

## Obesity – Can *Allium fistulosum* L. be a remedy?

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### Abstract

Obesity is one of the major problems facing human beings at present. Because of the consumption of refined sugar and foods rich in carbohydrates, as well as adoption of a more sedentary lifestyle (often by necessity as is the case with most office workers), people in all countries are increasingly getting obese, which in turn is leading to other disorders like diabetes and cardiovascular complications. Existing conventional drugs have adverse side-effects, which is the major cause for scientists to look towards the plant kingdom for discovery of newer drugs with less or no side-effects. The *Allium* genera of plants are widely known for their medicinal properties, in particular *Allium cepa* (onion) and *Allium sativum* (garlic), whose beneficial actions include anti-obesity effects. In this mini review, we examine a lesser known plant of the *Allium* genera, namely *Allium fistulosum* L. and review its anti-obesity potential. The conclusion of the present study is that the plant contains phytochemicals like ferulic acid and quercetin, which possess anti-obesity mechanisms of action thus rendering the plant to be of potential use against obesity.

**Key words:** obesity; adipose tissue; ferulic acid; quercetin; *allium fistulosum*

### Introduction

Obesity and overweight has been defined by World Health Organization (WHO) “as abnormal or excessive fat accumulation that may impair health”. The WHO factsheet of June 9, 2021 puts forth some statistics on obesity, which indicates a tripling of obese persons in the world since 1975; among people 18 years of age or older, more than 1.9 billion adults were overweight in 2016 with 650 million obese persons; these numbers in 2016 indicated that 39% of the world population were overweight and 13% suffered from obesity; 39 million children were obese or overweight in 2020; and over 340 million children and adolescents of the world aged 5-19 years were obese or overweight in 2016. The ironic part of the situation is that in countries with the most obese or overweight people, more people die of being obese than from malnutrition [1].

According to WHO “body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m<sup>2</sup>)”. Also, according to WHO, a BMI of 25 or more in adults is classified as overweight, and a BMI of 30 or more is classified as obesity [1]. The rapid rise in the numbers of obese and overweight persons is generally attributed to increased intake of foods that are high in fat and refined sugar, and a more sedentary lifestyle consisting of less outdoor activity and more armchair office and home activities. Foods that are high in fat and refined sugar may be sugary drinks, pizzas, white bread, fruit juices, sweetened breakfast cereals, pastries, cookies or

cakes and fried, grilled or boiled food [https://www.healthline.com/nutrition/20-foods-to-avoid-like-the-plague#TOC\_TITLE\_HDR\_7].

As per WHO, the risk of non-communicable diseases increases with BMI. These diseases include cardiovascular diseases [2], diabetes [3], musculoskeletal disorders (like osteoarthritis) [4], and cancers including endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and colon cancers [5]. Increased waist circumference of more than 40 inches in men (35 inches in women) is known as visceral adiposity and can be a cause for danger even though BMI is at normal level.

Pro-inflammatory cytokines are closely linked with obesity. A cross-sectional study comprising of 117 obese patients with a body mass index of 30 or above and 83 non-obese volunteer persons found that general obesity was closely linked with various interleukins (IL) like ILs 5, 10, 12, and 13 along with interferon- $\gamma$  (IFN- $\gamma$ ) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). General obesity patients with a low degree of physical activity had elevated levels of ILs 4, 10 and 13 [6]. The results are strongly suggestive that obesity cannot be simply explained away as the difference between energy intake and energy expenditures, rather more complex factors are at play. Adipocytes are not just fat reservoirs, but can secrete a wide range of bioactive peptides and proteins, which collectively are known as adipokines and can play a part in obesity [7].

Adeposinomes, which constitute the secretome of fat cells, release not only fatty acids and prostaglandins, but also proteins involved in the alternative complement system (adipsin, acylation-stimulating protein), insulin resistance, lipid metabolism (retinol-binding protein, cholesteryl ester transfer protein), vascular hemostasis (plasminogen activator inhibitor-1 or PAI-1), blood pressure regulation (angiotensinogen), glucose homeostasis (adiponectin), and angiogenesis (vascular endothelial growth factor or VEGF) [7]. Other proinflammatory cytokines that are released from adipokines include tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-1 $\beta$ , ILs 6, 8, and 10, transforming growth factor- $\beta$ , plasminogen activator inhibitor-1, haptoglobin, and serum amyloid A [8, 9]. Production of these factors and proteins are increased in obesity [7] and have been hypothesized to lead to a chronic low-grade inflammation leading to insulin resistance and metabolic syndrome like disorders. Obesity markers include IL-6, TNF- $\alpha$ , C-reactive protein, and haptoglobin [10, 11]. In fact, the hypothesis has reversed from obesity being the factor behind secretion of proinflammatory cytokines to obesity being an inflammatory disease that is obesity is an effect of proinflammatory cytokine(s) production in the body as a result of other factor(s) [11, 12].

Breast feeding has been shown to reduce obesity. Breast milk is rich in long-chain polyunsaturated fatty acids (LCPUFAs), which inhibit the production of proinflammatory cytokines and enhance the number of insulin receptors in various tissues [13, 14]. As such lack of LCPUFAs in the body/diet can lead to obesity. In rodent models, n3-LCPUFAs have been found to have a protective effect against high fat diet-induced insulin resistance. The protective action of n3-LCPUFAs has been attributed to the prevention of decrease of phosphatidylinositol 3' (PI3) kinase activity and the prevention of the depletion of glucose transporter 4 (GLUT4) in muscle, and the prevention of decreased expression of GLUT4 in adipose tissue. Additionally, n3-LCPUFA has been reported to stimulate fatty acid oxidation in the liver via the activation of peroxisome proliferator activated receptor- $\alpha$  (PPAR- $\alpha$ ) [15]. Development of insulin resistance, which was previously thought to be a consequence of excess dietary intake in obesity and a consequence of genetic, environmental, dietary, and sedentary factors in diabetes mellitus may now be taken as a consequence of factors that are being released by the adipokines, and which include a number of proinflammatory cytokines.

Some of the adipokines secreted from the white adipose tissue (WAT) are dependent on TNF $\alpha$ , which regulates synthesis of IL-6, acute phase protein, and haptoglobin [16]. Plasma levels of IL-6 reportedly increase during obesity [17], and IL-6 in addition to leptin, may convey information for regulation of energy balance from adipocytes to the hypothalamus. Circulating levels of IL-18 and IL-10 are also increased in obesity [18], and may play a role in the development of this disorder. The production of other cytokines including the ones mentioned has been attributed to hypoxia in areas of fat deposits with consequential increase in tissue mass with the increase in obesity. Hypoxia-inducible factor-1 (HIF-1), a transcriptional activation factor of leptin [19] may play a key role in the process.

### Some conventional medicines against obesity

A number of approaches have been taken for anti-obesity drugs or drugs that can reduce obesity. A number of such approaches along with current and emerging drugs have been reviewed by Williams and his group [20]. The United States Food and Drug Administration (USFDA) has thus far approved five drugs, namely orlistat, phentermine/topiramate, lorcaserin, naltrexone/bupropion, and liraglutide to treat obesity. On the other hand, the European Medicines Agency (EMA) has approved only three - orlistat, bupropion/naltrexone and liraglutide [21]. Orlistat is an inhibitor of pancreatic lipase thereby modulating the digestion and absorption of fat in the intestine. Side-effects of this drug include oily stools, diarrhea,

abdominal pain, fecal spotting. There has also been a few reports of adverse effects on the hepatic system like cholelithiasis, cholestatic hepatitis, and subacute liver failure [22]. The combination therapy of phentermine and topiramate results in minor effects like insomnia and dry mouth, but also can produce serious side effects in the form of cardiovascular complications [23]. Mitral regurgitation is a serious side effect of lorcaserin, which may lead to other complications like increased risk of other cardiovascular complications [24]. Naltrexone is an opioid antagonist used for treatment of opioid and alcohol dependency, while bupropion is used for treating depression and help giving up smoking. Individually, the drugs have no or little effect on obesity; used in combination, they form a safe anti-obesity polypharmacy drug with no serious side effects except nausea [25]. Liraglutide, originally developed for treatment of diabetes, has now been approved as an anti-obesity drug. Adverse reactions of this drug include a number of gastrointestinal complaints like nausea, abdominal pain, decreased appetite, diarrhea, and constipation. Thyroid C-cell tumors and acute pancreatitis are more severe effects that may arise from use of this drug [26].

Information sheet supplied by the National Institute of Diabetes and Digestive and Kidney diseases mention some more prescription drugs to treat obesity. These drugs include semaglutide, setmelanotide, benzphetamine, diethylpropion, and phendimetrazine. All these drugs have reported mild or serious adverse effects associated with their use [27]. Since anti-obesity drugs, despite their weight loss benefit can have adverse effects, and the only viable alternative to these drugs is bariatric surgery, scientists and traditional medicinal practitioners (TMPs) are taking a close look at the plant kingdom for plants that have the potential to reduce weight. Plants have the advantage of being easily available; an endangered plant can be cultivated to bring it out of its endangered status and increase availability. Moreover, any given plant can have hundreds of secondary metabolites, otherwise known as phytochemicals, with diverse pharmacological effects, one of which can be to reduce obesity.

### Anti-obesity plants and phytochemicals

Several plants/plant parts, plant formulations, and phytochemicals have been described as anti-obesity plants [28]. These plants include *Nigella sativa* L. (Ranunculaceae, black cumin), *Opuntia ficus-indica* (L.) Miller (Cactaceae, prickly pear), *Camellia sinensis* (L.) Kuntze (Theaceae, tea), *Crocus sativus* L. (Iridaceae, crocus), *Laminaria digitata* (Hudson) J.V. Lamouroux (Laminariaceae, oarweed), and *Lycium barbarum* L. (Solanaceae, goji berry). Family and English names of the plants are given in parenthesis. Another review article gives the names of sixty-three anti-obesity plants, including one *Allium* genus plant, namely *Allium victorialis* L. (Alliaceae, Alpine leek) [29]. Leaves of the plant (100 mg/kg) are consumed for two weeks to reduce weight. A very detailed review published in 2015 cites 118 plants/formulations, which are useful against obesity [30]. The review cites a number of useful *Allium* genus plants like *Allium cepa* L., *Allium fistulosum* L., *Allium nigrum* L., and *Allium sativum* L. Another review article on anti-obesity plants list 76 plants along with their geographic distribution [31]. This last review does not mention a single *Allium* genus plant as an anti-obesity plant. This is despite reports as to the efficacy of particularly *Allium cepa* and *Allium sativum* to reduce obesity.

The influence of quercetin-rich onion peel extracts have been examined on adipokine expression in visceral adipose tissue of rats in diet-induced obese rats. The extract influenced adipokine expressions, leading to moderation effect on obesity-induced inflammation [32]. Another study on the effect of quercetin-rich onion peel extract (OPE) supplementation to high fat-fed rats found that lipid accumulations and triglyceride concentrations in 3T3-L1 pre-adipocyte cells were suppressed; mRNA of activating protein-2 (AP-2) were down-regulated; mRNAs of carnitine palmitoyl transferase-1 $\alpha$  (CPT-1 $\alpha$ ) and fatty acid binding protein 4 (FABP4) were up-regulated; retroperitoneal and mesenteric fat levels

were lowered, which led the authors to conclude that quercetin-enriched OPE may inhibit obesity by “suppressing pre-adipocyte differentiation and inhibiting adipogenesis” [33]. A recent review on the effect of *Allium sativum* (garlic) on obesity mentions that garlic extract can reduce body weight, adipose tissue mass and improve lipid profiles in high fat diet fed rodents; ajoene and 1,2-vinyldithiin were among the active ingredients [34]. Because of the large number of papers already published on *Allium cepa* (1995 hits in PubMed Central with the search terms <Allium cepa, obesity>) and *Allium sativum* (3649 hits in PubMed Central with the search terms <Allium sativum, obesity>), we decided to concentrate on a lesser known species of *Allium* genus, namely *Allium fistulosum* and its effects on obesity.

### Allium fistulosum L. and its anti-obesity effects

*Allium fistulosum* L. belongs to the Alliaceae/Amaryllidaceae family of plants and is known in English as Welsh onion, bunching onion or long green onion. The plant, unlike the common onion (*Allium cepa*) does not have a bulb and has hollow leaves. The plant is used in culinary dishes of China, Japan, and Korea. It is also used in culinary dishes of Russia and Jamaica.

Phytochemicals reported in *Allium fistulosum* include allicin, p-coumaric acid, ferulic acid, isoquercitrin, quercitrin, kaempferol,  $\beta$ -sitosterol, campesterol, and stigmasterol [35]. A cyclic monoterpene D-limonene has also been identified from the plant [36]. Alliin, rutin, and quercetin are three other phytochemicals reported from the plant [37].

A study conducted on male 8-week-old C57BL/6 J mice fed a high fat diet with or without aqueous extracts of *Allium fistulosum* demonstrated beneficial effects of the extracts on reducing obesity and several parameters related to obesity. The ethanolic and aqueous extract (AFE and AFW, respectively) containing ferulic acid and quercetin decreased body weight and furthermore, decreased adipose tissue and liver weight, and adipocyte size. Improvement in serum lipid profiles and adiponectin were also observed with AFE. Both extracts attenuated high fat diet-induced changes in serum leptin and insulin-like growth factor 1 levels, liver expression of 5'-adenosine monophosphate-activated protein kinase (AMPK), and adipose tissue expression of UCP2 (mitochondrial uncoupling protein 2) [38].

An herbal extract combining extracts of *Allium fistulosum* and *Viola mandshurica* W. Becker (Violaceae) to high-fat diet-induced obese mice resulted in reduced body and tissue weights, adipocyte size, lipid accumulation in the liver, and serum triglyceride, total cholesterol and leptin levels. The extracts also increased the mRNA expression of peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ), UCP2 and adiponectin and decreased expression of leptin in the epididymal white adipose tissue, resulting in reduction of obesity [39]. In this context it is to be noted that leptin is the gene product of the obesity gene, and plays a role in the regulation of human adipose tissue mass and body weight [40]. Adiponectin in combination with PPAR- $\gamma$  plays a major role in the functioning of adipose tissue and ameliorating non-alcoholic fatty liver disease and the pathogenesis of obesity [41].

Ferulic acid, a phytoconstituent of *Allium fistulosum*, reportedly caused suppression in male C57BL/6N mice of high fat diet-induced weight gain and inhibited fatty acid biosynthesis [42]. Flavonols like quercetin (another phytoconstituent of *Allium fistulosum*) can inhibit adipogenesis by inhibiting uptake of methyl glucose in adipocytes [43], and induce apoptosis in mouse pre-adipocytes [44], or improve glucose uptake without adipogenesis activity in 3T3-L1 adipocytes [45]. Apoptosis was due to antioxidant activity of quercetin, which lead to down-regulation of PARP (poly (ADP-ribose) polymerase) and Bcl-2 proteins, and activation of caspase-3, Bax and Bak proteins. A phase 2 clinical trial is underway as to whether quercetin can change the absorption of glucose by the body

in obese subjects [46]. There is indeed a high possibility of discovery of other flavonoid compounds playing a distinct role in reducing obesity.

Poor gut absorption and low bioavailability of flavonoids along with destruction of flavonoids during cooking are important factors raised by scientists in the use of flavonoid compounds to control obesity. Quercetin glycosides are generally more easily absorbed. The role of gut microbiota is another factor that needs to be examined in more detail. It is to be expected that administration of flavonoid compounds with specific side groups attached, use of probiotics to change gut microbiota composition, and finding out alternate routes of delivery of flavonoid compounds are the next phases of research that needs to be taken into consideration for control of obesity and obesity-induced disorders.

### Conclusion

Obesity is a complicated disorder and which can lead to a number of non-communicable diseases, including cancer, arthritis, and cardiovascular problems. Conventional medicines have moderate to serious side effects; plant-based medications like phytochemicals can offer a solution for reducing obesity. In this review, we show that *Allium fistulosum* and at least two of its reported phytochemicals, namely ferulic acid and quercetin can play a role in decreasing weight and obesity.

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### Conflicts of interest

The authors declare no conflicts of interest.

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