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Review Article

VEGETABLE JUICES – THE MOST AWAITED THERAPEUTICS FOR A HIGHLY PRIZED TARGET, PTP 1β

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ABSTRACT

Constitution of the World Health Organization (WHO) defines health as, "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." According to views like this, we shouldn't think in terms of health and disease alone, rather in terms of 'health', 'disease' and 'normality'. Vegetables have been identified as an economical natural source of potent antioxidants and considered important in the maintenance of health and prevention of several diseases. Although, they were well reported for their beneficiary effects in diabetics, their mechanism-based therapeutics was not completely understood. In this study, an attempt was made to present the potential of these vegetable juices in becoming functional foods and also to discover the mechanism behind their preventive and therapeutic properties against diabetes and associated complications. Several scientific reports proved vegetables to be very good inhibitors of the most desired drug target, PTP 1β, both in-vitro and in-vivo; research finds vegetables' juices helping not only to improve the diseased state but also in promoting good 'health' rather than just 'normality' thus serving as a functional food.

Key words:*Health, Disease, Normality, Functional food, PTP 1β inhibition, Vegetable juices*

INTRODUCTION

Health and disease are two critical concepts in bioethics. Modern medicine sees a disease as essentially a process that recurs across individuals in slightly different forms: A disease is an abstract kind that is realized in different ways. Disorder is another important and neglected topic in health and well-being[1].One way of thinking about health says that it is just a little more complex than that of disease; so if disease is a biological malfunction or abnormality, it follows that a healthy person is someone whose biological systems are all in order.

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But another way of looking at health insists that it is not just an absence of disease but the presence of something more – a positive state. Constitution of the World Health Organization (WHO) defines health as, "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." [2]. According to views like this, we shouldn't think in terms of health and disease alone, rather in terms of health, disease and normality[1].

Of the 57 million global deaths in 2008, 36 million (or) 63% were due to non-communicable diseases (NCDs), principally being cardiovascular diseases, diabetes, cancers and chronic respiratory diseases. As the impact of NCDs increases, and as populations' age, annual NCD deaths are projected to continue to rise worldwide, and the greatest increase is expected to be seen in

low- and middle-income regions. While popular belief presumes that NCDs afflict mostly high-income populations, the evidence tells a very different story. Nearly 80% of NCD deaths occur in low- and middle-income countries and NCDs are the most frequent causes of death in most countries [3].

DIABETES MELLITUS (DM)

'Diabetes' is a polygenic metabolic disorder [Latin: siphon, Greek: a passing through (referring to the excessive urination)] [4] caused by impaired insulin secretion and variable degrees of peripheral insulin resistance leading to hyperglycemia. Early symptoms are related to hyperglycemia and include polydipsia, polyphagia, polyuria, and blurred vision. Later complications include vascular disease, peripheral neuropathy, nephropathy and predisposition to infection. Complications can be delayed or prevented with adequate glycemic control; heart disease remains the leading cause of mortality in DM [5].

Diabetes Mellitus is currently the 3rd leading cause of death after heart disease and cancer and affects over 135 million people worldwide. Complications from diabetes kills 2.8 million people worldwide per year. In 2010, about 1.9 million people ages 20 or older were diagnosed with diabetes. The number of people diagnosed with diabetes has risen from 1.5 million in 1958 to 18.8 million in 2010, an increase of epidemic proportions. It is estimated that 79 million adults aged 20 and older have prediabetes. Prediabetes is a condition where blood glucose levels are higher than normal but not high enough to be called diabetes. Studies have shown that by losing weight and increasing physical activity people can prevent or delay prediabetes from progressing to diabetes.

Diabetes is a group of diseases marked by high levels of blood glucose where in insulin is not produced and secreted often enough (Type 1 diabetes) or insulin receptors are not abundant enough or do not respond and initiate signals when insulin binds to it (Type 2 diabetes). Gestational diabetes is a form of glucose intolerance diagnosed during pregnancy. Other types of diabetes result from specific genetic conditions (such as maturity-onset diabetes of youth), surgery, medications, infections, pancreatic disease and other illnesses. Such types of diabetes account for 1-5% of all diagnosed cases[6].

While the management of hyperglycemia, the hallmark metabolic abnormality associated with type 2 DM has historically had center stage in the treatment of diabetes, therapies directed at other coincident features such as dyslipidemia, hypertension, hypercoagulability, obesity and insulin resistance have also been a major focus of research and therapy.

Although, oral anti-hyperglycemic agents/ insulin are the mainstay of treatment of diabetes and are effective in controlling hyperglycemia, they have prominent side effects and fail to significantly alter the course of diabetic complications. The common side effects associated with the main classes of drugs used for the treatment of type 2 diabetes mellitus are hypoglycemia, weight gain, gastrointestinal disorders, peripheral edema and liver disease[7].

In view of these shortcomings, herbal pharmacotherapy is often explored by diabetic patients. Many natural products and herbal medicines have been recommended for the treatment of diabetes[8]. In spite of the worldwide use of herbs and medicinal plants, the effective treatment of diabetes with phytochemicals has not been validated with scientific criteria which may support their substitution for the current therapy[9]. Metformin is the only ethical drug so far approved for treatment of Type 2 DM and is derived from a medicinal plant (*Galegosofficinalis*) historically used to treat diabetes[10]. World Health Organization expert committee on diabetes has listed as one of its recommendations that traditional methods of treatment for diabetes should be further investigated[11]. Hence in this context there is an immense need for the search of novel herbal drugs who possess anti-diabetic activity.

UNDERSTANDING INSULIN AND INTRIGUING TARGETS

Insulin is a pancreatic hormone that controls energy metabolism in liver, muscle and adipose tissue. Insulin is the most potent anabolic hormone known and is essential for appropriate tissue development, growth and maintenance of whole-body glucose homeostasis. Insulin regulates glucose homeostasis at many sites reducing hepatic glucose output (via decreased gluconeogenesis and glycogenolysis) and increasing the rate of glucose uptake, primarily into striated muscle and adipose tissue[12]. Insulin also profoundly affects lipid metabolism, increasing lipid synthesis in liver and fat cells and attenuating fatty acid release from triglycerides in fat and muscle. This acts on cells to stimulate glucose, protein and lipid metabolism as well as RNA and DNA synthesis by modifying the activity of a variety of enzymes and transport processes[13].

Without enough insulin being produced in the pancreas or without enough insulin receptors on cells, excess glucose accumulates in the bloodstream which causes water to move from cells into the bloodstream. The kidneys remove this excess fluid volume from the blood by increasing urine output. The cells which are supposed to receive glucose are starved and are forced to use glycogen and fat as an energy source. This causes triacylglycerol hydrolysis, fatty acid oxidation, gluconeogenesis and ketone body formation to be accelerated. These processes lead to a high amount of H^+, Na^+, K^+ and water secretion in the urine, which leads to dehydration and potentially life-threatening problems[13].

The Insulin Receptor

Insulin action is initiated through the binding to and activation of its cell-surface receptor, which consists of two α subunits and two β subunits that are disulfide linked into a 'β-α-α-β' heterotetrameric complex.

As a first step in initiating its responses, insulin binds to its plasma membrane receptor. Insulin binds to the extracellular α subunits, transmitting a signal across the plasma membrane that activates the intracellular tyrosine kinase domain of the β subunit. The receptor then undergoes a series of intramolecular transphosphorylation reactions in which one β-subunit phosphorylates its adjacent partner on specific tyrosine residues stimulating the tyrosine-kinase activity of the receptor, which has a crucial role in the transmission of the signal [14]. Termination of the signal involves inactivation of the insulin receptor (IR) kinase by dephosphorylation of three tyrosine residues located in the activation loop of the receptor [15].

Some evidence suggests that different tyrosine residues account for distinct functions. For example, phosphorylation of COOH-terminal tyrosines mediates the mitogenic actions of insulin. The phosphorylated tyrosines in the juxtamembrane domain may participate in substrate binding, whereas those found within the kinase domain regulate the catalytic activity of the insulin receptor β-subunit [16].

Insulin Resistance – An Understanding

Insulin resistance occurs when normal circulating concentrations of the hormone are insufficient to regulate these processes appropriately. Thus, by definition, insulin resistance is a defect in signal transduction[16].

Some forms of insulin resistance may involve the receptor itself. Alterations in insulin receptor expression, binding, phosphorylation state and/or kinase activity could account for many insulin-resistance phenotypes. In addition, it is possible that the selected blockade of distinct phosphorylation sites selectively inhibits certain actions of insulin. In this regard, individuals have been identified with rare genetic defects in the insulin receptor that influence expression, ligand binding and tyrosine kinase activity. These patients demonstrate severe insulin resistance, manifest as clinically diverse syndromes including the type-A syndrome, leprechaunism, Rabson-Mendenhall syndrome and lipoatropic diabetes [17, 18].

A number of protein tyrosine phosphatases (PTPases) have been described that can

dephosphorylate the insulin receptor, reducing its kinase activity and thereby attenuating insulin action. Two PTPases have been implicated in the negative regulation of the insulin receptor, PTP 1β and LAR. Elevated expression of each these phosphatases has been reported in insulin-resistant patients[19, 20]. In cultured systems, increased expression of these enzymes prevents insulin receptor kinase activation and insulin signaling. More recently, a PTP 1β knockout in mice resulted in enhanced insulin sensitivity suggesting that the regulation of PTP 1β function could represent an important target for insulin-sensitizing agents[21].

PROTEIN-TYROSINE PHOSPHATASE 1B AS A NOVEL TARGET FOR DIABETES

Protein-tyrosine phosphorylation plays an important role in regulating many cellular processes. The level of phosphotyrosine in the cell is a balance between the actions of PTKases and PTPases. As the role of PTKases in signal transduction is now understood in some detail, increasing attention is being focused on the role of PTPases. It has been shown that internalized insulin receptors are fully active tyrosine kinases that are deactivated as they traverse intracellular structures[22].

Protein-tyrosine phosphatase 1β (PTP 1β) is a protein-tyrosine phosphatase predominantly localized on intracellular membranes by means of a hydrophobic carboxy-terminal targeting sequence[23]. PTP 1β is targeted to the cytoplasmic face of membranes of the endoplasmic reticulum (ER) where it functions in a "dephosphorylation compartment" in which it acts to terminate signaling from receptor PTKs that have undergone endocytosis following ligand stimulation [24, 25]. This ER localization exposes PTP 1β essentially to the entire cytoplasm.

The extent of tyrosyl phosphorylation on a given protein is controlled by the reciprocal action of protein-tyrosine kinase and protein-tyrosine phosphatase (PTP) activities. PTP 1β has received significant attention in the regulation of normal IR signaling because it is an abundant enzyme expressed in all insulin-sensitive tissues. PTP 1β is an abundant, widely expressed non-receptor tyrosine phosphatase thought to be a key negative regulator of insulin signaling. It has previously been shown that PTP 1β overexpression results in the inhibition of IR and IRS; furthermore, introduction of anti–PTP 1β antibodies into cells enhances IR signaling. The increased insulin sensitivity is attributed to the absence of PTP 1β and results from failure to dephosphorylate the IR[26].

PTP 1β is a key regulator of insulin and leptin signaling[27]. PTP 1β acts as a physiological antagonist of the insulin receptor and its signal by dephosphorylating both the insulin receptor and the insulin receptor substrates [28, 29]. Increased PTP 1β levels or an increased activity of this enzyme were found in insulin-resistant and obese patients [30].

Nevertheless, considering the importance of PTP 1β as a therapeutic target, there is a compelling need to explore innovative ideas and schemes to target the enzyme for generating novel, potent and selective inhibitors. Because PTP 1β could be a potential therapeutic target, a better understanding of the interaction between the IR and PTP 1β is an important requirement for the development of compounds to improve insulin sensitivity[31].

Several studies suggest that the reduction in PTP 1β expression and activity is sufficient to enhance the insulin signaling pathway and to improve insulin sensitivity [32]. Reduced PTP 1β activity is directly associated with increased insulin sensitivity. The insulin signaling pathway and tyrosine phosphorylation of the insulin receptor and its substrates and finally glucose uptake into the cell via GLUT4 can be amplified by the inhibition of PTP 1β [28, 33]. Therefore, the inhibition of PTP 1β or the reduction in PTP 1β levels is a potential target for the prevention and treatment of insulin resistance and type 2 diabetes.

Protein tyrosine phosphatase 1β (PTP 1β) is considered as a major negative regulator of insulin receptor (IR) signaling. IR signaling in

retina has been demonstrated to be neuroprotective. Photoreceptor specific deletion of PTP 1β results in enhanced retinal IR-mediated neuroprotection indicating the importance of PTP 1β as a negative regulator in the retina. Elevated levels of retinal PTP 1β activity has been observed in mice lacking retinal pigment epithelium and diabetic retinopathy animal models. This enhanced PTP 1β activity could down regulate the IR signaling which may contribute to the death of photoreceptor neurons and ultimately lead to retinal degenerations[34]. The potential therapeutic agents that specifically reduce or inhibit the PTP 1β activity could be beneficial in protecting or delaying the photoreceptor cell death in the retinal degenerative diseases.

Consequently, it became a highly prized target in the pharmaceutical industry for therapeutic intervention in diabetes, diabetic complications and obesity. Years of work have failed to deliver a good PTP 1β inhibitor. The biggest underlying problem is probably the binding site that a drug would have to target. A phosphatase has to recognize protein that's already in its place and that means a very polar binding pocket with a good positive charge – a poor fit with most compound screening libraries. In addition, the tendency of potent active-site-directed inhibitors to be highly charged, presents problems with respect to oral bioavailability that limit drug development potential[35, 31].

DIET & DIABETES

People consume too much of sugar-sweetened beverages per day. It is estimated in a study that an individual on an average consumes about (not less than) 11.9 tea-spoons of sugar [36] while our 5 liters of blood just need (no more than) one tea-spoon of sugar for all the regular physiological functions[37]. In order to keep the amount of sugar floating through the blood vessels at around a teaspoon, insulin works by stimulating cells to sponge up this excess sugar out of the bloodstream. If this happens regularly, our body will have released so much insulin that it will begin to lose its sensitivity to insulin in other words, causing insulin resistance[38].

In animals, or at least in laboratory rats, it is clear that if glucose hits the liver in sufficient quantity and with sufficient speed, the liver will convert much of it to fat[37]. This apparently induces a condition known as insulin resistance, which is now considered the fundamental problem in obesity, and the underlying defect in heart disease and in the type 2 DM, that is common to obese and overweight individuals.

A simple meal plan of 'eating vegetables before carbohydrate'[39] achieved better glycemic control as evident from 2h OGTT[40]. A recent research over vegetables identified them to be selectively and differently inhibiting PTP 1β enzyme of various tissues[41].They have proved to be very good inhibitors of the most desired drug target, PTP 1β[41]. Furthermore, vegetables juice can also prevent development of diabetic complications by their inherent antioxidant and antioxidative stress properties[42].

SUMMARY & CONCLUSION

Indian systems of medicine believe that complex diseases can be treated with complex combination of botanicals unlike in west, with single drugs. Whole foods are hence used in India as functional foods rather than supplements[43], contributing to the prevention and reduction of risk factors for several diseases or enhancing certain physiological functions[44, 45].

In functional foods, one component might alter ability of another to reach its target, components bind separate sites on same target to create a combination effect and increase pharmacological action. Therefore, no single chemical component can be held responsible for activities displayed by complex plant mixtures because combination of whole might display more potential activity than sum of the parts[46, 47]. These fundamentals have been the basis of oriental traditional medicines.

Vegetables have been identified as an economical natural source of potent antioxidants[48]and important in the maintenance of health and prevention of several diseases[49]. Furthermore, eating

vegetables before carbohydrate rich meals have been found to improve postprandial glycaemic excursion in clinical settings[47].Recently, certain vegetables' juice has been identified to display anti-hyperglycemic activities through various mechanisms[41]. Vegetables' juice has also been observed to reduce development of hyperglycaemia induced oxidative stress and imbalance in physiological functions.Above all, if the active principles of vegetables juices were identified, they would become the most awaited therapeutics for the highly prized target PTP 1β.

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