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Review Article

# ADIPONECTIN-A PLEIOTROPIC BIOMARKER IN MULTISYSTEM PATHOLOGIES & INFLUENCE OF AYURVEDIC HERBS: A SCIENTIFIC APPRAISAL

**K. V. Narasimha Raju[1*], Pawan Kumar Godatwar[2]**

[*1]Chief Consultant – Kayachikitsa, M.J.F. Ayurvedic - Multispeciality Hospital & College, Chomu, Jaipur, Rajasthan, India.

[2]Associate Professor & Head, Dept of Roga Vijnan & Vikruti Vijnan, National Institute of Ayurveda, Jaipur, Rajasthan, India.

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**ABSTRACT**

The understanding of metabolic pathologies is made easy with the emergence of the most luring cytokine - Adiponectin, which is produced exclusively by adipocytes and which enhances insulin sensitivity and inhibits many steps in the inflammatory process by exerting its action through its receptors AdipoR1, AdipoR2, and T-cadherin. AdipoR1 is expressed abundantly in muscle, whereas AdipoR2 is predominantly expressed in the liver. In liver, Adiponectin inhibits the expression of gluconeogenic enzymes and the rate of glucose production. In muscle, Adiponectin increases glucose transport and enhances fatty acid oxidation, partially due to activation of AMP kinase.

These above physiological activities and many more are performed with the normal or high levels of Adiponectin in the blood whereas the decreased levels of the same leads to various metabolic disorders. The present article encompasses various researches and recent progress made in understanding the biological effects of Adiponectin. These studies confer Adiponectin's role as biomarker and mediator in multiple systemic pathophysiologies, thereby establishing its clinical and therapeutic value in the conditions ranging from metabolic syndrome to malignancies. Also presented in this paper is the contribution of Ayurveda in the form of single herbal drugs which show the therapeutic modulation on Adiponectin.

**KEYWORDS:** Adiponectin, Pathophysiology, Pleiotropic Biomarker, Ayurvedic herbs.

## INTRODUCTION

The fascinating molecule and White Adipose Tissue Hormone, Adiponectin, is also known as Gelatin- Binding Protein-28 (GBP28), ADIPO-Q, C1Q and Collagen Domain Containing,[1] Adipocyte Complement-Related Protein (ACRP30), or APM1.

Adiponectin is reduced in the metabolic disorders.[2] Apart from causing metabolic dysfunction, Adiponectin deficiency may also contribute to Coronary Heart Disease, Steatohepatitis, Insulin Resistance, Nonalcoholic Fatty Liver Disease, and a wide array of cancers.[3]

There are many emerging studies which highlight the clinical importance of Adiponectin in human pathologies of various metabolic diseases. Primarily Hypoadiponectemia was found to be associated with obesity and diabetes, indicating it's relation to systemic insulin sensitivity and the ability to directly regulate whole body energy metabolism. In healthy lean humans, circulating Adiponectin levels range from 2-30 mg/L.[4]

Adiponectin has attracted much attention lately because of its clinical importance, attributed to its anti-

inflammatory, insulin sensitizing and antiatherogenic properties.[5]

Adipose tissue is not simply an inert storage depot for lipids but is also an important endocrine organ that plays a vital role in the integration of endocrine, metabolic, and inflammatory functions to control energy homeostasis. Adipocytes secrete a variety of bioactive secretory proteins into the circulation which are collectively named as Adipocytokines which include Leptin, Tumor Necrosis Factor (TNF)-A, Plasminogen-Activator Inhibitor Type 1 (PAI-1), Adipsin, Resistin and Adiponectin.

Adiponectin, the gene product of the adipose tissue's most abundant gene transcript 1 (apM1), is a novel and important member of the Adipocytokine family. Adiponectin cDNA was first isolated by large-scale random sequencing of the human adipose tissue cDNA library [6]. It is a collagen-like protein that is exclusively synthesized in white adipose tissue, induced during adipocyte differentiation, and circulates at relatively high concentrations in the serum.

Adiponectin has been postulated to play an important role in the modulation of glucose and lipid metabolism in insulin-sensitive tissues in both humans and animals. Decreased circulating Adiponectin levels have been demonstrated in genetic and diet-induced murine models of obesity, as well as in diet-induced forms of human obesity.[7] Low Adiponectin levels have also been strongly implicated in the development of insulin resistance in mouse models of both obesity and lipoatrophy. Plasma Adiponectin levels in diabetic subjects with coronary artery disease (CAD) are lower than in diabetic patients without CAD, suggesting that low Adiponectin levels are associated with an atherogenic lipid profile and improved levels of Adiponectin have anti-atherogenic properties.[8] In studies done on human aortic endothelial cells, Adiponectin has been shown to dose-dependently decrease the surface expression of vascular adhesion molecules known to modulate endothelial inflammatory responses. It also inhibits proliferation of vascular smooth muscle cells and concentrates within the vascular intima of catheter-injured vessels.[9]

The association of low Adiponectin levels with obesity, insulin resistance, CAD, and dyslipidemia indicates that this novel protein can be an important marker of the metabolic syndrome.[61]

From the inferences of researches till date on Adiponectin, it is clear that the serum levels of Adiponectin are negatively / inversely related to the clinical manifestation of multiple diseases like DM 2, Obesity, CVD, NAFLD, Cancer, etc., encompassing different systems of the body. Hence, the very purpose in dealing the untoward clinical outputs of Adiponectin lies in improving the levels of Adiponectin either through natural or conservative methods.

In this article we present the scientific appraisal of Adiponectin for its central role in the pathophysiology of multisystem diseases and the scientific update on some of the Ayurvedic herbs for their effect on the maintenance of the healthy levels of Adiponectin. The drugs reviewed herein are *Haridra, Amalaki, Pippali, Pushkaramula, Guduchi, Musta* and *Aardraka,* which are part of an Extra-mural research project on Pre-Diabetes done in N.I.A., Jaipur.

**STRUCTURE & FUNCTIONS OF ADIPONECTIN**

In 1995, P.E. Scherer, Lodish et al., identified a secretory protein from murine 3T3-L1 adipocytes and named it Adipocyte complement-related protein of 30 kDa (Acrp30). It is a structural homolog to complement factor C1q and to a hibernation-specific protein isolated from the plasma of Siberian chipmunks. It forms large homo-oligomers that undergo a series of posttranslational modifications. Using the mRNA differential display technique, it was cloned and called adipoQ. Thus, a

description of the cDNA encoding Adiponectin was first reported.[10]

In 1999, a group at Osaka University isolated the human adipose-specific transcript, the apM1 gene product, which was found to be a soluble matrix protein, and named it Adiponectin. It was identified as a distinct protein among the adipokines because the plasma concentration of Adiponectin decreases upon accumulation of visceral fat.

Adiponectin is a protein hormone consisting 247 amino acids and the corresponding gene is found in chromosome 3q27 (long (q) arm of chromosome 3 at position 27), which is considered to be a locus that is highly susceptible for the development of metabolic diseases.

Adiponectin structurally is associated with the complement 1q (C1q) family and consists of a Carboxy terminal globular domain and an Amino terminal collagenous domain. The full length Adiponectin (fAd) consists of an N-terminal stalk made of 22 collagen repeats and a highly conserved globular domain at the C-terminal. Proteolytic cleavage of fAd by leukocyte elastase produces smaller globular Adiponectin (C-terminal) fragments (gAd). Adiponectin receptors 1 (AdipoR1) and 2 (AdipoR2) are expressed ubiquitously in most organs, especially in skeletal muscle in AdipoR1, and liver in AdipoR2.[4]

HMW form is found to be inversely correlated in patients with different systemic diseases while the circulating LMW form remains unchanged. HMW forms have been shown to significantly improve circulating glucose in diabetic humans and animal models, suggesting that HMW is the most active form of Adiponectin. Furthermore, significant weight reduction in patients elevates the circulating HMW form of Adiponectin.

The pharmacological effects of Adiponectin have been studied at animal, tissue, and cellular levels using a variety of recombinant Adiponectin products. It is possible that Adiponectin exists as variable protein complexes that exert different effects in various tissues. The globular head domain of Adiponectin has been shown to be more potent than the full-length form in ameliorating hyperglycemia and hyperinsulinemia in diet-induced and genetic forms of murine obesity and in decreasing elevated plasma free fatty acids in mice fed a high-fat meal or given intravenous intralipid injections.[11]

In skeletal muscle of mice, Adiponectin has been shown to increase expression of the genes encoding proteins involved in fatty acid transport and oxidation, such as CD36, acyl-CoA oxidase, and uncoupling protein, resulting in enhanced fat combustion and energy dissipation.[12]

In the liver, low doses of Adiponectin decreased the expression of proteins involved in fatty acid transport, such as CD36, leading to reduced fatty acid influx into the liver and hepatic triglyceride content. Improved hepatic insulin sensitivity occurred, leading the investigators to postulate that the primary effects of Adiponectin on muscle are to augment uptake and combustion of free fatty acids (FFAs), whereas decreased liver triglyceride content results from secondary reductions in serum FFA and triglyceride levels.

Single nucleotide polymorphisms in the Adiponectin gene have been reported in humans. Some of these polymorphisms markedly reduce plasma Adiponectin levels and predispose the carriers to insulin resistance. I164T polymorphism is one such mutation (isoleucine is substituted by threonine at the 164th position) that is reported to be a causative factor for hypoadiponectemia and the development of type 2 diabetes. Furthermore, individuals with this mutation are highly susceptible for the development of hypertension and coronary artery disease, suggesting the protective role of Adiponectin against development of metabolic disease in humans.

It can be deduced from the above discussion that the mechanism of action of Adiponectin principally involves Insulin-

sensitizing actions, activation of PPARα & AMP kinase and Antiatherosclerotic actions leading to a myriad of protective roles in varied pathophysiologies.[13]

**PATHOPHYSIOLOGIES: PLEIOTROPIC ROLE OF ADIPONECTIN**

A continuous research on Adiponectin for over 2 decades has established its role as a biomarker in major pathophysiologies of human body. The pleiotropic role of Adiponectin is proved In-Vivo and In-Vitro in Type II Diabetes, Obesity, Dyslipidaemias, Hypertension, Multiple Sclerosis (MS), Cancer, Non-Alcoholic Fatty Liver Disease, Cardio Vascular Diseases and Inflammations etc., encompassing different organ systems of the body.

- Adiponectin in Obesity and Type II Diabetes: Mediator of Insulin Action / Resistance.

As Adiponectin is produced exclusively by the adipocyte, its concentration in the serum is affected by changes in adipose tissue mass. However, unlike most adipose-derived hormones and secreted proteins, Adiponectin mRNA and serum levels are decreased in obesity.[14], [15] And, Plasma levels of Adiponectin exhibit strong negative correlations with direct (via computerized tomography scan) and indirect (waist-to-hip ratio, waist circumference) measures of intra-abdominal fat (IAF) mass.[16], [17]

The expression of the receptors AdipoR1 and AdipoR2 decline by 30% in the subcutaneous fat of obese individuals, while they normalize following weight loss.

The most significant role played by Adiponectin is that of its insulin-sensitizing effect. Total Adiponectin, HMW Adiponectin, and HMW ratio are inversely related to homeostasis model assessment (HOMA) of Insulin Resistance Index. A strong correlation between Adiponectin and systemic insulin sensitivity has been well established both in vivo and in vitro in mice, other animals, and humans.

In a study conducted on Pima Indians and Caucasians where the individuals have varied levels of glucose tolerance it is observed that decreased Adiponectin levels are closely related to the degree of Insulin Resistance and Hyperinsulinemia.[18]

Adiponectin administration to rodents has been shown to increase insulin-induced tyrosine phosphorylation of the insulin receptor in skeletal muscle in association with increased whole-body insulin sensitivity.[12] Stimulation of glucose utilization and fatty acid oxidation in skeletal muscle and liver by Adiponectin may also have occurred through activation of 5′-AMP kinase.

In experiments conducted by Berg et al.[19] intraperitoneal injection of mammalian-extracted full-length Adiponectin into fasting male wild-type mice and two models of type 1 diabetes—insulinopenic nonobese diabetic and streptozotocin-induced diabetic mice—produced a significant transient reduction of glucose levels. Adiponectin injection into a type 2 diabetic model (*ob/ob* mice) also lowered glucose levels.

Circulating Adiponectin levels have been shown to decrease in parallel with progression of insulin resistance during development of type 2 diabetes in rhesus monkeys genetically predisposed to develop insulin resistance.[20] In this study, there was a negative correlation of Adiponectin levels with body weight and fasting insulin levels and a positive correlation with insulin-stimulated glucose uptake (a marker of insulin sensitivity). In these monkeys, the decline in Adiponectin levels preceded overt hyperglycemia.

Adipocyte insulin action or signal transduction rather than absolute levels of insulin may regulate Adiponectin secretion. In support of this contention, Bogan and Lodish [21] have shown that secretion of Adiponectin by 3T3-L1 adipocytes requires

phosphatidylinositol 3-kinase (PI-3K), a major intermediate of insulin signalling activity. Insulin-stimulated insulin receptor substrate 1 (IRS-1)-associated PI-3K activity has been shown to be decreased in adipocytes of type 2 diabetic subjects. Thus it is possible that the decreased adipocyte PI-3K activity in type 2 diabetic patients may contribute to the decreased Adiponectin levels.

The connection between Adiponectin levels and insulin resistance has been further confirmed by data obtained from treatment with Thiazolidinediones (TZDs). TZDs are specific synthetic ligand activators of PPAR-γ (Peroxisome Proliferator-Activated Receptor (PPAR)-γ is a ligand-activated transcription factor and regulator of adipocyte differentiation and multiple adipocyte genes) that improve glucose tolerance and insulin sensitivity in muscle and fat tissue in type 2 diabetic patients.

In support of an important role for PPAR-γ in regulation of Adiponectin synthesis, circulating Adiponectin levels were found by Combs et al.[18] to be suppressed fivefold in patients with severe insulin resistance in association with dominant-negative PPAR-γ mutations. Thus, induction of adipose tissue Adiponectin expression and consequent increases in circulating Adiponectin levels could potentially represent a novel potential mechanism for PPAR-γ-mediated enhancement of whole-body insulin sensitivity.

Adiponectin is considered as a reliable marker for Insulin Resistance in type 2 diabetes. Tajiri et al.[22] used the hyperinsulinemic-euglycemic clamp to quantify Glucose Infusion Rate (GIR) as an index for insulin sensitivity in 16 patients with type 2 diabetes. GIR was most strongly correlated with circulating Adiponectin levels and fasting plasma glucose.

The role of Adiponectin in mitigating insulin resistance has been further substantiated by studies in humans and mice with lipodystrophies.[23], [24]

Lipodystrophies are characterized by selective but variable loss of body fat and insulin resistance. Serum Adiponectin levels are extremely low in patients with generalized lipodystrophies and may be related to the general absence of adipose tissue and/or associated severe insulin resistance.

Adipose tissue expression and circulating Adiponectin concentrations have also been found to be significantly decreased in HIV-positive patients with lipodystrophy treated with highly active antiretroviral therapy. Thus, it may be reasonable to surmise that decreased production of Adiponectin in lipoatrophic adipose tissue may contribute to the development of insulin resistance in these patients.

Visceral fat appears to be an important link between the many facets of the metabolic syndrome, including glucose intolerance, hypertension, dyslipidemia, and insulin resistance.[25] Visceral adiposity is characterized by enhanced lipolysis and augmented plasma FFA flux, especially into the portal circulation. Increased inflow of FFAs into the liver from the portal circulation is thought to retard insulin clearance and to enhance lipid synthesis, which may result in peripheral hyperinsulinemia and hyperlipidemia. FFAs have also been shown to induce hepatic insulin resistance by inhibiting insulin suppression of glycogenolysis during euglycemic-hyperinsulinemic clamp studies and to directly stimulate glycogenolysis and gluconeogenesis, thus contributing to mild fasting hyperglycemia in euglycemic subjects given lipid infusions.[26]

Adiponectin mRNA and protein levels have been found to be reduced in omental fat compared with subcutaneous fat. Visceral fat may also produce an as-yet-unidentified factor that destabilizes Adiponectin mRNA.[27] The inverse correlation between serum Adiponectin levels and intra-abdominal fat mass hints at a strong link between visceral fat and insulin resistance.

Although Adiponectin is secreted only from adipose tissue, its levels are paradoxically lower in obese than in lean humans. This is in contrast to most other adipocytokines, whose levels are increased in obesity in proportion to an increased total body fat mass. It is possible that although Adiponectin expression is activated during adipogenesis, a feedback inhibition on its production occurs during the development of obesity.

- **Adiponectin in Cardiovascular diseases**

The potential role of adiponectin in cardiovascular diseases has been observed in patients with coronary artery diseases (CAD), as they have lower levels of adiponectin irrespective of ethnic group.[28]

Intriguingly, HWM adiponectin has been linked to CAD. However, the hexamers are not affected and trimers increase, underlining the importance of HMW adiponectin in CAD in addition to the other obesity-related disorders/diseases, perhaps due to the functional priorities and tissue specificity shown by the adiponectin isoforms.[29]

Adiponectin deficiency in ischaemia-reperfusion mice caused myocardial infarct and aggravation was up to 78%, with a surge in TNFα levels and a decrease in activation of AMPK activity. It should be noted here that mice deficient in adiponectin suffer from myocardial ischaemia and injury due to reduced levels of cyclooxygenase-2 (COX-2), suggesting that adiponectin regulates COX-2 production.[30]

A possible role of adiponectin in atherosclerosis has been observed, in which activated macrophages attach to the vascular walls and convert into foam cells. These cells mass lipid droplets and recruit other macrophages to the site, ultimately leading to localized inflammation. Adhesion of monocytes to human aortic endothelial cells (HAECs), facilitated by TNFα, is inhibited by adiponectin by reducing the expression of vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and intercellular adhesion molecule-1 (ICAM-1) on the surface of HAECs.[31]

Some findings suggest a role of adiponectin in atherosclerosis by inhibiting binding of LDL to biglycan, which is a vascular proteoglycan. This ultimately decreases lipid accumulation in the subendothelial space, the cause of atherosclerotic plaque formation.[32]

In addition, single nucleotide polymorphisms (SNPs) at position +276 in the adiponectin gene have been associated with CAD. T/T homozygous is at a lower risk of developing CAD than G/G or G/T variants of the genes. A “C” to “G” variant at position 11,377 in the promoter region of adiponectin has been linked to coronary atherosclerosis and other related diseases. T-cadherin expression is higher in athero-resistant than atherosclerosis susceptible coronary arteries, which indicates that its expression is involved in the progression of atherosclerosis.[33] Both T-cadherin and adiponectin have been found in the vicinity of injured vessels, which suggests that they have a role in atherosclerosis.

Paradoxically, recent studies have determined that adiponectin has cardioprotective effects owing to its anti-inflammatory, anti-oxidant and anti-apoptotic properties. Further findings suggest that locally produced adiponectin in cardiomyocytes are functional and biologically significant. The ectopic derived adiponectin exerts its protective effects through the autocrine mechanism.

Some of the scientific proofs are: Matsubara et al.[34] demonstrated that plasma adiponectin concentrations were not only inversely related to triglyceride levels, atherogenic index (total:HDL cholesterol), and apolipoproteins (apos) B and E, but also positively correlated to serum HDL cholesterol and apo A-1 in nondiabetic female patients. These findings suggest that the hypoadiponectinemia observed in

dyslipidemia may accelerate the atherosclerotic changes.

Severe neo-intimal thickening and increased proliferation of vascular smooth muscle cells has been demonstrated in mechanically injured arteries of adiponectin knockout mice. Supplementation of adiponectin in this mouse model attenuated the neointimal proliferation.[35] This has been the first in vivo evidence that adiponectin might serve as a critical link bridging the adipose tissue-vascular axis.

High-sensitive C-reactive protein (hs-CRP) is a well-known marker and risk factor for coronary artery disease. It was recently shown that CRP mRNA is expressed in human adipose tissue. A significant inverse correlation has been observed between CRP and adiponectin mRNA levels in subcutaneous adipose tissue of human subjects with angiographically demonstrated coronary atherosclerosis[36]. This reciprocal association between adiponectin and CRP levels in both human adipose tissue and plasma is supportive of a role for adiponectin against the development of atherosclerosis and vascular inflammation.

Levels of Adiponectin are also lower in patients with essential hypertension [37] and in diabetic patients compared with nondiabetic subjects, and are particularly low in subjects with CAD. Decreased levels are found in men compared with women which may be androgen induced[38]. The incidence of cardiovascular death has been found to be higher in patients with renal failure who have decreased adiponectin levels (hypoadiponectinemia). [39]

- **Adiponectin in Cancer**

Studies have shown that individuals with low levels of adiponectin (hypoadiponectinaemia) could be at higher risk of developing malignancies linked to obesity, insulin resistance, endometrial cancer, postmenopausal breast cancer, leukaemia, colon, gastric, and prostate cancer.

The conditions like polycystic ovary syndrome (PCOS) can also result due to hypo levels of adiponectin. PCOS is characterized by hyperandrogenism, where high levels of circulating insulin stimulate the ovary to produce more androgens and decreases the production of Sex Hormone Binding Globulin (SHBG), leading to an even higher hyperandrogenic state.[40] This confers the low level of adiponectin, inversely proportional to that of insulin.

Also, the expression of adiponectin receptors in lung tissues was apparent particularly in the areas of cancerous lesions (64.2% AdipoR1 and 61.9% AdipoR2). [41]

As Adiponectin modulates several intracellular signaling pathways and stimulates AMPK, PPARγ, and MAPK in insulin target organs such as the liver and skeletal muscles, it can inhibit cancer progression and invasion through its receptors (AdipoR1, AdipoR2). [42]

- **Adiponectin in Non-Alcoholic Fatty Liver Disease (NAFLD)**

NAFLD encompasses a spectrum of conditions associated with lipid deposition in hepatocytes. It ranges from steatosis / Non alcoholic fatty liver (NAFL / simple fatty liver), to Non Alcoholic Steato Hepatitis (NASH—fatty changes with inflammation and hepatocellular injury or fibrosis), to advanced fibrosis and cirrhosis. NAFLD is characterized by insulin resistance and is associated with metabolic risk factors such as obesity, diabetes mellitus, and dyslipidemia.

Serum adiponectin level has been found to be significantly lower in the early-stage NASH group compared to the simple steatosis group ($P < 0.001$).[43]

In the liver, adiponectin acts through the activation of the AMPK and PPAR-α pathways and inhibition of toll-like receptor-4 mediated signaling.[44] It is believed that adiponectin attenuates liver inflammation and fibrosis, possibly through the decrement in the hepatic and insulin resistance.

Adiponectin is considered to have insulin sensitizing, antifibrogenic, and anti-inflammatory properties by acting on hepatocytes, hepatic stellate cells, and hepatic macrophages (Kupffer cells), respectively. Adiponectin decreased gluconeogenesis, decreased free FFA influx into the liver, and increased FFA oxidation. In addition, adiponectin has antifibrotic action in the liver, mainly through down-regulating the expression of aldehyde oxidase, TGF and CTGF, and anti-inflammatory action by suppressing TNF-α and other proinflammatory cytokines and by inducing anti-inflammatory cytokines, such as IL-10.[45]

**ADIPONECTIN: CLINICAL ASSOCIATION**

Genetic studies have mapped a susceptibility locus for type Metabolic Syndrome, 2 diabetes, and Coronary Heart Disease to Chromosome 3q27, where the gene encoding Adiponectin is located.[46]

Hara et al. found that genetic variations resulting in reduced serum adiponectin levels are associated with increased risk for type 2 diabetes.[47] In another study, Japanese subjects carrying a mis-sense mutation in the adiponectin gene associated with hypoadiponectinemia exhibited the phenotype of the metabolic syndrome, including Insulin Resistance and Coronary Artery Disease. Thus genetic polymorphisms of the adiponectin gene that result in lower production and secretion of adiponectin may be responsible, at least in part, for the pathogenesis of the various metabolic pathologies.

Improvement in insulin sensitivity by weight reduction in obese subjects with gastric bypass surgery [48] has been reported to increase adiponectin levels. In view of its potential beneficial effects, any measure that increases adiponectin levels would likely have therapeutic significance. In addition to hypolipidemic and antidiabetic effects, the therapeutic advantages of adiponectin include potential anti-inflammatory properties that might prevent or retard Atherogenesis, without increasing body weight.

Hence, replenishment of adiponectin clearly represents a novel treatment strategy for insulin resistance and related metabolic diseases.

**ADIPONECTIN: APPLICATION OF AYURVEDIC HERBS**

The following herbs considered for the scientific review are a part of Extra-Mural Project conducted in National Institute of Ayurveda, Jaipur, Rajasthan. Apart from their therapeutic effect on blood glucose and lipid levels, these drugs were found to have cumulative positive feedback effect on the basal metabolism and constitution of the subject with improved levels of Adipocytokines, particularly Adiponectin.

***Haridra (Curcuma longa)***

Curcumin helps lower inappropriately high levels of leptin (reducing leptin resistance) while boosting the all-important levels of the adiponectin (which lowers insulin resistance). The study conducted by Somlak et. al., on the extract of curcuma longa in type II Diabetes mellitus revealed that Curcumin intervention significantly increased adiponectin levels.[49]

In another study where abdominal subcutaneous adipose tissue and perirenal adipose tissue were collected from the operating-patients were cultured for 6 and 24 hours with different concentrations of curcumin (10 and 100 μg/ml) in vitro, revealed that 100 μg/ml curcumin can increase adiponectin secretion and decrease IL-6 secretion in human adipose tissues cultivated in vitro.[50]

Curcumin also prevents High Fat Diet Induced Insulin Resistance and Obesity via Attenuating Lipogenesis in Liver and Inflammatory Pathway in Adipocytes.[51]

***Amalaki (Emblica officinalis)***

T.P. Rao et.al., stated the medicinal qualities of Amla that it significantly improves the serum adiponectin levels.[52]

K.H. Khan stated that Amla extracts orally administered to the diabetic rats slightly improved body weight gain and also significantly increased various oxidative stress indices of the serum of the diabetic rats along with a significant increase in serum adiponectin levels.[53]

As deduced by Islam, Aminul. et al. Thiobarbituric acid-reactive substance levels were significantly reduced with Emblica officinalis extract, indicating a reduction in lipid peroxidation. With this, the serum adiponectin levels also improved significantly.[54]

***Pippali (Piper nigrum)***

Following the studies of Zhang H et.al., it is understood that Several amide constituents (piperlonguminine and retrofractamides A, B, and C) from the fruit of Piper promoted adipogenesis of 3T3-L1 cells. Among them, retrofractamide A was the most active and significantly increased the amount of adiponectin released into the medium and the uptake of 2- deoxyglucose into the cells. Retrofractamide A also increased mRNA levels of adiponectin, peroxisome proliferator-activated receptor gamma2 (PPARgamma2), glucose transporter 4 (GLUT4), and insulin receptor substrate 1 (IRS-1), but did not act as a PPARgamma agonist different from troglitazone.[55]

***Pushkaramula (Inula racemosa)***

Insulin can produce its effect on blood glucose level, insulin and lipid profile through its ability to change the blood level of adipocytokines.[56]

***Guduchi (Tinospora cordifolia)***

Choi, Bong-Hyuk et.al., during their study on the inhibition of inflammatory molecule expression discovered that Berberine in Tinospora cordifolia prevents and suppresses proinflammatory cytokines, E-selectin and genes, and increases adiponectin expression.[57]

***Musta (Cyperus rotundus)***

Pharmacological studies by Mahishankar, Dharashive Vishweshwar on the effect of aqueous extracts of Cyperus rotundus Linn. on plasma Adiponectin levels and glucose tolerence in diet fed obese Wistar rats revealed that the improved levels of serum adiponectin helped in regulating the normal levels of glucose.[58]

***Aardrak (*Zingiber officinale*)***

Insulin sensitizing is an important therapeutic mechanism against NAFLD, where the key role in the pathology is of insulin resistance and resulting hyperinsulinemia with hepatic triglyceride accumulation,. A previous preliminary study reported that the insulin sensitivity to adipocytes could be improved using ginger, with gingerol as its active component for this effect.[59]

PPARγ agonists have been hypothesized to be of therapeutic importance in NAFLD and ginger's 6-Shogaol has been reported to be a significant agonist of PPARγ in adipocytes.[60]

**CONCLUSION**

The correlations between hypoadiponectinaemia, Insulin Resistance, Dyslipidaemia and Cardiovascular diseases are well established from various researches. Owing to its pleiotropic effects as a biomarker in different systemic pathologies, Adiponectin has the potential to become a clinically relevant parameter to be considered for the evaluation of metabolic diseases.

Adiponectin administration as well as regulation of the pathways controlling its metabolism, represents a promising target for managing the aforementioned metabolic pathologies. In this regard Ayurvedic herbs were found to provide a serious contribution to the homoeostasis of adipocytokines, specifically Adiponectin, for curbing metabolic pathologies.

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***Address for correspondence**
Dr.K.V.Narasimha Raju
# C-31
Doctor's Residential Quarters
Gole market, Jawahar nagar
Jaipur 302004,Rajasthan, India
Mob: +919799025140
Email: drkvnr_june@yahoo.com
raju.vihaan@gmail.com