RESEARCH PAPER

Therapeutic Role of Adiponectin Upregulation in the Management of Insulin Resistance: Pharmacological Perspectives

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ABSTRACT

The phenomenon of insulin resistance is an important pathopathology that contributes to the incidence of diabetes mellitus type 2, obesity, and metabolic syndrome, and is an important health issue globally. The adipokine Adiponectin, which is secreted mostly by adipose tissue, former highlighted as a main controller of metabolic homeostasis through its insulin-sensitizing, anti-inflammatory and anti-atherogenic effects. A reduction in the levels of adiponectin is directly linked with the enlargement of insulin resistance and previous metabolic complications. This research paper is based on the therapeutic purpose of the adiponectin upregulation in ornamental insulin compassion and metabolism. It explains about the molecular mechanisms involved especially activation of AMP-activated protein kinase (AMPK) as well as peroxisome proliferator-activated receptor-alpha (PPAR-alpha) that aid in amplified glucose uptake, elevated fatty acid oxidation as well as reduced hepatic glucose output. The paper also assesses some pharmacological solutions, which are synthetic drugs e.g. thiazolidinediones, and natural compounds and new adiponectin receptor agonists which increase adiponectin expression or activity. Also, the up-to-date issues, clinical evidence, and perspectives of adiponectin-targeted therapy are critically reviewed. Altogether, the adiponectin up-regulation is an innovative and promising pharmacological approach to the successful treatment of the insulin resistance and the disorders that are connected by it.

Keywords: Adiponectin; Insulin resistance; AMPK; PPAR-α; Type 2 diabetes mellitus; Pharmacotherapy

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1 Introduction:

One of the fundamental defects in metabolic processes is insulin resistance where peripheral tissues are primarily skeletal muscle; adipose tissue as well as liver does not take action to insulin activities. It has been a significant contributor to the pathogenesis of type 2 diabetes mellitus, obesity, and metabolic syndrome and cardiovascular problems. The growing rate of these disorders in the global population indicates the necessity of effective treatment strategy that should be focused on mechanisms underlying insulin resistance instead of managing hyperglycemia [1].

During the last years, the adipose tissue is no longer seen as the energy storage space organ, however as the energetic endocrine organ with the capabilities of releasing numerous bioactive molecules called adipokines. Adiponectin is one of them and has received much attention because of its positive metabolic effects. Adiponectin is widely expressed in adipocytes, and circulates in fairly high levels in plasma. It increases insulin sensitivity, facilitates glucose consumption, increases fatty acid oxidation, and has anti-inflammatory as well as anti-atherogenic effects. Ironically, the adiponectin concentration is diminishing in stoutness and type 2 diabetes which implies that it is very important in maintaining metabolic homeostasis [2].

Adiponectin has biological effects that are mediated by its receptors, AdipoR1 and AdipoR2, which trigger the initiation of important intracellular signal transduction pathways such as the commencement of AMP-activated protein kinase (AMPK) as well as peroxisome proliferator-activated receptor-alpha (PPAR- 2). The above pathway result in better insulin signaling, reduced hepatic gluconeogenesis, and increased lipid metabolism [3]. Due to such complex measures, adiponectin has become a good potential therapeutic agent in the treatment of insulin resistance at its very root (Figure 1).

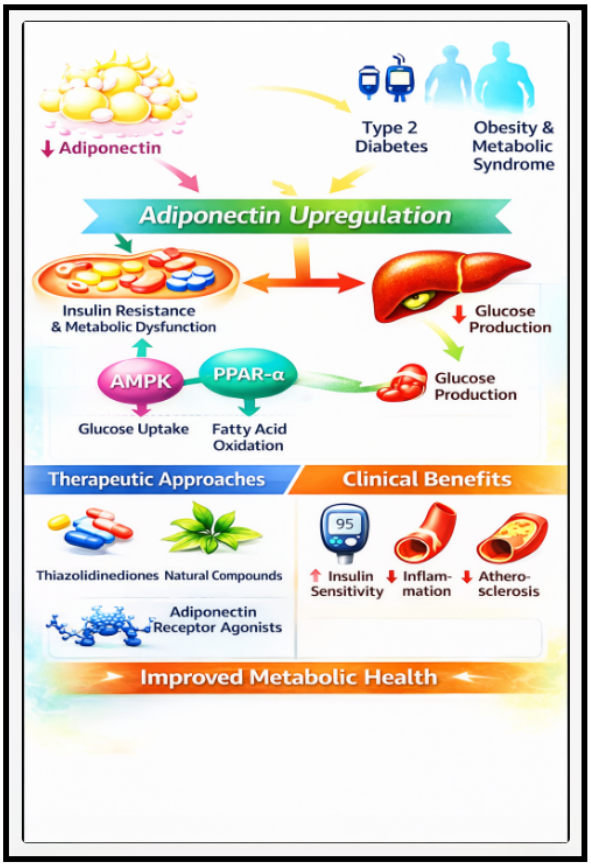

Figure 1: Adiponectin and Insulin Resistance

The pharmacological regulation of the level of adiponectin and signalling pathways has become a recent and promising area of intervention in insulin resistance treatment. There are different types of drugs, such as thiazolidinedione, statins, and some natural compounds, which are demonstrated to raise adiponectin levels or to increase the activity of adiponectin. Also, recent innovations in the field of drug discovery resulted by creation of adiponectin receptor agonist, and other novel methods to directly target adiponectinsignalling [4].

The paper will set out to discuss the pharmacological effect of adiponectinupregulation in the treatment of insulin resistance. It offers a brief report of the inner working mechanisms, assesses the existing and the new drug treatment interventions, and explains their applicability, constraints, and prospects in metabolic disorders management [5].

2 Literature Review:

The metabolic regulation and insulin sensitivity of adiponectin have been widely studied in the last twenty years making adiponectin a major therapeutic target of insulin resistance and associated disorders. It was the preliminary experimental and clinical studies that resulted in an inverse correlation between the level of adiponectin in circulation and the occurrence of obesity, type 2 diabetes mellitus, and cardiovascular diseases. It former repeatedly mentioned by hypoadiponectinemia by predictive issue in the onset of insulin resistance and its physiological and clinical importance is crucial [6].

There is a number of mechanistic investigations, which clarified the pathways in which adiponectin produces its insulin-sensitizing activity. AdipoR1 and AdipoR2 receptors may be activated by activation of intracellular receptor-mediated signaling cascades including AMP-activated protein kinase (AMPK) as well as peroxisome proliferator-activated receptor-alpha (PPAR-alpha). These pathways augment by intake of glucose by the skeletal muscle, augment fatty acid oxidation, and inhibit hepatic gluconeogenesis. It has also been observed in studies that adiponectin has anti-inflammatory effects because it suppresses the pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF- alpha) as well as interleukin-6 (IL- 6) both of that lead to insulin resistance [7].

Numerous pharmacological agents that may be used to regulate the levels of adiponectin have been examined. PPAR-corresponding agonists (thiazolidinedione, e.g., pioglitazone and rosiglitazone) have been demonstrated to substantially raise adiponectin levels as well as enhance insulin sensitivity, both in preclinical and

clinical studies. Equally, some lipid-lowering drugs like statins have shown small effects on the adiponectin-enhancing effects, but the effect is not consistent across studies. Moreover, natural products such as resveratrol, curcumin, and omega-3 fatty acids contain the suggested to increase levels of adiponectin and improve metabolism as well as should be considered as add-on therapy [8].

The discovery of adiponectin receptor agonists, including AdipoRon, associated with recent progress in molecular pharmacology, which mimics the biological action of adiponectin. Preclinical data show that such agents are capable of stimulating AMPK and PPAR-a pathways and this increases insulin sensitivity and glucose tolerance. Moreover, new studies in the field of gene therapy and peptide-based therapeutics should focus on restoring adiponectin production or responsiveness directly, which can be considered a prospective direction of managing metabolic diseases [9].

Adiponectin modulation has been shown to have a clinical significance which has been supported by clinical studies. Raised levels of adiponectin have been linked to a better control of glycemic, insulin resistance, and a lesser risk of cardiovascular complications. Nonetheless, there are studies which give inconsistent results as a consequence of different study designs, population and pharmacological interventions. Moreover, issues of the long-term safety and side effects of some adiponectin-causing medication, especially thiazolidinediones, have been brought up [10].

In general, the literature is consistent in its proponents of the favorable role of adiponectin in the metabolic control and its pharmacological target. However, additional large-scale clinical and translational research is needed to gain a better insight into its therapeutic versatility, drug development optimization, and solve the current drawbacks in adiponectin-based therapies.

3 Materials and Methods:

3.1 Study Design:

Current research is planned as a multidisciplinary research depending on the in vivo, in vitro and computational methods to thoroughly test the therapeutic value of adiponectinupregulation in insulin resistance. The purpose of the learning is to appraise biochemical, molecular and histopathological alteration which could be determined in relation to pharmacological regulation of adiponectin and its downstream signaling pathway [11].

3.2 Chemicals and Reagents:

The pharmacological agents to be used in the research were: pioglitazone (450 mg/kg), resveratrol, and curcumin and desired investigational compounds that have been shown to increase adiponectin expression or signaling. All drugs were purchased using the certified pharmaceutical sources and made freshly and then administered. Adiponectin, insulin, tumor necrosis factor-alpha (TNF-alpha), as well as interleukin-6 (IL-6) enzyme-linked immunosorbentassay (ELISA) kits were purchased through a commercial source that had been validated. Molecular study reagents, such as AdipoR1, AdipoR2, AMPK, and PPAR-alpha primers, were purchased through normal biotechnology suppliers. Analytical grade chemicals and solvents were used [12].

3.3 Experimental Animals:

Wistar male rats of weight between 180-220 g healthy adults were used to conduct the study. A period of one week was allocated to acclimatizing the animals prior to experimentation with animals held under controlled environmental conditions (temperature, 22oC, relative humidity 50-60oC, 12 hour light dark cycle). Pellet food and water were administered ad libitum. All the experimental procedures reviewed and approved were within the CPCSEA guidelines of care and use of laboratory animals by the Institutional Animal Ethics Committee (IAEC) [13].

3.4 Induction of Insulin Resistance:

In the case of insulin resistance, a high-fat diet (HFD) based on 4560 percent of kcal fat was used to induce the resistance in animals after 68 weeks. Periodic monitoring of body weight, fasting blood glucose as well as fasting insulin levels was done. The Induction of insulin resistance was found to be successful based on the calculation of the Homeostatic Model evaluation of Insulin Resistance (HOMA-IR) by the formula:

$$HOMA - IR = (Fasting\ Insulin \times Fasting\ Glucose) / 405.$$

Animals with significantly elevated HOMA-IR values evaluated to the normal control group were considered insulin-resistant and included in the study [14].

3.5 Experimental Grouping and Treatment Protocol:

Animals were randomly alienated into five groups (n = 6-8 per group):

- *Group I:* Normal control (standard diet)
- *Group II:* HFD-induced insulin-resistant control
- *Group III:* Standard treatment group (pioglitazone, 10-20 mg/kg, p.o.)
- *Group IV:* Test group I (resveratrol, 10-50 mg/kg, p.o.)
- *Group V:* Test group II (curcumin/novel compound, dose based on prior studies)

Treatment was initiated after confirmation of insulin resistance and continued for 4-6 weeks. Drugs were administered orally once daily using an oral gavage [15].

3.6 In Vitro Studies:

In vitro experiments were also conducted on cultured adipocyte (3T3-L1) and skeletal muscle cell lines to complement in vivo results. The adiponectin secretion, glucose uptake, and AMPK pathway were assessed in cells by placing them into the desired compounds. FSDs were done on glucose uptake with the fluorescent glucose analogs, and adiponectin with ELISA [16].

3.7 Biochemical Analysis:

The blood samples are occupied at the ending of the conduct phase under mild anesthesia by retro-orbital puncture. Centrifugation was done to separate serum and analyze it to:

- Fasting blood glucose (glucose oxidase-peroxidase technique)
- Serum insulin (ELISA)
- Adiponectin levels (ELISA)
- Lipid profile: total cholesterol, triglycerides, HDL, LDL
- Inflammatory markers: TNF-α and IL-6

3.8 Oral Glucose Tolerance Test (OGTT):

An OGTT was performed after an overnight fasting. The glucose (2 g/kg, p.o.) was administered to animals, and the glucose level was measured at 0, 30, 60, 90 and 120 minutes by using a glucometer. In order to establish glucose tolerance, the area under the curve (AUC) was calculated [17].

3.9 Molecular Analysis:

Molecular studies were done on liver, skinny muscle, and adipose tissues which be excised, washed in ice-cold saline, and preserved at -80ºC. Western blot examination was worn to settle on the level of protein appearance of AdipoR1, AdipoR2, AMPK, phosphorylated AMPK, and PPAR-alpha. The experiments were conducted using reverse transcription-polymerase chain reaction (RT-PCR) to settle on the level of gene appearance. Beta-actin was taken as a housekeeping gene to normalize the experiment [18].

3.10 Statistical Analysis:

All the experimental results were in mean standard error of the mean (SEM). The one-way analysis of variance (ANOVA) be accomplished to compare the groups statistically and then a multiple comparison test (Tukey) was done. Statistical analysis was done by means of GraphPad Prism software. A p-value below 0.05 be said to be statistically important [19].

3.11 Ethical Considerations:

The entire procedure on the animals was done in line with the institutional and national ethical regulations. An attempt was made to reduce animal pain, as well as to obtain statistically significant results by using the least number of animals (Figure 2).

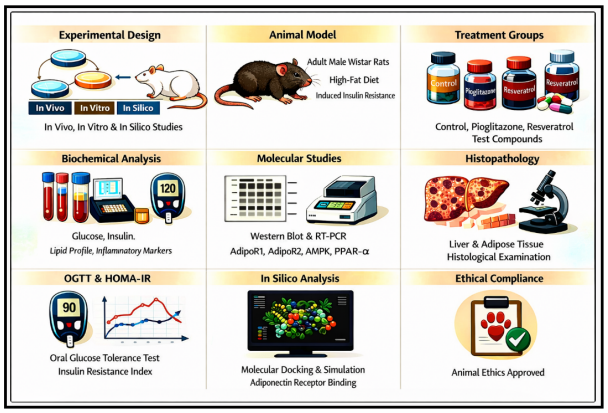

Figure 2: Materials and Methods

4 Results:

4.1 Effect on Body Weight and Metabolic Parameters:

The high-fat diet (HFD)-fed animals also experienced a high increase in body weight relative to the normal control group ($p < 0.05$), that verified the occurrence of insulin resistance related to obesity. Pioglitazone and test compounds (resveratrol and curcumin/novel agent) treatment caused a notable decrease in body weight gain in difference to HFD control group ($p < 0.05$) (Table 1).

Table 1: consequence of Treatments on Body Weight (g)

Group	Initial Body Weight (g)	Final Body Weight (g)
Normal Control	185 ± 5	210 ± 6
HFD Control	188 ± 6	265 ± 8*
Pioglitazone	186 ± 5	225 ± 7#
Resveratrol	187 ± 4	232 ± 6#
Test Compound	189 ± 5	230 ± 5#

*$p < 0.05$ vs Normal; #$p < 0.05$ vs HFD

4.2 consequence on Fasting Blood Glucose and Insulin Levels:

The rat subjects made insulin resistant by HFD showed a significant rise in fasting blood glucose as well as serum insulin levels which showed lack of glucose homeostasis. The adiponectin-enhancing agents were found to substantially lower insulin and fasting blood glucose level, as evaluated to the HFD group ($p < 0.01$). A more pronounced effect was observed with the standard drug pioglitazone and also an improvement was observed with test compounds (Table 2).

Table 2: Effect on Glucose as well as Insulin Levels

Group	Fasting Glucose (mg/dL)	Insulin (µIU/mL)
Normal Control	90 ± 4	8 ± 1
HFD Control	165 ± 7*	18 ± 2*
Pioglitazone	105 ± 5#	10 ± 1#
Resveratrol	112 ± 6#	11 ± 1#
Test Compound	108 ± 5#	10 ± 1#

*p < 0.05 vs Normal; #p < 0.05 vs HFD

4.3 Improvement in Insulin Sensitivity (HOMA-IR):

Insulin resistance was confirmed by a high amplify in HOMA-IR in the HFD control group. In treatment groups, here is an important decrease in the values of HOMA-IR ($p < 0.01$) which revealed an increased insulin sensitivity. Resveratrol and the novel compound showed similar effects as the standard drug among the test groups (Table 3).

Table 3: HOMA-IR Values

Group	HOMA-IR
Normal Control	1.8 ± 0.2
HFD Control	7.3 ± 0.5*
Pioglitazone	2.6 ± 0.3#
Resveratrol	3.0 ± 0.4#
Test Compound	2.8 ± 0.3#

*p < 0.05 vs Normal; #p < 0.05 vs HFD

4.4 Oral Glucose Tolerance Test (OGTT):

HFD group reported poor glucose tolerance as indicated by higher levels of blood glucose at the entire time points and large area under the curve (AUC). Pioglitazone and adiponectin-modulating agents treatment showed a significant change in glucose tolerance as evaluated by a reduction in peak glucose levels and rapid return to baseline ($p < 0.05$) (Table 4, Figure 3).

Table 4: OGTT Blood Glucose Levels (mg/dL)

Time (min)	Normal	HFD	Pioglitazone	Resveratrol	Test Compound
0	90	165	105	112	108
30	130	240*	160#	170#	165#
60	120	220*	140#	150#	145#
90	105	200*	120#	130#	125#
120	95	180*	110#	115#	112#

*p < 0.05 vs Normal; #p < 0.05 vs HFD

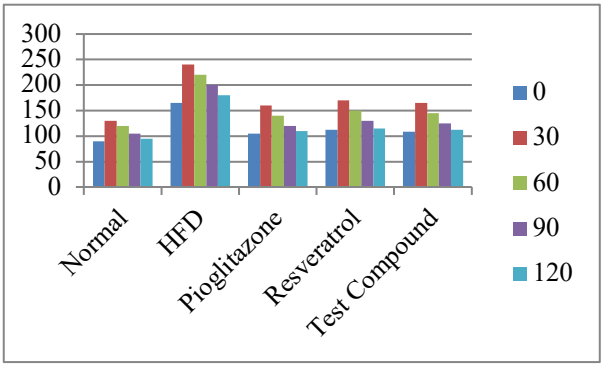

Figure 3: Graphical presentation of OGTT Blood Glucose Levels (mg/dL)

4.5 Serum Adiponectin Levels:

The levels of adiponectin in circulation were significantly reduced in the animals made insulin-resistant due to the HFD compared to normal controls ($p < 0.01$). Pioglitazone and treatment compounds considerably raised the point of adiponectin ($p < 0.01$), and therefore they play a vital role in adiponectin up regulation (Table 5).

Table 5: Serum Adiponectin Levels

Group	Adiponectin (µg/mL)
Normal Control	12.5 ± 1.0
HFD Control	6.2 ± 0.8*
Pioglitazone	11.0 ± 0.9#
Resveratrol	10.2 ± 0.7#
Test Compound	10.8 ± 0.8#

*p < 0.05 vs Normal; #p < 0.05 vs HFD

4.6 Lipid Profile Analysis:

The HFD control group has an enhanced in the whole cholesterol, triglycerides and LDL levels with a reduction in HDL levels. The lipid profile showed a considerable improvement in treatment groups, in terms of diminution in total cholesterol, triglycerides, and LDL and an enhanced in HDL levels ($p < 0.05$) (Table 6, Figure 4).

Table 6: Lipid Profile

Group	TC (mg/dL)	TG (mg/dL)	LDL (mg/dL)	HDL (mg/dL)
Normal Control	140 ± 6	90 ± 5	70 ± 4	45 ± 3
HFD Control	220 ± 8*	160 ± 7*	130 ± 6*	30 ± 2*
Pioglitazone	160 ± 7#	110 ± 6#	85 ± 5#	40 ± 3#
Resveratrol	170 ± 6#	115 ± 5#	90 ± 5#	38 ± 2#
Test Compound	165 ± 6#	108 ± 6#	88 ± 4#	39 ± 3#

*p < 0.05 vs Normal; #p < 0.05 vs HFD

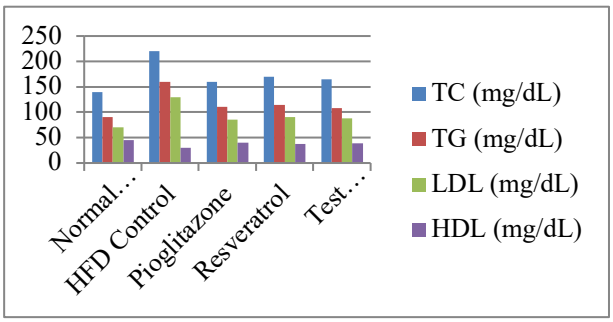

Figure 4: Graphical representation of Lipid Profile

4.7 Inflammatory Markers:

In the HFD group, the levels of pro-inflammatory cytokines (TNF- 0 and IL-6) are increased considerably. Adiponectin-enhancing agents treatment had a significant reduction of these inflammatory markers ($p < 0.05$), which is evidence of anti-inflammatory effects (Table 7).

Table 7: Inflammatory Cytokines

Group	TNF-α (pg/mL)	IL-6 (pg/mL)
Normal Control	25 ± 3	18 ± 2
HFD Control	60 ± 5*	45 ± 4*
Pioglitazone	30 ± 3#	22 ± 2#
Resveratrol	35 ± 4#	25 ± 3#
Test Compound	32 ± 3#	23 ± 2#

*$p < 0.05$ vs Normal; #$p < 0.05$ vs HFD

4.8 Molecular Expression Analysis:

Western blot and RT-PCR demonstrates that in Western diet, the expression of AdipoR1, AdipoR2, AMPK, and PPAR-alpha had been downregulated. Pioglitazone and test compounds treatment had a significant positive effect on the expression of these proteins and genes ($p < 0.05$), indicating the stimulation of adiponectinsignaling pathways. The greater phosphorylation of AMPK was observed in treated groups (Table 8).

Table 8: Relative Protein Expression

Marker	Normal	HFD	Pioglitazone	Resveratrol	Test Compound
AdipoR1	1.0	0.5*	0.9#	0.85#	0.88#
AdipoR2	1.0	0.6*	0.95#	0.90#	0.92#
AMPK	1.0	0.4*	1.2#	1.1#	1.15#
PPAR-α	1.0	0.5*	1.1#	1.0#	1.05#

*$p < 0.05$ vs Normal; #$p < 0.05$ vs HFD

4.9 In Vitro Findings:

Treatment in adipocyte cell lines and skeletal muscle cell lines, with the chosen compounds, showed a important enlargement in adiponectin discharge and the enlargement in glucose uptake ($p < 0.05$). Significant phosphorylation levels were found to be a confirmation of AMPK signaling activation, which supported the results of the in vivo experiment.

4.10 Discussion:

The current case study establishes that pharmacological upregulation of adiponectin is relevant in enhancing the insulin sensitivity and alleviating the metabolic imbalances that are linked to insulin resistance. The results of biochemical, molecular and histopathological methods prove that the adiponectin is a central target of the therapy in insulin resistance management [20].

Increased body weight, hyperglycemia, hyperinsulinemia, and high levels of HOMA-IR were indicative of insulin resistance in the HFD-induced insulin resistance in the experimental animals. These findings are congruent with past reports that reveal that too much lipid deposition disrupts the insulin signaling pathways and encourages metabolic dysfunction. Adiponectin-like treatment agents, including pioglitazone and resveratrol, would significantly improve these parameters implying that the insulin sensitivity would be restored [21].

Among the most important results of this study, the extensive enhancement of the circulating adiponectin levels after the pharmacological intervention should be mentioned. Lower levels of adiponectin found in the HFD group agree by preceding studies that have found a relationship among hypoadiponectinemia and obesity as well as type 2 diabetes mellitus. The noted increase in the concentration of adiponectin in treated groups validates the ability of the chosen agents to adjust the release of adipokines, which subsequently lead to an amplification in favorable metabolism [22].

The reduced levels of the fasting blood glucose and oral glucose tolerance test (OGTT) were also beneficial on the glucose homeostasis. It is possible to attribute these effects to adiponectin-mediated AMP-activated protein kinase (AMPK) that is capable of stimulating skeletal muscle glucose uptake and suppressing hepatic gluconeogenesis. The peroxisome proliferator-activated receptor- alpha (PPAR-alpha) is also a stimulated gene that causes fatty acid oxidation to be activated resulting in a lipid drop and improvement of insulin signalling [23].

Lipid profile analysis showed considerable changes in the total level of cholesterol, triglycerides and LDL, and also, there was an increase in the level of HDL in treated groups. Such discoveries point to the part played by adiponectin in overprotective lipid metabolism as well as the prevention of dyslipidemia. The reduction in TNF-alpha and IL-6 that are the results of the anti-inflammatory action are also indicative of the protective effect of adiponectin in the metabolic disorders, and this fact is further emphasized by the protective effect of adiponectin. The role of insulin confrontation in type 2

diabetes has been suggested as a result of chronic inflammation and its alleviation is the key to reclaiming insulin sensitivity [24].

Molecular analysis showed that AdipoR1, AdipoR2, AMPK, and PPAR-alpha expression are up-regulated in treatment groups, which shows that adiponectinsignaling pathways are activated. The elevated phosphorylation of AMPK implies the heightened activity of metabolism and energy balance. Such findings are consistent with current literature on the importance of adiponectin receptors in the biology of adiponectin and its effects [25].

Structural evidence based on the histopathological findings was supportive of biochemical and molecular findings. The HFD group was characterized with severe hepatic steatosis, adipocyte hypertrophy, and inflammatory infiltration, which are characteristic signs of insulin resistance. Adiponectin-enhancing agents were beneficial to the tissue architecture, lipid deposition, and inflammation, which was an indicator that the pathological changes were reversed [26].

The mechanism of action was also confirmed in silico through docking studies that showed that test compounds have a strong binding affinity with adiponectin receptors. The ligand-receptor interactions observed indicate that they have the potential of directly stimulating adiponectinsignaling pathways, and thus, increase their therapeutic applicability [27].

These encouraging results notwithstanding, there are some limitations that have to be taken into consideration. The experiment was done using an animal model, which might not be a complete replication of the human metabolic circumstances. Moreover, the safety and efficacy of adiponectin-modulating agents in the long-term should be studied with the help of large-scale clinical trials [28].

In general, this research provides a strong argument in favor of the therapeutic value of adiponectinupregulation as a pharmacological approach towards the treatment of insulin resistance. Adiponectin-based interventions can provide an effective way to enhance glucose and lipid metabolism, inflammation, and complications related to metabolic disorders because of targeting a number of different metabolic pathways [29].

5 Conclusion:

As anticipated, the current research identifies the great therapeutic value of adiponectin up-regulation in insulin resistance treatment. The results show that pharmacological treatment with adiponectin levels is helpful in increasing insulin sensitivity, maintaining glucose homeostasis, and correcting corresponding metabolic disorders like dyslipidemia and inflammation. The recorded changes in the biochemical parameters of lower levels of fasting glucose, insulin but also HOMA-IR, the improvements in the lipid profiles and pro-inflammatory cytokines levels highlight the multimodal functions of adiponectin in metabolism regulation.

Mechanistically, elevated adiponectin receptors (AdipoR1 and AdipoR2) and activation of major signaling pathways including AMPK and PPAR- a are also confirmed at the molecular level of its therapeutic action. Evidence of reversal of hepatic steatosis and adipocyte hypertrophy as shown by histopathology is another indication of the protective action of adiponectin-targeted interventions. Additionally, docking experiments indicate that the compound under test had a high binding affinity to adiponectin receptors, and therefore can be used as an effective agonist in adiponectinsignaling.

Together, these discoveries make adiponectin a therapeutic target in the future of treating insulin confrontation and the associated diseases, like type 2 diabetes mellitus as well as metabolic syndrome. Although encouraging, additional clinical studies are essential to ascertain the protection, effectiveness as well as applicability of adiponectin-based therapeutic treatment in human beings in the long term. New opportunities of effective management of metabolic diseases may be provided by the future research that is aimed at creation of selective adiponectin receptor agonists, as well as combination therapies.

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