Recent advance in treatment of osteoarthritis by bioactive components from herbal medicine

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Abstract
Osteoarthritis (OA) is a common chronic articular degenerative disease, and characterized by articular cartilage degradation, synovial inflammation/immunity, and subchondral bone lesion, etc. The disease affects 2–6% of the population around the world, and its prevalence rises with age and exceeds 40% in people over 70. Recently, increasing interest has been devoted to the treatment or prevention of OA by herbal medicines. In this paper, the herbal compounds with anti-OA activities were reviewed, and the cheminformatics tools were used to predict their drug-likeness properties and pharmacokinetic parameters. A total of 43 herbal compounds were analyzed, which mainly target the damaged joints (e.g. cartilage, subchondral bone, and synovium, etc.) and circulatory system to improve the pathogenesis of OA. Through cheminformatics analysis, over half of these compounds have good drug-likeness properties, and the pharmacokinetic behavior of these components still needs to be further optimized, which is conducive to the enhancement in their drug-likeness properties. Most of the compounds can be an alternative and valuable source for anti-OA drug discovery, which may be worthy of further investigation and development.

Keywords: Herbal medicine, Osteoarthritis, Bioactive components, Drug discovery, Drug-likeness properties, Pharmacokinetics

Background
Osteoarthritis (OA) is a common chronic articular degenerative disease, and characterized by articular cartilage degradation, synovial inflammation/immunity, and subchondral bone lesion, etc. [1, 2] The disease affects 2–6% of the population around the world, and its prevalence rises with age and exceeds 40% in people over 70 [1]. Treatment for OA can be divided into non-surgical (e.g. acetaminophen, nonsteroidal anti-inflammatory drugs, and hyaluronic acid, etc.) and surgical (e.g. osteotomy, unicompartmental knee arthroplasty, and total knee arthroplasty) management [1]. However, these current treatments are also accompanied by a series of complications, such as pain, infection, blood problem, and so on [1]. Thus, it can be seen that exploring more safe and effective treatments for OA still need to be carried out on an ongoing basis.

The smooth progress of drug research and development needs the support of the corresponding pathological models. The commonly used methods of mimicking OA include surgical (e.g. Hulth technique, joint immobilization, and destabilization of the medial meniscus, etc.) and non-surgical (e.g. monosodium iodoacetate, papain, and collagenase, etc.) induction [3–8]. The model animals (e.g. mouse, rat, and rabbit, etc.) and human biological samples (e.g. cartilage, peripheral blood mononuclear cell, and fibroblast-like synoviocytes, etc.) are selected as the research object to evaluate the anti-OA mechanism of the drug.
In recent years, increasing interest has been devoted to the treatment or prevention of OA by herbal medicines. OA is a kind of “deficiency syndrome” in traditional Chinese medicine theory [9]. A variety of traditional Chinese medicines with tonifying deficiency effects show the potentials to treat OA [10, 11]. Additionally, herbal compounds with cartilage-protective, anti-inflammatory or antioxidant effects have also been widely used in the treatment of OA [12–14]. Therefore, the herbal compounds with anti-OA activities were reviewed in this paper, and the cheminformatics tools were used to predict their drug-likeness properties and pharmacokinetic parameters, so as to provide the references for their follow-up researches and developments.

**The anti-OA activities of bioactive components from herbal medicines**

Information on the treatment of OA by bioactive components from herbal medicines was collected by using Google Scholar (http://scholar.google.com) and PubMed (https://www.ncbi.nlm.nih.gov/pubmed). From herbal medicines, 43 bioactive components with anti-OA activities have been isolated, including 11 terpenoids, 10 flavonoids, 7 alkaloids, 6 phenols, 3 quinones, 2 coumarins, 2 lignans, 1 steroids, and 1 furans (Additional file 1: Figure S1). The networks of OA pathogenesis and compound targets were constructed by Cytoscape software (version 3.8.0). OA is mainly characterized by joint degeneration, meanwhile accompanied by the changes of the related indicators in circulatory system (Fig. 1). Multiple pathological processes are involved in the pathogenesis of OA, such as inflammation, apoptosis, and oxidative stress, etc. (Figure 1). These bioactive components (such as resveratrol, curcumin, and isofraxidin, etc.) mainly target the damaged joints (e.g. cartilage, subchondral bone, and synovium, etc.) and circulatory system to improve the pathogenesis of OA, which mainly exert anti-inflammatory, anti-apoptotic, and anti-oxidative stress effects through interleukin (IL), nuclear factor-κB (NF-κB), and matrix metalloproteinase (MMP) pathways (Figs. 2 and 3). The effective doses of these compounds for the experiment are shown in Table 1.

**The effects of bioactive components on cartilage in OA**

Cartilage is pivotal to the normal function of synovial joints. Cartilage covers and protects the ends of long
bones permitting friction-free locomotion and movement at the joints. A dysfunction in the cartilage is one of the important inducing factors and pathological features of OA [14]. Cartilage consists of chondrocytes that generate a large of collagenous extracellular matrix, proteoglycans, and elastin fibers. Histological analysis shows that various components can repair the damage of chondrocytes in OA, including resveratrol [14], curcumin [15], icariin [16], berberine [17], sinomenine [18], tetramethylpyrazine [19], halofuginone [20], quercetin [21], psoralen [22], and magnoflorine [23].

Fig. 2 The overview of targets and effects of bioactive components with anti-OA activities. Green circular node: herbal compound; yellow circular node: target; red rectangle node: anti-inflammatory effect; green rectangle node: anti-apoptosis; blue rectangle node: antioxidation; pink rectangle node: anticatabolic effect; purple rectangle node: antiangiogenesis; orange rectangle node: antisteoclastogenesis; yellow rectangle node: anti-endoplasmic reticulum stress

The inflammatory mediators lead to articular cartilage damage and the clinical manifestations of OA [24]. Resveratrol attenuates inflammation through NF-κB, toll-like receptor 4 (TLR4)/tumor necrosis factor receptor–associated factor 6 (TRAF6), and Wnt/β-catenin signaling pathways [12, 24–26]. Curcumin reduces the expression of pro-inflammatory mediators via inhibiting the activation of NLR pyrin domain containing 3 inflammasome and NF-κB [15, 27, 28]. Cryptotanshinone [29] and cinnamophilin [30] inhibit IL-1β-induced cartilage inflammation through suppressing NF-κB and mitogen-activated protein kinase (MAPK) activation. Geniposide may have anti-inflammatory potential on OA, and p38 MAPK signaling is a crucial pathway for this effect [31]. Harpagoside exerts anti-inflammatory effect via suppressing c-fos/activator protein-1 activity in OA chondrocytes [32]. Isofraxidin targets the TLR4/myeloid differentiation protein-2 axis and NF-κB signaling pathway to prevent OA inflammation [33, 34]. Shikonin inhibits chondrocyte inflammation by the regulation of the phosphatidylinositol-3-kinase (PI3K)/Akt signaling pathway in OA rats [35]. Anti-inflammatory effects of licochalcone A are associated with NF-κB and nuclear
Fig. 3 The overview of anti-OA activities of a resveratrol, b curcumin, c isofraxidin, d berberine, e emodin, and f icarin. Yellow circular node: target; red rectangle node: anti-inflammatory effect; green rectangle node: anti-apoptosis; blue rectangle node: antioxidation; pink rectangle node: anti-catabolic effect; purple rectangle node: anti-angiogenesis; orange rectangle node: anti-osteoclastogenesis; yellow rectangle node: anti-endoplasmic reticulum stress.
Table 1 The effective doses for the experiment on anti-OA activities of the herbal compounds

| No. | Herbal compounds                        | In vivo           | In vitro                                      |
|-----|-----------------------------------------|------------------|-----------------------------------------------|
| 1   | 2,3,5,4′-Tetrahydroxystilbene-2-O-β-D-glucoside | 10–50 mg/kg (rat) [60] | 10–400 μg/ml (chondrocyte) [60] |
| 2   | Acetylshikonin                          | 5 mg/kg (rat) [86] | 3 μM (chondrocyte) [86] |
| 3   | Anemonin                                | 2 mg/kg (mouse) [49] | 10 μM (chondrocyte) [49] |
|     |                                        |                  | 10 μM (cartilage explant) [49] |
| 4   | Arasaponin R1                          |                  | 125 mg/l (chondrocyte) [41] |
| 5   | Artesunate                             | 25–300 mg/kg (rat) [57, 100] | 25–500 mmol/l (chondrocyte) [52, 81, 90] |
| 6   | Astragaloside IV                       |                  | 50 μg/ml (chondrocyte) [73] |
| 7   | Berberine                               | 10–50 mg/kg (rat) [17] | 20–100 μM (OA synovial fibroblasts) [17] |
|     |                                        | 10—200 μM/50 μl (rat) [67, 68] | 25–100 μM (chondrocyte) [67–69] |
|     |                                        | 7–28 μg/kg (rat) [69] | 25–100 μM (cartilage explant) [68] |
| 8   | Butein                                  | 20 mg/kg (mouse) [46] | 10–50 μM (chondrocyte) [46] |
| 9   | Celastrol                               | 1 mg/kg (rat) [84] | 0.1–1 μM (chondrocyte) [54] |
| 10  | Cinnamophilin                           |                  | 5–30 μM (SW1353 cell) [30] |
| 11  | Compound K                              |                  | 0.01–10 μM (MC3T3-E1 cell) [37] |
| 12  | Coptisine                               |                  | 2.5–10 μg/ml (chondrocyte) [44] |
| 13  | Crocin                                  | 5–100 μM/0.3 ml (rabbit) [43] | 50–100 μM (chondrocyte) [43] |
|     |                                        | 30 mg/kg (rat) [110] |                  |
| 14  | Cryptotanshinone                        | 10 mg/kg (mouse) [29] | 5–20 μM (chondrocyte) [29] |
| 15  | Curcumin                                | 50 μM (mouse) [15] | 10 μM (THP-1 cell) [15] |
|     |                                        | 50–100 mg/kg (mouse) [27, 65, 66] | 50–100 μM (chondrocyte) [27, 28] |
|     |                                        | 200 mg/kg (rat) [96] | 40 μM (synoviocyte) [97] |
| 16  | Emodin                                  | 5–25 μM/50 μl (rat) [39] | 5–30 μg/ml (chondrocyte) [38, 39] |
| 17  | Ferulic acid                            |                  | 40 μM (chondrocyte) [55] |
| 18  | Gastrodin                               | 100 μg/kg (rat) [51] | 10–50 μM (chondrocyte) [51] |
| 19  | Geniposide                              | 40 mg/kg (rabbit) [31] | 80 μg/ml (chondrocyte) [31] |
| 20  | Genistein                               | 0.3–0.5 mg/kg (rabbit) [58] |                  |
| 21  | Ginsenoside Rb1                         | 80 μM/0.3 ml (rat) [76] | 20–80 μM (SW1353 cell) [76] |
|     |                                        | 300 μM/200 μl (rat) [87] |                  |
| 22  | Ginsenoside RgS                         | 10–15 mg/kg (rat) [74] |                  |
| 23  | Halofuginone                            | 0.2–2.5 mg/kg (mouse) [20, 82, 91] |                  |
| 24  | Harpagoside                             |                  | 300 μg/ml (chondrocyte) [32] |
| 25  | Honokiol                                |                  | 2.5–10 μM (chondrocyte) [50] |
| 26  | Icarin                                  | 10–40 μg/ml (rat) [9] | 20 μM (SW1353 cell) [16, 79] |
|     |                                        | 20 μM (rat) [16] | 12.5 mg/l (chondrocyte) [41] |
|     |                                        | 1–6 g/kg (rabbit) [40] | 12 μg/ml (SW1353 cell) [92] |
|     |                                        | 10–25 mg/kg (mouse) [78, 108] | 0.5–1 μM (OA fibroblast-like synoviocyte) [95] |
| 27  | Isofraxidin                             | 20 mg/kg (mouse) [34] | 1–50 μM (chondrocyte) [33, 34] |
| 28  | Kaempferol                              |                  | 25–100 μM (chondrocyte) [47] |
| 29  | Licochalcone A                         |                  | 5–20 μM (chondrocyte) [36] |
| 30  | Magnoflorine                            | 50 ng/2 μl (pig) [23] | 25 μg/ml (MC3T3-E1 cell) [23] |
| 31  | Naringin                                | 100 mg/kg (mouse) [42] | 5 μM (chondrocyte) [42] |
|     |                                        | 5–10 mg/kg (rat) [106] |                  |
| 32  | Paeonol                                 | 20 mg/kg (rat) [56] | 50 μM (chondrocyte) [56] |
|     |                                        | 0.2–0.8 mg/kg (rabbit) [71] |                  |
| 33  | Piperine                                |                  | 10–100 μg/ml (chondrocyte) [45] |
| 34  | Psoralen                                | 1 mg/kg (rat) [22] | 10 μM (chondrocyte) [22] |
|     |                                        |                  | 10 μM (synoviocyte) [22] |
|     |                                        |                  | 10–6 mol/l (chondrocyte) [75] |
factor (erythroid-derived 2)-like 2 signaling pathways [36]. Compound K, an IkBα kinase inhibitor, may alleviate inflammatory response in cartilage [37]. Emodin ameliorates OA cartilage inflammation by inhibiting NF-κB and Wnt/β-catenin signaling [38, 39]. NF-κB signaling pathway is also involved in the treatment of cartilage inflammation by icariin [40, 41], arasaponin R1 [41], berberine [17], tetramethylpyrazine [13], naringin [42], coptisine [44], piperine [45], butein [46], kaempferol [47], tectorigenin [48], honokiol [50], and gastrodin [51]. In addition, some molecules have been reported to reduce the expression of inflammatory factors in OA cartilage, but the related pathways still need to be further explored, such as astragaloside IV [52], puerarin [53], celastrol [54], ferulic acid [55], paeonol [56], artesunate [57], genistein [58], theaflavin-3,3′-digallate [59], and 2, 3, 5,4′-tetrahydroxystilbene-2-O-β-D-glucoside [60].

In the progressive stage of OA, apoptosis destroys chondrocyte homeostasis [61]. Resveratrol inhibits chondrocyte apoptosis in OA through a variety of signaling pathways, including nitric oxide (NO) [61], NF-κB [26], sirtuin 1 [62, 63], Wnt/β-catenin [62], bal-2/bax [64], TLR4 [12], and PI3K/Akt signaling pathways [12]. Curcumin reverses apoptosis of chondrocytes via modulating the balance of antiapoptotic and proapoptotic proteins [15]. This is related to janus kinase 2/signal transducer and activator of transcription 3 [65], extracellular signaling-regulated kinase (ERK) 1/2, and Akt/mamalian target of rapamycin (mTOR) pathways [66]. Berberine prevents NO-induced chondrocyte apoptosis via AMP-activated protein kinase (AMPK) and p38 MAPK signaling [67, 68], and promotes cell survival through activating Akt signaling in OA model [69]. Tetramethylpyrazine inhibits the chondrocytes apoptosis through suppressing the production of reactive oxygen species (ROS) [70] and inactivating NF-κB signaling pathway [13]. Paeonol alleviates chondrocyte apoptosis by regulating the levels of ROS, bcl-2, and bax [56, 71]. Some components (icariin [9], sinomenine [72], astragaloside IV [73], quercetin [21], shikonin [35], tectorigenin [48], gastrodin [51], and ginsenoside Rg5 [74]) also exert antiapoptotic effects on chondrocytes through various mechanisms. The promoting effects of puerarin [53], psoralen [75], magnoflorine [23], and emodin [38] on proliferation may be also beneficial to reverse cartilage apoptosis.

The extracellular matrix of articular cartilage is mainly composed of type II collagen and aggrecan. Catabolic reactions take place in the OA cartilage, in which collagen and aggrecan are degraded [63]. MMPs are a family of zinc containing, calcium-dependent neutral proteases which can initiate the cleavage of type II collagen and aggrecan [76]. In OA chondrocytes, resveratrol may reverse the decrease in the levels of type II collagen, aggrecan, and glycosaminoglycan by regulating silent information regulator 2 type 1, hypoxia-inducible factor-2α, and MMPs expression [24, 62, 63, 77]. Curcumin [28], naringin [42], icariin [16, 78, 79], berberine [68, 69], sinomenine [72], tetramethylpyrazine [13, 70, 80], astragaloside IV [81], halofuginone [82], puerarin [83], quercetin [84], celastrol [54, 85], harpagoside [32], ferulic acid [55], shikonin, acetylshikonin [86],

### Table 1 (continued)

| No. | Herbal compounds | In vivo | In Vitro |
|-----|------------------|---------|----------|
| 35  | Puerarin         | 25–50 mg/kg (mouse) [53] | 50 nM (chondrocyte) [53] |
|     |                  | 30–200 mg/kg (rat) [83, 88] |              |
| 36  | Quercetin        | 50–100 mg/kg (rat) [21, 84] | 25 μM (chondrocyte) [21] |
|     |                  | 25 mg/kg (rabbit) [98] |              |
| 37  | Resveratrol      | 10–100 μg/8 μl (mouse) [77] |              |
| 38  | Shikonin         | 10 mg/kg (rat) [35] | 50 μM (chondrocyte) [86] |
| 39  | Sinomenine       | 2 mg/kg (rabbit) [99] | 10–250 μM (chondrocyte) [72] |
|     |                  | 5 mg/0.2 ml (rabbit) [102] | 10–250 μM (cartilage explant) [72] |
| 40  | Tectorigenin     | 0.75–1.5 μg/kg (rat) [48] | 0.25 mM (mesenchymal stem cell) [93] |
| 41  | Tetramethylpyrazine | 30–100 mg/kg (rat) [19, 89] | 0.5–200 μM (chondrocyte) [13, 70] |
|     |                  | 2.1 mg/0.1 ml (rat) [80] | 50–200 μM (cartilage explant) [70] |
| 42  | Theaflavin-3,3′-digallate | 25–75 μg/ml (chondrocyte) [59] |              |
| 43  | Triptolide       | 0.35 μg (mouse) [107] | 20 ng/ml (THP-1 cell) [107] |
ginsenoside Rb1 [76, 87], cinnamophillin [30], honokiol [50], 2, 3, 5, 4′-tetrahydroxystilbene-2-O-β-d-glucoside [60], geniposide [31], ginsenoside Rg5 [74], cryptotanshinone [29], isofoxadin [33], paenol [56], crocin [43], cop- tisine [44], piperine [45], butein [46], licochalcone A [36], tectorigenin [48], theaflavin-3,3′-dигаллат [59], anemonin [49], gastrogdin [51], compound K [37], and emodin [38, 39] inhibit the expression of MMPs through a variety of pathways, such as IL-1β signaling, NF-κB signaling, AMPK signaling, MAPK signaling, and NO signaling, etc. The inhibition of cartilage catabolic processes by resveratrol [24], curcumin [66], and astragaloside IV [73] may also be related to their regulation on autophagy, activation of which may reduce the severity of OA. Additionally, Artesunate [57] and psoralen [75] can markedly enhance the expression of type II collagen as well.

Oxidative stress plays a crucial role in the progression of OA, and the dysregulation of various oxidative stress indices occurs in cartilage, such as NO, inducible NO synthase (iNOS), and ROS, etc. [54]. Resveratrol [61], tetramethylpyrazine [13, 70], celastrol [54], isofoxadin [33, 34], paenol [56], shikonin [35], coptisine [44], piperine [45], butein [46], genistein [58], kaempferol [47], licochalcone A [36], honokiol [50], 2, 3, 5, 4′-tetrahydroxystilbene-2-O-β-d-glucoside [60], compound K [37], geniposide [31], emodin [38], and curcumin [65] may reverse the abnormal expression of these indexes. Mitochondrial dysfunction in chondrocytes is associated with OA, and induces oxidative stress [88]. Puerrarin [88] and quercetin [84] may attenuate mitochondrial dysfunction in OA rats. Subsequently, oxidative stress induces endoplasmic reticulum stress in OA, and quercetin may also repress this process by activating the sirtuin1/AMPK signaling pathway [21].

Abnormal angiogenesis is also closely related to the development of OA [57]. Some herbal compounds (e.g. sinomenine [18], tetramethylpyrazine [89], astragaloside IV [90], and artesunate [57]) may suppress aberrant angiogenesis by interfering with a variety of targets, such as vascular endothelial growth factor (VEGF), miR20b, and nerve growth factor (NGF), etc.

The effects of bioactive components on subchondral bone in OA
Besides cartilage, subchondral bone lesions are the characteristic pathological changes in OA as well [91]. The micro-computed tomography scan shows that halofuginone restores coupled bone remodelling and aberrant angiogenesis in subchondral bone [82, 91]. Osteoclast is a type of bone cell breaking down bone tissue, and collagen degradation mediated by which is also involved in the pathophysiology of OA [57]. Icariin [92] and sinomenine [93] suppress osteoclastogenesis through osteoprotegerin-NF-κB system. Halofuginone suppresses Th17-induced osteoclastogenesis via inhibition of TGF-β signaling [82]. Artesunate interrupts anterior cruciate ligament transection-associated osteoclastogenesis [57]. In addition to osteoclasts, osteoblasts are also the major cellular component of bone, which synthesize dense and crosslinked collagen and reshape bone tissue. Magnoflorine [23] and compound K [37] stimulate osteoblast proliferation, differentiation, and mineralization. Resveratrol may play the roles on alkaline phosphatase activity, osteocalcin release, and mineralization in osteoblasts via promoting the Wnt/β-catenin signaling pathway [94]. Histological analysis indicates that cryptotanshinone [29], isofoxadin [34], and resveratrol [77] may reduce subchondral bone plate thickness.

The effects of bioactive components on synovium in OA
Synovium supplies nutrients to cartilage and protects the joint structures and the adjoining musculoskeletal tissues [95]. OA is a classic degenerative synovial disease. Synovitis affects both symptoms and progression of OA [95]. Curcumin [96, 97], icariin [95], psoralen [22], berberine [17], quercetin [98], geniposide [31], sinomenine [99], and artesunate [57, 100] produce anti-inflammatory activity in synoviocytes/synovia by regulating the levels of various inflammatory factors, such as MMPs, ILs, and tumor necrosis factor (TNF)-α, etc. Synovial proliferation is induced by inflammation in OA [101]. The antiproliferative effects of curcumin [97] and icariin [95] may reverse this process. Likewise, angiogenesis and inflammation are closely associated in OA [57]. Sinomenine [18] and artesunate [57] may prevent the expression of angiogenic factors (e.g. VEGF, NGE, and angiopoietin-1, etc.). Oxidative stress and inflammation promote each other in joints [98]. Quercetin [98] and geniposide [31] may inhibit oxidative stress in synovial region. Glucose-regulated protein-78 aggregates in the endoplasmic reticulum, which is widely used as a marker for endoplasmic reticulum stress. Icariin can reduce Glucose-regulated protein-78 expression in synovium of OA [95]. Geniposide [31] and sinomenine [102] can decrease the levels of MMPs and cartilage oligomeric matrix proteins in synovial fluid, which may help to alleviate the process of cartilage degradation in OA. Insulin-like growth factor-1 accelerates the differentiation of chondrocytes, stimulates the synthesis of cartilage matrix, and inhibits the matrix decomposition, the up-regulation of which by artesunate may facilitate cartilage protection in OA [100].

The effects of bioactive components on circulatory system in OA
Circulatory pathology is closely related with OA [103]. A variety of herbal compounds can reverse some
pathological processes in serum of OA model. Quercetin [104], resveratrol [63, 105], sinomenine [99], puera-
in [53], isofraxidin [34], naringin [106], ginsenoside Rb1 [87], triptolide [107], and icariin [108] can reduce the serum levels of inflammatory cytokines, such as ILs, TNF-α, and hsa-miR-20b, etc. Sinomenine [102], quercetin [98, 104], and artesunate [100] may regulate the expressions of cartilage catabolic factors (e.g. MMPs, tissue inhibitors of MMP, and a disintegrin and metalloproteinase with thrombospondin motifs, etc.) in serum. Icariin reduces VEGF and hypoxia-inducible factor-α levels in the peripheral blood, which may help to inhibit the formation of new blood vessels in the synovial tissue of joints [9]. Resveratrol effectively improves the blood rheology, which facilitates to prevent and delay the degenerative changes in the articular cartilage of OA model [109]. Additionally, quercetin increases serum superoxide dismutase level, which is a major active molecule to scavenge free radical [98].

The effects of bioactive components on muscle in OA
Muscle weakness and inflammation also play a role in OA development and progression [110]. Crocin attenuation of OA symptoms through alleviating muscle oxidative stress (targets: nuclear factor (erythroid-derived 2)-like 2, superoxide anion, and glutathione, etc.) and inflammation (pathways: c-Jun N-terminal kinase, NF-κB, and MAPK, etc. signaling pathways) induction [110].

Pharmacokinetic parameters and drug-likeness properties prediction of bioactive components with anti-OA activities
In addition to their therapeutic activities, the pharmacokinetic behaviors of these components are also the key factors affecting their ability to develop drugs. Only the compounds with good drug-likeness properties have the possibility to be further investigated and developed. Thus, in the following section, the cheminformatics tools were applied to predict the pharmacokinetic parameters and drug-likeness properties of these compounds.

The pharmacokinetic parameters of these compounds were calculated by using pkCSM (http://biosig.unimelb.edu.au/pkcsmprediction) [111]. The compounds depicted as 2D structures in the MDL Molfile format were imported into the website. The water solubility of the compounds can influence their efficacy in vivo. The good aqueous solubility can facilitate the molecules dispersing into biological body fluids, thereby expediting their absorption and distribution processes [112]. Water solubility assessment showed that most of herbal compounds (38/43) were soluble in water (>−4 log mol/L), while five of 43 molecules were low soluble in water (<−4 log mol/L, Table 2). The low solubility of curcumin is one of the factors affecting its oral bioavailability. Reportedly, the solubility of curcumin can be significantly improved by addition of an electron-withdrawing group. A chemically modified curcumin, TRB-n0224, also has good therapeutic effects on OA model [113].

The main pathological features of OA are the degenerative lesions of cartilage and synovium in the joint. It is not conducive to the treatment of local lesions of OA if the distribution of drug molecules in the blood is more than that in the lesion tissues. VDss index can be used to predict the distribution of molecules in tissue and plasma. VDss analysis showed that thirty-six of 43 herbal compounds were mainly distributed in the circulatory system (<0.45 log L/kg, Table 2). This may require some measures to increase their levels in local tissues. Intra-articular injection allows the molecules to accumulate in the joint cavity, thus enhancing their effects on local lesions. Intra-articular delivery of resveratrol [77], tetramethylpyrazine [80], and anemonin [49] may enhance their articular cavity retention for treating OA.

In addition to intra-articular injection, transdermal delivery of joint is also one of the local administration methods. Extra-articular percutaneous approach has advantages over intra-articular injection, such as greater safety, easier use, better patient compliance, and so on. Skin permeability is the necessary requirement for transdermal drug delivery. Skin permeability estimation indicated that almost all of these herbal molecules (42/43) were easy to penetrate into the epidermis (prediction value less than −2.5, Table 2), especially anemonin, sinomenine, and triptolide.

The low clearance rate of drugs results in the prolongation of their half-life in vivo. This may produce a sustained and stable curative effect on the chronic diseases, such as OA. At the same time, however, attention should also be paid to the cumulative dose of herbal components with low total clearance. These compounds may also cause cumulative toxicity when they are used for long-term therapeutic purposes. Total clearance prediction showed that fifteen of 43 herbal compounds have the low hepatic clearance and renal clearance rates (prediction value less than 0.25, Table 2), especially celastrol, curcumin, and butein.

The drug-likeness properties prediction of these herbal compounds was analyzed by using MolSoft online tools (http://molsoft.com/mpred/) [114]. The input for the analysis was the MDL Molfile format of these compounds. Over half of these molecules (26/43) had the great possibility of becoming the drugs (prediction value between 0 and 2, Table 2), which have the possibility of being further studied and developed. However, of these compounds, nine molecules had poor drug-likeness properties (prediction value between −3 and −0.5,
| No. | Herbal compounds                                      | Botanical source                                      | Water solubility (log mol/L) | Skin permeability (log Kp) | VDss (human) (log L/kg) | Total clearance (log ml/min/kg) | DL |
|-----|------------------------------------------------------|-------------------------------------------------------|------------------------------|---------------------------|-------------------------|---------------------------------|----|
| 1   | 2, 3, 5, 4'-Tetrahydroxystilbene-2-O-β-d-glucoside | Polygonum multiflorum Thunb.                          | −3.227                       | −2.735                    | −0.109                  | 0.219                           | 0.16 |
| 2   | Acetylshikonin                                       | Lithospermum erythrorhizon Sieb.                     | −3.022                       | −3.188                    | 0.084                   | 0.336                           | 0.41 |
| 3   | Anemomnis                                           | Clematis L.                                          | −1.436                       | −3.646                    | −0.005                  | 0.431                           | −1.57 |
| 4   | Arasaponin R1                                       | Panax notoginseng (Burk) F. H. Chen                 | −2.765                       | −2.735                    | −0.239                  | 0.497                           | 0.24 |
| 5   | Artesunate                                           | Artemisia annua L.                                   | −3.125                       | −2.734                    | 0.286                   | 0.973                           | −0.39 |
| 6   | Astragaloside IV                                     | Astragalus membranaceus (Fisch.) Bge.               | −2.693                       | −2.735                    | −0.507                  | 0.147                           | 0.05 |
| 7   | Berberine                                            | Hydrastis canadensis L., Phellodendron amurense Ruhr., and Coptis chinensis Franch. | −3.341                       | −2.734                    | 0.764                   | 1.272                           | 0.91 |
| 8   | Butein                                               | Rhus verniciflua Stokes                              | −2.857                       | −2.835                    | 0.003                   | 0.062                           | 0.82 |
| 9   | Celastrol                                            | Celastrus aculeatus Merr.                            | −4.584                       | −2.720                    | −0.987                  | −0.090                          | 0.63 |
| 10  | Cinnamophilin                                        | Cinnamomum philippinense (Merr.) C. E. Chang        | −4.465                       | −3.051                    | 0.195                   | 0.215                           | 0.76 |
| 11  | Compound K                                           | Panax ginseng C. A. Mey.                             | −3.683                       | −2.735                    | −0.627                  | 0.475                           | 0.34 |
| 12  | Copatine                                             | Coptis chinensis Franch.                             | −3.325                       | −2.734                    | 0.636                   | 1.298                           | −0.08 |
| 13  | Crocin                                               | Scutellariae sativis L.                               | −2.804                       | −2.735                    | −0.294                  | 1.768                           | −0.27 |
| 14  | Cryptotanshinone                                      | Salvia miltochrista Bunge                           | −4.571                       | −2.563                    | 0.689                   | 0.841                           | 0    |
| 15  | Curcumin                                             | Curcuma longa L.                                     | −4.926                       | −2.913                    | −0.184                  | 0.033                           | −0.66 |
| 16  | Emodin                                               | Rheum palmatum L.                                    | −3.179                       | −2.764                    | 0.045                   | 0.348                           | −0.72 |
| 17  | Ferulic acid                                         | Oldenlandia diffusa (Wild.) Roxb.                    | −1.737                       | −2.621                    | −0.642                  | 0.653                           | −0.44 |
| 18  | Gastrodin                                            | Gastrodia elata Blume                                | −1.354                       | −2.985                    | −0.463                  | 0.234                           | −1.19 |
| 19  | Geniposide                                           | Gardenia jasminoides J. Ellis                        | −2.534                       | −2.914                    | −0.415                  | 1.408                           | 0.51 |
| 20  | Genistein                                            | Glycyrrhiza uralensis L.                             | −3.533                       | −2.737                    | −0.709                  | 0.232                           | 0.71 |
| 21  | Ginsenoside Rb1                                      | Panax ginseng C. A. Mey.                             | −2.839                       | −2.735                    | −0.440                  | 0.570                           | 0.28 |
| 22  | Ginsenoside Rg5                                      | Panax ginseng C. A. Mey.                             | −3.520                       | −2.735                    | −1.033                  | 0.513                           | 0.44 |
| 23  | Halofuginone                                         | Dichroa fehniifuga Lour.                             | −3.613                       | −2.960                    | 0.593                   | 1.134                           | 0.91 |
| 24  | Harpagoside                                          | Harpagophyllum procumbens DC.                        | −3.181                       | −2.751                    | −0.332                  | 1.057                           | −0.96 |
| 25  | Honokiol                                             | Magnolia officinalis Rehd. et Wils.                  | −3.862                       | −2.795                    | 0.350                   | 0.377                           | −0.33 |
| 26  | Icariin                                              | Epimedium brevicaur Maxim.                           | −2.930                       | −2.735                    | −0.278                  | 0.076                           | 1.09 |
| 27  | Isoflavadin                                           | Acanthopanax senticosus (Rupr. & Maxim.) Harms      | −2.37                        | −2.728                    | −0.382                  | 0.762                           | −0.88 |
| 28  | Kaeperferol                                           | Kaempferia rotunda L.                                 | −3.176                       | −2.735                    | −0.107                  | 0.558                           | 0.77 |
| 29  | Licochalcone A                                       | Glycyrrhiza uralensis L.                             | −4.161                       | −2.808                    | 0.092                   | 0.482                           | −0.16 |
| 30  | Magnoflorin                                          | Phellodendron chinense Schned.                       | −3.447                       | −2.954                    | 1.306                   | 1.102                           | 0.8  |
| 31  | Naringin                                              | Citrus plants                                        | −3.103                       | −2.735                    | 0.157                   | 0.685                           | 1.21 |
| 32  | Paeonol                                              | Paeonia suffrutcosa Andr.                            | −1.606                       | −2.758                    | 0.137                   | 0.630                           | 0.01 |
| 33  | Piperine                                              | Piper nigrum L.                                      | −3.799                       | −2.824                    | 0.266                   | 0.240                           | −0.02 |
| 34  | Psoralen                                              | Psoralea corylifolia L.                               | −2.688                       | −2.271                    | −0.284                  | 0.738                           | −0.93 |
| 35  | Puerarin                                             | Pueraria lobata (Willd.) Ohwi                        | −3.845                       | −2.735                    | −0.217                  | 0.183                           | 0.04 |
| 36  | Quercetin                                             | Cudraria tricuspidata (Carr.) Bur.                    | −2.942                       | −2.735                    | 0.134                   | 0.515                           | 0.93 |
| 37  | Resveratrol                                           | Polygonum cuspialatum Sieb., Veratrum album var. grandiflorum Maxim., and Vitis vinifera L. etc. | −3.285                       | −3.132                    | 0.118                   | 0.141                           | −0.94 |
| 38  | Shikonin                                              | Lithospermum erythrorhizon Sieb.                     | −2.535                       | −2.775                    | 0.297                   | 0.105                           | 0.36 |
| 39  | Sinomenine                                            | Sinomenium acutum (Thunb.) Rehd. et Wils.            | −2.276                       | −3.550                    | 0.673                   | 0.921                           | 0.87 |
| 40  | Tectorigenin                                          | Belamcanda chinensis (L.) Redouté                    | −3.580                       | −2.737                    | −0.644                  | 0.166                           | 0.58 |
Table 2 (continued)

| No. | Herbal compounds | Botanical source            | Water solubility (log mol/L) | Skin permeability (log Kp) | VDss (human) (log L/kg) | Total clearance (log ml/min/kg) | DL |
|-----|------------------|-----------------------------|-------------------------------|---------------------------|------------------------|-------------------------------|----|
| 41  | Tetramethylpyrazine | *Ligusticum chuanxiong* Hort. | −0.786                        | −2.671                    | −0.136                 | 0.551                         | −1.53|
| 42  | Theaflavin-3,3′-digallate | Black tea                  | −2.892                        | −2.735                    | −0.087                 | 0.242                         | 0.47|
| 43  | Triptolide        | *Tripterygium wilfordii* Hook.f. | −3.657                        | −3.202                    | 0.465                  | 0.484                         | −0.32|

Water solubility: the solubility of the molecule in water at 25 °C; less than −10: insoluble; between −10 and −6: poorly soluble; between −6 and −4: moderately soluble; between −4 and −2: soluble; between −2 and 0: very soluble; more than 0: highly soluble

Skin permeability: the human skin permeability of compounds in vitro; more than −2.5: low skin permeability; less than −2.5: high skin permeability

VDss (human): the volume of compounds distributed in tissue; less than −0.15: low distribution; more than 0.45: high distribution

Total clearance: a combination of hepatic clearance and renal clearance; less than 0.25: low total clearance; more than 0.25: high total clearance

DL: drug-likeness model score; between 0 and 2: very drug-like molecules; between −3 and −0.5: non-drug like molecules

Table 2), which may require some measures to optimize their pharmacokinetics parameters, such as molecular modification, drug administration route change, and drug dosage form optimization, etc.

Conclusion and future directions

In this review, we have summarized and analyzed 43 herbal compounds with anti-OA activities. The main therapeutic sites of these molecules for the treatment of OA are articular cartilage, subchondral bone, synovial membrane, and circulatory system, etc. Over half of these compounds have good drug-likeness properties (e.g. naringin, icariin, and quercetin, etc.), which may be worthy of further investigation and development. In addition, these compounds are mainly isolated from *Araliaceae*, *Leguminosae*, and *Polygonaceae* plants, etc., which would get more attention in the following researches.

Through cheminformatics analysis, the pharmacokinetic behavior of these components still needs to be further optimized, which is conducive to their enhancement in their drug-likeness properties. The water solubility of molecules can be changed by mean of structural modification, so as to enhance their oral absorption process. In the subsequent distribution process, the accumulation of drug molecules in the joint tissues is conducive to the treatment of the main lesion sites of OA. Both intra-articular injection and articular percutaneous administration can increase the levels of drug molecules in the joint, between which the latter one has a stronger application potential in the treatment of OA. Additionally, the retention time of the components with low clearance rate is increased in vivo, which is conducive to the continuous treatment of OA. However, when used for a long time, their doses should be properly adjusted to avoid cumulative toxicity.

At present, the application of herbal compounds in the treatment of OA has made some progress. However, compared to other arthritis (such as rheumatoid arthritis (RA)), the application of herbal compounds in OA is still inadequate. There is some common pathogenesis between OA and RA, such as inflammation, apoptosis, and oxidative stress, etc. [112]. Therefore, the potential of anti-RA drugs in the treatment of OA would be further explored in future researches. In addition, some new research patterns can be used to speed up the exploration of the mechanism and chemical basis of herbs in the treatment of OA, such as biolabelled research pattern [115, 116], chinmedomics [117], and systems pharmacology [118], etc.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13020-020-00363-5.

Additional file 1: Figure S1. Molecular structures of bioactive components isolated from herbal medicines treating OA.
Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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