REVIEW

Journal of Cachexia, Sarcopenia and Muscle 2017; **8**: 19–24
Published online 22 September 2016 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.12140

Curcumin: An effective adjunct in patients with statin-associated muscle symptoms?

Amirhossein Sahebkar[1,2*†], Nikou Saboni[3*†], Matteo Pirro[4] & Maciej Banach[5]

[1]*Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad 9177948564, Iran;* [2]*Metabolic Research Centre, Royal Perth Hospital, School of Medicine and Pharmacology, University of Western Australia, Perth, Australia;* [3]*Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad 9177948564, Iran;* [4]*Unit of Internal Medicine, Angiology and Arteriosclerosis Diseases, Department of Medicine, University of Perugia, Perugia, Italy;* [5]*Department of Hypertension, Chair of Nephrology and Hypertension, Medical University of Lodz, Łódź, Poland*

Abstract

In spite of the unequivocal efficacy of statins in reducing primary and secondary cardiovascular events, the use of these drugs in a considerable number of patients is limited because of statin intolerance, mainly statin-associated muscle symptoms (SAMS). SAMS encompass a broad spectrum of clinical presentations, including mild muscular aching and other types of myalgias, myopathy with the significant elevation of creatine kinase, and the rare but life-threatening rhabdomyolysis. Among several pathophysiologic mechanisms of SAMS, mitochondrial dysfunction is thought to be one of the main one. Curcumin is the polyphenolic ingredient of *Curcuma longa* L., which has various pharmacological properties against a vast range of diseases. Curcumin has several mechanisms of actions relevant to the treatment of SAMS. These effects include the capacity to prevent and reduce delayed onset muscle soreness by blocking the nuclear factor inflammatory pathway, attenuation of muscular atrophy, enhancement of muscle fibre regeneration following injury, and analgesic and antioxidant effects. Curcumin can also increase the levels of cyclic adenosine monophosphate, which leads to an increase in the number of mitochondrial DNA duplicates in skeletal muscle cells. Finally, owing to its essential lipid-modifying properties, curcumin might serve as an adjunct to statin therapy in patients with SAMS, allowing for effective lowering of low-density lipoprotein cholesterol and possibly for statin dose reduction. Owing to the paucity of effective treatments, and the safety of curcumin in clinical practice, proof-of-concept trials are recommended to assess the potential benefit of this phytochemical in the treatment of SAMS.

Keywords Statin; Myopathy; Curcumin; Myalgia; Mitochondria; Statin intolerance

Received: 19 May 2016; Accepted: 12 July 2016
**Correspondence to: Amirhossein Sahebkar, PharmD, PhD, Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, PO Box: 91779-48564, Iran. Tel: 985118002288; Fax: 985118002287, Email: sahebkara@mums.ac.ir; amir_saheb2000@yahoo.com; amirhossein.sahebkar@uwa.edu.au; Nikou Saboni, MD, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, PO Box: 91779-48564, Iran. Tel: 985118002288; Fax: 985118002287.*
†These authors have contributed equally to this manuscipt.

Statins and their side effects

Statins are the cornerstone of pharmacotherapy for dyslipidemia, and their efficacy in both primary and secondary prevention of atherosclerotic cardiovascular disease is well established.[1] There are, however, unfavourable side effects to statin therapy, sometimes leading to statin intolerance with muscular symptoms, which are the most common and of critical importance.[2] Statin-associated muscle symptoms (SAMS) comprise a diverse spectrum and encompass heterogeneous clinical presentations.[3,4] These presentations include: (i) mild forms of muscle weakness and aching, with the prevalence of even up to 29%; (ii) other forms of myopathy and myositis accompanied by the rise of creatine kinase (CK)[5] to more than 10 times the upper limit of normal, with the prevalence about 1/10 000 to 1/1000 of the consuming population per year[6]; and (iii) life-threatening rhabdomyolysis, which is fortunately very rare.[5] From this point of view, SAMS are one of the major reasons for drug non-adherence and discontinuation in even 75% of the statin users during the first 2 years of treatment.[7,8] Nonetheless, the diagnosis of SAMS is not simple because the symptoms are subjective and difficult to be judged, and also there is no gold standard diagnostic test currently available.[9] Additionally, in a relatively large percentage of patients on statin therapy we might observe the so-called *nocebo effect*, when the patients expect to have statin-associated symptoms,

what might be excluded after careful interview and physical examination in selected cases.[10] Finally, a relevant 22% of patients reporting statin-associated symptoms do not confirm their persistence after statin re-challenge, whereas up to 7% of patients still report adverse effects after placebo administration.[11] An overview of the scientific knowledge on the pathophysiology of SAMS, as well as guidance for clinicians on their management, has been recently issued.[3,4] Occurrence of SAMS is dependent on the potency, metabolism, and dose of different statins, and their interactions with other drugs.[12,13] Furthermore, patients' demographics, such as age, gender, co-morbidities (e.g. diabetes, HIV infection, severe renal failure, hypothyroidism, hepatic dysfunction, and undergoing surgery), genetic susceptibility, and race, have been proposed as other predisposing factors for SAMS.[13–17] Several pathophysiologic mechanisms have been suggested to underlie SAMS. Among these mechanisms, mitochondrial dysfunction has gained widespread attention as the main player in the etiopathogenesis of SAMS. A number of studies have indicated that physical exercise can lead to disturbances in mitochondrial function in patients on statins.[18] Analyses of muscle biopsies taken from patients with SAMS and normal CK levels have revealed mitochondrial dysfunction in muscle fibres.[19,20] On the other hand, histological findings of patients with SAMS and abnormally high CK levels showed no abnormalities in the configuration of muscle fibres.[21] In addition, mitochondrial damage by statins appears to be drug specific as muscle biopsies taken from patients treated with simvastatin 80 mg daily or atorvastatin 40 mg daily for 8 weeks showed a decline in the number of mitochondrial DNA duplicates in the simvastatin-treated group but not in the atorvastatin-treated group.[22]

In spite of its clinical importance, pharmacotherapy options for patients with SAMS are very limited. There is evidence showing that low vitamin D levels are associated with myalgia in patients on statin therapy[23]; in addition, a role for vitamin D supplementation in resolving SAMS has been proposed.[24] Also, statin-induced depletion in coenzyme-Q_{10} (CoQ_{10})[25] has been suggested as a causal mechanism for SAMS[18,26] and prompted several investigations on the therapeutic role of CoQ_{10}.[27–30] However, contrariwise, the results of randomized controlled trials (RCTs) have been highly ambiguous, and a recent meta-analysis concluded that treatment with CoQ_{10} does not play a significant role in lessening SAMS.[31]

Curcumin in patients with statin-associated muscle symptoms

Curcumin is a natural dietary polyphenol, extracted from *Curcuma longa* L., which has been extensively studied for the treatment of various diseases owing to its numerous pharmacological properties[32] including, but not limited to, antioxidant,[33] anti-inflammatory,[34–38] immunomodulatory,[39] anti-cancer,[40] anti-pruritic,[41] antidepressant,[42,43] and anti-arthritic[44] effects. Excessive physical pressure on skeletal muscles triggers an inflammatory cascade and rise in reactive oxygen species, which are all boosted up *via* nuclear factor kappa-B (NF-κB) pathway.[45–47] Activation of the inflammatory pathway results in delayed onset muscle soreness (DOMS).[48] One of the documented properties of curcumin, according to studies carried out in both humans and animals, is that it can prevent and reduce DOMS, which happens after unusual forceful exercise.[49–52] In a *proof-of-concept* study in C57BL/6 male mice (4–6 weeks old) with freeze injury in their masseter muscles, intraperitoneal injection of 20 μg/kg curcumin for 10 days caused regeneration of muscle fibres whereas the control group showed no signs of forming rejuvenated muscle fibres.[53] The efficacy of curcumin in diminishing DOMS has also been verified in humans, and attributed to the blockade of the NF-κB inflammatory pathway,[54,55] which consequently lowers the level of inflammatory cytokines such as interleukin 6 and tumour necrosis factor-α.[56,57] A study by Nicol *et al.* showed that oral use of curcumin (2.5 g twice daily) for 5 days can alleviate DOMS symptoms and heal muscular injuries in humans.[58] NF-κB is also involved in skeletal muscle atrophy during catabolism.[59] Therefore, inhibition of the NF-κB pathway by curcumin, which is a well-established effect of this phytochemical,[54,55] could justify the potential benefit of curcumin supplementation to attenuate muscular atrophy in catabolic conditions.[60] Moreover, curcumin can compensate for traumatized muscle fibres owing to its inflammatory suppressive features.[61]

Notably, the analgesic effect of curcumin has been shown in several RCTs and in different painful conditions including osteoarthritis,[44] rheumatoid arthritis,[62] fibromyalgia,[63] gout,[63] burning,[64] and post-surgical state.[65] Findings of a recent systematic review and meta-analysis of these RCTs implied a significant pain-relieving effect of curcumin that appeared to be independent of dose and duration of supplementation with this phytochemical.[66] Trials in osteoarthritis have shown that addition of curcumin to the treatment regimen leads to either reduction or discontinuation of the use of analgesics such as non-steroidal anti-inflammatory drugs.[67] The analgesic effects of curcumin, which can be favourable for the management of statin-induced myalgia, are thought to be because of the inhibition of cyclooxygenase-2 and prostaglandin E_2, stimulation of cortisol release, and enhancement of substance P depletion from nerve endings.[68,69]

As mentioned above, mitochondrial dysfunction has been suggested to play a key role in the development of SAMS. Mitochondrial activities are subject to oxidative stress[70–72] and are related to nuclear factor erythroid-2-related factor 2,[73–75] which acts as one of the key regulators of biological antioxidant defence.[76] Curcumin is a strong antioxidant that is known to counterbalance oxidative stress through several mechanisms including scavenging free radicals, chelating the

DOI: 10.1002/jcsm.12140

Table 1 Summary of studies investigating the impact of curcumin treatment in models of muscular injury

Reference	Model	Curcumin dose	Type of injury	Duration of treatment	Route of administration	Main result
[53]	C57BL/6 mice	20 μg/kg/day	Freeze injury in masseter muscle	Single dose	Intraperitoneal injection	Regeneration of muscle fibres
[83]	C57BL/6 mice	1500 mg/kg/day	Muscular atrophy because of streptozotocin-induced diabetes	2 weeks	Oral	Improvement of muscular atrophy
[84]	C57BL/6 mice	5% of daily diet	—	21 days	Oral	Reduced mitochondrial apoptosis No change in mitochondrial biogenesis adaptations in muscles
[85]	Wistar rats	50–100 mg/kg/day	Endurance exercise training	28 days	Intraperitoneal injection	Increase in cyclic adenosine monophosphate level and mitochondrial biogenesis in skeletal muscles
[50]	Randomized controlled trial	200 mg twice daily	Downhill running test	4 days	Oral	Reduced muscle pain and significant reduction in muscle injury in the lower limb
[58]	Randomized controlled trial	2.5 g twice daily	Eccentric single-leg press exercise	5 days	Oral	Reduced muscular pain

metal ions, up-regulation of antioxidant enzymes, and enhancement of nuclear factor erythroid-2-related factor 2 pathway.[77,78] The latter is a chief pathway through which many of the antioxidant enzymes such as superoxide dismutase, catalase, glutathione reductase, and glutathione peroxidase are up-regulated.[79]

It is known that cyclic adenosine monophosphate is dynamically involved in muscle development, adaptation, and regeneration,[80] and among different types of polyphenols, curcumin is known to be one of the most effectual ones in increasing the level of cyclic adenosine monophosphate.[81,82] Significant improvement in muscular atrophy in C57BL/6 mice suffering from streptozotocin-induced diabetes has been reported following supplementation with curcumin (1500 mg/kg/day) for a period of two weeks.[83] In another experimental study on old C57BL/6 mice (24 months), although curcumin supplementation (5% of diet) for a period of 21 days did not change mitochondrial biogenesis adaptations in muscles, it reduced mitochondrial apoptotic proteins compared with the control group.[84] While the above-mentioned findings are encouraging, more studies are still needed to be carried out in order to clarify the impact of curcumin supplementation on mitochondrial biogenesis and function in skeletal muscle fibres.[85]

Curcumin supplementation is not only believed to attenuate SAMS, but also may enhance the lipid-modifying properties of statins, and thus reduce the need for statin dose escalation (and in the consequence might allow statin dose reduction without significant risk increase), which is itself a contributing factor to myalgia and myopathies.[86] Several lines of experimental and clinical evidence have shown that curcumin can improve lipid profile by decreasing serum levels of LDL-C (by 15–20 mg/dL), total cholesterol (by about 10 mg/dL), and triglycerides (even by over 60 mg/dL in patients with metabolic syndrome).[87–89] At the molecular level, these lipid-regulating effects have been well characterized. Curcumin can down-regulate 3-hydroxy-3-methylglutaryl-coenzyme A reductase, sterol regulatory element-binding protein-1, fatty acid synthase, and apolipoprotein B100, and enhance the expression and/or activity of LDL receptor, peroxisome proliferator-activated receptor-α, and AMP-activated protein kinase as key targets involved in the regulation of lipid homeostasis.[88,90,91] Among the lipid-modifying effects of curcumin, triglyceride-lowering activity is of particular importance as statin therapy has moderate effect in correcting hypertriglyceridemia, and hypertriglyceridemia in statin-treated subjects has been suggested as an important cause of residual cardiovascular risk despite attainment of therapeutic LDL goals.[92]

Last, but not the least notable advantage of curcumin is its safety. Numerous trials have shown that curcumin is well tolerated and does not cause any serious side-effects even at high doses.[93,94] However, the safety at high-dose still needs to be affirmed in long-term uses,[87] as well as its safety in combination with statins (Table 1).

Conclusions

In conclusion, enhancement of mitochondrial biogenesis and function, along with analgesic, anti-inflammatory, antioxidant, and lipid-modifying properties jointly supports the potential benefit of curcumin supplementation as an adjunct to statin therapy in patients with SAMS, as well as in the individuals with a residual cardiovascular risk. Because accumulating clinical data has supported the safety of this polyphenol, *proof-of-concept* RCTs are recommended to unlock the potential of curcumin as a preventive and/or therapeutic strategy for SAMS.

Acknowledgements

The authors certify that they comply with the ethical guidelines for publishing in the *Journal of Cachexia, Sarcopenia and Muscle*, update 2015.[95]

Conflict of interests

The authors have no competing interests to declare.

References

1. Hobbs FR, Banach M, Mikhailidis DP, Malhotra A, Capewell S. Is statin-modified reduction in lipids the most important preventive therapy for cardiovascular disease? A pro/con debate. *BMC Med* 2016;**14**:1–8.
2. Abdulrazaq M, Hamdan F, Al-Tameemi W. Electrophysiologic and clinico-pathologic characteristics of statin-induced muscle injury. *Iran J Basic Med Sci* 2015;**18**:737.
3. Banach M, Rizzo M, Toth PP, Farnier M, Davidson MH, Al-Rasadi K, *et al*. Statin intolerance—an attempt at a unified definition. Position paper from an International Lipid Expert Panel. *Arch Med Sci* 2015;**11**:1–23.
4. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, *et al*. Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J* 2015;**36**:1012–22.
5. Alfirevic A, Neely D, Armitage J, Chinoy H, Cooper RG, Laaksonen R, *et al*. Phenotype standardization for statin-induced myotoxicity. *Clin Pharmacol Ther* 2014;**96**:470–476.
6. Law M, Rudnicka AR. Statin safety: a systematic review. *Am J Cardiol* 2006;**97**: S52–S60.
7. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users. *J Clin Lipidol* 2012;**6**:208–215.
8. Chodick G, Shalev V, Gerber Y, Heymann AD, Silber H, Simah V, *et al*. Long-term persistence with statin treatment in a not-for-profit health maintenance organization: a population-based retrospective cohort study in Israel. *Clin Ther* 2008;**30**:2167–2179.
9. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA. An assessment by the statin muscle safety task force: 2014 update. *J Clin Lipidol* 2014;**8**:S58–S71.
10. Banach M, Aronow WS, Serban C, Sahabkar A, Rysz J, Voroneanu L. Lipids, blood pressure and kidney update 2014. *Pharmacol Res* 2015;**95–96**:111–125.
11. Moriarty PM, Thompson PD, Cannon CP, Guyton JR, Bergeron J, Zieve FJ, *et al*. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: the ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol* 2015;**9**:758–69.
12. Hoffman KB, Kraus C, Dimbil M, Golomb BA. A survey of the FDA's AERS database regarding muscle and tendon adverse events linked to the statin drug class. *PLoS One* 2012;**7**:e42866.
13. Abd TT, Jacobson TA. Statin-induced myopathy: a review and update. *Expert Opin Drug Saf* 2011;**10**:373–387.
14. Taha DA, De Moor CH, Barrett DA, Gershkovich P. Translational insight into statin-induced muscle toxicity: from cell culture to clinical studies. *Transl Res* 2014;**164**:85–109.
15. Mancini GJ, Tashakkor AY, Baker S, Bergeron J, Fitchett D, Frohlich J, *et al*. Diagnosis, prevention, and management of statin adverse effects and intolerance: Canadian Working Group Consensus update. *Can J Cardiol* 2013;**29**:1553–1568.
16. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, *et al*. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *Circulation* 2007;**116**:1971–96.
17. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. *Cardiovasc Drugs Ther* 2005;**19**:403–414.
18. Marcoff L, Thompson PD. The role of coenzyme Q10 in statin-associated myopathy: a systematic review. *J Am Coll Cardiol* 2007;**49**:2231–2237.
19. Phillips PS, Haas RH, Bannykh S, Hathaway S, Gray NL, Kimura BJ, *et al*. Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med* 2002;**137**:581–585.
20. Mohaupt MG, Karas RH, Babiychuk EB, Sanchez-Freire V, Monastyrskaya K, Iyer L, *et al*. Association between statin-associated myopathy and skeletal muscle damage. *Can Med Assoc J* 2009;**181**: E11–E18.
21. Hanai J-i, Cao P, Tanksale P, Imamura S, Koshimizu E, Zhao J, *et al*. The muscle-specific ubiquitin ligase atrogin-1/MAFbx mediates statin-induced muscle toxicity. *J Clin Invest* 2007;**117**:3940–3951.
22. Schick B, Laaksonen R, Frohlich J, Päivä H, Lehtimäki T, Humphries K, *et al*. Decreased skeletal muscle mitochondrial DNA in patients treated with high-dose simvastatin. *Clin Pharmacol Ther* 2007;**81**:650–653.
23. Michalska-Kasiczak M, Sahebkar A, Mikhailidis DP, Rysz J, Muntner P, Toth PP, *et al*. Analysis of vitamin D levels in patients with and without statin-associated myalgia—a systematic review and meta-analysis of 7 studies with 2420 patients. *Int J Cardiol* 2015;**178**:111–6.
24. Khayznikov M, Hemachrandra K, Pandit R, Kumar A, Wang P, Glueck CJ. Statin intolerance because of myalgia, myositis, myopathy, or myonecrosis can in most cases be safely resolved by vitamin D supplementation. *N Am J Med Sci* 2015;**7**:86–93.
25. Banach M, Serban C, Ursoniu S, Rysz J, Muntner P, Toth PP, *et al*. Statin therapy and plasma coenzyme Q10 concentrations—a systematic review and meta-analysis of placebo-controlled trials. *Pharmacol Res* 2015;**99**:329–36.
26. Sirvent P, Mercier J, Lacampagne A. New insights into mechanisms of statin-associated myotoxicity. *Curr Opin Pharmacol* 2008;**8**:333–338.
27. Silver MA, Langsjoen PH, Szabo S, Patil H, Zelinger A. Effect of atorvastatin on left ventricular diastolic function and ability of coenzyme Q10 to reverse that dysfunction. *Am J Cardiol* 2004;**94**:1306–10.
28. Miyake Y, Shouzu A, Nishikawa M, Yonemoto T, Shimizu H, Omoto S, *et al*. Effect of treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on serum coenzyme Q10 in diabetic patients. *Arzneimittelforschung* 1999;**49**:324–329.
29. Folkers K, Langsjoen P, Willis R, Richardson P, Xia L-J, Ye C-Q, *et al*. Lovastatin decreases coenzyme Q levels in humans. *Proc Natl Acad Sci* 1990;**87**:8931–8934.
30. Bargossi A, Grossi G, Fiorella P, Gaddi A, Di Giulio R, Battino M. Exogenous CoQ 10 supplementation prevents plasma ubiquinone reduction induced by HMG-CoA reductase inhibitors. *Mol Aspects Med* 1994;**15**:s187–s193.

31. Serban C, Sahebkar A, Antal D, Ursoniu S, Banach M. Effects of supplementation with green tea catechins on plasma C-reactive protein concentrations: a systematic review and meta-analysis of randomized controlled trials. *Nutrition* 2015;**31**:1061–71.
32. Epstein J, Sanderson IR, MacDonald TT. Curcumin as a therapeutic agent: the evidence from in vitro, animal and human studies. *Br J Nutr* 2010;**103**:1545–1557.
33. Panahi Y, Ghanei M, Hajhashemi A, Sahebkar A. Effects of curcuminoids–piperine combination on systemic oxidative stress, clinical symptoms and quality of life in subjects with chronic pulmonary complications due to sulfur mustard: a randomized controlled trial. *J Diet Suppl* 2016;**13**:93–105.
34. Sahebkar A. Are curcuminoids effective C-reactive protein-lowering agents in clinical practice? Evidence from a meta-analysis. *Phytother Res* 2014;**28**:633–642.
35. Panahi Y, Sahebkar A, Parvin S, Saadat A. A randomized controlled trial on the anti-inflammatory effects of curcumin in patients with chronic sulphur mustard-induced cutaneous complications. *Ann Clin Biochem* 2012;**49**:580–588.
36. Panahi Y, Saadat A, Beiraghdar F, Sahebkar A. Adjuvant therapy with bioavailability-boosted curcuminoids suppresses systemic inflammation and improves quality of life in patients with solid tumors: a randomized double-blind placebo-controlled trial. *Phytother Res* 2014;**28**:1461–1467.
37. Panahi Y, Hosseini MS, Khalili N, Naimi E, Majeed M, Sahebkar A. Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: a randomized controlled trial and an updated meta-analysis. *Clin Nutr* 2015;**34**:1101–1108.
38. Panahi Y, Ghanei M, Bashiri S, Hajihashemi A, Sahebkar A. Short-term curcuminoid supplementation for chronic pulmonary complications due to sulfur mustard intoxication: positive results of a randomized double-blind placebo-controlled trial. *Drug Res* 2015;**65**:567–573.
39. Srivastava RM, Singh S, Dubey SK, Misra K, Khar A. Immunomodulatory and therapeutic activity of curcumin. *Int Immunopharmacol* 2011;**11**:331–341.
40. Shanmugam MK, Rane G, Kanchi MM, Arfuso F, Chinnathambi A, Zayed M, *et al*. The multifaceted role of curcumin in cancer prevention and treatment. *Molecules* 2015;**20**:2728–2769.
41. Panahi Y, Sahebkar A, Amiri M, Davoudi SM, Beiraghdar F, Hoseininejad SL, *et al*. Improvement of sulphur mustard-induced chronic pruritus, quality of life and antioxidant status by curcumin: results of a randomised, double-blind, placebo-controlled trial. *Br J Nutr* 2012;**108**:1272–1279.
42. Panahi Y, Badeli R, Karami GR, Sahebkar A. Investigation of the efficacy of adjunctive therapy with bioavailability-boosted curcuminoids in major depressive disorder. *Phytother Res* 2015;**29**:17–21.
43. Esmaily H, Sahebkar A, Iranshahi M, Ganjali S, Mohammadi A, Ferns G, *et al*. An investigation of the effects of curcumin on anxiety and depression in obese individuals: a randomized controlled trial. *Chin J Integr Med* 2015;**21**:332–338.
44. Panahi Y, Rahimnia AR, Sharafi M, Alishiri G, Saburi A, Sahebkar A. Curcuminoid treatment for knee osteoarthritis: a randomized double-blind placebo-controlled trial. *Phytother Res* 2014;**28**:1625–1631.
45. Tauler P, Aguiló A, Cases N, Sureda A, Gimenez F, Villa G, *et al*. Acute phase immune response to exercise coexists with decreased neutrophil antioxidant enzyme defences. *Free Radic Res* 2002;**36**:1101–1107.
46. Pizza FX, Peterson JM, Baas JH, Koh TJ. Neutrophils contribute to muscle injury and impair its resolution after lengthening contractions in mice. *J Physiol* 2005;**562**:899–913.
47. Aoi W, Naito Y, Takanami Y, Kawai Y, Sakuma K, Ichikawa H, *et al*. Oxidative stress and delayed-onset muscle damage after exercise. *Free Radic Biol Med* 2004;**37**:480–487.
48. Ferrer MD, Tauler P, Sureda A, Pujol P, Drobnic F, Tur JA, *et al*. A soccer match's ability to enhance lymphocyte capability to produce ROS and induce oxidative damage. *Int J Sport Nutr Exerc Metab* 2009;**19**:243–58.
49. Enns DL, Tiidus PM. The influence of estrogen on skeletal muscle. *Sports Med* 2010;**40**:41–58.
50. Drobnic F, Riera J, Appendino G, Togni S, Franceschi F, Valle X, *et al*. Reduction of delayed onset muscle soreness by a novel curcumin delivery system (Meriva®): a randomised, placebo-controlled trial. *J Int Soc Sports Nutr* 2014;**11**:10.1186.
51. Dieli-Conwright CM, Spektor TM, Rice JC, Schroeder ET. Hormone therapy attenuates exercise-induced skeletal muscle damage in postmenopausal women. *J Appl Physiol* 2009;**107**:853–858.
52. Davis JM, Murphy EA, Carmichael MD, Zielinski MR, Groschwitz CM, Brown AS, *et al*. Curcumin effects on inflammation and performance recovery following eccentric exercise-induced muscle damage. *Am J Physiol Regul Integr Comp Physiol* 2007;**292**:R2168–R2173.
53. Thaloor D, Miller KJ, Gephart J, Mitchell PO, Pavlath GK. Systemic administration of the NF-kB inhibitor curcumin stimulates muscle regeneration after traumatic injury. *Am J Physiol Cell Physiol* 1999;**277**: C320–C329.
54. Singh S, Aggarwal BB. Activation of transcription factor NF-kB is suppressed by curcumin (diferuloylmethane). *J Biol Chem* 1995;**270**:24995–25000.
55. Jobin C, Bradham CA, Russo MP, Juma B, Narula AS, Brenner DA, *et al*. Curcumin blocks cytokine-mediated NF-kB activation and proinflammatory gene expression by inhibiting inhibitory factor I-kB kinase activity. *J Immunol* 1999;**163**:3474–3483.
56. Cho JW, Lee KS, Kim CW. Curcumin attenuates the expression of IL-1beta, IL-6, and TNF-alpha as well as cyclin E in TNF-alpha-treated HaCaT cells; NF-kappaB and MAPKs as potential upstream targets. *Int J Mol Med* 2007;**19**:469–74.
57. Aggarwal S, Ichikawa H, Takada Y, Sandur SK, Shishodia S, Aggarwal BB. Curcumin (diferuloylmethane) down-regulates expression of cell proliferation and antiapoptotic and metastatic gene products through suppression of IkBα kinase and Akt activation. *Mol Pharmacol* 2006;**69**:195–206.
58. Nicol LM, Rowlands DS, Fazakerly R, Kellett J. Curcumin supplementation likely attenuates delayed onset muscle soreness (DOMS). *Eur J Appl Physiol* 2015;**115**:1769–1777.
59. Lecker SH, Goldberg AL, Mitch WE. Protein degradation by the ubiquitin–proteasome pathway in normal and disease states. *J Am Soc Nephrol* 2006;**17**:1807–1819.
60. Poylin V, Fareed MU, O'Neal P, Alamdari N, Reilly N, Menconi M, *et al*. The NF-. *Mediators Inflamm* 2008;**2008**.
61. Shehzad A, Lee YS. Molecular mechanisms of curcumin action: signal transduction. *Biofactors* 2013;**39**:27–36.
62. Chandran B, Goel A. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. *Phytother Res* 2012;**26**:1719–1725.
63. Appelboom T, MsciBiost CM. *Flexofytol, a Purified Curcumin Extract, in Fibromyalgia and Gout: A Retrospective Study*; 2013;**3**:104–107.
64. Cheppudira B, Fowler M, McGhee L, Greer A, Mares A, Petz L, *et al*. Curcumin: a novel therapeutic for burn pain and wound healing. *Expert Opin Investig Drugs* 2013;**22**:1295–303.
65. Agarwal KA, Tripathi C, Agarwal BB, Saluja S. Efficacy of turmeric (curcumin) in pain and postoperative fatigue after laparoscopic cholecystectomy: a double-blind, randomized placebo-controlled study. *Surg Endosc* 2011;**25**:3805–3810.
66. Broncel M, Gorzelak-Pabiś P, Sahebkar A, Serejko K, Ursoniu S, Rysz J, *et al*. Sleep changes following statin therapy: a systematic review and meta-analysis of randomized placebo-controlled polysomnographic trials. *Arch Med Sci* 2015;**11**:915–26.
67. Appelboom T, Maes N, Albert A. A new curcuma extract (Flexofytol®) in osteoarthritis: results from a Belgian real-life experience. *Open Rheumatol J* 2014;**8**:77.
68. Moini Zanjani T, Ameli H, Labibi F, Sedaghat K, Sabetkasaei M. The attenuation of pain behavior and serum COX-2 concentration by curcumin in a rat model of neuropathic pain. *Korean J Pain* 2014;**27**:246–252.
69. Enyeart JA, Liu H, Enyeart JJ. Curcumin inhibits bTREK-1 K+ channels and stimulates cortisol secretion from adrenocortical cells. *Biochem Biophys Res Commun* 2008;**370**:623–628.
70. Zúñiga-Toalá A, Zatarain-Barrón ZL, Hernández-Pando R, Negrette-Guzmán M, Huerta-Yepez S, Torres I, *et al*. Nordihydroguaiaretic acid induces Nrf2 nuclear translocation in vivo and attenuates

renal damage and apoptosis in the ischemia and reperfusion model. *Phytomedicine* 2013;**20**:775–779.
71. Tapia E, Soto V, Ortiz-Vega KM, Zarco-Márquez G, Molina-Jijón E, Cristóbal-García M, *et al*. Curcumin induces Nrf2 nuclear translocation and prevents glomerular hypertension, hyperfiltration, oxidant stress, and the decrease in antioxidant enzymes in 5/6 nephrectomized rats. *Oxid Med Cell Longev* 2012;**2012**.
72. Rojo AI, Medina-Campos ON, Rada P, Zúñiga-Toalá A, López-Gazcón A, Espada S, *et al*. Signaling pathways activated by the phytochemical nordihydroguaiaretic acid contribute to a Keap1-independent regulation of Nrf2 stability: role of glycogen synthase kinase-3. *Free Radic Biol Med* 2012;**52**:473–487.
73. Negrette-Guzmán M, Huerta-Yepez S, Tapia E, Pedraza-Chaverri J. Modulation of mitochondrial functions by the indirect antioxidant sulforaphane: a seemingly contradictory dual role and an integrative hypothesis. *Free Radic Biol Med* 2013;**65**:1078–1089.
74. Holmström KM, Baird L, Zhang Y, Hargreaves I, Chalasani A, Land JM, *et al*. Nrf2 impacts cellular bioenergetics by controlling substrate availability for mitochondrial respiration. *Biol Open* 2013;**2**:761–770.
75. Hayes JD, Dinkova-Kostova AT. The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. *Trends Biochem Sci* 2014;**39**:199–218.
76. Kansanen E, Jyrkkänen H-K, Levonen A-L. Activation of stress signaling pathways by electrophilic oxidized and nitrated lipids. *Free Radic Biol Med* 2012;**52**:973–982.
77. Derochette S, Franck T, Mouithys-Mickalad A, Ceusters J, Deby-Dupont G, Lejeune J-P, *et al*. Curcumin and resveratrol act by different ways on NADPH oxidase activity and reactive oxygen species produced by equine neutrophils. *Chem Biol Interact* 2013;**206**:186–193.
78. Ak T, Gülçin İ. Antioxidant and radical scavenging properties of curcumin. *Chem Biol Interact* 2008;**174**:27–37.
79. Panchal HD, Vranizan K, Lee CY, Ho J, Ngai J, Timiras PS. Early anti-oxidative and anti-proliferative curcumin effects on neuroglioma cells suggest therapeutic targets. *Neurochem Res* 2008;**33**:1701–1710.
80. Berdeaux R, Stewart R. cAMP signaling in skeletal muscle adaptation: hypertrophy, metabolism, and regeneration. *Am J Physiol Endocrinol Metab* 2012;**303**:E1–17.
81. Park S-J, Ahmad F, Philp A, Baar K, Williams T, Luo H, *et al*. Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting cAMP phosphodiesterases. *Cell* 2012;**148**:421–433.
82. Chowanadisai W, Bauerly KA, Tchaparian E, Wong A, Cortopassi GA, Rucker RB. Pyrroloquinoline quinone stimulates mitochondrial biogenesis through cAMP response element-binding protein phosphorylation and increased PGC-1α expression. *J Biol Chem* 2010;**285**:142–152.
83. Ono T, Takada S, Kinugawa S, Tsutsui H. Curcumin ameliorates skeletal muscle atrophy in type 1 diabetic mice by inhibiting protein ubiquitination. *Exp Physiol* 2015;**100**:1052–1063.
84. Wawrzyniak N, Duarte A, Nguyen L, Joseph A-M, Layne A, Criswell D, *et al*. Effect of short-term dietary curcumin supplementation on mitochondrial regulatory proteins in muscle and brown adipose tissue of aged mice (1159.4). *FASEB J* 2014;**28**:1159.4.
85. Hamidie RDR, Yamada T, Ishizawa R, Saito Y, Masuda K. Curcumin treatment enhances the effect of exercise on mitochondrial biogenesis in skeletal muscle by increasing cAMP levels. *Metabolism* 2015;**64**:1334–1347.
86. Ballantyne CM, Corsini A, Davidson MH, Holdaas H, Jacobson TA, Leitersdorf E, *et al*. Risk for myopathy with statin therapy in high-risk patients. *Arch Intern Med* 2003;**163**:553–564.
87. Sahebkar A. Why it is necessary to translate curcumin into clinical practice for the prevention and treatment of metabolic syndrome? *Biofactors* 2013;**39**:197–208.
88. Panahi Y, Khalili N, Hosseini MS, Abbasinazari M, Sahebkar A. Lipid-modifying effects of adjunctive therapy with curcuminoids–piperine combination in patients with metabolic syndrome: results of a randomized controlled trial. *Complement Ther Med* 2014;**22**:851–857.
89. Mohammadi A, Sahebkar A, Iranshahi M, Amini M, Khojasteh R, Ghayour-Mobarhan M, *et al*. Effects of supplementation with curcuminoids on dyslipidemia in obese patients: a randomized crossover trial. *Phytother Res* 2013;**27**:374–9.
90. Zingg JM, Hasan ST, Meydani M. Molecular mechanisms of hypolipidemic effects of curcumin. *Biofactors* 2013;**39**:101–121.
91. Sahebkar A. Curcuminoids for the management of hypertriglyceridaemia. *Nat Rev Cardiol* 2014;**11**:123–123.
92. Sahebkar A, Chew GT, Watts GF. New peroxisome proliferator-activated receptor agonists: potential treatments for atherogenic dyslipidemia and non-alcoholic fatty liver disease. *Expert Opin Pharmacother* 2014;**15**:493–503.
93. Eigner D, Scholz D. Ferula asa-foetida and *Curcuma longa* in traditional medical treatment and diet in Nepal. *J Ethnopharmacol* 1999;**67**:1–6.
94. Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: a component of tumeric (*Curcuma longa*). *J Altern Complement Med* 2003;**9**:161–168.
95. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2015. *J Cachexia Sarcopenia Muscle* 2015;**6**: 315–316.