

## **Can *Punica granatum* be a Miracle in Ameliorating Obesity? - A Short Review**

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### **Abstract**

Metabolic syndrome (MetS) is a combination of several biological and physiological abnormalities including insulin resistance, hypertension, obesity, adiposity, atherogenic dyslipidemia, endothelial dysfunction, which are interrelated. A combination of a number of these factors, all present in a single individual, not only lowers the life expectancy but also lowers the quality of life. MetS is becoming a grave concern and major scientific efforts are underway to treat MetS with plant-based extracts or phytochemicals. This review attempts to summarize some aspects of the current state of knowledge obtained with *Punica granatum* or pomegranate fruits and other parts of the plant in ameliorating obesity - a key component of MetS.

**Keywords:** Metabolic Syndrome; Obesity; *Punica granatum*; Pomegranate; Body Mass Index

### **Introduction**

Metabolic syndrome (MetS) is a combination of several biological and physiological abnormalities including insulin resistance, hypertension, obesity, adiposity, atherogenic dyslipidemia, endothelial dysfunction, which are interrelated [1,2]. This is now a concerning problem worldwide, which have become a challenge to prevent or cure. Prevalence of MetS ranges from below 10% to 84% worldwide depending on various factors like environment, profile of subjects (age, sex, health condition) and the region the data were collected from [3].

According to Adult Treatment Panel III report, obesity and abdominal obesity (measured by waist circumference) is considered as the main cause of MetS. It exacerbates the risk factors including non-esterified fatty acids, cytokines, PAI-1 and adiponectin of developing MetS by the products that are released from adipose tissue. All these risk factors are related with producing insulin resistance and cardiovascular diseases [4]. In obese people, C-reactive protein (CRP) level in serum, which is a marker of inflammation goes up due to inflammation in artery (happens because of accumulation of atherosclerotic plaque in artery); that signifies the presence of cardiovascular disease [5].

As obesity and MetS are interrelated, the global prevalence of these two has reached to an epidemic condition. A report in 2016 mentioned that approximately 2 billion people were being overweight and more than 650 million were obese. Among the whole adult population, obesity related metabolic abnormalities were found in 25% of the population [6-8]. By the year 2030, approximately 38%

of world population will be counted as overweight and 20% will be obese [9]. Bangladesh is a low-middle income country of South East Asia. Prevalence of overweight and obese people in Bangladesh has also been observed nowadays. An account showed that in 2004 the prevalence of obesity was 11.4% and it soared to 25.2% in 2014 [10]. Male adults having obesity were found in a major proportion than female (14.86% and 11.86%, respectively) because women are more conscious about their physical appearance. However, among urban women the percentage of overweight and obesity is an alarming 34% [11]. Increase of obesity among children of Bangladesh is also a fact of worry. Due to demographic and nutritional changes with changing life style, which encompasses high caloric food intake and leading a sedentary life, the rate of obesity and other chronic health problems are rising [12,13].

As obesity is reaching endemic proportion throughout the world, treatment or prevention of obesity has become a major concern. Diversifying the therapeutic strategies for the management of obesity has been studied for years. Some medications along with physical exercises have been suggested to control obesity, yet there is no specific medication to overcome this problem. Changing lifestyle and involving mainly in physical activities are the most suggested prescription by physicians [14,15]. Obesity not only affects on craving for food, but also it has an effect on brain functions like energy regulation. For this cause many suggest psychoactive drug such as Naltrexone HCl or bupropion HCl [16]. All the treatments ended up in showing adverse side effects and regaining weight.

Using synthetic drugs may cause other symptoms to arise, which is why people are now more interested in avoiding synthetic drugs and treating diseases through diet or by using natural products. *Punica granatum* or pomegranate is a well-known fruit throughout the world. Over the centuries various parts of this plant, namely, root, stem, bark, leaves, flower, fruits, and seeds have been used for the treatment of diseases such as diabetes, burns, cancer and cardiovascular diseases [17]. Besides, various parts of the plant can work as antimicrobial, antioxidant, anti-inflammatory, analgesic, hepatoprotective, anti-diarrheal, anti-obesity, and neuro-protective [18,19]. This review encompasses the anti-obesity property of *Punica granatum* (Figure 1A and 1B) along with the pharmacological evidences.



**Figure 1A:** Leaf and flower of *Punica granatum*.



**Figure 1B:** Fruit of *Punica granatum*.

## Obesity

Obesity can be defined as a chronic, multi-factorial disease where excess body fat is accumulated as measured by body mass index (BMI) of an individual. For an adult, BMI over 30 kg/m<sup>2</sup> is decided to be called obese [20,21]. Obesity is measured by the weight of major body parts such as legs, waist, and abdomen in relation to height. However, many studies conclude that waist circumference is a considerable indicator for obesity than BMI [22].

## Treatment of obesity

Existing anti-obesity drugs are absent, which do not have adverse effects. Anti-obesity drugs show adverse side effects, which outweigh their beneficial effects. From this point of view, plants have achieved a degree of confidence among users by giving satisfactory positive effects. To treat or reduce obesity tea of various plants such as *Camellia sinensis* and *Hibiscus sabdariffa* are very popular over the world. Besides these two plants, *Achyranthes aspera*, *Aegle marmelos*, *Carica papaya*, *Citrus limon* and *Punica granatum* possess anti-obesity activity. Phytochemicals for example flavonoids, phenolic acids, alkaloids, epigallocatechin-3-gallate, resveratrol, capsaicin, pro-cyanidins have anti-obesity effect [23-25]. *Punica granatum* or pomegranate is a potential source of phytochemicals that are effective to treat obesity. Camphor, benzaldehyde, phenolic compounds, flavonoids, gallic acid, catechins present in pomegranate peels are able to reduce lipase activity, thus having an anti-obesity effect [26-28].

## *Punica granatum*

*Punica granatum* is a plant belonging to the Lythraceae family, which has both medicinal and culinary purposes. Edible part (fruit, seed) as well as non-edible part (leaf, stem, bark, and root) contains a number of phytochemicals that can serve as both protective and therapeutic agents against different ailments [29].

### *Punica granatum* leaf extract

A study was conducted on obesity-induced mice (induced by giving high-fat diet) by treating with leaf extract of 400 or 800 mg/kg per day for 5 weeks. Result showed that leaf extract of pomegranate decreased body weight, appetite, and fat absorption [30]. Similar study was done by Adnyana., *et al.* in 2014, by using two different doses of 50 and 100 mg/kg body weight of leaf ethanol extract to obesity-induced mice. After 28 days of treatment, body weight was significantly reduced [31]. A randomized control trial was done on 21.13 million people having metabolic syndrome. They were treated with pomegranate leaf extract along with ascorbic acid of 10 - 20 mg in capsule or powder form. The result showed that extract of the plant leaf successfully reduced body weight of the subjects [32].

### *Punica granatum* fruit juice and vinegar

Pomegranate juice from two different regions (Taif and Egypt) was investigated to evaluate their anti-obesity effect by using high fat diet-induced obese rats. Body weight reduction, unwillingness to food consumption and decrease in serum level of lipid were found as a result of the study [33]. There is a traditional use of fruit vinegar to ameliorate obesity and obesity related complications. *Punica granatum* fruit vinegar was found effective as well. To evaluate the effect, 72 male rats were grouped equally into 12 groups in which one of the groups was treated with pomegranate vinegar along with high fat diet. After 18 weeks treatment, body weight and visceral adipose tissue mass were found to be significantly decreased by 0.2 - 0.5 fold and 0.7 - 1.8 fold, respectively [34]. Pomegranate vinegar was applied to high fat diet induced obese rat to evaluate if it can attenuate weight gaining and body fat accumulation. Rats were grouped into 5 groups and treated with the vinegar for 18 weeks. Observations displayed that the vinegar suppressed the increase of adiposity by increasing phosphorylation of AMP-activated kinase (AMPK) signaling. In this pathway mRNA for hormone sensitive lipase and mitochondrial uncoupling protein2 increases; the mRNA for transcription factor sterol regulatory element binding protein-1c (SREBP-1c) (major mediator of insulin action on the hepatic expression of glucokinase and lipogenesis-related genes) as well as peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) in adipose tissue decreases; mRNA increases for PPAR $\alpha$  and carnitinepalmitoyltransferase-1a (CPT-1a) and decrease for SREBP-1c in the liver. The net effect was lowering of body weight, fat mass, hepatic triglycerides and plasma triglycerides [35,36].

### *Punica granatum* seed oil

Pomegranate seed oil contains fatty acids such as punicic, oleic, and linoleic acids, which have anti-obesity effect. A combination of these three compounds were applied to check if it had an impact on the expression of proteins responsible for obesity and on the adipogenic differentiation of human adipose-derived mesenchymal stem cells (HADMSC). Study showed that 24 hours exposure to 10 mg/ml of the composition inhibited adipogenesis of HADMSC and generation of adipocytes from preadipocytes [37]. Xanthigen is a compound, found in pomegranate seed oil which stimulates weight loss, and reduce body fat [38]. In a study, this compound was detected to have effect of attenuating adipocyte differentiation and lipid accumulation as a treatment of obesity by various mechanisms such as down-regulating the activity of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) (a transcription factor in adipose tissue which plays a pivotal role in cell differentiation and function of mature adipocytes), down-regulating function of CCAAT/enhancer-binding proteins C/EBP $\gamma$  and C/EBP $\beta$  (transcriptional factors that induces pre-adipocyte differentiation), by up-regulating NAD-dependent deacetylase sirtuin-1 (SIRT1), and activating AMP-activated protein kinase (AMPK) signaling [39-41].

### *Punica granatum* peel extract

Fruit peels also possess therapeutic value such as managing metabolic syndromes and other life-threatening diseases. There are plenty of evidence supporting this theory [42,43]. Peel extract of pomegranate was tested *in vitro* on pre-adipocyte cell differentiation (3T3-L1 cell line). A probiotic strain *L. rhamnosus* GG ATCG 53103 along with peel extract was tested. Both peel extract and probiotic individually



and in combination significantly reduced triglyceride content and intracellular lipid accumulation. They also successfully lowered the mRNA expression of major transcriptional factors incriminated in adipocyte cell differentiation [44].

**Phytochemicals of pomegranate against obesity**

Pomegranate is rich in tannins and flavones. Mainly these two types of compounds act against obesity for pomegranate. Punicalgin, an ellagitannin that is found in pomegranate was tested to evaluate its anti-obesity efficacy. Administration of punicalgin to high-fat diet induced obese mouse for 12 weeks resulted in inhibition of increasing body weight. Liver fat was also reduced by the treatment of punicalgin. Administering of punicalgin in early stage of adipogenesis can stop further differentiation [45].

Polyphenols such as punicalgin, ellagic acid and a metabolite urolithin A were found inhibitory for lipase, α glucosidase, dipeptidyl peptidase-4 and adipogenesis. Especially urolithin A showed anti-adipogenic activity [46]. Investigations done with phytochemicals like tricetin, apigenin and luteolin for reduction of obesity found them safe for human use [47].

**Conclusion**

**Pomegranate against obesity related complications**

Obesity itself is a complicated disease. Obesity is a part of metabolic disorder where various diseases together increase mortality rate. Obesity can help in arising different complications, cardiovascular diseases, hypertension, diabetes, dyslipoproteinemia, cholelithiasis (formation of gallstone) [48]. The above review and Table 1 (below) suggests that pomegranate is effective for obesity management and obesity associated complications through various ways (Figure 2).

Pomegranate derivatives	Models	Pharmacological Effects	References
Pomegranate extract (with inulin)	High fat diet (HFD) fed male C57BL/6 mice	Decreased hepatic and serum level cholesterol. Increased gene expression of Cyp7a1 and Cyp7b1 (key regulator of bile acid synthesis pathway).	[49]
Seed oil, leave, juice, peel extract	<i>In vivo</i> and <i>in vitro</i> (high fat diet fed rats)	Neuroprotective effect by inhibiting cholinesterase and stimulating anti-oxidant capacity.	[50]
Juice	Sprague-Dawley rats	Prevent non-alcoholic fatty liver disease by reducing oxidative stress and inflammation.	[51]
Peel extract	Sprague-Dawley rats	Treat non-alcoholic fatty liver by modulating lipid metabolism.	[52]
Peel, flower extract, seed oil	High fat diet induced obese mice	Reduced fasting glucose level, increased glucose tolerance, and anti-inflammatory activity.	[53]
Pericarp methanolic extract	<i>In vitro</i> (human cancer cells MCF-7, MDA-MB 231, HEC-1A, SiHa, HeLa, SKOV3) and <i>in vivo</i> (Swiss albino mice)	Antagonized the effect of endogenous selective estrogen receptor modulator, 27-hydroxycholesterol, reduced breast cancer cell proliferation.	[54,55]
Pomegranate extract (40% Punicalgin)	HFD induced obese male rats (with cardiac metabolic disorders)	Decreased accumulation of cardiac triglyceride, cholesterol, myocardial damage. Activated AMP-kinase pathway, which upregulates mitochondrial biogenesis.	[56]
Ellagic acid	Obesity induced dyslipidemia and hepatic steatosis in KK-A(y) mice (a strain of KK diabetic mice and yellow obese mice)	Significantly suppressed serum resistin level, improved lipid profile and hepatic steatosis.	[57,58]

**Table 1:** Pomegranate derivatives against obesity related complications.



Figure 2: Anti-obesity mechanism of Pomegranate extracts.

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