



A Comprehensive Review Explaining the Detailed Mechanism of Actions of Various Lentils Like Soyabeans, Chickpeas in Improving Insulin Resistance

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Abstract

Insulin resistance (IR) stands as an important cause for type2 diabetes mellitus (T2DM) and metabolic syndrome. Right now treatment of IR is done with use of lifestyle modifications and or pharmacological treatment. It has been shown that leguminous plants like soyabeans and pulses that include dried beans dried peas, chickpeas, lentils can decrease IR along with related T2DM. But what is the mechanism of action of these soybeans and pulses in decreasing IR remains elusive. It has been considered that that it is the antioxidant action of these, that is responsible for the same, but there is evidence that independent methods might be there by which insulin sensitivity gets improved. On the bases of published studies using *in vivo* and *in vitro* models which represent IR states, the possible mechanism of action of soybeans, chickpeas along with their bioactive compounds are by increasing glucose transporter4 (GLUT-4), inhibiting adipogenesis by downregulation of peroxisome proliferator activated receptor gamma (PPAR- γ) decreasing adiposity, positively impacting adipokines and increasing short chain fatty acids producing beneficial bacteria in the gut. This review attempts to explain the detailed mechanism of action of how soybeans and chickpeas act to reduce IR.

Keywords: Soybeans; Chickpeas; Lentils; Insulin Resistance; GLUT4; PPAR γ ; Adipokines; SCFA Producing Bacteria

Introduction

Insulin resistance (IR), is well known to underlie the development of diseases like metabolic syndrome, type2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD) [1]. IR is characterized by decreased cellular response to insulin, for which the body needs to compensate by increasing insulin secretion to obtain biological effects that are normally achieved by a lower amount of insulin [2,3].

Recent management aims to attenuate IR by lifestyle modifications (like diet, exercise, weight loss) as first line of treatment before giving any pharmacological drugs (like insulin sensitizing agents) to patients [4]. Aim of this medicines is to restore the normal relationship between insulin sensitivity and secretion [5]. Yet due to complications associated with insulin sensitizing drugs, alternative treatments for attenuating IR in the form of dietary agents are getting a lot of interest, both among patients as well as practitioners [6].

Healthy diet has legumes as an important part, which are rich in protein, fibre, complex carbohydrates and micronutrients, and contain no cholesterol [7,8]. Besides the nutritional benefits, most legumes contain a number of bioactive compounds which may add to their functional health benefits [9]. Legumes like soyabeans and pulses have been known to have beneficial effects in T2DM management, because of their low glycemic index [10,11], i.e produce a relatively low rise in blood glucose following their intake [12]. Main difference between soyabeans and pulses is that soybeans are oil producing plants commonly harvested for the aim of producing soybean oil, while pulses (dried beans, dried peas, chickpeas, lentils) are harvested dry as edible seeds [12]. Both remain important sources of plant based dietary protein worldwide [13,14]. In Asian countries, soybeans especially are the major protein source for one billion people [14]. Besides their T2DM, management properties, there is support that soybean intake and that of pulses helps by attenuating IR as shown by the improvements in the homeostasis

modeling assessment –IR (HOMA-IR) index of fasting insulin levels [4,15-24]/although some studies have shown opposite [22] or null effects [23 25-27]. Thus aim of this review is to understand the mechanisms of actions for soybean, pulses along with their bioactive compounds, for reducing IR efficiently.

Methods

A search was done using the Pubmed search engine using the MeSH Terms soybeans; pulses; lentils; beans; chickpeas, peas; legumes; insulin resistance, insulin sensitivity. Secondary search was done using identified bioactive compounds like isoflavones, anthocyanins, galactooligosaccharides.

Results

A total of 92 articles were identified of which primary 15 articles were used for detailed mechanism of action studies. No meta-analysis was done.

Bioactive compounds of Soyabeans and Pulses

Isoflavones

Isoflavones are bioactive compounds which belong to a class of secondary metabolites known as flavonoids, which are a different varieties of polyphenolic compounds which are found in plants [28]. Isoflavones are there in >300 various types of plants [29], with legumes, like soyabeans and chick peas, being the major sources [29-31].

Soyabeans are the best source of Isoflavones, that are known, which includes the main Isoflavone aglycones, genistein, daidzein and glycitein, and their respective glycoside conjugates, genistin, daidzin and glycitin [29, 32]. Chickpeas also contain genistein and daidzein, though the major Isoflavones present in chickpeas are biochanin A (aglycone and glucoside forms) and formononetin [30]. see figure 1 for these Isoflavones in soyabeans and chickpeas.

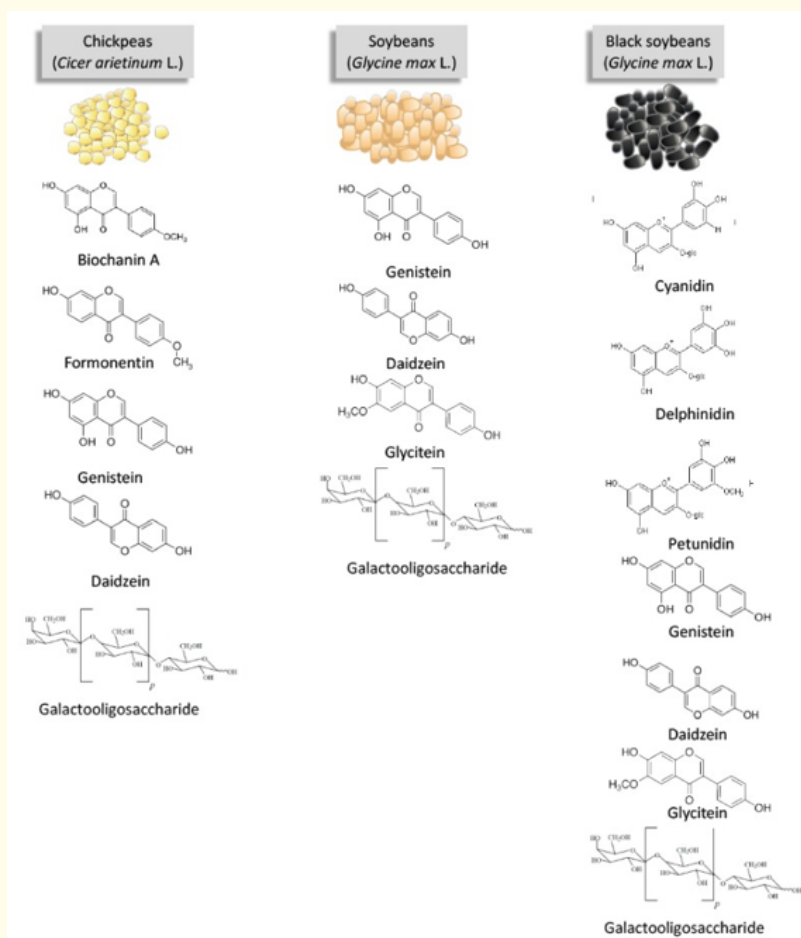


Figure 1: Courtesy ref 114-The bioactive compounds present in soybeans and chickpeas.

Important role of Isoflavones is their phytoestrogen activity, that is secondary to their weak affinity for estrogen receptors [31, 33]. Because of which Isoflavones have been used for cancers, cardiovascular disease, inflammation and diabetes [31,33]. How they act as antidiabetics is by attenuating insulin resistance and improving insulin secretion [30], which is supported by different clinical trials [4,15-17].

Anthocyanins

Anthocyanins represent the most vibrant types of flavonoids, and give the red, blue and purple pigments to plants [28]. Commonest sources of Anthocyanins are black soyabeans, black beans and red kidney beans [34,35].

Commonest Anthocyanins found in plants are cyaniding, delphinidin, pelargonidin, peonidin, petunidin and malvidin [36]. Types of Anthocyanins that are present in black soyabeans is not clear, though consistently various studies report presence of cyaniding-3-glucoside, delphinidin-3 glucoside, and petunidin -3 glucoside (figure 1) [37,38]. Anthocyanins like isoflavones are effective in CVD, cancer, inflammation and diabetes which is mainly secondary to their antioxidant activity [37]. Since dietary Anthocyanins improve insulin sensitivity [37], they constitute important way that diet can be used to combat IR.

Galactooligosaccharides

Galactooligosaccharides (GOS) describes a heterogenous group of carbohydrates that are composed of 1-10 galactosyl molecules [39,40]. GOS sources are human and bovine milk [40,41], but also found in foods like chickpeas and soya beans [17,38], and get commercially manufactured using β -galactosidase from lactose [40].

These GOS act as very potent prebiotics and their health benefits include promotion of gastrointestinal tract (GIT) health, weight management, prevention of carcinogenesis, etc [42]. Role of GOS in improving insulin sensitivity has also been proposed.

Mechanism of Action of reduced insulin resistance by Soyabeans and Pulses

Glucose transporter -4 and glucose utilization

Normally, pancreatic β -cells release insulin in amounts which correspond to changes in plasma glucose concentrations [43]. Then glucose gets removed from circulation by uptake into the cells of insulin sensitive tissues (skeletal muscle, adipose tissues) via glucose transporter -4 (GLUT-4) for energy utilization or storage [44]. Circulating insulin stimulates roughly 50% of intracellular GLUT-4 that has to be redistributed from storage vesicles in

the cytosol to the plasma membrane [44,45]. According to studies patients having T2DM, where IR is present, both expression as well as translocation of GLUT-4 is decreased markedly [30,44]. Hence increasing the levels and translocation of GLUT-4 is an important factor required for controlling glucose tolerance and Insulin sensitivity for preventing the development of insulin resistance (IR) [44-46].

Various investigators have studied the bioactive compounds present in soybeans and pulses, regarding how they work in improving glucose utilization and insulin sensitivity through increasing GLUT-4 gene expression as well as plasma membrane levels. Black soybean koji e. a fermented black soybean product was used for preparing an extract by Huang *et al* [47] for treating 3T3-L1 preadipocytes. These preadipocytes are usually made use of for studying insulin resistance to see the effect on adipogenesis along with related processes like glucose uptake [48,49]. To induce IR, preadipocytes got treated with dexamethasone and insulin for 60h (8days are needed to get mature adipocytes under culture conditions), by a method that has been shown to promote IR in this cell line [50]. An increase in protein levels of GLUT-4 was induced by black koji extract in a dose dependent manner from 25 to 200 μ g/ml as compared with vehicle treatment. The highest concentration i. e 200 μ g/ml increased glucose utilization in the preadipocytes significantly as compared to vehicle treatment. An analysis for isoflavone content of black soybean extract was done by Huang *et al* [47] but not of other flavonoids like anthocyanins, responsible for the black seed coat colour of this particular soybean and have been shown to increase GLUT-4 expression in some other studies [35]. Similarly, Inaguma, *et al.* [51] showed that it is the anthocyanins in black soyabeans which are responsible for increased glucose uptake. On treating adipocytes (3T3-L1 cells) with the anthocyanin, cyaniding-3-glucoside (20 and 100 μ M) after extraction from black soyabeans Inaguma, *et al.* [51] found that both cyaniding-3-glucoside concentrations increased mRNA levels of GLUT-4 compared to the vehicle treatment.

Further glucose utilization increase secondary to black soybean anthocyanins was also shown in a diabetic rodent model *in vivo* [35]. Sprague Dawley (SD) rats that were made diabetic by injection of streptozotocin (50mg/kg) had an increase in blood glucose levels, decreased blood insulin concentrations, along with a decrease in cardiac and skeletal muscle GLUT 4 protein [35]. Oral gavage of anthocyanins (50mg/kg) that was extracted from black soyabeans to these diabetic rats for 30 days decreased blood glucose levels, increased circulating insulin concentrations, along with

raised GLUT -4 translocation and insulin receptor phosphorylation in heart and skeletal muscle, compared to the diabetic control group [35].

Using anthocyanins (50mg/kg) that was extracted from a non-legume source by Luna-Vital et al supported that anthocyanins are the class of compounds which improve the GLUT-4 levels [52]. An anthocyanin rich purple corn water extract markedly increased glucose uptake in insulin resistant adipocytes compared to vehicle treatment [46]. Cyanidin -3-glucoside that is the major anthocyanin present in purple corn extract, administered by itself, also raised glucose uptake in IR adipocytes [52].

Reversely Gao., et al. showed that treating 3T3L1 adipocyte cells with isoflavones extracted from chickpeas (in concentrations of 50µg/ml and 100µg/ml) decreased GLUT4mRNA and protein levels in a dose dependent manner, when compared to vehicle treated adipocytes. Although chickpea isoflavones reduced GLUT-4 levels [30], with adipocytes not made IR as occurred with anthocyanins [33,37,51,52]. Thus in all it is the anthocyanins which are the compounds that cause the translocation of, and expression of GLUT-4 in adipocytes under conditions of IR as per these studies [30,35,47,51,52].

Per oxisome Proliferator Activated Receptor γ (PPAR)

PPAR belongs to a nuclear receptor family of ligand activated transcription factors [53]. Of the 3 different isoforms of PPARs, PPAR α and PPAR γ are the ones commonly studied for insulin sensitivity [53,54]. PPAR γ is mainly found in adipose tissue, and regulates adipocyte differentiation, and hence is an indirect regulator of glucose as well as lipid homeostasis [55, 56]. Once activated PPAR γ helps in normal insulin sensitivity that is by modulation of activation of specific insulin signaling molecules [30,55,56].

There has been a suggestion that isoflavones may bind to and activate PPAR γ [57]. Huang., et al. study [47], the black soybean koji extract (200µg/ml), which was rich in isoflavones markedly reduced PPAR γ protein levels in 3T3L1 preadipocytes, that were insulin resistant, as compared to control. Similarly Gao., et al. reported the chickpea isoflavones (50 and 100µg/ml) caused a reduction in PPAR γ mRNA levels as well as protein levels of CCAT-enhancer protein - α (C/EBP α), (which is a transcription factor that controls the PPAR γ expression) were also reduced by chickpea isoflavones. Also anthocyanins that were extracted from black soyabeans (50µg/ml) also reduced PPAR γ protein levels in differentiated 3T3L1 adipocytes [58]. This anthocyanin extract from these black soyabeans, consisted of cyaniding-3-glucoside (68. 3%), delphinidin -3 glucoside (25. 2%) and pentunidin-3 glucoside (6. 5%) [58].

Two questions got raised by both the studies of Gao., et al. [30], as well as that of Huang., et al. [47], both showing that there was improvement of insulin sensitivity regarding i) is adipocyte maturity a factor in insulin sensitivity ii) will anthocyanins also inhibit adipocyte differentiation by effecting downregulation of PPAR γ in preadipocytes, or would isoflavones continue to downregulate PPAR γ in mature adipocytes?

PPAR γ gets activated after binding of insulin sensitizing drugs like thiazolidenediones (TZDs), which further stimulates adipocyte differentiation, which =>increased accumulation of fat depots [59,60]. Kadowasi suggested that TZDs mechanism of action is by increasing the number of small adipocytes via. PPAR γ , and simultaneously reducing the number of large adipocytes [57]. Both actions would have an effect on alleviating IR [59]. Thus one could propose that the down regulation of, PPAR γ by isoflavones from chickpeas and soyabeans in preadipocytes, might prevent the development of large, dysfunctional adipocytes commonly associated with obesity and IR [61]. Thus isoflavones by inhibiting lipid accumulation, improve glucose utilization and insulin sensitivity [47]. None of the studies reported whether PPAR γ got activated or some other genes got activated, thus further research on this would clarify how isoflavones improve insulin sensitivity via PPAR γ .

Fat Deposition and Metabolism

In obesity once chronic energy consumption occurs there is spillover of triglycerides and other lipid metabolites into non adipose tissues like liver and muscle [53]. The deposition of lipids ectopically has an effect of interfering with intercellular signaling in these tissues, resulting in IR [53].

Legumes and bioactive isoflavone compounds have been shown to decrease fat deposition [30, 62-64]. 8week old male SD rats received high fat diet supplemented with raw, crushed chickpea seeds as studied by Yang et al [64]. Following 8mths of dietary supplementation, rats fed chick peas had markedly decreased body weight, epididymal fat pad weights (that is an indicator of visceral adiposity), along with reduced levels of triglycerides in liver and muscle as compared to non-supplemented rats fed a high fat diet [64]. Also postprandial plasma glucose and insulin levels were lower in chickpea supplemented rats in contrast to non supplemented rats [64]. Thus, chickpeas can blunt the hyperglycaemic and hyperinsulinemic effects of a long term high fat diet, and simultaneously decrease visceral adiposity and ectopic lipid accumulation [64]. Interestingly Yang et al used raw chickpea seeds in their study. In some countries raw chickpeas are taken, normally it is advised to cook chickpeas for destroying antinutritional factors which might

=>undesirable GIT side effects if taken raw [65,66]. What was not clear from this study was, is the good effect seen secondary to chickpeas or the antinutritional factors in this study. But treatment of 3T3L1 adipocytes with isoflavones extracted from chickpeas (extra-c concentration of 50µg/ml and 100µg/ml) caused a reduction of intracellular lipid accumulation in a dose dependent manner in comparison to control adipocytes as shown by Gao., *et al.* [30].

In vivo effects on fat deposition with subsequent IR was studied regarding soy isoflavones. Male SD rats that had high fat diet induced IR, received soya bean isoflavones in a dose of 150mg/kg and 450mg/kg by oral gavage x 30days. They had markedly decreased white adipose tissue weight that included epididymal and perirenal fat pad weights in contrast to IR control group with no difference in body weights among the groups [1]. Also fasting insulin levels and HOMA-IR were significantly lower in the rats that received soya bean isoflavones, as compared to their IR control counterparts [1]. Effects of soy isoflavones was also studied in obese and lean spontaneously hypertensive/NIH corpulent (SHR/N-cp) rats [62]. Supplementation of dietary soy isoflavones in both lean and obese SHR/N-cp rats markedly decreased fat deposition in various fat depots, as compared to control rats [62]. This soy isoflavone mixture consisted of genistein, daidzen, and glycitein, which was administered at 0. 1% w/w (100mg isoflavones/kg of diet) in AIN-93-G semipurified diet [62]. This amount equated to approximately 2. 5mg isoflavone/day based on an average of 25 g diet/day approximately [67]. Though there was no data for confirming the presence of IR in the obese rats, these data in obese SHR. N-cp rats are interesting as they are the IR phenotypes and thus the results imply soy isoflavone are helpful in decreasing adiposity in an IR state [62].

Genistein comprises of the main isoflavone glucoside compounds found in isoflavones seen in soya beans and lesser amounts in chickpeas [1,30,59]. Utilizing genistein (90%) as a pure dietary supplement (0. 1%w/w in high fat diet) for 4 weeks, in female ovariectomized SD rats, significantly smaller adipocyte but not fat padmass was found by Choi., *et al.* [63], as compared to their ovariectomized control counterparts. Since smaller adipocytes are more insulin sensitive, it is not surprising that HOMA-IR index was significantly reduced in ovariectomized rats supplemented with genistein, reaching a level comparable with the non ovariectomized sham group fed the high fat diet [63]. Also adding genistein to the HFD =>positive changes in the enzymes related to fat synthesis and oxidation, for e. g reduced hepatic fatty acid synthase activity and increased carnitine palmitoyl transferase, β -oxidation, and succinate dehydrogenase activity in adipose. Down regulation of genes

responsible for fatty acid synthesis was also a sequence of genistein supplementation, besides upregulation of genes responsible for fat utilization [63]. Although in this study genistein was not extracted from soybeans or chickpeas, it does help in giving the mechanism by which genistein treatment effects fat metabolism, with subsequent improvement in IR.

A positive effect of soy and soy-derived isoflavones on fat deposition has not been found in all studies. In male C57BL/6 mice fed a low fat diet containing soybean (8. 5% w/w) for 21 weeks had significantly increased total fat mass and fat pad weights, but not lean mass or total body weight, was shown by Zaniella., *et al.* [68], as compared to mice fed the soy free diet. Similarly when additional genistein was supplemented (5mg/kg/day) by oral gavage, same results were found. Neither the soy, nor genistein treatments influenced glucose metabolism or insulin sensitivity, as is determined by postprandial glucose and insulin tolerance testing respectively [68].

From these findings on soy [56,57,62], it is clear that with respect to adiposity, no benefit of soy is found in non diseased animal models consuming a low fat diet [70]. But evidence supports the conclusion that under conditions of a HFD, supplementing soy, chickpeas and/or their respective isoflavones can attenuate IR, possibly by reducing adiposity [30,62-64].

Adipokines

It is well known that relationship exists between adipose tissue and IR. With increased adipose mass =>weight gain impairment of insulin action occurs, which =>IR [69]. Yet increased mass is just one part of the game regarding role of adipose in IR. Adipose tissue is an active endocrine organ, which produces and secretes proteins called adipokines [70,71]. Once adiposity increased adipocytes become dysfunctional and hypertrophic =>dysregulation of adipokines [72,73]. Adiponectin, leptin and resistin are the adipokines affected following increased adiposity and IR. [70,73]. With this connection between diet, adiposity and IR, it is not surprising that dietary components can influence adipokine levels [74] and thus play a role in IR.

Adiponectin

Adiponectin has many beneficial biological effects, that include antiinflammatory, antiatherogenic, and antidiabetogenic actions [75]. Measured Adiponectin levels in the circulation, along with in AT, are inversely related to IR [47,57]. Hence restoring Adiponectin levels is of benefit in attenuating IR and improving insulin sensitivity [76].

SD rats having IR induced by high fat diet, giving soybean isoflavones (150mg/kg/day and 450mg/kg/day) by oral gavage x 30days increased both circulating protein and mRNA levels of adiponectin in perirenal white adipose tissue (WAT) compared to the insulin resistant control group and there was a significant negative correlation between circulating Adiponectin levels and HOMA-IR [1].

Studying the effect of soybean extract in IR 3T3L1 adipocytes, *in vitro* [47,51], 60h treatment for 60h with isoflavone rich black soybean koji extract (50-200µg/ml) increased Adiponectin protein significantly as seen by Huang, *et al.* [47], as compared to vehicle treatment. The study carried out by Inaguma, *et al.* [51], a reference was given to a study by Han, *et al.* [77], in which cyaniding-3-glucoside, the anthocyanin extracted from black soybeans markedly raised Adiponectin mRNA levels in 3T3L1 cells in a dose dependent manner.

From the above studies it is not possible to find out which compounds present in soy (i. e. anthocyanins or isoflavones) is responsible for the observed rise in Adiponectin levels. But all studies did not report appositive effect of soy isoflavones on Adiponectin levels. On supplementation by diet genistein (90%pure) in a HFD as 0.1%w/w given to ovariectomized SD rats for 4wks, Choi, *et al.* [63] found no significant differences in the level of serum adiponectin between control and genistein supplemented groups. However an improvement in the IR index in ovariectomized rats supplemented with genistein was seen [63]. Similar results in adiponectin in mature, premenopausal, insulin resistant female monkeys supplemented with dietary soy isoflavones (155mg/day) for 4 mths was found by Kavanagh, *et al.* [78]. Although dietary supplementation had no effects on plasma adiponectin levels; it did increase insulin area under the curve compared to control group, though no differences in glucose area under the curve were seen [78]. This suggests soy isoflavones promote hypersecretion in postmenopausal female monkeys.

Both Choi, *et al.* [63] and Kavanagh, *et al.* [78] did not examine tissue levels of adiponectin. It has been reported that adiponectin circulates until it binds to specific cell surface receptors [70]. Adiponectin receptors have been found in insulin responsive tissues like liver, adipose and skeletal muscle [75]. Thus improved IR that was reported by Choi, *et al.* [63], might be explained by increasing adiponectin responsiveness in these tissues.

Leptin

Role of leptin in control of energy balance and hence weight gain and adiposity is well known [73,79].

Zhang, *et al.* [1], measured leptin levels in HFD induced IR rats. They found high dose of soy isoflavones (450mg/kg, day) x 30days increased both circulating protein as well as adipose mRNA levels of leptin, despite decreased adipose weight, as compared to IR control grup [1]. Although HOMA-IR levels were decreased with both medium and high dose of soy isoflavone (150 and 450mg/kg/dayrespectively) Zhang, *et al.* showed that the negative association between circulating leptin and HOMA-IR did not reach statistical significance (p=0. 053) [1]. Further Choi, *et al.* measured serum leptin following dietary supplementation of genistein on ovariectomized rats fed a HFD [63]. No differences were noted in serum leptin levels between the groups after 4 weeks of supplementation by them [63]. Yang, *et al.* studied 8week old old male SD rats fed a HFD, that were supplemented with raw crushed chickpea seeds (10% w/w) for 8 mths had lower leptin mRNA levels in adipose as compare to untreated HFD control group [64]. Also, chickpea supplementation =>lower HOMA-IR levels, showing improved insulin sensitivity [64]. Thus, there has been a discrepancy on the relationship between leptin and IR and the effects of chickpea and soyisoflavoneson leptin levels [1,63,64]. Zhang, *et al.* showed that although there was a trend, which was not statistically significant between increased leptin levels and improved insulin sensitivity, that is similar to what has been seen by other reearchers who showed leptin improved insulin sensitivity [73,80]. Though Zhang, *et al.* saw changes in leptin levels with soy isoflavones, Choi, *et al.* showed genistein improved insulin sensitivity, without having any effect on leptin levels. Although Yang, *et al.* [64] did find decreased leptin and HOMA-IR levels from chickpea isoflavones, they did not do any correlation analysis, hence their observations remain inconclusive on the impact of leptin on IR. Hence without this confirmed benefit on IR, conclusions can't be drawn if one isoflavone is better than the other.

Resistin

Resistin, an adipokine not wellknown for promoting IR [73], hence limited studies on effects of soybeans as wellas pulses on Resistin levels are available. Zhang, *et al.* found soy isoflavones markedly reduced plasma Resistin levels following 30days of treatment withboth doses (150mg/kg/day and 450mg/kg/day). Although only higher doses of soy isoflavones decreased adipose mRNA levels of resistin [1]. Also a positive correlation between plasma resistin levels and HOMA-IR, gave a suggestion that increased resistin secretion improves IR [1].

Thus above adipokine studies show that isoflavone compounds obtained from Soy, favourably impact insulin sensitivity, by upregulating adiponectin and down regulating resistin [1,47,51]. Yet ef-

fects of chickpea and soy isoflavones on leptin levels and their relation to IR remains not clear requiring further studies.

Gut microbes and short chain fatty acids (SCFA)

Diet strongly affects production of SCFA by having an impact on bacterial flora of the GIT, by changing intestinal fermentation [81,82]. These SCFA comprising of acetic acid, propionic and butyric acids give energy to colonic cells and hence change the acidity of luminal pH, hence suppress growth of pathogenic bacteria, which promotes the growth of beneficial bacteria, like bifidobacterium, bacteroides, lactobacillus [39,81]. HFD changes composition of these gut flora from having lesser beneficial bacteria. To >harmful ones like firmicutes, clostridium [39,82]. This change in bacterial flora acts as an important factor in IR development followed by many metabolic diseases [39,83].

Galactooligosaccharides (GOS) are believed to act as prebiotics by increasing the production of SCFA and thus growth of beneficial bacteria [39,82]. The effects of commercially available soybean GOS (SBOS) on the gut ecosystem of Huangjiang mini piglets which are an experimental model meant to study human intestinal physiology [84] was done by Zhou., *et al.* [85]. These piglets received a standard diet and randomly assigned to supplementation of corn starch (0.5% w/w; control group) or SBOS (0.5/Ww/w; experimental group) for 14 days [85]. They found that SBOS supplementation increased total SCFA, propionate, and butyrate concentrations on the ileum and colon, as well as acetate and valerate concentrations in the ileum as compared to the control group. Further SBOS addition also raised the beneficial bacteria numbers in the intestine that included Bifidobacterium, Faecalibacterium, Fusobacterium, and Roseburia, while decreasing the potentially harmful bacteria like Clostridium, Streptococcus, and E. Coli as compared to control group [85]. Dai., *et al.* studied the effects of alpha GOS (α -GOS) extracted from dried chickpea powder in CD-1 IGS mice fed a HFD for 6 weeks. This CD1-IGS mouse is an outbred, general multipurpose model which presents which presents as a healthy phenotype [86]. Intake of a HFD for 6 weeks decreased SCFA and decreased total bacterial quantity along with altering the gut microbial composition as expected [39]. Once chickpea α -GOS (0.083g/kg/day) was given concurrent with HFD for 6 weeks promoted the secretion of SCFA in a dose dependent manner as compared to HFD and normal chow groups. All chickpea α -GOS treatments further stimulated the growth of beneficial bacteria like Bifidobacterium and Lactobacillus act the HFD group significantly. Though the HOMA-IR values were elevated in the HFD group act the normal control group, all the chickpea α -GOS groups had HOMA-IR values intermediate between the HFD group and the normal control group although this was not

considered statistically significant [39]. Another study where male C57BL/6mice were used, a longer duration, i. e. 18 weeks were seen as compared to 6 weeks of HFD feeding was needed to get statistically significant effects in insulin parameters for dietary GOS supplementation (7%w/w) [86]. The supplemented dose of GOS was greater in the study done by Kavadi., *et al.* [87], approximately 210-350mg/day (based on an average food intake of 3-5g/day [88], as compared to roughly 21mg/day in the study by Dai., *et al.* [39]. Hence it is possible that carrying out a longer study duration and or/higher dose of GOS treatments could =>reaching statistical significance for HOMA-IR. No significant differences in body weight among the HFD and 3 α -GOS treatment groups was found by Dai., *et al.* [39]. Thus lack of statistical effect on HOMA-IR by chickpea α -GOS; though adiposity was not checked in this study.

Despite a connection between GOS consumption of GOS from soy beans and chickpeas along with improved IR was not studied by Zhou., *et al.* [84] and Dai., *et al.* [39] respectively, other studies did examine the mechanism by which SCFA improved IR. Supplementing a HFD over the course of 20 weeks with 5%w/w SCFA (acetate and propionate) in male C57BL/6mice decreased HOMA-IR levels to those that were comparable with mice fed a low fat diet, which indicated an improved insulin sensitivity [82]. Also SCFA supplementation besides decreasing the total adipocyte numbers, also promoted smaller adipocytes as compared to abundant larger adipocytes seen in mice which were supplemented with a free HFD [82]. Further SCFA promoted adiposity browning, associated with increased cytochrome c oxidase activity (an indicator of mitochondrial respiratory capacity) along with expression of browning markers (like Pgc1 α). Further it has been thought that propionate plays an important role in the mechanism by which SCFA prevents IR, as seen by increased levels of hepatic odd chain-fatty acids- (a biomarker of propionate formation) and negative correlation between the formation of those odd chain fatty acids in the liver and the secretion of insulin during oral glucose tolerance test (GTT) [82].

Compared to these other studies have also shown that GOS from sources different from soybeans and chickpeas had no effect on improving insulin sensitivity. Stahl., *et al.* [89], conducted a study in SD rats, given a diet supplemented with GOS (15%w/w) for 9 weeks. GOS improved insulin sensitivity, act control group (supplemented with 15% w/w methyl cellulose) [91]. AS found in Dai., *et al.* study. study length might not have been optimal for seeing a change in insulin sensitivity in a population without IR. But similar changes were seen in overweight or obese prediabetic men who received GOS supplements (15g/day) with their regular meals for

12 weeks [90]. Addition of GOS increased faecal Bifidobacterium spp, but no changes in insulin sensitivity were seen [90]. Thus probably the GOS from legumes, rather than milk sources, might be more beneficial for improving insulin sensitivity; variability in the properties (structural, functional) of GOS from different sources might play a role in their beneficial effects. More work is needed to confirm the effect of SBOS and chickpea α -GOS on insulin sensitivity, along with conditions needed for SBOS and chickpea α -GOS to get optimal effect.

Conclusions

Thus this review summarizes how soya beans, chickpea along with their related bioactive compounds improve insulin sensitivity. Importantly soyabeans and chickpea showed effect of increasing insulin sensitivity only when a disease condition was present [1,36,39,47,62,64]. Models where disease condition was there soyabeans, chickpeas and/or bioactive compounds decreased adiposity [1,30,60,62], had influence on adipokines positively [1,47], inhibited adipogenesis (by downregulating PPAR γ [30,58], raised GLUT-4 levels [36,47,51], along with increasing SCFA producing benefitting bacteria in the GIT [39]. Similar results were not seen in absence of disease like increased adiposity [68], and reduced leptin levels [64] with soyabeans, chickpea addition. Thus possibly in absence of disease condition these soyabeans, chickpea only give nutritive value of legumes. Lot of studies have proved that good effects of soybeans/pulses is secondary to their high antioxidant activity of their bioactive compounds like anthocyanins and isoflavones [12,91,92]. Though oxidative stress gets taken care of which is associated with IR [93], actions of these bioactive compounds are beyond improving antioxidant activity and add to improving insulin sensitivity needs emphasis. As outlined isoflavones from both soyabeans, chickpea, decreased adiposity, important for betterment of IR. Isoflavones inhibit lipid accumulation in adipocytes via inhibiting PPAR- γ , that is a marker of early and mid-stage differentiation [47,60], glycerol-3 phosphate dehydrogenase (marker of late stage differentiation [86], and by causing apoptosis of mature adipocytes [94]. Isoflavones regulate PPAR γ by inhibiting tyrosine phosphorylation of C/EBP, besides activating Wnt signaling and adenosine monophosphate-activated protein kinase (AMPK) pathways [95,96]. These actions cause antiadipogenic effects which improve IR. Similarly, anthocyanins might act by AMPK activation. The AMPK activation caused by anthocyanins [97,98], increases GLUT-4 translocation=>increased glucose uptake along with improved insulin sensitivity [97,99]. Anthocyanins might also indirectly activate AMPK by increasing adiponectin secretion [99].

Soybeans seem to have greater effect on insulin sensitivity though both soyabeans, chickpea, are effective.

Considering importance in humans, it has been seen that mean intake of isoflavones from soy sources is <5mg/day in US and across European countries [100-103]. Among Asian populations the intake of isoflavones from diet is between 22-47mg/day [102-103], in vegetarian based diets roughly 22mg/day [103]. When external supplements were used in western countries mean isoflavone intake was 50mg/day [103]. Highest dose given to SD rats which got an effect 450mg/kg was =68-81mg/day that is similar to that of isoflavones given to participants of clinical studies [4,16,18]. Regarding anthocyanins average US intake is 12mg/day [104], and 30mg/day in Europeans [105]. No recommendations for Canada, US or European union (EU) as per anthocyanin intake though for China it is 50mg/day that is recommended [104]. No toxic effects have been seen with high doses of anthocyanins both in humans along with rodents i. e 9g/kg for rodents and 2g/day in humans [104,106]. Blueberries, blackberries and black soyabeans contain roughly 353mg, 529mg and 23 mg/100g of anthocyanins respectively [107]. In animal studies [35], animals took 50mg/kg/day of anthocyanins from black soybeans= to 11-12. 5mg anthocyanins/day. As per oligosaccharides not much knowledge is there though it has been suggested that 3g/day in European diets is required for healthy GIT microflora [108]. In Dai's study [39] mice took 0.083-0.83g/kg alphaGOS from chickpeas=2.1-21mg/day. As per Han and Baik [109] there were 144.9mg/g of total oligosaccharides in dry chick peas meaning one cup (250g) of dry chickpeas would have roughly 36 g of oligosaccharides. Though importantly oligosaccharides content decreases after cooking [109].

CVD is a well known cause of mortality and morbidity for diabetics [110]. Intake of soybeans and other pulses can improve vascular function [111-114]. Thus importantly soybeans, chickpeas besides improving insulin sensitivity these and other pulses might attenuate CVS risk associated with IR.

More studies are needed with other pulses besides the information on soybean and chickpeas on IR and insulin sensitizing effects.

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