Effect of H. sabdariffa Extract on Obesity

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H. sabdariffa derived bioactive compounds are potent in the treatment of obesity with an evident reduction in body weight, inhibition of lipid accumulation and suppression of adipogenesis through the PPARγ pathway and other transcriptional factors.

H. sabdariffa | Obesity | Weight | H. sabdariffa Extracton

1. Effect of H. sabdariffa Extracton (HSE) Body Weight

As aforementioned, obesity can be characterized by chronic energy imbalance and excessive body weight [1][2]. This disruption in energy homeostasis results in abnormal adipocyte differentiation, which is characterized by hyperplasia and hypertrophy of adipocytes [3]. The potentiality of polyphenols in *H. sabdariffa* to regulate energy metabolism and its beneficial effect on lipid management and weight loss as studied by several authors will be examined in this section.

Villalpando-Arteaga et al. [4] reported a reduction in body weight in relation to inhibition of fat accumulation of obese C57BL/6NHsd mice after treating with 33 mg/kg three times a week for 8 weeks. Impressively, Alarcon-Aguilar et al., [5] recorded a 9.6% decrease in body weight of obese Monosodium glutamate (MSG) mice with daily administration of 33.64 mg/kg/day for 8 weeks. A significant shift in body weight was noticed from the 7th week, which was attributed to a reduction in food with a consequent increase in liquid intake.

Herrara-Arellano et al., [6] who also reported a similar observation, attributed this result to the diuretic effect of *H. sabdariffa*. In spite of these observations, the author suggested that further long-term toxicity studies should be performed on this plant, especially since the previous study by Akindahunsi and Olaleye [7] have identified in their study that prolonged usage of this extract at a 15-dose level caused liver injury while the effect was mild at small dose levels (1–10). Carvajal-Zarrabal et al., [8] also reported that HSE administered at concentrations of 5% to 15% was effective in body weight reduction at intermediate and greater concentrations of 10% and 15% used in their experiment. In vitro and in vivo studies showed that HSE (or tea) inhibited the activity of a-amylase, blocking sugars and starch absorption, which may assist in weight loss [9][10]. Overall, in most studies, the ability of HSE to reduce body weight was attributed to *H. sabdariffa* polyphenols and flavonoids, through the inhibition of fat accumulation [5][4].

2. Effect of HSE on Lipid Accumulation, Cholesterol Metabolism and Plasma Parameters

Other factors are also involved in causing the onset of obesity. The major mark of obesity is abnormal or excessive fat accumulation in adipose tissue. The amount of excess fat in absolute terms, and its distribution in the body—either around the waist and trunk (abdominal, central or android obesity) or peripherally around the body (gynoid obesity) have important health implications [11]. The effect of *H. sabdariffa* on weight loss in early studies prompted further studies on its effect on lipid profile. Quite a number of studies have emphasized HSE as having an effect on inhibiting and/or reducing fat accumulation.

Bioactive compounds (polyphenolic and flavonoids) in *H. sabdariffa* have been reported to decrease oxysterols (a derivative cholesterol) in bile acid metabolism and block lipid accumulation in the liver [12]. In a study conducted by Carvajal et al., [8] on the modulation of fat absorption in rats by HSE, it was reported that HSE modulated fat absorption by increasing palmitic acid excretion in feces, accompanied by a decrease in triglycerides and cholesterol levels, including low-density lipoproteins (LDL) cholesterol. Another study carried out to evaluate the effects of HSE powder on the lipid profiles of individuals with and without metabolic syndrome (MS) showed that HSE significantly reduced glucose and total cholesterol levels, increased HDL levels, and triglycerides/HDL ratio in patients with MS [13]. In cholesterol-fed rabbits and high fructose-fed rats, HSE also decreased the number of oxidized LDL positive foam cells and total cholesterol and triglycerides concentrations in plasma [14]. According to Morales-Luna et al., [15], it was reported that 22.5 mg aqueous HSE of the white variety of Roselle prevented the increase in body weight of rats that were fed a high-fat fructose diet.

A more recent study investigated the effect of HSE in the reduction of fat tissue accumulation in high fat diet-induced obese C57BL/6NHsd mice [4]. A high-fat diet (HFD), along with reduced physical activity, induces excessive storage of triglycerides in adipocytes that leads to hypertrophy of the adipose tissue (AT). The study reported that HSE greatly diminished the accumulation of fat in the cytoplasm of hepatocytes. A significant reduction ($p < 0.05$) was observed in the gene expression of both transcription factors PPARγ and SREBP-1c in obese mice supplemented with HSE compared to obese mice. These authors claimed that HSE regulated the lipid homeostasis through SREBP-1c and PPARγ inhibition by blocking the increase of IL-1, TNF-α mRNA and lipoperoxidation and increased catalase mRNA; counteracting liver damage in an agonist-dependent manner. Hence, they concluded that HSE possesses an anti-steatogenic effect in the liver besides the anti-lipidemic and anti-obesogenic effects in the HFD-induced obese mouse model. Considering that fat accumulation is highly associated with obesity, accumulations of fat in organs have been a major concern in obesity management.

In liver steatosis, the anti-steatogenic effect of HSE on fatty liver (caused by fat accumulation in the liver) was recently conducted on humans. A clinical study conducted on patients with fatty liver within the age of 18–65 revealed that 2 HSE capsule-dose (1 g) after meals, 3 times a day significantly reduced the level of serum free fatty acid (FFA), exerting a beneficial effect on metabolic regulation, while improving the liver steatosis. However, this study observed no significant difference in the lipid profile except for FFA [16]. Furthermore, it was inferred in this study that polyphenol was mainly responsible for the clinical effect of HSE capsule and hence an increase in its dose could be more effective. A dose-dependent decrease in triglycerides levels, fatty acid concentrations and cholesterol contents of plasma lipids and liver lipids were observed in an in-vivo study of high-fat induced male Syrian hamsters fed with HSE [17]. HSE effectively inhibited lipid accumulation from fat-feeding and decrease the

cholesterol in plasma and organs (liver) [17]. Affirmatively, these authors also attributed the effects observed in HSE-fed hamsters to the presence of polyphenols in HSE. Clinical studies on patients with metabolic syndrome, an obesity-associated disorder, further supported arguments of previous reports that polyphenols may be responsible for the therapeutic effect in HSE [18].

Based on these studies, it can be inferred that the presence of natural bioactive compounds such as polyphenols, flavonoids, and organic acids in HSE could be used as a preventive therapy in combating fat-induced obesity.

3. Inhibitory Effect of HSE on Pancreatic Lipase

Another strategy that has been proposed for the treatment of obesity is to inhibit pancreatic lipase, which consequently decreases lipid absorption in the intestine [19]. The underlying concept is that for any dietary fat being absorbed in the human intestine, the fat should be broken down enzymatically by the action of pancreatic lipase [20]. Pancreatic lipase activity is therefore widely considered as one of the most important indicators for the determination of the anti-obesity potential of natural products [21]. Orlistat, a potent, specific, and irreversible inhibitor of pancreatic and gastric lipases, is a weight-loss agent with a novel mechanism of action for the treatment of obesity. It inhibits gastric and pancreatic lipases in the lumen of the gastrointestinal tract to decrease systemic absorption (30%) of dietary fat [22]. However side effects such as diarrhea, fecal incontinence, flatulence, bloating and dyspepsia are commonly developed [23]. Due to these adverse effects, there has been a long-standing interest in discovering well-tolerated natural inhibitors for nutrient digestion and absorption.

The potential inhibitory activity against pancreatic lipase was also reported by examining the effect of HSE on fat absorption-excretion and body weight in rats [8]. Thus, continuous administration of *H. sabdariffa* polyphenols might improve obesity-related metabolic disorders in a similar manner to orlistat [24]. While this action may be viewed as a potential strategy in obesity management, its mechanism in obesity therapy is yet to be explored.

4. Effect of HSE on Adipocyte Differentiation (Adipogenesis)

Adipogenesis is the process by which cells differentiate into adipocytes. This process involves the conversion of preadipocytes into mature adipocytes with intracellular lipid accumulation [25]. Adipocytes are cells that primarily compose adipose tissue, specialized in storing energy as fat [26]. They play an important role in regulating adipokine secretion which promotes adipogenesis. Therefore, understanding the molecular mechanisms that regulate adipogenesis is important for exploring anti-obesity therapy [27].

Adipocyte differentiation is a critical phenomenon in the development and progression of obesity [28]. Adipocyte differentiation has been reported to be mainly mediated by the transcription factors PPARγ and C/EBPα [25]. These adipogenic transcription factors that are implicated to activate a number of genes induced during adipocyte differentiation is a master regulator of adipogenesis [29][30][31]. Hence, a down-regulation of PPARγ and C/EBPα has been viewed as a strategy to obstruct adipogenesis in adipocytes. Several studies have reported that extract of various medicinal plants attenuates expression of PPARγ and C/EBPα [32][4][33][34][35][36].

So far, only a few studies have reported and confirmed the effect of HSE on adipocyte differentiation. Kim et al., [37] first reported the effect of HSE treatment on adipocyte differentiation from 3T3-L1 preadipocytes and found that HSE blocked adipogenesis, possibly mediated through the suppression of adipogenic transcription factor expression. HSE treatment (100 mg/mL) inhibited the expression of major adipogenic transcription factors PPAR-γ and C/EBP-α, nuclear hormone receptors that regulate adipogenesis during differentiation. The authors further stated that this inhibitory effect of HSE on the transcription factors was target specific [37]. Further studies by Kim et al. [32], also confirmed that HSE can inhibit the adipogenic transcription factors by blocking the MAPK-mediated signaling pathway during adipocyte differentiation. They reported that HSE significantly decreased the mRNA levels of leptin (a hormone predominantly made by adipose cells that helps to regulate energy balance) during differentiation. Hence, suggesting that the effect of HSE on adipocyte differentiation was also mediated by the regulation of leptin [32].

A recent study performed on 3T3-L1 pre-adipocytes cells revealed that *H. sabdariffa* aqueous extract and *H. sabdariffa* polyphenols at concentrations 500 µg/mL and 10 µg/mL significantly inhibited adipogenic differentiation of pre-adipocytes [38]. These authors concluded that polyphenols contained in *H. sabdariffa* are mainly accountable for its effect on adipogenesis. Kao et al. [17], also showed that *H. sabdariffa* polyphenolic extract (HPE) was more efficient in suppressing adipogenesis than HSE as markers of adipocyte differentiation, while SREBP 1 was found to decrease in a concentration-dependent manner following treatment with both HSE and HPE. The authors reported in their study that after inducing maturation of preadipocyte, HPE suppressed the adipogenesis of mature adipocyte cells. This corroborates with the previously reported findings that polyphenols are the major active components in HSE that are responsible for its anti-obesogenic effect.

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