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RESEARCH PAPER

Effect of Nano-Chlorogenic Acid Versus Conventional Chlorogenic Acid on Ampk Activity in Type 2 Diabetes under Different Therapeutic Conditions

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ABSTRACT

The lack of activity of adenosine monophosphate-activated protein kinase (AMPK) is the main reason for cellular energy dyshomeostasis in type 2 diabetes mellitus (T2DM). In this study, metformin partially stimulates AMPK but does not restore it to normal levels. In contrast to AMPK, native chlorogenic acid (CGA) is pharmacologically limited and is unable to uptake cellular energy in a cell. In this study, we compare the effect of conventional CGA with silver-nanoformulated CGA to stimulate AMPK in human serum. The study population consisted of 120 participants and was divided into three groups: a healthy control group, a metformin-treated T2DM group, and an untreated T2DM group. In vitro treatments to the serum were performed with 8 ppm of conventional CGA and 16 ppm of its silver nano-formulation. Enzyme levels were measured and data were statistically analyzed to identify significant differences. The primary findings were that diabetic patients experience a significant decline in AMPK activity compared to healthy controls, with the lowest levels in the untreated group. Treatment with the conventional form led to a significant increase in enzyme activity in all groups; however, the nano-formulation worked better ($p < 0.001$) in the diabetic group. The most striking finding was that the nano-intervention did not only bridge the metabolic gap between diabetic patients, but it also corrected the differences between the two patient groups from 0.889 to 0.506 in enzyme levels. This difference was not statistically significant for the healthy group ($p = 0.088$), suggesting that the efficacy of the nano-formulation is dependent on the extent to which metabolic dysregulation is not corrected. These findings demonstrate that nano-engineering of CGA is able to bypass cellular obstacles and significantly increases bioavailability compared with the free compound. It is thus an effective adjunct to the treatment of T2DM by resetting energy homeostasis in compromised cells and can be a natural treatment.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a growing global health concern for which the medical community and international health organizations are concerned. As the most prevalent form of diabetes, T2DM is a metabolic disorder characterized by chronic hyperglycemia. It imposes substantial economic burden on patients and is costly to their quality of life. It's more than just glycemic control: lipid and protein metabolism dysregulations lead to micro- and macrovascular diseases in the heart, kidneys, nerves and

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retina [1]. The most important of the metabolic disturbances is adenosine monophosphate-activated protein kinase (AMPK), an enzyme that plays a crucial role in cell energy homeostasis. As a novel serine/threonine kinase, AMPK is a crucial protein in energy balance and has become an important therapeutic target in many metabolic diseases such as diabetes, obesity, and inflammation. AMPK is activated in skeletal muscles when cellular energy is depleted and it is able to promote glucose uptake, oxidation of fatty acids and hepatic gluconeogenesis are inhibited. It is well-known that AMPK activity is inhibited in T2DM as a function of chronic energy surplus and hence AMPK activation is a key pharmacological target [2]. Even addressing the AMPK pathway needs to mention metformin (Glucophage, also known as Glucophage) as the first-line treatment for T2DM worldwide. Metformin is used primarily to inhibit hepatic glucose production and hepatic gluconeogenesis, and is the most active in this area [3]. At the molecular level, a landmark study demonstrated that the low blood-level concentrations of metformin are able to suppress the PEN2 protein on the lysosomal membrane and thus initiate a signalling cascade that allows AMPK action in a non-AMP-dependent manner [4]. The long-term use of metformin, however, is associated with gastrointestinal side effects and may eventually be less therapeutic in some patients [5]. Chlorogenic acid (CGA) has gained renewed interest in recent years as a natural phenolic compound with pleiotropic properties. It is found in coffee and in various fruits and vegetables and has an ester bond between caffeic and quinic acids. It improves insulin signaling, AMPK activation and intestinal glucose absorption. CGA also prevents diabetes complications due to its antioxidant and anti-inflammatory properties [6]. Numerous studies have shown that CGA stimulates AMPK and suppresses hepatic gluconeogenesis and de novo lipogenesis, and this makes it an appropriate natural addition to normal treatment [7]. The clinical efficacy of CGA is limited by its pharmacokinetic challenges as well, and like other phenolics it is also very weak in aqueous solubility, rapidly degrades and is unstable within the gastrointestinal tract and thus is very hard to deliver to the tissues [8]. Nanotechnology plays a new role to overcome these challenges. The incorporation of CGA as nanoparticles leads to enhanced bioavailability and the delivery of CGA to the tissues or organs and has been used to improve diabetes management in the past decades and is also a paradigm shift of nanotechnology-based drug delivery for diabetes. Phytochemical-engineered nanoparticles have shown the ability to improve the effectiveness, bioavailability and safety of natural drugs in preclinical diabetes [9,10]. Nano-formulated chlorogenic acid can be a key player to harness this natural compound and its nano-engineered form will address the bioavailability problem that exists in the conventional form. Building on all these findings, in this study we compare and contrast nano-formulated CGA with conventional CGA for circulating AMPK activity in three different groups of humans: healthy individuals (control group), T2DM patients on metformin therapy, and treatment-naïve T2DM patients. In the end, we aim to analyze the effectiveness of nano-formulation in the metabolic response compared to conventional CGA.

MATERIALS AND METHODS

Study Population

The samples were collected from patients in Al-Khalis General Hospital between June 10, 2024 and August 20, 2025 who were diagnosed with type 2 diabetes mellitus (T2DM). The participants were divided into three groups: Group I (P+M) consisted of 40 T2DM patients aged 44-55 years of both sexes who were receiving regular metformin (Glucophage) therapy; Group II (P-M) consisted of 40 T2DM patients of both sexes aged 38-56 years at the time of diagnosis who did not have any medication; and Group III (a healthy control group) consisted of 40 patients of both sexes aged 35-50 years with no clinical conditions which could potentially influence the study findings. The total population of 120 participants was then included in the study.

Sample Collection and Laboratory Processing

Ten milliliters (10 mL) of venous blood were drawn from each participant using disposable 10 mL plastic syringes fitted with 21-gauge (G21) needles. Each blood sample was subsequently divided into two aliquots: 2 mL were transferred into a plastic tube containing an anticoagulant for the determination of CBC and HbA1c levels. The remaining 8 mL were transferred into a plain plastic tube (anticoagulant-free) and allowed to clot at 37°C for 20–30 minutes. Serum was separated via

centrifugation at 3000 rpm for 10 minutes, divided into microcentrifuge tubes (Eppendorf tubes), and stored at -20°C until further analysis. The collected serum was used to determine levels of the AMPK enzyme and the following biochemical variables: fasting blood glucose (FBG), blood urea, creatinine, total bilirubin, liver enzymes (SGOT, SGPT, and ALP), lipid profile (levels of LDL, VLDL, HDL, triglycerides, and total cholesterol), fasting insulin, and insulin resistance (calculated HOMA-IR).

Synthesis of Silver-Chlorogenic Acid Nanoparticles

The CGA-PVP-silver nitrate complex was created following the modified protocols for the green synthesis of silver nanoparticles. 0.085 g of chlorogenic acid (98% purity) was mixed and dissolved in 123 mL of deionized distilled water while being magnetically stirred. The mixture was stirred for 15 minutes [11] and the complete dissolution of the chlorogenic acid was confirmed. Then, in another beaker, 0.30 g of polyvinylpyrrolidone (PVP) was dissolved in 70 mL of deionized distilled water. The PVP solution was added to the CGA solution and stirred. The solution was stirred for 30 minutes to allow maximum interaction between the CGA and PVP, as PVP is a steric stabilizer, which means it prevents NP agglomeration and improves size distribution [12]. After this, 7 mL of 0.1 M silver nitrate ($AgNO_3$) solution was added dropwise while stirring, and after this, the mixture was stirred for another 30 minutes to evenly distribute silver ions and start complex formation [13]. All steps of this preparation took place in the same lab under normal room light and temperature. After stirring the solution, it was sealed in a bag and kept at 4 °C for 48 hours to allow the last of the reaction to take place and the complexes containing silver to precipitate.

Characterization of Nanoparticles

The UV-Visible spectrophotometric method was applied to analyze and describe the liquid sample of nanochlorogenic acid. In the next step, the solvent was stripped off from the suspension of colloidal silver nanoparticles and the powder obtained was placed on the glass slide for future investigation via FTIR spectrometry, AFM, XRD, and FESEM [14].

Statistical Analysis

All values were represented as mean ± standard error of the mean. Group means were compared by Student's t-test. The criterion for significance was set at $p<0.05$. Analyses were performed using Microsoft Office Excel 2010.

RESULTS AND DISCUSSION

Normality Testing of AMPK Enzyme

Shapiro-Wilk Test indicated that the AMPK enzyme concentration had normal distribution in all groups irrespective of the treatments applied ($p > 0.05$). Therefore, the application of parametric test was justified in all subsequent analysis phases, as shown in Table 1.

Descriptive and Statistical Analysis of AMPK Enzyme

The results presented in Table 2 show different

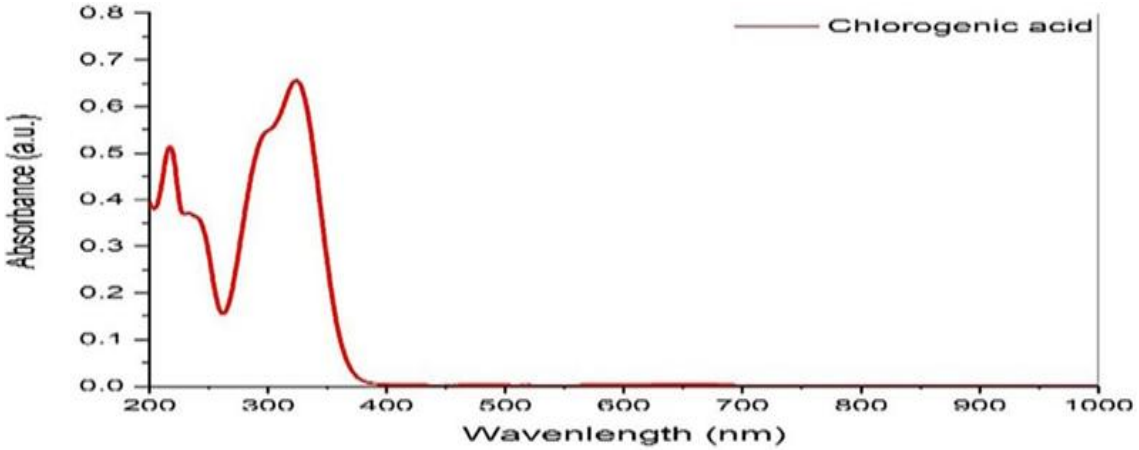

Fig. 1. UV visible spectra of chlorogenic acid as silver nanoparticle.

levels of activity of AMPK enzyme among the three study groups depending on the treatments received by the groups. In terms of non-treatment (no add.), the mean activity of the control was significantly high (3.187 ± 0.083) compared to those obtained for the P+M (1.054 ± 0.002) and P-M (0.165 ± 0.015) groups, and statistical significance was attained ($F = 1024.435$, $p < 0.001$). After treatment with normal chlorogenic acid (8 ppm CA), the mean values became higher for all groups, specifically, 6.471 ± 0.075 for the control, 2.270 ± 0.110 for the P+M, and 1.368 ± 0.077 for the P-M, all having a significant effect on AMPK ($F = 943.188$, $p < 0.001$). Silver nano-chlorogenic acid (16 ppm nano CA) had an even higher level of activity on the two diabetic groups, especially

Table 1. Normality Testing of AMPK Enzyme Across Groups and Treatment Conditions Using the Shapiro-Wilk Test.

Vars.		Control		P+M		P-M	
		Statistic	P value	Statistic	P value	Statistic	P value
AMPK	No add.	0.979	0.669	0.945	0.051	0.954	0.105
	8ppm CA	0.964	0.227	0.946	0.056	0.950	0.073
	16 ppm nano CA	0.968	0.316	0.953	0.098	0.956	0.130

Table 2. Descriptive and Statistical Analysis of AMPK Enzyme Levels Across Groups and Treatment Conditions.

MajorG	SubG	Minimum	Maximum	Mean	±SE	F	P value
No add.	Control	2.656	3.889	3.187	0.083	1024.435	0.000
	P+M	1.033	1.066	1.054	0.002		
	P-M	0.034	.270	0.165	0.015		
8ppm CA	Control	5.890	6.998	6.471	0.075	943.188	0.000
	P+M	1.056	2.988	2.270	0.110		
	P-M	1.003	2.079	1.368	0.077		
16 ppm nano CA	Control	5.566	6.897	6.236	0.077	925.609	0.000
	P+M	2.778	3.088	2.952	0.018		
	P-M	1.788	2.966	2.446	0.087		

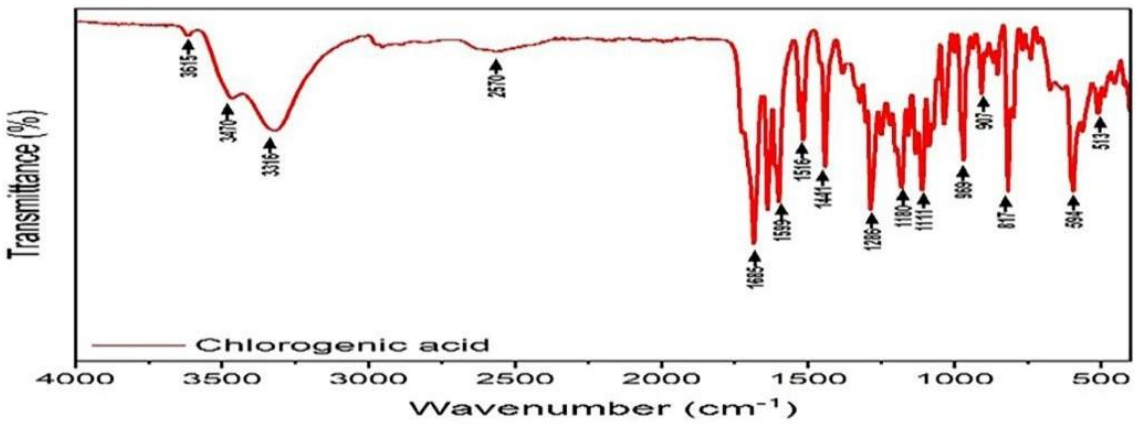

Fig. 2. FT-IR spectrum of chlorogenic acid.

P+M (2.952 ± 0.018) and P-M (2.446 ± 0.087), which were statistically significant (F = 925.609, p < 0.001).

Pairwise Comparison of AMPK Enzyme Between Treatment Conditions

The results presented in Table 3 illustrate the pairwise comparisons between the three treatment conditions within each subgroup, conducted using Dunnett's T3 test. In the control group, the mean difference between the no-treatment condition and the 8 ppm CA treatment was (−3.284), reaching high statistical significance (p < 0.001), while the difference between the no-treatment condition and the 16 ppm nano CA treatment was (−3.049), likewise achieving statistical significance (p < 0.001); however, the difference between the two treatment conditions did not reach the threshold of statistical significance (p = 0.088). In the P+M group, the mean difference between the no-treatment condition and the 8 ppm CA treatment was (−1.217) with high statistical significance (p < 0.001), and the difference between the no-treatment condition and the 16 ppm nano CA treatment was (−1.899), also yielding high statistical significance (p < 0.001); furthermore, the difference between the two treatments (−0.682) was statistically significant (p < 0.001). In the P-M group, the mean difference between the no-treatment condition and the

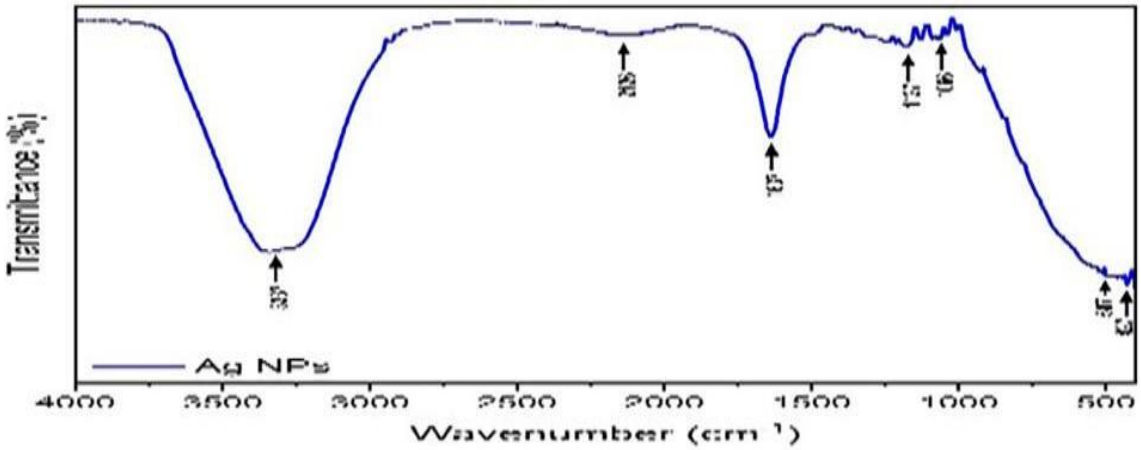

Fig. 3. FT-IR spectrum of chlorogenic acid as silver nanoparticle.

Table 3. Pairwise Comparison of AMPK Enzyme Levels Between Treatment Conditions Within Each Group Using Dunnett's T3 Test.

SubG	(I) MajorG	(J) MajorG	Statistics	Mean Difference (I-J)	P value	95% Confidence Interval	
						Lower Bound	Upper Bound
Control	No add.	8ppm CA	F=551.804, p value=0.000	-3.284	0.000	-3.556	-3.013
		16 ppm nano CA		-3.049	0.000	-3.323	-2.774
	8ppm CA	16 ppm nano CA		0.235	0.088	-.025	.496
P+M	No add.	8ppm CA	F=223.968, p value=0.000	-1.217	0.000	-1.490	-.943
		16 ppm nano CA		-1.899	0.000	-1.942	-1.855
	8ppm CA	16 ppm nano CA		-0.682	0.000	-.959	-.405
P-M	No add.	8ppm CA	F=284.276, p value=0.000	-1.203	0.000	-1.398	-1.008
		16 ppm nano CA		-2.281	0.000	-2.500	-2.062
	8ppm CA	16 ppm nano CA		-1.078	0.000	-1.361	-.794

8 ppm CA treatment was (−1.203) with high statistical significance ($p < 0.001$), the difference between the no-treatment condition and the 16 ppm nano CA treatment reached (−2.281) with high statistical significance ($p < 0.001$), and the difference between the two treatment conditions (−1.078) was equally statistically significant ($p < 0.001$).

Pairwise Comparison of AMPK Enzyme Between Subgroups

The data presented in Table 4 illustrate the results of pairwise comparisons among the three groups (Control, P+M, and P-M) within each treatment condition, conducted using Dunnett's T3 test. Under the no-treatment condition, the mean difference between the control group and the P+M group was (2.133) with high statistical significance ($p < 0.001$), between the control group and the P-M group was (3.022) with high statistical significance ($p < 0.001$), and between the P+M group and the P-M group was (0.889), equally achieving statistical significance ($p < 0.001$). Upon treatment with 8 ppm CA, the inter-group differences increased considerably, with the mean difference between the control and P+M groups reaching (4.201), between the control and P-M groups (5.103), and between the P+M and P-M groups (0.902), all attaining high statistical significance ($p < 0.001$). Under treatment with 16 ppm nano CA, the mean difference between the control and P+M groups was (3.284) and between the control and P-M groups was (3.790), both with high statistical significance ($p < 0.001$), while the difference between the P+M and P-M groups was (0.506), also reaching statistical significance ($p < 0.001$). These findings suggest a notable convergence in AMPK enzyme levels between the

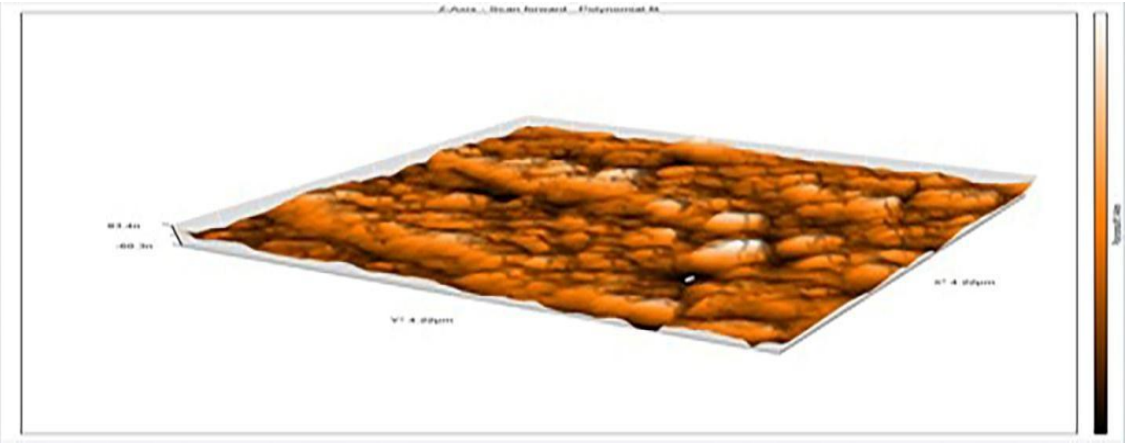

Fig. 4. AFM of chlorogenic acid as silver nanoparticle.

Table 4. Pairwise Comparison of AMPK Enzyme Levels Between Subgroups Using Dunnett's T3 Test.

MajorG	(I) SubG	(J) SubG	Mean Difference (I-J)	P value	95% Confidence Interval	
					Lower Bound	Upper Bound
No add.	Control	P+M	2.133	0.000	1.928	2.339
		P-M	3.022	0.000	2.813	3.231
	P+M	P-M	0.889	0.000	.850	.927
8ppm CA	Control	P+M	4.201	0.000	3.876	4.526
		P-M	5.103	0.000	4.841	5.365
	P+M	P-M	0.902	0.000	.574	1.230
16 ppm nano CA	Control	P+M	3.284	0.000	3.089	3.478
		P-M	3.790	0.000	3.507	4.072
	P+M	P-M	0.506	0.000	.286	.726

two diabetic groups when the nano formulation was applied, compared to the other treatment conditions.

The current study identified a clearly different pattern of AMP-Activated Protein Kinase (AMPK) enzyme activity among the three studied groups. Participants from the control group had the highest mean activity level of the enzyme (3.187 ± 0.083), the metformin group (P+M) of diabetic disease reported considerably lower mean (1.054 ± 0.002), and the diabetic untreated group (P-M) showed the lowest mean (0.165 ± 0.015), and their statistically significant differences were a very high difference ($F = 1024.435$, $p < 0.001$). AMPK, a serine/threonine kinase that is evolutionarily conserved, serves as a critical mediator of cellular energy homeostasis and new studies have demonstrated non-classical activation pathways through glucose, fatty acid, and glycogen sensing, as well as the classical AMP/ATP ratio mechanisms [15]. In type 2 diabetes mellitus, reduced AMPK activity sets off a complex series of metabolic disturbances such as an increase in hepatic glucose production, reduction in skeletal muscle glucose uptake and disrupted fatty acid metabolism, leading to an increase in insulin resistance and hyperglycemia [16]. Clinical and experimental data have pointed to the fact that the chronic energy surplus present in the disease has sustained the inhibition of the AMPK pathway by the rise in lipotoxic intermediates like diacylglycerol and ceramide that activate the protein kinase C isoforms and inhibit enzyme activation, and which suggests that AMPK represents a main treatment target through which to treat the condition [17]. The findings also support the idea that the diabetic AMPK level in metformin treated patients who were medicated maintained higher levels compared to untreated diabetic patients, since metformin stimulates the AMPK pathway via a multifaceted mechanism (fusing mitochondrial respiratory chain inhibition with lysosomal receptor targeting to indirectly activate AMPK) [18]. Recent studies demonstrate that such mechanisms depend on dose and duration of treatment, and metformin has effects from many extrahepatic sites including (but not limited to) gastrointestinal tract, gut microbiome, and tissue-resident immune cells [19]. However, the restoration of activity found in the P+M cohort did not reach levels seen in healthy patients, in agreement with reports showing that even if metformin does improve insulin sensitivity and reduce insulin resistance several multiple ways, it fails to restore AMPK activity to healthy levels in all patients which requires complementary therapeutic therapies [20]. In comparison, in the treatment with conventional chlorogenic acid at 8 ppm, AMPK levels appeared to increase significantly in all groups; the control group mean increased from 3.187 to 6.471, P+M group mean from 1.054 to 2.270, and P-M group mean from 0.165 to 1.368 and the difference was statistically significant ($p < 0.001$). This effect results from this phenolic compound's ability to activate AMPK by enhancing its phosphorylation and GLUT4 (glucose transporter GLUT4) activation in the skeletal muscle cells which results in an increase of insulin-independent glucose uptake in the body

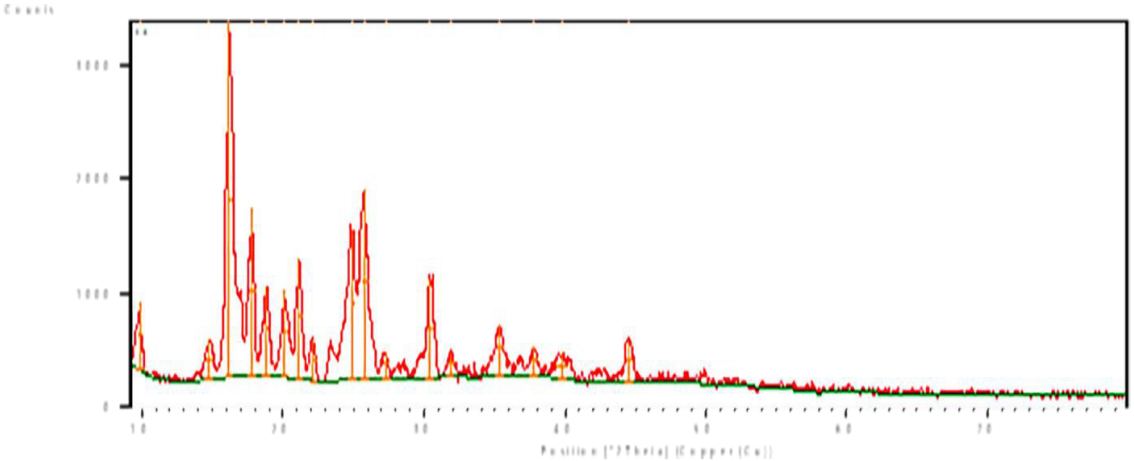

Fig. 5. XRD analysis of chlorogenic acid as silver nanoparticle.

[21]. In addition, chlorogenic acid suppresses hepatic gene expression of glucose-6-phosphatase and reduces ceramide accumulation, a major molecular mediator of glucagon-induced glucose production [22]. Moreover, this chemical supports oxidative defense mechanisms and suppresses the NF-κB pathway to reduce inflammation that impedes insulin signaling, generating an overall and coordinated metabolic benefit [23]. The most significant discovery found was that treatment with silver nano-chlorogenic acid at a 16 ppm dilution produced a significantly higher level of AMPK when compared to the usual formulation in both diabetic groups. The mean for the control group reached (6.236 ± 0.077), for the P+M group reached (2.952 ± 0.018) versus the conventional formulation (2.270 ± 0.110), and for the P-M group the mean rose to (2.446 ± 0.087), as compared to (1.368 ± 0.077) for the conventional formulation ($p < 0.001$). The nano formulation is based on 16 ppm because this must be equal to the real bioavailable concentration of the traditional formulation at 8 ppm, suggesting that the pharmacokinetic properties of nanoparticles compensate for the quantitative difference, making the enhanced effect a product of delivery efficiency rather than dosage [24]. To better understand the rationale for this superiority; phenolic compounds have specific limitations for bioavailability of the compounds in terms of poor aqueous solubility, early metabolic degradation and reduced stability in digestion. It has been recently confirmed that AMPK activation by plant-derived phenolic compounds is dependent on the appropriate delivery of the compound to its intracellular sites of action that is enabled by nanoparticles that can bypass intestinal absorption barriers and first-pass hepatic metabolism [25]. In this work, the silver nano formulation resolves these limitations by improving the penetration of the compound and providing a substantial amount of effective surface area and a synergistic particle stability that results in the antioxidant and anti-inflammatory activity that supplements AMPK activation [24]. Besides, treatment with a nano formulation resulted in a significant convergence of AMPK levels between the two different diabetic groups, with the inter-group difference being reduced to (0.506) versus (0.889) without treatment, which suggested that the nano form may have successfully bridged the metabolic gap between the two groups irrespective of metformin presence. Mechanistically, there is increased ability for nanoparticles to permeate through the cellular membrane and to access intracellular AMPK sites in a more direct and more effective way compared to the free compound. This phenomenon is more pronounced under the metabolomic circumstances of disturbed metabolic status, inflammatory dysregulation, oxidative stress and ceramide clustering together to impair AMPK signaling, and nanoparticles should be used more effectively for the restoration of the enzyme activity [15]. The therapeutic relevance of these results is also highlighted by the observation that the difference between the two medication types in the group with no diabetes did not reach statistical significance ($p = 0.088$), and in the two diabetic groups it did ($p < 0.001$), suggesting that compared to preclinical data, the relative superiority of the nano formulation is more pronounced in clinically dysfunctional conditions where the barrier of cellular access to free phenolic compounds is the greatest. As to next steps, these results suggest the need for extensive quality controlled clinical trials when it comes to the formulation of silver nano-chlorogenic acid, the safety profile beyond long-term clinical trials, and the possibility of a synergistic effect between this compound and metformin in order to establish secure and impactful natural therapeutics that may aid the improved management of type 2 diabetes mellitus [26].

CONCLUSION

These findings show that type 2 diabetes mellitus is associated with a considerable loss of AMPK enzyme activity, with the greatest losses present in patients with no prior treatment. While AMPK activity was shown to recover partially with metformin treatment, it was still not enough to restore enzyme activity to normal physiological levels.. The chlorogenic acid in both its formulations actually had a real effect on increasing enzyme activity for all groups but only silver nano-chlorogenic acid showed distinct qualitative superiority strongly in both diabetic groups, with silver nano-chlorogenic acid at 16 ppm enabling them to circumvent the bioavailability barrier and get direct intracellular access to the enzyme's sites of action. The convergence in AMPK between diabetic groups at nano formulation application (when the inter-group difference decreased from 0.889 to 0.506) demonstrates the same, this formulation reaches

metabolic equilibration, regardless of the effect of metformin. Integrating with the recent data, these results provide a potential solution for the use of silver nano-chlorogenic acid as a natural therapeutic adjunct in the treatment of type 2 diabetes mellitus if further clinical studies are performed to investigate the optimal dosage, long-term safety and potential interaction with a pre-existing pharmaceutical treatment plan.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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