The Role of Traditional Chinese Medicines in Osteogenesis and Angiogenesis

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The article aims to review various Traditional Chinese Medicines (TCMs) with both osteogenic and angiogenic effects, alone and in combination, and to consider whether these TCMs promote osteogenesis via angiogenesis and vascular endothelial growth factor (VEGF). Each of the TCMs involving in osteogenesis was searched through PubMed and CBMDisc using its Latin name and English name, and keywords such as ‘osteogenesis’, ‘bone’, ‘osteoblast’, ‘angiogenesis’, ‘VEGF’ were used. A total of 241 articles were screened from PubMed and CBMDisc. The articles were only chosen if they discussed the relationship of the TCMs with bone formation and/or angiogenesis. Twenty-seven articles were chosen, of which 16 were in English and 11 were in Chinese with English abstract. As a result, the TCMs (Danshen or Salvia miltiorrhiza Bunge, Danggui or Angelica sinensis, Astragalus membranaceus Bunge or Huangqi, and Ge Gan or Puerariae radix) that have a relationship with both osteogenesis and angiogenesis were screened out. It is found that the aforementioned TCMs enhance angiogenesis and osteogenesis. They show a positive effect on bone formation, and the possible mechanisms may be related to their ability to promote angiogenesis via an effect on substances such as VEGF.

Keywords: traditional Chinese medicines (TCMs); osteogenesis; angiogenesis; osteoblast; vascular endothelial growth factor (VEGF).

Abbreviations: Traditional Chinese medicines (TCMs); osteogenesis; angiogenesis; osteoblast; vascular endothelial growth factor (VEGF).

Received 31 October 2012
Revised 04 February 2013
Accepted 04 February 2013

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BACKGROUND

Bone is a highly vascularized tissue. In order for it to maintain homeostasis and regeneration, the development of microvasculature and microcirculation is crucial (Schmid et al., 1997). The process by which this occurs is known as angiogenesis. The formation of new vasculature transports oxygen, nutrients, and non-differentiated mesenchymal cells to the bone tissues that later can differentiate into cells such as osteoblasts, chondroblasts, or osteoclasts (Dai and Rabie, 2007). Many reports over the years demonstrated a close relationship between angiogenesis and fracture healing and bone formation. Experimental studies have shown that endothelial cells provide a microvasculature during bone remodeling (Erlebacher et al., 1995), and this vascular invasion is necessary for bone formation (Guenther et al., 1986; Rabie et al., 2002a; Augustin et al., 2007). Hence, the process of osteogenesis and angiogenesis are closely correlated (Rabie, 1997).

The underlying mechanism for angiogenesis lies in the action of VEGF. VEGF is a potent angiogenic peptide with mitogenic and chemotactic effects on endothelial cells (Gerber et al., 1999; Street et al., 2000; Geiger et al., 2005).

Many authors have reported VEGF’s effects on skeletal growth (Gerber et al., 1999; Ryan et al., 1999; Haigh et al., 2000; Street et al., 2000; Zelzer et al., 2002) and repair (Chu et al., 2002; Peng et al., 2002; Street et al., 2002). Some of them (Midy and Plouet, 1994; Wang et al., 1997; Ferrara, 1999; Gerber et al., 1999; Carlevaro et al., 2000; Deckers et al., 2000; Rabie et al., 2002b; Leung et al., 2004) have suggested a dual function of VEGF in bone growth including mandibular condylar growth: to recruit new blood supply and to help differentiation of osteoprogenitor cells. Yang et al. (2012) reviewed the role of VEGF in ossification and concluded that VEGF not only functions in bone angiogenesis but also in various aspects of bone development.

Mayr-Wohlfart et al. (2002) and Midy and Plouet (1994) have shown that VEGF can stimulate chemotactic migration of primary human osteoblasts. Also, it can stimulate cell proliferation by up to 70%, which suggests this hormone’s key role in bone formation and remodeling. In a research by Deckers et al. (2000), it was found that during bone formation and fracture healing, the VEGF produced by osteoblast-like cells in turn enhances osteoblastic differentiation by stimulating endothelial cells to secrete growth factors and cytokines that influence differentiation of mesenchymal cells to enter the osteogenic route (Wang et al., 1997; Trifitt et al., 1998;
Deckers et al. (2000) and thus amplifying this process (Głowacki, 1998). Gerber et al. (1999, 2000) and Street et al. (2002) found that not only did inhibition of VEGF during periods of rapid growth lead to inhibition of angiogenesis but it also led to decrease levels of osteoblast at growth plates in mice. Tan et al. (2010) found by an in vitro study that VEGF promoted bone remodeling by direct effects on osteoblastic cells via regulating gene expression of alkaline ALP, OCN, and OPG through VEGFR2 signaling pathway. All these studies give further credence to the role of VEGF as an essential coordinator of angiogenesis and osteogenesis.

Traditional Chinese Medicines (TCMs) have been used for centuries among the Chinese population to treat a variety of diseases and conditions. They may be used individually or in combination to form a formula in disease treatment. The wide variety of conditions that TCMs are used includes promotion of fractured bone healing and bone diseases such as osteoporosis (Li et al., 1998).

Many in vitro and in vivo studies have shown the positive effects of Chinese herbs on bone formation, namely, by the promotion of osteoblastic proliferation and inhibition of osteoclastic formation (Wong and Rabie, 2006). Several TCMs that have these bone promoting properties have also been widely used to treat ischemic myocardium and peripheral ischemia. The mechanism of this may be due to the angiogenic effects that these herbs have. Angiogenesis has been found to be one of the primary prerequisites in bone formation via the increase expression of VEGF. Whether causation exists between the angiogenic properties and bone forming properties of these Chinese herbs still remains in question.

The aim of this article was to review various TCMs with both osteogenic and angiogenic effects, alone and in combination, and to consider whether these TCMs promote osteogenesis via angiogenesis and VEGF.

**MATERIAL AND METHODS**

Wong and Rabie (2006) reviewed the TCMs that are involved in osteogenesis. On the basis of this, each TCM was searched through PubMed and CBMdisc using its Latin name and English name, and keywords such as ‘osteogenesis’, ‘bone’, ‘osteoblast’, ‘angiogenesis’, ‘VEGF’ were used. A total of 241 articles were screened from PubMed and CBMdisc. The articles were only chosen if they discussed the relationship of the TCMs with bone formation and/or angiogenesis. Finally, 27 articles were chosen, of which 16 were in English, 11 were in Chinese with English abstract.

**RESULTS**

As a result, the TCMs (Danshen or Salvia miltiorrhiza Bunge, Danggui or Angelica sinensis (AS), Astragalus membranaceus Bunge or Huangqi, and Ge Gan or Puerarin radix) that have a relationship with both osteogenesis and angiogenesis were screened out. For Danshen or Salvia miltiorrhiza Bunge, there were 64 search results but only eight were chosen. For Astragalus membranaceus Bunge or Huangqi, four out of a total of 19 studies were chosen. For Ge Gan or Puerarin radix, three articles out of 97 were used. Finally, the papers that discussed the combination of the herbs were found during the search for each individual TCM mentioned earlier. Two articles discussed the combinational use of Astraglaus membranaceus and AS, whereas one article investigated on the combined effects of Angelica and Radix Chuanxiong. The active components of the four TCMs that were screened out are shown in Table 1. The reference studies that discussed the TCMs reviewed in this article and their relationship with angiogenesis and osteogenesis are summarized in Table 2.

**Puerariae radix (Ge Gen)**

Puerariae radix (PR), also known as Ge Gen, comes from the root of Pueraria lobata (Wild) Ohwi, a wild creeper leguminous plant. It is one of the earliest and most important crude herbs used in Chinese medicine for treatment of fever, pain, diabetes, and so forth (State Pharmacopoeia Committee, 2000; Wang et al., 2003), which is mainly produced in the Henan, Hunan, Zhejiang, and Sichuan provinces in China (Dai and Rabie, 2007). PR contains a high concentration of isoflavonoids such as daidzein and genistein. For the past few decades, it has been widely used in China for treating cardiovascular diseases such as hypertension, angina pectoris (Fan et al., 1985), and arrhythmia (Chai et al., 1985). Previous reports also found that this medicine is important in preventing bone loss induced by estrogen deficiency.

Wang et al. (2003) examined the possible role of PR in bone metabolism by feeding OVX mice a diet containing different doses of the herb for 4 weeks. The decrease in total femoral BMD caused by OVX was significantly inhibited and prevented with the intake of different doses of PR; therefore, the researchers suggest that PR may prevent osteoporosis in post-menopausal women. In a study by Huh et al. (2006), they found that PR significantly increased the mRNA expression of VEGF and dose-dependently increased ALP activity that is related to osteoblastic activity. Meanwhile, it significantly upregulated the mRNA expression of type I collagen, OPN (a bone matrix protein secreted by osteoblasts and regarded as the last in a chronological sequence of markers of osteoblastic differentiation) and OCN (a later marker of osteoblastic differentiation and closely related to osteoblastic maturation) in human osteoblast-like SaOS-2 cells.

In a study by Zhang et al. (2006), PR was found to be able to induce angiogenesis in ischemic myocardium and non-ischemic myocardium zones of rat myocardial infarction model. It can promote endothelial cell proliferation and formation of new blood vessels (Li and Fan, 2004). Zhang also found that PR augmented VEGF mRNA expression in ischemic and non-ischemic rat myocardium following myocardial infarction.

Therefore, it is concluded by the aforementioned studies that PR plays a vital role in osteoblastic bone formation and that this may be related to the herb’s angiogenic property via the increase expression of VEGF mRNA.
Table 1. Active components of the TCMs related to both angiogenesis and osteogenesis

<table>
<thead>
<tr>
<th>Active components</th>
<th>Puerariae radix extract</th>
<th>Puerarin</th>
<th>Aqueous extract</th>
<th>SBD.4A</th>
<th>Astragalus polysaccharides-chitosan</th>
<th>Astragalus membranaceus injection</th>
<th>Astragalus polysaccharides</th>
<th>F1</th>
<th>Dangui Buxue Decoction, Xuefu Zhuyu Decoction, and Xiongshao Capsule</th>
<th>RS-9403</th>
<th>DS-9403</th>
<th>Salvia miltiorrhiza extract</th>
</tr>
</thead>
</table>

**Angelica sinensis**—(Danshen)**

*Angelica sinensis*, also known as Danshen, is the root of *A. sinensis* (Oliv) Diels that is an herbaceous perennial plant belonging to the Umbelliferae Family (Hsieh et al., 2000). It has been long used in Chinese medicine for its effects of blood cleansing and increase in circulation. It is a valuable remedy for anemia, menstrual irregularities, and constipation (Ji et al., 1999; Yim et al., 2000; Liu et al., 2001; Ye et al., 2001). In addition, the herb is frequently prescribed for bone and tendon injuries. Regarding its relation to bone, Yang et al. (2002) studied the possible direct effect of AS on bone cells. They found that at low concentrations, the aqueous extract has an accelerating effect on the proliferation of bone cells. It increased the total amount of protein produced in human osteoprecursor cells (OPC-1), stimulated ALP activity (the messenger related to osteoblastic activity and initiating calcification) and type I collagen production. The latter two are important proteins made by bone cells, namely osteoblasts during osteogenesis.

With regards to promoting angiogenesis, Meng et al. (2006, 2008) reported that Danshen can increase the number of vessels in chick embryo CAM, stimulate proliferation of cardiac microvascular endothelial cells obtained from rats, and increase VEGF expression in rats.

In a study by Zhao et al. (2008, 2006), the researchers investigated the effect of SBD.4A, a non-proteinaceous multi-component botanical growth factor isolated from AS, on periodontal regeneration by testing its bone related activities such as osteoblast proliferation and differentiation, and hyaluronic acid (HA) secretion by fibroblasts. HA is an extracellular matrix GAG, whose destruction by hyaluronidase-overexpressing periodontal pathogens contributes to the physiopathology of periodontitis; and in this study, it was found that SBD.4A stimulates HA in a dose-dependent manner. Moreover, the SBD.4A was formulated in a slow release matrix and tested in a rat calvarial defect model by placing it into the periodontal defects. The results indicate that SBD.4A can stimulate osteoblast proliferation (because of the increase in ALP activity—a marker for osteoblast differentiation), enhance activity of fibroblasts, endothelial cells, and angiogenesis both in *vitro* and *in vivo*, all of which are crucial for periodontal ligament repair and overall periodontal healing (Cochran and Wozney, 1999; Benatti et al., 2007). These results demonstrated that the herb has a bone generation-stimulatory activity that is consistent with preliminary *in vitro* findings using MC3T3 osteoblasts. Combined with previous findings on SBD.4A wound healing activities (Zhao et al., 2006), these data also indicated that there is a beneficial effect on periodontal defect and/or bone regeneration *in vivo*. However, the existence of a direct relationship that Danshen promote bone formation via the increase in VEGF and thus angiogenesis still remains unconfirmed.

**Astragalus membranaceus Bunge (Huangqi)**

*Astragalus membranaceus* Bunge (a perennial plant in the pulse family, Leguminosae), contains glycosides and flavonoides, particularly isoflavonoides as its principle components. As a tonic used to strengthen muscles and bones, it is one of the most widely used medicinal herbs in Asian traditional medicine. Previous studies reported that the herb can also promote new bone formation in periodontal defects (Xu et al., 2004, 2006). In another study, the same researchers found that astragalus polysaccharides with a lower concentration in a short-term culture may promote cultured dog bone marrow stem cells proliferation and differentiation into osteoblast *in vitro* (Xu et al., 2007). Kim et al. (2003) investigated its effects on osteoblast proliferation by an *in vivo* experiment using ovariectomized rats for 9 weeks and reported that the herbal extract F1, obtained from *Astragalus membranaceus Bunge*, inhibited tibia and lumbar bone loss. Compounds of Astragalus have also been found to improve VEGF mRNA expression in placental trophocyte and vascular endothelial cell in early pregnancy that helps to increase placental blood supply (Wang et al., 2005). Because of its effects on bone and VEGF, *Astragalus* may be related to bone formation via angiogenesis. However, more research would be needed to confirm its effects.

**Salvia miltiorrhiza Bunge (Danshen)**

*Radix Salvia miltiorrhiza Bunge* (SM) or Danshen is a common TCM that has been used for thousands of years to treat cardiovascular diseases, to improve perfusion of ischemic myocardium, and to enhance blood circulation (Zhu, 1998). It has also been shown to enhance wound healing in rabbits with second degree burn (Hu and
Table 2. Studies that discuss the TCMs related to both angiogenesis and osteogenesis

<table>
<thead>
<tr>
<th>Osteogenesis</th>
<th>Active components</th>
<th>Experiment design</th>
<th>Angiogenesis and VEGF</th>
<th>Active components</th>
<th>Experiment design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puerarin radix (Ge Gan)</td>
<td>Puerariae radix extract</td>
<td>In vitro (SaOS-2 cells)</td>
<td>Zhang et al. (2006)</td>
<td>Puerarin</td>
<td>Animal study (Sprague-Dawley male rats)</td>
</tr>
<tr>
<td>Wang et al. (2003)</td>
<td>N/A</td>
<td>Animal study (female mice)</td>
<td>Huh et al. (2006)</td>
<td>Puerariae radix extract</td>
<td>In vitro (SaOS-2 cells)</td>
</tr>
<tr>
<td>Angelica sinensis (Danggui)</td>
<td>Aqueous extract</td>
<td>In vitro (human osteoprecursor cells)</td>
<td>Meng et al. (2006, 2008)</td>
<td>N/A</td>
<td>In vitro, 2006 (rat cardiac microvascular endothelial cells) Animal study, 2008 (Rats)</td>
</tr>
<tr>
<td>Zhao et al. (2006, 2008)</td>
<td>SBD,4A</td>
<td>In vitro, 2006 (MC3T3 osteoblasts) Animal study, 2008 (Wistar Rats)</td>
<td>N/A</td>
<td>N/A</td>
<td>Animal study (rats)</td>
</tr>
<tr>
<td>Astragalus membranaceus (Huangqi)</td>
<td>Astragalus polysaccharides-chitosan</td>
<td>Animal study (dog and in vitro (bone marrow stem cells))</td>
<td>Wang et al. (2005)</td>
<td>N/A</td>
<td>Animal study (rats)</td>
</tr>
<tr>
<td>Xu et al. (2004)</td>
<td>Astragalus membranaceus injection</td>
<td>In vitro (bone marrow stem cells)</td>
<td>May improve VEGF mRNA expression in placental trophocyte and vascular endothelial cell in early pregnancy</td>
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<tr>
<td>Xu et al. (2007)</td>
<td>Astragalus polysaccharides</td>
<td>In vitro (dog bone marrow stem cells)</td>
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<tr>
<td>Kim et al. (2003)</td>
<td>F1</td>
<td>In vitro human osteoblast-like cell lines, MG-63 and Saos-2 and in vivo (ovariectomized rats)</td>
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</tbody>
</table>

(Continues)
| **Salvia miltiorrhiza** (Danshen) | Hu (1993) | Stimulates more rapid growth of osteoblast-like cells in chicken embryo calvariae cultured *in vitro* | N/A | *In vitro* (osteoblast-like cells isolated from chicken embryo calvariae cultured) | Lay *et al.* (2003a) | Enhances angiogenesis in murine SVR endothelial cell line by up-regulating VEGF and VEGF-R2 gene expression | Sal B | *In vitro* (murine SVR endothelial cell line) |
|---|---|---|---|---|---|---|---|
| **Ding *et al.* (1995)** | Stimulates ALP activity in MC3T3-E1 cells | N/A | *In vitro* (MC3T3-E1 cells) | Meng *et al.* (2006) | Promotes angiogenesis by stimulating proliferation of cardiac microvascular endothelial cells in CAM model and increasing blood vessels | N/A | *In vitro* (rat cardiac microvascular endothelial cells) |
| **Qin and Wang (1992)** | Promotion of fracture healing is related to increase in calcium, zinc contents, and Zn/Cu ratio in rat tibial fracture | N/A | Animal study (rats) | Gao *et al.* (2005) | Promotes angiogenesis in chicken embryo chorioallantoic membrane (CAM) | Danggui Buxue Decoction, Xuefu Zhuyu Decoction and Xiongshao capsule | Animal study (mice) and Chicken CAM model |
| **Shi *et al.* (2000)** | Affects procollagens expression to enhance bone fracture healing in rat radial fractures | RS-9403 | Animal study (Wistar rats) | Lay *et al.* (2003b) | Enhances angiogenesis and ischemic reperfusion of skin flap in rats | Animal study (Male Sprague-Dawley rats) and *in vitro* (murine endothelial cell line SVR) |
| **Fu *et al.* (1999)** | Increases strength of fracture healing site in rats’ radial fractures | DS-9403 | Animal study (Wistar rats) | | | |
| **Wong and Rabie (2008)** | Promotes new bone formation in bone defects during bone grafting | *Salvia miltiorrhiza* extract | Animal study (New Zealand White rabbits) | | | |
| **Chin *et al.* (2011)** | Enhances bone remodeling by regulating the gene expression of ALP, OCN, OPG, and RANKL | N/A | *In vitro* (MC3T3-E1 cells) | Lei *et al.* (2003a) | Angelica sinensis and Astragalus membranaceus used in a 5:1 ratio have a promotive effect on capillary formation in CAM, a more significant result in promoting endothelial cell growth and increase cell population in S phase. | N/A | 2003a (Chick embryo chorioallantoic membrane model) *in vitro*, 2003b (human umbilical vein endothelial cell) |

*(Continues)*
Over the years, many papers have reported the beneficial effects of this herb on bone healing in fractures by inhibiting osteoclastic activity and enhancing osteoblasts. Compounds isolated from the root of SM include tanshinone I, tanshinone IIA, cryptotanshinone, and dihydrotanshinone (Kim et al., 2008).

Several studies have examined the effectiveness of SM in promoting healing in bone fracture. Qin and Wang (1992) found that after the administration of SM, the contents of calcium, zinc, and Zn/Cu ratio increased significantly, whereas serum copper content was inhibited. The authors believed that the enhanced fracture healing was related to the increased zinc content in serum and the increased mobilization of zinc in fractured bone. Another mechanism is that SM affects the pro-collagen expression to enhance the bone fracture healing by the modulation of transforming growth factor beta 1 expression at the site of fracture (Shi et al., 2000). Fu et al. (1999) also found that SM increased the strength of fracture healing site in rats fed with SM.

In a study by Hu (1993), it was found that SM stimulated a more rapid growth of osteoblast-like cells in early stage of culture of chicken embryo calvariae. Ding et al. (1995) investigated the effect of SM on ALP activity of MC3T3-E1 cells and reported that SM caused a significant increase in ALP activity (135%) at 72 h up to a maximum concentration of 5 mg/mL. Chin et al. (2011) reported by an in vivo study that SM enhanced bone remodeling by regulating the gene expression of ALP, OCN, OPG, and RANKL. Wong and Rabie (2008) found by an in vivo study that SM significantly promoted 478% new bone formation when SM extract in collagen matrix was placed in bone defects.

Because of the link between osteogenesis and angiogenesis, the effect of SM on angiogenesis was investigated. Salvia miltiorrhiza Bunge has a positive effect on promoting angiogenesis. This was shown by Lay et al. (2003a) in which SM crude extract and salvianolic acid B (a component of SM) enhanced angiogenesis in murine SVR endothelial cell line by up-regulating VEGF and VEGF-R2 gene expression. This finding was also supported by another paper (Lay et al., 2003b) in which the authors found SM enhanced angiogenesis and ischemic-reperfusion of skin flap in Sprague–Dawley rats. Meng et al. (2006) also reported that Danshen increased the number of vessels in chick embryo CAM, and Gao et al. (2005) found that it promotes angiogenesis in CAM. These studies suggested that SM extract can increase bone formation through a combination of increase angiogenesis and increased osteoblastic activity.

### Table 2. (Continued)

<table>
<thead>
<tr>
<th>Osteogenesis</th>
<th>Angiogenesis and VEGF</th>
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<tr>
<td>Combination of Chinese herbs</td>
<td>Combination of Chinese herbs and Angelica sinensis</td>
</tr>
</tbody>
</table>

**Combination of Chinese herbs**

It is common that traditional prescriptions combine three to ten herbal medicines. The art of combining two or more herbs involves the idea of increasing or promoting therapeutic effectiveness, minimizing toxicity or side effects, and changing the major functions of the herbs (Zhu, 1998). Although may be only one or two are responsible for the central effect, the supplemental ingredients are important in achieving the goal of the remedy. The combination of herbs may have a synergistic effect to enhance the treatment outcome or may
In regard to the combination usage of herbs, Lei et al. (2003a) adopted chicken embryo CAM models and found by an in vivo study that when rat blood serum containing *Astragulus membranaceus* (Huangqi) and AS (Danggui) are used in a 5:1 ratio, there was a promotive effect on the formation of capillary in CAMs at 72 h after incubation. Compared with the non-stimulated control group and the other groups with different ratio of *Astragulus membranaceus* to AS, the group with ratio of 5:1 achieved better effects on the formation of capillary and the amount of blood vessel in CAM. Although *Astragulus membranaceus* and AS used singly can also promote endothelial cell growth and increase cell population in S phase and DNA synthesis, Lei et al. (2003b) showed a more significant synergistic effect when the two herbs were used in combination by observing the cell proliferation using the cultured human umbilical vein endothelial cell as an in vitro model. They also reported that VEGF expression in all medicated group was up-regulated.

For the other combination strategy, when *Angelica* and *Rhizoma* chuanxiong were combined, Meng et al. (2008) found that there was a significant enhancement in endothelial cell proliferation, increase in VEGF expression and stimulated quantity of vessels in rats treated acutely with the herbs and revascularization in CAM.

**CONCLUSION**

The theories and practice of TCMs have in no doubt survived the test of time. Through the course of Chinese history, it has arisen from a mythical medicine to a modern system of herbal medicine used to treat a variety of diseases and conditions. The effects that TCMs have on angiogenesis and osteogenesis cannot be denied. Numerous studies and experiments have been carried out to find what relationship of various TCMs has on these two physiological processes. Many have found a positive effect on bone formation, and the possible mechanisms may be related to their ability to promote angiogenesis via an effect on substances such as VEGF. However, the exact mechanism is yet to be confirmed and possibly, there are still more wisdom behind these once-considered mythical herbs, waiting to be discovered.

**Acknowledgement**

This work is supported by Small Project Funding, HKU (201007176194).

**Conflict of Interest**

The authors have declared that there is no conflict of interest.

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