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POTENTIAL ROLE OF PHYTOCOMPOUNDS IN METABOLIC DISEASE

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ABSTRACT

Metabolic disease can be defined as co-occurrence of diseases that serve as risk factors for cardiovascular events and include insulin resistance, dyslipidemia, hypertension and obesity which are interrelated in mechanism and pathways. Interleukins, tumor necrosis factor α, C – reactive protein (CRP) are some inflammatory mediates common among these pathways bridging one another. Obesity remains the major burden for initialization of metabolic disease as this pays way for excess circulation of free fatty acids. Abundance of free fatty acid serves as a contributor of insulin resistance which alter RAAS pathway leading to consequences. CRP affects insulin signaling pathway leading to hyperglycemic condition and serve as marker for development of cardiovascular events. Interleukin 6 (IL-6) is associated with insulin resistance. IL-6 on contact with CRP further aggravates cardiovascular events. Hyperglycemia elevates interleukin 18 (IL-18) concentrations through oxidative stress which is responsible for atherosclerotic plaque deposition. Higher concentrations of IL-18 increase the synthesis of IL-6 and CRP thus worsening the condition. Serine phosphorylation of insulin receptors prevent interaction with insulin resulting in insulin signal impairment. IRS-1 phosphorylation is driven by JNK, IKKβ, and TNFα. As diabetic patient express many inflammatory features, designing therapy including compounds

that target inflammatory pathways of metabolic disease emerges to provide potential benefits. Anti inflammatory compounds derived from plant source are of higher preference accounting to their minimal side effect.

KEYWORDS: Anti-inflammatory compounds, cardiovascular events, Interleukins, Insulin resistance, Obesity, Serine phosphorylation.

INTRODUCTION

Metabolic diseases are major surge in health care system that is characterized by pattern of interconnected physiological functioning and directly related to cardiovascular disease, type 2 diabetes mellitus and their consequences.[1] Metabolic abnormalities induces stress reactions of cells resulting in inflammatory factors promotion.[2] Cytokines, adipokines and eicosanoids are the inflammatory mediators associated with progress of metabolic diseases.[3] Obesity results in increased pro inflammatory mediator TNF alpha which interfere with insulin resistance resulting in type 2 diabetes mellitus[4] and increases the level of leptin which is the key factor for induction of cardiovascular disease.[5] Leukocytic endogenous mediator is elevated by oxidative stress leading to cardiovascular disease.[6] Insulin resistance along with obesity affects renin angiotensin system (RAS) and elevates angiotensinogen II availability. Excess angiotensinogen II results in generation of reactive oxygen species[7] which accounts for atherosclerosis by oxidizing poly unsaturated lipids in addition to the progression of diabetic nephropathy.[8]

Inflammatory pathway

The mechanism of insulin resistance is associated with activation Protein Kinase-C [PKC] through IKKβ or JNK pathway resulting in increased serine phosphorylation of Insulin Receptor Substrate [IRS]. Serine phosphorylation of IRS diminishes tyrosine phosphorylation which impairs PI 3-kinase, subsequently inhibiting insulin signaling which results in insulin resistance. Serine phosphorylation of IRS-1 is enhanced by c-Jun NH_2-terminal kinase [JNK] that is activated by free fatty acids, oxidative stress and inflammation in company with stress-activated protein kinases and tumor necrosis factor [TNFα].[9] Inhibition of insulin signaling by serine phosphorylation of IRS-1 occurseither by intercession with insulin receptor or by increased IRS-1 degeneration.[10,11] The most common inflammatory factors involved in metabolic disease includes interleukin-1β [IL-1β], interleukin 6 [IL-6], interleukin 18 [IL-18], and tumor necrosis factor α [TNF-α] in addition to elevated level of C-Reactive Protein[12,13] which is induced by cytokines and ROS. CRP act as primary inflammatory factor in

induction of type 2 diabetes mellitus. Hypertension and obesity results in elevated level of CRP.[14] C- Reactive Protein serves as a biomarker in development of CVD by promoting endothelial dysfunction, increased LDL uptake. It also inhibits synthesis of nitric oxide thus contributing to platelet aggregation.[15] C-Reactive Protein pays way for type 2 diabetes mellitus by impairing insulin signaling through regulation of spleen tyrosine kinase and insulin receptor substrate 1[IRS-1].[16,17] CRP produced in the liver is stimulated further by IL 6 produced in adipose tissue where obesity exerts one of its contributions in metabolic disease.[18] Higher level of interleukin 6 in circulation is strongly bonded to insulin resistance which is the early manifestation of metabolic disease by increasing insulin production and inhibiting insulin mediated glucose uptake.[19] IL 6 can be determined as an exasperate factor in development of cardiovascular events and progression of metabolic disease. IL 6 elevation along with C-Reactive Protein is associated with reduced high density lipoprotein and raised triglyceride level contributing to cardiovascular diseases.[20,21] IL 6 increases suppressor of cytokine signaling proteins in liver cells which induces hepatic insulin resistance.[22] Interleukin 18 plays a vital role in regulation of immune responses by enhancing the action of T cells. IL 18 level elevates with acute hyperglycemic condition through oxidative stress mechanism.[23] Over time this results in insulin resistance and atherosclerotic plaque.[24] IL 18 exerts its action by inducing production of interferon gamma which inhibit fibrous cap formation and ends in rupture.[25] IL-18 is a pro inflammatory cytokine activate Nuclear Factor – kappa β(IKKβ) cell pathway that further synthesize IL-6 and CRP worsening the condition.[26]

Pharmacological approaches targeting inflammatory pathway

Inflammation remains as key in pathophysiology of metabolic disease. Activated inflammatory factors play a vital role in initiation of diabetic complications. Hence targeting inflammatory pathways gain attention in management of metabolic disease. Compounds derived from natural source are better alternatives to existing drugs as natural compounds were observed to show anti- inflammatory and anti-diabetic properties with least side effects.[27]

S.no	Compounds	Target	Effect
1.	Allicin	PKC pathway.[28]	Reduce hypertension and glucose level.[29]
2.	Apigenin	NF- Kappa β cells.[30]	Suppress oxidative stress and vascular injury.[31]
3.	Baicalein	TNF-α and gluconeogenesis.[32]	Reduce triglyceride and total cholesterol levels.[33]
4.	Berberine	AMPK pathway, NF- Kappa β cells.[34]	Alleviate triglyceride and insulin resistance.[35]
5.	Capsicum oleoresin	PPAR α.[36]	Decrease serum concentration of LDL.[37]
6.	Chrysin	TNF- α, IL-1β and IL-6 levels.[38]	Alleviate serum LDL and insulin levels.[39]
7.	Curcumin	IL-1 and TNF α concentrations.[40]	Reduce total cholesterol and increase HDL concentration.[41]
8.	Ellagic acid	TNF-α and NF- Kappa β pathway.[42]	Decrease Fetuin-A level and insulin resistance.[43]
9.	Eriocitrin	TNF-α.[44]	Attenuate dyslipidemia and lipogenesis.[45]
10.	Hesperiden	IL-6, TNF-α.[46]	Reduce circulating VLDL and triglyceride concentration.[47]
11.	Kaempferol	NF- Kappa β pathway, IL-6.[48]	Decrease plasma triglyceride concentration.[49]
12.	Naringenin	AMPK pathway and NF-Kappa β system.[50]	Alleviate LDL level and improve HDL concentration.[51]
13.	Resverastrol	AMPK and NF- Kappa β pathway.[52]	Improve glucose tolerance.[53]
14.	Silymarin	TNF-α, IL-6, IL-1 β.[54]	Alleviate dyslipidemia.[55]
15.	Trigonelline	TNF-α and leptin.[56]	Increase insulin sensitivity and reduce triglyceride level.[57]

CONCLUSION

Metabolic disease increases the risk of cardiovascular complications about 2 to 3 folds thus existing as a global burden. Untreated metabolic disease leads to critical health concern and increased mortality. Appropriate pharmacological therapy in addition to certain lifestyle modification helps in management of metabolic disease and prevention of major consequences. Anti-inflammatory compounds derived from natural source were proven to show insulin sensitivity and come out with minimal side effects helping in improving therapy of metabolic disease. Obstecle to achieve target is low bioavailability of natural compounds, hence formualting phyto compounds into nanomolecules and encapsulations aids in better bioavailability and positive outcome. Understanding the inflammatory mediator interactions with immune response and metabolisms enable individualization of therapeutic regimen and aids in minimizing the burden of health care system.

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