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Short Communication

Bioactive Compounds within Herbs and Spices Contributing to Anti Diabetic Action in Type2 Diabetes Mellitus (T2DM) - A Short Communication

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Culinary herbs and spices are utilized as traditional medicine for ages for the therapy of diabetes mellitus (DM) along with its comorbidities, with various publications that propose use of medicinal plants. But mostly exactly what are the biologically active substances of these herbs and spices with their mode of action is not clear. We ourselves reviewed roles of monoterpenes, PTP1B Inhibitors, other plant products like soya bean pulses, aloe vera etc [1-5].

The antidiabetic action of usually used herbs and spices got analyzed in the study by Pereira *et al.*, utilizing virtual screening regarding 18 anti diabetes mellitus (DM) drug targets utilizing the DIA-DB webserver. Basically they wanted to find the bioactive agents of these plants and get the understanding of their molecular mode of working against diabetes mellitus (DM).

Primary *in vivo* model observed for examining the antidiabetic action of plant extracts used to be streptozotocin –induced or alloxan induced diabetic rats. Aniseed, bay leaves [6], cardamom [7], cinammon [7], cumin [8,9], dill [10], ginger [7], hops, rosemary [11], saffron [7,12], sage [13], and turmeric [14] have also been examined in type2 diabetes mellitus (T2DM) patients. Main *in vivo* results seen for herbs and spices are fall in hyperglycemia and hyperliidemia. Hyperglycemia seen in T2DM occurs secondary to pancreatic functional impairment along with insulin resistance (IR), correlated with imbalance in glycogenolysis and gluconeogenesis rates =>enhanced endogenous glucose synthesis [15]. Decrease in lipid was seen in total cholesterol, low density lipoproteins (LDL), very low density lipoproteins (VLDL), and triglycerides amounts with escalation of high density lipoproteins (HDL) amounts. DM presents with low plasma HDL with high triglycerides (TG), total cholesterol (TC), and LDL amounts [16]. Escalated LDL prevents insulin release and causes pancreatic B –cell apoptosis, although rise in HDL helps against apoptosis along with increase in pancreatic B –cell function, decreased plasma glucose and enhanced insulin. Collection of TG in liver, pancreas and muscles is associated with IR and the TC levels in adipocytes enhancement with > amts of TG's [17].

As DM represents a complicated disease, there is requirement for agents that have multiple targets instead of single target approach by one drug [18]. In view of this plants like herbs and spices represent a very lucrative therapy for DM since variety of protein targets might be controlled with >1 agent. In the study of Pereira., et al. almost 50% of the herbs and spices were shown to be having a good percentage that have multiple targets that are cinnamon, cumin, fennel, fenugreek, lemon balm, liquorice, oregano, lemon grass, saffron, marjoram, rosemary, sage, thyme. The main antidiabetic actions seen in earlier works were a decrease in hyperglycemia and hyperliidemia, along with control in insulin secretion. In figure 1, actions of each herb and spices on these 3 DM hallmarks based on the protein targets of the DIA-DB webserver is observed. All herbs and spices were shown to be potential controllers of ≥12 protein targets except paprika and cardamom, whose agents were only observed as potential controllers of 5 and 9 targets, respectively. Decrease in hyperglycemia can be due to the control of the protein targets that take part in glucose metabolism. AMY2A and MGAM Inhibition delays digestion of the carbohydrates, and hence reduces the postpartum blood glucose amount [19]. FBP1 and PYGL inhibition inhibits endogenous glucose synthesis through liver via inhibition of gluconeogenesis and glycogenolysis respectively and hence decreasing blood glucose [15]. PDK's get upregulated in DM and thus cause inhibition of pyruvate dehydrogenase kinase complex which in turn causes pyruvate → Acetyl CoA conversion, which then enters the Kreb's cycle [20]. With inhibition of PDK2, serum glucose might be decreased via inhibiting the amount of pyruvate present in liver for gluconeogenesis [21]. GCK activation also causes decrease of serum glucose amounts by helping glycogenesis and glycolysis via phosphorylation of glucose to glucose-6-phosphate.

Decrease in hyperliidemia can be explained by control of protein targets NR5A2, the PPARs and RXRA which are responsible for lipid metabolism. PPARs have variety of actions in lipid metabolism via genes which control and participate in lipogenesis, TG generation, reverse cholesterol transport, lipolysis and FA oxidation. PPARG stimulation => expression of cluster of differentiation 36 (CD36) which helps in clearing away the oxidized LDL through blood via macrophages [22]. Further PPARG stimulates expression of liver X receptor (LXR) which then stimulates the expression of reverse cholesterol transporter ABCA1, that liberates HDL into the blood

Figure 1: Protein-compound target networks identified for each herb and spice. The number below each protein target denotes the number of potential bioactive compounds identified [35].

stream, where cholesterol get concerted to bile salts in the liver and then excreted. Moreover PPARG promotes adipogenesis, making new adipocytes which can pick up extra lipids through plasma at the time promoting apoptosis of lipid –saturated adipocytes [23]. In the liver PPARA helps in fatty acid (FA) oxidation, enhances FA uptake by escalating the expression of FA transport along with FA translocase, enhancing apolipoprotein A1 (Apo-A1, i.e. a part of HDL) reduces Apo-C2 (part of VLDL) and, enhancing LPL (helping in breaking of TG → FA) [23].

Like PPARA, PPARD stimulates FA oxidation via upregulating of the target gene carnitine palmitoyl transferase A1 and reduces TG amounts via downregulation of target protein angiopoietin –like 4 protein which normally inhibits breaking and removal of TG [23]. Therapy with PPAR agonists hence will cause reduced cholesterol, TG, LDL, VLDL amounts at the same time escalating HDL amounts. NR5A2 is markedly expressed in liver which targets the bile synthesizing enzymes cholesterol 7 –alpha hydroxylase (CYP7A1) along with sterol 12 –alpha hydroxylase (CYP8B1). Rest of the target genes are mediators of cholesterol uptake and efflux, HDL synthesis, cholesterol exchange among lipoproteins, and FA generation [24]. Therapy with NR5A2 agonists hence would help in decreasing hyperlipidemia.

The targeting of proteins PTPN9, DPP4, HSD11B1, RBP4, FFAR1, and INSR would help in insulin liberation from the B-cells and enhance insulin sensitivity. This will then help in sustaining glucose homeostasis and thus decrease hyperglycemia.

- Protein tyrosine phosphatase non receptor type 9 (PTPN9) interferes with the insulin signaling pathway and hence therapy utilizing inhibitors would cause insulin sensitization and enhance glucose homeostasis [25].

- Half-life of the incretin hormones would be escalated by Inhibition of dipeptidyl peptidase (DPP4) and thus, result in escalated insulin secretion and give time to for blood glucose levels to touch normal levels [26].

- Compounds that have the ability of inhibiting hydroxysteroid Dehydrogenase 11 B1 (HSD11B1). can inhibit glucose synthesis by the liver and enhance glucose-dependent insulin sensitivity [27].

- Enhanced levels of retinol binding protein 4 (RBP4) have a correlation with insulin resistance (IR) where RBP4 acts as an adipokine and thus interferes with insulin signaling and decreases glucose uptake in the muscles [28,29]. RBP4 further assists glucose generation by the liver thus enhancing plasma glucose levels. Compounds thus having the capacity of binding RBP4 might interfere with its correlation with transthyretin, causing excessive clearance of the enhanced serum RBP4via the kidneys [30].

- Treatment with FFAR1 agonists will potentiate glucose-dependent insulin secretion via the pancreatic B-cells and in the gastrointestinal tract (GIT) will help in the liberation of the incretin hormones [31].

Stimulation of INSR by agonists would activate insulin signaling pathway, thus enhance insulin sensitivity and aid in glucose uptake by the tissues [32]. Some separate bioactive compounds for some of the herbs and spices have been isolated in earlier work. But the results given here point that the anti-diabetic actions of these plants get initiated from various compounds that control multiple protein targets having intertwined biological actions. Extracts made from these herbs and spices can hence comprehensively correct the multiple impaired functions which are correlated with diabetes. The results given in Figure 1 helps in understanding the anti-diabetic activity of allspice, aniseed, basil, bay leaves, black pepper, caraway, cardamom, dill, fennel, lemongrass, parsley, saffron, sage, star anise, thyme, and yarrow, in which anti-diabetic activity has been found but studies analyzing their anti-diabetic modes of action are missing. Regarding herbs and spices such as cinnamon, clove, cumin, fenugreek, ginger, liquorice, marjoram, nutmeg, oregano, rosemary, and turmeric, the data given here gives novel understanding and provides evidence regarding their well-known anti-diabetic action. For example, *in vivo* studies have observed that therapy with rosemary manipulates the action of GCK and FBP1. Although no agonists for GCK were found by the DIA-DB webserver, agonists for NR5A2 and peroxisome proliferator activated receptor gamma (PPARG) which can control the action of GCK were isolated [24]. This was also seen regarding fenugreek in which 33 liver receptor homolog1 (NR5A2) and 2PPARG agonists were isolated. Regarding FBP1 inhibition by rosemary, 19 compounds were found to be acting as potential inhibitors and these were various flavonoid glucosides like 6-hydroxyluteolin-7-O-glucoside, Apigenin-7-O-glucoside, hispidulin-rutinoside, hesperidin and luteolin-7-O-glucoside, luteolin-7-Oglucuronide and luteolin-7-O-rutinoside. Treatment with rosemary has also been associated with *in vitro* and *in vivo* alpha-glucosidase inhibitory activity and this study corroborates since 61 compounds were found to be probable inhibitors of MGAM. Hops compounds have been found to manipulate the expression of various proteins related to lipogenesis, triglyceride synthesis, reverse cholesterol transport, lipolysis, and fatty acid (FA) oxidation. The three PPARs have been demonstrated to interfere with the expression of these target proteins and in this experiment 19 PPARA, 4 PPARD, and 1 PPARG agonists were isolated were mainly the geranyl- and prenyl-tetrahydroxychalcones and the xanthohumols. Just like that, as has been found in earlier publications, regarding, fenugreek, PPARA, and PPARG agonists were also found, just like PYGL, AMY2A, and intestinal maltose—gluco amylase (MGAM) inhibitors.

Hierarchical clustering analysis

Hierarchical clustering analysis of the bioactive compounds isolated from every herb and spice was carried out utilizing Tanimoto similarities to find if the bioactive compounds found showed some chemical similarity in structure. No clustering was found for caraway, cardamom, cinnamon, marjoram, nutmeg, oregano, and paprika. The total amount of chemically resembling compounds within these herbs and spices may be insufficient for making any clusters from which any useful conclusions can be drawn. The two main chemical groups observed in the herbs and spices were the sesquiterpenoids and the flavonoids/flavonoid glycosides. The sesquiterpenoids represent one of the main kinds of agents that can be identified in the volatile oils of plant extracts and have been observed to possess anti-diabetic action [32]. The volatile oils present in basil, bay leaves, black pepper, clove, lemongrass, and turmeric were identified to possess anti-diabetic action in vitro and/or *in vivo* [33]. The flavonoids and flavonoid glycosides were a major representative chemical class of the bioactive agents identified in aniseed, bay leaves, clove, cumin, dill, fennel, fenugreek, lemon balm, lemongrass, liquorice, parsley, rosemary, saffron, sage, thyme, and yarrow. Various publications studies are present on the anti-diabetic activity of flavonoids and their glycosides [34].

Thus in summary, a library of 2300 compounds obtained from 30 usual herbs and spices had a screening in silico utilizing the DIA-DB web server against 18 drug targets that are recognized for DM, >900 Compounds from the herbs and spices library were seen to be containing potential anti DM action with liquorice, hops, fennel, rosemary, and fenugreek seen to be especially rich in potential anti DM compounds. A great percentage of the compounds were seen to be potential poly pharmacological agents that controlled 3 or > anti DM drug targets which were achillin B from yarrow, asparasaponin 1 from fenugreek, bisdimethoxy curcumin from turmeric, carniloside from lemon grass, cinammtannin B1 from cinammom, crocin from saffron and glbridin from liquorice. Main targets found for herbs and spices compounds were dipeptidyl peptidase (DPP4), intestinal maltose—gluco amylase (MGAM), liver receptor homolog 1 (NR5A2), pancreatic alpha amylase (AM2A), peroxisome proliferatlor activated receptor alpha (;PRPPA), protein tyrosine phosphatase non receptor type 9 (PTPN9), retinol binding protein -4 (RBP4) with >250 compounds seen to be potential inhibitors of these special protein targets. Bay leaves, liquorice and thyme were the only ones that possessed compounds which could potentially control all 18 protein targets and then came black pepper, cumin, dill, hops and marjoram having 17 protein targets. Mostly >1 compound within a particular plant could potentially control a special protein target. It was seen that via this multi - compound - multi – target control of these particular protein targets that the main, anti DM action of decreased hyperglycemia and hyperliidemia, of the herbs and spices could be accounted for. Data from this study, along with known scientific results, suggest that anti DM potential of usually used culinary herbs and spices was due to a collective effect of >1 bioactive compound controlling and restoring various downregulated and intertwined diabetic biological processes [35].

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