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Advances in the Management of Obesity and Type 2 Diabetes Mellitus: Recent Studies of Non-Medicinal Agents



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Abstract

The prevalence of obesity and related metabolic disorders, particularly type 2 diabetes mellitus, is rising worldwide at an alarming rate. These used to mainly affect adults and older adults and were more prevalent in certain geographic regions; however, recent data confirm that a significant number of children and adolescents across the globe are also affected. Modern medicine has significantly improved in offering either medicinal and/or medical procedures to combat these health threats. At the same time, alternative and traditional medicine have also generously helped in the management of such disorders. In this paper, we summarize advances from the past 5 years in the applications of non-medicinal agents for the treatment and/or prevention of obesity and related metabolic disorders (particularly type 2 diabetes mellitus). In particular, the roles of anti-inflammatory, whole-food, and plant-based food diets, along with selected phytochemicals, certain gut bacterial species, and others are discussed.

Keywords: Obesity; Type 2 Diabetes; Diets; Phytochemicals; Insulin; Glucose

Abbreviations: BMI: Body Mass Index; CRP: C-Reactive Protein; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; IL: Interleukin; LDL-C: Low Density Lipoprotein Cholesterol; T2DM: Type 2 Diabetes Mellitus; TNF: Tumor Necrosis Factor; WHO: World Health Organization; OFIF: Opuntia Ficus Indica Fruit; KB: kukoamine B

Introduction

The World Health Organization (WHO) updated its report on global body weight concerns on May 7, 2025 to emphasize that the prevalence of “unhealthy” weight is increasing at an alarming rate [1]. In 2022, 12.5% of the world’s population was identified as obese. Since 1990, adult obesity rates have doubled worldwide [2]. More troublesome is the fact that this rate was quadrupled

among adolescents. For adults with “unhealthy” weight in 2022, 2.5 billion were overweight and 890 million were obese. In 2024, 35 million children were overweight by the age of 5; while in 2022, 390 million children and adolescents aged 5-19 were overweight, and 160 million were obese [1]. The increased rates in “unhealthy” weight have been associated with increased rates of type 2 diabetes globally [2]. The main biochemical mechanism

of increased blood glucose levels (hyperglycemia) relates to interruptions in the clearance of blood glucose [3]. While in healthy individuals, skeletal muscle and adipose tissue efficiently contribute to the removal of glucose from blood (through glucose transporter 4 system) in response to insulin, this mechanism is impaired for the overweight and obese [4]. In addition to this mechanism, impairments in other pathways caused by “unhealthy” weight may also significantly contribute to the development of insulin resistance and type-2 diabetes.

WHO still recommends the application of Body Mass Index (BMI) numbers to define overweight and obesity states; in this system, adults with a BMI of >25 and <30 are categorized as “overweight,” while those adults having a BMI of greater than 30 are categorized as obese [1]. The principal reason for developing these “unhealthy” weight conditions is the accumulation of adipose tissue in the body. It is now well established that obesity is associated with an increased risk of several metabolic disorders such as cardiovascular disease, type 2 diabetes mellitus (T2DM), reproductive system disorders, impaired bone metabolism, sleep problems, and others that collectively reduce quality of life in affected individuals [5,6].

Over the past decade, significant advances have been made in the management of such chronic disorders with modern medicine. In parallel, alternative and traditional medicine have also expanded their contributions. Many phytochemicals and botanical remedies have been tested and promoted against obesity and T2DM.

This article presents a summary and discussion of studies published over the past 5 years (2020-2025), pertaining to the application of non-medicinal approaches in the management of obesity and T2DM.

Experimental Studies

In its August 2025 issue, Nature Communication reported the effectiveness of *Phaleria nisidai* extract against T2DM [7]. The leaves of this plant have traditionally been used for tea. This study reported that genkwanin glycosides from these leaf extracts are responsible for antidiabetic effects observed in both in vivo and in vitro settings. The investigators showed that in male mice with diet-induced obesity, the extract significantly improved insulin sensitivity and glucose uptake in adipose tissue. In in vitro studies using murine and human adipocytes, the investigators observed increased glucose uptake by these cells in response to treatment with the leaf extract. The mechanism of these effects was reported to be through the upregulation of Glut1 expression via PKC-ERK1/2 signaling.

Another article published in August 2025 in Journal of Biological Chemistry reported glucose modulating effects of andrographolide in a mouse model of Alzheimer’s disease with diet-induced obesity [8]. A dose of 2 mg/kg of andrographolide 3 times weekly for 16 weeks prevented the effects of high-fat diet on

glucose metabolism. This treatment was associated with reduced glucose oxidation and ATP production. The effects of opuntia Ficus-indica fruit (OFIF) on obesity, insulin resistance, and diabetes were tested in a diet-induced obesity mouse model. The addition of OFIF resulted in improvements in glucose tolerance and insulin sensitivity as assessed by HOMA-IR. These changes were accompanied by increased expression of insulin receptors in adipose and hepatic tissues. Furthermore, overall reductions in markers of oxidative stress and inflammation were observed in the hepatic and adipose tissues of OFIF-treated mice. These changes were associated with beneficial modifications in the abundance and diversity of fecal bacteria.

The anti-obesity effects of an ethyl-amide derivative of oleanolic acid-derived triterpenoids, 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acids have been investigated in a diet-induced obesity mouse model [9,10]. The anti-obesity effect was associated with reduced energy intake along with reductions in serum levels of glucose and insulin in the high-fat-diet-treated animals. Interestingly, these researchers observed that prevention of weight gain was limited only to the high-fat-diet group. The anti-obesity effects of *kukoamine B* (KB), a major component of the *Lycii Radicis Cortex* were tested in ovariectomized and high-fat diet-induced obese mice [11]. The treatment with KB was associated with a dose-dependent reduction in lipid droplet formation along with downregulation of adipogenesis-related genes, including Pparg, Cebpa, Srebp1, Fasn, and Plin2. Furthermore, KB treatment significantly decreased the expression of adipogenic factors, such as phosphorylated CREB, CEBPB, PPARG, and CEBPA. These changes were accompanied by reduced body weight gain, hepatic steatosis, and adipocyte hypertrophy. The investigators suggested that KB merits further investigation in the management of obesity.

Raw and fermented chickpea extracts were tested for their potential anti-adipogenic and anti-obesity properties, using 3T3-L1 pre-adipocyte cells [12]. The cells treated with fermented extract had lower lipid accumulation, along with downregulation of adipogenesis-related genes. These *in vitro* findings were further supported by *in vivo* studies in which the diet-induced obese mice treated with the fermented extract had reduced weight gain and lower amounts of adipose tissue, plus improved serum cholesterol, triglycerides, and glucose levels. Ganoderma resinaceum-derived resinacein S positively impacted thermogenesis in a mouse model of diet-induced obesity [13]. This effect was associated with inhibition of weight gain in mice fed a high-fat-diet. These effects were mediated through the expression of thermogenic genes and related proteins, such as uncoupling protein 1 and mitochondrial biogenesis, by activating the AMPK-PGC1 α signaling pathway. In particular, this study reported that Res S may promote brown adipose tissue activation and browning of inguinal white adipose tissue, improving glucose and lipid homeostasis. Similar effects on brown fat, body weight gain, and glucose hemostasis were observed when the mice were treated with radish seed extract and its major phytochemical sulforaphane [14].

The effects of coumarin-derived aesculetin were tested in rats treated with high-fat-diet and streptozotocin [15]. The treatment with aesculetin was associated with decreased body weight, lower HbA1c and cholesterol levels, along with increased insulin secretion. These changes were accompanied by improvements in the renal and hepatic function and prevention of cardiac tissue injury. It was suggested that these beneficial effects were most likely mediated through enhanced endogenous antioxidant capacity and reduced inflammation. Treatment of diet-induced obese mice with *Pleurotus ferulae* extract over 8 weeks resulted in reduced weight gain and adipose tissue accumulation [16]. These changes were accompanied by reduced serum total cholesterol and low-density lipoprotein cholesterol levels. Additional in vitro studies using 3T3-L1 adipocytes showed that the extract can inhibit adipocyte differentiation and lipid accumulation by downregulating key adipogenic transcription factors, such as PPAR γ and C/EBP α , plus related genes involved in fat synthesis and storage, including Fabp4, Fasn, and Scd1.

Clinical Studies

A randomized clinical trial involving 169 adults with T2DM were assigned to groups receiving either standard medical care (n=90) or a whole-food plant-based diet with exercise (n=79) for 24 weeks [17]. Parameters pertaining to glycemic control (HbA1c, glucose, insulin, and HOMA-IR), serum lipids, and C-reactive protein were measured. This study concluded that a whole-food plant-based diet in combination with exercise was more effective for improving glycemic control than standard medical care. Additional benefits in regard to medical management of diabetes and cardiovascular medications were also noted in the diet-lifestyle group. Therefore, lifestyle changes including whole-food plant-based diets and regular physical exercise may be an effective approach in the management of chronic diseases.

The addition of 8.5g D-allulose to the diabetic diets resulted in improved postprandial hyperglycemia in patients with T2DM as compared with a strictly energy-controlled diabetic diet [18]. This effect was speculated to be related to increased endogenous pancreatic insulin secretory capacity owing to reduced insulin requirement. In a double-blind, randomized, cross-over clinical trial, the combination of diets moderate in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs), and metformin resulted in beneficial changes in the gut microbiome plus postprandial glycaemia in 26 subjects with prediabetes [19]. The investigators suggested that increased GLP-1 secretion plus increased *Butyricimonas virosa* abundance may play a role in reduced postprandial glycaemia in these subjects.

Eighty-one young-adult subjects were enrolled in a two-arm randomized controlled trial to investigate the effects of an energy-reduced anti-inflammatory diet on liver function over a 6-month period [20]. The consumption of the calorie-restricted anti-inflammatory diet was associated with significant reductions in

weight loss (7%), visceral adiposity (22%), HOMA-IR (15%), total cholesterol (5%), LDL-C (5%), triglycerides (12%), hs-CRP (29%), IL-6 (16%), and TNF- α (34%), plus significant improvements in liver function markers. This study concluded that anti-inflammatory diets may effectively prevent complications associated with “unhealthy” weight. Similar observations were noticed in 74 women and 7 men with obesity who consumed anti-inflammatory diets over 24 weeks [21]. Observations from these 2 independent studies endorse the beneficial effects of anti-inflammatory diets in weight management and related metabolic abnormalities impacting the liver, cardiovascular, and metabolic systems.

Fifty-four newly diagnosed male (n=26) and female (n=28) subjects with impaired fasting glucose were randomly divided into treated (n=27) or placebo (n=27) groups [22]. The treated group received diets supplemented with of *Cynara scolymus* extract containing chlorogenic acid and dicaffeoylquinic acid derivatives. Compared with the placebo group, the treated group showed significant improvements in markers of oxidative stress, inflammation, serum lipids, insulin, glycated hemoglobin, and waist circumference. These data suggest consumption of *Cynara scolymus* extract may help with the prevention of metabolic disorders, including T2DM.

Closing Remarks

Appropriate lifestyle and diet play a crucial role in maintaining health and optimal physiological function. Therefore, these measures could be among the first-line practices for the prevention and/or treatment of mild non-communicable chronic disorders, including “unhealthy” weight and associated conditions such as T2DM, cardiovascular disease, dyslipidemia, and others. Otherwise, the use of medicinal treatments and/or other medical procedures should be advised by practicing healthcare providers. Many patients and their relatives may prefer the use of approved non-medicinal agents and natural health products over conventional medications, provided that their conditions can be managed by such agents. The literature increasingly reports the effectiveness of various diets, dietary agents, phytochemicals, and plant extracts in the management of obesity and related T2DM. These agents may produce therapeutic effects through several distinct but interrelated mechanisms such as antioxidant, anti-inflammatory, and microbiome-modulating pathways. While they may deem effective in the management of symptoms, they may also produce adverse or toxic effects. Therefore, all subjects are strongly advised to avoid self-treatment and to consult with their health care professionals, including registered dietitians, before consuming any natural health products, phytochemicals, or nutraceuticals, and before making major modifications to their dietary habits. The risk for experiencing unwanted and/or toxic effects is significantly higher in specific groups of subjects such as pregnant and lactating women, children and adolescents, cancer

patients and other patients with compromised immune systems, as well as older adults.

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