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The natural compound dimethylsimmondsin present in jojoba reveals food restricting properties

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Abstract: Obesity has become a serious medical problem in developed countries. Currently marketed anti-obesity drugs have limited efficacy and significant adverse effects, creating a significant need for a new generation of anti-obesity therapeutics. For optimal efficacy, new drugs should aim to both reduce appetite and increase energy expenditure, or at minimum, counteract the reduction in energy expenditure resulting from decreased food intake.

Prevention is often more effective than a cure, and this study proposes a natural method using the Jojoba seed, specifically its simmondsins components, to reduce food intake by activating Cholecystokinin neuropeptide (CCK).

Keywords: Simmondsin, Cholecystokinin, Jojoba, Functional food, Obesity, appetite.

Review: The Jojoba plant is a dioecious evergreen shrub that is native to the deserts of southern Arizona, northwestern Mexico, and neighboring regions. It is known botanically as Simmondsia chinensis, a name assigned to it mistakenly by botanist Link, who had mixed up its seeds with those of a different plant collected from China. The Jojoba plant produces one of the most valuable berries. Its seed is an oblong berry, approximately the size of a hazelnut kernel, with a red-brown outer layer and white interior. The seed has an oily taste that is not disagreeable, according to the earliest references on the plant by Clavigero and Barco. [1,2]

Image 1. Jojoba seed and female plant

The oil derived from Jojoba seeds is unique, it is not a typical oil but rather a liquid ester, which is a yellow liquid wax with a low melting point of 7°C. Unlike vegetable oils, which have several alcohol groups on the molecule and can become rancid due to oxidation, Jojoba consists mainly of fatty acid esters of decyl alcohol, which contain two double bonds in each constituent molecule, making it resistant to oxidation. Notably, early research has revealed that Jojoba nuts contained about 50% liquid oil with analytical characteristics similar to sperm whale oil. [3]

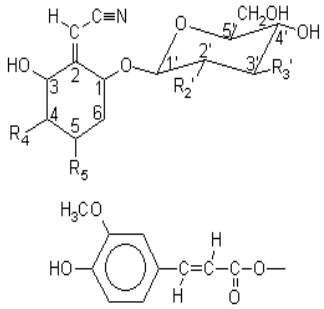
Esters	**Percentage**
Composition	
C34-C36	0.2
C38	6.6
C40	30.2
C42	50.9
C44	9
C46-C50	0.9
Properties	
Melting Point (ºC)	9
Density (g/ml)	0.862
Iodine value (g/100g)	83
Acid value	0.36
Viscosity (cSt)	26.6
Moisture (%)	0.03
Flash point (ºC)	225
CFPP (ºC)	10
Oxidation stability (h)	41.3

Table 1. Composition and properties of jojoba oil

Jojoba has multiple culinary and medicinal benefits. The oil derived from its seeds is commonly used in salads as a substitute for olives, and the seeds themselves can be consumed raw or roasted. Historically, it has also been used to treat conditions such as the suppression of urine caused by mucous concretions and to facilitate childbirth. Additionally, jojoba is known for its beneficial properties for skin and hair health, as well as its hydrating and anti-inflammatory effects. [4]

After extracting the oil from Jojoba seeds, the residue left behind is known as Jojoba meal or Jojoba flour. In addition to being eaten by animals, the leaves and fruits of the Jojoba plant are also a traditional food source for indigenous communities. These communities roast and grind the seeds, mixing them with hard-boiled egg yolks to make a coffee substitute. After extracting oil, a by-product (more less 50% in weight) has potential value as livestock feed, especially in arid areas where such feeds are scarce. Jojoba meal is rich in protein (about 30%), fiber, and carbohydrates. While its protein content has a good amount of lysine, the methionine content is low. However, the use of Jojoba meal as animal feed is currently uncertain due to the presence of four unpalatable compounds known as simmondsin. Subsequently, microbial processes were developed in order to reduce the amount of simmondsin to a level where it can be safely consumed by animals without affecting their appetite [5].

There is a major problem associated with incorporating jojoba meal into animal diets. When laboratory mice were fed jojoba meal, they stopped eating and eventually starved to death. This led to further investigation, which ultimately revealed that Simmondsin, a compound found in jojoba meal, could contain cyanide and be toxic at certain concentrations [6]. The jojoba bean contains 2 glycosides with toxic effects: simmondsin [2-(cyanomethylene)-3-hydroxy-4,5-dimethoxycyclohexyl-D- glucoside] at 2.3% and simmondsin-2'-ferulate at 1% [7], but simmondsin are not cyanogens, because the cyano group cannot be eliminated as hydrogen cyanide by lack of a hydrogen atom in alpha position (the alpha carbon atom is tetra-substituted). There are no indications that HCN causes the food intake reduction on weight loss after simmondsin intake in rats. [8]



trans ferulic acid moiety

$R_{2'}$ = H	$R_{3'}$ = OH	R_4 = OCH_3	R_5 = OCH_3	simmondsin
$R_{2'}$ = H	$R_{3'}$ = OH	R_4 = OH	R_5 = OCH_3	4-demethylsimmondsin
$R_{2'}$ = H	$R_{3'}$ = OH	R_4 = OH	R_5 = OH	didemethylsimmondsin
$R_{2'}$ = fer. ac. moiety	$R_{3'}$ = OH	R_4 = OCH_3	R_5 = OCH_3	simmondsin 2'-trans-ferulate
$R_{3'}$ = fer. ac. moiety	$R_{2'}$ = OH	R_4 = OCH_3	R_5 = OCH_3	simmondsin 3'-trans-ferulate
$R_{2'}$ = fer. ac. moiety	$R_{3'}$ = OH	R_4 = OCH_3	R_5 = OH	5-demethylsimmondsin 2'-trans-ferulate
$R_{2'}$ = fer. ac. moiety	$R_{3'}$ = OH	R_4 = OH	R_5 = OCH_3	4-demethylsimmondsin 2'-trans-ferulate

Image 2. Simmondsins and ferulates

It's important to be cautious about using simmondsin as an emaciation product for human consumption because commercial preparations may contain other types of simmondsin besides dimethylsimmondsin. Even if formulations are prepared using pure dimethylsimmondsin, it may have inhibitory effects on both food intake and angiogenesis, making it unsuitable for pregnant women or children. [9,10]

Previous studies have described the food intake control properties of orally administered 4, 5-dimethylsimmondsin and its ferulate present in jojoba meal. In the 1990s, it was discovered that simmondsin acted as a hunger satiation ingredient, which allowed for the reinterpretation of earlier experiments with mice and cattle fed diets supplemented with jojoba meal. Rather than being toxic, the ingredient satisfied the animals' hunger, leading to a decline in feed intake. As a result, researchers are exploring the possibility of using simmondsin as a safe appetite suppressant.

Cholecystokinin: One of the first gut hormones involved in the control of appetite is cholecystokinin (CCK). CCK is an important neurointestinal peptide hormone produced by endocrine cells primarily in the upper part of the small intestine. CCK plays multiple regulatory roles in many target organs and tissues. Plasma CCK levels significantly increase after consuming a meal containing a high amount of fat and protein. CCK also alters appetite. Gibbs et al. (1973) first demonstrated a dose-dependent effect of exogenous CCK in reducing food intake in rats and monkeys. [11,12]

This effect occurred without evidence of toxicity and was specific to food intake, as CCK had no effect on water intake in water-deprived rats. This finding was subsequently confirmed in humans, where an intravenous infusion of the terminal octapeptide of CCK reduced meal size and duration. The reason why Simmodsina acts as an inhibitor is precisely due to CCK neuropeptide that is activated and sends a signal to the brain of satiety. Thus, food intake is reduced because the individual feels satisfied or satiated with the food intake. [13]

Simmondsin may reduce food intake by affecting the cholecystokinin (CCK) pathway. The acute toxicity of simmondsin is low, and it does not cause any pathological changes. However, the food intake reduction is temporary and returns to normal once simmondsin is removed from the diet. Although two different peripherally acting CCK-A receptor antagonists, 2-NAP and devazepide, do not fully eliminate the anorexic effect of simmondsin, it appears that some physiological effects of simmondsin are CCK-A receptor dependent. The findings of these experiments suggest that simmondsin reduces food intake by stimulating CCK receptors either directly or indirectly. In rats, simmondsin administration orally induces a dose-dependent decrease in food intake, which can be counteracted by the i.p. injection of devazepide, a specific antagonist of CCK receptors. [14]. In the past, Glaxo Smith Kline collaborated with a CCK1R agonist (GI-181771) that was found to promote significant weight loss after 8 weeks in a Phase II trial conducted in 2002. However, the small therapeutic window and side effects such as nausea and vomiting led to the discontinuation of GI-18177 [15]. Given this background, the potential inclusion of simmondsin in future work should be evaluated with caution.

Although jojoba has been utilized for its medicinal properties by indigenous people for centuries, there has been limited research on the effects of simmondsin on humans, with only anecdotal evidence available. Nonetheless, jojoba remains a valuable source of molecules that modulate angiogenesis. [16]

In the 1990s, Kalman et al. from Miami Research Associates investigated the effects of 40 and 120mg/day of simmondsin on 31 healthy obese subjects for 4 weeks. Both groups experienced weight loss and a decrease in

caloric intake, with no significant adverse events reported. [17]

A recent unpublished study conducted in Pamplona, Spain, has found that the combination of chocolate, Spirulina, and Jojoba seed presents a promising opportunity to create a novel and effective anti-obesity product. This blend of natural ingredients offers a synergistic effect that can help combat metabolic syndrome, which is not achievable with single-component treatments. When combined, the unique properties of each component are enhanced, resulting in a more potent therapeutic agent that can reduce food intake and increase energy expenditure. In particular, the simmondsin components in Jojoba seed activate the Cholecystokinin neuropeptide (CCK), which leads to reduced food intake. The study revealed that consuming a bonbon containing this blend of ingredients 30 minutes before meals resulted in an average weight loss of 1.012kg per week, 0.694kg of them were fat. These findings suggest that the combination of chocolate, Spirulina, and Jojoba seed could be a promising solution to address the growing problem of obesity.

Conclusion: The issue of obesity is a major health concern that calls for effective anti-obesity medications. However, current drugs have limited effectiveness and notable adverse effects, underscoring the need for the development of novel therapeutic approaches. This research suggests a natural solution utilizing simmondsin compounds found in Jojoba seeds to stimulate CCK and decrease food consumption, which could provide a potential remedy to this escalating problem. To validate the appetite-reducing properties of jojoba as a CCK activator, it would be highly valuable to conduct human trials. Jojoba seed with other components, as spirulina, can be developed as an interesting Functional Food.

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