the analysis. A 25% of the patients treated with statins were exposes to pDDis: 37 serious and significant interactions in 31 of the statins prescriptions. The statins involved were atorvastatin, simvastatin, and rosuvastatin.	Badiu, Bucsa, Mogosan, and Dumitrascu (2016)

(continued on next page)

Table 4 (*continued*)

Drugs involved in drug-drug interactions (DDIs)	Models/dose	Statins	Aim	Results	Reference
				Between others, most cases of pDDIs were associated with the concurrent use of fenofibrate (serious muscular toxicity). Amiodarone (decreased metabolism of the statin, muscular toxicity increased). Acenocoumarol (increased anticoagulant effect; diltiazem (muscular toxicity increased).	
Berberine (an alkaloid available from the medicinal plant *Coptis chinensis,* widely used clinically in the treatment of gastrointestinal infections, diabetes, hypertension and hyper-cholesterolemia	Drug metabolism study *in vitro* (HepG2 cell) in relation to a drug pharmacokinetics study *in vivo* (male Sprague-Dawley rats).	Lovastatin	To evaluate *in vivo* e *in vitro* drug-drug interactions between lovastatin and berberine-lovastatin comparing the main pharmacokinetics parameters obtained *in vivo* against the metabolic activity obtained *in vitro* using HepG2 cell line	*In vitro* HepG2 cells, berberine increased the metabolic activity. *In vivo* berberine altered the pharmacokinetics of lovastatin. Lovastatin pharmacokinetic parameter t½β was increased, while the AUC and Cmax were decreased. These results revealed a potential drug-drug interaction between berberine and lovastatin. The data suggest that berberine may slow the adverse effects caused by continuous dosing of lovastatin such as myopathy.	Cui et al. (2016)
Fluoxetine Paroxetine (selective serotonin re-uptake inhibitors with protective effect against myocardial infarction)	Male Wistar rats treated intraperitoneally with atorvastatin (10 mg/kg BW) fluoxetine (10 mg/kg BW) and paroxetine (10 mg/kg BW) per day for 28 days.	Atorvastatin in combination with fluoxetine or paroxetine	To examine oxidative stress parameters in the blood of rats after 28 days treatment with atorvastatin combined with fluoxetine or paroxetine. The activity of GPX, GR and TAS in serum were determined	Fluoxetine,paroxetine: Concomitant administration of atorvastatin with fluoxetine caused an increase in the GPX activity and the TAS. Concomitant administration of atorvastatin with paroxetine increased the activities of GPX and GR. The results suggest a drug-drug interaction having an effect on the blood redox equilibrium	Herbet, Izdebska, et al., 2016
Voriconazole Lansoprazol	Human (patient, 44-year-old Caucasian man) treated with voriconazole for 1 year due to pulmonary aspergillosis, and lansoprazole (30 mg per day) due to gastro-esophageal reflux symptoms. Sixteen months later, the patient was given simvastatin (10 mg per day) for hyperlipidemia.	Simvastatin	To examine a case of recurrent cholestatic hepatitis, while on voriconazole induced initially by concomitant use of lansoprazole and the later use of simvastatin to prevent cardiovascular disease.	Two episodes of cholestatic hepatitis were observed with nearly identical clinical symptoms precipitated by the addition of a single medication prescribed voriconazole, 16-months apart. The similar clinical presentation and the two different P450 pathways of voriconazole metabolism (2C19 and 3A4) suggest that all patient medications must be monitored to prevent adverse drug-drug interactions. The use of either proton pump inhibitors or HMG CoA reductase inhibitors must be done with the most caution in patients on anti-fungal therapy.	Lopez and Tayek (2016)
Danshensu, a tradicional Chinese medicine, (3,4-dihydroxy- phenyl lactic acid)	*In vitro* studies: primary rat hepatocytes incubated with Danshensu (20, 40 and 80 μM) and, HEK293T cells with over-expression of OATP1B1*a and OATP1B1*5 for determining the effects of Danshensu on the uptake of rosuvastatin.	Rosuvastatin	To explore the changes of rosuvastatin pharmacokinetics in presence of Danshensu in rats. To explore the effects of Danshensu on the uptake of rosuvastatin by hepatocytes. To explore the effects of Danshensu on the uptake of rosuvastatin in HEK293T cells with overexpression of OATP1B1*a and OATP1B1*5	Danshensu increased rosuvastatin pharmacokinetic parameters such as Cmax, AUC_{0-t} and $AUC_{0-\infty}$ about 123%, 194% and 195% in rats, respectively in the presence of 20, 40 and 80 μM of Danshensu. Danshensu significantly altered the pharmacokinetics of rosuvastatin in rats.	Wen et al. (2016)
GSK2647544 [a selective lipoprotein-associated phospholipase A2 (Lp-PLA2) inhibitor]	Human (healthy male volunteers) treated with repeated doses of GSK2647544 (80 mg per day).	Simvastatin	To assess the overall safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) profiles of GSK2647544 in healthy subjects	GSK2647544 concomitant administration with simvastatin increased AUC and Cmax of simvastatin and simvastatin acid by 3.6- to 4.3-fold and 1.5- to 3.1-fold, respectively.	Wu et al. (2016)
Peficitinib (inhibitor of the hepatic uptake transport organic anion transporting polypeptide, OATP1B1)	Human (24 healthy adults of East Asian and non-East Asian origin) received a single dose of rosuvastatin 10 mg on days 1 and 10. On days 5-13, subjects received a daily dose of 150 mg peficitinib.	Rosuvastatin	To report a clinical study evaluating the effects of peficitinib on the pharmacokinetics of rosuvastatin.	Peficitinib: co-administration of peficitinib with rosuvastatin, increased AUC and Cmax of rosuvastatin by 18 and 15%, respectively, and increased AUC and Cmax of peficitinib by 16 and 28%, respectively.	Zhu et al. (2016)

				Once –daily oral administration of peficitinib had no clinically significant effect of rosuvastatin pharmacokinetics. It is unlikely that peficitinib will have clinically significant effect on the exposure of other substrates for OATP1B1	
Raltegravir [Human immune-deficiency virus (HIV) inhibitor]	Human (24 healthy male and female subjects, age range 18 and 55 years) treated with Raltegravir, 400 mg two times a day, for 7 days Atorvastatin, 20 mg once a day for 7 days, and combination of atorvastatin, 20 mg once a day + raltegravir, 400 mg two times a day for 7 days.	Atorvastatin	To investigate the influence of a frequently used statin, atorvastatin on the pharmacokinetics of raltegravir and viceversa.	For raltegravir, the $AUC_{0\text{-}12h}$ was 1.00 (0.68-1.51). For atorvastatin, the $AUC_{0\text{-}24h}$ was 1.00 (0.90-1.11). The $AUC_{0\text{-}24h}$ metabolite-to-parent ratio for atorvastatin lactone, *ortho*-hydroxy- and *para*-hydroxy-atorvastatin did not change during concomitant raltegravir use. The effect of atorvastatin on low-density lipoprotein cholesterol was not significantly different when combined with raltegravir *versus* atorvastatin alone. Atorvastatin 20 mg has no clinically relevant effect on raltegravir pharmacokinetics and viceversa. The combination was well tolerated and can be administered without dose adjustments.	Blonk, van Beek, Colbers, Schouwenberg, and Burger (2015)
Evacetrapib [Cholesteryl ester-transfer protein (CETP) inhibitor]	*In vitro* studies: human hepatic microsomes, CYP3A4, CYP2C9 Two clinical studies:(A) Human (healthy adult subjects) treated with evacetrapib (100 or 300 mg per day for 15 days): pharmacokinetics of midazolam and tolbutamide prior to administration of evacetrapib and on day 15 after evacetrapib. (B) Human (adult subjects with hypercholesterolemia) treated: ● with evacetrapib (30, 100 or 500 mg per day for 15 days) as monotherapy, ● with simvastatin (40 mg) as monotherapy, or ● in combination with evacetrapib (100 mg)	Simvastatin	To evaluate the potential for evacetrapib to cause clinically important drug-drug interactions (DDIs) with cytochromes P450 (CYP) determining by pharmacokinetic analysis, the interaction of evacetrapib with midazolam and tolbutamide in healthy adult subjects, and the interaction of evacetrapib with simvastin in dyslipidaemic patients	Evacetrapib: plasma AUC and Cmax for midazolam and tolbutamide showed that pharmacokinetics of both drugs were not affected by evacetrapib. Evacetrapib: co-administration of evacetrapid with simvastatin caused minimal changes en Cmax of simvastatin. In patients receiving simvastatin alone or in combination with evacetrapib, no clinically important differences were found regarding clinical laboratories or treatment emergent adverse events. *In vitro*, in liver microsomes and cultured hepatocytes, a weak interaction with CYP3A4 occurred at both 100 and 300 mg doses of evacetrapib, whereas the AUC ratios for CYP2C9 ranged from 0.85 to 1.06, indicating minimal interaction with CYP2C9. Thus, these studies suggested a low risk of clinically relevant DDIs between evacetrapib and CYP3A4 and CYP2C9 substrates that may be taken as concomitant medications	Cannady et al. (2015)
Rifampin (potent inhibitor for OATP1B)	Male cynomolgus monkeys (*Macaca fascicularis*) 7–10 years of age, treated with rifampin (18 mg/kg BW, orally)	Rosuvastatin Atorvastatin	To measure rifampin effect on plasma exposure of endogenous substrates of hepatic transporters. To further evaluate whether cynomolgus monkeys are a suitable translational model to study OATP1B- mediated DDIs, the inhibitory effect of rifampin on *in vitro* transport and pharmacokinetics of rosuvastatin and atorvastatin were also determined	Rifampin: significantly decreased plasma clearance and increased AUC of intravenously administered rosuvastatin by 2.8- and 2.7-fold, and increased the AUC and Cmax of orally administered rosuvastatin by 6-and 10.3-fold, respectively. In contrast, rifampin did not significantly increase plasma exposure of orally administered atorvastatin, indicating species differences in the rate-limiting elimination pathways. Rifampin strongly inhibited the uptake of rosuvastatin and atorvastatin by cynomolgus monkey cOATP1B1 and cOATP1B3 *in vitro*. Both cOATP1B1 and cOATP1B3 are functionally similar to their human orthologs.	Chu et al. (2015)

(continued on next page)

Table 4 (*continued*)

Drugs involved in drug-drug interactions (DDIs)	Models/dose	Statins	Aim	Results	Reference
Ticagrelor (CYP3A4 inhibitor)	Human (62-year-old woman) treated with ticagrelor (90 mg) twice daily, atorvastatin 80 mg) once daily, metoprolol (25 mg) twice daily, and aspirin (81 mg) daily, during 2 months	Atorvastatin	To report a case of rhabdomyolysis possibly caused by interaction of ticagrelor with high-dose atorvastatin.	Ticagrelor: rhabdomyolysis was diagnosed based on the symptoms combined with elevated creatine kinase, urine myoglobin, and serum creatinine. A drug interaction between once-daily ticagrelor and atorvastatin 80 mg can be the cause of the observed rhabdomyolisis	Kido et al. (2015)
ACT-178882 (a direct renin inhibitor that has shown to influence the activity of CYP3A4 *in vitro* and *in vivo*)	Human (32 healthy male subjects) received atorvastatin 20 mg simvastatin 20 mg on 1, 9, 31, and 41 days. ACT-178882 500 mg once daily, on days 6 to 33,	Atorvastatin Simvastatin	To evaluate possible inhibitory and inductive effects of ACT-178882 on pharmacokinetics of simvastatin and atorvastatin. This design enabled the study of complex time-dependent effects on CYP3A4 activity with clinically relevant substrates.	ACT-17888: In the presence of ACT-178882, mean simvastatin and metabolite concentrations were markedly higher on day 9 when compared to day 1, resulting in values for AUC and Cmax that were about 2.5-fold and 4.0-fold greater. In the presence of ACT-178882 on day 9, Cmax was lower, but AUC was similar, Tmax delayed, and t½ of elimination slightly prolonged when compared to atorvastatin alone on day 1. On day 31, after prolonged administration of ACT-178882, exposure to atorvastatin, *ortho*-hydroxy-atorvastatin, simvastatin, and 6β-hydroxy acid simvastatin decreased by 14, 19, 21, and 27 %, respectively, when compared to day 9.However, on this day, exposure to simvastatin and its metabolite was still markedly higher when compared to day 1.	Dingemanse, Nicolas, & van Bortel (2014)
Ginkgo biloba extract (GBE)	Human (14 healthy subjects) received simvastatin 40 mg once daily, co-treated with GBE 120 mg twice daily.Each treatment was administered for 14 days, separated by a wash-out period of 1 month.	Simvastatin	To determine the influence of GBE on the pharmacokinetics and pharmacodynamics of simvastatin.	GBE administration reduced mean simvastatin AUC and Cmax by 39% and 32%, respectively, but did not cause significant differences in simvastatin acid pharmacokinetics or its cholesterol-lowering efficacy. However, we cannot rule out the possibility for a pharmacodynamics interaction between GBE and simvastatin *in vivo*.	Dai et al. (2013)

Note: OATP1B1: organic anion transporting polypeptide 1B1; CQ: chloroquine; SCH: human sandwich-cultured hepatocytes; LCZ696: a novel angiotensin receptor neprilysin inhibitor; AUC: area under the plasma concentration curve; Cmax: peak concentration; pDDIs: potential drug-drug interactions; DDIs: drug-drug interactions; CYP: cytochromes P450; PK: pharmacokinetics; PD: pharmacodynamic; GPX: glutathione peroxidase; TAS: total antioxidant status; GBE: Ginkgo biloba extract; GR: glutathione reductase; SSRIs: selective serotonin reuptake inhibitors; GSK2647544: a selective lipoprotein-associated phospholipase A2.

the risk of statin-induced myopathy to some extent. However, in a study to investigate the interaction between atorvastatin and fenofibrate, when considering Cmax and AUC of combining atorvastatin and fenofibrate *versus* only atorvastatin, it was documented that there was no relevant clinical-pharmacokinetic drug interaction between them when healthy Mexican volunteers were treated with only atorvastatin (20 mg) or the combination of atorvastatin (20 mg) and fenofibrate (160 mg) (Patino-Rodriguez et al., 2015). Pretreatment of amiodarone (400 mg/day) for three days increased the AUC, Cmax, and elimination half-life of simvastatin acid (40 mg), whereas it did not significantly alter pravastatin pharmacokinetics, suggesting that pravastatin should be preferred to simvastatin when simultaneously prescribed with amiodarone to avoid a drug interaction (Becquemont et al., 2007). The combination of sitagliptin with atorvastatin might lead to the acute breakdown of the skeletal musculature, such as the generalized weakness, muscle aches, and atypical chest pain observed in a 60-year-old female (Khan, Kurian, & Bishnoi, 2016). The co-administration of statins with fluconazole, a known moderate inhibitor of CYP3A4 that is a strong inhibitor of cytochrome P450 (CYP) 3A4, or certain potent azoles, like itraconazole or ketoconazole, can increase the levels of a patient's statin-induced rhabdomyolysis (Charokopos, Muhammad, Surbhi, & Brateanu, 2017).

8.3. Oxidative stress during the combination of drugs with statins

Various studies have documented that the combination of statins and other kinds of drugs could alter the imbalance in prooxidant and antioxidant levels (Table 4). For example, after rats were treated with either rosuvastatin (10 mg/kg BW) or citalopram (10 mg/kg BW) for 14 days, the simultaneous administration of rosuvastatin with antidepressant drugs, paroxetine or citalopram, caused an increase in blood GPx and serum GR activities, whereas the GPx and GR levels were not affected when only rosuvastatin or citalopram were administered, and the 14-day application of paroxetine (10 mg/kg BW) significantly decreased GPx activity, while GR activity was increased (Herbet, Izdebska, Piatkowska-Chmiel, Poleszak, & Jagiello-Wojtowicz, 2016). Additionally, a combined 14-day treatment of rosuvastatin (10 mg/kg BW) and fluoxetine (10 mg/kg BW) significantly increases GPx and GR activities while decreasing the level of total antioxidant status (TAS). Perhaps, these differences result from the shared metabolism of rosuvastatin and fluoxetine and these drugs are biotransformed by cytochrome P450 izoenzyme CYP2C9 (Herbet, Gawronska-Grzywacz, & Jagiello-Wojtowicz, 2015). To investigate the impact of the combination of rosuvastatin (10 mg/kg BW) and amitriptyline (10 mg/kg BW) on the oxidation-reduction status in rats, it was documented that the combination significantly increased the GPX activity compared to the group receiving only rosuvastatin, and decreased the GR activity compared to the groups receiving only rosuvastatin or amitriptyline (Herbet, Gawronska-Grzywacz, Graca, & Jagiello-Wojtowicz, 2013). A recent study revealed that after the rats were injected with aqueous solutions of atorvastatin (10 mg/kg BW), fluoxetine (10 mg/kg BW), and paroxetine (10 mg/kg BW) once a day for 28 days, separately or concomitantly, the concomitant administration of atorvastatin with fluoxetine increased the blood GPX activity and serum TAS, and the combination of atorvastatin with paroxetine increased the blood GPX and serum GR activities, whereas the use of atorvastatin or other drugs separately did not significantly change the investigated oxidative stress parameters, suggesting that drug-drug interactions might have an effect on the oxidation-reduction balance and increase the antioxidant status, therefore resulting in oxidative stress-related toxicity (Herbet, Gawronska-Grzywacz, Izdebska, & Piatkowska-Chmiel, 2016).

The co-administration of simvastatin and *Crotalus durissus terrificus* venom (*vCdt*) led to renal oxidative stress and protein increase in envenomed patients while mitigating uricosuria, which altered urinary creatinine and urea, membranal protein in the cortex and medulla, plasma neutral and dipeptidyl IV Aps, and most of the renal APs in nonenvenomed patients, and also exacerbated hypercreatinemia, which limits its use in antivenom therapy (Yamasaki, Villarroel, Barone, Zambotti-Villela, & Silveira, 2008). Strikingly, simvastatin and atorvastatin had a toxic effect to prevent dopaminergic cell death in the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine mouse model of Parkinson's disease (Kreisler et al., 2007). Lovastatin did not inhibit palmitate-induced apoptosis in cardiomyocytes, but rather induced significant apoptosis itself; the combination of lovastatin palmitate increased the level of apoptosis to one that was equal to the sum of palmitate alone and lovastatin alone (Kong & Rabkin, 2002). ATV, at the highest dose used, induced hepatic lipid peroxidation and injury, suggesting a role for oxidative stress in ATV-induced hepatotoxicity.

8.4. No interaction with statins

Additionally, the clinical use of statins in combination with certain drugs does not reduce the efficacy of statins or their toxic effects. As reported, the choline salt of fenofibric acid, ABT-335, had no clinically significant pharmacokinetic interaction with rosuvastatin (Zhu et al., 2009), nor did the oral direct Factor Xa inhibitor, rivaroxaban, with atorvastatin (Kubitza, Becka, Roth, & Mueck, 2012). Aleglitazar, a balanced PPARalpha/gamma agonist, has no clinically relevant pharmacokinetic interaction with high-dose atorvastatin or rosuvastatin (Foley-Comer, Young, Russell-Yarde, & Jordan, 2011). As an orally active, potent inhibitor of the cholesteryl ester transfer protein for the treatment of dyslipidaemia, anacetrapib has been documented to possess no clinically meaningful effect on the pharmacokinetic parameters of simvastatin (Krishna et al., 2009).

There is no evidence for the need to avoid the co-prescription of various statins and several kinds of antibiotics with an increased risk of statin-induced adverse drug reactions (Settergren et al., 2013). Although there is a small pharmacokinetic drug interaction between extended-release niacin and ezetimibe/simvastatin, the concomitant use of them was mentioned to be appropriately monitored, especially during the niacin titration period (Kosoglou et al., 2011). In a study to reveal the sacubitril/valsartan (LCZ696), approved for the treatment of heart failure patients with co-medication of simvastatin, it was documented that LCZ696 and simvastatin (Ayalasomayajula et al., 2016) or atorvastatin (Ayalasomayajula et al., 2017) were generally well-tolerated when administered alone or in combination. The previous study concluded that the co-administration of fluvastatin and clopidogrel has no clinically relevant effect on fluvastatin pharmacokinetics (Ayalasomayajula et al., 2007).

As an orally active, potent, and selective inhibitor of dipeptidyl peptidase IV (DPP-4), vildagliptin had no effects on the pharmacokinetics of simvastatin, and its major active metabolite, simvastatin β-hydroxy acid, also exhibited no effects when vildagliptin and simvastatin were co-administered (Ayalasomayajula et al., 2007). Similarly, raltegravir, an HIV-integrase inhibitor, showed no clinically relevant effect on the pharmacokinetics of atorvastatin (Blonk et al., 2015). This study also confirmed that rivaroxaban does not interact with the substrates for permeability, either (P)-glycoprotein alone (digoxin) or P-glycoprotein and cytochrome P(450) (CYP)3A4 (atorvastatin) (Kubitza et al., 2012). A recent study revealed that there was no potential DDI between telmisartan and pitavastatin (Coss, Jones, & Dalton, 2016).

Enobosarm, known as a first in class selective androgen receptor modulator, has been documented to show no effect on the pharmacokinetics of rosuvastatin (Coss et al., 2016). Canagliflozin does not show clinically relevant drug interactions with simvastatin (Devineni & Polidori, 2015). The safety and tolerability of pitavastatin is not affected by co-administration with itraconazole, indicating that pitavastatin is not a CYP3A4 substrate in humans (Nakagawa, Gosho, Inazu, & Hounslow, 2013). Setipiprant has little impact on simvastatin pharmacokinetics, because it does not modulate CYP3A4 in a clinically relevant manner (Gehin et al., 2015). Piragliatin is reported to have no clinically relevant effect on the pharmacokinetics of simvastatin, even though

they are CYP3A substrates (Georgy, Zhai, Liang, Boldrin, & Zhi, 2016). Idelalisib, a potent phosphatidylinositol-3-kinase delta (PI3Kdelta) inhibitor, is metabolized to a lesser extent by CYP3A, whereas both valsartan, an angiotensin-receptor blocker, and fimasartan, an angiotensin II type 1 (AT1) receptor blocker, did not affect rosuvastatin pharmacokinetics (Jin et al., 2015; Jung et al., 2015; Kang et al., 2016).

Doravirine, a nonnucleoside reverse transcriptase inhibitor, has been reported to have no clinically relevant effect on atorvastatin pharmacokinetics in healthy subjects (Khalilieh et al., 2017). Additionally, compared with simvastatin alone, a single-dose simvastatin administration seven days after a single-dose sarilumab administration in patients with rheumatoid arthritis (RA) resulted in reduced simvastatin and β-hydroxy-simvastatin acid exposure in plasma (Lee et al., 2017). Eslicarbazepine decreases plasma exposure of simvastatin in a dose-dependent fashion (Bialer & Soares da Silva, 2012).

However, due to individual differences and a variety of unknown factors, care should be taken when using the above-mentioned drugs together with statins, as consideration needs to be placed on metabolism-related gene polymorphism associated with statins.

9. Conclusions

Statins are widely used as anti-hyperlipidemic agents worldwide, and are also potent drugs used as lipid-lowering agents in cardiovascular diseases. However, side effects such as muscle toxicity, hepatotoxicity and nephrotoxicity caused by statins alone or in combination with other drugs have been widely reported. This review shows that oxidative stress imbalance and statin metabolism abnormality are partial mechanisms of statin-induced toxicity. Statins can induce ROS production, mediate lipids damage, DNA damage, protein damage and other oxidative damage, resulting in cell antioxidant imbalance, mitochondrial membrane potential imbalance, activation of some oxidative stress signal pathways, which leads to oxidative stress and cell damage. It is worth noting that pravastatin, rosuvastatin and pitavastatin may be less prone to produce myotoxicity, hepatotoxicity and nephrotoxicity, than simvastatin, atorvastatin, fluvastatin, cerivastatin and lovastatin by oxidative stress. Interestingly, the adverse effects induced by statins show organ specific, such as myopathy and liver adverse reactions which occur mostly in patients with multiple diseases and/or multiple drugs. Therefore, on the one hand, in order to avoid statin-induced the adverse effect, it is necessary to require candid patient counseling, shared decision-making, eliminating contributing factors, careful clinical assessment and the use of a myalgia index score, and isolating potential muscle-related adverse events by gradually reintroducing drug therapy with the utilization of intermittent dosing of lipid altering agents. On the other hand, statins combined with other drugs such as diazepam or fluoxetine (Table 3) may cause some adverse effect, which will provide important guidance for the use of statins. In all, this will provide an important reference for screening and developing antioxidant products or reagents.

The common adverse reactions of statins are closely related to the dosage of statins. It is necessary to be vigilant against myopathy and liver adverse reactions (Du Souich et al., 2017). Statins are used to treat cardiovascular diseases and can cause side effects even in the normal dose range (Fig. 1). In addition, taking high-dose or long-term low doses of these drugs can also cause some organ toxicity (Backes et al., 2017). Interestingly, the side effects of drugs are also related to the patient's physical condition (Profumo et al., 2014). Therefore, it seemed that the side effects of statins are not a dose-dependent increase.

Importantly, abnormal drug metabolism is closely related to oxidative stress, because drug metabolism may produce a large number of free radicals, resulting in imbalance in cell redox. Therefore, abnormal drug metabolism may be the source of side effects of statins. In addition, other drugs may inhibit or accelerate the metabolism of statins by transporters, liver and intestinal metabolic enzymes, thereby increasing the exposure of drugs or metabolites in organs or blood. Interestingly, genetic polymorphisms affect the pharmacokinetics and pharmacodynamics of statins, thereby affecting the efficacy of statins. It is worth noting that the combination of other drugs and statins may also lead to toxic and side effects, which will provide a basis for statins use. Constructively, organ-specific toxicity and toxicity mechanism of statins metabolic abnormalities will provide important value for the fundamental treatment and prevention of statins side effects, and provide some warning and instructive value for the use of statins.

Furthermore, the nuclear encoded genes essential for synthesis of the electron transport chain complexes in mitochondria require more attention during statin-induced ROS generation, oxidative stress, and toxicities. Polymorphisms within these nuclear encoded genes are being increasingly implicated in statin-induced toxicities. A previous study revealed that the phenotype associated with single nucleotide polymorphisms (SNPs) in the human Elongation Factor Gene (EF-G) 2mt gene might be a pharmacogenetic candidate gene for statin toxicity. Therefore, it has been suggested that these SNPs may be the obvious markers to distinguish whether the patient showed side effects after they were exposed to the statins by checking these gene sequences using the advanced sequencing technology. However, future studies should be carried out to reveal the relationship between the SNPs with statin-induced toxicities.

The combination of various kinds of drugs generally used in clinical practices, and therefore, the combined effects of statins with other drugs are worthy of further investigations. Long-term polypharmacotherapy, such as the combination of statins and citalopram, fluoxetine, amitriptyline, or paroxetine, has been suggested to cause drug-induced oxidative stress. Additionally, the synergistic hepatotoxicity observed in clinical settings during therapy with the combination of statin and fibrate shows that the hepatotoxic actions of lipophilic statins were augmented by fenofibrate. Considering that oxidative stress might be one potential toxic mechanism for the various toxicities induced by statins, it has been suggested that the reason for the imbalance between oxidation and reduction, and the increased antioxidant status, needs further investigation, as well as the role of the metabolism of statins during the combined therapy.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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