Review

The Protective Effect of Bee Venom on Fibrosis Causing Inflammatory Diseases

Woo-Ram Lee 1, Sok Cheon Pak 2 and Kwan-Kyu Park 1,*

1 Department of Pathology, College of Medicine, Catholic University of Daegu, 3056-6, Daemyung-4-Dong, Nam-gu, Daegu 705-718, Korea; E-Mail: woolamee@cu.ac.kr
2 School of Biomedical Sciences, Charles Sturt University, Panorama Avenue, Bathurst, NSW 2795, Australia; E-Mail: spak@csu.edu.au

* Author to whom correspondence should be addressed; E-Mail: kkpark@cu.ac.kr; Tel.: +82-53-650-4149; Fax: +82-53-650-4843.

Academic Editor: Ren Lai

Received: 14 August 2015 / Accepted: 5 November 2015 / Published: 16 November 2015

Abstract: Bee venom therapy is a treatment modality that may be thousands of years old and involves the application of live bee stings to the patient’s skin or, in more recent years, the injection of bee venom into the skin with a hypodermic needle. Studies have proven the effectiveness of bee venom in treating pathological conditions such as arthritis, pain and cancerous tumors. However, there has not been sufficient review to fully elucidate the cellular mechanisms of the anti-inflammatory effects of bee venom and its components. In this respect, the present study reviews current understanding of the mechanisms of the anti-inflammatory properties of bee venom and its components in the treatment of liver fibrosis, atherosclerosis and skin disease.

Keywords: bee venom; inflammation; liver fibrosis; atherosclerosis; skin disease

1. Introduction

Bee venom is a natural toxin produced by the honey bee and it has a prime role of defense for the bee colony [1–3]. It has an efficient and complex mixture of substances designed to protect bees against a broad diversity of predators [2]. Bee venom possesses various peptides including melittin, apamin, adolapamin and mast cell degranulating peptide [4,5]. It also contains enzymes, biologically activity
amines and non-peptide components. Enzymes are composed of phospholipase A2 (PLA2), hyaluronidase, acid phosphomonesterase, α-D-glucosidase and lysophospholipase, as well as non-peptides such as histamine, dopamine and norepinephrine [6]. Bee venom therapy is a treatment modality that may be thousands of years old and involves the application of live bee stings to the patient’s skin or, in more recent years, the injection of bee venom into the skin with a hypodermic needle [7]. Many experiments on the biological and pharmacological activities of bee venom have been carried out [2–8]. Majority of these studies have proven the effectiveness of bee venom in treating pathological conditions such as arthritis [9], pain [10,11] and cancerous tumors [12,13] among others.

The major component of bee venom is melittin, which comprises approximately 50% of the dry weight of bee venom. It is a small linear peptide composed of 26 amino acid residues [14]. Melittin has multiple effects, including anti-bacterial, anti-viral and anti-inflammatory, in various cell types [15,16]. Recent studies have shown that melittin can induce cell cycle arrest, cell growth inhibition and apoptosis in various tumor cells [17–19]. When several melittin peptides accumulate in the cell membrane, phospholipid packing is severely disrupted, thus leading to cell lysis [16]. Melittin triggers not only the lysis of a wide range of plasmatic membranes but also of intracellular ones such as those found in mitochondria. PLA2 and melittin act synergistically, breaking up membranes of susceptible cells and enhancing their cytotoxic effect [20]. However, other paper reported that melittin at concentrations below 2 μM does not disrupt cell membranes of leukocytes [21]. In addition, another paper reported that an optimal dose of melittin protects TGF-β1-induced apoptotic activation of hepatocytes by inhibiting the activation of the Bcl-2 family of proteins, caspases and poly (adenosine diphosphate-ribose) polymerase (PARP) cleavage [22].

Apamin is an integral part of bee venom, accounting for about 2%–3% of its dry weight [3]. It is a peptide neurotoxin comprising 18 amino acid residues that is tightly cross-linked by the presence of two disulphide bonds [5]. Apamin is well known for its pharmacological property of irreversibly blocking Ca\(^{2+}\)-activated K\(^+\) (SK) channels [23]. These channels link intracellular calcium transients to changes of the membrane potential by promoting K\(^+\) efflux following increases of intracellular calcium during an action potential [24]. In a previous paper, it was reported that apamin inhibited pro-inflammatory cytokines in lipopolysaccharide (LPS) with fat diet-induced atherosclerotic animal model [25]. Furthermore, a recent study has examined its biological and pharmacological activities [26]. However, little is known about the molecular mechanisms and the levels of gene regulation involved in the anti-inflammatory process. As such, this review focuses on overview of recent research on anti-inflammatory properties of bee venom and its components in liver fibrosis, atherosclerosis and inflammatory skin disease. Moreover, we review possible mechanisms of bee venom for alleviating or preventing the inflammatory diseases.

2. Anti-Inflammatory Effect of Bee Venom on Liver Fibrosis

Liver fibrosis occurs with chronic hepatic damage in a variety of liver diseases including viral hepatitis, alcoholic hepatitis and primary sclerosing cholangitis [27]. In these conditions, fibrotic liver shows changes in tissue architecture and extracellular matrix composition that ultimately compromise organ function [28–31]. The processes of liver repair and of fibrogenesis resemble that of a wound-healing process. Viral infection, alcoholic or drug toxicity, or any other factors that cause damage to hepatocytes, elicit an inflammatory reaction in the liver [14]. Following injury, an acute inflammation response takes
place resulting in moderate cell necrosis and extracellular matrix damage [32]. Chronic ethanol consumption is associated with serious and potentially fatal alcohol-related liver diseases such as fatty liver, alcoholic hepatitis and cirrhosis [33]. It is currently understood that the pathogenesis of these diseases is related to apoptosis [34]. Pro-inflammatory cytokine, TNF-α can induce multiple mechanisms that initiate apoptosis in hepatocytes, which leads to liver injury [35]. A paper reported that an optimal dose of bee venom exerts anti-apoptotic effects against ethanol-induced injury to hepatocytes via the mitochondrial pathway [34]. Thus, bee venom protects hepatocyte against TNF-α with actinomycin D induced apoptosis. Low concentrations of bee venom resulted in anti-apoptotic effects that were associated with a decrease in the level of proteolytic fragments of caspases and PARP [36]. Furthermore, a recent study indicates that bee venom inhibits CCL4-induced hepatic fibrosis through suppression of fibrogenic cytokines in liver fibrosis animal model. This study shows that bee venom down-regulated pro-inflammatory cytokines such as TNF-α and IL-1β. It has been demonstrated that collagen gene expression is regulated by TNF-α at a transcription level and IL-1β exerts a stimulatory effect on the synthesis of extracellular matrix components [37]. Transforming growth factor (TGF)-β is a multifunctional cytokine that mediates cellular differentiation, growth and apoptosis [38]. Park et al. reported that TGF-β1 decreased cell viabilities and induced hepatocyte apoptosis. However, adding the 10 ng/mL of bee venom significantly increased the viability of TGF-β1-treated hepatocyte [39]. In addition, Lee and colleagues demonstrated that an optimal dose of melittin exerts anti-apoptotic effects against TGF-β1-induced injury to hepatocytes via the mitochondrial pathway [22]. As such, these papers found that an optimal dose of bee venom and melittin can serve to protect cells against TGF-β1-mediated injury.

The nuclear transcription factor NF-κB is the key player in the development of chronic inflammatory diseases [40]. This transcription factor-involved-pathway is one of the main signaling pathways activated in response to pro-inflammatory cytokines. In addition, activation of this pathway plays a central role in inflammation through the regulation of genes encoding various growth factors [41]. Park et al. suggested that melittin attenuates liver injury in thioacetamide-treated mice through modulating inflammation and fibrogenesis [14]. These authors investigated the mechanism for suppression of NF-κB transcription by melittin in TNF-α-treated hepatocytes, examining the effect of melittin on NF-κB promoter activity by transiently transfected luciferase reporter plasmid containing the NF-κB promoter sequence. Melittin significantly inhibited NF-κB promoter activity and NF-κB DNA binding activity in TNF-α-treated hepatocytes. These results suggest that melittin suppresses NF-κB activation, leading to an inhibition of hepatocyte apoptosis [42].

Hepatic stellate cells (HSCs) are perisinusoidal cells residing in the space of Disse. During injury, in response to inflammatory and other stimuli, these cells adopt a myofibroblast-like phenotype and represent the cornerstone of the fibrotic response in the liver [42,43]. Once activated, HSCs up-regulate gene expression of extracellular matrix (ECM) components, matrix-degrading enzymes and their respective inhibitors, resulting in matrix remodeling and accumulation at sites with abundant activated HSCs [31,44]. Park et al. reported that melittin inhibited TNF-α secretion in the TNF-α-treated HSCs. Furthermore, melittin inhibited the TNF-α-induced expression of IL-1β and IL-6, especially with 0.5 mg/mL of melittin. This article also showed that melittin protected against thioacetamide-induced liver fibrosis by suppressing liver inflammation and fibrogenesis through the NF-κB signaling pathway. In addition, its anti-fibrotic effect may be attributed to modulation of the inflammatory effect in the activated HSC [14].
Acute hepatic failure is characterized by hepatic encephalopathy, severe coagulopathy, jaundice and hydroperitoneum [45,46]. Administration of a subtoxic dose of D-galactosamine together with LPS has often been used for preparing an animal model with endotoxemic shock and acute liver failure [47]. Upon stimulation with D-galactosamine and LPS, secretion of various pro-inflammatory cytokines and hepatic necrosis occur, which leads to the decreased levels of antioxidant enzymes [48,49]. This liver injury has been associated with significant increases in alanine aminotransferase (ALT) activity and TNF-α level in serum, ultimately leading to extremely high lethality [50]. Park and co-investigators found that melittin prevents D-galactosamine/LPS-induced liver failure by suppressing apoptosis and the inflammatory response in the mouse liver [51]. Melittin decreased the high rate of lethality, alleviated hepatic pathological injury, attenuated hepatic inflammatory responses and inhibited hepatocyte apoptosis. This study provides evidence that melittin may offer an alternative for the prevention of acute hepatic failure.

Some evidence suggests that adult hepatocytes play a role by way of epithelial mesenchymal transition (EMT) in the accumulation of activated fibroblasts [52,53]. EMT is a dynamic cellular program in which polarized epithelial cells lose epithelial properties, undergo morphological changes and acquire mesenchymal characteristics [54]. Hepatocytes can transdifferentiate into mesenchymal cells by EMT and deposit collagen in the liver during chronic injury [55]. A recent study has investigated the anti-fibrosis or anti-EMT mechanism by examining the effect of apamin on TGF-β1-treated hepatocytes or CCl₄-injected animal model. This article demonstrated that administration of apamin significantly increased the expression of epithelial marker E-cadherin and decreased mesenchymal marker vimentin in the TGF-β1-treated hepatocytes. In particular, apamin suppressed the expression of Smad-independent and Smad-dependent signaling pathways in hepatocytes. These results demonstrate the potential of apamin for the prevention of EMT progression induced by TGF-β1 in vitro [26].

PLA2 from bee venom is a prototypic group III enzyme that hydrolyzes fatty acids and it has been reported that melittin in bee venom enhances the activity of PLA2 [56,57]. In addition, it has been shown that PLA2 prevents neuronal cell death and spinal cord injury [58,59]. Kim et al. demonstrated that PLA2 protects against hepatic dysfunction and induces anti-inflammatory cytokine production in acetaminophen-injected mice. This study suggests that PLA2 may have therapeutic potential in preventing acetaminophen-induced hepatotoxicity [60].

3. Anti-Inflammatory Effect of Bee Venom on Atherosclerosis

Atherosclerosis is a chronic inflammatory disease of the arteries resulting from interactions among lipids, monocytes and arterial wall cells [61]. The early stage of atherosclerosis involves the activation of the vascular endothelium in response to many stimuli, such as low-density lipoproteins, free radicals, infectious microorganisms, shear stress, hypertension and toxins from smoking [62]. In the progression of atherosclerosis, the proliferation and migration of vascular smooth muscle cell (VSMC) play an important role in causing stenosis or intimal thickening [63]. The migration and proliferation of VSMC is caused by pathological phenomena such as the accumulation of inflammatory cells and the release of pro-inflammatory cytokines [64,65]. In addition, abundance of macrophages is observed in atherosclerotic lesions, and early lesions of atherosclerosis are characterized by the infiltration of monocyte/macrophages and the presence of macrophage foam cells [63]. Macrophages are multi-potent inflammatory cells with
the capacity for synthesis and secretion of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-8 and IL-6 [61,66]. Particularly, TNF-α is reportedly involved in the development of early atherosclerosis by up-regulating vessel wall chemokine and expression of adhesion molecules such as intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 in the aorta [67,68]. The up-regulation of the endothelial adhesion molecules promotes the development of atherosclerotic lesions in rabbits [69], subhuman primates [70] and humans [71,72]. Therefore, the suppression of cell adhesion molecule expression and macrophage accumulation at the level of the endothelium is of particular significance with respect to the management of the vascular inflammatory process. Some of study demonstrated that bee venom inhibits the development of atherosclerosis in C57BL/6 mice induced by injected LPS with feeding of an atherogenic diet. This is likely due to mechanisms involving anti-hypertriglyceridemic and anti-inflammatory effects of bee venom [73]. This study suggested that reduction of adhesion molecules and inflammatory factors by bee venom may be a protection against the atherosclerotic lesion formation.

The increased potential for growth of VSMC is a key abnormality in the development of atherosclerotic lesions [63]. It is well known that, in response to a platelet-derived growth factor (PDGF), VSMC can initiate highly conserved signaling events, which lead to either cell migration or proliferation [74]. Given the nature of VSMC in atherosclerosis, its apoptosis is beneficial in that it offers protection to the walls of arteries against proliferative restenosis induced by arterial injury, including arterial balloon angioplasty or stent implantation [75–80]. Son et al. reported that the anti-atherosclerotic effects of melittin were identified by interfering with the induction of apoptosis, inhibiting the proliferation of aortic VSMC and inhibiting downstream molecules of the PDGF receptor [8]. In addition, several studies have investigated the role of type IV collagenase or gelatinase (MMP-2 and 9) in the regulation of VSMC behavior both in vitro and in vivo [81,82]. MMP-9 is expressed in the initial stage of the smooth muscle cell (SMC) migration, whereas the MMP-2 activity is observed at a later stage after arterial injury [83]. The synthesis and secretion of MMP-9 can be stimulated by various stimuli, including TNF-α and PDGF, during pathological processes such as atherosclerosis and inflammation [82,84,85]. Jeong et al. investigated the effects of melittin on TNF-α-induced migration of human aortic SMCs. The study found that melittin suppresses TNF-α-induced MMP-9 expression by inhibiting its gene transcription, but not by regulating the tissue inhibitor or metalloproteinases. Additionally, suppression of the human aortic SMC migration by melittin appeared to block the MMP-9 expression by inhibiting the NF-κB signaling pathway. This study suggested that melittin is a potential agent for the prevention of vascular disorders related to the VSMC migration [65]. Recently, numerous basic research studies have indicated that TNF-α accelerates atherosclerosis in mice. Moreover, IL-1β, which plays an important role in the mediation of inflammatory responses and in the pathogenesis of atherosclerosis, is secreted by macrophages in atherosclerotic lesions [86,87]. Kim et al. investigated the protective effects of melittin on serum lipid profiles, pro-inflammatory cytokines, pro-atherosclerotic proteins and adhesion molecule levels in an LPS/high fat-induced mouse model of atherosclerosis and monocyte-derived macrophages. The major finding is that melittin inhibits LPS/high fat-induced expression levels of inflammatory cytokines and adhesion molecules such as TNF-α, IL-1β, ICAM and VCAM. Furthermore, the mechanisms are partly attributable to the inhibition of the NF-κB signaling pathway in LPS-treated monocyte-derived macrophages [88].
Several studies have confirmed that some calcium channel blockers can decrease the area of atherosclerotic lesions, production of oxidative stress and expression of inflammatory cytokines without conspicuously affecting blood lipid levels [89]. Kim et al. valuated the anti-atherosclerotic or anti-apoptotic mechanisms of apamin in THP-1-derived macrophages. Treatment of cells with oxLDL significantly promoted the accumulation of lipids and expression of apoptotic proteins. However, treatment of macrophages with apamin inhibited apoptosis through the regulation of Bel-2 family, caspase-3 and PARP apoptotic pathway. In vivo, apamin attenuated apoptotic cell death in atherosclerotic mice [90]. These authors also investigated the protective effect of apamin on LPS/fat-induced atherosclerotic mice. The treated mice showed a large number of atherosclerotic lesions in the aorta. However, treatment with apamin predominantly attenuated atherosclerotic lesions, lipid, Ca2+ levels, pro-inflammatory cytokines, adhesion molecules, fibrotic factors and macrophage infiltrations. In regard to mechanism, it was found that treatment with apamin in THP-1-derived macrophages suppresses inflammatory responses by a decrease of the NF-κB signal pathway. Therefore, this study suggests that apamin plays an important role in monocyte/macrophage inflammatory processing and may be of potential value for preventing atherosclerosis [25].

The proliferation of VSMC is governed by the cell cycle, a common convergent point for proliferative signaling cascades [91]. The cell cycle, which consists of three distinct sequential phages (G0/G1, S and G2/M), regulates cellular proliferation [92]. Generally, the cell cycle is tightly regulated by the activity of cycle-dependent kinase (CDK) and the specific regulatory cyclin complex. Specific CDKs are sequentially activated during different phases of the cell cycle [93]. A recent study examined the cellular mechanisms by which apamin inhibits cell cycle progression of the cells exposed to PDGF. This study also investigated the inhibitory effect of apamin on PDGF-induced VSMC proliferation and migration. The results showed that PDGF-treated-VSMC was decreased in cell proliferation and migration through the regulation of cyclin D1, CDK 4, cyclin E and CDK 2. Notably, 2 μg/mL of apamin inhibited the PDGF stimulated proliferation of VSMC through blocking PDGF signaling pathway [94].

4. Anti-Inflammatory Effect of Bee Venom on Skin Disease

Acne vulgaris is the most common skin disease of the pilosebaceous follicle and results in non-inflammatory and inflammatory lesions [95]. Propionibacterium acnes (P. acnes) is a major contributing factor to the inflammatory component of acne [96]. P. acnes contributes to the inflammatory reaction of acne by inducing monocytes and keratinocytes to produce pro-inflammatory cytokines, including IL-1β, IL-8 and TNF-α [97]. The induction of these cytokines by P. acnes is mediated by Toll-like receptor (TLR) 2 [98]. Various therapeutic agents, including antibiotics for acne, have been used to inhibit inflammation or bacteria growth. However, antibiotics may lead to the emergence of resistant pathogens and side effects [99]. Thus, research recently focused on the anti-inflammatory property of bee venom. This included the effect of heat-killed P. acnes on human keratinocyte and monocyte cell lines. Kim et al. investigated the anti-inflammatory effects of bee venom in heat-killed P. acnes-treated HaCaT and THP-1 cells, as revealed by ELISA analysis and Western blotting by measuring the pro-inflammatory cytokines and chemokines. Heat-killed P. acnes markedly increased the secretion of TNF-α, IL-8 and IFN-γ in HaCaT and THP-1 cells. However, bee venom treatment decreased the secretion of those cytokines. In addition, bee venom inhibited heat-killed P. acnes-induced TLR2 expression in HaCaT cells. These results suggest that bee venom blocked TLR2 expression and
suppressed the production of pro-inflammatory cytokines induced by *P. acnes* in HaCaT and THP-1 cells [100]. Another recent study conducted by An *et al.* reported that bee venom has a potential anti-bacterial effect against inflammatory skin disease. In this context, *P. acnes* was intradermally injected into ears of ICR mice. Following the injection, bee venom mixed with vaseline was applied to the skin surface of the ear. Histological observation revealed that the *P. acnes* injection induced a considerable increase in the number of infiltrated inflammatory cells and inflammatory cytokines. By contrast, the bee venom treated ears showed noticeably reduced ear thickness. Additionally, bee venom significantly inhibited the number of TNF-α and IL-1β positive cells [101]. Han *et al.* investigated the biological effect of bee venom treatment on keratinocyte migration *in vitro*. Migration assays showed that the distance of cell migration was dramatically increased in the experimental cells exposed to bee venom. This finding suggests that human epidermal keratinocyte migration occurred more rapidly in the bee venom treated cell, indicating that bee venom stimulates keratinocyte migration. Therefore, bee venom could be applied topically to accelerate wound healing by cell regeneration process [6].

During an inflammatory response, TLR activation results in the activation of the MAPK and the transcription factor NF-κB signaling pathways. These pathways then modulate inflammatory gene expression, which is crucial in shaping the innate immune response within the inflammatory skin disease [102]. Lee *et al.* investigated the effects of melittin in the production of inflammatory cytokines in heat-killed *P. acnes*-treated HaCaT cells. Furthermore, the molecular pathogenesis of anti-inflammatory effects of melittin was investigated in living *P. acnes*-induced inflammatory skin disease animal model. Administration of heat-killed *P. acnes* increased expression of IKK, IκB and NF-κB in HaCaT cells. However, the addition of melittin reduced IKK, IκB and NF-κB phosphorylation. These results indicate that treatment with melittin abrogated the effect of *P. acnes* in altering the expression through NF-κB signaling. The same study investigated whether melittin modulates MAPK signaling in heat-killed *P. acnes*-treated HaCaT cells. Findings showed that phosphorylated p38 was markedly increased after treatment with heat-killed *P. acnes*; however, phosphorylated p38 was decreased after treatment with melittin. These results underscore the theory that melittin inhibits pro-inflammatory cytokine expression by suppression of p38 MAPK phosphorylation in heat-killed *P. acnes*-treated HaCaT cells [103].

### 5. Conclusions

Due to the rising prevalence of side effects from pharmacological approach to inflammatory disease, there is a pressing need for better treatment to alleviate the symptoms of these disorders. The present review is the first to focus on how bee venom and its major components may be incorporated into therapy for inflammatory diseases. We propose that bee venom may serve as an inflammation modulator that subsequently affects the liver fibrosis, atherosclerosis and skin disease. Bee venom and its components regulate pro-inflammatory cytokines in hepatocyte and liver fibrosis animal model. In the atherosclerosis animal model, bee venom appears to inhibit the inflammatory reactions and VSMC proliferation. Furthermore, bee venom seems to accelerate wound healing and antibacterial therapy for the treatment of inflammatory skin disease through the regulation of inflammatory signaling pathway. Collectively, therapy using bee venom and its major components is considered a useful clinical approach for the treatment of inflammatory diseases. In addition, further studies including experimental elucidation of optimal dose, allergic reaction and side effects will lead to a potential therapeutic alternative for inflammatory disease.
Since bee venom contains a number of other components, advances in modern sequencing techniques will provide an arsenal of new possibilities to combat other inflammation related diseases.

Acknowledgments

This work was carried out with the support of “Cooperative Research Program for Agriculture Science and Technology Development (Project No. PJ01132501)” Rural Development Administration, Korea.

Author Contributions

All three authors wrote the manuscript and approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. An, H.J.; Kim, K.H.; Lee, W.R.; Kim, J.Y.; Lee, S.J.; Pak, S.C.; Han, S.M.; Park, K.K. Anti-fibrotic effect of natural toxin bee venom on animal model of unilateral ureteral obstruction. *Toxins* **2015**, *7*, 1917–1928.

2. Orsolic, N. Bee venom in cancer therapy. *Cancer Metastasis Rev.* **2012**, *31*, 173–194.

3. Son, D.J.; Lee, J.W.; Lee, Y.H.; Song, H.S.; Lee, C.K.; Hong, J.T. Therapeutic application of anti-arthritis, pain-releasing, and anti-cancer effects of bee venom and its constituent compounds. *Pharmacol. Ther.* **2007**, *115*, 246–270.

4. Karimi, A.; Ahmadi, F.; Parivar, K.; Nabiuni, M.; Haghighi, S.; Imani, S.; Afrouzi, H. Effect of honey bee venom on lewis rats with experimental allergic encephalomyelitis, a model for multiple sclerosis. *Iran. J. Pharm. Res.: IJPR* **2012**, *11*, 671–678.

5. Moreno, M.; Giralt, E. Three valuable peptides from bee and wasp venoms for therapeutic and biotechnological use: Melittin, apamin and mastoparan. *Toxins* **2015**, *7*, 1126–1150.

6. Han, S.M.; Park, K.K.; Nicholls, Y.M.; Macfarlane, N.; Duncan, G. Effects of honeybee (apis mellifera) venom on keratinocyte migration *in vitro*. *Pharm. Mag.* **2013**, *9*, 220–226.

7. Castro, H.J.; Mendez-Lnocencio, J.I.; Omidvar, B.; Omidvar, J.; Santilli, J.; Nielsen, H.S., Jr.; Pavot, A.P.; Richert, J.R.; Bellanti, J.A. A phase i study of the safety of honeybee venom extract as a possible treatment for patients with progressive forms of multiple sclerosis. *Allergy Asthma Proc.: Off. J. Reg. State Allergy Soc.* **2005**, *26*, 470–476.

8. Son, D.J.; Ha, S.J.; Song, H.S.; Lim, Y.; Yun, Y.P.; Lee, J.W.; Moon, D.C.; Park, Y.H.; Park, B.S.; Song, M.J.; et al. Melittin inhibits vascular smooth muscle cell proliferation through induction of apoptosis via suppression of nuclear factor-kappab and akt activation and enhancement of apoptotic protein expression. *J. Pharmacol. Exp. Ther.* **2006**, *317*, 627–634.

9. Park, H.J.; Lee, S.H.; Son, D.J.; Oh, K.W.; Kim, K.H.; Song, H.S.; Kim, G.J.; Oh, G.T.; Yoon, D.Y.; Hong, J.T. Antiarthritic effect of bee venom: Inhibition of inflammation mediator generation by suppression of nf-kappab through interaction with the p50 subunit. *Arthritis Rheum.* **2004**, *50*, 3504–3515.
10. Kwon, Y.B.; Ham, T.W.; Kim, H.W.; Roh, D.H.; Yoon, S.Y.; Han, H.J.; Yang, I.S.; Kim, K.W.; Beitz, A.J.; Lee, J.H. Water soluble fraction (<10 kDa) from bee venom reduces visceral pain behavior through spinal alpha 2-adrenergic activity in mice. Pharmacol. Biochem. Behav. 2005, 80, 181–187.

11. Kim, H.W.; Kwon, Y.B.; Ham, T.W.; Roh, D.H.; Yoon, S.Y.; Lee, H.J.; Han, H.J.; Yang, I.S.; Beitz, A.J.; Lee, J.H. Acupoint stimulation using bee venom attenuates formalin-induced pain behavior and spinal cord fos expression in rats. J. Vet. Med. Sci./Jpn. Soc. Vete. Sci. 2003, 65, 349–355.

12. Putz, T.; Ramoner, R.; Gander, H.; Rahm, A.; Bartsch, G.; Thurnher, M. Antitumor action and immune activation through cooperation of bee venom secretory phospholipase a2 and phosphatidylinositol-(3,4)-bisphosphate. Cancer Immunol. Immunother.: CII 2006, 55, 1374–1383.

13. Russell, P.J.; Hewish, D.; Carter, T.; Sterling-Levis, K.; Ow, K.; Hattarki, M.; Doughty, L.; Guthrie, R.; Shapira, D.; Molloy, P.L.; et al. Cytotoxic properties of immunoconjugates containing melittin-like peptide 101 against prostate cancer: In vitro and in vivo studies. Cancer Immunol. Immunother.: CII 2004, 53, 411–421.

14. Park, J.H.; Kum, Y.S.; Lee, T.I.; Kim, S.J.; Lee, W.R.; Kim, B.I.; Kim, H.S.; Kim, K.H.; Park, K.K. Melittin attenuates liver injury in thioacetamide-treated mice through modulating inflammation and fibrogenesis. Exp. Biol. Med. (Maywood) 2011, 236, 1306–1313.

15. Terra, R.M.; Guimaraes, J.A.; Verli, H. Structural and functional behavior of biologically active monomeric melittin. J. Mol. Gr. Model. 2007, 25, 767–772.

16. Raghuraman, H.; Chattopadhyay, A. Melittin: A membrane-active peptide with diverse functions. Biosci. Rep. 2007, 27, 189–223.

17. Jeong, Y.J.; Choi, Y.; Shin, J.M.; Cho, H.J.; Kang, J.H.; Park, K.K.; Choe, J.Y.; Bae, Y.S.; Han, S.M.; Kim, C.H.; et al. Melittin suppresses egf-induced cell motility and invasion by inhibiting pi3k/akt/mtor signaling pathway in breast cancer cells. Food Chem.Toxicol.: Int. J. Publ. Br. Ind. Biol. Res. Assoc. 2014, 68, 218–225.

18. Park, J.H.; Jeong, Y.J.; Park, K.K.; Cho, H.J.; Chung, I.K.; Min, K.S.; Kim, M.; Lee, K.G.; Yeo, J.H.; Chang, Y.C. Melittin suppresses pma-induced tumor cell invasion by inhibiting nf-kappab and ap-1-dependent mmp-9 expression. Mol. Cells 2010, 29, 209–215.

19. Shin, J.M.; Jeong, Y.J.; Cho, H.J.; Park, K.K.; Chung, I.K.; Lee, I.K.; Kwak, J.Y.; Chang, H.W.; Kim, C.H.; Moon, S.K.; et al. Melittin suppresses hif-1alpha/vegf expression through inhibition of erk and mtor/p70s6k pathway in human cervical carcinoma cells. PLoS ONE 2013, 8, e69380.

20. Damianoglou, A.; Rodger, A.; Pridmore, C.; Dafforn, T.R.; Mosely, J.A.; Sanderson, J.M.; Hicks, M.R. The synergistic action of melittin and phospholipase a2 with lipid membranes: Development of linear dichroism for membrane-insertion kinetics. Protein Pept. Lett. 2010, 17, 1351–1362.

21. Pratt, J.P.; Ravnic, D.J.; Huss, H.T.; Jiang, X.; Orozco, B.S.; Mentzer, S.J. Melittin-induced membrane permeability: A nonosmotic mechanism of cell death. In Vitro Cell. Dev. Biol. Anim. 2005, 41, 349–355.

22. Lee, W.R.; Park, J.H.; Kim, K.H.; Park, Y.Y.; Han, S.M.; Park, K.K. Protective effects of melittin on transforming growth factor-betal injury to hepatocytes via anti-apoptotic mechanism. Toxicol. Appl. Pharmacol. 2011, 256, 209–215.
23. Thompson, J.M.; Ji, G.; Neugebauer, V. Small-conductance calcium-activated potassium (sk) channels in the amygdala mediate pain-inhibiting effects of clinically available riluzole in a rat model of arthritis pain. Mol. Pain 2015, 11, 51, doi:10.1186/s12990-015-0055-9.

24. Bond, C.T.; Herson, P.S.; Strassmaier, T.; Hammond, R.; Stackman, R.; Maylie, J.; Adelman, J.P. Small conductance Ca^2+^-activated k^+ channel knock-out mice reveal the identity of calcium-dependent afterhyperpolarization currents. J. Neurosci.: Off. J. Soc. Neurosci. 2004, 24, 5301–5306.

25. Kim, S.J.; Park, J.H.; Kim, K.H.; Lee, W.R.; Pak, S.C.; Han, S.M.; Park, K.K. The protective effect of apamin on lps/fat-induced atherosclerotic mice. Evid.-Based Complement. Altern. Med.: eCAM 2012, 2012, 305454, doi:10.1155/2012/305454.

26. Lee, W.R.; Kim, K.H.; An, H.J.; Kim, J.Y.; Lee, S.J.; Han, S.M.; Pak, S.C.; Park, K.K. Apamin inhibits hepatic fibrosis through suppression of transforming growth factor beta1-induced hepatocyte epithelial-mesenchymal transition. Biochem. Biophys. Res. Commun. 2014, 450, 195–201.

27. Chen, M.H.; Chen, J.C.; Tsai, C.C.; Wang, W.C.; Chang, D.C.; Tu, D.G.; Hsieh, H.Y. The role of tgf-beta 1 and cytokines in the modulation of liver fibrosis by sho-saiko-to in rat’s bile duct ligated model. J. Ethnopharmacol. 2005, 97, 7–13.

28. Wallace, K.; Burt, A.D.; Wright, M.C. Liver fibrosis. Biochem. J. 2008, 411, 1–18.

29. Kim, K.K.; Wei, Y.; Szekeres, C.; Kugler, M.C.; Wolters, P.J.; Hill, M.L.; Frank, J.A.; Brumwell, A.N.; Wheeler, S.E.; Kreidberg, J.A.; et al. Epithelial cell alpha3beta1 integrin links beta-catenin and smad signaling to promote myofibroblast formation and pulmonary fibrosis. J. Clin. Investig. 2009, 119, 213–224.

30. Choi, S.S.; Diehl, A.M. Epithelial-to-mesenchymal transitions in the liver. Hepatology 2009, 50, 2007–2013.

31. Bataller, R.; Brenner, D.A. Liver fibrosis. J. Clin. Investig. 2005, 115, 209–218.

32. Friedman, S.L. Mechanisms of disease: Mechanisms of hepatic fibrosis and therapeutic implications. Nat. Clin. Pract. Gastroenterol. Hepatol. 2004, 1, 98–105.

33. Gao, B.; Bataller, R. Alcoholic liver disease: Pathogenesis and new therapeutic targets. Gastroenterology 2011, 141, 1572–1585.

34. Kim, K.H.; Kum, Y.S.; Park, Y.Y.; Park, J.H.; Kim, S.J.; Lee, W.R.; Lee, K.G.; Han, S.M.; Park, K.K. The protective effect of bee venom against ethanol-induced hepatic injury via regulation of the mitochondria-related apoptotic pathway. Basic Clin. Pharmacol. Toxicol. 2010, 107, 619–624.

35. Li, J.; Yang, S.; Billiar, T.R. Cyclic nucleotides suppress tumor necrosis factor alpha-mediated apoptosis by inhibiting caspase activation and cytochrome c release in primary hepatocytes via a mechanism independent of akt activation. J. Biol. Chem. 2000, 275, 13026–13034.

36. Park, J.H.; Kim, K.H.; Kim, S.J.; Lee, W.R.; Lee, K.G.; Park, K.K. Bee venom protects hepatocytes from tumor necrosis factor-alpha and actinomycin d. Arch. Pharm. Res. 2010, 33, 215–223.

37. Kim, S.J.; Park, J.H.; Kim, K.H.; Lee, W.R.; Chang, Y.C.; Park, K.K.; Lee, K.G.; Han, S.M.; Yeo, J.H.; Pak, S.C. Bee venom inhibits hepatic fibrosis through suppression of pro-fibrogenic cytokine expression. Am. J. Chin. Med. 2010, 38, 921–935.

38. Imamura, T.; Oshima, Y.; Hikita, A. Regulation of tgf-beta family signalling by ubiquitination and deubiquitination. J. Biochem. 2013, 154, 481–489.

39. Park, J.H.; Kim, K.H.; Kim, S.J.; Lee, W.R.; Lee, K.G.; Park, K.K. Effect of bee venom on transforming growth factor-beta1-treated hepatocytes. Int. J. Toxicol. 2010, 29, 49–56.
40. Tak, P.P.; Firestein, G.S. Nf-kappab: A key role in inflammatory diseases. *J. Clin. Investig.* 2001, 107, 7–11.
41. De Martin, R.; Hoeth, M.; Hofer-Warbinek, R.; Schmid, J.A. The transcription factor nf-kappa b and the regulation of vascular cell function. *Arterioscler. Thromb. Vasc. Biol.* 2000, 20, E83–E88.
42. Park, J.H.; Lee, W.R.; Kim, H.S.; Han, S.M.; Chang, Y.C.; Park, K.K. Protective effects of melittin on tumor necrosis factor-alpha induced hepatic damage through suppression of apoptotic pathway and nuclear factor-kappa b activation. *Exp. Biol. Med. (Maywood)* 2014, 239, 1705–1714.
43. Sarem, M.; Znaidak, R.; Macias, M.; Rey, R. Hepatic stellate cells: It’s role in normal and pathological conditions. *Gastroenterol. Hepatol.* 2006, 29, 93–101.
44. Zhang, Y.; Wang, Y.; Di, L.; Tang, N.; Ai, X.; Yao, X. Mechanism of interleukin-1beta-induced proliferation in rat hepatic stellate cells from different levels of signal transduction. *APMIS: Acta Pathol. Microbiol. Immunol. Scand.* 2014, 122, 392–398.
45. Sun, H.; Chen, L.; Zhou, W.; Hu, L.; Li, L.; Tu, Q.; Chang, Y.; Liu, Q.; Sun, X.; Wu, M.; et al. The protective role of hydrogen-rich saline in experimental liver injury in mice. *J. Hepatol.* 2011, 54, 471–480.
46. Choi, E.Y.; Hwang, H.J.; Kim, I.H.; Nam, T.J. Protective effects of a polysaccharide from hizikia fusiformis against ethanol toxicity in rats. *Food Chem. Toxicol.: Int. J. Publ. Br. Ind. Biol. Res. Assoc.* 2009, 47, 134–139.
47. Silverstein, R. D-galactosamine lethality model: Scope and limitations. *J. Endotoxin Res.* 2004, 10, 147–162.
48. Gong, X.; Luo, F.L.; Zhang, L.; Li, H.Z.; Wu, M.J.; Li, X.H.; Wang, B.; Hu, N.; Wang, C.D.; Yang, J.Q.; et al. Tetrandrine attenuates lipopolysaccharide-induced fulminant hepatic failure in d-galactosamine-sensitized mice. *Int. Immunopharmacol.* 2010, 10, 357–363.
49. Sass, G.; Heinlein, S.; Agli, A.; Bang, R.; Schumann, J.; Tiegs, G. Cytokine expression in three mouse models of experimental hepatitis. *Cytokine* 2002, 19, 115–120.
50. Yamada, I.; Goto, T.; Takeuchi, S.; Ohshima, S.; Yoneyama, K.; Shibuya, T.; Kataoka, E.; Segawa, D.; Sato, W.; Dohmen, T.; et al. Mao (ephedra sinica staph) protects against d-galactosamine and lipopolysaccharide-induced hepatic failure. *Cytokine* 2008, 41, 293–301.
51. Park, J.H.; Kim, K.H.; Lee, W.R.; Han, S.M.; Park, K.K. Protective effect of melittin on inflammation and apoptosis in acute liver failure. *Apop.: Int. J. Program. Cell Death* 2012, 17, 61–69.
52. Zeisberg, M.; Yang, C.; Martino, M.; Duncan, M.B.; Rieder, F.; Tanjore, H.; Kalluri, R. Fibroblasts derive from hepatocytes in liver fibrosis via epithelial to mesenchymal transition. *J. Biol. Chem.* 2007, 282, 23337–23347.
53. Dooley, S.; Hamzavi, J.; Ciuclan, L.; Godoy, P.; Ilkavets, I.; Ehnert, S.; Ueberham, E.; Gebhardt, R.; Kanzler, S.; Geier, A.; et al. Hepatocyte-specific smad7 expression attenuates tgf-beta-mediated fibrogenesis and protects against liver damage. *Gastroenterology* 2008, 135, 642–659.
54. Thiery, J.P.; Sleeman, J.P. Complex networks orchestrate epithelial-mesenchymal transitions. *Nat. Rev. Mol. Cell Biol.* 2006, 7, 131–142.
55. Copple, B.L. Hypoxia stimulates hepatocyte epithelial to mesenchymal transition by hypoxia-inducible factor and transforming growth factor-beta-dependent mechanisms. *Liver Int.: Off. J. Int. Assoc. Study Liv.* 2010, 30, 669–682.
56. Zhao, H.; Kinnunen, P.K. Modulation of the activity of secretory phospholipase a2 by antimicrobial peptides. *Antimicrob. Agents Chemother.* **2003**, *47*, 965–971.

57. Monti, M.C.; Casapullo, A.; Santomauro, C.; D’Auria, M.V.; Riccio, R.; Gomez-Paloma, L. The molecular mechanism of bee venom phospholipase a2 inactivation by bolinaquinone. *Chembiochem* **2006**, *7*, 971–980.

58. Lopez, F.O.; Lopez O’Rourke, V.J.; Fernandez Mariscal, E.; Vilarraza Sauquet, R.; Sanudo Martin, I. [c3 spinal cord ependymoma c03]. *Med. Clin.* **2011**, *136*, 605.

59. Jeong, J.K.; Moon, M.H.; Bae, B.C.; Lee, Y.J.; Seol, J.W.; Park, S.Y. Bee venom phospholipase a2 prevents prion peptide induced-cell death in neuronal cells. *Int. J. Mol. Med.* **2011**, *28*, 867–873.

60. Kim, H.; Keum, D.J.; Kwak, J.; Chung, H.S.; Bae, H. Bee venom phospholipase a2 protects against acetaminophen-induced acute liver injury by modulating regulatory t cells and il-10 in mice. *PLoS ONE* **2014**, *9*, e114726.

61. Ross, R. Atherosclerosis--an inflammatory disease. *N. Engl. J. Med.* **1999**, *340*, 115–126.

62. Stoll, G.; Bendszus, M. Inflammation and atherosclerosis: Novel insights into plaque formation and destabilization. *Stroke* **2006**, *37*, 1923–1932.

63. Ross, R. The pathogenesis of atherosclerosis: A perspective for the 1990s. *Nature* **1993**, *362*, 801–809.

64. Gerthoffer, W.T. Mechanisms of vascular smooth muscle cell migration. *Circ. Res.* **2007**, *100*, 607–621.

65. Jeong, Y.J.; Cho, H.J.; Whang, K.; Lee, I.S.; Park, K.K.; Choe, J.Y.; Han, S.M.; Kim, C.H.; Chang, H.W.; Moon, S.K.; *et al.* Melittin has an inhibitory effect on tnf-alpha-induced migration of human aortic smooth muscle cells by blocking the mmp-9 expression. *Food Chem. Toxicol.: An Int. J. Publ. Br. Ind. Biol. Res. Assoc.* **2012**, *50*, 3996–4002.

66. Cipollone, F.; Iezzi, A.; Fazia, M.; Zucchelli, M.; Pini, B.; Cuccurullo, C.; de Cesare, D.; de Blasis, G.; Muraro, R.; Bei, R.; *et al.* The receptor rage as a progression factor amplifying arachidonate-dependent inflammatory and proteolytic response in human atherosclerotic plaques: Role of glycemic control. *Circulation* **2003**, *108*, 1070–1077.

67. Zhang, L.; Peppel, K.; Sivashanmugam, P.; Orman, E.S.; Brian, L.; Exum, S.T.; Freedman, N.J. Expression of tumor necrosis factor receptor-1 in arterial wall cells promotes atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **2007**, *27*, 1087–1094.

68. Ohta, H.; Wada, H.; Niwa, T.; Kirii, H.; Iwamoto, N.; Fujii, H.; Saito, K.; Sekikawa, K.; Seishima, M. Disruption of tumor necrosis factor-alpha gene diminishes the development of atherosclerosis in apoE-deficient mice. *Atherosclerosis* **2005**, *180*, 11–17.

69. Li, H.; Cybulsky, M.I.; Gimbrone, M.A., Jr.; Libby, P. An atherogenic diet rapidly induces vcam-1, a cytokine-regulatable mononuclear leukocyte adhesion molecule, in rabbit aortic endothelium. *Arterioscler. Thromb.: A J. Vasc. Biol./Am. Heart Assoc.* **1993**, *13*, 197–204.

70. Shi, Q.; Vandeberg, J.F.; Jett, C.; Rice, K.; Leland, M.M.; Talley, L.; Kushwaha, R.S.; Rainwater, D.L.; Vandeberg, J.L.; Wang, X.L. Arterial endothelial dysfunction in baboons fed a high-cholesterol, high-fat diet. *Am. J. Clin. Nutr.* **2005**, *82*, 751–759.

71. Poston, R.N.; Haskard, D.O.; Coucher, J.R.; Gall, N.P.; Johnson-Tidey, R.R. Expression of intercellular adhesion molecule-1 in atherosclerotic plaques. *Am. J. Pathol.* **1992**, *140*, 665–673.
vascular formation and remodeling. us muscle cell

83. Hwang, S.J.; Ballantyne, C.M.; Sharrett, A.R.; Smith, L.C.; Davis, C.E.; Gotto, A.M., Jr.; Boerwinkle, E. Circulating adhesion molecules vcam-1, icam-1, and e-selectin in carotid atherosclerosis and incident coronary heart disease cases: The atherosclerosis risk in communities (aric) study. Circulation 1997, 96, 4219–4225.

84. Lee, B.; Kim, S.J.; Park, J.H.; Kim, K.H.; Chang, Y.C.; Park, Y.Y.; Lee, K.G.; Han, S.M.; Yeo, J.H.; Pak, S.C.; et al. Bee venom reduces atherosclerotic lesion formation via anti-inflammatory mechanism. Am. J. Chin. Med. 2010, 38, 1077–1092.

85. Jung, F.; Haendeler, J.; Goebel, C.; Zeiher, A.M.; Dimmeler, S. Growth factor-induced phosphoinositide 3-oh kinase/akt phosphorylation in smooth muscle cells: Induction of cell proliferation and inhibition of cell death. Cardiovasc. Res. 2000, 48, 148–157.

86. Yang, B.; Kim, H.S.; Park, K.W.; You, H.J.; Jeon, S.I.; Youn, S.W.; Kim, S.H.; Oh, B.H.; Lee, M.M.; Park, Y.B.; et al. Celecoxib, a cycloxygenase-2 inhibitor, reduces neointimal hyperplasia through inhibition of akt signaling. Circulation 2004, 110, 301–308.

87. Lesauskaite, V.; Ivanoviene, L.; Valanciute, A. Programmed cellular death and atherogenesis: From molecular mechanisms to clinical aspects. Medicina (Kaunas) 2003, 39, 529–534.

88. Hofmann, C.S.; Sonenshein, G.E. Green tea polyphenol epigallocatechin-3 gallate induces apoptosis of proliferating vascular smooth muscle cells via activation of p53. FASEB J.: Off. Publ. Fed. Am. Soc. Exp. Biol. 2003, 17, 702–704.

89. Curcio, A.; Torella, D.; Cuda, G.; Coppola, C.; Faniello, M.C.; Achille, F.; Russo, V.G.; Chiariello, M.; Indolfi, C. Effect of stent coating alone on in vitro vascular smooth muscle cell proliferation and apoptosis. Am. J. Physiol. Heart Circ. Physiol. 2004, 286, H902–H908.

90. Chen, J.H.; Wu, C.C.; Hsiao, G.; Yen, M.H. Magnolol induces apoptosis in vascular smooth muscle. Naunyn-Schmied. Arch. Pharmacol. 2003, 368, 127–133.

91. Perlman, H.; Sata, M.; Krasinski, K.; Dorai, T.; Buttyan, R.; Walsh, K. Adenovirus-encoded hammerhead ribozyme to bcl-2 inhibits neointimal hyperplasia and induces vascular smooth muscle cell apoptosis. Cardiovasc. Res. 2000, 45, 570–578.

92. Newby, A.C.; Zaltsman, A.B. Molecular mechanisms in intimal hyperplasia. J. Pathol. 2000, 190, 300–309.

93. Cho, A.; Reidy, M.A. Matrix metalloproteinase-9 is necessary for the regulation of smooth muscle cell replication and migration after arterial injury. Circ. Res. 2002, 91, 845–851.

94. Bendeck, M.P.; Zempo, N.; Clowes, A.W.; Galardy, R.E.; Reidy, M.A. Smooth muscle cell migration and matrix metalloproteinase expression after arterial injury in the rat. Circ. Res. 1994, 75, 539–545.

95. Chen, Q.; Jin, M.; Yang, F.; Zhu, J.; Xiao, Q.; Zhang, L. Matrix metalloproteinases: Inflammatory regulators of cell behaviors in vascular formation and remodeling. Med. Inflamm. 2013, 2013, 928315, doi:10.1155/2013/928315.

96. Moon, S.K.; Cha, B.Y.; Kim, C.H. Erk1/2 mediates tnf-alpha-induced matrix metalloproteinase-9 expression in human vascular smooth muscle cells via the regulation of nf-kappab and ap-1: Involvement of the ras dependent pathway. J. Cell. Physiol. 2004, 198, 417–427.

97. Branen, L.; Hovgaard, L.; Nitulescu, M.; Bengtsson, E.; Nilsson, J.; Jovinge, S. Inhibition of tumor necrosis factor-alpha reduces atherosclerosis in apolipoprotein e knockout mice. Arterioscler. Thromb. Vasc. Biol. 2004, 24, 2137–2142.
87. Canault, M.; Peiretti, F.; Mueller, C.; Kopp, F.; Morange, P.; Rihs, S.; Portugal, H.; Juhan-Vague, I.; Nalbone, G. Exclusive expression of transmembrane tnf-alpha in mice reduces the inflammatory response in early lipid lesions of aortic sinus. Atherosclerosis 2004, 172, 211–218.

88. Kim, S.J.; Park, J.H.; Kim, K.H.; Lee, W.R.; Kim, K.S.; Park, K.K. Melittin inhibits atherosclerosis in lps/high-fat treated mice through atheroprotective actions. J. Atheroscler. Thromb. 2011, 18, 1117–1126.

89. Mancini, G.B. Antiatherosclerotic effects of calcium channel blockers. Prog. Cardiovasc. Dis. 2002, 45, 1–20.

90. Kim, S.J.; Park, J.H.; Kim, K.H.; Lee, W.R.; An, H.J.; Min, B.K.; Han, S.M.; Kim, K.S.; Park, K.K. Apamin inhibits thp-1-derived macrophage apoptosis via mitochondria-related apoptotic pathway. Exp. Mol. Pathol. 2012, 93, 129–134.

91. Braun, K.; Ehemann, V.; Waldeck, W.; Pipkorn, R.; Corban-Wilhelm, H.; Jenne, J.; Gissmann, L.; Debus, J. Hpv18 e6 and e7 genes affect cell cycle, prb and p53 of cervical tumor cells and represent prominent candidates for intervention by use peptide nucleic acids (pnas). Cancer Lett. 2004, 209, 37–49.

92. Elledge, S.J. Cell cycle checkpoints: Preventing an identity crisis. Science 1996, 274, 1664–1672.

93. Fuster, J.J.; Fernandez, P.; Gonzalez-Navarro, H.; Silvestre, C.; Nabah, Y.N.; Andres, V. Control of cell proliferation in atherosclerosis: Insights from animal models and human studies. Cardiovasc. Res. 2010, 86, 254–264.

94. Kim, J.Y.; Kim, K.H.; Lee, W.R.; An, H.J.; Lee, S.J.; Han, S.M.; Lee, K.G.; Park, Y.Y.; Kim, K.S.; Lee, Y.S.; et al. Apamin inhibits pdgf-bb-induced vascular smooth muscle cell proliferation and migration through suppressions of activated akt and erk signaling pathway. Vasc. Pharmacol. 2015, 70, 8–14.

95. Leyden, J.J. The evolving role of propionibacterium acnes in acne. Semin. Cutan. Med. Surg. 2001, 20, 139–143.

96. Jung, M.K.; Ha, S.; Son, J.A.; Song, J.H.; Houh, Y.; Cho, E.; Chun, J.H.; Yoon, S.R.; Yang, Y.; Bang, S.I.; et al. Polyphenon-60 displays a therapeutic effect on acne by suppression of tlr2 and il-8 expression via down-regulating the erk1/2 pathway. Arch. Dermatol. Res. 2012, 304, 655–663.

97. Vowels, B.R.; Yang, S.; Leyden, J.J. Induction of proinflammatory cytokines by a soluble factor of propionibacterium acnes: Implications for chronic inflammatory acne. Infect. Immun. 1995, 63, 3158–3165.

98. Kim, J. Review of the innate immune response in acne vulgaris: Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. Dermatology 2005, 211, 193–198.

99. Aslam, I.; Fleischer, A.; Feldman, S. Emerging drugs for the treatment of acne. Expert Opin. Emerg. Drugs 2015, 20, 91–101.

100. Kim, J.Y.; Lee, W.R.; Kim, K.H.; An, H.J.; Chang, Y.C.; Han, S.M.; Park, Y.Y.; Pak, S.C.; Park, K.K. Effects of bee venom against propionibacterium acnes-induced inflammation in human keratinocytes and monocytes. Int. J. Mol. Med. 2015, 35, 1651–1656.

101. An, H.J.; Lee, W.R.; Kim, K.H.; Kim, J.Y.; Lee, S.J.; Han, S.M.; Lee, K.G.; Lee, C.K.; Park, K.K. Inhibitory effects of bee venom on propionibacterium acnes-induced inflammatory skin disease in an animal model. Int. J. Mol. Med. 2014, 34, 1341–1348.
102. Grange, P.A.; Raingeaud, J.; Calvez, V.; Dupin, N. Nicotinamide inhibits propionibacterium acnes-induced IL-8 production in keratinocytes through the NF-kappab and MAPK pathways. *J. Dermatol. Sci.* **2009**, *56*, 106–112.

103. Lee, W.R.; Kim, K.H.; An, H.J.; Kim, J.Y.; Chang, Y.C.; Chung, H.; Park, Y.Y.; Lee, M.L.; Park, K.K. The protective effects of melittin on propionibacterium acnes-induced inflammatory responses *in vitro* and *in vivo*. *J. Investig. Dermatol.* **2014**, *134*, 1922–1930.

© 2015 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/4.0/).