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Natural Fatty Acid Synthase Inhibitors From Traditional Chinese Medicines and Functional Foods*

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Abstract The increasing prevalence of obesity and related diseases has made it imperative to address obesity as a pressing public health concern. Urgent attention is needed to develop innovative treatment options and strategies for obesity-related diseases. Fatty acid synthase (FAS) is a complex multiple enzyme that plays a critical role in the biosynthesis of long-chain fatty acids. Its dysregulation has been implicated in various human diseases, including obesity, type 2 diabetes, cancer, inflammation, and cardiovascular disease. Consequently, research on FAS inhibitors has received increasing attention over the past 30 years. In China, traditional Chinese medicines (TCMs) and functional foods are being recognized for their potential to alleviate disease status, particularly chronic diseases like obesity. Several TCMs have been found to have a strong inhibitory effect on FAS. This review aims to summarize the literature on the role of FAS as a biomarker and therapeutic target in obesity and related diseases while providing evidence to support the anti-obesity potential of TCMs and functional foods with FAS inhibitory activities.

Key words fatty acid synthase, inhibitor, cancer, obesity, traditional Chinese medicine, functional food
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Obesity is a significant public health challenge and a major risk factor contributing to the global burden of disease[1]. In China, there has been a rapid increase in obesity and overweight over the past 40 years[2]. The latest national adult obesity rate, according to Chinese criteria, is 16.4%, with an overweight rate of 34.3%[3]. Epidemiological studies have shown that obesity is associated with hypertension, dyslipidemia, cardiovascular and cerebrovascular diseases, non-alcohol fatty liver disease (NAFLD), type 2 diabetes, and cancer[4-5].

Elevated *de novo* lipogenesis, which leads to an increase in fat mass and obesity, is closely linked to the activity of fatty acid synthase (FAS, EC 2.3.1.85)[6]. Thus, FAS is an attractive target for therapeutic intervention. In recent years, there has been a growing interest in the use of traditional Chinese medicines (TCMs) and functional foods as alternative or complementary treatments for a variety of disorders, including obesity and obesity-related diseases[7-8]. These natural remedies contain a diverse array of biologically active compounds, such as flavonoids, xanthones, alkaloids, terpenoids, stilbenes, quinones, saponins, and phenylpropanoids. These constituents have been studied for their potential to regulate FAS activity and lipid metabolism[9].

In the last three decades, multiple studies have explored the potential inhibitory effects of extracts derived from various TCMs and functional foods on FAS[10-20]. These findings suggest that natural remedies could be a promising avenue for developing therapeutic interventions against obesity and related disorders.

This brief review aims at summarizing the resourse, chemical structures, functions, and the application potential of natural FAS inhibitors isolated from TCMs and functional foods.

1 FAS is related to human diseases

1.1 FAS is a key enzyme for fatty acid biosynthesis

Lipids play a crucial role in various biological processes, serving as important components of cellular structures and performing a range of functions

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such as energy storage, plasma membrane formation, signal transduction, and protein acylation[21]. Fatty acids and their residues are key components of lipids, with saturated or unsaturated long-chain hydrocarbon tails of varying lengths and carboxylic acid groups at the ends[22]. Fatty acid biosynthesis occurs in all plants and animals, catalyzed by FAS, which utilizes nicotinamide adenine dinucleotide phosphate (NADPH)-dependent condensation of acetyl coenzyme A (CoA) and malonyl-CoA to synthesize saturated 16-carbon palmitic acid[23-25].

Mammalian FAS is a complex homodimeric enzyme consisting of two identical subunits, each containing a 270 ku polypeptide chain and seven independent functional domains: malonyl acetyl transferase (MAT), β-ketoacyl synthase (KS), β-ketonyl reductase (KR), β-hydroxyacyl dehydratase (DH), enoyl reductase (ER), thioesterase (TE), and acyl carrier protein (ACP)[26].

The precursor is elongated through cyclic decarboxylation condensation of acyl-CoA and malonyl-CoA, initiated by acetyl CoA[26]. Acetyltransferase loads acetyl coenzyme A onto the phosphoubiquitin cofactor of ACP's terminal mercaptan, and ACP transfers the acetyl group to the active site of KS cysteine. Then, MAT transfers malonyl from malonyl-CoA to ACP, and KS partially decarboxylates acetyl and malonyl to ACP-bound β-ketonyl intermediate. The sequence of NADPH-dependent KR, DH, and ER modifies the β-carbon position to produce a saturated acyl product elongated by two carbon units. This acyl group serves as the starting substrate for the next round of extension until the fatty acid chain reaches 16 to 18 carbon atoms and is released from ACP as a free fatty acid through the TE domain[26].

1.2 FAS is a therapeutic target for treating human diseases

Synthetic palmitate is a crucial precursor in the synthesis of complex lipids, including glycerol phospholipids and cholesterol, and is involved in membrane protein palmitoylation[27]. Thus, FAS plays a vital role in the human lipid metabolism cycle. However, FAS has also been linked to numerous human diseases and adverse health conditions, such as obesity, hypertension, cardiovascular diseases, NAFLD, and cancer[28-29].

Obesity is characterized by an increase in adipose tissue mass resulting from an imbalance between energy intake and expenditure, leading to an increase in both the number and size of adipocytes[30]. Studies have shown that FAS is over-activated in the adipose tissue of obese rats[31]. Adipose tissue is composed of various cell types, including preadipocytes, mature adipocytes, endothelial cells, macrophages, fibroblasts, and adipose stem cells[32]. The number of adipocytes is determined by the differentiation of preadipocytes into mature adipocytes throughout an individual's lifespan[32]. The expansion of adipose tissue is considered a hallmark of obesity, with the increase in adipocyte size primarily resulting from intracellular lipid accumulation[33]. Thus, inhibiting preadipocyte differentiation into mature adipocytes or reducing intracellular lipid accumulation may help improve adipose tissue quality.

Increased expression of FAS during hepatitis C virus (HCV) infection leads to changes in cellular lipid concentrations and promotes steatosis[34]. FAS overexpression has also been observed in mice models of liver steatosis, demonstrating its involvement in this disease *in vivo*[35]. Moreover, FAS overexpression has been implicated in many types of cancer, where it plays a critical role in tumor cell survival, proliferation, and metastasis[36-37]. Consequently, FAS has become a promising therapeutic target for these diseases. Due to its low or absent expression in most normal human tissues, FAS is being considered as a potential diagnostic marker and therapeutic target[29, 37]. Various FAS inhibitors have been developed and tested in preclinical and clinical studies, demonstrating promising results in reducing tumor growth and improving metabolic disorders[38]. However, optimizing the efficacy and safety of FAS inhibitors remains a challenge, particularly in minimizing off-target effects and optimizing drug delivery[38]. Nonetheless, continued research in this field holds great promise for the development of novel therapies for a range of human diseases.

2 Classical FAS inhibitors

Numerous inhibitors have been reported that target the catalytic sites of FAS, with most of them exhibiting binding affinity to these sites.

The first identified inhibitor of FAS is the natural

compound cerulenin, which has been discovered in the fungus *Cephalosporium caerulens*[39]. Cerulenin has been shown to covalently bind to the KS domain of FAS, disrupting the condensation reaction between acetyl-CoA and malonyl-CoA, which subsequently inhibits the biosynthesis of fatty acids and sterols in yeast[40]. *In vivo* studies have demonstrated that cerulenin treatment in *ob/ob* mice leads to significant body weight reduction[41]. Specifically, weight loss is observed after 2 d of treatment compared to the control group, and a slowed rate of weight gain is observed after 7 d of prolonged treatment. Daily or alternate-day administration of 60 mg/kg cerulenin resulted in a significant increase in ATP content by 58.1% and 61.5%, respectively, after 7 d of treatment. Additionally, a significant increase in ATP is also observed after 2 d of treatment with 60 mg/kg cerulenin. In contrast, administration of 30 mg/kg cerulenin for 2 or 7 d does not result in a significant change in cell ATP content[41].

C75 is the first synthesized FAS inhibitor to solve the chemical instability of reactive epoxides in cerulenin[42]. C75 acts on different domains including KR, TE and ACP of FAS in an irreversible manner[43]. It was first discovered by chemists in 1994 and has since been extensively studied for its potential therapeutic applications in treating cancer and obesity[44]. C75 works by targeting FAS, leading to a decrease in the production of fatty acids and subsequent inhibition of tumor cell growth and proliferation[45]. C75 retards growth of human melanoma cells, involving activation of caspase-dependent apoptosis[46]. It has also been shown to have anti-obesity effects in animal studies by reducing food intake and increasing energy expenditure[47].

Orlistat is an FDA-approved pharmaceutical compound that is widely used for weight loss by inhibiting pancreatic lipase, an enzyme that breaks down dietary fats in the gut. Studies have suggested that orlistat also acts as an inhibitor of FAS[48-49]. Orlistat has been shown to reduce fatty acid synthesis and lipid accumulation in various cell types by inhibiting FAS[48]. This additional mechanism of action has led to investigations into the potential of orlistat as a treatment for cancer[48]. Preclinical studies have demonstrated that orlistat can induce apoptosis in cancer cells and inhibit tumor growth in various animal models[50]. Furthermore, orlistat has been found to possess anti-inflammatory properties by reducing the production of inflammatory cytokines in macrophages, which may be mediated by its FAS inhibitory activity[51]. These findings suggest that orlistat may have potential applications in the treatment of both cancer and inflammatory diseases.

Platensimycin, a natural component isolated from *Streptomyces platensis*, shows inhibitory effect on the type II FAS, which catalyzes the long chain fatty acid biosynthesis in prokaryote[52]. This inhibition leads to a decrease in the production of bacterial fatty acids, ultimately resulting in cell death. Since bacterial and mammalian fatty acid synthesis pathways share similarities, platensimycin has been investigated for its potential as an inhibitor of mammalian FAS[52]. *In vitro* studies have demonstrated that platensimycin can inhibit FAS activity, specifically by targeting the KR domain of FAS[53]. Platensimycin’s ability to inhibit FAS has led to its investigation as a potential therapeutic agent for metabolic disorders, such as obesity and type 2 diabetes[54]. Preclinical studies in animal models have shown that platensimycin can reduce body weight and improve glucose metabolism[54].

Triclosan is a synthetic compound that has been widely used as an antibacterial and antifungal agent in various consumer products such as soaps, toothpaste, and cosmetics[55]. Triclosan has been studied for its potential as an inhibitor of mammalian FAS[56]. *In vitro* studies have shown that triclosan can inhibit the activity of FAS, specifically by targeting the enzyme’s KR domain. This inhibition leads to a decrease in the production of fatty acids, which is believed to contribute to triclosan’s antibacterial activity. In addition, triclosan has been shown to have anti-inflammatory effects, which may be mediated by its inhibition of FAS activity. Studies have demonstrated that triclosan can reduce the viability of cancer cells via inhibiting the ER domain of FAS[57].

TVB-2640 is a potent inhibitor of both FAS and the enzyme stearoyl-CoA desaturase-1 (SCD1), which is involved in the synthesis of monounsaturated fatty acids from saturated fatty acids[58]. In preclinical studies, TVB-2640 has been shown to reduce body weight and improve glucose metabolism in animal models of obesity and type 2 diabetes. TVB-2640 has also been shown to reduce liver fat accumulation and improve liver function in animal models of NAFLD. Clinical trials have demonstrated the safety and tolerability of TVB-2640 in humans. In a phase 1

study, TVB-2640 was well-tolerated and demonstrated a dose-dependent reduction in SCD1 activity in healthy volunteers. In a phase 2a study, TVB-2640 improved insulin sensitivity and reduced liver fat accumulation in patients with non-alcoholic fatty liver disease[58].

The chemical structures and the IC_{50} values of the above classical FAS inhibitors are summarized in Figure 1 and Table 1.

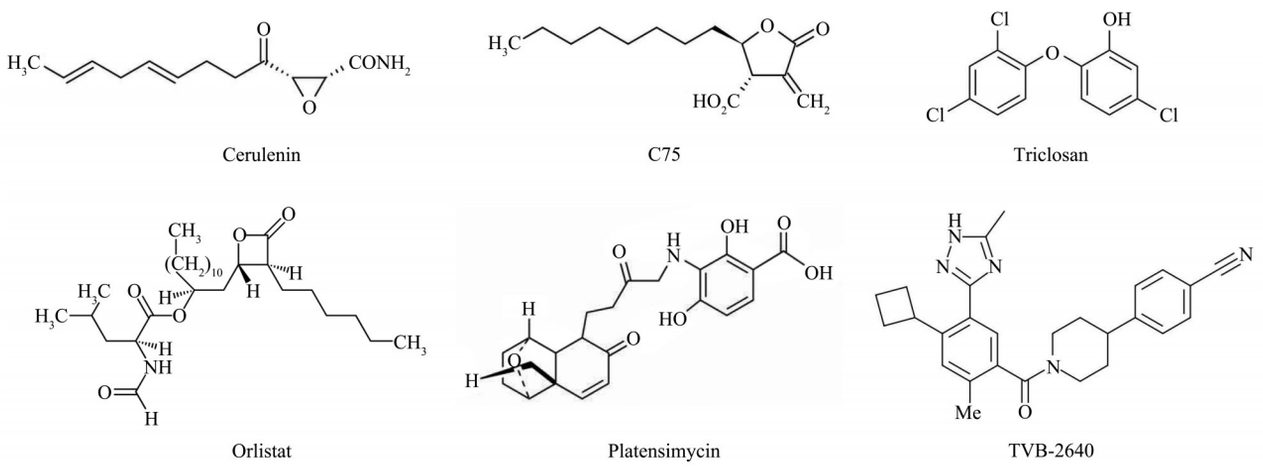

Fig. 1 The chemical structures of classical FAS inhibitors

Table 1 Classical FAS inhibitors

No.	Compound	Activity（IC_{50}）	Resource	Year
1	Cerulenin	20 mg/L	*Cephalosporium caerulens*	1972
2	C75	>200 μmol/L	Synthesis	2000
3	Triclosan	10−50 μmol/L	Synthesis	2002
4	Orlistat	0.9 μmol/L	Synthesis	2004
5	Platensimycin	0.3 μmol/L	*Streptomyces platensis*	2007
6	TVB-2640	0.052 μmol/L	Synthesis	2015

These classical FAS inhibitors have attracted the interest of pharmaceutical developers in the past 30 years. Up to now, however, no FAS inhibitors are developed as new drugs for treating obesity or related diseases. Cerulenin has limitations for use in human medications due to several reasons. Firstly, it can covalently bind to other thiol-containing proteins, causing off-target effects and toxicity. Secondly, its short half-life and rapid clearance make it difficult to maintain effective concentrations *in vivo*. Thirdly, its inhibitory effect on FAS can lead to liver toxicity. Finally, its poor solubility and stability limit its clinical use. One of the main limitations for C75 is its toxicity, which has been observed in animal studies. C75 has been shown to induce weight loss and improve insulin sensitivity in animals, but it also causes systemic toxicity, including hepatotoxicity and neurotoxicity. While triclosan has shown potential as an FAS inhibitor and a potential therapeutic agent for metabolic disorders, its use has been limited by its potential health risks. For platensimycin, a main limitation is its poor pharmacokinetic profile, as it has a short half-life and low oral bioavailability, making it difficult to maintain therapeutic concentrations *in vivo*. Additionally, platensimycin’s mechanism of action is not fully understood. As a proved drug, a major limitation of orlistat is its gastrointestinal side effects, including diarrhea, flatulence, and fecal incontinence, which can cause discomfort and reduce patient compliance. Although TVB-2640 shows promise as a potential therapeutic agent for metabolic disorders, particularly NAFLD, there are still some unresolved issues. One of the main challenges is optimizing its pharmacokinetic profile to ensure sufficient exposure and bioavailability *in vivo*. Another consideration is the potential for drug-drug interactions, as TVB-2640 may interact with other medications that affect lipid metabolism or liver

function.

It should be noted that, most of the classical FAS inhibitors are synthetic compounds, which raises concerns about their biocompatibility in the medical field. Therapeutic drugs and medical devices often need to interact with the human body, and it's essential to ensure that they do not cause adverse reactions or harm to patients. In contrast, natural compounds are chemical substances found in nature, such as those derived from plants, animals, and microorganisms. They have been extensively utilized in pharmaceuticals and medicine due to their superior biocompatibility compared to synthetic compounds.

3 Natural FAS inhibitors derived from TCMs and functional foods

TCMs and functional foods have been widely used for the treatment of chronic diseases, such as obesity and related metabolic disorders[7-8]. TCM employs a holistic approach to treatment and uses natural ingredients, such as herbs, roots, and mushrooms, to regulate metabolic pathways and improve overall health[7]. Some commonly used TCM ingredients could treat obesity and related conditions by affecting gut microbiota[59]. These ingredients have been shown to reduce body weight, improve insulin sensitivity, and lower blood lipid levels in animal and human studies[59]. The goal of TCM is to restore balance and harmony to the body by addressing imbalances through three major approaches: optimizing external factors and environment, enhancing emotional wellbeing by managing stress and improving lifestyle factors such as diet and exercise. Functional foods, on the other hand, are products fortified with bioactive compounds, such as polyphenols and omega-3 fatty acids, which have beneficial effects on health[60]. Functional foods have gained popularity in recent years as a convenient and effective way to supplement the diet and manage chronic diseases. Some examples of functional foods used for the treatment of obesity and related conditions include green tea, black tea, and fish oil[61]. These foods have been shown to improve lipid metabolism, reduce inflammation, and promote weight loss in animal and human studies[62].

TCMs and functional foods offer a rich source of herbs for drug discovery and TCM formulas show great potential for developing effective and less toxic treatments for various diseases[63-64]. The growing interest and advancements in natural product research have not only led to a deeper understanding of the chemical properties and therapeutic benefits of herbal medicines, but have also contributed to the expansion of the chemical library for drug discovery[65].

By screening a variety of TCMs and functional foods, there is a finding of many crude extracts and pure compounds that could inhibit FAS activity. Among them,

3.1 Flavonoids

Flavonoids demonstrate diverse biological activities, such as antioxidation, anticancer, anti-inflammatory, cardiovascular protection, and neuroprotection. Flavonoids are the main active compounds existing in parasitic loranthus, Chinese wolfberry, galangal, strawberry and maple leaf. Natural flavonoids in these plants are reported to inhibit FAS activity[10-12]. Furthermore, the extracts from *Citrus reticulata Blanco* (Rutaceae) and *Canarium album Raeuseh* (Burseraceae) leaves, which mainly contain flavonoids, exhibit a stronger inhibitory effect on FAS compared to C75[13]. Flavonoids exist in ginkgo leaf, and *Parasite scurrula*, show both strong FAS inhibitory effect and weight loss effect in obese mice[14]. Natural flavonoids, such as luteolin, apigenin, baicalein, quercetin, myricetin, kaempferol, morin, and fisetin, abundant in traditional Chinese herbal medicine and functional foods, have the ability to inhibit FAS activity[15].

3.2 Catechins

Catechin compounds exist mainly in different kinds of teas. The inhibitory potencies of the active components of green tea, and black tea are similar to or greater than classical FAS inhibitors such as cerulenin. Epigallocatechin gallate (EGCG), a main component in green tea, is the first reported FAS inhibitor that isolated from plant[16]. The subsequent research has found that other catechins, such as epigallocatechin (EGC), epicatechin gallate (ECG), gallocatechin gallate (GCG) and catechin gallate (CG) in green tea also show FAS inhibition with IC_{50} values of 10 to 100 μmol/L[17]. Theaflavins, which exist in black tea, have also been reported to inhibit both the expression level and activity of FAS[18].

3.3 Stilbenes

Stilbene and stilbene glycosides obtained from

the traditional Chinese herbs have the ability to inhibit FAS activity. One of the most common stilbene compounds, resveratrol, can inhibit the activity of FAS with an IC_{50} value of 11.1 mg/L (48.7 μmol/L)[19]. 2,3,5,4'-tetrahydroxy stilbene-2-O-β-D-glucoside from the root of *Polygonum multiflorum* Thunb. shows inhibitory effect on FAS[20]. Vitisin B, isolated from *Iris lactea* Pall, inhibits FAS activity with an IC_{50} value of 0.617 mg/L (0.681 μmol/L) [66]. Vitisin B could inhibit intracellular FAS activity, down-regulate the expression level of FAS, and then reduce the viability of human breast cancer cells[66]. Two natural stilbene glycosides, desoxyrhaponticin and rhaponticin, possess an inhibitory function on FAS activity with IC_{50} values of 172.6 μmol/L and 73.2 μmol/L. These two compounds could induce human cancer cell apoptosis *via* inhibiting intracellular FAS[67].

3.4 Xanthones

Xanthones exist mainly in Gambogaceae plants. A number of xanthones show inhibitory effect on FAS. Several studies have investigated the inhibitory effects of α-mangostin, the compound with the highest content in mangosteen pericarp, on FAS[68]. It has been found that α-mangostin significantly inhibits FAS activity and suppresses the growth of human cancer cells. Further studies reveal that α-mangostin inhibits FAS primarily by acting more strongly on the KS domain and less strongly on the MAT domain[69]. In addition, α-mangostin induces apoptosis and inhibits cell migration and invasion *via* both inhibiting intracellular FAS activity and down-regulating the expression level of FAS[69-70]. Furthermore, a serious of other xanthones isolated from the pericarp of mangosteen show FAS inhibitory effects, such as β-mangostin, γ-mangostin, garcinone E, 2, 4, 6, 7-tetrahydroxyxanthone[68].

3.5 Diarylheptanoids

Curcumin, a famous diferuloylmethane compound, can inhibit FAS activity by several mechanisms[71]. Firstly, it can directly bind to and inhibit FAS activity. Secondly, curcumin can downregulate the expression of FAS by inhibiting its promoter activity, resulting in a decrease in FAS protein levels. Thirdly, curcumin can modulate signaling pathways involved in FAS expression and activity, such as the AMP-activated protein kinase (AMPK) pathway, the mammalian target of rapamycin (mTOR) pathway, and the peroxisome proliferator-activated receptor (PPAR) pathway[72].

3.6 Terpenoids

Terpenoids are a diverse group of natural compounds. They are widely distributed in plants and are known for their pharmacological properties. Several natural terpenoids have been used in TCMs, and some of them show inhibitory effect on FAS. Ursolic acid, a natural triterpenoid compound found in various TCMs and foods, has been shown to have multiple effects on lipid metabolism, adipogenesis, and cancer cells. With regards to lipid metabolism, ursolic acid has been found to inhibit the activity of FAS, with an IC_{50} value of 6 mg/L. Its main target is the MAT domain, with a weaker effect on the KS domain[73]. Oleanic acid, isolated from peels of pomegranate, is also evaluated for inhibitory activities on FAS. The results show that oleanic acid can inhibit FAS activity with an IC_{50} value of 68.4 μmol/L[74].

3.7 Thioethers

Several thioethers, sulfur-containing compounds found Liliaceae *Allium* plants such as garlic, onion, and Chinese green onion, have been shown to have beneficial effects on lipid metabolism and adipogenesis[75]. Among them, diallyl trisulfide shows the strongest inhibitory effect. One of the primary ways in which allicin exerts its effects is through the inhibition of FAS[76]. Through inhibition kinetics, substrate protection analysis, and stoichiometric assays, it has been revealed that diallyl trisulfide interacts with the essential sulfhydryl groups present on both the ACP and the KS domain of FAS, leading to the inactivation of the enzyme. This inactivation of FAS by diallyl trisulfide is a result of affinity-labeling kinetics[76].

3.8 Tannins

Tannins are water-soluble components that are widely present in TCMs and foods. Researches have indicated that both condensed and hydrolysable tannins can effectively inhibit FAS activity[77]. Condensed tannins primarily target the MAT domain, with trimeric condensed tannins inhibiting β-ketoacyl reduction by competing with NADPH, achieving an IC_{50} value of 0.65 μmol/L[78]. Various tannins, such as ellagitannins, casuarinin, gemin G, gemin A, pedunculagin, potentillin, and ellagic acid, exhibit potent inhibitory activity against FAS, with IC_{50} values ranging from 0.21 to 41.4 μmol/L[78-80].

3.9 Fatty acids

Alpha-linolenic acid (ALA) is a polyunsaturated omega-3 fatty acid that is essential for human health. It is not produced by the body, and therefore must be obtained through dietary sources such as flaxseeds, chia seeds, walnuts, and fatty fish. ALA is converted in the body into two other important omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These fatty acids have been found to have numerous health benefits, including reducing inflammation, improving brain function, and reducing the risk of heart disease. The inhibitory effect of ALA on intracellular FAS is found recently[81]. By calculating and determining the binding energy between ALA and palmitic acid with TE domain of FAS, ALA occupies hydrophobic pocket A and forms a broad hydrophobic interaction with several amino acids. The carboxyl group of ALA also forms a salt bridge with the guanidyl groups in TE[81]. Notably, the catalytic triad of Ser2308-His2481-Asp2338 does not play a role in binding ALA to the TE domain. Molecular docking by means of computer simulation show that KS domain of FAS may also be an action site by ALA[82].

Natural FAS inhibitors isolated from TCMs and functional foods are widely distributed in plants. Some representative naturally derived FAS inhibitors are summarized in Figure 2 and Table 2.

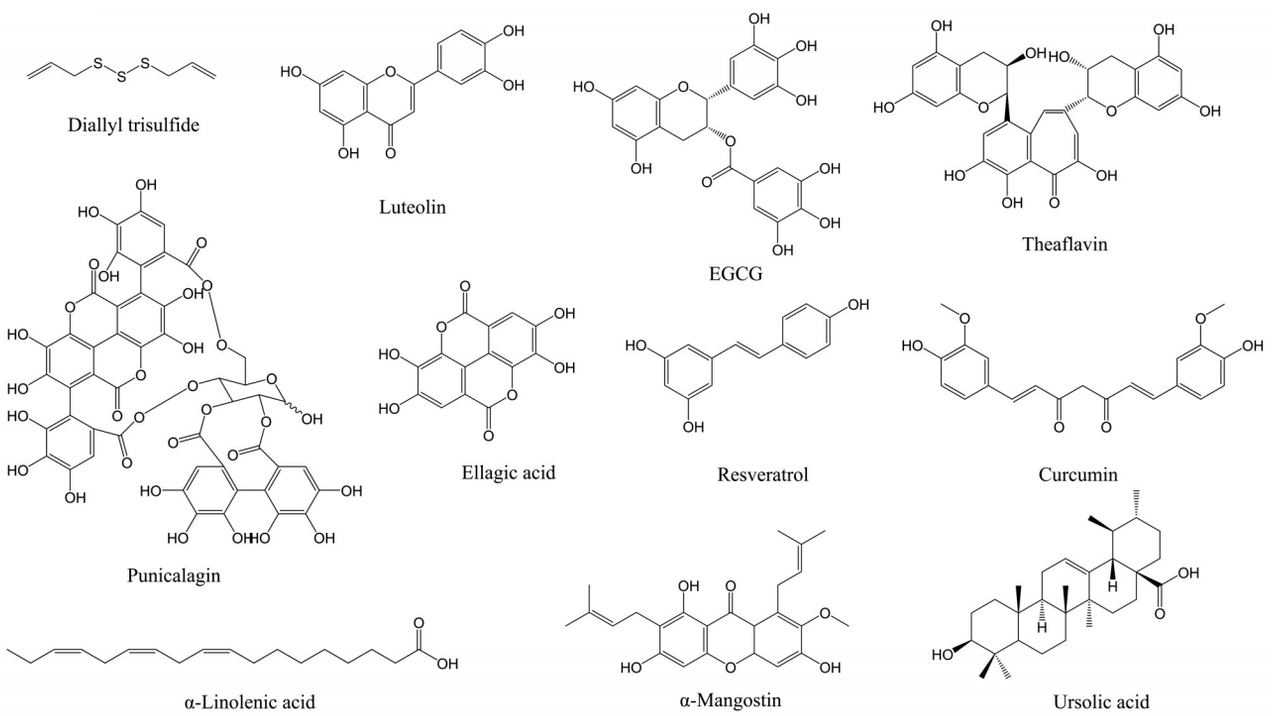

Fig. 2 The chemical structures of representative FAS inhibitors from TCMs and functional foods

Table 2 Representative natural components with FAS inhibitory activity

No.	Compound	Activity (IC_{50})/(μmol·L^{-1})	Resource	Reference
1	Tannic acid	0.14	Oak bark	[80]
2	Vitisin B	0.681	*Iris lactea* Pall	[66]
3	γ-Mangostin	1.24	Mangosteen pericarp	[68]
	Theaflavins	1.77	Black tea	[18]
4	Morin	2.33	Osage orange	[15]
5	Garcinone E	3.30	Mangosteen pericarp	[68]
6	Punicalagin	4.3	*Punica granatum* L.	[74]
7	α-Mangostin	5.54	Mangosteen pericarp	[68]
8	Avicularin	6.15	*Polygonum aviculare* L.	[11]

Continued to Table 2

No.	Compound	Activity (IC_{50})/(μmol·L^{-1})	Resource	Reference
9	Diallyl trisulfide	8.37	Gallic	[76]
10	CG	10.0	Green tea	[17]
11	Amentoflavone	13.0	*Ginkgo biloba*	[14]
12	Ursolic acid	13.16	*Eriobotrya japonica* Thunb.	[73]
13	Curcumin	24.0	*Curcuma longa* L.	[71]
14	β-Mangostin	24.8	Mangosteen pericarp	[68]
15	Emodin	25.0	*Polygonum multiflorum* Thunb.	[20]
16	Luteolin	31.47	*Paspalum conjugatum*	[15]
17	Quercetin	45.6	Apple peel	[15]
18	Resveratrol	48.7	Grape skin	[19]
19	EGCG	52.0	Green tea	[16]
20	Ellagic acid	66.2	Pomegranate	[79]
21	Oleanic acid	68.4	Olive oil	[74]
22	Rhaponticin	73.2	Sea-buckthorn	[67]
23	Baicalein	92.6	*Scutellaria baicalensis* Georgi	[15]
24	Apigenin	138.9	Celery	[15]
25	Kaempferol	165.6	Broccoli	[15]
26	Desoxyrhaponticin	172.6	Sea-buckthorn	[67]

4 Biological activity of natural FAS inhibitors isolated from TCMs and function foods

4.1 Effects of natural FAS inhibitors on adipocytes

FAS plays an important role in the whole life of adipocytes (fat cells). The fatty acids synthesized by FAS are then incorporated into triacylglycerols (TAGs) and stored in lipid droplets within adipocytes. During adipocyte development, FAS plays a critical role in the synthesis and accumulation of TAGs, which are the major energy storage form in adipocytes[83]. FAS expression and activity are tightly regulated by hormonal and nutritional signals, such as insulin and glucose, respectively. In response to insulin, FAS activity is upregulated, leading to increased synthesis and storage of TAGs in adipocytes.

In addition, FAS also plays a role in adipocyte differentiation. Adipocyte differentiation involves the conversion of preadipocytes, which are undifferentiated precursor cells, into mature adipocytes that are capable of storing lipid droplets. During this process, FAS expression and activity increase, leading to the accumulation of lipids in the developing adipocytes.

Furthermore, FAS has been implicated in the regulation of adipocyte size and lipid metabolism. Studies have shown that FAS expression and activity are elevated in obese adipose tissue, which is characterized by enlarged adipocytes and impaired lipid metabolism. Inhibition of FAS activity has been shown to reduce adipocyte size and improve lipid metabolism in obese animals[84]. Since FAS plays a critical role in the regulation of lipid metabolism and adipocyte function, dysregulation of FAS activity has been implicated in the development of obesity and metabolic disorders, making it a potential therapeutic target for these conditions.

As a high active FAS inhibitor, α-mangostin exhibits cytotoxicity that is associated with various apoptotic events, such as an increase in cell membrane permeability, nuclear chromatin condensation, and loss of mitochondrial membrane potential in adipocytes. This cytotoxicity is proven to be linked to the inhibition of FAS activity in cells, which is in turn rescued by the addition of exogenous palmitic acids at concentrations of 50 mmol/L or 100 mmol/L. This indicates that α-mangostin induced apoptosis in 3T3-L1 preadipocytes *via* FAS inhibition. Additionally, α-mangostin is found to suppress intracellular lipid accumulation during adipocyte differentiation and stimulate lipolysis in mature adipocytes, both of which are associated with its FAS inhibitory activity. Moreover, 3T3-L1 preadipocytes

are more vulnerable to α-mangostin induced cytotoxicity than mature adipocytes. These findings suggest that α-mangostin has potential as a preventive or therapeutic agent for obesity[69]. Resveratrol is found to inhibit FAS activity, down-regulate the expression level of FAS, and thus significantly suppress adipocyte differentiation and lipid accumulation in adipocytes[19].

With a strong inhibitory effect on FAS, diallyl trisulfide has also been shown to suppress the differentiation of preadipocytes into adipocytes, thereby reducing the overall number of adipocytes. This is thought to be due to its ability to inhibit the expression of adipogenic transcription factors, which are responsible for promoting the differentiation of preadipocytes into adipocytes. It has been demonstrated that diallyl trisulfide can directly bind to and inhibit FAS activity, thereby reducing the synthesis of fatty acids and the accumulation of fat in cells. This inhibition of FAS has been shown to be dose-dependent, with higher doses of diallyl trisulfide resulting in greater inhibition of FAS activity[76].

During early-stage differentiation, tannic acid, a potent FAS inhibitor, significantly reduces lipid accumulation, but has no effect during mid- and late-stages. Several genes associated with lipid metabolism are identified after tannic acid treating adipocytes. Compared to the control group, mRNA levels of FAS, C/EBPα, and PPARγ are significantly decreased (P<0.05), while mRNA levels of adipsin and ap2 are increased (P<0.05), although *ACC1* and *ACC2* mRNA levels are not affected. Western blot results demonstrate that tannic acid down-regulates the expression of PPARγ, a major factor in preadipocyte differentiation[85].

4.2 Effects of natural FAS inhibitors on cancer cells

Fatty acids are essential components of cancer cell membranes. Overexpression of FAS has been observed in many types of cancer cells and is associated with tumor growth and metastasis. Therefore, natural FAS inhibitors have been extensively studied for their potential anticancer effects. A variety of natural FAS inhibitors have been shown to induce apoptosis in cancer cells by inhibiting FAS activity.

Curcumin is found to induce apoptosis in human liver cancer HepG2 cells, with an IC_{50} value of 8.84 mg/L[86]. It demonstrates a dose-dependent inhibition of intracellular FAS activity and downregulates the expression and mRNA levels of FAS. Furthermore, the apoptotic effect of curcumin on HepG2 cells could be reversed by the addition of sodium palmitate. Treatment with curcumin decreases the levels of the anti-apoptotic protein Bcl-2 and increases the levels of the pro-apoptotic protein Bax in breast cancer cells. As a result, there is a significant increase in the Bax/Bcl-2 ratio, which is consistent with the effects observed with FAS siRNA treatment[86].

As one of the most potent natural FAS inhibitors, α-mangostin induces apoptosis of many cancer cells by blocking the fatty acid biosynthesis. Meanwhile, α-mangostin triggers endoplasmic reticulum (ER) stress and autophagy in human breast cancer cells, which counteracts its apoptotic effects. Interestingly, the end product of the FAS catalyzed reaction, palmitic acid, reverses both the ER stress and autophagy caused by α-mangostin. Inhibition of ER stress and autophagy significantly increases cell apoptosis in response to α-mangostin treatment[87].

ALA is a novel FAS inhibitor and could induce breast cancer cell apoptosis, inhibit the invasion and metastasis, and arrest cell cycle in human breast cancer cells *via* inhibiting FAS[81]. ALA also suppresses the proliferation and invasion in osteosarcoma MG63, 143B, and U2OS cells by down-regulating FAS expression[82].

4.3 Possible mechanisms of action of FAS inhibitors on adipocytes and cancer cells

Targeting intracellular FAS activity can be a potential strategy to prevent or treat obesity and related diseases. In previous study, scientists have demonstrated that many FAS inhibitors isolated from TCMs and foods decreases the viability, arrests cell cycle, and induces apoptosis in human cancer cells by inhibiting intracellular FAS activity and down-regulating FAS expression[43, 82]. In this progress, FAS inhibitors could induce autophagy and ER stress, which are related to the FAS inhibitory effect. The reason why FAS inhibition can activate autophagy and ER stress in cancer cells is still speculative. Among intracellular nutrients, fatty acids play a crucial role in cancer cells, and cancer cells increase their synthesis to maintain growth and proliferation[21]. FAS is the only enzyme known to catalyze the *de novo* synthesis of endogenous long-chain fatty acids and plays an essential role in cell division and intracellular lipid

synthesis[6]. The deficiency of intracellular fatty acid, caused by the inhibition of FAS, stimulates autophagy. Treatment of cancer cells with FAS inhibitors leading to a reduction in the amount of free fatty acids.

FAS inhibitors also induce apoptosis in cancer cells through the modulation of B-cell lymphoma 2 (Bcl-2) family proteins. The Bcl-2 family proteins play a crucial role in regulating the intrinsic apoptotic pathway by modulating the balance between pro-survival and pro-apoptotic signals. Fatty acid synthase inhibitors have been found to increase the expression of pro-apoptotic Bcl-2 family proteins such as Bax, while decreasing the expression of anti-apoptotic Bcl-2 family proteins such as Bcl-2. This shift in the balance of Bcl-2 family proteins towards pro-apoptotic signals results in the activation of caspases and subsequent apoptosis in cancer cells[67, 70].

Additionally, FAS inhibitors are found to induce apoptosis in cancer cells by causing mitochondrial damage. Mitochondria are responsible for generating energy in cells through oxidative phosphorylation, and they play a critical role in apoptosis signaling. Studies have shown that FAS inhibitors can disrupt the normal function of mitochondria, leading to the release of cytochrome c and activation of caspases, which are key players in the apoptotic pathway[81].

In addition, FAS inhibitors induce ER stress in cancer cells, which can also contribute to apoptosis. ER stress is caused by the accumulation of misfolded proteins in the ER lumen, leading to the activation of the unfolded protein response (UPR) pathway. The UPR pathway can either promote cell survival or induce cell death depending on the severity and duration of the stress. FAS inhibitors have been found to induce prolonged and severe ER stress in cancer cells, leading to the activation of the apoptotic pathway through the activation of caspases. The induction of apoptosis in cancer cells through the modulation of Bcl-2 family proteins and the induction of ER stress provides a promising therapeutic strategy for the treatment of cancer using FAS inhibitors[87].

Moreover, FAS inhibitors play an important role in cancer therapy by reducing the intracellular levels of fatty acids, which in turn leads to a decrease in cancer cell invasion and metastasis. By inhibiting FAS activity, these inhibitors disrupt the synthesis of fatty acids, which are essential components for cell membrane structure and function, energy metabolism, and signaling pathways in cancer cells. As a result, cancer cells become more sensitive to chemotherapy and immunotherapy, and are less likely to metastasize and invade surrounding tissues[81-82].

A diagrammatic sketch of the possible mechanisms of FAS inhibitors derived from TCMs and functional foods in the treatment of human breast cancer is shown in Figure 3.

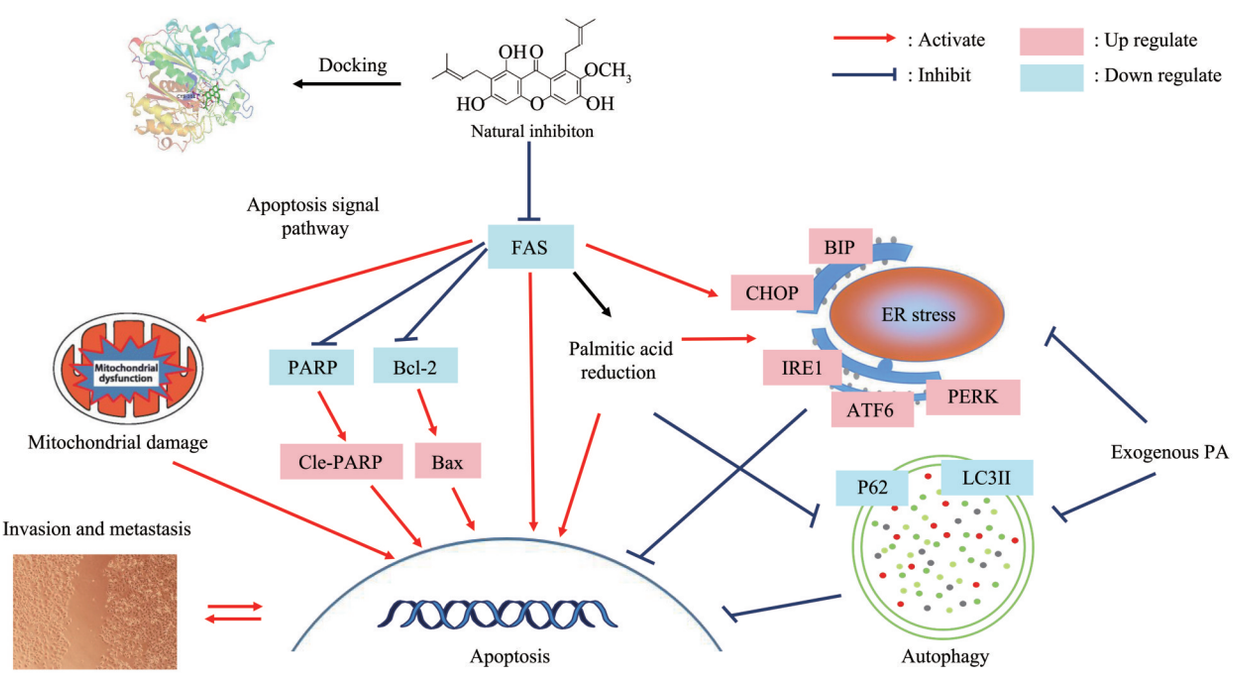

Fig. 3 The possible mechanisms of FAS inhibitors derived from TCMs and functional foods in the treatment of human breast cancer

5 Prospects for the application of natural FAS inhibitors isolated from TCMs and function foods

As mentioned above, a large number of TCMs and functional foods have been found to inhibit FAS activity. The potential use of natural FAS inhibitors derived from TCMs and functional foods is an area of active investigation. With the increasing prevalence of obesity and related metabolic disorders, there is a growing interest in identifying natural compounds that can modulate lipid metabolism and reduce adiposity. Several natural compounds including curcumin, resveratrol, and quercetin have been shown to reduce lipid accumulation in adipocytes, suggesting that they may be useful for the prevention and treatment of obesity.

In addition to their effects on lipid metabolism, natural FAS inhibitors have also been studied for their potential anti-cancer properties. FAS is known to be upregulated in many types of cancer, and inhibition of FAS activity has been shown to induce apoptosis in cancer cells. Several natural FAS inhibitors, including EGCG and ursolic acid, have been found to have anti-cancer activity in preclinical studies.

As a target for drug therapy, the possible side effects of inhibiting FAS are noteworthy and can not be ignored. One question that needs to be addressed is whether FAS inhibitors as a group have any side effects. There is a belief that inhibiting FAS through natural sources of inhibitors does not cause adverse reactions. As mentioned above, numerous reported natural FAS inhibitors are derived from foods, and there is ample evidence of their safety. For instance, green tea, black tea, grape, and garlic have been used for thousands of years, and there have been no reports of toxicity associated with their consumption[17-19, 75]. Another question is what potential side effects inhibiting FAS may have on the human body, as it is a critical enzyme in synthesizing fatty acids *in vivo*. Inhibiting its activity may lead to the inability of the body to synthesize fatty acids. Despite the complexity of the fatty acid biosynthesis process, there are several factors to consider when inhibiting FAS. FAS expression is regulated by diet, and it is only expressed when there is a lack of exogenous fatty acids. There is extensive experimental evidence indicating the safety of inhibiting fatty acid synthase in animals[12, 47]. When FAS activity is partially inhibited, it has no adverse effects on normal physiological activities[12]. Additionally, FAS is highly expressed in adipose tissue and cancer cells, making its regulation more targeted and less impactful on normal tissues[6, 29, 37]. So FAS represents a relatively ideal target for drug therapy.

In summary, the natural FAS inhibitors have shown potent inhibition on FAS with less toxicity, and hold promise in the development for effective and inexpensive therapeutics. These FAS inhibitors offer a versatile approach to inhibiting FAS at three levels: as isolated compounds, crude extracts, and in food. This approach provides several advantages, including ease of application and cost-effectiveness. Overall, the use of natural FAS inhibitors from TCMs and functional foods represents a promising avenue for the development of novel therapeutics for obesity and cancer. However, further research is needed to fully elucidate the mechanisms of action and potential clinical applications of these compounds.

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来源于中药和功能性食品的脂肪酸合酶抑制剂*

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摘要　肥胖症及其相关疾病已成为迫切需要解决的公共卫生问题。脂肪酸合酶（fatty acid synthase，FAS）是一种多功能复合酶，对长链脂肪酸的生物合成发挥至关重要的作用，是治疗肥胖、2型糖尿病、癌症、炎症和心血管疾病等的潜在靶点。在过去的30年里，FAS抑制剂的研究受到越来越多的关注。在中国，传统中药和功能性食品广泛被应用于慢性疾病的预防和治疗，其中有多种天然产物对FAS的活性表现出很强的抑制作用。本文综述了来源于中药和功能性食品中的FAS抑制剂结构和活性特点，为天然来源的FAS抑制剂治疗肥胖症和相关疾病提供了依据。

关键词　脂肪酸合酶，抑制剂，癌症，肥胖，中药，功能性食品
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