ACTA SCIENTIFIC NUTRITIONAL HEALTH

Volume 3 Issue 4 April 2019

Research Article

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

**Kulvinder Kochar Kaur[1]*, Gautam Allahbadia[2] and Mandeep Singh[3]**

[1]*Scientific Director, Dr Kulvinder Kaur Centre for Human Reproduction, Punjab, India*

[2]*Rotunda-A Centre for Human Reproduction, Mumbai, India*

[3]*Consultant Neurologist, Swami Satyanand Hospital, Jalandhar, Punjab, India*

***Corresponding Author:** Kulvinder Kochar Kaur, Scientific Director, Dr Kulvinder Kaur Centre for Human Reproduction, Punjab, India.

**Received:** January 21, 2019; **Published:** March 15, 2019

## 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 arttempts to explain the detailed mechanism of action of how soybeans and chickpeas act to reduce IR.

**Keywords:** Soybeans; Chickpeas; Lentils; Insulin Resistance; GLUT4; PPARγ; 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 paharmacological 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, fried 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 buiactuve 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 >300various 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 formonentin [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 dietry 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 changesin 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 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 soyabean koji e. a fermented black soyabean 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 200μg/ml as compared with vehicle treatment. The highest concentration i. e 200 μg/ml increased glucose utilization in the preadipocytes significantly as compared to vehicle treatment. An analysis for isoflavone content of black soyabean extract was done by Huang eral [47] but not of other flavonoids like anthocyanins, responsible for the black seed coat colourof this particular soyabean 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-L1cells) with the anthocyanin, cyaniding-3 –glucoside (20and 100μM) 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 soyabean anthocyanins was also shown in a diabetic rodent model *in vivo* [35]. Sprague Dawley (SD) rats that were made diabetic by injection of steptozotocin (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 30days 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 etal 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 anthrocyanin 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, PPARα and PPAR γ are the ones commonly studied for insulin sensitivity [53,54]. PPARγ 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 PPARγ 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 PPARγ [57]. Huang., *et al*. study [47], the black soybean koji extract (200µg/ml), which was rich in isoflavones markedly reduced PPARγ 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 PPARγ mRNA levels as well as protein levels of CCAT-enhancer protein –α (C/EBPα), (which is a transcription factor that controls the PPARγ expression) were also reduced by chickpea isoflavones. Also anthocyanins that were extracted from black soyabeans (50µg/ml) also reduced PPARγ 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 PPARγ in preadipocytes, or would isoflavones continue to downregulate PPARγ in mature adipocytes?

PPARγ 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. PPARγ, 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, PPARγ 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 PPARγ got activated or some other genes got activated, thus further research on this would clarify how isoflavones improve insulin sensitivity via PPARγ.

## 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 etal [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 liverand muscle as compared to non-supplemented rats fed a high fat diet [64]. Also postprandial plasma glucose and insulin levels were lower in chiclpea 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 sumultaneously decrease visceral adiposity and ectopic lipid accumulation [64]. Interestingly Yang etal used raw chickpea seeds in their study. In some countries raw chickpeas are taken, normally it is ad vised tocook chockpeas 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 epidydimal 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 glyciten, 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 isoflovanes seen in soya beans and lesser amounts ln chickpeas [1,30,59]. Uililizing 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 relatipnship 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 dysfunctionaland 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 antinflammatory, 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 attaenuating 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 anthrocyanin 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 bydiet 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 grpup [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 reaearchers 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 aceric acid, propionic and butyric acids give energy to colonic cells and hence change the acidityod luminal pH, hence suppress growth of pathogenic bacteria, which promotes the growth of beneficial bacteria, like bifidobaterium, 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 gtoup. Further SBOS addition also raised the beneficial bacteria numbers in the intestine that included Bifidobacterium, Faecalibacterium, Fusobacterium, and Rose buria, 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 6weeks. 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 6weeks 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 Lactobacullus 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 20weeks woth 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 supplelemention 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 Pgc1α). 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 benefical effects More work is needed to confirm the effect of SBOS and chicpea 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 PPARγ [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 PPARγ 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/kgwas =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. e9g/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 insilun 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.

## Bibliography

1. Zhang HM., *et al*. "The effects of soy isoflavone on insulin sensitivity and adipocytokines in insulin resistant rats administered with high fat diet". *Natural Product Research* 22.18 (2008): 1637-1649.

2. Artune F., *et al*. "The impact of insulin resistance on the kidney and vasculature". *Nature Reviews Nephrology* 12.12 (2016): 721-737.

3. Park SE., *et al*. "Biomarkers of insulin sensitivity and insulin resistance: Past, present and future". *Critical Reviews in Clinical Laboratory Sciences* 52 (2014): 180-190.

4. Llaneza P., *et al*. "Soy isoflavones improve insulin sensitivity without changing serum leptin among postmenopausal women". *Climacteric* 15.6 (2012): 611-620.

5. Medscape. "Insulin Resistance" (2017).

6. Gandhi GR., *et al*. "Gallic acid attenuates high fat diet fed streptozotocin –induced insulin resistance via partial agonismpf PPAR γ in experimental type2 diabetic rats and enhances glucose uptake through translocation and activation of GLUT -4 in PI3K/p-Aktsignaling pathway". *European Journal of Pharmacology* 745 (2014): 201-216.

7. Afshin A., *et al*. "Consumption of nuts and legumesand risk of incident ischaemic heart disease, stroke and diabetes. A systematic review and meta-analysis". *The American Journal of Clinical Nutrition* 100 (2014): 278-288.

8. Polak R., *et al*. "Legumes: Health benefits and culinary approaches to increase intake". Clinical Diabetes 33.4 (2015): 198-205.

9. Rebello CJ., *et al*. "A review of the nutritional value of legumes and their effects on obesity and its related comorbiditiesm". *Obesity Review* 15 (2014): 392-407.

10. Blair RM., *et al*. "Soyfoods have low glycemic and insulin response indices in normal weight subjects". *Nutrition Journal* 5 (2006): 35.

11. Mudryj AN., *et al*. "Nutritional and health benefits of pulses". *Applied Physiology, Nutrition, and Metabolism* 39.11 (2014): 1197-1204.

12. Thompson SV., *et al*. "Bean and rice meals reduce posprandial glycemic response in adults with type 2 diabetes: A crossover study". *Nutrition Journal* 11 (2012): 23.

13. Anderson JW., *et al*. "Cardiovascular and renal benefits of dry bean and soybean intake". *The American Journal of Clinical Nutrition* 70.3 (1999): 464s-474s.

14. Brar GS and Carter TEJr. "Soybean: Glycine max (L) Merrill". In Genetic Improvement of Vegetable Crops; Kalloo G, Bergh BO, Eds; Pergamon Press: Oxford, UK, Chapter 30 (1993): 427-463.

15. Choi MS., *et al*. "The beneficial effects of soybean (Glycine max (L.) Merrill) leaf extracts in adults with prediabetes arandomized placebo controlled trial". *Food Function* 5.7 (2014): 1621-1630.

16. Choquette S., *et al*. "Effects of soya isoflavones and exercise on body composition and clinical risk factors of Cardiovascular diseases on overweight premenopausal women: A 6mth-double blind controlled trial". *British Journal of Nutrition* 105.8 (2011): 1199-1209.

17. Fei BB., *et al*. "Effects of soy oligosaccharides on antioxidant enzyme activities and insulin resistance in pregnant women with gestational diabetes mellitus". *Food Chemistry* 158 (2014): 429-432.

18. Jamilian M and Asemi Z. "The effects of soya isoflavones on metabolic status of patients with polycystic ovary syndrome". *The Journal of Clinical Endocrinology and Metabolism* 101.9 (2016): 3386-3394.

19. Nilsson A., *et al*. "Effects of a brown beans evening meal on metabolic risk markers and appetite regulating hormones at a subsequent standardized breakfast: A randomized cross over study". *PLoS ONE* 8 (2013): e59985.

20. Reverri EJ., *et al*. "Black beans, fober and antioxidant capacitypilot study: Examination of whole foods vs functional components on postprandial metabolic oxidative stress, and inflammation in adults with metabolic syndrome". *Nutrients* 7.8 (2015): 6139-6154.

21. Mariangeli CP., *et al*. "Whole and fractionated yellow pea flours reduce fasting indulin and insulin resistance in hypercoleterolaemic and overweight human subjects". *British Journal of Nutrition* 105.1 (2011): 110-117.

22. Johnson SK., *et al*. "Palatability and glucose, insulin and satiety responses of chickpea floru and ectracted chi ckpea florur bread eaten as part of a breakfast". *European Journal of Clinical Nutrition* 59.2 (2005): 169-176.

23. Nestel P., *et al*. "Effects of long term consumption and single meals of chickpeas on plasma glucose, insulin and triacylglycerol concentrations". *The American Journal of Clinical Nutrition* 79.3 (2004): 390-395.

24. Pittaway JK., *et al*. "Chickpeas may influence fatty acids and fiber intake in ad libitim diet, leading to small improvements in serum lipid profile and glycaemic control". *Journal of the American Dietetic Association* 108.6 (2008): 1009-1013.

25. Ye YB., *et al*. "Daidzen and genstein fail to improve glycemic control and insulin sensitivity in Chinese women with impaired glucose regulation: A double blind, randomized, placebo controlled trial". *Molecular Nutrition and Food Research* 59.2 (2015): 240-249.

26. Bourdon I., *et al*. "Beans, as a source of dietary fibre, increase cholecystokinin and apolipoprotein B48 response to test meals in men". *Journal of Nutrition* 131.5 (2001): 1485-1490.

27. Win ham DM., *et al*. "Pinto bean consumption reduces biomarkers for heart disease risk". *The Journal of the American College of Nutrition* 26.3 (2007): 243-249.

28. Clark JL., *et al*. "Efficacy of flavonoids in the management of high blood pressure". *Nutrition Review* 73.12 (2015): 799-822.

29. Ko KP. "Isoflavones Chemistry, analysis, functions and effects on health and cancer". *Asian Pacific Journal of Cancer Prevention* 15.17 (2014): 7001-7010.

30. Gao Y., *et al*. "Isoflavones in chickpeas inhibit adipocyte differentiation and prevent insulin resistance in 3T3L1 cells". *Journal of Agricultural and Food Chemistry* 63 (2015): 9696-9703.

31. Yu J., *et al*. "Isoflavones: Antiinflammatorybenefit and possible caveats". *Nutrients* 8.6 (2016): 361.

32. Kim UH., *et al*. "Pterocarpan-enriched soy leaf extract ameliorates insulin sensitivity and pancreatic β-cell proliferation in type 2 diabetic mice". *Molecules* 19.11 (2014): 18493-18510.

33. Ridriques –Morato J., *et al*. "Pharmacokinetic comparison of soy isoflavines exacts in human plasma". *Journal of Agricultural and Food Chemistry* 63 (2015): 6946-6953.

34. Hu J., *et al*. "Anthrocyanin composition and expression analysis of Anthrocyanin biosynthetic genes in kidney mean pod". *Plant Physiology and Biochemistry* 97 (2015): 304-312.

35. Nizamutdinova IT., *et al*. "The antidiabetic effect of Anthrocyanins in strptozotocin –induced diabetic rats through glucose transporter 4 regulation and prevention of insulin resistance and pancreatic apoptosis". *Molecular Nutrition and Food Research* 53.11 (2009): 1419-1429.

36. Belwal T., *et al*. "Dietary anthrocyanins and insulin resistance. When food becomes a medicine". *Nutrients* 9.10 (2017): 1111.

37. Koh K., *et al*. "Identification of anthrocyanins in black soyabean (Glycine max (L.) Merrill) varirties". *Journal of Food Science Technology* 51.2 (2014): 377-381.

38. Lee JH., *et al*. "Characteristics of anthocyanins in the black soybeans (Glycine max (L.) by HPLC-DAD-ESI/MS analysis". *Food Chemistry* 112.1 (2009): 226-231.

39. Dai Z., *et al*. "Effect of aα-galacto-oligosaccharides from chickpeas on high fat diet induced metabolic syndrome in mice". *Journal of Agriculture and Food Chemistry* 65.15 (2017): 3160-3166.

40. Niittynen L., *et al*. "Galacto-oligosaccharidesand bowel function". *Scandinavian Journal of Nutrition* 51.2 (2007): 62-66.

41. US Food and Drug Administration (2017).

42. Sangwan V., *et al*. "Hypoglycaemic effects of galactooligosaccharides in alloxan induced diabetic rats". *Journal of Dairy Research* 82 (2015): 70-77.

43. Fu Z., *et al*. "Regulation of insulin synthesis ans secretionand pancreatic β celldysfinction in diabetes". *Current Diabetes Reviews* 9.1 (2013): 25-53.

44. Shan WF., *et al*. "Effect of GLUT 4 expression on insulin resistance in patients with advanced liver cirrhosis". *Journal of Zhejiang University Science B* 12 (2011): 677-682.

45. Mueckler M. "Insulin resistance and disruption of GLUT-4 trafficking in skeletal muscles". *Journal of Clinical Investigation* 107.10 (2001): 1211-1213.

46. Gannon NP., *et al*. "Dietary stimulators of GLUT 4 expressionand translocation in skeletal muscles. A mini review". *Molecular Nutrition and Food Research* 59.1 (2015): 48-64.

47. Huang CC., *et al*. "Effect of black soyabeanskoji extraction on glucose utilization and adipocyte differentiation in 3T3L1 cells". *International Journal of Molecular Sciences* 15 (2014): 8280-8292.

48. Sanchez-Solana B., *et al*. "Mouse raistin modulates adipogenesis and glucose uptake to 3T3L1 preadipocytes through the ROR1 receptor". *Molecular Endocrinology* 26 (2012): 110-127.

49. Zhou Y., *et al*. "Establishment of the insilun resistance induced by inflammatory response in 3T3L1 preadipocytes cell line". *Inflammation* 31 (2008): 355-364.

50. Lo KA., *et al*. "Analysis of in vitro insulin resistance models and their physiological relevance to in vivodiet induced adipose insulin resistance". *Cell Report* 5 (2013): 259-270.

51. Inaguma T., *et al*. "Improvement of insulin resistance by cyanidin3-glucosiide, anthocyaninfrom black beans through te upregulation of GLUT-4 gene expression". *BMC Process* 5 (2011): 21.

52. Luna-Vital D., *et al*. "Anthocanins from purple corn ameliorated tumor necrosis factor α induced inflammation and insulin resistance in 3T3L1 adipocytes via activation of insulin signaling and enhanced GLUT translocation". *Molecular Nutrition and Food Research* 61 (2017): 1700362.

53. Halzuik MM and Halzuik M. "PPAR –α and insulin sensitivity". *Physiology Review* 55.2 (2006): 115-122.

54. Ferre P. "The biology of peroxisome prolferator activated receptots: Relationshup woth lipid metabolismand insulin sensitivity. *Diabetes* 53 (2004): S43-S50.

55. Leonardini A., *et al*. "Cross talk between PPAR γand insulin signaling and modulation of insulin sensitivity". PPAR Res 2009 (2009): 1-12.

56. Olefsky JM and Saltiel AR. "PPAR γ and the treatment of insulin resistance". *Trends in Endocrinology and Metabolism* 11 (2000): 362-368.

57. Wagner JD., *et al*. "Effects of soy protein and isoflavones on insulin resistance and adiponectin in male monkeys". *Metabolism* 57 (2008): 524-531.

58. Kim HK., *et al*. "Black soybean anthocyanins inhibit adipocyte didderentiation in 3T3L1 cells". *Nutrition Research* 32 (2012): 770-777.

59. Kadowaki T., *et al*. "The role of PPAR γ in high fat diet –induced obesity and insulin resistance". *Journal of Diabetes and its Complication*s 16 (2002): 41-45.

60. Metzger D., *et al*. "Functional role of RXR's and PPAR γ in mature adipocytes". *Prostaglandins, Leukotrienes and Essential Fatty Acids* 73 (2005): 51-58.

61. Kubota N., *et al*. "PPARγ mediates high –fat diet indiced adipocyte hye pertrophy and insulin resistance". *Molecular Cell* 4 (1999): 597-609.

62. Ali AA., *et al*. "Effects of soybean isoflavones, probiotic s, and their interactions on lipid metabplism end endocrine system in an animal model of obesity and diabetes". *The Journal of Nutritional Biochemistry* 15 (2004): 583-590.

63. Choi JS., *et al*. "Genistein reduced insulin resistance index through modulating lipid metabolism in ovriectomized rats". *Nutrition Research* 32 (2012): 844-855.

64. Yang Y., *et al*. "Dietary chickpea reverse visceral adiposity, dyslipidaemia and insulin resistance in rats induced by a chronic high fat diet". *British Journal of Nutrition* 98 (2007): 720-726.

65. El-Adawy TA. "Nutrutional composition and antinutritional factors and chickpea s (Cicer arietinum L) undergoing different cooking methods and germination". *Plant Foods for Human Nutrition* 57 (2002): 83-92.

66. Pulse Canada (2018).

67. Hernandez CM., *et al*. "Spontaneoisly hypertensive rats: Further evaluation of age related memory performance and clinergic marker expression". *Journal of Psychiatry and Neuroscience* 28 (2003): 197-209.

68. Zanella I., *et al*. "Soy and soy isoflavone genostein promotes adipose tissue development in male mice on a low fat diet". *European Journal of Nutrition* 54 (2015): 1095-1107.

69. Vidal- Puigi A., *et al*. "Resistin: A new link between obesity and insulin resistance". *Clinical Endocrinology* 55 (2001): 437-438.

70. Kwon H and Pessin JE. "Adipokinesmediate inflammation and insulin resistance". *Front Endocrinol (Laussane)* 4 (2013): 71.

71. Rabe K., *et al*. "Adipokines and insulin resistance". *Molecular Medicine* 14 (2008): 741-751.

72. Guilherme A., *et al*. "Adipocyte dysfunctions linking obesity to insulin resistance and type2 diabetes". *Nature Reviews Molecular Cell Biology* 9 (2008): 367-377.

73. Jung UJ and Choi MS. "Obesity and its metabolic complications: The role of adipokines and the relationship between obesity, inflammation, insulin resistance., dyslipidaemia, and nonalcoholic fatty liver disease". *International Journal of Molecular Sciences* 15 (2014): 6184-6223.

74. Kashino L., *et al*. "Association of dietary patterns with serum adupokines among Japanese: A cross-sectional study". *Nutrition Journal* 14 (2015): 58.

75. Clark JL., *et al*. "Exoliring the cardiometabolic relevance of T-cadherin: A pleiotropic adiponectin receptor". *Endocrine, Metabolic and Immune Disorders* 17 (2017): 200-206.

76. Balsan GA., *et al*. "Relationship between adiponectin, obesity and insulin resistance". *Revista da Associação Médica Brasileira* 61 (2015): 72-80.

77. Han J., *et al*. "Cyanidin-3-glicoside anthocyanin from black beans has potential to protect insulin resistance on 3T3L1 adipocytes by inhibiting TNFα release". *British Journal of Nutrition* (2018).

78. Kavanagh K., *et al*. "High isoflavone soy diet increases insulin secretion without decreasing insulin sensitivity to premenopausal nonhuman primates". *Nutrition Research* 28.6 (2008): 368-376.

79. Antuna –Puente B., *et al*. "Adipokine: The missing link between insulin resistance and obesity". *Diabetes Metabolism* 34 (2008): 2-11.

80. Paz-Filho G., *et al*. "Leptin therapy, insulin sensitivity, and glucose homeostasis". *Indian Journal of Endocrinology and Metabolism* 16 (2012): S549-S555.

81. O'Connor S., *et al*. "Prebiotics in the management of components of the metabolic syndrome". *Mauritas* 104 (2017): 11-18.

82. Weitkunat K., *et al*. "Short chain fatty acids and insulin, but not guar gum, precent diet induced obesity and insulin resistance. through differential mechanism in mice". *Science Report* 7 (2017): 6109.

83. Murphy EA., *et al*. "Influence of high fat diet on gut microbiota: A sriving force for chronic disease risk". *Current Opinion in Clinical Nutrition and Metabolic Care* 18.5 (2015): 515-520.

84. Fu D., *et al*. "Molecular cloning and expression profiling of weaned Huangjiang mini piglets with large or small body weight at birth". *Molecular Biology Reports* 40 (2012): 3341-3350.

85. Zhou XL., *et al*. "Dietary supplementation with soybean oligosaccharides increases Short chain fatty acids but decreases ptotein derived catabolites in the intestinal luminal content of weaned Huangjiang mini piglets". *Nutrition Research* 34 (2014): 780-788.

86. Charles River. (2017).

87. Kavadi PK., *et al*. "Dietary incorporation of whey protein isolates and galactooligosaccharides exhibit improvement in glucose homeostasis and insulin resistance in high fat fed mice". *Journal of Intercultural Ethnopharmacology* 6 (2017): 326-332.

88. Research Diets. (2018).

89. Stahel P., *et al*. "Of the milk sugars, galactose, bit not prebiotic galactooligosaccharide improves insulin sensitivity in male Sprague Dawley rats". *Plos One* 12.2 (2017): e012260.

90. Canfora EE., *et al*. "Supplementation of diet with galactooligosaccharides increases Bifidobacteria, but not insulin sensitivity, in obese prediabetic individuals". *Gastrienterology* 153 (2017): 87-97.

91. Wang Q., *et al*. "Soya usoflavines: the multipurpose phytochemical (review)". *BioMed Research* (2013): 697-701.

92. Yoon GE and Park S. "Antioxidant actionof soy isoflavines 0n oxidative stressand antioxidant activities in exercised rars". *Nutrition Research and Practice* 8 (2014): 618-624.

93. Zhang ZF., *et al*. "Purple sweet potato color attenuates hepatic insulin resistance via blocking oxidative stress in high fat –diet treated mice". *Journal of Nutritional Biochemistry* 21 (2013;): 1008-1018.

94. Medjakovin S., *et al*. "Potential health modulating effects of isoflavones and metabolites via activation of PPAR and AhR". *Nutrients* 2 (2010): 241-279.

95. Feng S., *et al*. "Potential of Natural products in the inhibition of adipogenesis through regulation of PPAR γ expression and /or its transcriptional activity". *Molecules* 21 (2016): 1278.

96. Hossan MK., *et al*. "Molecular mechanisms of the antiobesity and antidiabetic properties of flavonoids". *International Journal of Molecular Sciences* 17 (2016): 569.

97. Li D., *et al*. "Health benefits of anthocyaninds and molecular mechanisms Update from recent decade". *Critical Reviews in Food Science and Nutrition* 57 (2017): 1729-1741.

98. Tsuda T., *et al*. "Anthicyanins enhances adipokines secretion and adupocyte specific gene expression in isolated rat adipocytes". *Biochemical and Biophysical Research Communications* 316 (2004): 148-157.

99. Huang B., *et al*. "Anti-diabetic effects purple corn extract on C57BL/Ksj db/dbmice". *Nutrition Research and Practice* 9 (2015): 22-29.

100. Chun OK., *et al*. "Urinary isoflavones and their metabolites-validate the diatary isoflavones intake in USadults". *Journal of the American Dietetic Association* 109 (2009): 245-254.

101. Filberto AC., *et al*. "Habitual dietary isoflavone intake is associated with decreased C rective protein concentrations among healthy premenooausal women". *Journal of Nutrition* 143 (2013): 900-906.

102. Pop EA., *et al*. "Effects of a high daily dose of soy isoflavones on DNA damage, apoptosis and estrogenic outcomes in healthy, postmenopausal women-A Phase 1 clinical trial". *Menopause* 15 (2008): 684-692.

103. Van der Velpen V., *et al*. "Large interindividual variation in isoflavone plasma concentrations limitsue of isoflavone intke data forrisk assessment". *European Journal of Clinical Nutrition* 68 (2014): 1141-1147.

104. Wallace TC. "Anthocyanins". *Advances in Nutrition* 6 (2015): 620-622.

105. Grosso G., *et al*. "Estimated dietary intake and major food sources of polyphenols in the Polish arm of the HAPIEE study". *Nutrition* 30 (2014): 1398-1403.

106. Khoo HE., *et al*. "Anthocyanidins and anthocyanins. Colored pigmentsas food pharmaceutical ingredients, and the potential health benefits". *Food and Nutrition Research* 61 (2017): 1361779.

107. Wu X., *et al*. "Concentrarions of anthocyanins in common foods in United States and estimation of normal consumption". *Journal of Agricultural and Food Chemistry* 54 (2006): 4069-4075.

108. Larentin A., *et al*. "Carbohydrates: Resistance starch and oligosaccgarides". In Guide to Nutritional Supplements; Caballero E, Ed; Elsevier Ltd; Oxford, UK (2009): pp84-92.

109. Han JH and Baik. BY. "Oligosaccharide content and composition of legumes and their reduction of soaking, cooking, ultrasound, and high hydrostatic pressure". *Cereal Chemistry* 83 (2006): 428-433.

110. Leon BM and Maddox TM. "Diabetes and cardiovascular disease. Epidemiology, biological mechanisms, treatment recommendations and future research". *World Journal of Diabetes* 6 (2015): 1246-1258.

111. Beavers DP., *et al*. "Exposure to isoflvone containingsoy products and endothelial function: A Bayesian meta-analysis if randomized controlled trials". *Nutrition, Metabolism and Cardiovascular Diseases* 201; 22 (2012): 182-191.

112. Hanson MG., *et al*. "Lentil-based diets attenuate hypertension and large artery remodellng in spontaneously hypertensive rats". *British Journal of Nutrition* 111 (2014): 690-698.

113. Hanson MG., *et al*. "Lentil consumption reduces resistance artery remodeling and restores arterial compliancein the spontaneously hypertensive rat". *Journal of Nutritional Biochemistry* 37 (2016): 30-38.

114. Clark JL., *et al*. "Rebelling against the (Insulin) Resistance: A Review of the proposed insulin sensitizing actions of Soybeans, Chickpeas, nd their bioactive Compounds". *Nutrients* 10 (2018): 434.

**Volume 3 Issue 4 April 2019**