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Therapeutic Effects of Phytochemicals of *Brassicaceae* for Management of Obesity

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SSM, TAK and ALA designed the study. Authors AK and SSIR wrote the first draft of the manuscript. Authors YQA, SSY and YAM reviewed and corrected the manuscript. Authors MNH, ABA and HMA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Cruciferous vegetables are rich in glucosinolates, carotenoids, chlorophylls and ascorbic acid which play a major role in the modulation of lipid metabolism and are therefore involved in the lowering of total cholesterol levels in the blood. *Cruciferous* diet has an inverse relationship with the obesity which has been attributed to the indoles and isothiocyanates derived from the glucosinolates, such as indole-3-carbinol (I3C) and sulforaphane. Obesity and overweight still remain one of the leading causes of "preventable" deaths worldwide exerting a great deal of strain on the healthcare systems. It is ironic to note that there are nearly 100 drugs available in the market for the obesity related diseases like hypertension, but only 6 medications have been approved for the treatment of obesity in the long run. Since obesity is a chronic and permeant disease, it puts an individual to a risk of 30 more chronic diseases like hypertension, type 2 diabetes, cancers, degenerative joint diseases and cardiovascular diseases. Hence, there is a desperate need to find an alternative supporting strategy to support the current medications. In this communication, we have explored the role of phytochemicals from *cruciferous* diet in exerting hypolipidemic effects, which may open up nascent avenues for therapeutic intervention to tackle obesity.

Keywords: Cruciferous; brassicaceae; hyperlipidemia; cholesterol; indole-3-carbinol; brassica; hypercholesterolemia.

1. INTRODUCTION

Obesity and Overweight have dramatically increased in the recent times and have been recognized as a topic of considerable research interest globally. Moreover, the adiposity goes undetected in significant proportion of population in developed countries. In 2014 alone, more than 1.9 billion adults aged 18 years and older were overweight, of these over 600 million (11% of men and 15% of women of the world's adult population) adults were obese [1].

Previously, obesity was considered as a problem only in developed and affluent countries. But now, it has become a major concern in developing, low- and middle-income countries, particularly in urban settings. In Saudi Arabia, it has been reported that, from 1988 to 2005, the prevalence of obesity among young people increased significantly [2]. It is quite dejecting to note that the incidences of pre-mature morbidity and mortality rate is rising exponentially. It has been observed that the overall overweight/obesity prevalence has risen from 20% in 1996 [3] to 35% in 2005 to 59.4% in 2013 [4] and nearly 75% of Gulf cooperation council (GCC) population has been collectively included [5].

The National Growth Study reported that the overall prevalence of obesity in children and adolescents from 5 to 18 years was 11.3%. Among the age group of 5–12 years, the prevalence of obesity in females was 11% and that of male was 7.8%. While, it was interesting to note that among the age group of 13–18 years, the prevalence of obesity in female was 12.1% and that of male was 13.8% [2,6]. It is agonizing to report that in GCC, an estimated 20,000 deaths per year take place due to obesity and related comorbidities [5]. Obesity and Overweight have been proved to be major risk factors for many chronic diseases, including diabetes [7], cardiovascular diseases [8], cancer [9], obstructive sleep apnea [10] and osteoarthritis [11].

People are generally considered obese when their body mass index (a measurement obtained by dividing a person's weight (in kilograms) by the square of the person's height in meters), is over 30 kg/m^2 and with the range 25–30 kg/m^2, they are categorized as overweight [12]. Some East Asian countries use lower values than that as mentioned above [13].

In order to maintain the quality of life for the population and decrease the economic burden on the health system, there is an urgent need for more powerful dietary strategies to keep obesity related diseases at bay. With this perspective in focus, considerable interest has been aroused worldwide to tap the hidden potential of dietary phytochemicals to help counteract obesity.

Vegetables are major dietary source for phytochemicals with potential anti-obesity properties, with the types and levels varying markedly between species and even cultivar [22]. *Cruciferous* vegetables belong to the family of *Brassicaceae* (also called *Cruciferae*) with many genera, species, and cultivars being raised for food production such as *cauliflower*, *cabbage*, *garden cress*, *bok choy*, *broccoli*, *brussels sprouts* and similar green leafy vegetables. The family takes its alternate name (*Cruciferae*, New Latin for "cross-bearing") from the shape of their flowers, wherein the four petals resemble a cross. *Cruciferous* vegetables are one of the dominant food crops worldwide. They are high in vitamin C, soluble fiber and they contain multiple nutrients and phytochemicals.

2. OBESITY

2.1 Causes and Preventive Measures

Obesity is most commonly caused by a combination of excessive food intake, lack of physical activity, and genetic susceptibility [12] [14]. Few cases are primarily attributed to the genetic makeup, while others are endocrine disorders and the rest are related to medications or prolonged mental illness [15]. The myth that “obese people eat little yet gain weight due to a slow metabolism” is invalid and unsupported [16]. On an average, obese people have a greater energy expenditure than their lean counterparts due to excess energy required to maintain an increased body mass [16,17].

Obesity can be effectively prevented through a combination of social changes and personal choices [12]. Changes in diet and exercise are the primary strategies [7]. Quality of diet can be ameliorated by cutting down the consumption of energy-dense foods, such as those high in fat and sugars, and by increasing the intake of dietary fiber [12]. Medications may be taken along with a suitable diet to reduce appetite or decrease fat absorption [18]. If diet, exercise, and medication are not effective, a gastric balloon surgery may be performed to reduce stomach volume or bowel length, which may later make the individuals feel full sooner while eating or reduce ability to absorb nutrients from food [19].

2.2 Molecular Mechanism

Obesity is characterized at the cellular level by an increase in the number and size of adipocytes (fat storage cells) that have differentiated from pre-adipocytes in the adipose tissue [20]. This transition from undifferentiated pre-adipocytes into mature adipocytes constitute the adipocyte lifecycle, and hence treatments that regulate both the size and number of adipocytes may provide a valuable adjunct to reduce dietary energy in combating obesity. The relationship between adiposity and inflammation is also being gradually unraveled with the recognition that adipocytes also produce inflammatory cytokines, suggesting that obesity induces an inflammatory state which may lead to further disease progression [21].

3. DIABETES AND CRUCIFEROUS DIET

In the last few years, there has been a steep rise in the premature morbidity and mortality cases related to Type 2 diabetes (T2D). It has been estimated that the number of affected adults from T2D will swell up to 439 million by 2030 [53]. The increase in the calorie-rich foods like fast foods, meat and animal products, sugar-sweetened beverages have increased the risk of T2D in especially aging and more sedentary population. This has gathered the attention of researchers globally to overcome this crisis by a suitable diet. Intervention of lifestyle by slight alteration in the dietary factors have proved to be beneficial in reversing this global epidemic. In a recent study, it has been mentioned that the daily WHO recommended intake of more than 400g or 5 portions of combined fruits and vegetables have been quite effective in reducing the incidences of T2D [54]. In a diabetes prevention program, it was interesting to note that nearly 20% of the population which aged 60 and above could reduce the risk of T2D to 71% by just alteration in the lifestyle [55].

Several studies are in the progress to find the exact link between the cruciferous diet and the T2D through meta-analysis and prospective cohort studies [56–59].

4. COMPOSITION AND ROLE OF PHYTOCHEMICALS OF *BRASSICACEAE*

Brassicas contain glucosinolates, carotenoids, chlorophylls, ascorbic acid, sinigrin; gluconapin, glucobrassicanapin, progoitrin, phenolics like hydroxycinnamic acids (sinapic, ferulic, p-coumaric and caffeic acids), glycosides of quercetin, kaempferol and derivatives of p-coumaric, ferulic, sinapic and caffeic acid [23, 24].

An interesting randomized double-blind placebo-controlled trial showed that, with supplementation of extract of *Brassica Rapa turnip* for 10 weeks, there was an increase in the high-density lipoprotein (HDL) and a considerable reduction in the total-Cholesterol (TCh)/HDL ratio, free fatty acid and adipsin levels [25]. *Red cabbage*, rich in anthocyanin, has been reported to increase fecal lipid excretion and thus prevent atherogenic diet-induced serum/tissue lipids elevation, cardiac and hepatic peroxidation and injuries [26].

Extracts of *Kale* leaves inhibited lipid peroxidation in both isolated very low-density lipoprotein (VLDL) and Low-density lipoprotein (LDL) [27], while gluconapin (3-butenyl glucosinolale) and sinigrin (2-Propenyl glucosinolale), extracted from *Brassica Rapa L. oleifera,* suppressed postprandial hypertriglyceridemia in mice [26,28]. *Brassica olearaceae L.* combined with hydro soluble chitosan synergistically decreased serum TCh, LDL, VLDL and triglycerides [29].

Dietary phytochemicals might be employed as anti-obesity agents, as they may suppress the growth of the adipose tissue, inhibit differentiation of preadipocytes, stimulate lipolysis, and induce apoptosis of existing adipocytes, thereby reducing the mass of adipose tissue. Overview of the different pathways leading to obesity and obesity-related diseases are depicted in Fig. 1.

5. VITAL ROLE OF THE CHIEF CONSTITUENT - INDOLE-3-CARBINOL

Indole-3-carbinol (I3C) is a phytochemical present chiefly in *cruciferous* vegetables of the genus *Brassica*, which includes *kohlrabi* [30], *cabbage*, *cauliflower, turnip, broccoli, kale and brussels sprouts* [31]. It has been reported that I3C treatment significantly lowered weight gain, visceral fat pad weights and plasma lipid levels in high fat diet (HFD)-induced obesity mice through normalizing the mRNA levels of uncoupling proteins 1 and 3. The crucial factors of thermogenesis in visceral adipose tissue and their regulators such as sirtuin 1, peroxisome proliferator-activated receptor (PPAR) α and

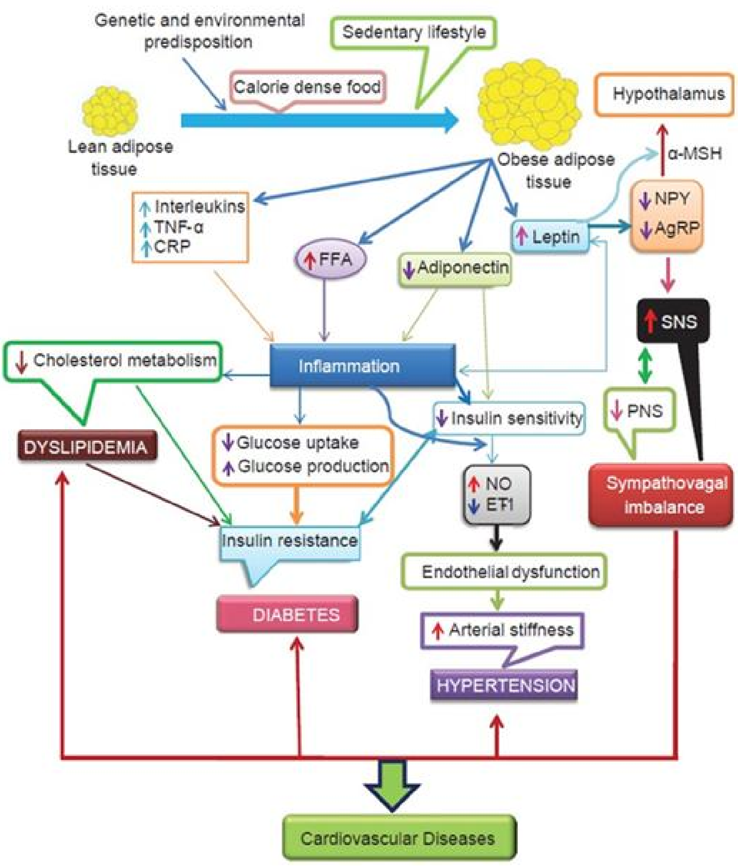

Fig. 1. Overview of the different pathways resulting in the development of obesity and related chronic diseases [51]

PPARγ coactivator 1α, were also down-regulated by HFD. After I3C treatment, the expression levels of a key adipogenic transcription factor, PPARγ2, and its target genes, such as leptin and adipocyte protein 2, in the visceral adipose tissue of mice significantly decreased in mice maintained on the HFD diet. Furthermore, HFD-induced up-regulation in mRNA levels of inflammatory cytokines (tumor necrosis factor α, interferon β and interleukin 6) was significantly improved by I3C [32].

Y Choi et al. analyzed the anti-obesity activity of I3C using 3T3-L1 cell lines and targeted silent mating type information regulation 2 homolog 1 (SIRT1), a $NADP^+$-dependent deacetylase sirtuin, as a novel therapeutic target for metabolic diseases. They discovered that I3C binds to SIRT1 and activates SIRT1 deacetylase activity in 3T3-L1 cells. Reverse transcriptase polymerase chain reaction analysis showed that I3C treatment reduced mRNA levels of adipogenic genes which encode for C/EBPa, PPARg2, FAS, and Adipokines in 3T3-L1 cells. Interestingly, I3C did not inhibit adipocyte differentiation in SIRT1 knockdown 3T3-L1 cells [33].

Another study revealed the effects of I3C on 3T3-L1 cells. It was observed that the aryl hydrocarbon receptor (AhR), AhR nuclear translocator (ARNT), Cytochrome P450 1B1, hormone-sensitive lipase (HSL), glycerol-3-phosphate dehydrogenase, nuclear factor erythroid-derived factor 2, and vascular endothelial growth factor receptor protein expression in differentiated adipocytes were analyzed and resulted in reduced lipid droplet accumulation in adipocytes and suppressed adipocyte-stimulated angiogenesis in endothelial cells [34].

Adipokines and lipogenic-associated gene products, including acetyl coenzyme A carboxylase (ACC) and PPAR-g were studied in a HFD induced obesity mice model treated with I3C. The I3C treatment decreased body weight and fat accumulation and infiltrated macrophages in epidydimal adipose tissue of HFD induced obesity mice, and these reductions were associated with improved glucose tolerance and with modulated expression of Adipokines, ACC mRNAs and PPAR-g protein [35],[36]. The results revealed that I3C significantly inhibited triglyceride accumulation in mature adipocytes in association with significantly increased expression of AhR and Cytochrome P450 1B1 proteins. Moreover, there was a slight decrease in the nuclear factor erythroid-derived factor 2–related factor-2, hormone-sensitive lipase, and glycerol-3-phosphate dehydrogenase expression in mature adipocytes. Fig. 2. shows the pathways of AhR activation induced by I3C from *cruciferous* diet.

Furthermore, I3C inhibited conditioned medium-stimulated endothelial tube formation, which was accompanied by the modulated secretion of angiogenic factors in adipocytes, including vascular endothelial growth factor, interleukin-6, matrix metalloproteinases, and nitric oxide. In summary, I3C reduced lipid droplet accumulation in adipocytes and suppressed adipocyte-stimulated angiogenesis in endothelial cells.

6. RECENT DEVELOPMENTS IN *IN-VITRO* AND *IN-VIVO* STUDIES

Red cabbage microgreen supplementation attenuated HFD induced weight gain, significantly lowered circulating LDL levels, reduced hepatic cholesterol ester and triacylglycerol levels and expression of inflammatory cytokines in the liver [37,38]. Phytochemicals of *Brassica campestris spp. rapa* were extracted from roots with ethanol and the molecular mechanism of the anti-obesity effect was investigated in *in-vitro* and *in-vivo* studies. It was demonstrated that in *in-vitro* studies, the activation of cyclic AMP-dependent protein kinase, HSL and extracellular signal-regulated kinase were induced in 3T3-L1 cells. Additionally, both weight gain and epididymal fat accumulation were highly suppressed by the daily oral administration of extract for 8 weeks in the obese mouse model. Whereas, the overall amount of food intake was not affected. Extract treatment induced the expression in white adipocytes of lipolysis-related genes, including b3-adrenergic receptor, HSL, adipose triglyceride lipase, and uncoupling protein 2 [39]. Aqueous extract of *Broccoli,* regulated glucose homeostasis via reduction of serum resistin, leptin and adiponectin in HFD-induced obesity rats [40].

Few studies have investigated the effect of *Broccoli sprouts* on lipid profiles. In an animal experiment, administration of ethanol extract of *Broccoli sprouts* in two doses (200 and 400 g/kg) for 4 weeks in rats fed with HFD, resulted in decreased levels of serum TCh, LDL, triglycerides and cardiac risk factors (TCh/HDL), and increased HDL [41]. In this study, HFD increased the levels of total cholesterol and TG

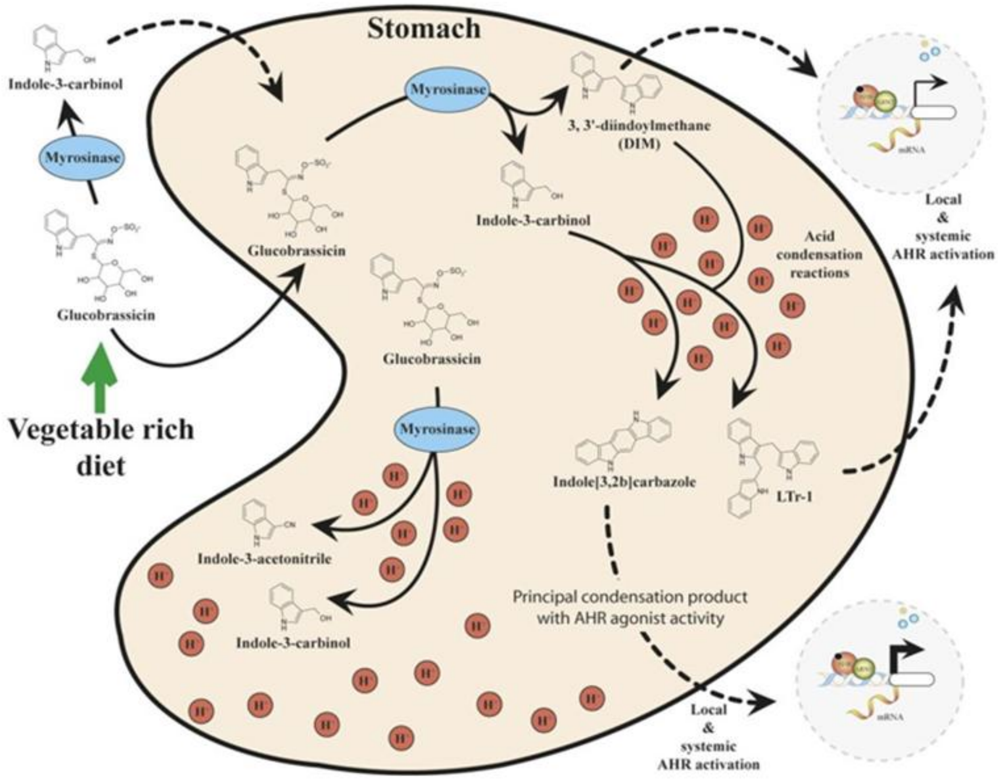

Fig. 2. Indole-3-carbinol present in the vegetable diet plays a major role in the activation of AHR resulting in decreased triglyceride accumulation in mature adipocytes [52]

in the liver and adipose tissue, but the activities of heparin-releasable lipoprotein lipase and total extractable lipoprotein lipase in adipose tissue decreased in the *Broccoli sprout* group [41]. *Broccoli* is a good source of sulforaphane which was used as a functional food in a study wherein the rat model showed that *Broccoli* decreased hepatic triglyceride [42]. When *Broccoli sprouts* were used as an ingredient of a supplementary food for HFD induced mice obesity model, it altered hepatic fat concentrations, gene expression patterns, and fatty acid concentrations [43].

Raphanus sativus cv. Sango Sprout Juice was used in HFD-Induced Obesity in Sprague Dawley Rats. Surprisingly, it improved the obesity related disorders such as lowering total cholesterol level, food intake and liver weight and up-regulated the antioxidant enzymes like catalase, NAD(P)H:quinone reductase, oxidised glutathione reductase and superoxide dismutase, as well as the phase II metabolic enzyme UDP-glucuronosyl transferase (up to about 43%)[44].

Spinach, kale, brussels sprouts, broccoli, mustard greens, green bell pepper, cabbage and collards were investigated for their bile acid binding ability and the study demonstrated that after binding with bile acids, these vegetables could prevent bile acid reabsorption and stimulate plasma and liver cholesterol conversion to additional bile acid [45].

7. RECENT UPDATE OF THE CLINICAL TRIALS

Since *cruciferous* vegetables contain carotenoids such as lutein, zeaxanthin and beta-carotene, it has been a hot topic of research among the scientists worldwide to study their bioactivity [46]. However, in recent few years, the bioavailability of carotenoids and the protective effect exerted by black (*Brassica oleracea L. var. acephala subvar. Laciniata L*) and red cabbage (*Brassica oleracea L. var. capitata L.f. rubra*) against lipoprotein peroxidation were investigated for the first time in humans. Plasma lutein, β-carotene levels and total antioxidant capacity in healthy volunteers were significantly increased and TCh, LDL and oxidized LDL were decreased after dietary intervention for 2 weeks [47].

A single blind and randomized controlled clinical trial was done by a research team targeting hypocholesterolemic activity of *Komatsuna (Brassica rapa L. var. perviridis)* on healthy men. After 4 weeks of intervention, serum cholesterol levels were significantly reduced [48]. In a different study, *Broccoli sprouts* powder was used as a supplementary treatment in a randomized double-blind placebo-controlled clinical trial and the improvement of serum triglyceride and oxidized LDL/LDL-cholesterol ratio were investigated [49]. While in a separate clinical study of 12 subjects, it was demonstrated that the consumption of *Broccoli sprouts* for only 1 week, reduced markers of oxidative stress along with increased metabolism of cholesterol [50].

8. CONCLUSION

Cruciferous vegetables are rich in bioactive phytochemicals and can be used as an alternative dietary supplement for anti-obesity purposes. However, the bioavailability and absorption of the nutrients depend upon the method employed for processing before consumption, as overboiling or overcooking render the phytochemicals inactive. Apart from maintaining a *cruciferous* diet, physical activity and exercise play a vital role in fighting obesity, which is in agreement with the adage “suffer the pain of discipline or suffer the pain of regret”. The obesity in individuals with genetic susceptibility and endocrine disorders can be treated early in childhood with personalized medicine and controlled hormonal balance to maintain homeostasis of blood glucose levels. During the recent few years, research on the use of *cruciferous* vegetables against obesity have caught the attention of many scientists around the globe and the clinical trials and progressive cohort studies are under progress which gives us a dawn of hope for the alternative and effective strategies.

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CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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