Nanomed. J. 10(2): 122-130, Spring 2023

RESEARCH PAPER

Effects of *Curcumin* and *Nanocurcumin* supplementation on serum brain-derived neurotrophic factor and some complications in type 2 diabetic rats

Ali Shamsi-Goushki [1, 2], Zinat Mortazavi [3]*, Fatemeh Behrasi [1], Ali Ebrahimkhani [4], Razieh Hosseini [1]

[1]Department of Nutrition, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran
[2]Department of Nutrition, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Health Promotion Research Center, Zahedan University of Medical Sciences, Zahedan, Iran
[4]Nutrition Department, School of Public Health, Iran University of Medical Sciences, Tehran, Iran

ABSTRACT

Objective(s): One of the most important neurotrophins is brain-derived neurotrophic factor (BDNF) that is closely associated with insulin resistance and Type 2 Diabetes Mellitus (T2DM). This study was done under the objective of investigating the effects of curcumin (CUR) and nano-curcumin (nCUR) on serum levels of BDNF, fasting blood sugar (FBS), water and food intake, and body weight in T2DM rats.

Materials and Methods: Our work required the division of 48 male Wistar rats into the 6 groups of Control, diabetic, diabetic treated with two doses of CUR and nCUR (100 and 200 mg/kg), T2DM induced rats by intraperitoneal injection of Streptozotocin, and nicotinamide in the fasting state. Once the rats received nCUR and CUR doses through gavage for 28 days, their Serum level of BDNF was measured at the end of intervention period, while their body weight, FBS, and food and water intake were also examined at both onset and ending of this period.

Results: Considering the effect of curcumin and nano-curcumin administration on the induced significant increase in serum BDNF and decrease in FBS, food, and water intake in T2DM rats ($P<0.05$), we can confirm the superior effectiveness of nano-curcumin 100 in serum BDNF elevation than curcumin ($P<0.05$). It is also notable that the body weight of intervention groups did not face any significant reduction when compared to that of diabetic control group.

Conclusion: These findings provide evidence for the beneficial effects of CUR and nCUR as an antidiabetic agent, which can be potentially considered as an adjunct for the available diabetes therapies.

Keywords: *Brain-derived neurotrophic factor, Nano-curcumin, Rat, Type 2 diabetes*

How to cite this article
Shamsi-Goushki A, Mortazavi Z, Behrasi F, Ebrahimkhani A, Hosseini R. Effects of Curcumin and Nanocurcumin supplementation on serum brain-derived neurotrophic factor and some complications in type 2 diabetic rats. Nanomed J. 2023; 10(2): 122-130. DOI: 10.22038/NMJ.2023.69556.1742

INTRODUCTION

Reported with a death rate of over one million per year, Diabetes is the ninth leading cause of mortality worldwide [1] and Type 2 diabetes (T2DM) is known as one of the multifactorial expanding burdens on the health system due to being reported in 5-8% of adults. Many well-defined complex etiologies are responsible for hyperglycemia, as the hallmark of this disease, and probably macrovascular and microvascular complications [2]. It is believed both genetic and environmental factors including obesity and excessive energy intake, inactive lifestyle, and also pancreatic beta-cell dysfunction are responsible for T2DM, which consequently lead to metabolic disorders and glucose homeostasis impairments [3].

A number of human and animal model studies are investigating the effect of nutritions on the management of T2DM [4]. An increasing range of evidences has raised the interest of many in regards to the probable role of some medicinal plant supplements on the prevention and management of T2DM, while curcumin (CUR) stands as the most leading option [5]. The data of a published review in 2020 introduced the antidiabetic effects of CUR and also discussed its ability to protect patients

* *Corresponding author: Email: zimoiran@yahoo.com*
Note. This manuscript was submitted on December 10, 2022; approved on February 12, 2023

against macro and microvascular complications [6]. In addition to the probable improvement in beta-cell function and reducing inflammation, CUR can lower the number of prediabetics that progress into T2DM as well [7].

Nowadays, the decreased levels of brain-derived neurotrophic factor (BDNF), which is already known to implicate Alzheimer's and depression pathogenesis, seem to be also linked to T2DM [8]. Several studies approved the probable advantageous impacts of BDNF on fasting, postprandial glucose, hyperinsulinemia [8,9]. and some other conditions, and mentioned the the positive impact of CUR on serum BDNF levels [10].

Currently, there is an expanding preference for investigating the association of CUR with insulin resistance and also some glycemic control indices such as FBS [11]. It seems that CUR can have a potential effect on the reduction of insulin resistance [12] and act as a modifier for FBS as well [11]. For instance, curcuminoids supplementation can significantly decrease the fasting blood glucose and HOMA-IR of overweight and obese T2DM patients [13]. A systematic review and meta-analysis conducted on human randomized controlled trials in 2018 revealed the significant impact of CUR supplementation on reducing FBS three times in a day for 10 weeks [14]. According to a wide array of animal model studies, the application of various doses of CUR with different intervention periods can reduce the glucose levels and improve the rate of insulin resistance [15]. In addition, an assessment on the connection of CUR and weight as an anthropometric index was indicative of its potential effects on reducing obesity and overweight [16].

Some studies explained the poor bioavailability of CUR through certain reasons, including poor absorption, rapid metabolism, and rapid systemic elimination, and proclaimed "nanotechnology" as a solution for minimizing these challenges. Apparently, the exertion of nanoparticles may increase the therapeutic role of CUR to some extent [17], while nano-curcumin (nCUR) can perform deliveries with more potential biological and pharmacological advantages [18]. Considering these facts, we preferred to examine both cases of CUR and nCUR in our study. Despite the invested interest in the role of CUR on diabetes management among researchers, the results are not still clearly elucidated. Upon this basis, we decided to design this animal model study to investigate the role of CUR as an antidiabetic agent under the objective of determining the probable impact of both conventional CUR and nCUR on BDNF and some other diabetes complications.

MATERIALS AND METHODS

Study details

In this experimental study, three-month-old male Wistar rats (200-250 g, N=48) were purchased from Zahedan University of Medical Sciences research center. All stages of the research were carried out in 2020 in accordance to the instructions of Ethics committee recommendations for laboratory animals in Zahedan University of Medical Sciences (IR.ZAUMS.REC.1397.357). All animals were fed through a normal diet along with water ad libitum in the course of the study. Rats were exposed to dark/light cycle, suitable environmental conditions (temperature 24 ± 2°C and 60 ± 5% of humidity), and fine ventilation [19].

Induction of T2DM

The induction of T2DM in rats was completed by the intraperitoneal injection of 110 mg/kg Nicotinamide (NA) (Merck, Germany) and 45 mg/kg Streptozotocin (STZ) (Sigma Aldrich, USA) in a fasting state. STZ was dissolved in 0.1 mol/l cold citrate buffer (pH = 4.5) and subsequent to 72 hr, their blood glucose was measured through the tail vein by the usage of a glucometer (Accu-Chek Performa, USA). Every rat with non-fasting blood glucose greater than 250 mg/dL was considered to be diabetic [19].

Experimental protocol and dietary regimen

The rats were divided into six equal groups of eight rat members. Subsequent to acclimatization for 2 weeks, the rats were treated daily with 100 or 200 mg/kg of CUR or 100 or 200 mg/kg of nCUR by oral gavage (using Needle Gavage) for 28 days. The control and diabetic control groups received equal volumes of normal saline.

Preparation of curcumin and nanocurcumin

Despite the insoluble characteristic of CUR in water, it can be easily dissolved in organic solvents such as dimethyl sulfoxide (DMSO). A stock solution of CUR (Sigma Aldrich, USA, batch No: C7727) and Nano-micelle of curcumin (Exir Nano Sina, Iran, batch No: 1,228,225,765) was prepared at 100 mmol/L in DMSO. Thereafter, two different doses of CUR and nCUR (100 and 200 mg/kg of body

weight) were selected as the designed treatment [19, 20].

Blood collection and measurement of variables

At the end of intervention period, the rats were anesthetized with Ketamine (60 mg/kg, Alfasan, Woerden, Netherlands) and Xylosine (5 mg/kg, Alfasan, Woerden, Netherlands) after 12 hr of overnight fasting [19]. Then, Blood samples were collected via cardiac puncture and centrifuged at 3000 rpm for 10 min. Serum samples were immediately stored at 75 °C for the upcoming evaluation of biochemical indicators [19].

At the beginning and end of intervention, the body weight was also measured by the digital scale (EK610i; A&D, Tokyo, Japan), while the average water (CC) and food consumption (gr) were evaluated at the first and fourth weeks of intervention.

Plasma biochemical assays

The biochemical assessment required the measurement of serum BDNF (Bioassay Technology Laboratory, Shanghai, China) by using the rat ELISA kit and ELISA reader (Stat Fax 2100; Awareness Technology, Palm City, FL, USA) [21]. To evaluate the FBS, blood samples were taken from the tail vein in the fasting state at the beginning and ending of intervention period, which was followed by measuring the blood glucose through the exertion of a glucometer (Accu-Chek Performa, USA) [22].

Statistical analysis

The data were analyzed by PRISM GraphPad version 8 (GraphPad, San Diego, CA, USA). One-way ANOVA was performed to assess the significancy ($P<0.05$) and then, Tukey's test was applied in order to examine the differences among groups. $P<0.05$ was considered as statistically significant and the sign of a significant difference between the group means [19].

Once again, the data analysis was completed by PRISM GraphPad version 8 (GraphPad, San Diego, CA, USA). One-way ANOVA was used to compare the multiple data sets and when the P. value obtained from ANOVA was significant ($P<0.05$), Tukey's test was applied to assay the differences among groups. $P<0.05$ was considered as an indicator of significant differences between group means [19].

RESULTS

Effects of CUR and nCUR on serum levels of BDNF

The effects of different doses of CUR and nCUR on the serum levels of BDNF were measured and the results were provided in Fig. 1. The Serum level of BDNF was significantly increased in the intervention groups when compared to diabetic controls ($P<0.05$). According to outputs, nCUR is more preferable than CUR due to its superior capability to ameliorate the BDNF levels ($P<0.05$).

Effects of CUR and nCUR on FBS

In conformity to the exhibited effects of different doses of CUR and nCUR on FBS in Fig. 2, there was a lack of any significant difference in FBS before the intervention, which was significantly decreased at the end of intervention period when compared to the diabetic control group ($P <0.05$). However, there was no significant difference between CUR and nCUR groups.

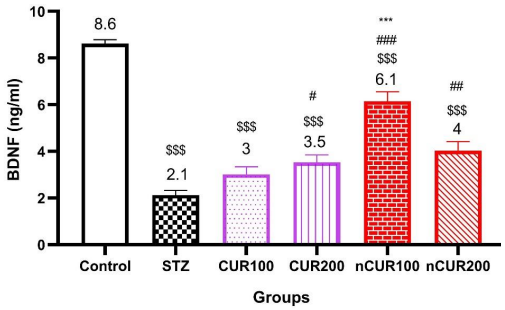

Fig. 1. Effects of curcumin and nano-curcumin on BDNF in studied rats $$$P<0.001 in comparision with control group. ###P<0.001, ##P<0.01 and #P<0.05 in comparision with STZ group. ***P<0.001 Nano-curcumin in comparision with curcumin group. Data are expressed as Mean ± SD (n=8), and analyzed by the One-way ANOVA and Tukey's *post hoc* tests
Ctrl: Control group, STZ: Diabetic control group, CUR: Curcumin, nCUR: Nano-curcumin

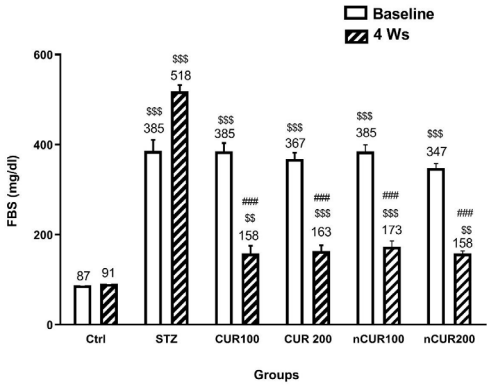

Fig. 2. Effects of curcumin and nano-curcumin on FBS in studied rats $$$P<0.001 and $$P<0.01 in comparision with control group. ###P<0.001 in comparision with STZ group. Data are expressed as Mean ± SD (n = 8), and analyzed by the One-way ANOVA and Tukey's *post hoc* tests
Ctrl: Control group, STZ: Diabetic control group, CUR: Curcumin, nCUR: Nano-curcumin

Effects of CUR and nCUR on body weight

According to the presented data on the effects of CUR and nCUR on body weight in Fig. 3, there was no significant difference in this factor among the results of experimental groups in prior to study initiation. However at the end of intervention period, the rates of body weight in diabetic control and intervention groups were significantly decreased when compared to the control group (P<0.05). Also, the body weight of intervention groups was not significantly reduced when compared to the diabetic control group. The significant weight loss was observed in the nCUR 200 group (P<0.05).

Effects of CUR and nCUR on food intake

Considering the provided information on food intake in response to our intervention in Fig. 4, the mean food intake in the first week of intervention faced a significant increase in diabetic control group when compared to the control group, CUR 100 and 200 (P<0.05), while there was a lack of any notable difference between the nCUR group 100 and 200. Besides, the food intake of intervention groups (CUR 100 and 200 and nCUR 100 and 200) was significantly reduced in contrast to the diabetic control group (P<0.05)at the end of the intervention period (fourth week). Also, a significant increase in food intake was observed in nCUR group 100 when compared to nCUR groups 200 and CUR 100 and 200 (P<0.05).

Effects of CUR and nCUR on water intake

Mean water consumption in the first week of intervention in the diabetic control group was significantly increased when compared to the control, CUR 100, and 200 groups (P<0.05), however, there was no significant difference between the nCUR 100 and 200 groups (Fig. 5). According to our final data, the water consumption of intervention groups (CUR 100, 200, and nCUR 100) faced a significant decrease in contrast to the diabetic control group (P<0.05), while there was a lack of any difference between the nCUR 200 and diabetic control groups.

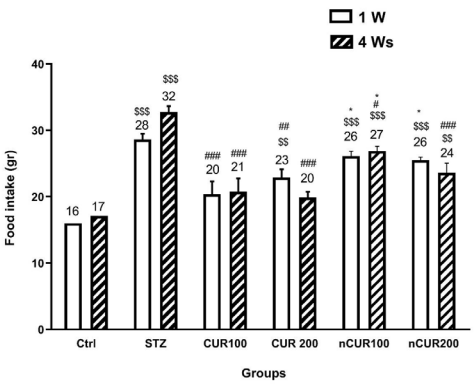

Fig. 4. Effects of curcumin and nano-curcumin on food intake in studied rats. $$$P<0.001 and $$P<0.01 in comparision with control group. ###P<0.001, ##P <0.01 and #P<0.05 in comparision with STZ group. *P<0.05 Nano-curcumin in comparision with curcumin group. Data are expressed as Mean ± SD (n = 8), and analyzed by the One-way ANOVA and Tukey's *post hoc* tests
Ctrl: Control group, STZ: Diabetic control group, CUR: Curcumin, nCUR: Nano-curcumin

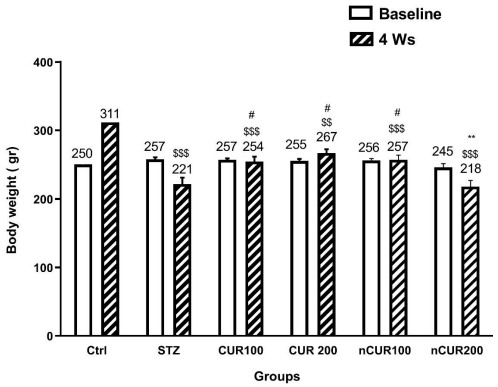

Fig. 3. Effects of curcumin and nano-curcumin on body weight in studied rats. $$$P<0.001 and $$P<0.01 in comparision with control group. #P<0.05 in comparision with STZ group. **P<0.01 Nano-curcumin in comparision with curcumin group. Data are expressed as Mean ± SD (n = 8), and analyzed by the One-way ANOVA and Tukey's *post hoc* tests
Ctrl: Control group, STZ: Diabetic control group, CUR: Curcumin, nCUR: Nano-curcumin

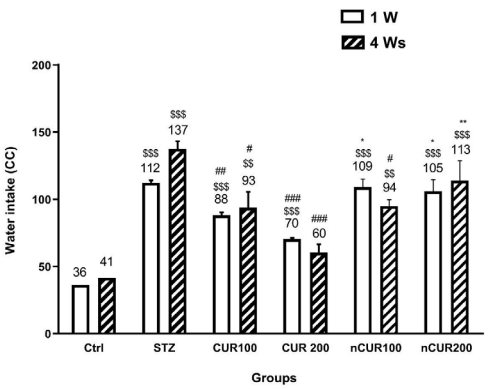

Fig. 5. Effects of curcumin and nano-curcumin on water intake in studied rats. $$$P<0.001 and $$P<0.01 in comparision with control group. ###P<0.001, ##P<0.01 and #P<0.05 in comparision with STZ group. **P<0.01 and *P<0.05 Nano-curcumin in comparision with curcumin group. Data are expressed as Mean ± SD (n = 8), and analyzed by the One-way ANOVA and Tukey's *post hoc* tests
Ctrl: Control group, STZ: Diabetic control group, CUR: Curcumin, nCUR: Nano-curcumin

DISCUSSION

The outcomes of this experimental study indicated the positive effects of CUR and nCUR supplementations on increasing the rates of BDNF and body weight. Moreover, our intervention is capable of decreasing the intake of FBS, food, and water in Streptozotocin-nicotinamide-induced diabetic rats. Our study is the very first to report the effects of CUR and nCUR on serum levels of BDNF, food and water intake, and body weight in T2DM rats.

According to several related studies, the pharmacological effects of CUR on improving serum levels of BDNF, FBS, and insulin resistance in diabetes mellitus are generated by increasing the PPARγ activation, inducing NF-kB inhibition, regulating the expression of AMP-activated protein kinase (AMPK), triggering glucokinase activity in the liver, and attenuating tumor necrosis factor-alpha (TNF-α) [23, 24].

The considerable limitation of CUR after oral administration is its poor bioavailability due to containing a low gastrointestinal absorption, rapid metabolism, and fast systemic elimination [24]. Nano micelles containing CUR (SinaCurcumin®) were designed for oral administration to improve the poor bioavailability of CUR, which are prepared from GRAS (generally recognized as safe) pharmaceutical excipients and C3-complex form of CUR [19, 25]. The percentage of CUR encapsulation in these nano micelles is about 100% and their sizes are around 10 nm [19, 25]. The application of nCUR instead of CUR seems to provide a significantly higher bioavailability after oral administration [24]. For example, some studies claimed that the nanoencapsulation of curcumin can increase its bioavailability by 9 times [26].

In the current study, the serum levels of BDNF in CUR (200 mg/kg dose) and nCUR treated groups were significantly increased when compared to the diabetic control group, which is probably due to the decreased insulin resistance and FBS. Some clinical and experimental studies reported a decrease in the BDNF serum levels of diabetes and insulin-resistant cases [9, 27]. In addition to its protective effects on central nervous system, synaptic plasticity, learning, and memory, BDNF has the potential to display protective behaviors in obesity and diabetes as well [28, 29]. It is also abled to play a role in metabolic control, especially glucose metabolism and insulin resistance [8]. Numerous studies have confirmed the antioxidant, anti-inflammatory neuroprotection, and anti-diabetic properties of CUR [19,24]. CUR and nCUR can indirectly increase the serum levels of BDNF by reducing hyperglycemia, hyperlipidemia, FBS, and insulin resistance [24].

Several studies pointed put the effect of CUR supplementation on significantly increasing the serum concentrations of BDNF [10, 30], which has an important role in the functions of brain, synaptic plasticity, and neurotransmission [31]. Wang et al. reported the ability of CUR to develop some neuroprotective impacts through the activation of brain-derived neurotrophic factor/Tyrosine kinase B (TrkB)-dependent Mitogen-activated protein kinase (MAPK) and Phosphoinositide-3 kinase (PI-3K) cascades in rodent cortical neurons [32]. Furthermore, the benefits of this product on the improvement of BDNF level throughout cAMP elevation and activation of extracellular signal-regulated kinases (ERKs) and p38 kinase, or decreasing the oxidative damage in obesity and diabetes, were discussed by Sarraf et al [10]. In line with our research, the outcomes of Osali et al study on women with metabolic syndrome in 2020 indicated that taking 80 mg of nCUR per day for 6 weeks can increase the serum level of BDNF and also decrease inflammatory indices. According to their conclusions, nCUR increases the serum level of BDNF by reducing the expression of Toll-like receptor and inhibiting NF-κB [33].

Our observations implicated a significant decrease in the serum FBS of CUR and nCUR groups when compared to the diabetic control group. These effects were probably induced by the increased activation of PPARγ, inhibition of NF-κB, and the antioxidant and anti-inflammatory properties of CUR and nCUR. Several studies reported that different doses of CUR can decrease the HOMA-IR and FBS of patients with diabetes and metabolic syndrome [11, 14].

A randomized, double-blind, placebo-controlled trial performed by Hodaei et al investigated the effect of CUR supplementation on HOMA-IR, FBS, body weight, and oxidative stress of 53 T2DM patients. All participants were randomly assigned to receive either 1500 mg/day of CUR or placebo three times a day for 10 weeks. In conformity to their data, the CUR-treated group resulted in a lower FBS and body weight without facing any alteration in its insulin resistance. This study claims the capability of CUR in inhibiting the gene expression of inflammatory cytokines such as certain Interleukins (Interleukin-1, Interleukin-2,

Interleukin-6, Interleukin-8, Interleukin-12) and Tumor necrosis factor-alpha (TNF-α) through NF-ĸB inactivation [11]. In another study, Flores et al. revealed the effect of Standard diets with CUR consumption for 8 weeks on increasing PPARγ through the activation of AMPK and decreasing lipid peroxidation in diabetic mice [23]. Also according to the report of Sushil et al., the consumption of 100 mg/day of CUR for 7 weeks can decrease MCP-1, HbA1C, TNF-a, IL-6, and lipid peroxidation [31]. Rahimi et al. attempted to determine the effects of nCUR on diabetes treatment and discovered that this supplementation can have a significant impact on FBS reduction [25]. In another study conducted on type 1 diabetic rats, a significant decrease was observed in FBS by 32 and 37% in response to the consumption of 10 and 50 mg of nCUR , respectively [34].

We also evaluated the factor of food and water intake and observed a significant decrease in CUR and nCUR groups in contrast to the diabetic control group. Besides, the body weights of intervention groups were not significantly reduced in comparison to the diabetic control group. These effects of CUR and nCUR are probably due to the reduced FBS, HOMA-IR, urinary sugar, and inflammatory reactions. Previous studies were indicative of an increase in the water and food intake of diabetic patients and also reported their evident weight loss [35].

According to the literature, the intake of CUR promotes the weight loss of obese/overweight patients [36] and fatty liver diseases [37] without altering their water and food intake [36]. Moreover, certain studies on diabetes reported the effect of CUR on preventing diabetes-related weight loss and reducing their other complications such as overeating, polydipsia, and polyuria [15,35,38].

Another assessment investigated the effects of curcumin and nanocurcumin on the body weight of diabetic rats. Considering their outcomes, the case of diabetes resulted in facing weight loss while the intervention group with curcumin and nanocurcumin did not affect the weight loss [39]; these observations were consistent with the data of our study.

The study of Ejaz et al. on rats fed with high-fat diet implicated the consumption of 500 mg/BW of CUR for 12 weeks, which did not effect the food intake while leading to the suppression of weight gain, activation of AMPK (5-adenosine monophosphate-activated protein kinase), up-regulation of impolitic genes, and suppression of endoplasmic reticulum stress as the potential CUR-mediated mechanisms of this treatment [40].

A meta-analysis study denoted that CUR administration can significantly reduce body weight, however, this result was insignificant in the cases that involved an intervention duration of fewer than 8 weeks. According to this assessment, the underlying mechanism behind the effects of CUR on body weight may be associated with the down-regulation of Janus-kinase (JNK) enzyme by CUR, which has been suggested to have a significant role in obesity pathogenesis. Besides, CUR may suppress 11β-hydroxysteroid dehydrogenase type 1 (11ßHSD1) enzyme and contribute to cortisol activation, as well as reduces obesity through the inhibition of adipocyte differentiation in the early stages by suppressing PPAR-γ, enhancing MAPK, and consequently inducing lipolysis [36].

However, the intake of CUR in a randomized crossover trial did not change the body weight of obese adults [41]. In addition, another randomized, double-blind, placebo-controlled trial revealed the significant effect of this product on the body weight of patients with metabolic syndrome [42]. Since the short duration of these two studies is considered as a limitation, further long-term trials are needed to clarify this issue.

The administration of CUR and nCUR to rats with aluminium chloride toxicity did not cause any significant changes in body weight and food and water intake [43].

Furthermore, the report of Assis et al. claimed that the anti-hyperglycemic effects of CUR-enriched yogurt may increase the rates of peripheral insulin sensitivity and glucose tolerance in STZ-diabetic rats, which is probably due to the link between AKT phosphorylation and GLUT4 transcription that can improve glycaemic control and subsequently ameliorate weight gain, food and water intake, and urine volume [38].

The impact of CUR on type 1 diabetic rats was investigated in another study and resulted in reporting a notable lower body weight and blood glucose levels in the CUR-treated samples. Also, their outcomes was accompanied by an elevation in food and water intake up to the 9th day, which was subsequently decreased after the 12th, 15th, 18th and 21st days [35].

Due to few available studies on the effect of CUR supplementation on body weight, water and food intake in diabetic rats and human, further

researches are required to reach a firm conclusion in these areas.

Next to the involvement of certain limitations in our study, such as the unidentified histopathological condition of the pancreas, our results also indicated the necessity of considering lower doses of CUR and nCUR (10, 25, and 50 mg/kg).

CONCLUSIONS

Based on our intervention data, it can be concluded that the oral administration of CUR and nCUR can potentially cause an increase in serum BDNF and also decrease the FBS and food and water intake in diabetic rats. Also, nCUR 100 seemed to be more effective on the elevation of serum BDNF than CUR, which is possibly due to the increased solubility and bioavailability. Our data demonstrated the superior efficacy of nCUR 100 than nCUR 200 in improving these variables that may be attributable to the dose-dependent effects of nCUR. Although our findings provided evidence for the antidiabetic potentials of CUR and nCUR, yet the limited number of assessments on CUR and nCUR as complementary therapies for diabetic complications stands as a concern. Therefore, the conduction of more research is recommended to investigate the therapeutic effects of lower doses of nCUR in diabetic rats.

ACKNOWLEDGMENTS

The authors acknowledge the Zahedan University of Medical Science that provided facility and financial support for this study.

CONFLICTS OF INTEREST

The authors declared no conflicts of interest in this study.

REFERENCES

1. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends. J Epidemiol Glob Health. 2020;10(1):107-111.
2. Lin X, Xu Y, Pan X, Xu J, Ding Y, Sun X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. Sci Rep. 2020;10(1):14790.
3. DeFronzo RA, Ferrannini E, Groop L, Henry RR, Herman WH, Holst JJ, et al. Type 2 diabetes mellitus. Nature Reviews Disease Primers. 2015;1(1):15019.
4. Ojo O. Dietary Intake and Type 2 Diabetes. Nutrients. 2019;11(9):2177.
5. Pivari F, Mingione A, Brasacchio C, Soldati L. Curcumin and Type 2 Diabetes Mellitus: Prevention and Treatment. Nutrients. 2019;11(8):1837.
6. Oliveira S, Monteiro-Alfredo T, Silva S, Matafome P. Curcumin derivatives for Type 2 Diabetes management and prevention of complications. Arch Pharm Res. 2020;43(6):567-581.
7. Adibian M, Hodaei H, Nikpayam O, Sohrab G, Hekmatdoost A, Hedayati M. The effects of curcumin supplementation on high-sensitivity C-reactive protein, serum adiponectin, and lipid profile in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial. Phytother Res. 2019;33(5):1374-1383.
8. Krabbe KS, Nielsen AR, Krogh-Madsen R, Plomgaard P, Rasmussen P, Erikstrup C, et al. Brain-derived neurotrophic factor (BDNF) and type 2 diabetes. Diabetologia. 2007;50(2):431-438.
9. Rozanska O, Uruska A, Zozulinska-Ziolkiewicz D. Brain-Derived Neurotrophic Factor and Diabetes. Int J Mol Sci. 2020;21(3):841.
10. Sarraf P, Parohan M, Javanbakht MH, Ranji-Burachaloo S, Djalali M. Short-term curcumin supplementation enhances serum brain-derived neurotrophic factor in adult men and women: A systematic review and dose-response meta-analysis of randomized controlled trials. Nutr Res. 2019;69:1-8.
11. Hodaei H, Adibian M, Nikpayam O, Hedayati M, Sohrab G. The effect of curcumin supplementation on anthropometric indices, insulin resistance and oxidative stress in patients with type 2 diabetes: a randomized, double-blind clinical trial. Diabetol Metab Syndr. 2019;11:41.
12. Altobelli E, Angeletti PM, Marziliano C, Mastrodomenico M, Giuliani AR, Petrocelli R. Potential Therapeutic Effects of Curcumin on Glycemic and Lipid Profile in Uncomplicated Type 2 Diabetes-A Meta-Analysis of Randomized Controlled Trial. Nutrients. 2021;13(2):404.
13. Na LX, Li Y, Pan HZ, Zhou XL, Sun DJ, Meng M, et al. Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: a double-blind, placebo-controlled trial. Mol Nutr Food Res. 2013;57(9):1569-1577.
14. Azhdari M, Karandish M, Mansoori A. Metabolic benefits of curcumin supplementation in patients with metabolic syndrome: A systematic review and meta-analysis of randomized controlled trials. Phytother Res. 2019;33(5):1289-1301.
15. Zhang DW, Fu M, Gao SH, Liu JL. Curcumin and diabetes: a systematic review. Evid Based Complement Alternat Med. 2013;2013:636053.
16. Hariri M, Haghighatdoost F. Effect of Curcumin on Anthropometric Measures: A Systematic Review on Randomized Clinical Trials. J Am Coll Nutr. 2018;37(3):215-222.
17. Ghalandarlaki N, Alizadeh AM, Ashkani-Esfahani S. Nanotechnology-applied curcumin for different diseases therapy. Biomed Res Int. 2014;2014:394264.
18. Karthikeyan A, Senthil N, Min T. Nanocurcumin: A Promising Candidate for Therapeutic Applications. Front Pharmacol. 2020;11:487.
19. Shamsi-Goushki A, Mortazavi Z, Mirshekar MA, Mohammadi M, Moradi-Kor N, Jafari-Maskouni S, et al. Comparative Effects of Curcumin versus Nano-Curcumin on Insulin Resistance, Serum Levels of Apelin and Lipid Profile in Type 2 Diabetic Rats. Diabetes Metab Syndr Obes. 2020;13:2337-2346.
20. Hossaini Alhashemi S, Mohammadpour AH, Heidari R, Nikoo MH, Nemati MH, Vazin A. The effect of nanocurcumin on the incidence of atrial fibrillation, and markers of inflammation and oxidative stress level after coronary artery bypass graft surgery: A randomized, double-blind, placebo-controlled clinical study. Avicenna J Phytomed.

2022;12(5):503-513.
21. Elfving B, Plougmann PH, Wegener G. Detection of brain-derived neurotrophic factor (BDNF) in rat blood and brain preparations using ELISA: pitfalls and solutions. J Neurosci Methods. 2010;187(1):73-77.
22. Zou W, Yang Y, Gu Y, Zhu P, Zhang M, Cheng Z, et al. Repeated Blood Collection from Tail Vein of Non-Anesthetized Rats with a Vacuum Blood Collection System. J Vis Exp. 2017(130):55852.
23. Jiménez-Flores LM, López-Briones S, Macías-Cervantes MH, Ramírez-Emiliano J, Pérez-Vázquez V. A PPARγ, NF-κB and AMPK-dependent mechanism may be involved in the beneficial effects of curcumin in the diabetic db/db mice liver. Molecules. 2014;19(6):8289-8302.
24. Boarescu PM, Boarescu I, Bocșan IC, Gheban D, Bulboacă AE, Nicula C, et al. Antioxidant and Anti-Inflammatory Effects of Curcumin Nanoparticles on Drug-Induced Acute Myocardial Infarction in Diabetic Rats. Antioxidants (Basel). 2019;8(10):504.
25. Rahimi HR, Mohammadpour AH, Dastani M, Jaafari MR, Abnous K, Ghayour Mobarhan M, et al. The effect of nano-curcumin on HbA1c, fasting blood glucose, and lipid profile in diabetic subjects: a randomized clinical trial. Avicenna J Phytomed. 2016;6(5):567-577.
26. Quispe C, Herrera-Bravo J, Javed Z, Khan K, Raza S, Gulsunoglu-Konuskan Z, et al. Therapeutic Applications of Curcumin in Diabetes: A Review and Perspective. Biomed Res Int. 2022;2022:1375892.
27. Eyileten C, Kaplon-Cieslicka A, Mirowska-Guzel D, Malek L, Postula M. Antidiabetic Effect of Brain-Derived Neurotrophic Factor and Its Association with Inflammation in Type 2 Diabetes Mellitus. J Diabetes Res. 2017;2017:2823671.
28. Skibinska M, Kapelski P, Rajewska-Rager A, Szczepankiewicz A, Narozna B, Duda J, et al. Elevated brain-derived neurotrophic factor (BDNF) serum levels in an acute episode of schizophrenia in polish women: Correlation with clinical and metabolic parameters. Psychiatry Res. 2019;271:89-95.
29. Akça İ, Bodur A, Kahraman C, Abidin İ, Aydın-Abidin S, Alver A. The regulation of adipokines related to obesity and diabetes is sensitive to BDNF levels and adipose tissue location. Hormones (Athens). 2022;21(2):295-303.
30. Xu Y, Ku B, Tie L, Yao H, Jiang W, Ma X, et al. Curcumin reverses the effects of chronic stress on behavior, the HPA axis, BDNF expression and phosphorylation of CREB. Brain Res. 2006;1122(1):56-64.
31. Kuipers SD, Bramham CR. Brain-derived neurotrophic factor mechanisms and function in adult synaptic plasticity: new insights and implications for therapy. Curr Opin Drug Discov Devel. 2006;9(5):580-586.
32. Wang R, Li YH, Xu Y, Li YB, Wu HL, Guo H, et al. Curcumin produces neuroprotective effects via activating brain-derived neurotrophic factor/TrkB-dependent MAPK and PI-3K cascades in rodent cortical neurons. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34(1):147-153.
33. Osali A. Aerobic exercise and nano-curcumin supplementation improve inflammation in elderly females with metabolic syndrome. Diabetol Metab Syndr. 2020;12:26.
34. Ganugula R, Arora M, Jaisamut P, Wiwattanapatapee R, Jørgensen HG, Venkatpurwar VP, et al. Nano-curcumin safely prevents streptozotocin-induced inflammation and apoptosis in pancreatic beta cells for effective management of Type 1 diabetes mellitus. Br J Pharmacol. 2017;174(13):2074-2084.
35. Xie Z, Wu B, Shen G, Li X, Wu Q. Curcumin alleviates liver oxidative stress in type 1 diabetic rats. Mol Med Rep. 2018;17(1):103-108.
36. Mousavi SM, Milajerdi A, Varkaneh HK, Gorjipour MM, Esmaillzadeh A. The effects of curcumin supplementation on body weight, body mass index and waist circumference: a systematic review and dose-response meta-analysis of randomized controlled trials. Crit Rev Food Sci Nutr. 2020;60(1):171-180.
37. Jalali M, Mahmoodi M, Mosallanezhad Z, Jalali R, Imanieh MH, Moosavian SP. The effects of curcumin supplementation on liver function, metabolic profile and body composition in patients with non-alcoholic fatty liver disease: A systematic review and meta-analysis of randomized controlled trials. Complement Ther Med. 2020;48:102283.
38. Assis RP, Arcaro CA, Gutierres VO, Oliveira JO, Costa PI, Baviera AM, et al. Combined Effects of Curcumin and Lycopene or Bixin in Yoghurt on Inhibition of LDL Oxidation and Increases in HDL and Paraoxonase Levels in Streptozotocin-Diabetic Rats. Int J Mol Sci. 2017;18(4):332.
39. Dadgar H, Kermanshahi H, Jaafari MR, Javadmanesh A. Effects of curcumin and its nano-micelle formulation on body weight, insulin resistance, adiponectin, and blood biochemical parameters of streptozotocin-induced diabetic rats. Iranian Journal of Veterinary Science and Technology. 2022;14(3):38-45.
40. Ejaz A, Wu D, Kwan P, Meydani M. Curcumin inhibits adipogenesis in 3T3-L1 adipocytes and angiogenesis and obesity in C57/BL mice. J Nutr. 2009;139(5):919-925.
41. Mohammadi A, Sahebkar A, Iranshahi M, Amini M, Khojasteh R, Ghayour-Mobarhan M, et al. Effects of supplementation with curcuminoids on dyslipidemia in obese patients: a randomized crossover trial. Phytother Res. 2013;27(3):374-379.
42. Yang YS, Su YF, Yang HW, Lee YH, Chou JI, Ueng KC. Lipid-lowering effects of curcumin in patients with metabolic syndrome: a randomized, double-blind, placebo-controlled trial. Phytother Res. 2014;28(12):1770-1777.
43. Ibrahim RM, Elaal F, Zaki S. Effect of Curcumin and Nano-curcumin on Reduce Aluminum Toxicity in Rats. Int J Food Sci Bioechnol. 2019;4:64.