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Traditional Chinese Medicines With Anti-inflammatory Functions and Their Inhibitory Effects on Fatty Acid Synthase*

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Abstract As the prevalence of obesity and related diseases continues to rise, obesity accompanied chronic inflammation becomes a non-neglect public health problem. Innovative treatment options and strategies for obesity-related chronic inflammation are urgently needed. Fatty acid synthase(FAS) is a multiple enzyme complex which has been recognized as a potential therapeutic target for obesity, inflammation, diabetes, non-alcohol fatty liver disease(NAFLD), and cancer. Research on FAS inhibitors has attracted increasing attention in recent years. Several key inflammatory markers have been consistently associated with obesity, which suggests that a persistent inflammatory response is a potentially modifiable risk factor. In China, traditional Chinese medicines (TCMs) have been applied clinically to treat inflammation. Among them there are several TCMs with strong inhibitory effect on FAS. This brief review aims at summarizing literatures concerning the recognized role of FAS as a biomarker and therapeutic target in obesity and related inflammation as well as providing evidence to support the anti-inflammation potential of TCMs with FAS inhibitory activities. FAS has emerged as a crucial target in anti-obesity therapies, and FAS inhibition might contribute to the treatment of inflammation.

Key words fatty acid synthase, inhibitor, inflammation, obesity, traditional Chinese medicine
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Metabolic disease is characterized by obesity, mitochondrial dysfunction, redox imbalance and chronic inflammation[1]. Elevated lipogenesis has been associated with a variety of diseases, including obesity, inflammation, diabetes, non-alcohol fatty liver disease(NAFLD), and cancer[2]. Obesity induces accumulation of adipose tissue macrophages and inflammatory responses that promote the development of glucose and lipid metabolism disorders[3]. Elevated *de novo* lipogenesis leads to the increase of fat mass and obesity[4]. The way in which obesity triggers the chronic inflammation that promotes the transition from obese/normoglycemic to obese/metabolically compromised, remains an important outstanding issue with significant clinical impact. The relationships amongst these physiological changes and how they promote metabolic dysfunction in obesity are not well understood.

Traditional Chinese medicine(TCM), including Chinese herbology and acupuncture, plays a crucial role in alternative and complementary medicines[5]. TCMs are being increasingly utilized and investigated in the management of a variety of disorders, including both obesity and inflammation. In TCM, there exists a wide range of biologically active constituents, such as flavonoids, alkaloids, isoprenoids, quinones, saponins

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and phenylpropanoids. Many of these active components have been reported to inhibit inflammation and activate inflammatory immune response[6]. Fatty acid synthase(FAS, EC 2.3.1.85) plays a pivotal role in *de novo* lipogenesis, making this multi-catalytic protein an attractive target for therapeutic intervention[7]. Over the past 20 years, it has been found that the extracts of a variety of TCMs illustrate potential inhibitory effects on FAS[8-10]. This brief review aims at summarizing the well-known involvement of fatty acid bio-synthesis in inflammation and the TCMs with FAS inhibitory activity, concerning their possible application in inflammation treatment.

1 FAS and FAS inhibitors

1.1 FAS is related to human diseases

FAS is a dimer multifunctional enzyme, which functions in the fatty acid synthesis from acetyl-CoA, malonyl-CoA and NADPH in animals[11]. Fatty acids are essential for membrane biogenesis, post-translational modifications of proteins, energy storage and generation of signaling molecules[12]. As a key enzyme for the *de novo* synthesis of fatty acid, FAS has been indicated to associate with a large number of human diseases and adverse health conditions such as obesity, inflammation, NAFLD, cardiovascular disease, and cancer[13]. Elevated saturated free fatty acid(FFA) levels during over-nutrition lead to inflammation, which perturbs energy homeostasis. Obesity is a result of increased adipose tissue mass, which is caused due to the rising of adipocyte numbers and size, accompanied with the imbalance between energy intake and expenditure[14]. Adipose tissue consists of mature adipocytes, preadipocytes, endothelial cells, macrophages, fibroblasts and adipose derived stem cells[15]. Preadipocytes are capable to propagate and differentiate into mature adipocytes, which determine the number of adipocytes throughout their entire lifespan[16]. Additionally, the increase in number and size of adipocytes in adipose tissues is regarded as cellular syndrome of obesity, and the increase of adipocytes size is the result of increased storage of lipids in the cell[15]. Meanwhile, the size of cell depends on the lipid accumulation in the adipocytes. Therefore, adipose tissue mass can be reduced by the inhibition of adipogenesis from preadipocytes to mature adipocytes or the prevention of intracellular lipid accumulation[17]. Increased FAS expression level has also been detected in many types of cancers, including breast, bladder, prostate, endometrium, ovary, colon, lung, and pancreas cancer cells[8,18]. Since FAS doesn't express or expresses at a low level in most normal tissues, it has been considered as a potential diagnostic marker.

1.2 Classical FAS inhibitors

A large number of inhibitors have been reported, most of which can bind to the catalytic sites of FAS. The first reported FAS inhibitor is cerulenin, which has been isolated from the fungi *Cephalosporium caerulens*[19]. Cerulenin is a promising FAS inhibitor that irreversibly binds to β - ketoacyl synthase(KS) domain of FAS. C75, the synthetic derivative of cerulenin, is more stable than cerulenin[20]. C75 acts on β - ketoacyl reductase(KR), acyl carrier protein (ACP) and thioesterase(TE) domains of FAS in a competitive and irreversible manner. Orlistat, an anti-obesity drug approved by Food and Drug Administration(FDA) of USA, has been reported as an irreversible FAS inhibitor with a half inhibitory concentration(IC_{50}) value of 0.9 μmol/L, mainly acts on the TE domain[19]. Platensimycin, a broad-spectrum antibiotic produced by *Streptomyces platensis*, inhibits the type II FAS, which is important in the fatty acid biosynthesis pathway in bacteria[21]. Triclosan inhibits enoyl reductase(ER) domain *in vitro* and is cytotoxic to human breast cancer MCF-7 and SK-Br-3 cells[22]. These classical FAS inhibitors are summarized in Table 1.

Table 1 Classical FAS inhibitors

No.	Compound	Activity (IC_{50})	Resource	Ref.
1	Cerulenin	20 g/L	*Cephalosporium caerulens*	[19]
2	Orlistat	0.9 μmol/L	Synthesis	[19]
3	C75	> 100 μmol/L	Synthesis	[20]
4	Platensimycin	0.3 μmol/L	*Streptomyces platensis*	[21]
5	Triclosan	10−50 μmol/L	Synthesis	[22]

Classical FAS inhibitors such as C75, cerulenin and triclosan demonstrate significant physiological functions. The body weight and food intake of obese mice are obviously reduced after treated with FAS

inhibitors. The actions are due to inhibition of the expression of signal neuropeptide Y in hypothalamus, which is mediated by malonyl-CoA, one of the substrates of FAS. C75 and cerulenin have been reported to reduce lipid droplets accumulation in mice adipocytes[10,23].

1.3 Natural FAS inhibitors derived from TCMs

TCM is an ancient form of healthcare that dates back over 2 500 years and includes natural treatments such as acupuncture, herbal remedies, dietary advice, stress/emotional support, exercise, including Tai Chi, Qi Gong, also, treatments such as cupping and moxibustion. TCM treatments aim to correct imbalances in the body and primarily work in three major ways: a. Addressing a patient's external factors and environment; b. Helping patients relate to their internal emotions in a healthier way, including managing stress; c. Improving someone's lifestyle factors, including diet and exercise routine[24].

TCMs are abundant sources for herb selection of drug discovery. In addition, TCM formulas provide promising sources for a more effective and less toxic treatment option for diseases[25-26]. The increasing interest and progress in seeking natural products has not only provided a chemical understanding of herbal drugs and their therapeutic function, but also contributed to the chemical bank for drug discovery[25,27].

By screening a variety of TCMs, there is a finding of many crude extracts of TCM that could inhibit FAS activity. The tea polyphenols, such as epigallocatechin gallate(EGCG), catechins, flavones, theaflavins are reported to inhibit both the activity and the expression level of FAS[28]. *Polygonum multiflorum*, *Alpiniae officinarum*, and *Parasite scurrula*, show both strong FAS inhibitory effect and weight loss effect in animal models[28]. The inhibitory potencies of the active components of tuber fleeceflower root, parasitic loranthus, green tea leaf and ginkgo leaf are similar to or greater than classical FAS inhibitors such as cerulenin and C75.

Flavonoids are the main active compounds exist in the crude extracts of parasitic loranthus, polygonum multiforum, galangal, night kodo and maple leaf. The extracts of these TCMs are reported to inhibit FAS activity[29]. In addition, the extracts of *Citrus reticulate* Blanco (Rutaceae) and *Canarium album* Raeuseh (Burseraceae) leaves, mainly containing the flavonoids, reveal stronger inhibitory effect on FAS than C75[30].

Tannins are water-soluble polyphenols, widely existing in TCMs. It has been reported that both condensed and hydrolysable tannins could strongly inhibit FAS activity[30]. The condensed tannins mainly act on malonylacetyl transferase (MAT) domain. The trimeric condensed tannins inhibit β - ketoacyl reduction reaction by competing with NADPH with an IC_{50} value of 0.65 μmol/L[30]. Ellagitannins, casuarinin, gemin G, gemin A, pedunculagin, potentillin and ellagic acid, isolated from *Geum japonicum* Thunb. var. chinense F. Bolle (Rosaceae), exhibit strong inhibitory activity against FAS with IC_{50} values at the range of 0.21 to 41.4 μmol/L[31].

Stilbene and stilbene glucosides, isolated from traditional Chinese herb *Fallopia multiflora*(Thunb.) Harald, are reported to inhibit the FAS activity[32]. The crude extract of grape skin as well as resveratrol are reported to reduce the proliferation of adipocytes by inhibiting intracellular FAS[33]. Ursolic acid, exists in several TCMs, strongly inhibits FAS with an IC_{50} value of 6 mg/L, acting mainly on the MAT domain and weakly on the KS domain[30].

Natural FAS inhibitors isolated from TCMs are widely distributed in plants. They have shown potent inhibition on FAS with less toxicity, and hold promise in the development for effective and inexpensive therapeutics. Some TCMs derived FAS inhibitors are summarized in Table 2.

Table 2 Representative compounds with FAS inhibitory activity isolated from TCMs.

No.	Compound	Activity (IC_{50})	Resource	Ref.
1	EGCG	52 μmol/L	Green tea	[28−29]
2	Luteolin	31.47 μmol/L	*Paspalum conjugatum*	[30]
3	Punicalagin	4.3 μmol/L	*Punica granatum* L.	[32]
4	Resveratrol	11.1 g/L	Grape skin	[33]
5	Alpha-mangostin	5.54 μmol/L	Mangosteen skin	[8, 17]
6	Vitisin B	0.681 μmol/L	*Iris lactea* Pall	[9]
7	Ursolic acid	6.0 g/L	*Eriobotrya japonica* Thunb.	[10]
8	Curcumin	8.84 g/L	*Curcuma longa* L.	[30]
9	Emodin	25 μmol/L	*Polygonum multiflorum* Thunb.	[32]

2 The involvement of FAS in inflammation

2.1 FAS and inflammation are involved in many diseases

FAS plays an important role in inflammation activation. It is reported that knocked down FAS reduces the inflammation response, conversely overexpressed FAS increases inflammatory factors expression[34]. Obesity is in the chronic low-grade inflammation state, many inflammatory factors are overexpressed in obesity such as interleukin[35-36]. FAS involves in the *de novo* synthesis of endogenous lipids and regulate fatty acid synthesis and oxidation. Both the activity and the expression of FAS are higher in obese mouse in comparison with normal mouse. Inhibition of FAS could reduce the weight effectively in obesity mice[37]. Inflammation is also involved in the process of obesity, which related to FAS[38]. Inflammation response promotes tumor development[39], meanwhile FAS is one of the crucial factors in cancer[15]. Inflammation response and FAS are exceedingly important factors in many diseases such as diabetes, NAFLD, cancer and some metabolic diseases[40-41]. Growing evidences prove that FAS and inflammation promote the development of diseases at the same time. It is still unclear how FAS involved in inflammation.

2.2 FFA, the end product of FAS, induces inflammation

FAS catalyzes the synthesis of palmitic acid with acetyl-CoA and malonyl-CoA. Intracellular FFAs are elevated in type 2 diabetes and cancer and there is a remarkable decrease of it *via* inhibiting FAS activity[42]. Triglyceride and palmitate could cause inflammation directly[43]. FFA has been proposed to promote inflammatory responses by directly engaging toll-like receptors (TLRs) and then induce nuclear factor-κB(NF-κB)-dependent production of inflammatory as well. FFA activates the TLRs, which lead to JNK activation. In addition, FFA could activate NF-κB *via* TLRs pathway. While the inflammation emerging, some cytokines like IL-6 and TNF-α are secreted[44]. Fatty acid binding protein (FABP), a protein that transports FFAs, could be improved by FFA *in vitro*[45]. FABP deficiency causes inflammation to be inhibited *via* activation of SIRT3 with the involvement of ROS and mitochondrial dysfunction[46]. Supplementation with n-3 fatty acids resulted in changes of inflammatory-state related genes in the lung epithelial cells exposed to polycyclic aromatic hydrocarbons[47].

2.3 FAS mediates inflammatory response through lipid membrane

The cytoplasmic membrane is the most important part of the cell, almost all receptors are localized on the plasma membrane. The innate immune response is affected by cell membrane lipids, while the composition of membrane lipids changed, the inflammation would be elevated broadly *via* TLRs pathway[48]. The regulation of FAS substantially contributes to the inflammatory response of immune cells[49]. Endogenous fatty acid synthesis, mediated by FAS, affects membrane composition, FAS deletion changes the composition and order of the plasma membrane, meanwhile the Rho GTPase activity is suppressed, which inhibits the JNK pathway through the membrane subdomains[50]. On the other hand, restored Rho GTPase activity or intact FAS could trigger JNK signaling pathway[40].

2.4 Inflammatory signaling pathways involved in FAS

2.4.1 NF-κB

The central mediator of the inflammatory process is considered to be the NF-κB transcription factor family, which participants in innate and adaptive immune responses[51]. SREBP1-c, a nuclear transcription factor that regulates the expression of lipids in cells and the expression of FAS by co-expression with FAS. FAS expression is improved by increased SREBP1-c expression. Overexpression of SREBP1-c could enhance ROS levels, which induce inflammatory factors such as p-IκB, p-P65 and TLR4 overexpression[52]. FAS synthesizes *de novo* fatty acids, which are significant factors in activating inflammation responsible. FFA can aggravate the burden of mitochondria and cause mitochondria to produce ROS, which subsequently activates NF-κB pathway increased inflammation[53]. In addition, palmitate could active NF-κB pathway *via* PKC and JNK pathways. Inhibition of FAS could reduce NF-κB significantly through PI3K/AKT pathway[54]. The thermogenic markers related to fatty acid synthesis, mobilization, and oxidation in the ob/ob mice are decreased. There are also alterations in insulin signaling and protein and gene expressions of inflammation[55]. Reduced expression of the FAS gene

and increased expression of cytokine genes in adipose tissues of obese subjects are reported[56].

2.4.2 JAK-STAT

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway contributes to inflammation process and regulates some inflammatory factors expression[57]. FFA stimulates JAK/STAT expression by facilitated the IL-6 level. After IL-6 binding with JAK/STAT receptor, JAK/STAT could be activated. Then phosphorylated STAT enters the nuclear to regulate the inflammation cytokine gene expression[58].

2.4.3 TLR

A critical role of TLR and its downstream molecules such as tumor necrosis factor receptor-associated factor 6(TRAF6) has been documented in inflammatory response induced by FFA. TLR is usually a binding site for lipopolysaccharide, which in turn causes inflammatory responses in cells[59]. There are growing evidences illustrate that FAS produces FFA, which subsequently induces inflammation *via* TLR included TLR2 and TLR4. TLR could boost some signaling pathway such as MAPK, PI3K/AKT and NF-κB pathway[60].

3 TCMs with anti−inflammtion abilities

Numerous Chinese herbs have been shown to exert a medicinal effect on hepatic inflammation, fatty liver disease as well as preventing the accumulation of fat in the liver[61]. Studies demonstrate that TCMs protect against hepatic inflammation *via* different mechanisms based on their animal model[61]. Several TCMs have been found to reduce oxidative stress. Medicinal mushrooms promote stronger immunity, help to fight fatigue, have anticancer properties, help to balance hormones and control the body's stress response. *Monascus adlay* and *Monascus purpureus* are applied to lower lung inflammation and damage. Chinese gooseberries could lower hepatotoxin-induced liver inflammation. *Crataegi Fructus* (Shanzha) could treat symptoms of hyperactive bladder. Green tea extract and its active components are applied to protect the brain, reduce fatigue and regulate appetite. TCM formulas like Virgate wormwood decoction (Yinchenhao Tang) and Five Stranguries Powder (Wuli San) show antioxidant and anti-inflammatory abilities, then were used to lower liver damage[62].

4 Anti−inflammation function of FAS inhibitors derived from TCM： facts and perspectives

Inflammation is at the root of most diseases and tied to the majority of common health problems, including cancer, heart disease, autoimmune disorders, cognitive impairment and diabetes. TCM herbal treatments showed positive antioxidant, anti-inflammatory, anti-apoptotic and autophagic regulatory functions[63]. TCM treatments can also coordinate patients to overcome a variety of harmful lifestyle habits related to inflammation, such as resisting chronic pain, cigarette smoking, overeating, poor sleep, chronic stress, hormonal imbalances alcohol- and non-alcohol-induced liver damage[64-65].

Through systematic review of the literature, we found that FAS inhibitors, originated from TCMs show potent anti-inflammation activity. *Polygonum multiflorum*, the crude extract of which show strong inhibition on FAS, has been applied both clinical and preclinical to treat inflammation[66]. The main components *Polygonum multiflorum*, such as 2,3,5,4'-tetrahydroxystilbene-2-O-β-d-glucopyranoside and emodin, are contributed to inflammation[67]. The polyphenols isolated from *Loranthus micranthus* Linn. are high active FAS inhibitors and have anti-inflammatory activity as evidenced by the suppression of inducible nitric oxide and cytokine (TNF-α) levels in the culture supernatant of lipopolysaccharide-stimulated murine macrophages[68]. Thioether compounds exist in Allium could reduce both the expression level and the activity of FAS. They are reported to be potential preventive agents in inflammation[69]. The xanthones isolated from *Garcinia mangostana* Linn. pericarp demonstrate both anti-obesity and anti-cancer activity *via* inhibiting FAS[8]. The anti-inflammation effect of *Garcinia mangostana* Linn. pericarp extract is also reported[70]. Pomegranate (*Punica granatum*) peel has a wide range of clinical applications for the treatment and prevention of chronic inflammation in China[71]. The extract of pomegranate as well as the main components such as tannic acid and punicalagin show high active inhibition on FAS activity[72]. Loquat leaf (*Eriobotrya japonica* Thunb.) and its main component ursolic acid exhibit both strong inhibitory effect on FAS and anti-inflammation activity[30,73].

In summary, FAS inhibitors derived from TCMs have the application potential to treat inflammation. Inhibition of FAS activity by TCMs could reduce the amount of FFA and consequently reduce obesity. FFA could activate the inflammation factors and induce inflammation directly. Obesity and inflammation are mutually reinforcing and both have a positive impact on the development of cancer. FAS inhibitors indicate anti-obesity, anti-inflammatory and anti-cancer activity. Previous studies suggest that FAS may be a common target for the treatment of these diseases. The possible mechanisms of FAS inhibitors in the treatment of obesity, inflammation and cancer are shown in Figure 1.

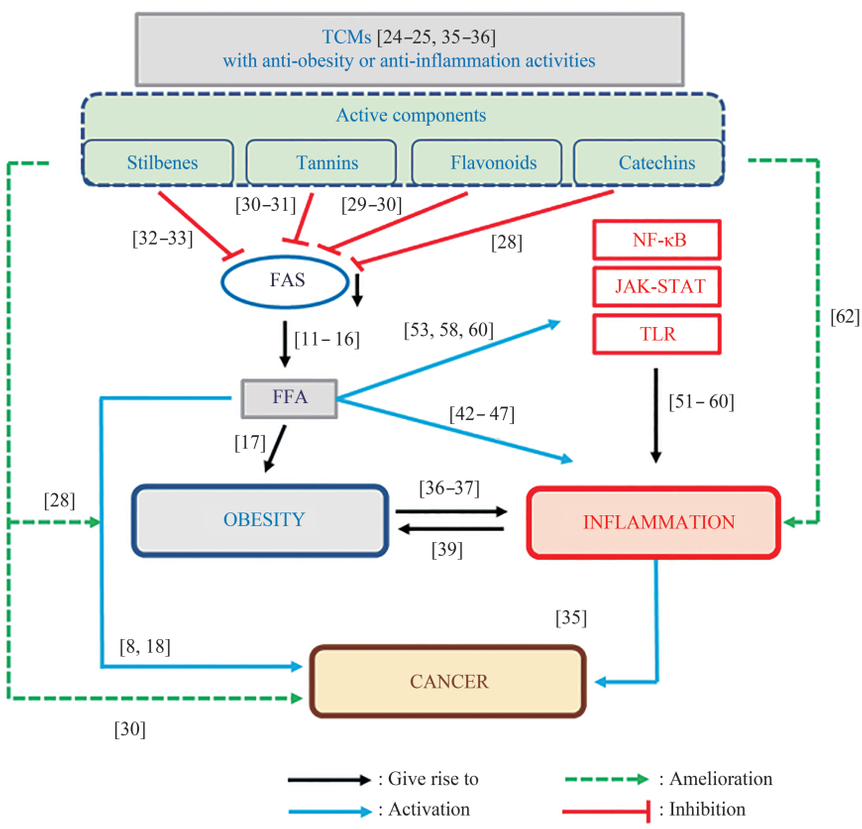

Fig. 1 The possible mechanisms of FAS inhibitors derived from TCMs in the treatment of obesity , inflammation and cancer

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具有抗炎活性的中药对脂肪酸合酶的抑制作用*

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摘要　随着肥胖及其相关疾病的患病率不断上升，肥胖并发的慢性炎症已成为一个不容忽视的公共卫生问题，迫切需要针对肥胖相关慢性炎症新的治疗方案和干预策略. 脂肪酸合酶（fatty acid synthase，FAS）是一种多功能复合酶，是治疗肥胖、糖尿病、非酒精性脂肪肝、炎症和癌症的潜在靶点. 持续的炎症反应是潜在的危险因素. 一些关键的炎症标志物与肥胖密切相关，其中特别是FAS抑制剂的研究受到越来越多的关注. 在我国，中药已广泛被应用于炎症的治疗，其中有多种中药对FAS表现出强抑制作用. 本文综述了中药FAS抑制剂的结构和活性特点，对于研发中药FAS抑制剂治疗炎症提供了依据.

关键词　脂肪酸合酶，抑制剂，炎症，肥胖，中药
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