The evidence for natural therapeutics as potential anti-scarring agents in burn-related scarring

M. Mehta1, O. A. Branford2 and K. J. Rolfe1*

Abstract

Though survival rate following severe thermal injuries has improved, the incidence and treatment of scarring have not improved at the same speed. This review discusses the formation of scars and in particular the formation of hypertrophic scars. Further, though there is as yet no gold standard treatment for the prevention or treatment of scarring, a brief overview is included. A number of natural therapeutics have shown beneficial effects both in vivo and in vitro with the potential of becoming clinical therapeutics in the future. These natural therapeutics include both plant-based products such as resveratrol, quercetin and epigallocatechin gallate as examples and includes the non-plant-based therapeutic honey. The review also includes potential mechanism of action for the therapeutics, any recorded adverse events and current administration of the therapeutics used. This review discusses a number of potential ‘treatments’ that may reduce or even prevent scarring particularly hypertrophic scarring, which is associated with thermal injuries without compromising wound repair.

Keywords: Burns, Hypertrophic scar, Natural therapeutics, Wound healing

Background

A burn is defined by the World Health Organisation (WHO) as 'an injury to the skin or other organic tissue primarily caused by heat or due to radiation, radioactivity, electricity, friction or contact with chemicals' [1]. It has been estimated that annually, there are 486,000 burn injuries in the USA that required medical attention with 40,000 requiring hospitalisation [2], with a global incidence in 2004 of approximately 11 million burn injuries requiring medical attention [3]. Non-fatal burns are one of the leading causes of disability in low- to middle-income countries [3]. Advances in medical treatment means that survival following extensive burns has improved over recent years though the incidence, treatment and prevention of scarring from thermal injuries has not improved over the same time frame [4].

Review

Hypertrophic scars

Hypertrophic scars are defined as visible raised scars which do not spread beyond the original injury margins. Hypertrophic scars are characterised by proliferation of the dermal tissue, excessive deposition of fibroblast-derived extracellular matrix (ECM) over a prolonged period of time and persistent inflammation and fibrosis [5]. Hypertrophic scars primarily contain collagen type III orientated parallel to the epidermal surface with abundant collagen nodules [6]. This structural realignment results in contracture, low tensile strength and raised scars.

The incidence of hypertrophic scars after a burn remains unclear, with estimates ranging from 26 % to 75 % depending on age, ethnicity and if healing was spontaneous or through surgical means (for example, skin grafting) [7–12].

Apart from the aesthetic problems, patients often complain of itching, redness and hard nodular scar tissue often with abnormal sensation. Hypertrophic scars following thermal injury are often associated with...
contractures, which can result in functional loss especially over joints such as in the hand [13].

**Scar formation**

Wound healing is an inherent process which aims to restore the integrity of the skin as rapidly as possible. Wound healing is divided into four stages: haemostasis, inflammation, proliferation and tissue remodelling. Within these four stages, which often overlap, there are numerous interactions between fibrotic and anti-fibrotic growth factors, cells, ECM components and numerous enzymes [14].

Fibroblasts derived from hypertrophic scars have demonstrated an altered phenotype compared to fibroblasts derived from normal scars and fibroblasts derived from uninjured tissue [6, 15]. Fibroblasts derived from hypertrophic scars have demonstrated both an increased expression of the pro-fibrotic cytokine, transforming growth factor beta 1 (TGF-β1), and a prolonged expression of the associated TGF-β receptors (Fig. 1) [16, 17]. Further, there appears to be an alteration in TGF-β signalling (via increased phosphorylation of the receptor Smad proteins) in hypertrophic-derived fibroblasts and a decreased expression of the inhibitory Smad 7 in hypertrophic scar-derived fibroblasts [18]. Studies have indicated that ectopic expression of Smad 7 prevents collagen contraction in both normal and hypertrophic scar-derived fibroblasts (FPCL: fibroblast-populated collagen lattice: model for contraction) [19].

A mouse model which lacked the receptor Smad, Smad 3, showed improved wound healing [20]. Conversely, exogenous Smad 3 (via an adenovirus-containing Smad 3 cDNA) in a rabbit dermal ulcer model showed increased granulation tissue and re-epithelisation [21]. Sumiyoshi and colleagues suggested that the differences in outcome may be that the adenovirus-containing Smad targeted mainly fibroblasts [21, 22], whereas in the mouse model lacking Smad 3, the deficiency was found in fibroblasts, keratinocytes and inflammatory cells.

**Fig. 1** Summary of TGF-β signalling in hypertrophic scars (Reprinted from Penn JW, Grobbelaar AO, Rolfe KJ. The role of TGF-β family in wound healing, burns and scarring: a review. Int J Burns Trauma. 2012;2:18–28. With permission). TGF-β1 transforming growth factor beta 1, HTS hypertrophic scar, LAP latency-associated peptide, LTBP latebt transforming growth factor-beta-1 binding portein, CTGF connective tissue growth factor, TIMP-1 tissue inhibitor of metalloproteinase-1.
Decorin, a proteoglycan found in the dermal ECM, binds and regulates TGF-β1 and plays a role in collagen fibrillogenesis. Decorin has been shown to be diminished in hypertrophic scars [23]. Zhang and his colleagues demonstrated that decorin inhibited both basal and TGF-β induced contraction in FPCL in normal and hypertrophic derived fibroblasts [24].

Linge et al. demonstrated that fibroblasts derived from hypertrophic scars failed to undergo apoptosis during FPCL contraction unlike fibroblasts derived from normal scars [25]. It was determined that the hypertrophic scar-derived fibroblasts were resistant to breakdown by collagenase D and matrix metalloproteinase-2 (MMP-2) due to excessive cross-linking of the FPCL. Linge and colleagues further found that hypertrophic scar-derived fibroblasts over-expressed tissue transglutaminase [25]. Reducing tissue transglutaminase in hypertrophic FPCL induced apoptosis on gel contraction [25]. Differences have been further identified in myofibroblasts, and these fibroblasts express alpha smooth muscle actin and are associated with wound contraction and maturation of the granulation tissue [26]. Myofibroblasts derived from hypertrophic scars appear to be less sensitive to apoptotic signals than fibroblasts derived from normal scars and express different levels of some apoptotic-related molecules [27].

Studies suggest that migrating fibrocytes, cells with a distinct cytokine and chemokine profile, may play a role in wound repair and therefore scarring [28]. Fibrocytes appear to be increased in number of healing burn wounds and were higher in hypertrophic scar than in mature scar tissue [29]. Fibrocytes from patients who have undergone thermal injury appear to differ in their paracrine effects on dermal fibroblasts by stimulating fibroblasts to proliferate, produce and contract the ECM and stimulate production of TGF-β1 and its downstream effector connective tissue growth factor (CTGF/CCN2) [30].

Matrix metalloproteinases are involved in the breakdown of the ECM during a number of physiological processes. MMP-1 is involved in the degradation of interstitial collagens, type I, II and III. Hypertrophic-derived fibroblasts appear to have reduced collagenase (MMP-1) activity [31]. Though other studies have shown an increase in expression of MMP-2 and low level of MMP-9 [32], MMP-2 has been demonstrated to effect matrix remodelling in late wound healing, degrading denatured collagen, whereas MMP-9 appears to be involved in early wound healing degrading collagen types IV and V, fibronectin and elastin [33, 34].

Evidence suggests that the immune response may play a role in scarring. Studies have suggested an abnormality in the role of Th1/Th2 paradigm after a thermal injury [30, 35]. Studies have implicated Toll-like receptors in fibrosis with recent studies implicating increased expression of toll-like receptor 4 (TLR4) mRNA and surface receptors implicating the Toll receptor system in potential activation of dermal fibroblast in hypertrophic scars [36].

**Treatment for scar**

Numerous treatments are used to reduce or prevent scarring [37, 38]. Identifying injuries, which if permitted to heal spontaneously may result in pathological scarring, is important to prevent unnecessary treatment as few treatments are without side effects [39, 40]. Compression therapy (pressure garments) has shown mixed results with a meta-analysis showing no alteration in scar scores [41], whereas a 12-year prospective study showed an overall significant improvement in scar appearance [42]. The mechanism for pressure in the reduction of scarring remains unclear though in vitro studies suggest a change in MMP, collagen and alpha smooth muscle actin expression [43, 44]. Patient compliance is often low due to discomfort which may affect the overall clinical result, but further compression therapy has well-recognised complications [45, 46].

Silicone gel is commonly used in the treatment or prevention of pathological scars. Results for the use of silicone gel either on its own or with compression garments remain conflicting [47], but this may in part be due to patient compliance [48]. The mechanism of action for silicone gel remains unclear though a recent study suggests that silicone gel alters the expression of TGF-β1, platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) 4 months after surgery for surgical scar revision though patient numbers were small (n=4) and the original injuries were not discussed [49].

Intra-lesional corticosteroids have shown to be useful in vivo through a number of mechanisms including reduction in the inflammatory process, decrease in collagen production and fibroblast proliferation [50, 51]. Scar response rates for triamcinolone acetone (10 to 40 mg/ml), the most common corticosteroid used for scar reduction, range from 50 % to 100 % with a recurrence rate of 9 %–53 % (reviewed in [50]). However, the use of corticosteroids is often associated with pain on injection and up to 50 % of patients report side effects [52].

Other treatments which are currently being studied include laser therapy [53], bleomycin, interferon, 5-fluorouracil, imiquimod, methotrexate and cryotherapy [54]. However, to date, there is no effective ‘gold standard’ for the treatment or prevention of any scarring.

**Plant-based products**

A number of plants with medical properties have been studied for their effectiveness in the prevention of scarring [55]. The present review provides in vitro and/or in vivo
Evidence supporting plant-based products as potential therapeutic agents.

**Quercetin**
Quercetin is a flavonoid found in plants, vegetables and fruits including onions, apples and berries [56]. Quercetin has been demonstrated in vitro to have a number of biological properties including tumour suppression and anti-inflammatory, anti-oxidant properties and is anti-bacterial [57–60]. However, the metabolism of quercetin in humans may reduce its biological effects [61].

Quercetin has been shown in vitro to reduce proliferation in fibroblasts derived from keloid scars and alter intracellular signalling pathways and collagen synthesis [62–64]. Phan and colleagues demonstrated that in fibroblasts derived from keloid and hypertrophic scars, quercetin not only inhibited fibroblast proliferation by inducing cell cycle arrest but also inhibited FPCL contraction, though both cell cycle arrest and FPCL could be reversed and though resumption of contraction was slowest in the quercetin treated group [65]. Saulis and colleagues showed in a rabbit model that Mederma (active compound allium cepa, a derivative of quercetin) improved collagen organisation and therefore may have an effect on the pathophysiology of hypertrophic scars [66].

**Onion extract**
Onion extract in in vitro studies suggest that it may have anti-inflammatory and anti-proliferative properties on fibroblasts and mast cells and increase the expression of MMP-1 [67, 68]. Quercetin and onion extract have both been shown to induce the up-regulation of MMP-1 in vitro and in vivo [68]. MMP-1 is known to play a role in ECM remodelling and therefore quercetin and onion extract may play a role in anti-fibrotic processes.

A small (n = 16) randomised controlled split scar study on Asian women undergoing a Pfannenstiel’s incision for caesarean section demonstrated a statistically significant reduction in scar height and symptoms at 4 and 12 weeks post-surgery in an onion extract group. However, there was no statistically significant reduction in redness or pliability of the scar over the time studied [69]. Ho et al. using a gel containing onion extract, heparin and allotoin found the gel significantly reduced the risk of scarring in 120 Chinese patients undergoing laser removal of their tattoos [70]. Wananukul et al., in a paediatric group (n = 39; mean age 4.3 years old) who underwent a median sternotomy in a split scar experimental study (onion extract versus placebo), demonstrated that onion extract in a silicone derivative gel significantly decreased the incidence of hypertrophic scars, whereas there was no significant difference in the incidence of keloid scars [71]. Other authors have used a combination of a silicone derivative plus onion extract in patients who had undergone a median sternotomy (n = 60) over a treatment period of 12 weeks. They found that itch and pain was less for the treated group, there was also an improved Vancouver Scar score in the treated group especially for pigmentation [72].

Beuth and colleagues compared hypertrophic scars treated with Contractubex® (cepae extract, heparin, allantoin; treatment group) for 28 days with one intraleisonal corticosteroid application (control group) [73]. Contractubex® demonstrated a significant shorter time for normalisation of the scar (erythema, pruritus and consistency) compared to the corticosteroid group. Contractubex® was further associated with less adverse events than corticosteroid application [73].

**Resveratrol**
Resveratrol is a natural plant polyphenol and phyto-oestrogen, present in grape skin, red wine, and peanuts [74, 75]. Resveratrol is noted to have a number of beneficial health effects including cardio-vascular, anti-inflammatory and anti-oxidant properties [74–78].

Resveratrol has been shown to reduce fibroblast cell proliferation through cell cycle arrest at G1 in fibroblasts derived from hypertrophic scars and normal skin fibroblasts and induce apoptosis [79]. Resveratrol further decreased hydroxyproline levels and down-regulated the expression of collagen type I and III mRNA [79].

Resveratrol has further shown beneficial effects in preventing surgical adhesions in an animal model [80]. Ikeda et al. demonstrated in vitro that resveratrol decreases TGF-β1, type 1 collagen and alpha smooth muscle actin in keloid-derived fibroblasts [81]. Further, resveratrol suppressed keloid-derived fibroblast proliferation and induced apoptosis. Interestingly, resveratrol did not have the same effects on alpha smooth muscle actin or type 1 collagen in fibroblasts derived from normal scars [81].

**Epigallocatechin gallate (EGCG)**
EGCG is a major catechin in green tea and has a number of biological properties; it has been shown to potentially play a role in preventing fibrosis in a number of organs [82].

EGCG has been shown in FPCL to abrogate contraction stimulated by PDGF and TGF-β1 [83, 84]. EGCG binds directly to PDGF-BB preventing the PDGF ligand binding to its receptor and therefore preventing both proliferation and FPCL contraction [83, 85]. EGCG has been shown to inhibit a number of intracellular signalling pathways and reduce expression of pro-fibrotic molecules (vascular endothelial growth factor (VEGF), TGF-β1, CTGF) in a number of organs [86–88]. Inhibition of TGF-β1 results in reduction of the synthesis of the ECM [84]. Interestingly, EGCG has been
demonstrated to improve re-epithelisation in a chronic wound model and the structural stability of collagen was shown to be enhanced with EGCG [89, 90].

**Oleanolic acid (OA)**

OA is a naturally occurring triterpenoid compound with a number of biological properties including anti-inflammatory and anti-tumour effects [91, 92]. In a rabbit ear model of hypertrophic scarring where OA was applied daily for 22 days, it was found to significantly inhibit hypertrophic scarring with a corresponding reduction in TGF-β1 and collagen type I and III and increase levels of MMP-1 [93]. Zhang et al. also used the rabbit ear model to study OA and repeated the observation that OA reduced the incidence of hypertrophic type scars [94]. They found that TGF-β1, MMP-1, TIMP-1 and collagen I and III were notably decreased though the number of apoptotic cells and mRNA expression of MMP-2, caspase-3 and caspase-9 were increased in the scar tissue [94].

**Curcumin**

Curcumin, a polyphenol, has been shown to induce apoptosis in a number of cell lines [95–97]. Curcumin has been shown in a rat wound healing model to increase contraction and reduce wound healing time [98]. The wounds showed increased fibronectin and collagen expression with increased collagen maturation and cross-linking increasing the wounds tensile strength after treating with curcumin for 12 days (200 μl at a concentration of 40 mg/kg body weight) [98].

Scharstuhl and colleagues showed that curcumin treatment (>25 μM for 48 h) induced fibroblast apoptosis and inhibited FPCL contraction via a reactive oxygen species (ROS)-mediated process in human dermal fibroblasts in vitro [99]. They concluded that curcumin at high concentrations may be a therapeutic strategy in the reduction or prevention of hypertrophic scarring and that the process can be regulated through the modulation of heme oxygenase(HO) molecule activity or the administration of HO effector molecules.

**Shikonin**

Shikonin is a natural naphthoquinone compound from the Chinese herb *Lithospermum erythrorhizon*. Shikonin has been demonstrated to have a number of molecular targets, inducing apoptosis, necrosis and necroptosis in cancer cells [100–102]. It has further been demonstrated that shikonin selectively kills cancer cells while maintaining normal cells [103]. Shikonin in cancer lines has been shown to alter a number of intracellular signalling pathways particularly those associated with apoptosis [103–105]. Fan and colleagues demonstrated that Shikonin keratinocytes did not respond to Shikonin unlike human scar-derived fibroblasts which where stimulated to undergo apoptosis [106]. Shikonin induced apoptosis by altering the expression of caspase-3, B-cell lymphoma (BCL)-2, phosphorylation of ERK1/2 and p38 [107]. Further, Shikonin down-regulates collagen (type I and III) and smooth muscle actin gene expression in scar-derived fibroblasts [107].

Normal skin fibroblasts (n = 3) were demonstrated to reduce TGF-β1 induced collagen production when cultured with Shikonin. This was demonstrated to be through alteration of the TGF-β1-SMAD intracellular signalling pathway [108]. This pathway further prevented FPCL by down-regulating alpha smooth muscle actin [108].

**Emodin**

Emodin is a resin derived from the Himalayan rhubarb, buckthorn and Japanese knotweed. It has been investigated for a number of therapeutic effects including asthma, arthritis and Alzheimer’s disease in a number of animal models [109–112]. Emodin has been shown to alter a number of intracellular signalling pathways including nuclear factor-kB and phosphoinositide 3 kinase/Akt [113], which plays a role in a number of cellular processes including the cell cycle. In vitro and in vivo studies have suggested that emodin may potentially play a role in preventing fibrosis in a number of organs [113–116].

Hypertrophic scars were developed through mechanical stress in an animal model, and emodin was administered intra peritoneally (10 mg/kg). Liu demonstrated that the emodin-treated hypertrophic scar group had an improved histopathological appearance compared to the control group; however, on removal of emodin at day 14, histopathology of the scar was only minimally improved at day 28 [113]. Emodin further inhibited the inflammatory response in the hypertrophic scars (tumor necrosis factor (TNF)-α monocyte chemoattractant protein (MCP)-1, interleukin (IL)-6). Emodin was shown to reduce the activation of PI3K and Akt in the hypertrophic fibroblasts, but this was not reciprocated in normal fibroblasts [113].

**Non-plant-based therapeutics**

**Honey**

Honey has been shown to have anti-bacterial properties through the presence of inhibines which consist of hydrogen peroxide, flavonoids, phenolic acids and other as yet unidentified substances [117, 118]. Other non-peroxide anti-microbial factors have been identified in honey depending on the floral sources, origin and processing [119–123]. However, studies have implicated that it is not simply its anti-microbial properties that confer its effectiveness in treating wounds [124]. Honey activates various components of the immune system in vitro...
Table 1 Natural therapeutics, where they originate from, their potential mechanism of action and known adverse events, bioavailability and drug interactions

| Natural therapeutic agent | Origin | Mechanism of action(s) | Administered | Known adverse effects or potential issue with use |
|---------------------------|--------|------------------------|--------------|--------------------------------------------------|
| Quercetin                 | Flavonoid found in plants, vegetables and fruits | • Blocks TGF-β (inhibits receptor expression and SMAD2/3 nuclear translocation)—in turn alters collagen expression [62]  
• Alters IGF-1 signalling (through reduction in receptor and intracellular signalling)—in turn affects keloid fibroblast proliferation [63]  
• Reduces collagen contraction [65] | In vitro [62, 63, 65] | Bioavailability is problematic though studies have suggested potential ways to improve its availability [152]  
• Adverse events appear mild [153, 154]  
• Interacts with some drugs, e.g. fluoroquinolones, taxol/paclitaxel [144, 145] |
| Onion extract (kaempferol, Mederma®, Contractubex®, Cybele®, Erasé gel, Kaloidon gel) | Onion | • Up-regulates MMP-1 [68] | In vitro (human skin fibroblasts) [68]  
In vivo (hairless mice administered with ointment) [68] | No adverse events [69, 72]  
• Moderate pruritus, all other adverse events less than the use of corticosteroids [73] |
| Resveratrol                | Grape skin, red wine and peanuts | • Inhibits fibroblast cell growth, causes cell cycle arrest and induces apoptosis which result in reduced collagen expression [79]  
• Reduced TGF-β1 protein in keloid fibroblasts (n = 5), reduced cell proliferation and induced apoptosis but did not decrease collagen type I, alpha smooth muscle actin or heat shock protein 47 in normal skin fibroblasts (n = 1) [81] | In vivo (hypertrophic-derived fibroblasts, normal skin fibroblasts) [79]  
In vitro (keloid fibroblasts) [81] | In vitro appears to have no genotoxic activity [155]  
Resveratrol (administered orally) in a number of studies in humans both symptomatic (e.g. Alzheimer’s patients, obese patients) and healthy showed minor adverse events, the most common being nausea, weight loss, diarrhoea and skin rash [140, 156, 157]  
• One individual showed elevated hepatic ALT and AST (grade 4) which returned to normal after stopping the medication [140]  
• Boocock et al. [149] suggested oral administration may not be sufficient for some therapeutic roles of resveratrol |
| Epigallocatechin gallate   | Green tea | • Prevents PDGF-BB binding to its receptor and leads to prevention of proliferation and collagen gel contraction [83, 85]  
• Known to inhibit a number of intracellular signalling pathways and thereby reducing pro-fibrotic gene expression [86–88] and ECM production [84] | In vitro (neonatal fibroblasts) [83]  
In vitro (human/rat vascular smooth muscle cells) [85]  
In vitro (post-natal human dermal fibroblasts) [84]  
In vitro (rat cardiac fibroblasts) [86]  
In vitro (human gingival fibroblasts) [87]  
In vitro (human umbilical vein endothelial cells) [88] | ECGC appears well tolerated with oral administration [158–160] or used on the skin [161]  
• Adverse events include mild gastrointestinal issues and skin rashes [158, 160, 161]  
• Polyphenon E has been linked to elevated liver function tests but this appeared related to the LOT [141] though a case study showed a case of drug-induced hepatitis [142] and other studies have shown minor increase in liver markers [162]  
• Number of chemotherapy agents [146]  
• Animal model associated with male infertility [163]  
• Oral administration in an animal model (dose, 225–135 mg/kg) for 5 days. Liver injury observed at doses of 90 mg/kg and above [138]  
• Bardoxolone methyl—semi-synthetic triterpenoid based on the scaffold of oleanolic acid—caused heart failure in patients with stage 4 chronic kidney disease [139] |
| Oleanolic acid             | Number of foods, for example, olive oil, garlic, etc | • Decreased TGF-β1 and collagen I and III and increased MMP-1 [93] possibly through decreased fibroblast proliferation, increased apoptosis and degradation of collagen types I and III through enhanced MMP-2 activity [94] | In vivo (rabbit ear model for hypertrophic scars; applied as an ointment) [93, 94] | • Animal model associated with male infertility [163]  
• Oral administration in an animal model (dose, 225–135 mg/kg) for 5 days. Liver injury observed at doses of 90 mg/kg and above [138]  
• Bardoxolone methyl—semi-synthetic triterpenoid based on the scaffold of oleanolic acid—caused heart failure in patients with stage 4 chronic kidney disease [139] |
and in vivo which not only activates the immune response but also tissue repair [125–129].

To date, there have been mixed results with the use of honey on wounds. Nakajima and colleagues using a mouse model and three forms of Japanese honey found that the use of honey had little benefit in wound healing [130]. Gupta and colleagues retrospectively compared the hospital records of burns patients who had been treated with either honey dressings or silver sulfadiazine dressings over a period of 5 years [131]. They found that honey enhanced healing, reduced contractures and had better overall outcome compared to silver sulfadiazine [131]. Others have confirmed the beneficial effects of honey and healing time when compared to other dressings including silver sulfadiazine-, film- and gauze-based dressings [132, 133]. However, silver sulfadiazine has been shown to delay healing and increase pain and infection rates and may therefore have not been the best comparator [134]. Honey’s anti-inflammatory effect is proposed as the reason why honey reduces fibrosis and scarring [135–137].

### Table 1: Natural therapeutics, where they originate from, their potential mechanism of action and known adverse events, bioavailability and drug interactions (Continued)

| Natural Therapeutic | Source/Origin | Mechanism of Action | Adverse Events/Bioavailability/Drug Interactions |
|---------------------|---------------|---------------------|-----------------------------------------------|
| Curcumin Rhizome of *Curcuma longa* and related species. | *Induces fibroblast apoptosis and reduced collagen gel contraction [99] via ROS mechanism* | Poor bioavailability especially after oral administration [164] | - Appears well tolerated up to 8 g/day up to 3 months [164, 165] - Adverse effects may change with adaptations that are used to improve bioavailability - Chelate iron suppresses hepcidin therefore potentially causing iron deficiency [166] - Interacts with 5-fluorouracil and vinorelbine [140, 147, 148, 156] |
| Shikonin Chinese herbRadix Arnebiae | *Induces apoptosis in fibroblasts [106]* | Low bioavailability due to high lipophility [167] altered through the formation of a complex with other proteins [150] | - Not known as yet |
| Emodin Derived from the Himalayan rhabarb, buckthorn and Japanese knotweed | *Alters the intracellular pathway of PI3K and Akt but only in hypertrophic scar-derived fibroblasts [113]* and this in turn inhibited the inflammatory response and improved the histopathology appearance of the scar [113] | | |
| Honey | *Accelerates wound healing due to its anti- bacterial activity, anti-oxidant activity, stimulator effects and anti-inflammatory effects [135–137]* | | |

**TGF-β1** transforming growth factor beta 1, **IGF-1** insulinlike growth factor-1, **MMP** matrix metalloproteinase, **PDGF-BB** platelet-derived growth factor-BB, **ECM** extracellular matrix, **RGCg** epigallocatechin gallate, **ROS** reactive oxygen species

**Adverse events, bioavailability interactions and synergistic effects**

Though considered ‘natural’, most of the products are synthetically manufactured; further, even some ‘natural’ products have been identified as causing toxicities (Table 1) [138, 139]. There have been limited toxicity studies conducted on the natural therapeutics discussed in this review, though those used in human studies appear to have mild adverse events recorded (such as honey, onion extract, quercetin; Table 1). Though there have been individuals who appear to have increased adverse events, resveratrol saw one individual in a study show grade 4 elevation of their liver function markers after 3 months treatment of 1 g of resveratrol daily [140]. The patient’s markers returned to normal after discontinuing the medication. EGCG has also shown in some individuals to elevate liver function tests though a case study did identify drug-induced hepatitis with the use of a concentrated green tea extract [142]. Oleanolic acid in animal studies suggests that repeated...
oral administration can cause liver injury [138]. Oleano-
lic acid derivatives have also been shown to be related to
fluid overload which in some individuals resulted in
heart failure in patients with stage 4 chronic renal dis-
ease (8.8 % of the treated group compared to 5 % of the
placebo group) [139].

It has been well recognised that some herbal products
can interact with medicinal drugs and reduce or prevent
their effectiveness, e.g. St John’s wort (Hypericum per-
foratum), and in some cases, alter the efficacy of medi-
cinal drugs [143]. A number of the products discussed in
this paper have also been shown to interact with
other drugs including antibiotics (fluoroquinolones) and
chemotherapy agents [144–148].

A number of the agents have been shown to have low
bioavailability (quercetin, curcumin, shikonin), and others
have been suggested that oral administration may not be
sufficient for therapeutic levels to be reached or indeed
maintained [149]. Further, those that have low bioavail-
ability which are then either manipulated or other pro-
tains added this structural alteration may affect both
adverse events and the actual therapeutic mechanisms
[150, 151]. To date, there remains a paucity of information
in regard to the safety of some of these agents in their use
as anti-scarring products.

Conclusions
In vitro and in vivo studies have shown that a number of
‘natural’ therapeutic agent and strategies may play a role
in the future treatment of scarring, particularly hyper-
trophic scarring which is so intrinsically linked with
burn injuries. There remains no gold standard in the
treatment or prevention of scarring. It remains problem-
atic comparing all products not just natural therapeutics
in part due to the number of methodologies used to
assess the effectiveness of anti-scarring therapeutics and
the number of models used. Further, those that do
undergo clinical trials, the variation in patients and out-
come measures is immense leading to problems in com-
paring agents and is often undertaken once the scar has
formed. There is a theoretical risk which agents that re-
duce or prevent scarring may in turn prevent or
lengthen the wound healing process, and this has yet to
be elucidated. However, it appears that there is a poten-
tial for a natural therapeutic as either a monotherapy or
as an adjunct to play a role in treating or even prevent-
ing hypertrophic scarring.

Abbreviations
ECM: extracellular matrix; FPCL: fibroblast-populated collagen lattice;
MMP: matrix metalloproteinase.

Competing interests
The authors declare they have no competing interests.

Authors’ contributions
KR conceived the idea and drafted the manuscript. MM and OB participated in
the design and coordination. All authors read and approved the final manuscript.

Author details
1British College of Osteopathic Medicine (BCOM), Finchley Road, London
NW3 5HR, UK. 2The Royal Marsden Hospital, Fulham Rd, London SW3 6JJ, UK.

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References
1. World Health Organization http://www.who.int/mediacentre/factsheets/
fs365/en/ Accessed 5th Jan 2016
2. American Burn Association. http://ameriburn.org/resources_fact sheet.php
accessed 9th Jul 2015
3. WHO http://www.who.int/violence_injury_prevention/other_injury/burns/
en/ Accessed 9th Jul 2015
4. Sheridan RL. Burn care: results of technical and organizational progress.
JAMA. 2003;290:719–22.
5. Singer AJ, Clark RA. Cutaneous wound healing. N Engl J Med. 1999;341:738–46.
6. Gauglitz GG, Korting HC, Pavicic T, Ruzicka T, Jeschke MG. Hypertrophic
Scarring and Keloids: Pathomechanisms and Current and Emerging
Treatment Strategies. Mol Med. 2011;17(1–2):113–25.
7. Deitch EA, Wheelahan TM, Rose MP, Clothier J, Cotter J. Hypertrophic burn
scars: analysis of variables. J Trauma. 1983;23:895–8.
8. McDonald WS, Deitch EA. Hypertrophic skin grafts in burned patients: a
prospective analysis of variables. J Trauma. 1987;27:147–50.
9. Spurr ED, Shakespeare PG. Incidence of hypertrophic scarring in burn-
injured children. Burns. 1990;16:79–81.
10. Dedovic Z, Koupilova I, Brychta P. Time trends in incidence of hypertrophic
scarring in children treated for burns. Acta Chir Plast. 1999;41(3):87–90.
11. Bombaro KM, Engrav LH, Carrougher GJ, Wiechman SA, Faucher L, Costa BA,
et al. What is the prevalence of hypertrophic scarring following burns?
Burns. 2003:299–302.
12. Gangemi EN, Gregori D, Bierchiala P, Zingarelli E, Cairo M, Bollero D, et al.
Epidemiology and the risk factors for pathologic scarring after burn
wounds. Arch Facial Plast Surg. 2008;10:93–102.
13. Schneider JC, Holvanahalli R, Helm P, Goldstein R, Kowalskie K. Contractures
in burn injury; defining the problem. J Burn Care Res. 2006;27:508–14.
14. Tredget EE. Pathophysiology and treatment of fibroproliferative disorders
following thermal injury. Ann N Y Acad Sci. 1999;888:165–82.
15. Ali SS, Hajrah NH, Ayoub NN, Mosthiff SS, Abuzinadah DA. Morphological
and morphometric study of cultured fibroblast from treated and untreated
abdominal scar. Saudi Med J. 2010;30:874–81.
16. Schmid P, Itin P, Bi C, Cox DA. Enhanced expression of transforming growth
factor-beta type I and type II receptors in wound granulation tissue and
hypertrophic scar. Am J Pathol. 1998;152:485–93.
17. Wang R, Ghahary A, Shen Q, Scott PG, Roy K, Tredget EE. Hypertrophic scar
in injured skin contracts more transforming growth factor-beta 1
mRNA and protein than normal skin and cells. Wound Repair and Regen.
2000;8:128–37.
18. Xie JL, Qi SH, Pan S, Xu YB, Li TZ, Liu XS, et al. Expression of Smad proteins
by normal skin fibroblasts and hypertrophic scar fibroblasts in response to
transforming growth factor beta 1. Dermatol Surg. 2008;34:1216–24.
19. Kopp J, Preis E, Said H, Hafemann B, Wickert L, Gresner MM, et al.
Abrogation of transforming growth factor-B signalling by SMAD 7 inhibits
collagen gel contraction of human dermal fibroblasts. J Biol Chem. 2006;
281(21):15708–6.
20. Ashcroft GS, Yang X, Glick AB, Weinstein M, Letterio JL, Mizel DE, et al. Mice
lacking Smad3 show accelerated wound healing and an impaired local
inflammatory response. Nat Cell Biol. 1999;1(5):260–6.
21. Sumiyoshi K, Nakao A, Setoguchi Y, Okumura K, Ogawa H. Exogenous
Smad3 accelerates wound healing in a rabbit derma ulcer model. J Invest
Dermatol. 2004;123:229–36.
22. Setoguchi Y, Jaffe HA, Daniel C, Crystel RG. Es vivo and in vivo gene transfer
to the skin using replication-deficient recombinant adenovirus vectors. J
Invest Dermatol. 1994;102:415–21.
23. Scott PG, Dodd CM, Tredget EE, Ghahary A, Rahemtulla F. Chemical
characterisation and quantification of proteoglycans in human post burn
hypertrophic and mature scars. Clin Sci (London). 1996;90:417–25.
24. Zhang Z, Garron TM, Li XJ, Liu Y, Zhang X, Li YY, et al. Recombinant human decorin inhibits TGF-beta 1 induced contraction of collagen lattice by hypertrophic scar fibroblasts. Burns. 2003;29(4):527–37.

25. Linge C, Richardson J, Vigor C, Clayton E, Hardas B, Rolfe K. Hypertrophic scars cells fail to undergo a form of apoptosis specific to contractile collagen–the role of transglutaminase. J Invest Dermatol. 2005;127:72–83.

26. Hinr Z, Gabbiani G. Cell-matrix and cell-cell contacts of myofibroblasts: role in connective tissue remodeling. Thromb Haemost. 2003;90(6):993–1002.

27. Moulin V, Larocheille S, Langlois C, Thibault I, Lopez-Valle CA, Roy M. Normal skin wound and hypertrophic scar fibroblasts have differential responses to apoptotic inducers. J Cell Physiol. 2004;198(3):350–8.

28. Yang L, Scott PG, Gujfe J, Shankowsky HA, Ghahary A, Tredget EE. Peripheral blood fibrocytes from burn patients: identification and quantification of fibrocytes in adherent cells cultured from peripheral blood mononuclear cells. Lab Invest. 2002;82:1183–92.

29. Yang L, Scott PG, Dodd C, Medina A, Jiao H, Shankowsky HA, et al. Identification of fibrocytes in post burn hypertrophic scar. Wound Repair Regen. 2005;13(4):398–404.

30. Wang J, Jiao H, Stewart TL, Shankowsky HA, Scott PG, Tredget EE. Increased TGF-beta-producing CD4+ T lymphocytes in post burn patients and their potential interaction with dermal fibroblasts in hypertrophic scar. Wound Repair Regen. 2007;15(4):530–9.

31. Eto H, Suga H, Aoi N, Kato H, Doi K, Kuno S, et al. Therapeutic potential of fibroblast growth factor-2 for hypertrophic scars: up regulation of MMP-1 and HGF expression. Lab Invest. 2012;92:214–33.

32. Neely AN, Olinger CE, Gardner J, Greenhalgh DG, Warden GO. Gelatinase activity in keloids and hypertrophic scars. Wound Repair Regen. 1999;7(3):166–71.

33. Mauviel A. Cytokine regulation of metalloproteinase gene expression. J Cell Biochem. 1993;53:288–95.

34. Zhang Y, McCluskey K, Fuji K, Wahl LM. Differential regulation of metalloproteinase and TIMP-1 production by TNF-alpha, granulocyte – macrophage CSF and IL-1 beta through prostaglandin dependent and independent mechanisms. J Immunol. 1998;161:3071–6.

35. Tredget EE, Yang L, Delechanty M, Shankowsky H, Scott PG. Polarized T helper cells Th2 cytokine production in patients with hypertrophic scar following thermal injury. J Interferon Cytokine Res. 2005;26:179–89.

36. Wang J, Hori K, Ding J, Huang Y, Kwan P, Lakad A, et al. Toll-like receptors expressed by dermal fibroblasts contribute to hypertrophic scar healing. J Cell Physiol. 2011;226(5):1265–73.

37. Liuza F, Chadwick S, Shah M. Paediatric post-burn scar management in the UK: A national survey. Burns. 2015;41(2):252–6.

38. Sidgwick GP, McGeorge D, Bayat A. A comprehensive evidence-based review on the role of topical and dressings in the management of skin scarring. Arch Dermatol Res. 2015;307:461–77.

39. Stewart TL, AS, Schenbri PJ, Hori K, Ding J, Shankowsky HA, et al. The use of laser Doppler imaging as a predictor of burn depth and hypertrophic scar post burn injury. J Burn Care. 2012;33(6):764–71.

40. Kwan PO, Ding J, Tredget EE. Serum decorin, IL-1β and TGF-β predict hypertrophic scar post burn. J Burn Care Res. In press.

41. Anzurat A, Olson J, Singh P, Rowe BH, Tredget EE. The effectiveness of pressure garment therapy for the prevention of abnormal scarring after burn injury: a meta-analysis. J Plast Reconstr Aesthet Surg. 2009;62(1):77–84.

42. Elav GH, Heimbach DM, Rivara FP, Moore ML, Wang J, Carroughe JJ, et al. Twelve-year within-wound study of the effectiveness of custom pressure garment use in burn rehabilitation. J Burn Care Rehab. 2003;24(6):411–7.

43. Choi J, Lee EH, Park SW, Chang H. Regulation of Transforming growth factor β1, platelet-derived growth factor, and basic fibroblast growth factor by silicone gel sheeting in early-stage scarring. Arch Plast Surg. 2015;42(1):120–7.

44. Gauglitz GG. Management of keloids and hypertrophic scars: current and emerging options. Clin Cosmet Invest Dermatol. 2013;6:103–14.

45. Roques C, Téot L. The use of corticosteroids to treat keloids: A review. Int J of Low Extrem Wounds. 2008;7(3):137–45.

46. Manuskiatti W, Fitzpatrick RE. Treatment response of keloidal and hypertrophic stromatoxyc scars: comparison among intralesional corticosteroid, 5-fluouracil, and 585 nm flashlamp-pumped pulse dye laser treatments. Arch Dermatol. 2002;138(9):1149–55.

47. Tredget EE, Levi B, Donelan MB. Biology and principles of scar management and burn reconstruction. Surg Clin North Am. 2014;94(4):793–815.

48. Rabello BF, Souza CD, Júnior JAF. Update on hypertrophic scar treatment. Clinics. 2014;69(8):565–573.

49. Ye Q, Wang S-J, Chen J-Y, Rahman K, Hai-Liang X, Zhang H. Medicinal plants for the treatment of hypertrophic scars. Evid Based Complement Alternat Med. 2015;2015:101340.

50. Ross JA, Kasum CM. Dietary flavonoids: bioavailability, metabolic effects, and safety. Annu Rev Nutr. 2003;22:19–34.

51. Bors W, Heller W, Michel C, Saran M. Flavonoids as antioxidants. Determination of radical-scavenging efficiencies. Methods Enzymol. 1990; 186:343–55.

52. Lamson DW, Brigman NS. Antioxidants and cancer, part 3: Quercetin. Altern Med Rev. 2000;5:196–208.

53. Prior RL. Fruits and vegetables in the prevention of cellular oxidative damage. Am J Clin Nutr. 2003;78:570–85.

54. Williams RJ, Spencer JP. Rice-Evans C. Flavonoids: antioxidants or signalling molecules? Free Radic Biol Med. 2004;36:7838–49.

55. Barnes S, Prasain J, D’Alessandro T, Arabahali A, Botting N, Lila MA, et al. The metabolism and analysis of isoflavones and other dietary polyphenols in foods and biological systems. Food Function. 2011:2(5):235.

56. Phan TT, Lim U, Chan SY, Tan EK, Lee ST, Longaker MT. Suppression of transforming growth factor beta/Smad signalling in keloid derived fibroblasts by quercetin: implications for the treatment of excessive scars. J Trauma. 2004;57(5):1032–7.

57. Phan TT, Sun L, Tran E, Nguyen TT, Chan SY, Lee ST, et al. Suppression of insulin like growth factor signalling pathway and collagen expression in keloid derived fibroblasts by quercetin: its therapeutic potential use in the treatment and/or prevention of keloids. Br J Dermatol. 2003;148(3):544–52.

58. Long X, Zeng X, Zhang QF. Influence of quercetin and aryan collagen synthesis of cultured human keloid fibroblasts. Chin Med Sci J. 2006;21(3):179–83.

59. Phan TT, Sun L, Bay BH, Chan SY, Lee ST. Dietary compounds inhibit proliferation and contraction of keloid and hypertrophic scar derived fibroblasts in vitro: therapeutic implications for excessive scarring. J Trauma. 2003;54(6):1212–24.

60. Saulis A, Mogford JH, Mustoe TA. Effect of Mederma on hypertrophic scar formation in the rabbit ear model. Plast Reconstr Surg. 2002;109(1):77–83.

61. Augusti T. Therapeutic values of onion (Allium cepa L.) and garlic (Allium sativum L.). Indian J Exp Biol. 1996;34(7):634–40.

62. Cho J-W, Cho S-Y, Lee S-R, Lee K-S. Onion extract and quercetin induce matrix synthesis of cultured human keloid fibroblasts in vitro and in vivo. Int J Mol Med. 2010;25:347–52.

63. Chanprapaph K, Tannattanakom S, Wattanakrai P, et al. Effectiveness of onion extract gel on surgical scars in Asians. Dermatol Res Pract. 2012;2012: 212945.

64. Ho WS, Ying SY, Chan PC, Chan HH. Use of onion extract, heparin, allantoin gel in prevention of scar in Chinese patients having laser removal of tattoos: A prospective randomized controlled trial. Dermatol Surg. 2006;32(7):1891–5.

65. Wananukul S, Chatpreedprai S, Peongujjarit D, Lertsapcharoen P. A prospective placebo-controlled study on the efficacy of onion extract in silicone derivative gel for the prevention of hypertrophic scar and keloid in median sternotomy wound in pediatric patients. J Med Assoc Thai. 2013; 96(11):1428–33.

66. Jenwitheesuk K, Surakunprapha P, Jenwitheesuk K, Kuptamond C, Prathanee S, Intanoo W. Role of silicone derivative plus onion extract gel in pretermal delivery.
hypertrophic scar protection: a prospective randomized, double blinded, controlled trial. Int Wound J. 2012;9:397–402.

73. Beuth J, Hunzelmann N, van Leendert R, Basten R, Noehle M, Schenider B. Safety and Efficacy of Local Administration of Contractubex® to Hypertrophic Scars in Comparison to Corticosteroid Treatment. Results of a Multicenter, Comparative Epidemiological Cohort Study in Germany. In: 2006;20:277–84.

74. George J, Singh M, Srivastava AK, Bhu K, Roy P, Chaturvedi PK, et al. Resveratrol and Black Tea Polyphenol Combination Synergistically Suppresses Mouse Skin Tumour Growth by Inhibition of Activated MAPKs and p53. PLoS ONE. 2011;6:e23395.

75. Hirota Y, Tadokoro K, Tuda T, Nakazoe E, Ohnaka K, Takayanagi R, et al. Resveratrol, a phytoestrogen found in red wine, down-regulates protein S expression in HepG2 cells. Thrombos Res. 2011;127:e1–7.

76. Olson ER, Naugle JE, Zhang X, Bomser JA, Meszaros JG. Inhibition of cardiac fibroblast proliferation and myofibroblast differentiation by resveratrol. Am J Physiol Heart Circ Physiol. 2005;288(3):1131–8.

77. Giller M, Fritsch-Breisch M, Lohberger B, Walther SM, Moazed-Fuerst F, Rinner B, et al. Influence of resveratrol on rheumatoid fibroblast-like synoviocytes analysed with gene chip transcription. Phytomedicine. 2013;20:43–50.

78. Yao J, Wang JY, Liu L, Li XY, Xun AY, Zeng WS, et al. Anti-oxidant effects of resveratrol on mice with DSS-induced ulcerative colitis. Arch Med Res. 2010;41(3):288–94.

79. Geng Z, Zhong F, Luo JL, Zhang P. Resveratrol mediated reduction of collagen by inhibiting proliferation and producing apoptosis in human hypertrophic scar fibroblasts. Biosci Biotechnol Biochem. 2013;77(12):2389–96.

80. Sogutlu G, Karabulut AB, Ara C, Cinpolat O, Isik B, Piskin T, et al. The effect of resveratrol on surgery induced periodontal adhesions in an experimental model. Cell Biochem Funct. 2007;25(2):217–20.

81. Ikeda K, Torioe T, Matsumoto Y, Fujita T, Sato N, Yotsuyanagi T. Resveratrol inhibits fibrogenesis and induces apoptosis in kciob fibroblasts. Wound Repair Regen. 2013;21:166–23.

82. Branford OA, Grobbelaar AO, Rolfe KJ. Epigallocatechin-3-gallate (EGCG), a constituent of green tea and its anti-fibrotic effect. In Tea Consumption and Health Nova. 2004:68:1817–20.

83. Suzuki Y, Hatton S, Isamura M. Epigallocatechin-3-O-gallate inhibits fibroblast contraction of floating collagen gel. Interaction between epigallocatechin-3-O-gallate and platelet derived growth factor. Biosci Biotechnol Biochem. 2004;68:1817–20.

84. Klass BR, Branford OA, Grobbelaar AO, Rolfe KJ. The effect of epigallocatechin-3-gallate, a constituent of green tea, on transforming growth factor-beta1-stimulated wound contraction. Wound Repair Regen. 2010;18(1):1–8.

85. Weber AA, Neuhaus T, Skach RA, Hatcher J, Ahn HY, Schörr K, et al. Mechanism of the inhibitory effects of epigallocatechin-3 gallate on platelet-derived growth factor-BB induced cell signalling and mitogenesis. FASEB J. 2004;18:128–30.

86. Ca’ Y, Yu SS, Chen TT, Gao S, Geng B, Yu Y, et al. EGCG inhibits CTGF expression via blocking NF-κB activation in cardiac fibroblast. Phytomedicine. 2013;20(2):106–13.

87. Wang CY, Deng YT, Huang SY, Liu OM, Chang HH, Wong MY. Epigallocatechin-3-gallate inhibits lypo-phosphatic acid-stimulated connective growth factor via JNK and Smad3 suppression in human gingival fibroblasts. J Formos Med Assoc. 2014;113(1):50–5.

88. Moyle CW, Cerezo AB, Winterborne MS, Hollands WJ, Alexeev Y, Needs PW, et al. Potent inhibition of VEGFR-2 activation by tight binding of green tea polyphenols. J Med Chem. 2007;50:7451–5.

89. Hafina LA, Elnour IA, El-Demady A. Inhibition of VEGFR-2 activation in cardiac fibroblast. J Biochem. 2014;155:123–7.

90. Wang R, Yin R, Zhou W, Xu D, Li S. Shi-Kionin and its derivatives: a patent review. Expert Opin Ther Pat. 2012;22:977–97.

91. Wang Y, Fabritius M.C. Chemotherapeutic sensitization by endoplasmic reticulum stress: increasing the efficacy of taxane against prostate cancer. Cancer Biol Ther. 2009;8:146–52.

92. Yang JT, Li ZL, Wu JY, Lu FJ, Chen CH. An oxidative stress mechanism of shikonin in human glioma cells. PLoS One. 2014;9:e94180.

93. Chang IC, Huang YJ, Chiang CW, Yeh LS. Shikonin induces apoptosis through reactive oxygen species/extracellular signal-regulated kinase pathway in osteosarcoma cells. Biomark Diagn. 2011;2:186–24.

94. Hashimoto S, Xu M, Masuda T, Auichi S, Iako J, Lu M, et al. Beta-hydroxyisovanillosilyshikonin inhibits the cell growth of various cancer cells line and induces apoptosis in leukemia HL-60 cells through a mechanism different from those of Fas and etoposide. J Biochem. 1999;125:17–23.

95. Gao D, Hiromura M, Yasui H, Sakarui H. Direct reaction between Shikonin and thiol induces apoptosis in H660 cells. Biol Pharm. 2002:25:827–82.

96. Fan C, Xie Y, Dong Y, Zou Y, Upton Z. Investigating the potential of Shikonin as a novel hypertrophic scar treatment. J Biomed Sci. 2015;22:70.

97. Xie Y, Fan C, Dong Y, Lynam E, Levesdale DI, Li K, et al. Functional and mechanistic investigation of Shikonin in scar. Chemico-Bio Interact. 2015;228:18–27.

98. Fan C, Dong Y, Xie Y, Su Y, Zhang X, Levesdale D, et al. Shikonin reduces TGF-β1-induced collagen production and contraction in hypertrophic scar derived fibroblasts. Int J Mol Med. 2015;36:985–91.

99. Wang T, Zhong XG, Li YH, Zhang SJ, Gao YS, et al. Protective effect of emodin against airway inflammation in the ovalbumin-induced mouse model. Chin J Integr Med. 2015;21:431–7.

100. Zhu X, Zeng K, Qiu Y, Yan F, Lin C. Therapeutic effect of emodin on collagen-induced arthritis in mice. Inflammation. 2013;36:1253–9.

101. Sun YP, Liu JP. Blockade of emodin on amyloid-β 26-35-induced neurotoxicity in AβPP/PS1 mice and PC12 cells through activation of the class III phosphatidylinositol 3-kinase/Beclin-1/B cells lymphoma 2 pathway. PLoS One. 2015;10:1–8.

102. Shimall D, Shanmugam MK, Kumar AP, Zhang J, Tan BK, Sethi G. Targeted abrogation of diverse signal transduction cascades by emodin for the treatment of inflammatory disorders and cancer. Cancer Lett. 2013;341:139–49.

103. Liu C. Inhibition of mechanical stress-induced hypertrophic scar inflammation by emodin. Molec Med Rep. 2015;11:4087–92.

104. Hu Q, Noor M, Wong YF, Hylands PJ, Simmonds MS, Xu Q, et al. In vitro anti-fibrotic activities of herbal compounds and herbs. Nephrol Dial Transplant. 2009;24:3033–41.

105. Chen XH, Sun RS, Hu JM, Mo ZF, Yang ZF, Jin GT, et al. Inhibitory effect of emodin on bleomycin-induced pulmonary fibrosis in mice. Clin Exp Pharmacol Physiol. 2009;36:146–53.

106. Dong MX, Jia Y, Zhang YB, Li CC, Geng YT, Zhou L, et al. Emodin protects against the development of skin fibrosis and induced fibrogenesis via inhibition of hepatic stellate cells activation. World J Gastroenterol. 2009;15:753–62.

107. Schepartz AI, Subers NH. Catecholase in honey. J Apic Res. 1996;35:57–43.
118. Subrahmanyan M. Addition of antioxidant and polyethylene glycol 4000 enhances the healing property of honey in burns. Ann Burns Fire Disast. 1996;93:3–5.

119. Brady NF, Molan PC, Harfoot CG. The sensitivity of dermatophytes to the antimicrobial activity of manuka honey and other honey. Pharm Sci. 1997:21–3.

120. Welhan H. Causes of the antimicrobial activity of honey. Infection. 1998;26:–31.

121. Lu J, Carter DA, Turnbull L, Rosendale D, Hedderley D, Stephens J, et al. The Effect of New Zealand Kanuka, Manuka and Clover Honeys on Bacterial Growth Dynamics; and Cellular Morphology Varies According to the Species. PLoS ONE. 2013;8(5):55988.

122. Rufian-Henares JA, Morales FJ. Functional properties of melanoids: In vitro antioxidant, antimicrobial and anthyptensive activities. Food Res Int. 2007; 40:999–1002.

123. Macedo E, Wittmann S, Barth G, Henke T. Identification and quantification of methylglyoxal as the dominant antibacterial constituent of Manuka (Leptospermum scoparium) honeys from New Zealand. Mol Nutr Food Res. 2008;52:483–9.

124. Kivlinn PH, lelVeld AA, de Boer L, Spejer D, Vandenbroucke-Grauls CM, Zaat SA. How honey kills bacteria. FASEB J. 2010;24:2576–82.

125. Subrahmanyan M, Hemmady A, Pawar SG. The sensitivity to honey of multidrug-resistant Pseudomonas Aeruginosa from infected burns. Ann Burns Fire Disasters. 2003;16:94–6.

126. Abuherf N, Al-Omran R, Abo-Shehada M. The effect of bee honey on the proliferative activity of human B- and T-lymphocytes and the activity of phagocytes. Food Agric Immunol. 1999;11:69–77.

127. Tonks A, Cooper RA, Price AJ, Molan PC, Jones KP. Stimulation of TNF-alpha production by human monocytes: effects on systemic sex ster.

128. Tonks AJ, Cooper RA, Jones KP, Blair S, Parton J, Tanks A. Honey stimulates proliferative activity of human B- and T-lymphocytes and the activity of phagocytes. Food Agric Immunol. 1999;11:69–77.

129. Tokns A, Cooper RA, Price AJ, Molan PC, Jones KP. Stimulation of TNF-alpha release in monocytes by honey. Cytokine. 2001;14:2420–2.

130. Tokns A, Cooper RA, Jones KP, Blair S, Parton J, Tanks A. Honey stimulates inflammatory cytokine production from monocytes. Cytokine. 2003;21:242–7.

131. Nakajima Y, Nakano Y, Fuwano S, Hayahi N, Kinosita A, Miyahara M, et al. Effects of three types of Japanese honey on full thickness wound in mice. Evid Based Complement Alternat Med. 2013;2013:504537.

132. Gupta SS, Singh O, Bhagel PS, Moses S, Shukla S, Mathur RK. Honey dressing prevents wound infection. Cochrane Database Syst Rev. 2010;17(3):CD006478.

133. Wasiak J, Cleland H, Campbell F. Dressings for superficial and partial thickness burns. Cochrane Database Syst Rev. 2010;3:CD001837.

134. Brady NF, Molan PC, Harfoot CG. The sensitivity of dermatophytes to the antimicrobial activity of manuka honey and other honey. Pharm Sci. 1997:21–3.

135. Subrahmanyan M. Oleanolic acid alters bile metabolism in human liver microsomes. J Chemother. 2003;15:266–74.

136. Liu J, Lu Y-F, Zhang Y, Wu KC, Fan F, Klaassen CD. Oleanolic acid alters bile metabolism in human liver microsomes. J Chemother. 2003;15:266–74.

137. Sak K. Chemotherapy and dietary phytochemical agents. Chem Res Practice. 2012;2:28570.

138. Bun SS, Ciccolini J, Bun H, Aubert C, Catalin J. Drug interactions of paclitaxel with Trolox. J Nutr Biochem. 2003;14:1343–50.

139. Wang CZ, Luo X, Zhang B, Song WX, Ni M, Mehande S, et al. Nonotoginseng enhances anti-cancer effect of 5-Fluorouracil on human colorectal cancer cells. Cancer Chemother Pharmacol. 2007;60:69–79.

140. Sen S, Sharma H, Singh N. Curcumin enhances Vincristine mediated apoptosis in NSCLC cells by the mitochondrial pathway. Biochem Biophys Res Commun. 2005;331:1245–52.

141. Boocock DJ, Faust GE, Patel KR, Schinas AM, Brown VA, Ducharme MP, et al. Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent. Cancer Epidemiol Biomarkers Prev. 2007;16:1246–52.

142. Chen CY, Chen FA, Wu AB, Hsu HC, Kang JJ, Cheng HW. Effect of hydroxypropyl-β-cyclodextrin on the solubility, photo stability and in vitro permeability of alkanin/shikonin enantiomers. Int J Pharm. 1996;141:171–8.

143. Xia H, Tang C, Gui H, Wang X, Qi J, Wang X, et al. Preparation, cellular uptake and angiogenic suppression of shikonin-containing liposomes in vitro and in vivo. Bioso Rep. 2013;33:e00020.

144. Oththof MR, Hollman PCH, Vree TB, Katan MB. Bioavailabilities of quercetin-3-glucoside and quercetin-4-glucoside do not differ in humans. J Nutr. 2000; 130:1200–3.

145. Kiesswetter H, Koscielny J, Kalus U, Vix JM, Petirini O, van Toor BS, et al. Efficacy of orally administered extract of red vine leaf AS 195 (folia vitis viniferae) in chronic venous insufficiency (stages I-II). A randomized, double-blind, placebo-controlled trial. Arzneimittelforschung. 2000;50:109–17.

146. Erfurd I, Kosonen T, Affth J, Mäenpää J, Pertunen K, Kenna L, et al. Pharmacokinetics of quercetin from quercetin aglycone and rutin in healthy volunteers. Eur J Clin Pharmacol. 2000;56:545–53.

147. Lombardi G, Vannini S, Blasi F, Marcotullio MC, Dominici L, Villarin M, et al. In Vitro Safety/Protection Assessment of Resveratrol and Pterostilbene in a Human Hepatoma Cell Line (HepG2). Nat Prod Commun. 2015;10:1403–8.

148. Turner RS, Thomas RG, Craft S, van Dyck CH, Mintzer J, Reynolds BA, et al. A randomised double-blind, placebo controlled trial of resveratrol for Alzheimer disease. Neurology. 2015;85:1383–91.

149. van der Made SM, Plat J, Mensink RP. Resveratrol does not influence metabolic risk markers related to cardiovascular health in overweight and slightly obese subjects: a randomized, placebo-controlled crossover trial. PLoS One. 2015;10:e0118393.

150. Joe AK, Schnol-Sussman F, Breashears AB, Abrams JA, Hibshoosh H, Cheung K, et al. Escalation Study of Polyphenon E in Patients with Barrett’s Esophagus. Cancer Prev Res. 2015;8:1131–7.

151. Chen Li, Liu CY, Chu JP, Hus CH. Therapeutic effect of high-dose green tea extract on weight reduction: A randomized, double-blind, placebo-controlled clinical trial. Clin Nutr. 2015; in press.

152. Chow HH, Cai Y, Hamkim IA, Crowell JA, Shahi F, Brooks CA, et al. Phase Ib Randomized, Double-Blinded, Placebo-Controlled, Dose Escalation Study of Polyphenon E in Patients with Barrett’s Esophagus. Res Commun. 2005;331:1245–9.

153. Wang CZ, Luo X, Zhang B, Song WX, Ni M, Mehendale S, et al. Nonotoginseng enhances anti-cancer effect of 5-Fluorouracil on human colorectal cancer cells. Cancer Chemother Pharmacol. 2007;60:69–79.

154. Xia H, Tang C, Gui H, Wang X, Qi J, Wang X, et al. Preparation, cellular uptake and angiogenic suppression of shikonin-containing liposomes in vitro and in vivo. Bioso Rep. 2013;33:e00020.

155. Mavric E, Wittmann S, Barth G, Henke T. Identification and quantification of methylglyoxal as the dominant antibacterial constituent of Manuka (Leptospermum scoparium) honeys from New Zealand. Mol Nutr Food Res. 2008;52:483–9.

156. Rufian-Henares JA, Morales FJ. Functional properties of melanoids: In vitro antioxidant, antimicrobial and anthyptensive activities. Food Res Int. 2007; 40:999–1002.

157. Mavric E, Wittmann S, Barth G, Henke T. Identification and quantification of methylglyoxal as the dominant antibacterial constituent of Manuka (Leptospermum scoparium) honeys from New Zealand. Mol Nutr Food Res. 2008;52:483–9.

158. Rufian-Henares JA, Morales FJ. Functional properties of melanoids: In vitro antioxidant, antimicrobial and anthyptensive activities. Food Res Int. 2007; 40:999–1002.
165. Goeal A, Kunnumakkara AB, Aggarwal BB. Curcumin as ‘Curemin’: from kitchen to clinic. Biochem Pharmacol. 2008;75:787–809.
166. Jiao Y, Wilkinson J, Di X, Wang W, Hatcher H, Kock ND, et al. Curcumin, a cancer chemopreventive and chemotherapeutic agent, is a biologically active iron chelator. Blood. 2009;113:462–9.
167. Albreht A, Vovk I, Simonovska B. Addition of β-lactoglobulin produces water-soluble shikonin. J Agric Food Chem. 2012;60:10834–43.
168. Su L, Liu L, Wang Y, Yan G, Zhang Y. Long-term systemic toxicity of shikonin derivatives in Wistar rats. Pharm Biol. 2014;52:486–90.
169. Simon A, Traynor K, Santos K, Blaser G, Bode U, Molan P. Medical Honey for Wound Care—Still the ‘Latest Resort’? Evid Based Complement Alternat Med. 2009;6:165–73.