IMMUNOLOGY, HEALTH AND DISEASE

Treatment of tibial dyschondroplasia with traditional Chinese medicines: “Lesson and future directions”

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ABSTRACT Tibial dyschondroplasia (TD) is a metabolic tibiotarsal bone disease in rapidly growing birds throughout the world, which is characterized by gait disorders, reduced growth, and in an unrecoverable lameness in many cases. The short production cycle in chickens, long metabolism cycle in most of the drugs with the severe drug residue, and high treatment cost severely restrict the enthusiasm for the treatment of TD. Traditional Chinese medicine (TCM) has been used for the prevention, treatment, and cure of avian bone diseases. Previously, a couple of traditional Chinese medicines has been reported being useful in treating TD. This review will discuss the TCM used in TD and the alternative TCM to treat TD. Selecting a TCM approach and its pharmacologic effects on TD chickens mainly focused on the differentiation, proliferation, and apoptosis of chondrocytes, angiogenesis, matrix metabolism, oxidative damage, cytokines, and calcification of cartilage in tibia.

Key words: chicken, pharmacologic effect, tibial dyschondroplasia, traditional Chinese medicine

TIBIAL DYSCHONDROPLASIA

Tibial dyschondroplasia (TD) is the most critical tibiotarsal bone disease in fast-growing poultry that disturbs the healthy development of the tibial growth plate (GP) (Nabi et al., 2016). Tibial dyschondroplasia is characterized by an avascular and nonmineralized GP, gait disorders, reduced growth, and unrecoverable lameness (Figure 1) (Mehmood et al., 2017). Previous research has indicated that almost 30% of bone diseases in poultry are due to TD and that this disease leads to greater than 10% morbidity in China, creating significant economic losses in the poultry industry (Li et al., 2008; Dan et al., 2009; Zhang et al., 2018b). Affected chickens are less disease resistant and show reductions in production performance and osteomyelitis (Shahzad et al., 2014, 2015).

Healthy GP development requires cartilage vascularization and mineralization with a well-structured morphology, whereas in TD, the differentiation of chondrocytes appears to be abnormal. The avian GP has random columns of chondrocytes along with deeply penetrating blood vessels (Pines et al., 2005). It has stated that the examination of a histologic section of GP illustrated that a large number of chondrocytes were in the resting zone of the normal broiler, and the chondrocytes regularly proliferated and differentiated from top to bottom (Piróg et al., 2010). Angiogenesis is increased in the cartilage profoundly in the hypertrophic zone to prepare the osteoblasts for calcification in normal bone ossification. The blood vessels are thick and rich in blood in normal bone ossification, whereas chondrocytes are small in size with large capsules, and nucleus present in the center.

In TD GP, the chondrocytes are unorganized and round in shape, having fewer blood vessels, and there is no demarcation between proliferative zone and hypertrophic zone (Mehmood et al., 2019a). The chondrocytes are immature and larger than normal chondrocytes. Tibial dyschondroplasia lesions are present in the proximal GP of the tibia bone, which includes avascular, nonmineralized (noncalcified) tissue, and dull cartilage. Histologically, cartilage does not show any blood vessels and vascularization because the prehypertrophic (avascular) zone enlarges and combines with avascular cartilage zones (Leach and Monsonego-Ornan, 2007; Nabi et al., 2016). The sketch of healthy and TD GP is shown in Figure 2.
PATHOGENESIS OF TD

Studies have shown that with TD, angiogenesis, and vascular development are inhibited in osteoblasts, osteoclasts, and mesenchymal stem cells, vascular infiltration in the hypertrophic zone of cartilage is reduced, and osteoclasts, osteoblasts, and mesenchymal stem cells lacked sufficient nutritional inputs. Consequently, calcified cartilage cannot complete the bone sedimentary process, which leads to white cartilage deposition (Rath et al., 2007; Borjesson et al., 2013). It is clear that the occurrence of TD in broilers is mainly associated with pathologic changes of tibial because of the following: 1) the apoptosis of chondrocytes, especially the nuclear dissolution, preventing the further development of a large number of chondrocytes; 2) chondrocytes in the resting and proliferative zone cannot further differentiate within the hypertrophic zone, and a large number of cells gather near the GP; 3) vascular endothelial cell impairment and reduced angiogenesis within the tibia GP. The accompanying deterioration of blood flow impairs or kills off chondrocytes within the zone of tibia GP osteogenesis; 4) the resulting failure of osteogenesis causes an accumulation of white cartilaginous tissue in place of healthy bone (Leach and Monsonego-Ornan, 2007; Nabi et al., 2016; Mehmood et al., 2018a, 2019a, 2019b; Yao et al., 2018; Zhang et al., 2018a, 2018b). Currently, research focuses on increasing the growth rate and feed conversion ratio of broilers; consequently, poultry bone disease incidence is also increasing in the broiler industry. It is reported that the chicken muscle tissue and bone growth and development destroy the original balance and are also a reason for the leg deformities in chicken. Previous studies indicated that GP were resistant to angiogenesis in TD chickens, and the chondrocytes around TD lesions failed to provide appropriate angiogenesis signals to stimulate normal GP vascularization. A reduction of blood vessels at the site of osteogenesis induces deterioration and necrosis of chondrocytes (Figure 1) (Zhang et al., 2018a, 2018b). Rath et al. (2007) have reported apoptosis of capillary endothelial cells in GP in thiram-induced TD chickens, and the mortality of cells increased with the duration of the thiram dosing period, accompanied by chondrocyte cell death. Previously, studies have found that the gene expression of tibial GP chondrocytes significantly changes during the occurrence of TD in chickens, and the cartilage matrix protein composition changes follow. Tibial dyschondroplasia triggers abnormal chondrocyte protein secretion in TD, including Col II, Col X, Aggrecan, and fibroblast growth factor, bone adhesion protein (osteonectin), osteopontin, conversion, transforming growth factor-β, insulin-like growth factor 1, epidermal growth factor, and tumor necrosis factor, and so on. (Tian et al., 2013). Meanwhile, changes of cartilage extracellular matrix (ECM) composition accompany abnormal chondrocyte protein secretion in TD lesion areas, including heat shock family proteins (HSP), extracellular matrix metalloproteinase 9, aggrecan, Col II, Runx2, P2RX7, caspases, BECN1, Sox9, Hif-1 alpha/vascular endothelial growth factor (VEGF), Cox-2, Wnt4, BMP2, MMP-13, and extracellular matrix metalloproteinase inducers (Tian et al., 2013; Shahzad et al., 2014, 2015; Iqbal et al., 2016; Nabi et al., 2016; Zhang...
et al., 2018a, 2018b; Mehmood et al., 2018b, 2019a, 2019b; Yao et al., 2018).

CAUSES OF TD

Since TD was reported in 1965, the factors related to TD occurrence have been discovered, including heredity (variety breeding), environment (temperature, light, feeding density), nutrient elements (electrolyte, calcium and phosphorus ratio), vitamin D3, and poisons (thiram in particular). (Zhang et al., 2018a, 2018b; Mehmood et al., 2019a, 2019b). Tibial dyschondroplasia appears to be induced by multiple factors, and causes are diverse. For example, soybean meal in feed has been linked to changes in TD incidence, along with other factors such as vitamin D deficiency, hyperthyroidism, and abnormal levels of biochemical markers such as IL-1 and nitric oxide. Rath et al. (2007) and Li et al. (2008) have demonstrated that thiram is highly effective in inducing TD and that the symptoms are nearly identical to naturally occurring TD signs (Zhang et al., 2019a). Our previous studies have also found that thiram can be used to induce TD in poultry efficiently, and thiram has been widely used to model TD in many controlled induction experiments (Zhang et al., 2018a). Our previous studies have indicated that thiram promotes apoptosis of chondrocytes, inducing nuclear dissolution, which serves to greatly the number of functioning chondrocytes within osteogenesis zones (Figure 3). In addition, thiram disrupts angiogenesis within the tibial GP, further impairing chondrocyte activity and undermining osteogenesis at that location (Figure 3) (Mehmood et al., 2018a,b; Zhang et al., 2018a, 2018b; Mehmood et al., 2019a).

PHARMACOLOGICAL MECHANISM OF TCM FOR THE TREATMENT OF TD

For the treatment of TD in chickens, there is still no specific drug widely available. Previous studies showed that administering vitamin C and vitamin D3 and changing the proportion of calcium and phosphorus in the diet reduces the incidence of TD in chickens (Leach and Monsonego-Ornan, 2007; Landy and Toghyani, 2018). Owing to the short production cycle in chickens, the long metabolism cycle of most drugs, high treatment costs, and issues regarding the accumulation of drug residues in commercial chickens serve as deterrents for the broad-scale application of drugs to combat TD. The application of traditional Chinese medicines (TCM) has a long history and has been used for the prevention, clinical treatment, and cure of disorders or diseases (Hao et al., 2015). Recently, some key TCM have come under scrutiny as potential tools for combating TD, application of which is not accompanied by the issues presented with the use of synthetic drugs. In particular, the application of a single herb or single TCM herb extract has generated significant interest (Nabi et al., 2016; Zhang et al., 2018a; Mehmood et al., 2019b). At present, the pharmacologic effects of TCM on TD chickens are mainly focused on the differentiation, proliferation, and apoptosis of chondrocytes, angiogenesis, matrix metabolism, oxidative damage, cytokine stimulation, and calcification of cartilage in the tibia (Leach and Monsonego-Ornan, 2007; Nabi et al., 2016; Zhang et al., 2018b; Yao et al., 2018; Mehmood et al., 2019a). Currently, there are several kinds of TCM reported to treat TD (Figure 4), which are as follows.

Tetramethyhyprazine

Tetramethyhyprazine (TMP) is one of the most important bioactive component extracted from the TCM herb Chuanxiong, has been found to function as a vasodilator, improving minicirculation, eliminating free radicals, and is antiapoptotic and anti-inflammatory (Liang et al., 2005; Mehmood et al., 2018a; Zhang et al., 2018c). Tetramethyhyprazine was reported to play an essential role in angiogenesis during the impairment and recovery of GP in TD chickens via regulating the expression of the relevant gene of the hypoxia inducible factor-1α (HIF-
1α/VEGF pathway (Mehmood et al., 2018a). Mehmood et al. (2019b) have reported that TMP treatment upregulates the expression of ITGB3 in TD chickens. Thus, TMP could be considered as an essential agent to avoid the losses and costs associated with TD.

**Tanshinone IIA**

Tanshinone IIA is a fat-soluble bioactive component of *Salvia miltiorrhiza*, which has anti-inflammatory property, can scavenge oxygen free radicals, and possesses antioxidant effects (La-Zhi et al., 2008). Tanshinone IIA can promote the increase of bone marrow mesenchymal differentiation, bone mineral density, bone strength, and fracture healing while preventing bone loss. In previous studies, we found that Tanshinone IIA can reduce the incidence of thiram-induced TD in chickens, significantly improve the development of tibial cartilage, and downregulate Hsp90 and VEGF in TD chickens (Mehmood et al., 2017). Studies have shown that Tanshinone IIA can significantly downregulate β-catenin, block Wnt/β-catenin signal pathway, as well as change the expression of downstream target genes, such as Hsp90 and VEGF, so it plays an essential role in protecting relevant tissues and organs (Liu et al., 2013; Mehmood et al., 2017). Recently, our study found that TD chickens treated by Tanshinone IIA can restore gene (WNT5α, β-catenin, and BMP-2) expression in Wnt/β-catenin pathway and improve GP development patterns in TD broilers (Yang et al., 2019).

**Celastrol**

Celastrol has been commonly used as an anti-inflammatory agent and immune regulator, including dermatitis, anticancer, Alzheimer disease, systemic lupus erythematosus, cartilage-protective, rheumatoid arthritis, and dermatomyositis in China (Nabi et al., 2016; Zhang et al., 2018d; Li and Hao, 2019). Nabi et al. (2016) reported that treatment with celastrol significantly inhibited the expression of Hsp90 and increased the expression of receptors Flk-1 in the GP in thiram-induced TD chickens. At the same time, celastrol could decrease the level of aspartic acid transaminase, alanine amino transferase, and malondialdehyde by reducing liver stress. Celastrol promotes broiler liver detoxification, restores antioxidative activity, reduces liver damage, and elevates the production of bone metabolism-related enzymes (Nabi et al., 2016). Meanwhile, administration of celastrol to TD chickens can promote the GP vascularization and restore the angiogenesis (Nabi et al., 2016).

**Chlorogenic Acid**

Chlorogenic acid (CGA), is known as one of the most common polyphenolic compounds, mainly in...
Eucommia, honeysuckle, and green tea. Pharmacologic studies have found that CGA plays an important and therapeutic role in antioxidation, anti-inflammatory, antiviral, antitumor, cardioprotection, and free radical scavenging activities. (Kwak et al., 2013; Han et al., 2017; Nabavi et al., 2017). Of note, CGA inhibits the expression of Jun-D, c-Jun, c-Fos, Fra-1, Fra-2, ALP, Runx2, and Osterix genes involved in the differentiation of preosteoblasts into osteoblasts (Yi, 2013). Zhang and Hu (2016) found that CGA can enhance the proliferation of osteoblasts and accelerate the transition process S phase. Chlorogenic acid may increase the expression of Bcl-2 and decrease the Bax expression during apoptosis, thereby inhibiting osteoblast apoptosis (Zhang and Hu, 2016). Zhang et al. (2019b) reported that CGA possesses a positive therapeutic effect on TD chickens via regulating caspase-3, caspase-9, MMP-9, MMP-10, MMP-13, and BECN1 expression.

Apigenin is one of the most common flavonoids compounds, mainly in Daphne, Verbenaceae, and Papyridae, and is widely distributed in warm tropical vegetables and fruits. Pharmacologic studies have found that apigenin plays several therapeutic roles in antitumor, cardiovascular and cerebrovascular protection, antiapoptosis, anti-inflammatory, and antioxidant functions. (Salehi et al., 2019). Our previous research found that administering the apigenin to TD chickens restored chondrocyte columnar organization with vascularization, which ultimately abrogated the lameness (Iqbal et al., 2016). Meanwhile, the expression levels of Hsp90 and VEGF were increased in thiram-treated chondrocytes culture medium, whereas apigenin therapy to chondrocytes reduced the Hsp90 and VEGF expression levels. Apigenin therapy is considered as a promising approach to control and treat TD in chickens (Mehmood et al., 2017).
GP cells in broilers, insufficient vascular formation in the proliferation zone of tibial epiphysis and hypoxia (Iqbal et al., 2016). However, epigallocatechin gallate (ICA) could promote or inhibit the proliferation of chondrocytes; Eucommia ulmoides increased the bone growth rate by promoting chondrogenesis or inhibiting the proliferation of chondrocytes, as well as increasing the expression levels of BMP-2 and insulin-like growth factor-1 (Kim et al., 2015). Puerarin increased the proliferation of chondrocytes in osteoarthritis (Peng et al., 2019b). Antler extracts promoted chondrocyte proliferation and differentiation and prevented chondrocyte apoptosis (Yao et al., 2019). Emodin can promote the proliferation of chondrocytes by inhibiting the expression of extracellular signal-regulated kinase and Wnt/beta-catenin pathways in chondrocytes and downregulate the expression of a series of inflammatory mediators (Liu et al., 2018). Psoralen, achyranthesaceae polysaccharide, and soya bean isoflavone promote osteoblast differentiation and proliferation by activating the Wnt/β-catenin signaling pathway (Weng et al., 2014; Yu et al., 2015; Zheng et al., 2017). Traditional Chinese medicine can be used for the prevention and treatment of TD by regulating the chondrocyte cycle, promoting chondrocyte proliferation.

Icariin

Icariin (ICA), extracted from Herba epimedii, has been shown to be effective for the treatment of various bone regeneration and repair (Zhang et al., 2018a). In recent years, studies have found that ICA has the following effects for treating bone diseases: 1) It can significantly improve bone density and bone formation; 2) Icariin has the function of promoting the metabolic activity of chondrocytes and the synthesis of cartilage matrix, promoting the proliferation of chondrocytes for the growth of cartilage, which can be used for the repair of cartilage tissue; 3) Promoting osteoblast differentiation; 4) Effective anti-inflammatory activity that can be used to treat osteoarthritis; 5) It can effectively inhibit the absorbance of mature osteoclasts and the formation of osteoclast-like cells (Xu et al., 2016; Wang et al., 2018). In our previous studies, we have found that ICA upregulated WNT4 and P2RX7 mRNA expressions and downregulated VEGF expression, as well as restored the GP width, reduced chondrocyte damage and “white cartilage mass,” promoted the development of blood vessels in GPs, increased growth performance, and reduced lameness in TD chickens. Meanwhile, ICA administration recovered GP lesion, improved the performance, and prevented lameness (Zhang et al., 2018a).

Epigallocatechin Gallate

Epigallocatechin gallate is the most effective active catechin in green tea. Epigallocatechin gallate as a potent antibacterial, antiviral, antiarteriosclerosis, anti-inflammatory, antioxidant, and antitumor agent has been reported (Chen et al., 2014a; Granja et al., 2017). Epigallocatechin gallate has a vigorous antioxidant activity and can protect cells and DNA from damage owing to its oxygen free radical scavenging ability (antioxidant) (Chen et al., 2014a). The occurrence of TD is also closely related to the expression of Hsps. The upregulated expression of Hsp90 affects the expression of VEGF and its receptor, resulting in obstructed vascular formation in the proliferation zone of tibial GP cells in broilers, insufficient oxygen supply of cells, and hypoxia (Iqbal et al., 2016). However, epigallocatechin gallate can inhibit aryl hydrocarbon receptor activity of Hsp90 client protein by binding to Hsp90c terminal. Epigallocatechin gallate can significantly increase the transcription level of VEGF in TD broilers and considerably reduce the transcription levels of Hsp90 and Flk-1. Therefore, the prevention and recovery of broiler TD can be achieved through epigallocatechin gallate (Iqbal et al., 2016).

BIOLOGICAL ACTIVITIES FOR THE SELECTION OF TCM TREATING TD

Research efforts of TCM use for treating TD have been made significant progress. Meanwhile, TCM application has little side effects, low price, low drug residue, and high safety margins, and TCM substances are easy to obtain. The use of TCM not only avoids the gastrointestinal reactions caused by oral drugs but also avoids the first-pass effect of liver metabolism (An et al., 2019; Zhang et al., 2019c). What is more? Chinese herbal medicine contains rich active ingredients, such as polysaccharides, alkaloids, volatile oils, and organic acids (Yu et al., 2019). These active ingredients are conducive for regulating immune function and improving the production performance of chickens. Keeping in view the characteristics of TCM, we have identified some protocols and features that should be kept in mind while selecting TCM (Table 1; Figure 5).

Promote the Proliferation of Chondrocytes and Inhibit the Apoptosis of Chondrocytes

Previous results showed that Eucommia ulmoides could promote or inhibit the proliferation of chondrocytes; Eucommia ulmoides increased the bone growth rate by promoting chondrogenesis or inhibiting the proliferation of chondrocytes, as well as increasing the expression levels of BMP-2 and insulin-like growth factor-1 (Kim et al., 2015). Puerarin increased the proliferation of chondrocytes in osteoarthritis (Peng et al., 2019b). Antler extracts promoted chondrocyte proliferation and differentiation and prevented chondrocyte apoptosis (Yao et al., 2019). Emodin can promote the proliferation of chondrocytes by inhibiting the expression of extracellular signal-regulated kinase and Wnt/beta-catenin pathways in chondrocytes and downregulate the expression of several inflammatory cytokines and prostanoids and proinflammatory activity that can promote or inhibit the proliferation of chondrocytes; Eucommia ulmoides increased the bone growth rate by promoting chondrogenesis or inhibiting the proliferation of chondrocytes, as well as increasing the expression levels of BMP-2 and insulin-like growth factor-1 (Kim et al., 2015). Puerarin increased the proliferation of chondrocytes in osteoarthritis (Peng et al., 2019b). Antler extracts promoted chondrocyte proliferation and differentiation and prevented chondrocyte apoptosis (Yao et al., 2019). Emodin can promote the proliferation of chondrocytes by inhibiting the expression of extracellular signal-regulated kinase and Wnt/beta-catenin pathways in chondrocytes and downregulate the expression of a series of inflammatory mediators (Liu et al., 2018). Psoralen, achyranthesaceae polysaccharide, and soya bean isoflavone promote osteoblast differentiation and proliferation by activating the Wnt/β-catenin signaling pathway (Weng et al., 2014; Yu et al., 2015; Zheng et al., 2017). Traditional Chinese medicine can be used for the prevention and treatment of TD by regulating the chondrocyte cycle, promoting chondrocyte proliferation.

Degradation and Synthesis of Extracellular Matrix

Extracellular matrix is a noncellular 3-dimensional macromolecular network composed of collagen, proteoglycan/glycosaminoglycan, elastin, fibronectin, laminin, and several other glycoproteins (Theocharis et al., 2016). Studies have shown that TCM can promote the synthesis of collagen and proteoglycan in cartilage matrix and inhibit its degradation, which may be one of the protective mechanisms of cartilage. Results showed that ICA promotes cartilage repair via regulating chondrocyte proliferation and differentiation, as well as ECM synthesis (Wang et al., 2016). Curcumin inhibits the production of proinflammatory cytokines and prostanoids and the degradation of matrix-metalloproteases (Henrotin et al., 2010). Psoralen can promote the synthesis of ECM and increase the expression of cartilage genes, which may be a useful bioactive component to activate...
## Table 1. Alternative traditional Chinese medicines for treating TD.

| Name                     | Active components | Biological activity | Mechanism of action | References |
|--------------------------|-------------------|---------------------|---------------------|------------|
| Morinda officinalis      | Iridoids glycoside| Antiapoptotic and   | ↓ Proinflammatory   | (Wang et al., 2014) |
|                          |                   | anti-inflammatory   | cytokines           |            |
| Resveratrol              | Phytoalexin, polyphenolic | Regulates apoptosis, | ↓ MMP-3 and MMP-13 | (Liu et al., 2017b; Jin et al., 2018; Wang and Bai, 2019) |
|                          |                   | degrades extracellular matrix and protects chondrogenesis | ↑ Sirt1 |            |
| Rhizoma atracetylodon macrocephalea | Sesquiterpene, atractylolide | Promotes chondrogenic differentiation | ↑ Type II collagen | (Li et al., 2012) |
| Fructus psoralaeae       | Volatile oil, coumarin, flavones, lipids, resins | Promotes viability and cartilaginous formation | ↑ Aggrecan, and Sox-9 | (Pan et al., 2016) |
| Semen plantaginis        | Flavonoids, triterpenoids, iridoid glycosides | Antioxidant | ↑ VEGF, HIF-1α | (Tzeng et al., 2016) |
| Hesperetin               | Flavonoids        | Antiapoptotic and   | ↑ VEGF/VEGFR2       | (Chen et al., 2019; Muhammad et al., 2019) |
|                          |                   | angiopotic          | ↓ Jagged1/Notch1    | (Yuan et al., 2018) |
| Daidzein                | Flavonoids, isoflavones | Antioxidant | ↑ Caspase-3 and caspase-8, ROS-mediated, ↓ Bcl-2 | (Yi et al., 2019) |
| Curculigo orchioides     | Phensols and phenolic glycosides | Antiapoptotic and angiopotic | ↑ IL-1β, ↓ ROS, apoptosis | (Hejazi et al., 2018) |
| Paeonol                 | Paeonol           | Antiapoptotic and   | ↑ mTOR, p70S6K, Notch1, ↓ BNIP3, hypoxia | (Xue et al., 2019) |
| Curculigo orchioides     | Lignans, iridoids, phenols, steroids, flavonoids | Antioxidant and angiopotic and bone formation | ↑ Cartilage metabolism, ↓ Apoptosis | (Lu et al., 2013; Li et al., 2014) |
| Tetrandrine              | Alkaloids         | Anti-inflammatory, antiapoptotic and antioxidan | ↑ MMP-1, -3 and -13, Apoptosis, ↓iNOS, COX-2, TNF-α | (Xie et al., 2002; Ng et al., 2006; Shine et al., 2018) |
| Puerarin                | Isoflavone        | Antioxidant, anti-inflammatory, anti-apoptotic and bone formation | ↑ Oxidative stress, ↓ nuclear factor-κB protein | (Zhao et al., 2016; Guo et al., 2018) |
| Naringin                | Flavanone glycoside | Angiogenesis, antioxidiant, and protects chondrocytes | ↓ Caveolin-1, p-p38, and p-ATF-2, TNF-α and p38MAPK pathways | (Su et al., 2014; Song et al., 2017) |
| Polygonon multilorum     | Polyphenol, tetrahydroxystibene, glucoside | Angiogenesis | ↑ Vascular endothelial growth factor, angiopoietin 1, and angiopoietin receptor-2 | (Mu et al., 2017) |
| Magnolia officinalis     | Neolignans, lignans, sesquiterpenes, alkaloids, and phenylethanoid | Antioxidant, extracellular matrix biosynthesis and protects chondrocytes | ↓ NF-kB | (Chen et al., 2014b; Amorati et al., 2015) |
| Berberine II             | Alkaloids (Isoquinoline) | Antiapoptotic, extracellular matrix biosynthesis and protects chondrocytes | ↓ NF-kB | (Zhou et al., 2015a; Lu et al., 2019) |
| Quercetin                | Flavonoid glycosides | Antioxidant, angiogenesis, and bone repair | ↓ IL-6, IL-1α, IL-3, ↓ IL-4, NF-κB | (Zhou et al., 2015b; Forte et al., 2016) |
| Betulinic acid           | Triterpene        | Antioxidant and extracellular matrix biosynthesis | ↓ Extracellular matrix (ECM) | (Yi et al., 2014; Jiang et al., 2019) |
| Sophoridine              | Matrine           | Antiapoptosis and antioxidiant | ↓ Caspase-3 and Bax, ↑ Bcl-2 | (Zhao et al., 2015) |
| Baiacalin                | Baiacalin         | Protects chondrocytes | ↑ H2O2, ↓ ECM-genes | (Cao et al., 2018) |
| Iso queretin             | Flavonoids        | Bone formation | ↑ RUNX2 | (Li et al., 2019) |
| Genistein                | Isoflavone        | Anti-inflammatory, angiogenesis, enhancing bone formation, and inhibiting bone resorption | ↑ BMP and angiogenesis pathways | (Cheng et al., 2014) |
| Bauhinia championii flavone | Flavonoids          | Antioxidant, anti-inflammatory, and antiapoptotic | ↓ Apoptosis, ↓ caspase-3 and TLR4, ↑ Bcl-2 | (Jian et al., 2016) |
| Velvet antler            | Amino acids, polypeptides and proteins | Angiogenesis, proliferation, and differentiation of chondrocytes | ↑ CEPCs and VEGF | (Li et al., 2018; Ma et al., 2019) |

(continued on next page)
the function of chondrocytes (Xu et al., 2015). Astragalo
dose IV significantly induced osteogenesis-related gene
expression, such as ALP, ColIa2, osteocalcin, and Runx2 (Bian et al., 2011). Chlorogenic acid has a positive
therapeutic effect on TD by regulating the caspase
and BECN1 expression, and regulating the degradation
of ECM.

**Angiogenesis**

Blood plays a role of nutrient transport in growth and
development, and blood vessel degeneration often leads
to severe damage to tissues and organs, as well as bone
development. The growth and development of bones
cannot be initiated and maintained without angiogenesis
(Mehmood et al., 2018a,b; Zhang et al., 2018b). Capil-
ary invasion mediated by VEGF is the key mechanism
linking chondrogenesis and osteogenesis, which deter-
mines the development and growth rate of bone
(Mehmood et al., 2018a,b). Thiram can change the
differentiation of abnormal chondrocytes by altering
the expression of the HIF-1α/VEGF pathway of
chondrocytes. Previously, *Drynaria fortunei* promoted
angiogenesis associated with modified MMP-2/TIMP-2
balance (Mehmood et al., 2018a; Huang et al., 2018).
Icarin can significantly improve abnormal angiogenesis
in the GP of TD and promote vascular recovery
(Zhang et al., 2018c). Mehmood et al. (2018a,b) demonstrated
that the TMP enhances angiogenesis in TD chickens via regulation of the HIF-1α/VEGF
signaling pathway. Administering celestrol to TD
chickens prevented unvascularized GP and reinstated
angiogenesis (Nabi et al., 2016). Screening the TCM
that promotes tibia angiogenesis is considered as another
important target in treating broilers TD.

**Scavenging Oxygen Free Radicals**

Free radicals can inhibit the synthesis of chondrocyte
data, matrix proteoglycan, and collagen and cause
severe damage to the membrane structure of cartilage.
In addition, free radicals can induce apoptosis in chon-
drocytes, resulting in high levels of cell count reductions
within critical zones of bone GP (Qin et al., 2019).
Administration of *Dendrobium officinale* polysaccha-
drides to aged mice significantly decreased oxidative
stress of bone marrow mesenchymal stem cell (Peng
et al., 2019a). Scutellarin reduced the levels of oxidative
stress in collagen-induced arthritis mice (Zhang et al.,
2017). Usually, chondrocyte proliferation and apoptosis
are in a dynamically balanced state; however, excessive
angiogenesis of chondrocytes in TD chickens reduces cell
density and numbers within bone GP resulting in
impairment of cartilage formation, as well as subsequent
ossification processes.

Meanwhile, oxygen-free radicals can also accelerate
the apoptosis of chondrocytes, reducing the content of
proteoglycan in the cartilage matrix. Some key selected
therapeutic TCM agents help prevent the occurrence
of TD in chickens via scavenging radical oxygen species,
thereby reducing oxidative damage to cartilaginous
chondrocytes. Li et al. (2007) reported that thiram
destroyed the oxidative balance via decreasing superox-
dide dismutase and GSH-Px content. Our previous study
found that the antioxidant index of the liver had signif-
cicant changes in TD chickens, the levels of superoxide
dismutase, glutathione peroxidase, and total antioxi-
dation were significantly reduced, and the content of malondialdehyde was increased considerably.
Icarin, anacardic acid, and tetramethylpyrazine can
restore the serum biochemical indexes and antioxidant
imbalance of TD broilers.

**CONCLUSION**

Currently, research on the mechanisms of TCM-
derived products for the treatment of TD is now
providing a strong foundation in efforts to uncover
potential treatments for TD. However, there are still

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**Table 1.** (continued)

| Name | Active components | Biological activity | Mechanism of action | References |
|------|-------------------|---------------------|---------------------|------------|
| Achyranthes bidentata | Phytosterone, phytocedrostoids, saccharides and saponins | Promotes chondrocyte proliferation, anti-inflammatory, and antiapoptotic | ↓ Wnt/β-catenin pathway, ↑ Frizzled-2, β-catenin and cyclin D1, ↓ glycogen synthase kinase 3β (GSK-3β), ↓ MMP-13, ↓ TIMP-1, ↓ Caspase-3 activity and apoptosis | (Weng et al., 2014; Zhang et al., 2014) |
| Sinomenine | Alkaloids | Anti-apoptotic of chondrocytes | ↓ Cell viability, ↑ Cell growth, ALP, Coll-I synthesis, ↑ MMP-2 and Runx2, ↓ ROS production, ↓ Hsp90 inhibitions | (Ju et al., 2010; Siddique et al., 2014; Kang et al., 2019; Nabi et al., 2016) |
| Ginsenosides | Saponins, ginsenoside | Angiogenesis, antioxidative possesses osteoblast differentiation and osteogenic stimulatory | ↓ Proteoglycans, ↑ Mineral density, ↓ Bone damage | (Yimam et al., 2015; He et al., 2018) |
| Gambogic acid | Gamboges, guttic acid | Angiogenesis, antioxidative possesses | | |
| White mulberry | Gallic acid, chlorogenic acid, protocatechue acid, rutin, caffeic acid | Immunomodulation, anti-inflammatory, antioxidation, and relieves cartilage degeneration | | |

**Abbreviations:** HIF-1α, hypoxia inducible factor-1α; TD, tibial dyschondroplasia; TNF, tumor necrosis factor.
many problems in the clinical application of TCM. For example, the composition of TCM and specific mechanisms of action are not clear; the chemical structure of polysaccharides, flavonoids, and glycoside monomers is complex, and large-scale (industrial) production is difficult; moreover, dosage of naturally occurring substances is not easily standardized, and lack of quantitative indicators and unified standards is difficult to implement on a large scale. Future research on the mechanism of TCM treatment should be combined with the latest scientific achievements to deepen further the understanding TCM derivative treatment and to lay the foundation.

Tibial dyschondroplasia is the most important tibiotarsal bone disease in fast-growing poultry that disturbs normal development of the tibial GP. The long metabolic cycles of most drugs combined with residue buildup and high treatment cost seriously restrict the utility of synthetic therapeutics for the treatment of TD. The use of TCM not only avoids the gastrointestinal reactions caused by oral drugs but also avoids the first-pass effects on liver metabolism. The principle of selecting TCM and its pharmacologic effects on TD chickens is primarily focused on the differentiation, proliferation, and apoptosis of chondrocytes, angiogenesis, matrix metabolism, oxidative damage, cytokines, and calcification of cartilage in tibia.

Figure 5. Mechanism of traditional Chinese medicines for improving bone remodeling in TD chickens. Abbreviation: TD, tibial dyschondroplasia.
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SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.psj.2020.08.055.

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