Review

Exploring the efficacy of traditional healing methods in bone fracture management, with emphasis on piper sarmentosum

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Osteoporosis is a socio-public health issue which led to a rise in risk of fractures with subsequent delay in fracture healing. Fracture healing is a complex physiological process which involves four overlapping phases that is, haematoma formation, inflammation, repair and remodelling phases. It involves a series of biological cascades which resemble tissues differentiation that occur during foetal skeletal development. Several studies have been carried out to investigate the different traditional medicines using plants known for their fracture healing properties. *Piper sarmentosum* (Daun Kaduk) is widely distributed in South East Asia and used traditionally to treat many diseases such as diabetes mellitus, fungoid dermatitis and joint ache. The high costs and adverse effects of conventional treatment modalities may favor the wide usage of traditional herbal medicines. The current review focused on the usage of traditional herbal medicine to treat fractures healing in osteoporotic state.

Key words: Bone, fracture healing, herbs, osteoporosis, *Piper sarmentosum*, traditional medicine.

INTRODUCTION

Fracture healing

A fracture is a loss of continuity in the substance of a bone following severe trauma. Postmenopausal osteoporosis is the commonest cause of pathological fracture whereby vertebral, wrist and hip fractures are the most frequent osteoporotic fractures which occur in the elderly (Schuit et al., 2004). Falls due to imbalance and physical instability are recognized as the primary risk factors for hip and wrist fractures in osteoporotic patients (Gardner et al., 2006). Bone is able to restore pre-fracture properties without leaving scar after trauma (Giannoudis et al., 2007). Fracture healing is a normal biological process after any trauma, involving a complex series of events. Tissue differentiation during fracture

healing is similar to the foetal skeletal development (Goldhahn et al., 2008). There are two basic types of fracture healing viz: (1) Primary (direct) fracture healing; is rare and involves direct contact of cells in compact bone to re-establish the continuity (Giannoudis et al., 2007). It requires absolute immobilization at fracture site (e.g. internal fixation), (2) secondary (indirect) fracture healing occurs in most of bone fractures and requires relative immobilization at the fracture site (e.g. cast or external fixation) (Jahagirdar and Scammell, 2009). Based on the histological observations, fracture healing (secondary healing) occurs in four overlapping phases which are haematoma formation phase; early inflammatory phase (2 to 4 weeks); repair phase (proliferation and differentiation) (1 to 2 months); and late remodelling phase (lasts for months or years) (Harwood et al., 2010).

Bone metabolism is regulated by local and systemic factors. Osteoblasts are the only bone cells which have

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parathyroid hormone (PTH) receptors to maintain the extracellular level of calcium. Activated vitamin D stimulates calcium absorption from the intestine and enhances calcium transport from the kidney. Calcitonin inhibits osteoclast activity, whereby it reduces bone resorption (Kalfas, 2001). Various local growth factors including bone morphogenic proteins (BMPs), transforming growth factor beta (TGF-β), insulin-like growth factors (I-LGF), platelet derived growth factor (PDGF), and fibroblast growth factors (FGF) which are secreted by osteoblasts and blood cells are involved in maintaining bone metabolism and in improving fracture healing by regulating the differentiation and activation of bone cells (Kalfas, 2001).

OSTEOPOROSIS

Osteoporosis is a major global health problem which leads to an increased risk of fractures (Giannoudis et al., 2007). Osteoporosis is the commonest metabolic bone disease affecting more than 200 million people worldwide (Lin and Lane, 2004). It is manifested by decreased bone mineral density (BMD), bone mass and microarchitectural deterioration of bone structure which leads to enhanced bone fragility (Raisz, 2005). Annually, 100 to 200 million people worldwide are at risk of having an osteoporotic fracture (Giannoudis et al., 2007). The incidence rate of hip fractures is higher in Caucasian people compared to other ethnicity (Cooper et al., 1992). As a result of the demographic changes and increased life expectancy, the incidence rate of hip fractures is predicted to be increased from 1.66 million in 1990 to 6.26 million by 2050 (Cooper et al., 1992). The pathogenesis of primary postmenopausal osteoporosis was first discovered by Albright (1947). Postmenopausal oestrogen decline results in increased bone remodelling and an uncoupling between resorption by osteoclasts and formation by osteoblasts which leads to bone loss (Wronski et al., 1989).

EFFECTS OF OESTROGEN DEFICIENT STATE ON BONE REPAIR

The ovariectomised rat is recognized as a useful model for postmenopausal osteoporosis, as the pathogenesis process is similar to that in osteoporotic women (Frost and Jee, 1992; Estai et al., 2011c). Influence of osteoporosis on fracture healing is not well understood. Previous researches proved that osteoporosis is associated with a delay in fracture healing (Qiao et al., 2005). Furthermore, earlier studies on animals revealed that osteoporosis following oestrogen loss influenced the early and late periods of fracture healing in ovariectomised rats (Namkung-Matthai et al., 2001; Kubo et al., 1999). Osteoporotic fractures carry a higher risk of substantial mortality and morbidity affecting the quality

of life (Kanis et al., 2000). It contributes to a large percentage of public and private health spending. In 2005, the disease burden from osteoporosis in the USA was more than 2 million fractures at a cost of 17 billion US dollars and annual incident fractures and expenditures are predicted to rise up to 50% by 2025 (Burge et al., 2007).

Postmenopausal oestrogen loss induced production of Macrophage colony-stimulating factor (M-CSF) and various cytokines such as interleukin-1 (IL-1), IL-6 and tumour necrosing factor alpha (TNF-α) from marrow stromal cells (Chen et al., 2009). These pro-inflammatory cytokines are involved in osteoclastogenesis (Weitzmann and Pacifici, 2006). Cenci et al. (2000) concluded that the oestrogen deficent state induced bone loss by enhancing TNF-α production hence it is involved in osteoclastogenesis (Cenci et al., 2000). Reactive oxygen species (ROS) physiologically play an important role in the remodelling process, whereby overproduction of ROS by osteoclasts accelerated bone resorption (Sontakke and Tare, 2002). In osteoporosis, the activity of osteoclasts was increased as a result of overproduction of ROS (Sheweita and Khoshhal, 2007).

Several studies have extensively investigated the relationship between oestrogen and oxidative stress. Oestrogen loss was found to decrease the level of antioxidants in rodent bone cells (Lean et al., 2003). Ovariectomy induces oxidative stress and subsequent bone loss by increasing the level of ROS such as hydrogen peroxide (H_2O_2) in rats (Muthusami et al., 2005). Oxidative stress induced bone loss by increasing the expression of TNFα in ovariectomised mice (Jagger et al., 2005). It was found that H_2O_2 had a role in osteoclastogenesis and signals bone loss in oestrogen deficiency state (Lean et al., 2005). Furthermore, H_2O_2 was reported to affect bone formation by inhibiting osteoblastic differentiation in mice (Liu et al., 2004). Accumulation of lipid peroxide in bone may play a role in the pathogenesis of osteoporosis by inducing differentiation of marrow stromal cells into adipocytes instead of osteoblasts. In addition, lipid peroxide induced further secretion of cytokines which induced osteoclastic differentiation (Parhami, 2003) (Figure 1).

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Complementary and alternative medicine (CAM) is acquiring respect worldwide due to its fewer side effect side effects, low costs and increased efficacy (Bussmann and Sharon, 2006).

The use of CAM is rapidly growing and used widely mainly in the developing countries. According to the WHO (2008), in some African and Asian countries, about 80% of population use traditional over conventional medicine as primary medicine. In China, traditional medicine account for 40% of health care expenditure (Bussmann and Sharon, 2006).
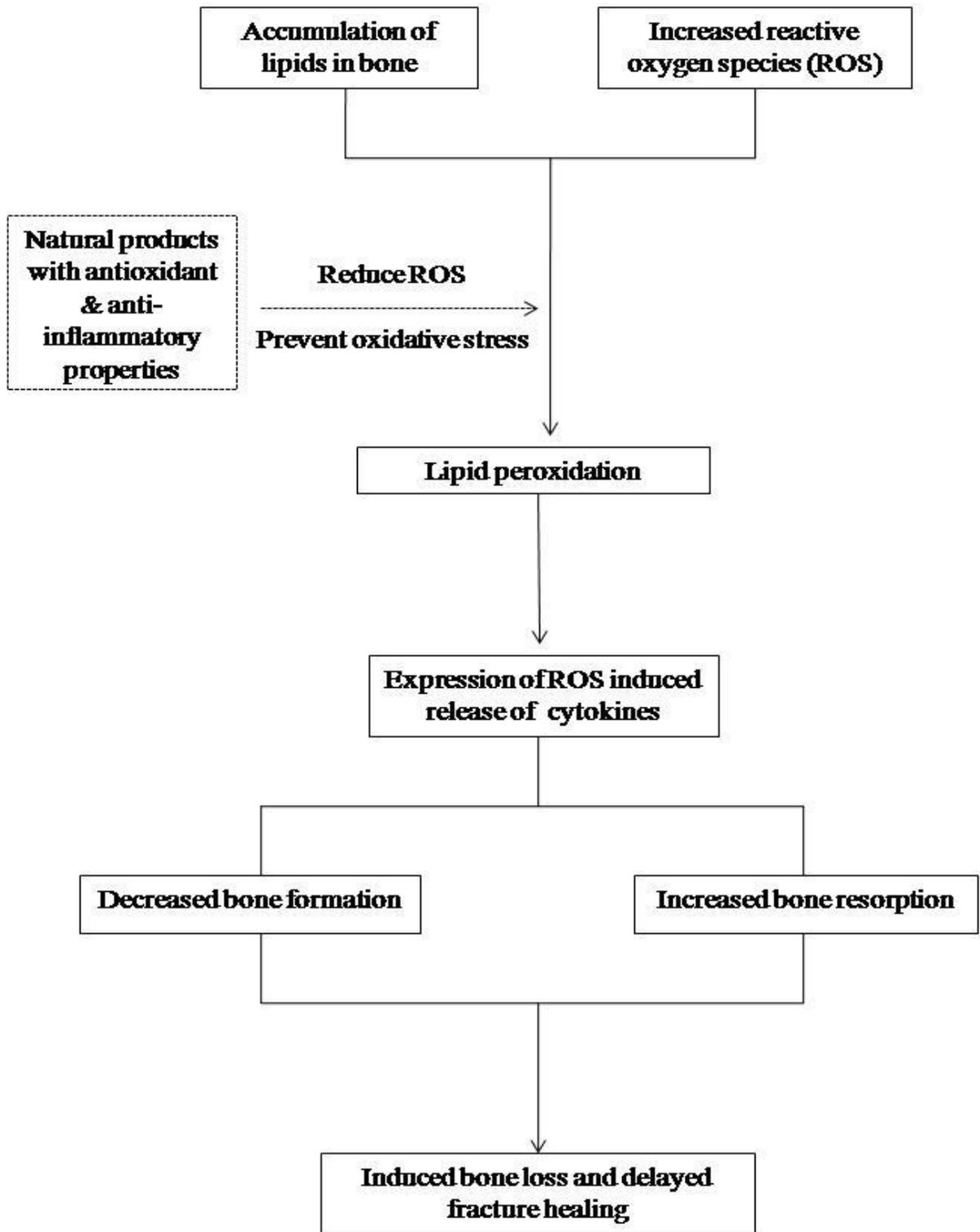
Figure 1. Flow chart showing effects of lipid peroxidation on bone following oestrogen deficiency and possible role of natural products in preventing oxidative stress.

Conventional medicine refers to all medicines given by medical doctors, doctors of osteopathy and allied health professionals. The term CAM is largely used instead of traditional medicines. National Center for Complementary and Alternative Medicine (NCCAM) defines CAM as "a group of diverse medical and health care systems,

practices, and products that are not generally considered part of conventional medicine". It was reported that the global sales of herbal products were accounted for about 60 billion US dollar (Brevoort, 1998).

In the past decades, numerous studies have been conducted to investigate the different medicinal plants in order to produce an effective agent to promote fracture healing in osteoporotic state (Koester and Spindler, 2006). Bisphosphonates, parathyroid hormone, selective oestrogen receptor modulators, vitamin D, calcium and fluoride are the main medications for treatment of osteoporosis and osteoporotic fractures (Fu et al., 2009). Bisphosphonates are considered as the drug of choice in treatment of osteoporosis and their intake has been linked to an increase in the risk of atrial fibrillation (Heckbert et al., 2008). In the other hand, use of sodium fluoride was found to increase the BMD; however, its use does not have positive effect on the risk of fractures (Kleerekoper et al., 1991). In addition, long-term use of oestrogen has been associated with development of tumours and uterine bleeding (Vecchia et al., 2001). Medical expenditures for the treatment of osteoporosis and osteoporotic fractures in USA were 17 billion US dollars in 2005 (Burge et al., 2007). Due to the high costs and the side effects that may follow long-term use of these agents, there is a need to discover natural products with minimal side effects and lower cost which can be used as adjuvant treatment besides the conventional treatment modalities.

Traditional Chinese medicine (TCM) was developed in China 2000 years ago. In Chinese culture, it is believed that diseases occur as a result of imbalance between opposing forces within the body (Carroll, 2007). Several techniques were developed in TCM such as herbal products, massage and acupuncture to restore the balance within the body (Carroll, 2007). TCM has been used earlier in treatment of bone fractures (Huang, 2003).

In Chinese folklore, there is a theory that the kidneys are related to bone, therefore the usage of herbal medicine which acts on *Shen* (kidneys) can be beneficial for bone (Huang, 2003).

A Chinese traditional herbal kidney tonic was reported to accelerate fracture healing in experimental animals by inducing the expression of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) (Luo et al., 2006). These neurotrophic factors are secreted by osteoblasts and chondrocytes during bone repair and it is thought to play role in promoting fracture healing (Luo et al., 2006). *Rhizoma curculiginis (*family-Amaryllidaceae), the dried rhizome of *Curculigo orchioidis* is extensively used in traditional Chinese medicine for treating bone fracture (Wong et al., 2007; Zhu, 1998). Earlier experimental studies showed that *R. curculiginis* and *Rhizoma drynariae* may be beneficial in fracture healing (Wong et al., 2007). *R. drynariae* (family-Polypodiaceae), the dried rhizome of *Drynaria fortunei* has been used earlier in the

traditional Chinese medicine to enhance bone healing (Dong et al., 2008). Earlier experimental studies had proven the beneficial effects of *D. fortunei* in promoting fracture healing (Wong and Rabie, 2006).

Ayurveda is a medical system adopted in India thousands of years ago and is still widely used in that country (Carroll, 2007). Ayurvedic medicine is based on breathing techniques, meditation and yoga (Carroll, 2007). In Ayurvedic culture, the young bark of *Ficus religiosa* (family-Moraceae) has been widely used in the treatment of bone fracture (Kirtikar and Basu, 1993). *Cissus quadrangularis* (family-Vitaceae) commonly known as the "bone setter," is an indigenous medicinal plant of India (Chopra et al., 1976). Previous researches showed that *C. quadrangularis* had fractured healing properties and antiosteoporotic effect (Deka et al., 1994; Shirwaikar et al., 2003).

Astragalus membranaceus (family-Fabaceae) is a plant known to have phytoestrogenic properties. The root of *A. membranaceus* is rich with formononetin which was reported to accelerate fracture repair in rats (Huh et al., 2009). The seeds of *Lepidium sativum* (family-Brassicaceae) and stems of *Sarsaparilla smilax* (family-Liliaceae) are used widely in Saudi Arabia as traditional Arab medicine to promote healing and strengthen bone after fracture (Juma, 2007; Ahsan et al., 1989). Furthermore, a mixture of the extracts of 6 herbs, *Radix dipsaci*, *Ramulus sambucus williamsii*, *Rhizoma notoginseng*, *Flos carthami*, *Rhizoma rhei* and *Fructus gardeniae*, was effectively used as a topical herbal paste to promote fracture healing in an experimental animals model (Peng et al., 2010) (Table 1).

Piper sarmentosum

P. sarmentosum (PS) (*Piperaceae,* Malay name: Kaduk), is a creeping shrub with erect branchlets that can grow up to 20 cm (Figure 2). It is widely distributed in the Southern East region of Asia. In Malay culture, the water decoction of its leaves is being used for treating diabetes, hypertension, cough and joint aches (Subramaniam et al., 2003).

Water decoction of its roots is being used to relieve dysmenorrhea and urinary symptoms (Azlina et al., 2009). In Thailand, the water extract of the whole plant has been used in treatment of diabetes mellitus (Peungvicha, 1998). In the past decades, it has been extensively investigated to assess its medicinal properties. The extract of the different parts of PS plant is known to have potential benefits. It possesses an antioxidant, antiplasmodial, antituberculosis, anti-inflammatory, anticarcinogenic and hypoglycemic properties (Peungvicha, 1998; Ariffin et al., 2009). Previous phytochemical studies on PS fruits has resulted in the isolation of phenylpropanoids, lignans and eight amides such as pellitorine, sarmentine and sarmentosine,

and other active compounds (Rukachaisirikul et al., 2004). An earlier pharmacokinetic study based on the three active amides compounds, pellitorine, sarmentine and sarmentosine, revealed that pellitorine and sarmentine have good bioavailability compared to sarmentosine (Hussain et al., 2011). Sarmentosine was neither detected in tissues nor plasma which may indicate that it is not absorbed from the gastrointestinal tract (Hussain et al., 2011). The methanolic extract of *Piper sarmentosum* consists of a high natural antioxidant scavenger, naringenin with high superoxide scavenging activity as compared to other phenolic compounds (Subramaniam et al., 2003). In general, the ethanolic extract of PS showed stronger antioxidant activity compared to its aqueous extract (Hussain et al., 2009). The extract of PS is rich in phenolic compounds such as naringenin, a flavonoid group with free radical-scavenging activity (Subramaniam et al., 2003). Flavonoids are a group of naturally occurring phenolic compounds (Seyoum et al., 2006). They have aromatic hydroxyl groups which are believed to inhibit the activity of enzymes involved in lipid oxidation (Miean and Mohamed, 2001). Hence, flavonoids may replace α-tocopherol as chain-breaking antioxidants (Van et al., 2000).

Several studies have been conducted to verify PS's antioxidant and anti- inflammatory properties. Free radical-scavenging activities of the PS flavonoids may play an important role in reducing ROS and preventing oxidative stress. An aqueous extract of PS was found to reduce the endothelial oxidative stress and induce antioxidant enzymes (Ugusman et al., 2011). Aqueous, methanol and hexane extracts of PS were reported to prevent cellular apoptosis induced by H_2O_2 in human umbilical vein endothelial cells through its antioxidative action (Hafizah et al., 2010). PS aqueous extract also enhanced the expression of nitric oxide which has anti-atherosclerotic properties (Ugusman et al., 2010). Ethanolic extract of PS roots showed anti-inflammatory, anti-nociceptive and antipyretic proprieties in animal models (Sireeratawong et al., 2010). Furthermore, aqueous extract of PS revealed anti-nociceptive and anti-inflammatory activities *in vivo* (Zakaria et al., 2010). In addition, aqueous extract of PS was found to be protective against atherosclerosis by reducing vascular cell adhesion molecule-1, intercellular adhesion molecule-1 and C-reactive protein in experimental rabbits (Amran et al., 2011).

The expression of 11β-hydroxysteroid dehydrogenase type 1, an enzyme which is linked with obesity, was found to be reduced following administration of PS aqueous extract to ovariectomised rats (Azlina et al., 2009). However, there are not many studies investigating fracture healing properties of PS extract. Past experimental studies showed that flavonoids prevented ovariectomy induced osteopenia and strengthened bone in ovariectomised animals (Horcajada et al., 2008). Thus,

fracture healing properties of PS may be attributed to the action of flavonoids present in the PS extract.

A previous study on experimental fractured animal models have revealed better fracture healing following PS administration during the late phase of fracture healing ((Estai et al., 2011a; Estai et al., 2011b)). In addition, Ima-Nirwana et al. (2009) had observed an antiosteoporotic effect of PS aqueous extract in the adrenalectomised rats. The beneficial effect of PS on osteoporosis and fracture healing is most probably attributed to the antioxidative actions of the PS flavonoids which may prevent oxidative stress. ROS are found to be associated with many age related degenerative diseases such as atherosclerosis, asthma, osteoporosis, arthritis, diabetes and cancer (Valko et al., 2007). ROS played an important role in bone metabolism during the remodelling process by promoting bone resorption (Bai et al., 2005). Normally, ROS are produced at low levels and are neutralized by antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase (Hamada et al., 2009). The oestrogen deficient state was shown to induce oxidative stress and osteopenia by increasing the level of ROS in animals (Muthusami et al., 2005). An earlier study found that the activity of intracellular antioxidant enzymes was significantly decreased in postmenopausal women (Ozgocmen et al., 2007). Postmenopausal women suffering from osteoporosis have been showed a significant decrease in plasma antioxidants (Maggio et al., 2003). The level of ROS was found to be higher after fracture which may react with free fatty acids found at the fracture site resulting in lipid oxidation (Prasad et al., 2003).

Reduced BMD is associated with an increase in oxidative stress (Basu et al., 2001). Dietary intake of antioxidant such as vitamin C has revealed a beneficial effect on BMD in postmenopausal women (Morton et al., 2001). Previous experimental studies on animals confirmed that osteopenia following oestrogen loss can be prevented by the supplementation of antioxidants (Lean et al., 2005). It has been also found that glutathione peroxidase, an antioxidant enzyme secreted by osteoclasts have a major role in reducing H_2O_2 (Muthusami et al., 2005). In addition, administration of palm oil tocotrienol was found to prevent bone loss induced by nitrilotriacetate (FeNTA) (an oxidizing agent) in experimental animals (et al., 2005). Hence, supplementation of antioxidants can strengthen the bone and promote fracture healing in osteoporotic patients (Sheweita and Khoshhal, 2007).

CONCLUSION

Previous studies have proved that osteoporosis following oestrogen deficiency is linked with a delay in fracture healing. In clinical practice, the impact of osteoporotic fracture is substantial as it is associated with higher

Table 1. Table revealing earlier studies on tradional medicinal plants with fracture healing properties.

Plant	Part used	System of medicine	References
Astragalus membranaceus	Root	Chinese	Huh et al. (2009)
Cissus quadrangularis	Stem/leaf	Ayurveda	Chopra et al. (1976) and Deka et al. (1994)
Ficus religiosa	Young bark	Ayurveda	Kirtikar and Basu (1993)
Lepidium sativum	Seeds	Arabic	Juma (2007)
Mixture of 6 herbs, *Radix dipsaci*, *Ramulus sambucus williamsii*, *Rhizoma notoginseng*, *Flos carthami*, *Rhizoma rhei* and *Fructus gardeniae*	Leaf	Chinese	Peng et al. (2010)
Rhizoma curculiginis	Rhizome	Chinese	Wong et al. (2007)
Rhizoma drynariae	Rhizome	Chinese	Dong et al. (2008)
Sarsaparilla smilax	Stem	Arabic	Ahsan et al. (1989)

Figure 2. *Piper sarmentosum* plant. Adopted from http://en.wikipedia.org/wiki/Piper_sarmentosum.

morbidity, mortality and expenditures as well as reducing the quality of life. Several studies have been conducted to investigate the different medicinal plants to evaluate their healing properties in order to produce a more effective or complementary treatment for fracture healing of osteoporotic patients. PS is rich in a natural antioxidant superoxide scavenger (Naringenin) which may have beneficial in promoting fracture healing most probably by reducing ROS through its free radical-scavenging activity. Hence, PS may have potential to be added as antioxidant supplements to the current treatment modalities.

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