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REVIEW

Effects of various antimicrobial agents on multi-directional differentiation potential of bone marrow-derived mesenchymal stem cells

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Abstract

Antimicrobial drugs of several classes play an important role in the treatment of bone and joint infections. In addition to fighting pathogenic microorganisms, the effects of drugs on local tissues and cells are also related to the course and prognosis of bone and joint infections. The multi-directional differentiation potential of bone marrow-derived mesenchymal stem cells (MSCs) is essential for tissue repair after local injury, which is directly related to the recovery of bone, cartilage, and medullary adipose tissue. Our previous studies and the literature indicate that certain antimicrobial agents can regulate the differentiation potential of bone marrow-derived MSCs. Here, in order to systematically analyze the effects of various antimicrobial drugs on local tissue regeneration, we comprehensively review the studies on the effects of these drugs on MSC differentiation, and classify them according to the three differentiation directions (osteogenesis, chondrogenesis, and adipogenesis). Our review demonstrates the specific effects of different antimicrobial agents on bone marrow-derived MSCs and the range of concentrations at which they work, and provides a basis for drug selection at different sites of infection.

Key words: Antimicrobial agents; Bone marrow mesenchymal stem cells; Osteogenesis; Chondrogenesis; Adipogenesis

Core tip: Bone marrow-derived mesenchymal stem cells (MSCs) are essential for tissue repair (bone, cartilage, and medullary adipose tissue) after local bone and joint infection. The effects of various antimicrobial agents on the three types of differentiation potential (osteogenesis, chondrogenesis, and adipogenesis) of bone marrow-derived MSCs are worth noting. Here in this paper, we collect the latest updates on the use of antimicrobial agents to regulate the differentiation of MSCs.

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INTRODUCTION

Antimicrobial drugs are referred to as drugs that exhibit an inhibitory or killing effect on bacteria and other pathogenic microorganisms. In clinic, the most commonly used antimicrobial agents are antibiotics, which include natural antibiotics and synthetic antibiotics. Penicillin is a typical natural antibiotic which is produced by fungal metabolism[1]. Synthetic antibiotics, such as quinolones, are the most common type of antibiotics today and play important roles in the treatment of clinical diseases[2]. Antimicrobial agents, in a broad sense, are not limited to antibiotics. Some peptides with antibacterial property and drugs that have been proven to have both antibacterial and other biological functions also fall under the category of antimicrobial agents[3,4]. In addition, extracts of certain plants or Chinese medicines have also been reported to have antimicrobial properties, and they have been speculated to play a role in killing pathogenic microorganisms in clinical and other fields[5]. Similar to bacteria, fungi, viruses, and other pathogenic microorganisms also pose significant challenges to human health, and their corresponding therapeutic drugs also play an important role in clinical and related fields[6,7]. As clinically common diseases, bone and joint infectious diseases can be caused by a variety of pathogenic microorganisms; they cause pain in patients and pose great challenges to clinicians. When using various antimicrobial drugs to treat bone and joint infections, close attention should be paid to the killing effects of these agents on pathogenic microorganisms and to their regulation in local tissues and cells[8]. After using local or systemic antibacterial drugs to treat osteomyelitis and effectively controlling the symptoms of infection, local bone marrow mesenchymal stem cells (BMSCs) diff-erentiate into osteoblasts and lipoblasts, and finally, differentiate into mature bone and adipose tissue to repair locally damaged sites[9]. Similarly, when the symptoms of intra-articular infection are improved, the damaged articular cartilage also needs to be repaired in an environment conducive to chondrogenic differentiation[10]. At this time, the effect of antimicrobial drugs on the differentiation potential of stem cells is crucial. If a drug can promote the differentiation of the stem cells in a direction favorable for tissue repair while also killing the pathogenic microorganisms, the treatment process and the therapeutic effect can be accelerated. On the contrary, if the drug inhibits the differentiation potential of stem cells, it may have undesirable effects on disease treatment.

Considering the multi-directional differentiation potential of bone MSCs and their three most common differentiation directions (osteogenesis, chondrogenesis, and adipogenesis)[11], we review the effects of different classes of antimicrobial agents on these three types of differentiation functions, and hope that it can produce certain ideas for the better drug-mediated treatment of bone and joint infectious diseases.

EFFECTS OF VARIOUS ANTIMICROBIAL AGENTS ON OSTEOGENIC DIFFERENTIATION

BMSCs are bone marrow-derived cells that play a key role in the renewal and regeneration of osteoblasts. BMSCs can differentiate into bone-forming osteoblasts and have been shown to be a primary source of osteoprogenitor cells[12]. Moreover, BMSCs can be used as bone graft materials to treat bone defects[13]. While the local osseous tissue is damaged by the pathogenic microorganism, BMSCs are activated and differentiate into osteoblasts to complete the repair of local bone dissolution. Failure of BMSCs to completely repair the local bone defects caused by infection may lead to local osteoporosis and even pathological fractures[13]. Therefore, while using various antimicrobial agents to control infection, the consideration of the effect of drugs on osteogenic differentiation of BMSCs is crucial. Drugs with antibacterial properties and osteoinductive ability may play a better therapeutic role in orthopedic infections, such as osteomyelitis; whereas drugs that inhibit the differentiation of stem cells into osteoblasts and destroy the osteogenic microenvironment may adversely

affect the repair of local osseous tissue. In this section, we will review the effects of different antimicrobial agents on osteogenic differentiation, and the overall situation is listed in Table 1.

Antibiotics

Antituberculosis drugs: As a representative drug for the treatment of tuberculosis, rifampicin has a strong bactericidal effect on *Mycobacterium tuberculosis*. In addition, rifampicin has also been shown to exhibit anti-Gram-positive bacteria activity and kill the intracellular bacteria hidden in cells, and has a wide range of clinical applications. To demonstrate the potential toxicity of rifampicin and its effects on osteogenic differentiation of osteoblasts, researchers studied osteoblasts treated with different concentrations of rifampicin. The results showed that rifampicin did not cause toxicity to osteoblasts or affect the level of alkaline phosphatase (ALP) in the cells when the concentration of rifampicin did not exceed 10 μg/mL. However, when the drug concentration reached 100 μg/mL and above, the number of osteoblasts and intracellular ALP levels decreased significantly, and the decrease was over 75%[14]. Another study demonstrated that rifampicin is cytotoxic to human bone marrow-derived MSCs at concentrations above 32 μg/mL and inhibited osteogenic differentiation potential of human bone marrow-derived MSCs in a concentration-dependent manner at concentrations ranging from 4-128 μg/mL. The collagen synthesis, mineralization effect, and expression levels of osteogenic genes in MSCs were inhibited to varying degrees with the increase in rifampicin concentration[15].

β-lactams: As a representative drug of β-lactam antibiotics, the discovery of penicillin has great significance in the history of human infectious diseases. It has been reported that penicillin, at a conventional blood concentration (30 μg/mL), does not inhibit the osteogenic differentiation process of human bone marrow-derived MSCs[16]. When penicillin was added during the culture of human osteoblasts, cytotoxicity was observed when the penicillin concentration reached 500 μg/mL. At the same time, the differentiation function of osteoblasts was also significantly inhibited after penicillin concentration exceeded 500 μg/mL, and the intracellular ALP level was significantly decreased (above 75%) compared with the control group[14]. Since penicillin cannot tolerate the enzymes produced by a variety of bacteria and is more likely to be destroyed, the probability of clinical drug resistance is increased and the clinical application is greatly limited. Therefore, some antibiotics that are artificially synthesized and can tolerate penicillinase are gradually replacing penicillin and play a greater role in the clinic. Both flucloxacillin and nafcillin are semi-synthetic penicillins that can tolerate penicillinase. It has been reported that flucloxacillin at conventional plasma concentrations (200 μg/mL) does not affect the osteogenic differentiation of human bone marrow-derived MSCs[16]. Nafcillin can still exert its antibacterial effect under acidic conditions, but it has been reported that nafcillin has a strong inhibitory effect on the proliferation and differentiation of human osteoblasts. When its concentration exceeds 10 μg/mL, the ALP level in osteoblasts was drastically reduced[14].

Cephalosporins are an important branch of β-lactam antibiotics and play an important role in the treatment of various infectious diseases. Cefazolin, cefuroxime, cefotaxime, and cefepime are representative drugs of first, second, third, and fourth generation cephalosporins, respectively, and their effects on the differentiation of osteoblasts have been reported. Previous studies showed that cefuroxime does not alter the osteogenic differentiation of human bone marrow-derived MSCs at conventional blood concentrations (50 μg/mL)[16]. Cefazolin and cefepime cause osteogenic inhibition (above 25% and 75%, respectively) at concentrations up to 200 μg/mL, and cefotaxime inhibits the differentiation of osteoblasts (above 75%) at concentrations up to 500 μg/mL[14].

Carbapenems are a new class of β-lactams that are known for their broad spectrum. These drugs have strong antibacterial activity against most Gram-positive, Gram-negative, aerobic, anaerobic, and multi-drug resistant bacteria, and are one of the most important antibacterial drugs employed for the treatment of serious bacterial infections. Imipenem and meropenem are representative drugs that fall under in this category. Studies on the effect of these two drugs on differentiation of human osteoblasts have shown that imipenem does not have a significant effect on the differentiation potential of osteoblasts[14], while meropenem inhibits the differentiation of osteoblasts to a certain extent at concentrations of more than 500 μg/mL[14].

Macrolides: Macrolide antibiotics, drugs that inhibit bacterial protein synthesis by blocking peptide acyltransferase in bacterial ribosomes, are a class of drugs with extensive antibacterial spectrum. Azithromycin is a drug commonly used in clinical practice, and has certain inhibitory effects on various bacteria, mycoplasma, and

Table 1 Effects of various antimicrobial agents on osteogenic differentiation

Agent		Ref.	Cell / animal	Effect	Concentration
Antituberculosis drugs	Rifampicin	[14]	Osteoblasts	Inhibition	≥ 100 μg/mL
		[15]	BMSCs	Inhibition	4-128 μg/mL
β-lactams	Penicillin	[16]	BMSCs	No effect	30 μg/mL
		[14]	Osteoblasts	Inhibition	≥ 500 μg/mL
	Flucloxacillin	[16]	BMSCs	No effect	200 μg/mL
	Nafcillin	[14]	Osteoblasts	Inhibition	≥ 100 μg/mL
	Cefazolin	[14]	Osteoblasts	Inhibition	≥ 200 μg/mL
	Cefuroxime	[16]	BMSCs	No effect	50 μg/mL
	Cefotaxime	[14]	Osteoblasts	Inhibition	≥ 500 μg/mL
	Cefepime	[14]	Osteoblasts	Inhibition	≥ 200 μg/mL
	Imipenem	[14]	Osteoblasts	No effect	0-1000 μg/mL
	Meropenem	[14]	Osteoblasts	Inhibition	≥ 500 μg/mL
Macrolides	Azithromycin	[14]	Osteoblasts	Inhibition	≥ 100 μg/mL
Aminoglycosides	Gentamicin	[14]	Osteoblasts	Inhibition	≥ 100 μg/mL
		[16]	BMSCs	Inhibition	≥ 75 μg/mL
		[17]	BMSCs	Inhibition	50-200 μg/mL
		[18]	C2C12	Inhibition	12.5-800 μg/mL
	Amikacin	[14]	Osteoblasts	No effect	0-1000 μg/mL
	Tobramycin	[20]	BMSCs	Inhibition	300-1000 μg/mL
		[14]	Osteoblasts	Inhibition	≥ 500 μg/mL
Tetracyclines	Tetracycline	[22]	BMSCs	Inhibition	10 μg/mL
	Doxycycline	[14]	Osteoblasts	Inhibition	≥ 100 μg/mL
	Minocycline	[14]	Osteoblasts	Inhibition	≥ 100 μg/mL
Quinolones	Levofloxacin	[14]	Osteoblasts	Inhibition	≥ 200 μg/mL
	Ciprofloxacin	[14]	Osteoblasts	Inhibition	≥ 100 μg/mL
Polypeptide antibiotics	Colistin	[14]	Osteoblasts	Inhibition	≥ 100 μg/mL
	Bacitracin	[23]	BMSCs	Promotion	0.1-10 μmol/L
	Vancomycin	[24]	BMSCs	No effect	0-500 μg/mL
		[24]	BMSCs	Inhibition	5000 μg/mL
		[14]	Osteoblasts	No effect	0-2000 μg/mL
		[25]	BMSCs	No effect	0-20 μg/mL
		[16]	BMSCs	Inhibition	200 μg/mL
Other types of antibiotics	Metronidazole	[16]	BMSCs	No effect	20 μg/mL
	Trimethoprim	[14]	Osteoblasts	Inhibition	≥ 500 μg/mL
	Linezolidone	[14]	Osteoblasts	Inhibition	≥100 μg/mL
	Salinomycin	[26]	BMSCs	No effect	10 μmol/L
Natural peptides	Lactoferrin	[27]	Adipose-derived stem cells	Promotion	10-100 μg/mL
		[29]	MC3T3-E1	Promotion	1-1000 μg/mL
	Hepcidin	[30]	BMSCs	Promotion	0.2 mmol/L
	LL-37	[31]	BMSCs	Promotion	5-20 μg/mL
	KR-12	[32]	BMSCs	Promotion	1-1000 μg/mL
Chinese traditional drug extracts	Cordycepin	[33]	Adipose-derived stem cells	Promotion	10 μg/mL
		[34]	BMSCs	Promotion	10 μg/mL
	Tanshinone IIA	[35]	BMSCs	Promotion	1-5 μmol/L
		[36]	C2C12	Promotion	2.5-10 μmol/L
	Andrographolide	[37]	Osteoblasts	Promotion	4.46 or 8.92 μmol/L
	Baicalin	[38]	Sprague-Dawley rats	Promotion	50 mg/kg
		[39]	Osteoblasts	Promotion	50 μmol/L
	Costunolide	[40]	C3H10T1/2	Promotion	1 ng/mL
	Extract of lithospermum	[41]	C2C12	Promotion	30 or 60 μg/mL

		[42]	C2C12	Promotion	2 or 4 μg/mL
	Naringin	[43]	Adipose-derived stem cells	Promotion	0.1 μmol/L
	Curcumin	[44]	Adipose-derived stem cells	Promotion	5-20 μmol/L
	Limonene	[45]	C2C12	Promotion	2.5-10 μL
	Extract of piperaceae	[46]	Sprague-Dawley rats	Promotion	100 or 200 mg/kg
	Eugenol	[47]	Dental pulp cells	Inhibition	0.1-1 mL
	Saikosaponin-A	[48]	BMSCs	Promotion	10-40 μL
	Licochalcone A	[49]	MC3T3-E1	Promotion	2.5-5 μL
Antifungal drugs	Trichostatin A	[50]	Adipose-derived stem cells	Promotion	75 nL
		[51]	Periodontal ligament cells	Promotion	100-400 nL
		[52]	Adipose-derived stem cells	Promotion	1 μL
	Voriconazole	[53]	Osteoblasts	Promotion	15 or 200 μg/mL
	Fluconazole	[53]	Osteoblasts	No effect	15 or 200 μg/mL

chlamydia. Studies have shown that azithromycin does not produce cytotoxicity in the concentration range of 0-200 μg/mL; however, it inhibits the differentiation potential of osteoblasts at very low concentrations. When its concentration exceeds 10 μg/mL, the differentiation of human osteoblasts grown in the osteogenic induction environment was significantly inhibited, and the level of intracellular ALP synthesis decreased by more than 75%[14].

Aminoglycosides: Aminoglycoside antibiotics are a class of drugs that are effective against Gram-negative bacteria and aerobic bacteria, and gentamicin is a representative drug of this category. Studies have shown that gentamicin inhibits the osteogenic differentiation of human osteoblasts. When the drug concentration is less than 100 μg/mL, the drug does not have a significant effect on osteogenic differentiation. However, when its concentration exceeds 100 μg/mL, gentamicin exhibits osteogenic inhibitory effects. When its concentration exceeds 500 μg/mL, the osteogenic differentiation potential is almost completely suppressed[14]. In another study, a similar phenomenon was observed in bone marrow-derived MSCs. When the gentamicin concentration reached 75 μg/mL, the proliferation and osteogenic differentiation activity of MSCs decreased significantly[16]. In addition, studies have shown that gentamicin can inhibit the osteogenic differentiation of human bone marrow-derived MSCs in a dose-dependent manner within a concentration range of 50-200 μg/mL[17]. The ALP level in the C2C12 cell line was similarly been reduced by gentamicin[18]. Amikacin is a drug commonly used for the treatment of gentamicin-resistant infectious diseases. Its most prominent advantage is that it remains stable and active against the aminoglycoside inactivating enzymes produced by many Gram-negative bacilli. In addition, its effect on osteoblast differentiation is also less severe than that of gentamicin. At an amikacin concentration of 1000 μg/mL, the osteogenic differentiation of osteoblasts is still not significantly inhibited. Osteogenesis inhibition is exhibited only after the amikacin level reaches a very high concentration of 2000 μg/mL[14]. As an aminoglycoside, tobramycin is often used for the treatment of gentamicin-resistant *Pseudomonas aeruginosa* infections. Studies have shown that tobramycin may have a lower cytotoxicity than gentamicin while exhibiting antibacterial effects[14]. However, the effect of tobramycin on osteogenic differentiation is still inhibitory[19]. When the concentration of tobramycin reaches 300 and 500 μg/mL, the osteogenic differentiation potential of human bone marrow-derived MSCs and osteoblasts is inhibited, respectively[14,20].

Tetracyclines: Tetracycline antibiotics exhibit a therapeutic effect on a variety of bacterial, rickettsial, chlamydial, and mycoplasma infections. Tetracycline is a representative member of such drugs. In addition to its role in killing various pathogenic microorganisms, tetracycline has been reported to exhibit bone tissue affinity and can, thus, be used for various targeted therapies[21]. Studies related to osteogenic differentiation have shown that 10 μg/mL tetracycline can promote osteogenic differentiation of rat bone marrow-derived MSCs, increase ALP and mineralized nodules, and upregulate the osteogenic gene expression levels in

MSCs[22]. Doxycycline is the most commonly used tetracycline antibiotic, but unlike tetracycline, it exhibits a strong inhibitory effect on osteoblast proliferation and osteogenic differentiation. When its concentration reaches 100 μg/mL, the differentiation of human osteoblasts is severely inhibited[14]. Minocycline is also widely used in clinical practice, and its antibacterial efficacy is relatively strong among tetracyclines. Similar to doxycycline, minocycline significantly inhibited the differentiation potential of osteoblasts (above 75%) at concentrations above 100 μg/mL[14].

Quinolones: Quinolones are a class of synthetic antibiotics that are widely used in a variety of clinical infectious diseases due to their excellent and broad-spectrum antimicrobial properties. Levofloxacin is a commonly used quinolone in the clinic. Studies have shown that it does not cause toxicity to human osteoblasts in the concentration range of 0-200 μg/mL, but when the drug concentration reaches 200 μg/mL or more, the differentiation potential of osteoblasts is significantly inhibited (above 75%)[14]. Ciprofloxacin is another representative drug of quinolones, which has poor biocompatibility and significantly inhibits the proliferation and differentiation of osteoblasts at concentrations above 10 μg/mL (above 75%)[14].

Polypeptide antibiotics: Polypeptide antibiotics are a class of antibiotics with structural features similar to those of polypeptides, and their main members include polymyxins, bacitracins, and vancomycins. Colistin is one of the more commonly used polymyxin antibiotics. It mainly acts on Gram-negative bacteria and works synergistically with gentamicin. It has been reported in the literature that when the concentration of colistin reaches 100 μg/mL, the differentiation ability of human osteoblasts is inhibited[14]. Bacitracin is a metal peptide antibiotic produced by *Bacillus subtilis* and *Bacillus licheniformis*; it can strongly inhibit Gram-positive bacteria and has antagonistic effects on the development of resistance to *Staphylococcus aureus*. Our previous studies have shown that bacitracin can promote the osteogenic differentiation of human bone marrow-derived MSCs in a dose-dependent manner, thus increasing intracellular ALP, collagen, and mineralization, and upregulating the levels of osteogenesis marker genes. When the concentration of bacitracin reached 100 μmol/L, its ability to promote bone differentiation decreased, but this effect was still stronger than that in the control group[23]. Vancomycin is mainly used for the treatment of methicillin-resistant *Staphylococcus aureus*. There have been several reports on the effects of vancomycin on osteogenic differentiation. The general view is that vancomycin does not adversely affect the osteogenic differentiation of human osteoblasts and human bone marrow-derived MSCs at effective antimicrobial concentrations and higher concentrations[14,24,25]. However, it has also been reported that vancomycin inhibits the osteogenic differentiation of bone marrow-derived MSCs at a concentration of 200 μg/mL[16]. Therefore, further research on the regulation of osteogenic differentiation by vancomycin needs to be conducted to determine whether the effect of this drug on osteogenic differentiation is related to cell type and drug concentration.

Other types of antibiotics: Metronidazole is a drug commonly used in the treatment of anaerobic infections in the clinic. Studies have shown that conventional plasma concentrations (20 μg/mL) of metronidazole do not affect the osteogenic differentiation potential of human bone marrow-derived MSCs[16]. Trimethoprim (TMP) is a well-known sulfa drug enhancer with an antibacterial spectrum similar to that of sulfonamides. When TMP is combined with a sulfa drug, the combined antibacterial properties of both are greatly enhanced, and the formation of resistant bacteria can be reduced. Studies have shown that TMP does not affect the differentiation potential of osteoblasts in the concentration range of 0-200 μg/mL. However, when the concentration of TMP reaches 500 μg/mL, the osteogenic differentiation of the cells is inhibited[14]. Linezolidone is a bacterial protein synthesis inhibitor and is a fully synthetic oxazolidinone antibiotic. The drug has good biocompatibility and does not affect the viability of osteoblasts between 0-500 μg/mL. However, when the concentration of linezolidone is greater than 10 μg/mL, osteogenic inhibition occurs[14]. Salinomycin is a polyether antibiotic produced by *Streptomyces albus*. Studies have shown that 10 μM of salinomycin does not affect osteogenic differentiation and cellular mineralization of human bone marrow-derived MSCs[26].

Natural peptides

In addition to the use of antimicrobial agents for the treatment of pathogenic microorganisms, which cause infection symptoms, activation of immune cells and secretion of some peptides with antimicrobial effects in the human body also play a decisive role in the elimination of infection. Lactoferrin is an important non-heme iron-binding glycoprotein found in milk, with powerful biological functions, such as

broad-spectrum antibacterial, anti-oxidation, anti-cancer effects, and immune system regulation. It has been reported that lactoferrin promotes the differentiation of human adipose-derived stem cells into osteoblasts in a concentration-dependent manner and also promotes the expression of osteogenic genes[27]. Similarly, other studies have found that lactoferrin promotes the proliferation of MC3T3-E1 osteoblast cells *via* the mitogen-activated protein kinase (MAPK) signaling pathway and promotes the differentiation of MC3T3-E1 into osteogenesis *via* the protein kinase A and p38 signaling pathways[28,29]. Hepcidin is a cysteine-rich polypeptide synthesized and secreted by the liver, which has a wide range of antibacterial and anti-protozoal functions. Studies have found that, in addition to regulating iron metabolism and antibacterial properties, hepcidin also regulates the function of rat bone marrow-derived MSCs. At a concentration of 0.2 mmol/L, hepcidin enhanced the mineralization ability of rat bone marrow-derived MSCs and upregulated the expression of osteogenic genes. The researchers found that this osteogenic differentiation may be related to the activation of the p38 signaling pathway[30]. As an important part of the immune system, antimicrobial peptides (AMPs) can destroy microbial membranes and induce the death of pathogenic bacteria, having the potential to become a substitute for traditional antibiotics. The only natural antimicrobial peptide, cathelicidin (hCAP18/LL-37), was confirmed in 1995 and proved to exhibit antibacterial activity both *in vitro* and *in vivo*. Moreover, in addition to its resistance to pathogenic microorganisms, LL-37 has also been shown to promote the proliferation, migration, and osteogenic differentiation of rat bone marrow-derived MSCs. In the concentration range of 5-20 μg/mL, LL-37 promoted the osteogenic differentiation potential of MSCs in a dose-dependent manner. More importantly, LL-37 at a concentration of 10 μg/mL can reverse the osteogenic inhibition caused by lipopolysaccharide[31]. However, since the peptide chain of LL-37 is too long and too difficult to synthesize, it is inconvenient to use it as a conventional therapeutic drug for bacterial infections and inflammatory diseases. Short-chain AMPs have recently attracted attention due to their lower production costs. Among the LL-37 active fragments of different lengths investigated, KR-12 is the shortest antimicrobial peptide with antibacterial activity. In our previous study, KR-12 stimulated osteogenic differentiation of human bone marrow-derived MSCs within an effective antimicrobial concentration (1-1000 μg/mL). This osteoinductive phenomenon also appears to be concentration-dependent[32].

Chinese traditional drug extracts

Chinese traditional drugs are mainly composed of botanicals (roots, stems, leaves, and fruits), animal drugs (viscera, skin, bone, organs, *etc*.,), and mineral medicines. Since such drugs are often present in a mixture rather than in a monomer form, their pharmacological effects are often studied by extracting the active ingredient of the drug. Similar to the above-mentioned antimicrobial drugs, some Chinese herbal extracts with antibacterial or anti-pathogenic properties have attracted a lot of attention in recent years[33-49]. Compared with traditional antibiotics, these Chinese traditional drug extracts exhibit less side effects and are less prone to drug resistance while exerting antibacterial effects. Among these herbal extracts, some promote osteogenic differentiation of bone marrow-derived MSCs, such as cordycepin, tanshinone, and baicalin[33-36,38,39]. If these extracts can exert stable antibacterial activity and simultaneously induce bone marrow-derived MSCs to differentiate into new osseous tissue by virtue of their osteoinductive properties, the clinical application prospects of these extracts will be more extensive. The Chinese traditional drug extracts that have been reported to regulate osteogenic differentiation and to exhibit antibacterial properties in recent years are also listed in Table 1.

Antifungal drugs

Local and systemic fungal infections are not uncommon, and with the increase in immunodeficiency diseases, such as acquired immunodeficiency syndrome, the harm caused by fungal infections is also more serious. Fungal infections of bone tissue are rare and often accompanied by systemic immunodeficiencies or inhibition. While antifungal agents are used to treat fungal infections, the effects of the drug itself on osseous tissue and osteogenic differentiation are equally noteworthy. Trichostatin A (TSA) is a drug that exhibits a therapeutic effect on mold. It has been found that TSA at 75 nmol/L can stimulate the osteogenic differentiation potential of rat adipose stem cells[50]; some scholars have found similar phenomena in human periodontal ligament cells (HPDLCs). TSA can promote the differentiation of such cells into osteoblasts in a concentration-dependent manner within a concentration range of 100-400 nmol/L[51]. As inhibitors of histone deacetylases, TSA (1 μmol/L) also increases bone formation during osteogenic differentiation of human adipose-derived stem cells[52]. Voriconazole is an antifungal drug commonly used to treat severe invasive infections caused

by fluconazole-resistant Candida. Studies on its effects on osteoblasts have shown that voriconazole at both 15 μg/mL and 200 μg/mL can stimulate osteogenic differentiation of human osteoblasts *in vitro*, whereas fluconazole exhibits no such effect of inducing differentiation[53].

EFFECTS OF VARIOUS ANTIMICROBIAL AGENTS ON CHONDROGENIC DIFFERENTIATION

As an important seed cell for local cartilage repair, the ability of bone marrow-derived MSCs to differentiate into chondrocytes in the direction of cartilage is essential[54]. After the cartilage tissue is damaged by factors such as trauma, inflammation, and infection, microfracture surgery is an important approach for clinical treatment of local cartilage defects[55]. Surgery can transport MSCs in the medullary cavity to the cartilage defect area and complete the repair of the local defect by dividing the cells into the cartilage direction[56]. During the treatment of joint infections, surgical treatment, such as debridement drainage, and the application of systemic or topical antibiotics are equally important. If the drug can effectively control the infection and promote the differentiation of MSCs into chondrocytes to repair the existing cartilage defects, its clinical application range will be greatly increased, and it will play a more important role in the process of infectious arthritis and tissue engineering cartilage repair. At present, there have been very few studies on the regulation of chondrogenic differentiation by various antibacterial drugs. In this section, we list antimicrobial drugs that have been shown to have an effect on chondrogenic differentiation, and the overall data are listed in Table 2. In the previous section, we discussed the inhibitory effect of doxycycline on human osteoblast differentiation. The effect of this drug on the chondrogenic differentiation potential of human bone marrow-derived MSCs has also attracted attention. It has been reported that doxycycline at 2 μg/mL can enhance the chondrogenic differentiation of MSCs *in vitro*. This phenomenon was further confirmed *in vivo*[57]. Oxytetracycline is another member of the tetracycline antibiotic class, and some scholars have reported its ability to promote cartilage differentiation in ATDC5 cell line (pre-chondrocyte cell line). Studies have shown that oxytetracycline can promote the differentiation of ATDC5 cells into cartilage in a dose-dependent manner within a concentration range of 0.01 to 10 μmol/L[58]. Cordycepin is a natural extract that has been extensively studied in recent years. Its broad-spectrum antibacterial, anti-fungal, and anti-viral capabilities have attracted the attention of the medical community. The positive effect of cordycepin on the osteogenic differentiation potential of various stem cells has been introduced in the previous section, and its regulatory effect on the chondrogenic differentiation of MSCs is also worthy of attention. Studies have shown that 1 μg/mL of cordycepin can promote the differentiation of MCSs into cartilage and increase the expression levels of intracellular cartilage genes. Further experiments have demonstrated that this phenomenon is mediated by the inhibition of Nrf2 and the activation of BMP signaling[59]. Similarly, some scholars have found that lactoferrin promotes early chondrogenic differentiation of ATDC5 cells by the activating Smad2/3-Sox9 signaling pathway while also exhibiting osteoinductive effects, and also inhibits excessive hypertrophy of chondrocytes[60].

Phorbol-12-myristate-13-acetate (PMA) is an antibiotic extracted from penicillium culture and the first antibiotic to treat human diseases. Very low concentrations of PMA (0.1 μmol/L) have a strong inhibitory effect on the chondrogenic differentiation potential of chick embryonic stem cells[61]. TSA exhibits osteogenic induction properties while possessing antibacterial properties. It can positively regulate osteogenic differentiation, but exhibits an inhibitory effect on chondrogenic differentiation. When the concentration of TSA reaches 100 nmol/L, the chondrogenic differentiation of human bone marrow-derived MSCs induced by transforming growth factor-β (TGF-β1) can be inhibited[62].

EFFECTS OF VARIOUS ANTIMICROBIAL AGENTS ON ADIPOGENIC DIFFERENTIATION

Adult bone marrow contains a variety of cells, such as endothelial-like cells, fibroblasts, macrophages, osteocytes, adipocytes, and MSCs. Among them, adipocytes are the most abundant and can occupy more than 50% of the volume of the bone marrow cavity. In old age, adipocytes can even occupy more than 90% of the volume of the marrow cavity[63]. Bone marrow adipocytes are also involved in bone meta-

Table 2 Effects of various antimicrobial agents on chondrogenic differentiation

Agent		Ref.	Cell	Effect	Concentration
Antibiotics	Doxycycline	[57]	MSCs	Promotion	2 μg/mL
	Oxytetracycline	[58]	ATDC5	Promotion	0.01-10 μmol/L
	PMA	[61]	Embryonic stem cells	Inhibition	0.1 μmol/L
Natural peptides	Lactoferrin	[60]	ATDC5	Promotion	1 μmol/L
Chinese traditional drug extracts	Cordycepin	[59]	MSCs	Promotion	1 μg/mL
Antifungal drugs	Trichostatin A	[62]	BMSCs	Inhibition	100 nmol/L

bolism. In the pathological state of advanced osteoporosis or osteonecrosis, the differentiation of bone marrow-derived MSCs into adipocytes is enhanced, resulting in an increased number of adipocytes and decreased bone mass[64]. As an important component of the bone marrow microenvironment, bone marrow adipocytes not only occupy the non-hematopoietic medullary cavity space, but also have many physiological functions and play an important role in the pathological process of various diseases[65]. Bone marrow-derived MSCs are the main source of bone marrow adipocytes, and their adipogenic differentiation potential plays a vital role in the physiological renewal of adipose tissue in the medullary cavity and the repair of fat necrosis caused by pathological factors, such as infection[66]. During the process of using antibacterial drugs to treat osteomyelitis caused by various pathogenic microorganisms, both the antibacterial properties of antimicrobial drugs and their effects on the adipose tissue repair process are worthy of attention. In this section, we will review the effects of various antimicrobial agents on adipogenic differentiation to provide a reference for clinical use (Table 3).

Antibiotics

Isoniazid is another important member of anti-tuberculosis drugs, and its inhibition of adipogenic differentiation has been reported in the literature. Isoniazid inhibited the adipogenic differentiation potential of 3T3-L1 pre-adipocytes in a concentration-dependent manner, in a concentration range of 0.5-10 mmol/L. A similar phenomenon was also observed in human adipose stem cells[67]. Streptomycin is an aminoglycoside antibiotic, but it is widely used in the treatment of tuberculosis because of its anti-tuberculosis effect. Some scholars have found that 100 μg/mL streptomycin can inhibit the expression of adipogenic genes and the adipogenic ability of human bone marrow-derived MSCs[68]. Spiramycin is a macrolide antibiotic that exhibits antibacterial properties in the body and can enhance the phagocytosis of phagocytic cells. Studies on the effects of this drug on adipogenesis have revealed that spiramycin inhibits adipogenesis both *in vivo* and *in vitro*. Spiramycin at concentrations of 2.5-20 μmol/L inhibited the adipogenic differentiation of 3T3-L1 pre-adipocyte cells in a dose-dependent manner, which was further confirmed in the high-fat diet-induced obese mice model[69]. It is reported in the above study that salinomycin at 10 μmol/L does not affect the osteogenic differentiation potential of human bone marrow-derived MSCs. At this concentration, the adipogenic differentiation activity of MSCs is also not affected[26]. However, we believe that this result does not represent the effect of thalimycin at different concentrations on the osteogenic and adipogenic differentiation of MSCs. Further studies are needed to demonstrate the effect of this drug on the multi-directional differentiation potential of bone marrow-derived MSCs. Geldanamycin is an antibiotic secreted by *Streptomyces hygroscopicus* and has been shown to exhibit antibacterial, antiprotozoal, and antitumor activities. Studies have shown that geldanamycin can inhibit the adipogenic differentiation of 3T3-L1 pre-adipocytes in a dose-dependent manner at very low concentrations (0.001-1 μmol/L). *In vivo* experiments in mice further confirmed the inhibitory effect of geldanamycin on adipogenic differentiation[70].

Natural peptides

The positive regulation of lactoferrin on osteogenic and chondrogenic differentiation has been mentioned in the previous section, and its regulation of adipogenic differentiation is also worthy of attention. More than one study has shown that lactoferrin negatively regulates the adipogenic differentiation potential of cells. Some scholars have found that MC3T3-G2/PA6 cells gradually lose their ability to differentiate into adipocytes under the action of 10-100 μg/mL lactoferrin[71]; the level of adipogenic genes in C1C12 pluripotent stem cells have also been found to

Table 3 Effects of various antimicrobial agents on adipogenic differentiation

Agent		Ref.	Cell / animal	Effect	Concentration
Antibiotics	Isoniazid	[67]	3T3-L1	Inhibition	0.5-10 mmol/L
		[67]	Adipose stem cells	Inhibition	2 or 10 mmol/L
	Streptomycin	[68]	BMSCs	Inhibition	100 μg/mL
	Spiramycin	[69]	3T3-L1	Inhibition	2.5-20 μmol/L
	Salinomycin	[26]	BMSCs	No effect	10 μmol/L
	Geldanamycin	[70]	3T3-L1	Inhibition	0.001-1 μmol/L
Natural peptides	Lactoferrin	[71]	MC3T3-G2/PA6	Inhibition	10-100 μg/mL
		[72]	C1C12	Inhibition	0.1-10 μmol/L
		[73]	Subcutaneous preadipocytes	Promotion	10 μmol/L
Chinese traditional drug extracts	Cordycepin	[74]	3T3-L1	Inhibition	10-100 μg/mL
	Tanshinone IIA	[75]	3T3-L1	Inhibition	2.5-10 μmol/L
		[76]	3T3-L1	Inhibition	1-10 μmol/L
	Andrographolide	[77]	3T3-L1	Inhibition	1-5 μg/mL
	Baicalin	[78]	3T3-L1	Inhibition	200 μmol/L
		[79]	Atherosclerosis mice	Inhibition	50 or 100 mg/kg
	Oleuropein	[80]	BMSCs	Inhibition	10 μmol/L
		[81]	3T3-L1	Inhibition	0.1-100 μmol/L
	Piperlonguminine	[82]	3T3-L1	Promotion	3-30 μmol/L
	Hydroxytyrosol	[83]	BMSCs	Promotion	1 or 100 mmol
		[84]	Omental pre-adipocyte cells	Inhibition	30 μg/mL
	Shikonin	[85]	3T3-L1	Inhibition	0.5-2 μmol/L
	Ursolic acid	[86]	3T3-L1	Inhibition	2.5-10 μmol/L
	Alpinia officinarum	[87]	3T3-L1	Inhibition	150-400 μg/mL
	Dioscin	[88]	3T3-L1	Inhibition	1-4 μmol/L
	Methyl cinnamate	[89]	3T3-L1	Inhibition	12.5-100 μmol/L
	Tetrandrine	[90]	3T3-L1	Inhibition	2.5-10 μmol/L
	Honokiol	[91]	3T3-L1	No effect	1-10 μmol/L
	Licochalcone A	[92]	3T3-L1	Inhibition	5 or 10 μmol/L
Antifungal drugs	Trichostatin A	[51]	Periodontal ligament cells	No effect	400 nmol/L
		[93]	3T3-L1	Inhibition	500 nmol/L
Antiviral drugs	Efavirenz	[94]	Pre-adipocytes	Inhibition	0.5-4 μmol/L
		[104]	SGBS pre-adipocytes	Inhibition	0.1-5 μmol/L
	Zidovudine	[95]	3T3-F442A	Inhibition	6-50 μmol/L
		[99]	3T3-F442A	Inhibition	1-6 μmol/L
	Stavudine	[95]	3T3-F442A	Inhibition	3-75 μmol/L
	Lamivudine	[95]	3T3-F442A	Inhibition	8-200 μmol/L
	Nelfinavir	[98]	3T3-L1	Inhibition	20 μmol/L
	Efavirenz	[96]	Adipocyte precursor cells	Inhibition	4 μmol/L
		[97]	Adipocyte precursor cells	Inhibition	2 or 4 μmol/L
	Maraviroc	[96]	Adipocyte precursor cells	No effect	0.1-4 μmol/L
	Nevirapine	[97]	Adipocyte precursor cells	Promotion	2 or 4 μmol/L
	Darunavir	[100]	3T3-L1	Inhibition	0.1-25 μmol/L
	Raltegravir	[101]	3T3-F442A	Inhibition	1-50 μg/mL
	Indinavir	[102]	3T3-L1 and 3T3-F442A	Inhibition	10 or 20 μmol/L
		[103]	3T3-F442A	Inhibition	1-50 μg/mL
	Elvitegravir	[104]	SGBS pre-adipocytes	Inhibition	0.1-5 μmol/L
Antimalarials	Amodiaquine	[105]	3T3-L1	Inhibition	0.1-10 μmol/L
	Quinine	[106]	Preadipocytes	Promotion	5-50 μmol/L
	Artemisinic Acid	[107]	Adipose-derived stem cells	Inhibition	50 or 200 μmol/L

downregulate under the action of nipple proteins, and instead, the cells differentiate into osteogenesis and cartilage[72]. However, studies have shown that lactoferrin at a concentration of 10 μmol/L can promote the adipogenic activity of subcutaneous preadipocytes, and the associated adipogenic protein levels are also increased[73]. These results suggest that more research on the regulatory effect of lactoferrin on adipogenic differentiation needs to be conducted.

Chinese traditional drug extracts

In Table 1, we list the Chinese traditional drug extracts that have been reported to have antibacterial properties and can regulate osteogenic differentiation in recent years. Among these Chinese traditional drug extracts, cordycepin, tanshinone, andrographolide, and baicalin have also been reported to exhibit the ability to regulate adipogenic differentiation[74-79]. In addition, other Chinese traditional medicines that have antimicrobial effects and have the opportunity to play a role in clinical infectious diseases have also been reported to regulate adipogenesis[80-92]. We summarize the regulation mediated by these Chinese traditional drug extracts on adipogenic differentiation in Table 3.

Antifungal drugs, antiviral drugs, and antimalarials

The promotion of TSA for osteogenic differentiation and inhibition of chondrogenic differentiation have been mentioned earlier in this paper. In a study of its effects on adipogenic differentiation, TSA at a concentration of 400 nmol/L did not promote differentiation of HPDLCs into adipogenic phase[51]. In another study, the researchers concluded that TSA at a concentration of 500 nmol/L inhibited the adipogenic differentiation activity of 3T3-L1 cells by inhibiting the activity of histone deacetylase[93].

Viruses and malarial parasites are not common pathogenic microorganisms of bone and joint infections. However, due to the particularity of the mechanism of pharmacological action, its related therapeutic drugs may have a significant impact on fat metabolism. We summarize the antiviral and antimalarial drugs that have been reported to regulate adipogenesis in recent years and list them in Table 3[94-107].

CONCLUSION

In order to achieve better results *via* the antimicrobial drug treatment of bone and joint infections, we should pay attention to the elimination of pathogenic microorganisms using various antimicrobial drugs while also taking into account the effects of these drugs on local tissue repair. Bone marrow-derived MSCs are used as core cells for the renewal and repair of local bone, cartilage, and medullary adipose tissue. The regulation of multiple differentiation potentials of MSCs by various antimicrobial agents affects recovery from bone and joint infectious diseases. In the course of clinical drug treatment, only by understanding the effects of antibacterial drugs on the osteogenic, cartilage, and adipogenic differentiation of bone marrow-derived MSCs and rationally selecting the antimicrobial drugs that are most beneficial for controlling infection as well as repairing local tissue according to the pathogens and infection sites involved, can effective treatment against infection with minimum damage to local tissue be achieved.

REFERENCES

1 **Barker CI**, Germovsek E, Sharland M. What do I need to know about penicillin antibiotics? *Arch Dis Child Educ Pract Ed* 2017; **102**: 44-50 [PMID: 27412043 DOI: 10.1136/archdischild-2015-309068]
2 **Rissing JP**. Antimicrobial therapy for chronic osteomyelitis in adults: role of the quinolones. *Clin Infect Dis* 1997; **25**: 1327-1333 [PMID: 9431371 DOI: 10.2307/4460225]
3 **Chen R**, Cole N, Dutta D, Kumar N, Willcox MDP. Antimicrobial activity of immobilized lactoferrin and lactoferricin. *J Biomed Mater Res B Appl Biomater* 2017; **105**: 2612-2617 [PMID: 27758034 DOI: 10.1002/jbm.b.33804]
4 **Bucki R**, Leszczyńska K, Namiot A, Sokołowski W. Cathelicidin LL-37: a multitask antimicrobial peptide. *Arch Immunol Ther Exp (Warsz)* 2010; **58**: 15-25 [PMID: 20049649 DOI: 10.1007/s00005-009-0057-2]
5 **Tomioka H**. Usefulness of Chinese Herbal Medicines as Host-Directed Therapeutics against Mycobacterial Infections: A Review. *Am J Chin Med* 2017; **45**: 1597-1611 [PMID: 29121801 DOI: 10.1142/S0192415X17500860]
6 **Ma H**, Lv G, Wang B. Does surgery influence the outcome of Aspergillus osteomyelitis? *Clin Microbiol Infect* 2014; **20**: O788 [PMID: 24666933 DOI: 10.1111/1469-0691.12588]
7 **Mirabet V**, Álvarez M, Luis-Hidalgo M, Galán J, Puig N, Larrea L, Arbona C. Detection of hepatitis B virus in bone allografts from donors with occult hepatitis B infection. *Cell Tissue Bank* 2017; **18**: 335-341 [PMID: 28748417 DOI: 10.1007/s10561-017-9644-3]

8 **Chakraborty PP**, Roy A, Bhattacharjee R, Mukhopadhyay S, Chowdhury S. Reversible Secondary Osteolysis in Diabetic Foot Infection. *J Am Podiatr Med Assoc* 2017; **107**: 538-540 [PMID: 29252019 DOI: 10.7547/16-004]

9 **Wu H**, Hu B, Zhou X, Zhou C, Meng J, Yang Y, Zhao X, Shi Z, Yan S. Artemether attenuates LPS-induced inflammatory bone loss by inhibiting osteoclastogenesis and bone resorption via suppression of MAPK signaling pathway. *Cell Death Dis* 2018; **9**: 498 [PMID: 29703893 DOI: 10.1038/s41419-018-0540-y]

10 **Yin H**, Wang Y, Sun Z, Sun X, Xu Y, Li P, Meng H, Yu X, Xiao B, Fan T, Wang Y, Xu W, Wang A, Guo Q, Peng J, Lu S. Induction of mesenchymal stem cell chondrogenic differentiation and functional cartilage microtissue formation for in vivo cartilage regeneration by cartilage extracellular matrix-derived particles. *Acta Biomater* 2016; **33**: 96-109 [PMID: 26802442 DOI: 10.1016/j.actbio.2016.01.024]

11 **Dominici M**, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop Dj, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* 2006; **8**: 315-317 [PMID: 16923606 DOI: 10.1080/14653240600855905]

12 **Kärner E**, Bäckesjö CM, Cedervall J, Sugars RV, Ahrlund-Richter L, Wendel M. Dynamics of gene expression during bone matrix formation in osteogenic cultures derived from human embryonic stem cells in vitro. *Biochim Biophys Acta* 2009; **1790**: 110-118 [PMID: 19007861 DOI: 10.1016/j.bbagen.2008.10.004]

13 **Chen D**, Shen H, He Y, Chen Y, Wang Q, Lu J, Jiang Y. Synergetic effects of hBMSCs and hPCs in osteogenic differentiation and their capacity in the repair of critical-sized femoral condyle defects. *Mol Med Rep* 2015; **11**: 1111-1119 [PMID: 25373389 DOI: 10.3892/mmr.2014.2883]

14 **Rathbone CR**, Cross JD, Brown KV, Murray CK, Wenke JC. Effect of various concentrations of antibiotics on osteogenic cell viability and activity. *J Orthop Res* 2011; **29**: 1070-1074 [PMID: 21567453 DOI: 10.1002/jor.21343]

15 **Zhang Z**, Wang X, Luo F, Yang H, Hou T, Zhou Q, Dai F, He Q, Xu J. Effects of rifampicin on osteogenic differentiation and proliferation of human mesenchymal stem cells in the bone marrow. *Genet Mol Res* 2014; **13**: 6398-6410 [PMID: 25158258 DOI: 10.4238/2014.August.25.3]

16 **Pountos I**, Georgouli T, Henshaw K, Howard B, Giannoudis PV. Mesenchymal Stem Cell physiology can be affected by antibiotics: An in vitro study. *Cell Mol Biol (Noisy-le-grand)* 2014; **60**: 1-7 [PMID: 25350512]

17 **Chang Y**, Goldberg VM, Caplan AI. Toxic effects of gentamicin on marrow-derived human mesenchymal stem cells. *Clin Orthop Relat Res* 2006; **452**: 242-249 [PMID: 16906089 DOI: 10.1097/01.blo.0000229324.75911.c7]

18 **Ince A**, Schütze N, Karl N, Löhr JF, Eulert J. Gentamicin negatively influenced osteogenic function in vitro. *Int Orthop* 2007; **31**: 223-228 [PMID: 16710734 DOI: 10.1007/s00264-006-0144-5]

19 **Martin B**, Tucci MA, Benghuzzi HA. In vitro evaluation of the effects of tobramycin and parathyroid hormone on mesenchymal stem cells. *Biomed Sci Instrum* 2014; **50**: 383-390 [PMID: 25405448 DOI: 10.5923/c.jce.201402.26]

20 **Glatt V**, Kwong FN, Park K, Parry N, Griffin D, Vrahas M, Evans CH, Harris M. Ability of recombinant human bone morphogenetic protein 2 to enhance bone healing in the presence of tobramycin: evaluation in a rat segmental defect model. *J Orthop Trauma* 2009; **23**: 693-701 [PMID: 19858977 DOI: 10.1097/BOT.0b013e3181b01b2f]

21 **Feng X**, Liu X, Cai X, Lin T, Xu W, Yang C, Liu Y, Yang S, Fu D. The Influence of Tetracycline Inducible Targeting Rat PPARγ Gene Silencing on the Osteogenic and Adipogenic Differentiation of Bone Marrow Stromal Cells. *Curr Pharm Des* 2016; **22**: 6330-6338 [PMID: 27396594 DOI: 10.2174/1381612822666160708223353]

22 **Zhang J**, Xue S, Luo Y, Zhi W. Tetracycline hydrochloride induces the osteogenic differentiation of rat bone marrow mesenchymal stem cells. *CJTER* 2017; **21**: 4605-4610 [DOI: 10.3969/1.issn.2095-4344.2017.29.003]

23 **Li H**, Nie B, Du Z, Zhang S, Long T, Yue B. Bacitracin promotes osteogenic differentiation of human bone marrow mesenchymal stem cells by stimulating the bone morphogenetic protein-2/Smad axis. *Biomed Pharmacother* 2018; **103**: 588-597 [PMID: 29677546 DOI: 10.1016/j.biopha.2018.04.084]

24 **Bariteau JT**, Kadakia RJ, Traub BC, Viggeswarapu M, Willett NJ. Impact of Vancomycin Treatment on Human Mesenchymal Stromal Cells During Osteogenic Differentiation. *Foot Ankle Int* 2018; **39**: 954-959 [PMID: 29620948 DOI: 10.1177/1071100718766655]

25 **Booysen E**, Sadie-Van Gijsen H, Deane SM, Ferris W, Dicks LMT. The Effect of Vancomycin on the Viability and Osteogenic Potential of Bone-Derived Mesenchymal Stem Cells. *Probiotics Antimicrob Proteins* 2018 [PMID: 30276719 DOI: 10.1007/s12602-018-9473-0]

26 **Scherzed A**, Hackenberg S, Froelich K, Rak K, Technau A, Radeloff A, Nöth U, Koehler C, Hagen R, Kleinsasser N. Effects of salinomycin on human bone marrow-derived mesenchymal stem cells in vitro. *Toxicol Lett* 2013; **218**: 207-214 [PMID: 23410960 DOI: 10.1016/j.toxlet.2013.02.001]

27 **Ying X**, Cheng S, Wang W, Lin Z, Chen Q, Zhang W, Kou D, Shen Y, Cheng X, Peng L, Zi Xu H, Zhu Lu C. Effect of lactoferrin on osteogenic differentiation of human adipose stem cells. *Int Orthop* 2012; **36**: 647-653 [PMID: 21713451 DOI: 10.1007/s00264-011-1303-x]

28 **Liu M**, Fan F, Shi P, Tu M, Yu C, Yu C, Du M. Lactoferrin promotes MC3T3-E1 osteoblast cells proliferation via MAPK signaling pathways. *Int J Biol Macromol* 2018; **107**: 137-143 [PMID: 28863893 DOI: 10.1016/j.ijbiomac.2017.08.151]

29 **Zhang W**, Guo H, Jing H, Li Y, Wang X, Zhang H, Jiang L, Ren F. Lactoferrin stimulates osteoblast differentiation through PKA and p38 pathways independent of lactoferrin's receptor LRP1. *J Bone Miner Res* 2014; **29**: 1232-1243 [PMID: 24877241 DOI: 10.1002/jbmr.2116]

30 **Lu H**, Lian L, Shi D, Zhao H, Dai Y. Hepcidin promotes osteogenic differentiation through the bone morphogenetic protein 2/small mothers against decapentaplegic and mitogen-activated protein kinase/P38 signaling pathways in mesenchymal stem cells. *Mol Med Rep* 2015; **11**: 143-150 [PMID: 25351366 DOI: 10.3892/mmr.2014.2769]

31 **Yu X**, Quan J, Long W, Chen H, Wang R, Guo J, Lin X, Mai S. LL-37 inhibits LPS-induced inflammation and stimulates the osteogenic differentiation of BMSCs via P2X7 receptor and MAPK signaling pathway. *Exp Cell Res* 2018; **372**: 178-187 [PMID: 30287143 DOI: 10.1016/j.yexcr.2018.09.024]

32 **Li H**, Zhang S, Nie Be, Du Z, Long T, Yue B. The antimicrobial peptide kr-12 promotes the osteogenic differentiation of human bone marrow stem cells by stimulating bmp/smad signaling. *RSC Advances* 2018; **8**: 15547-15557 [DOI: 10.1039/c8ra00750k]

33 **Yang J**, Cao Y, Lv Z, Jiang T, Wang L, Li Z. Cordycepin protected against the TNF-α-induced inhibition of osteogenic differentiation of human adipose-derived mesenchymal stem cells. *Int J Immunopathol Pharmacol* 2015; **28**: 296-307 [PMID: 26130747 DOI: 10.1177/0394632015592160]

34 **Wang F**, Yin P, Lu Y, Zhou Z, Jiang C, Liu Y, Yu X. Cordycepin prevents oxidative stress-induced inhibition of osteogenesis. *Oncotarget* 2015; **6**: 35496-35508 [PMID: 26462178 DOI: 10.18632/oncotarget.6072]

35 **Qian K**, Xu H, Dai T, Shi K. Effects of Tanshinone IIA on osteogenic differentiation of mouse bone marrow mesenchymal stem cells. *Naunyn Schmiedebergs Arch Pharmacol* 2015; **388**: 1201-1209 [PMID: 26231349 DOI: 10.1007/s00210-015-1154-x]

36 **Kim HJ**, Kim SH. Tanshinone IIA enhances BMP-2-stimulated commitment of C2C12 cells into osteoblasts via p38 activation. *Amino Acids* 2010; **39**: 1217-1226 [PMID: 20300786 DOI: 10.1007/s00726-010-0557-8]

37 **Jiang T**, Zhou B, Huang L, Wu H, Huang J, Liang T, Liu H, Zheng L, Zhao J. Andrographolide Exerts Pro-Osteogenic Effect by Activation of Wnt/β-Catenin Signaling Pathway in Vitro. *Cell Physiol Biochem* 2015; **36**: 2327-2339 [PMID: 26279437 DOI: 10.1159/000430196]

38 **Zhang G**, Li C, Niu Y, Yu Q, Chen Y, Liu E. Osteoprotective Effect of Radix Scutellariae in Female Hindlimb-Suspended Sprague-Dawley Rats and the Osteogenic Differentiation Effect of Its Major Constituent. *Molecules* 2017; **22**: pii: E1044 [PMID: 28671635 DOI: 10.3390/molecules22071044]

39 **Guo AJ**, Choi RC, Cheung AW, Chen VP, Xu SL, Dong TT, Chen JJ, Tsim KW. Baicalin, a flavone, induces the differentiation of cultured osteoblasts: an action via the Wnt/beta-catenin signaling pathway. *J Biol Chem* 2011; **286**: 27882-27893 [PMID: 21652696 DOI: 10.1074/jbc.M111.236281]

40 **Jeon WJ**, Kim KM, Kim EJ, Jang WG. Costunolide increases osteoblast differentiation via ATF4-dependent HO-1 expression in C3H10T1/2 cells. *Life Sci* 2017; **178**: 94-99 [PMID: 28435036 DOI: 10.1016/j.lfs.2017.04.012]

41 **Choi YH**, Kim GS, Choi JH, Jin SW, Kim HG, Han Y, Lee DY, Choi SI, Kim SY, Ahn YS, Lee KY, Jeong HG. Ethanol extract of Lithospermum erythrorhizon Sieb. et Zucc. promotes osteoblastogenesis through the regulation of Runx2 and Osterix. *Int J Mol Med* 2016; **38**: 610-618 [PMID: 27353217 DOI: 10.3892/ijmm.2016.2655]

42 **Choi YH**, Han Y, Jin SW, Lee GH, Kim GS, Lee DY, Chung YC, Lee KY, Jeong HG. Pseudoshikonin I enhances osteoblast differentiation by stimulating Runx2 and Osterix. *J Cell Biochem* 2018; **119**: 748-757 [PMID: 28657691 DOI: 10.1002/jcb.26238]

43 **Wang L**, Zhang YG, Wang XM, Ma LF, Zhang YM. Naringin protects human adipose-derived mesenchymal stem cells against hydrogen peroxide-induced inhibition of osteogenic differentiation. *Chem Biol Interact* 2015; **242**: 255-261 [PMID: 26482937 DOI: 10.1016/j.cbi.2015.10.010]

44 **Wang N**, Wang F, Gao Y, Yin P, Pan C, Liu W, Zhou Z, Wang J. Curcumin protects human adipose-derived mesenchymal stem cells against oxidative stress-induced inhibition of osteogenesis. *J Pharmacol Sci* 2016; **132**: 192-200 [PMID: 27840063 DOI: 10.1016/j.jphs.2016.10.005]

45 **Soundharrajan I**, Kim DH, Srisesharam S, Kuppusamy P, Sivanesan R, Choi KC. Limonene promotes osteoblast differentiation and 2-deoxy-d-glucose uptake through p38MAPK and Akt signaling pathways in C2C12 skeletal muscle cells. *Phytomedicine* 2018; **45**: 41-48 [PMID: 29573911 DOI: 10.1016/j.phymed.2018.03.019]

46 **Ngueguim FT**, Khan MP, Donfack JH, Tewari D, Dimo T, Kamtchouing P, Maurya R, Chattopadhyay N. Ethanol extract of Peperomia pellucida (Piperaceae) promotes fracture healing by an anabolic effect on osteoblasts. *J Ethnopharmacol* 2013; **148**: 62-68 [PMID: 23578859 DOI: 10.1016/j.jep.2013.03.063]

47 **Anpo M**, Shirayama K, Tsutsui T. Cytotoxic effect of eugenol on the expression of molecular markers related to the osteogenic differentiation of human dental pulp cells. *Odontology* 2011; **99**: 188-192 [PMID: 21706355 DOI: 10.1007/s10266-011-0009-2]

48 **Huang W**, Zheng X, Yang X, Fan S. Stimulation of Osteogenic Differentiation by Saikosaponin-A in Bone Marrow Stromal Cells Via WNT/β-Catenin Pathway. *Calcif Tissue Int* 2017; **100**: 392-401 [PMID: 28185033 DOI: 10.1007/s00223-017-0242-y]

49 **Kim SN**, Bae SJ, Kwak HB, Min YK, Jung SH, Kim CH, Kim SH. In vitro and in vivo osteogenic activity of licochalcone A. *Amino Acids* 2012; **42**: 1455-1465 [PMID: 21468757 DOI: 10.1007/s00726-011-0901-7]

50 **Hu X**, Zhang X, Dai L, Zhu J, Jia Z, Wang W, Zhou C, Ao Y. Histone deacetylase inhibitor trichostatin A promotes the osteogenic differentiation of rat adipose-derived stem cells by altering the epigenetic modifications on Runx2 promoter in a BMP signaling-dependent manner. *Stem Cells Dev* 2013; **22**: 248-255 [PMID: 22873791 DOI: 10.1089/scd.2012.0105]

51 **Huynh NC**, Everts V, Pavasant P, Ampornaramveth RS. Inhibition of Histone Deacetylases Enhances the Osteogenic Differentiation of Human Periodontal Ligament Cells. *J Cell Biochem* 2016; **117**: 1384-1395 [PMID: 27043246 DOI: 10.1002/jcb.25429]

52 **Maroni P**, Brini AT, Arrigoni E, de Girolamo L, Niada S, Matteucci E, Bendinelli P, Desiderio MA. Chemical and genetic blockade of HDACs enhances osteogenic differentiation of human adipose tissue-derived stem cells by oppositely affecting osteogenic and adipogenic transcription factors. *Biochem Biophys Res Commun* 2012; **428**: 271-277 [PMID: 23085045 DOI: 10.1016/j.bbrc.2012.10.044]

53 **Allen KC**, Sanchez CJ, Niece KL, Wenke JC, Akers KS. Voriconazole Enhances the Osteogenic Activity of Human Osteoblasts In Vitro through a Fluoride-Independent Mechanism. *Antimicrob Agents Chemother* 2015; **59**: 7205-7213 [PMID: 26324277 DOI: 10.1128/AAC.00872-15]

54 **Nasrabadi D**, Rezaeiani S, Eslaminejad MB, Shabani A. Improved Protocol for Chondrogenic Differentiation of Bone Marrow Derived Mesenchymal Stem Cells -Effect of PTHrP and FGF-2 on TGFβ1/BMP2-Induced Chondrocytes Hypertrophy. *Stem Cell Rev* 2018; **14**: 755-766 [PMID: 29691795 DOI: 10.1007/s12015-018-9816-y]

55 **Buckwalter JA**, Brown TD. Joint injury, repair, and remodeling: roles in post-traumatic osteoarthritis. *Clin Orthop Relat Res* 2004; 7-16 [PMID: 15232420 DOI: 10.1016/0024-3795(94)00233-4]

56 **Nakajima H**, Goto T, Horikawa O, Kikuchi T, Shinmei M. Characterization of the cells in the repair tissue of full-thickness articular cartilage defects. *Histochem Cell Biol* 1998; **109**: 331-338 [PMID: 9562382 DOI: 10.1007/s004180050233]

57 **Lee HH**, O'Malley MJ, Friel NA, Chu CR. Effects of doxycycline on mesenchymal stem cell chondrogenesis and cartilage repair. *Osteoarthritis Cartilage* 2013; **21**: 385-393 [PMID: 23186943 DOI: 10.1016/j.joca.2012.11.010]

58 **Hojo H**, Yano F, Ohba S, Igawa K, Nakajima K, Komiyama Y, Kan A, Ikeda T, Yonezawa T, Woo JT, Takato T, Nakamura K, Kawaguchi H, Chung UI. Identification of oxytetracycline as a chondrogenic

compound using a cell-based screening system. *J Bone Miner Metab* 2010; **28**: 627-633 [PMID: 20376510 DOI: 10.1007/s00774-010-0179-y]

59 **Cao Z**, Dou C, Li J, Tang X, Xiang J, Zhao C, Zhu L, Bai Y, Xiang Q, Dong S. Cordycepin inhibits chondrocyte hypertrophy of mesenchymal stem cells through PI3K/Bapx1 and Notch signaling pathway. *BMB Rep* 2016; **49**: 548-553 [PMID: 27439604 DOI: 10.5483/BMBRep.2016.49.10.071]

60 **Takayama Y**, Mizumachi K. Inhibitory effect of lactoferrin on hypertrophic differentiation of ATDC5 mouse chondroprogenitor cells. *Biometals* 2010; **23**: 477-484 [PMID: 20094900 DOI: 10.1007/s10534-010-9291-7]

61 **Garrison JC**, Pettit GR, Uyeki EM. Effect of phorbol and bryostatin I on chondrogenic expression of chick limb bud, in vitro. *Life Sci* 1987; **41**: 2055-2061 [PMID: 3118121 DOI: 10.1016/0024-3205(87)90480-2]

62 **Wang JP**, Wen MH, Chen YT, Lee HH, Chiang ER, Lee YT, Liu CL, Chen TH, Hung SC. Trichostatin A inhibits TGF-β1 induced in vitro chondrogenesis of hMSCs through Sp1 suppression. *Differentiation* 2011; **81**: 119-126 [PMID: 21074928 DOI: 10.1016/j.diff.2010.10.003]

63 **Gimble JM**, Robinson CE, Wu X, Kelly KA. The function of adipocytes in the bone marrow stroma: an update. *Bone* 1996; **19**: 421-428 [PMID: 8922639 DOI: 10.1016/S8756-3282(96)00258-X]

64 **Valenti MT**, Dalle Carbonare L, Mottes M. Osteogenic Differentiation in Healthy and Pathological Conditions. *Int J Mol Sci* 2016; **18**: pii: E41 [PMID: 28035992 DOI: 10.3390/ijms18010041]

65 **Naveiras O**, Nardi V, Wenzel PL, Hauschka PV, Fahey F, Daley GQ. Bone-marrow adipocytes as negative regulators of the haematopoietic microenvironment. *Nature* 2009; **460**: 259-263 [PMID: 19516257 DOI: 10.1038/nature08099]

66 **Wang C**, Meng H, Wang X, Zhao C, Peng J, Wang Y. Differentiation of Bone Marrow Mesenchymal Stem Cells in Osteoblasts and Adipocytes and its Role in Treatment of Osteoporosis. *Med Sci Monit* 2016; **22**: 226-233 [PMID: 26795027 DOI: 10.12659/MSM.897044]

67 **Chen Y**, Xue P, Hou Y, Zhang H, Zheng H, Zhou T, Qu W, Teng W, Zhang Q, Andersen ME, Pi J. Isoniazid suppresses antioxidant response element activities and impairs adipogenesis in mouse and human preadipocytes. *Toxicol Appl Pharmacol* 2013; **273**: 435-441 [PMID: 24128855 DOI: 10.1016/j.taap.2013.10.005]

68 **Goralczyk A**, van Vijven M, Koch M, Badowski C, Yassin MS, Toh SA, Shabbir A, Franco-Obregón A, Raghunath M. TRP channels in brown and white adipogenesis from human progenitors: new therapeutic targets and the caveats associated with the common antibiotic, streptomycin. *FASEB J* 2017; **31**: 3251-3266 [PMID: 28416581 DOI: 10.1096/fj.201601081RR]

69 **Kim MO**, Ryu HW, Choi JH, Son TH, Oh SR, Lee HS, Yuk HJ, Cho S, Kang JS, Lee CW, Lee J, Lee CK, Hong ST, Lee SU. Anti-Obesity Effects of Spiramycin In Vitro and In Vivo. *PLoS One* 2016; **11**: e0158632 [PMID: 27398599 DOI: 10.1371/journal.pone.0158632]

70 **Desarzens S**, Liao WH, Mammi C, Caprio M, Faresse N. Hsp90 blockers inhibit adipocyte differentiation and fat mass accumulation. *PLoS One* 2014; **9**: e94127 [PMID: 24705830 DOI: 10.1371/journal.pone.0094127]

71 **Yagi M**, Suzuki N, Takayama T, Arisue M, Kodama T, Yoda Y, Numasaki H, Otsuka K, Ito K. Lactoferrin suppress the adipogenic differentiation of MC3T3-G2/PA6 cells. *J Oral Sci* 2008; **50**: 419-425 [PMID: 19106469 DOI: 10.2334/josnusd.50.419]

72 **Yagi M**, Suzuki N, Takayama T, Arisue M, Kodama T, Yoda Y, Otsuka K, Ito K. Effects of lactoferrin on the differentiation of pluripotent mesenchymal cells. *Cell Biol Int* 2009; **33**: 283-289 [PMID: 19103298 DOI: 10.1016/j.cellbi.2008.11.013]

73 **Moreno-Navarrete JM**, Ortega F, Sabater M, Ricart W, Fernández-Real JM. Proadipogenic effects of lactoferrin in human subcutaneous and visceral preadipocytes. *J Nutr Biochem* 2011; **22**: 1143-1149 [PMID: 21295959 DOI: 10.1016/j.jnutbio.2010.09.015]

74 **Takahashi S**, Tamai M, Nakajima S, Kato H, Johno H, Nakamura T, Kitamura M. Blockade of adipocyte differentiation by cordycepin. *Br J Pharmacol* 2012; **167**: 561-575 [PMID: 22537056 DOI: 10.1111/j.1476-5381.2012.02005.x]

75 **Park YK**, Obiang-Obounou BW, Lee J, Lee TY, Bae MA, Hwang KS, Lee KB, Choi JS, Jang BC. Anti-Adipogenic Effects on 3T3-L1 Cells and Zebrafish by Tanshinone IIA. *Int J Mol Sci* 2017; **18**: pii: E2065 [PMID: 28953247 DOI: 10.3390/ijms18102065]

76 **Park SB**, Park JS, Jung WH, Park A, Jo SR, Kim HY, Dal Rhee S, Ryu SY, Jeong HG, Park S, Lee H, Kim KY. Identification of a novel 11β-HSD1 inhibitor from a high-throughput screen of natural product extracts. *Pharmacol Res* 2015; **102**: 245-253 [PMID: 26515507 DOI: 10.1016/j.phrs.2015.10.014]

77 **Jin L**, Fang W, Li B, Shi G, Li X, Yang Y, Yang J, Zhang Z, Ning G. Inhibitory effect of andrographolide in 3T3-L1 adipocytes differentiation through the PPARγ pathway. *Mol Cell Endocrinol* 2012; **358**: 81-87 [PMID: 22449851 DOI: 10.1016/j.mce.2012.02.025]

78 **Wu Y**, Wang F, Fan L, Zhang W, Wang T, Du Y, Bai X. Baicalin alleviates atherosclerosis by relieving oxidative stress and inflammatory responses via inactivating the NF-κB and p38 MAPK signaling pathways. *Biomed Pharmacother* 2018; **97**: 1673-1679 [PMID: 29793330 DOI: 10.1016/j.biopha.2017.12.024]

79 **Lee H**, Bae S, Kim K, Kim W, Chung SI, Yoon Y. Beta-Catenin mediates the anti-adipogenic effect of baicalin. *Biochem Biophys Res Commun* 2010; **398**: 741-746 [PMID: 20627088 DOI: 10.1016/j.bbrc.2010.07.015]

80 **Casado-Díaz A**, Anter J, Müller S, Winter P, Quesada-Gómez JM, Dorado G. Transcriptomic analyses of the anti-adipogenic effects of oleuropein in human mesenchymal stem cells. *Food Funct* 2017; **8**: 1254-1270 [PMID: 28243663 DOI: 10.1039/c7fo00045f]

81 **Kuem N**, Song SJ, Yu R, Yun JW, Park T. Oleuropein attenuates visceral adiposity in high-fat diet-induced obese mice through the modulation of WNT10b- and galanin-mediated signalings. *Mol Nutr Food Res* 2014; **58**: 2166-2176 [PMID: 25104077 DOI: 10.1002/mnfr.201400159]

82 **Yamaguchi I**, Matsuda H, Zhang H, Hamao M, Yamashita C, Kogami Y, Kon'I H, Murata M, Nakamura S, Yoshikawa M. Adipogenic effects of piperlonguminine in 3T3-L1 cells and plasma concentrations of several amide constituents from Piper chaba extracts after treatment of mice. *J Nat Med* 2014; **68**: 74-82 [PMID: 23584920 DOI: 10.1007/s11418-013-0770-3]

83 **Anter J**, Quesada-Gómez JM, Dorado G, Casado-Díaz A. Effect of Hydroxytyrosol on Human Mesenchymal Stromal/Stem Cell Differentiation into Adipocytes and Osteoblasts. *Arch Med Res* 2016; **47**: 162-171 [PMID: 27393375 DOI: 10.1016/j.arcmed.2016.06.006]

84 **Stefanon B**, Colitti M. Original Research: Hydroxytyrosol, an ingredient of olive oil, reduces triglyceride accumulation and promotes lipolysis in human primary visceral adipocytes during differentiation. *Exp Biol*

Med (Maywood) 2016; **241**: 1796-1802 [PMID: 27287014 DOI: 10.1177/1535370216654226]
85 **Gwon SY**, Ahn JY, Jung CH, Moon BK, Ha TY. Shikonin suppresses ERK 1/2 phosphorylation during the early stages of adipocyte differentiation in 3T3-L1 cells. *BMC Complement Altern Med* 2013; **13**: 207 [PMID: 23919458 DOI: 10.1186/1472-6882-13-207]
86 **He Y**, Li Y, Zhao T, Wang Y, Sun C. Ursolic acid inhibits adipogenesis in 3T3-L1 adipocytes through LKB1/AMPK pathway. *PLoS One* 2013; **8**: e70135 [PMID: 23922935 DOI: 10.1371/journal.pone.0070135]
87 **Jung CH**, Jang SJ, Ahn J, Gwon SY, Jeon TI, Kim TW, Ha TY. Alpinia officinarum inhibits adipocyte differentiation and high-fat diet-induced obesity in mice through regulation of adipogenesis and lipogenesis. *J Med Food* 2012; **15**: 959-967 [PMID: 23126661 DOI: 10.1089/jmf.2012.2286]
88 **Poudel B**, Lim SW, Ki HH, Nepali S, Lee YM, Kim DK. Dioscin inhibits adipogenesis through the AMPK/MAPK pathway in 3T3-L1 cells and modulates fat accumulation in obese mice. *Int J Mol Med* 2014; **34**: 1401-1408 [PMID: 25189808 DOI: 10.3892/ijmm.2014.1921]
89 **Chen YY**, Lee MH, Hsu CC, Wei CL, Tsai YC. Methyl cinnamate inhibits adipocyte differentiation via activation of the CaMKK2-AMPK pathway in 3T3-L1 preadipocytes. *J Agric Food Chem* 2012; **60**: 955-963 [PMID: 22273148 DOI: 10.1021/jf203981x]
90 **Jang BC**. Tetrandrine has anti-adipogenic effect on 3T3-L1 preadipocytes through the reduced expression and/or phosphorylation levels of C/EBP-α, PPAR-γ, FAS, perilipin A, and STAT-3. *Biochem Biophys Res Commun* 2016; **476**: 481-486 [PMID: 27246736 DOI: 10.1016/j.bbrc.2016.05.150]
91 **Atanasov AG**, Wang JN, Gu SP, Bu J, Kramer MP, Baumgartner L, Fakhrudin N, Ladurner A, Malainer C, Vuorinen A, Noha SM, Schwaiger S, Rollinger JM, Schuster D, Stuppner H, Dirsch VM, Heiss EH. Honokiol: a non-adipogenic PPARγ agonist from nature. *Biochim Biophys Acta* 2013; **1830**: 4813-4819 [PMID: 23811337 DOI: 10.1016/j.bbagen.2013.06.021]
92 **Quan HY**, Baek NI, Chung SH. Licochalcone A prevents adipocyte differentiation and lipogenesis via suppression of peroxisome proliferator-activated receptor γ and sterol regulatory element-binding protein pathways. *J Agric Food Chem* 2012; **60**: 5112-5120 [PMID: 22563885 DOI: 10.1021/jf2050763]
93 **Kim SN**, Choi HY, Kim YK. Regulation of adipocyte differentiation by histone deacetylase inhibitors. *Arch Pharm Res* 2009; **32**: 535-541 [PMID: 19407971 DOI: 10.1007/s12272-009-1409-5]
94 **Gallego-Escuredo JM**, Del Mar Gutierrez M, Diaz-Delfin J, Domingo JC, Mateo MG, Domingo P, Giralt M, Villarroya F. Differential effects of efavirenz and lopinavir/ritonavir on human adipocyte differentiation, gene expression and release of adipokines and pro-inflammatory cytokines. *Curr HIV Res* 2010; **8**: 545-553 [PMID: 21073442 DOI: 10.2174/157016210793499222]
95 **Stankov MV**, Panayotova-Dimitrova D, Leverkus M, Schmidt RE, Behrens GM. Thymidine analogues suppress autophagy and adipogenesis in cultured adipocytes. *Antimicrob Agents Chemother* 2013; **57**: 543-551 [PMID: 23147731 DOI: 10.1128/AAC.01560-12]
96 **Díaz-Delfín J**, Domingo P, Giralt M, Villarroya F. Maraviroc reduces cytokine expression and secretion in human adipose cells without altering adipogenic differentiation. *Cytokine* 2013; **61**: 808-815 [PMID: 23357304 DOI: 10.1016/j.cyto.2012.12.013]
97 **Díaz-Delfín J**, del Mar Gutiérrez M, Gallego-Escuredo JM, Domingo JC, Gracia Mateo M, Villarroya F, Domingo P, Giralt M. Effects of nevirapine and efavirenz on human adipocyte differentiation, gene expression, and release of adipokines and cytokines. *Antiviral Res* 2011; **91**: 112-119 [PMID: 21619898 DOI: 10.1016/j.antiviral.2011.04.018]
98 **Dowell P**, Flexner C, Kwiterovich PO, Lane MD. Suppression of preadipocyte differentiation and promotion of adipocyte death by HIV protease inhibitors. *J Biol Chem* 2000; **275**: 41325-41332 [PMID: 11018036 DOI: 10.1074/jbc.M006474200]
99 **Stankov MV**, Schmidt RE, Behrens GM, German Competence Network HIV/AIDS. Zidovudine impairs adipogenic differentiation through inhibition of clonal expansion. *Antimicrob Agents Chemother* 2008; **52**: 2882-2889 [PMID: 18474584 DOI: 10.1128/AAC.01505-07]
100 **Pérez-Matute P**, Pérez-Martínez L, Blanco JR, Oteo JA. Minimal effects of Darunavir on adipocyte differentiation and metabolism in 3T3-L1 cells. *J Infect Chemother* 2012; **18**: 485-493 [PMID: 22245882 DOI: 10.1007/s10156-011-0361-8]
101 **Pérez-Matute P**, Pérez-Martínez L, Blanco JR, Oteo JA. Neutral actions of Raltegravir on adipogenesis, glucose metabolism and lipolysis in 3T3-L1 adipocytes. *Curr HIV Res* 2011; **9**: 174-179 [PMID: 21585335 DOI: 10.2174/157016211795945278]
102 **Stankov MV**, Schmidt RE, Behrens GM. Impact of stimulatory pathways on adipogenesis and HIV-therapy associated lipoatrophy. *Exp Biol Med (Maywood)* 2009; **234**: 1484-1492 [PMID: 19934369 DOI: 10.3181/0907-RM-205]
103 **Caron M**, Auclair M, Vigouroux C, Glorian M, Forest C, Capeau J. The HIV protease inhibitor indinavir impairs sterol regulatory element-binding protein-1 intranuclear localization, inhibits preadipocyte differentiation, and induces insulin resistance. *Diabetes* 2001; **50**: 1378-1388 [PMID: 11375339 DOI: 10.2337/diabetes.50.6.1378]
104 **Moure R**, Domingo P, Gallego-Escuredo JM, Villarroya J, Gutierrez Mdel M, Mateo MG, Domingo JC, Giralt M, Villarroya F. Impact of elvitegravir on human adipocytes: Alterations in differentiation, gene expression and release of adipokines and cytokines. *Antiviral Res* 2016; **132**: 59-65 [PMID: 27216995 DOI: 10.1016/j.antiviral.2016.05.013]
105 **Kim TH**, Kim HK, Hwang ES. Novel anti-adipogenic activity of anti-malarial amodiaquine through suppression of PPARγ activity. *Arch Pharm Res* 2017; **40**: 1336-1343 [PMID: 29071567 DOI: 10.1007/s12272-017-0965-3]
106 **Ning X**, He J, Shi X, Yang G. Regulation of Adipogenesis by Quinine through the ERK/S6 Pathway. *Int J Mol Sci* 2016; **17**: 504 [PMID: 27089323 DOI: 10.3390/ijms17040504]
107 **Lee J**, Kim MH, Lee JH, Jung E, Yoo ES, Park D. Artemisinic acid is a regulator of adipocyte differentiation and C/EBP δ expression. *J Cell Biochem* 2012; **113**: 2488-2499 [PMID: 22396222 DOI: 10.1002/jcb.24124]

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