Original Research

URTICA PILULIFERA MAY BE AN ALTERNATIVE FOR METFORMIN IN PATIENTS WITH KIDNEY DISEASE

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ABSTRACT: There is a debate about the possibility of adjusting or discontinuing metformin treatment among patients with impaired kidney function attributed to lactic acidosis. *U. pilulifera* is an alternative with potential therapeutic options. The main objectives of the present study are to investigate the effects of both the extract of *U. pilulifera* and metformin in reducing some kidney parameters and the second objective is to raise the issue about the necessity of giving more concern to herbal treatment and to go more advanced steps towards formulating these herbal treatments. The methodology included collecting *U. pilulifera* and preparing its extract, induction of diabetic model using alloxan and biochemical testing of urea, uric acid and creatinine. Fifty Wistar rats were randomly assigned into the following groups: Group I: control group; Group II: diabetic group; Group III: diabetic treated with 1.25 mg/kg of body weight *U. pilulifera*; Group IV: diabetic treated with 1.88 mg/kg of body weight *U. pilulifera*; Group V: diabetic group treated with 14.2 mg/kg metformin. Study findings showed that kidney function parameters under study, urea, uric acid and creatinine were significantly increased in diabetic group. On the other hand, treatment using either metformin or *U. pilulifera* was able to decrease significantly study parameters to levels approximate to that in control group. Taken together, the present study showed that both metformin and *U. pilulifera* were successfully able to restore kidney parameters urea, uric acid and creatinine in diabetic group to almost levels of control group.

KEYWORDS: Diabetes, Lactic acidosis, Metformin, *U. pilulifera*, Kidney function test, Uric acid, Creatinine.

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INTRODUCTION

Metformin therapy and renal failure

According to study of Kajbaf et al (2013), there are criteria for withdrawing of metformin which are mainly qualitative (kidney failure), mainly quantitative in which a suggested threshold—mostly based on serum creatinine values—for withdrawing metformin, and quantitative with indication of a chronic kidney disease (CKD) threshold for withdrawal and/or adjustment of the metformin dose.

It has been pointed to large degree of agreement that thresholds of serum creatinine ≥ 1.5mg/dl in male patients and ≥ 1.4mg/dl in female patients, the eGFR thresholds varied from 60 ml/min per 1.73m2 to stage 5 CKD (Lalau et al., 2014)

Several studies in literature have witnessed a debate regarding the beneficial and harmful effects of metformin. It has been pointed to the necessity of including a serious analysis of present guidelines that are mainly applied to patients with renal impairment (Holstein et al., 1999; Macklin, Alexander, 2005; Nye and Herrington, 2011). These findings were consistent with findings of large study of Ekstrom et al (2012) in which use of metformin was proved to be efficient and safe in patients at varying CKD stages.

Across the literature, there was a trend showing increased beneficial outputs attributed to metformin treatment among patients with type 2 diabetes irrespective to the presence of chronic kidney disease and cardiovascular disease, which, in turn, has plausibly let researchers to reconsider its in this high-risk population (Rocha et al., 2013). Several studies from the United kingdom have shown that metformin treated patients to have decreased risk of diabetes-related death, incident myocardial infarction, fatal and non-fatal strokes and heart failure (Salpeter et al., 2003; Stades et al., 2004; Bodmer et al., 2008; Nye and Herrington, 2011; Sharif, 2011).

Other studies put more emphasis on the consideration that metformin is still remaining the only glucose-lowering treatment having cardio-protective outputs and is suitable for the 20% to 40% of patients with diabetes who are going to develop diabetic nephropathy (Pilmore, 2010). According to Rocha et al (2013), although metformin is recommended as the antiglycemic agent of choice in the general population, but guidelines on chronic renal disease do not approve metformin with equal importance.

According to Dell'Aglio (2009), metformin use in patients with renal impairment is limited due to perceived risk of lactic acidosis as indicated through numerous case reports in which it is used. Furthermore, current National Institute for Health and Clinical Excellence guidelines recommend that the dose of metformin should be reviewed if the estimated glomerular filtration rate (eGFR) is <45 mL/min/1.73 m^2 and that metformin should be discontinued in patients in whom the eGFR falls to <30 mL/min/1.73 m^2 (Rocha et al., 2013).

In their study, Lalau and Race (2001) reported that metformin has no nephrotoxic impacts. Furthermore, Frid et al (2010) showed that metformin has certain characteristics among which are it is not metabolized, its association with plasma proteins is low, and it is mainly excreted through kidneys (90%). It has also been reported by the same authors that its half life is about 6.5 hours in patients with normal kidney function and it is prolonged in patients with severe renal failure.

According to Dell'Aglio et al (2009), pharmacokinetic studies of metformin have suggested that metformin doses to be lowered by one third in patients with eGFRs of <45 mL/min/1.73 m^2. Furthermore, metformin is tolerable at eGFRs of <30 mL/min/1.73 m^2, if patients have stable chronic kidney disease without having other failures in liver or respiratory systems.

In their study, Frid et al (2010), metformin serum concentrations were analyzed in 137 type 2 diabetic patients. Serum metformin, cystatin C, and creatinine were also analyzed. Study findings showed that metformin may be used at eGFR above 30 mL/min/1.73 m^2 and this study indicated that patients above this GFR limit were not likely to have metformin levels above 20 µmol/L, which is considered a safe level.

Tsuda et al (2009) conducted a study to investigate the correlation between overdose of metformin and mortality. Study data showed that survivors had metformin level of 254 µmol/L, whereas nonsurvivors had metformin level of 302 µmol/L. Taken together, high levels of serum metformin are associated with lactic acidosis.

According to Pilmore (2010), it has been indicated that the use of metformin is limited in patients with kidney disease due to possible risk of lactic acidosis. It seems that treatment by metformin is useful for large proportion of patients with CKD. Another study by Agrawal et al (2009) has pointed

to little beneficial effects of metformin use in renal parameters among patients with metabolic syndrom

According to previous considerations, it is plausible to think of other therapeutic options. Previous studies have found that some herbal treatments may be good alternatives. Among these herbal treatments is *Urtica pilulifera*. Studies have shown that the extracts of *U.pilulifera* was used to treat various diseases including Diabetes Mellitus (Kavalali et al., 2003; Lopatkin et al., 2005). Urtica pilulifera, is a well-known plant in Palestinian and in Sinai (Ali-Shtayeh etal., 2000). It belongs to family Urticaceae and it is characterized morphologically by the stinging hairs carried by its leaves and flowers which cause irritation to the skin (Fu etal., 2006). A tea made from the leaves of Urtica pilulifera has traditionally been used as a stimulating tonic, blood purifier and hemostatic and for enhancement of hemoglobin concentration (Chrubasik etal., 2007).

Dina et al (2013) conducted a study to evaluate the potential effects of ethylacetate (EA), chloroform (CHLOR) and hexane (HEXA) extracts of *Urtica pilulifera* as oral anti-diabetic agents as well as to evaluate their possible anti- oxidant and anti-inflammatory effects in type 2 diabetic rat model. The researchers induced the model of Type2 diabetes through a high fat diet and low dose streptozotocin (STZ). Diabetic adult male albino rats were allocated into groups and treated according to the following schedule; Pioglitazone HCL (PIO), EA, CHLOR and HEXA extracts of Urtica pilulifera at two doses of 250 and 500mg/kg were used. Control groups were included as normal and diabetic control. Blood glucose, insulin resistance, antioxidant enzymes, 8-hydroxy-2-deoxyguanosine (8-OHdG) as well as C-reactive protein and tumor necrosis factor-a levels were evaluated. Study findings indicated to significant hypoglycemia associated with antioxidant and anti-inflammatory effects in diabetic rats in EA and CHLOR extracts of *Urtica pilulifera*. It is believed that these activities are responsible, at least partly, for improvements that have been seen in hyperglycemia and insulin resistance of diabetic rats. Taken together, the previous findings encourage the traditional use of *Urtica pilulifera* extract as an antioxidant and anti-inflammatory agent as an additional therapy of diabetes (AlShuwayeb and Al-Khatib, 2013).

Study objectives

The main objectives of the present study are to investigate the effects of both the extract of *U. pilulifera* and metformin in reducing some kidney parameters including the second objective is to raise the issue about the necessity of giving more concern to herbal treatment and to go more advanced steps towards formulating these herbal treatments.

METHODOLOGY

Plant collection and preparing of its extract

U. pilulifera was collected from different places that are well-known to have *U. pilulifera* in Jordan. *U. pilulifera* was air-dried in shade well-ventilated area and then ground into fine powder. About 350 g of powder was put in a Soxhlet cold extractor using absolute methanol as solvent and remained for three consecutive days (Sadki et al., 2001). The extract was concentrated to dryness in rotary evaporator under reduced pressure and controlled temperature (45°C) to yield an 11.4% viscous greenish-colored extract. The extract was kept at 4°C in a glass container until use. Wister rats were used in this study, in which their average weight was 170 g. The animals were carefully checked and monitored every day for any changes. After determination of lethal dose (LD50), two doses were selected 1.25 g/kg and 1.88 g/kg of body weight. Doses were prepared through dissolving required amount of the viscous extract in 10 mL Tween-20: 0.9% NaCl (1:9, V/V).

Diabetic model

Diabetes was induced employing alloxan so that rats were injected by alloxan monohydrate "B.O.H chemical LTD England" intraperitoneally at a dose of 150 ml/kg body weight (dissolved in fresh normal saline) to 18 hr fasted rat. Rats were monitored for blood glucose and rats with blood glucose level over 200 mg/ml, were considered diabetic and employed in the study.

Animals were assigned into the following groups:

Group I: control group; Group II: diabetic group; Group III: diabetic treated with 1.25 mg/kg of body weight; Group IV: diabetic treated with 1.88 mg/kg of body weight; Group V: diabetic group treated with 14.2 metformin.

STATISTICAL ANALYSIS

Data analysis was carried out using SPSS 20. Data were presented as mean and standard deviation. T test was used to investigate the difference between kidney function tests in study groups. Significance level was considered at alpha level ≤ 0.05.

RESULTS

The effects of treatment of *U. pilulifera* and metformin on urea in study groups

As shown in table 1, the mean concentration of urea in control group is 26.92 ± 1.83 mg/dl which is increased significantly (P <0.05) to 39.62 ± 3.16 in diabetic group. Treatment using *U. pilulifera* (1.25 mg/kg) decreased significantly (P <0.05) the mean concentration of Urea to 25.52± 1.62 compared with diabetic group. Treatment using *U. pilulifera* (1.88mg/kg) decreased significantly (P <0.05) the mean concentration of Urea to 28.32 ± 2.41compared with diabetic group. The data of the present study, showed that treatment using metformin 14.2 mg/kg decreased significantly (P <0.05) the mean concentration of urea to 22.54± 1.80 mg/dl compared with diabetic group.

The effects of treatment of *U. pilulifera* and metformin on uric acid in study groups

As seen in table 1, the mean concentration of uric acid in control group was 1.61± 0.22 mg/dl, and this was increased significantly (P <0.05) in diabetic group to 2.34 ± 0.16 mg/dl. Data showed positive outcome from treatment with *U. pilulifera* 1.25 mg/dl which was able to decrease significantly (P <0.05) the mean concentration of uric acid to 1.42 ± 0.06 mg/dl. It was also observed that treatment with 1.88 mg/dl of *U. pilulifera* to decrease significantly (P <0.05) the mean concentration of uric acid level acid level to 1.62 ± 0.12 mg/dl compared with diabetic group. Treatment with 14.2 mg/kg metformin was able to decrease significantly (P <0.05) the mean concentration of uric acid level to 1.18± 0.04 mg/dl compared with diabetic group.

The effects of treatment of *U. pilulifera* and metformin on creatinine in study groups

In control group, the concentration of creatinine was 0.98 ± 0.08 mg/dl, and creatinine level was increased significantly (P <0.05) in diabetic group to 2.16± 0.12 mg/dl. In the present study, diabetic group treated with 1.25 mg/dl *U. pilulifera* had decreased significantly (P <0.05) the mean concentration of creatinine level to 1.39 ± 0.06 mg/dl compared with diabetic group. The same trend was observed in using treatment with 1.88 mg/dl *U. pilulifera* which decreased the mean concentration of creatinine level to 1.26 ± 0.14 mg/dl. This variation was statistically significant (P <0.05). Using treatment with 14.2 mg/kg metformin was able to decrease significantly (P <0.05) the mean concentration of creatinie to 1.22± 0.09 mg/dl compared with diabetic group (table 1).

Table1:The effect of treatment with U. pilulifera and metformin on some kidney parameters in study groups.

Group	Treatment	Urea (M± SD) (mg/dl)	Uric acid (M± SD) (mg/dl)	Creatinine (M± SD) (mg/dl)
I	Control	26.92 ± 1.83	1.61± 0.22	0.98 ± 0.08
II	Diabetic (alloxan)	39.62 ± 3.16*	2.34 ± 0.16*	2.16± 0.12*
III	Treated group (1.25 mg/kg)	25.52± 1.62**	1.42 ± 0.06**	1.39 ± 0.06**
IV	Treated group (1.88 mg/kg)	28.32 ± 2.41**	1.62 ± 0.12**	1.26 ± 0.14**
V	Treated group with metformin 14.2 mg/kg	22.54± 1.80**	1.18± 0.04**	1.22± 0.09**

*compared with control group.
**compared with diabetic group.

DISCUSSION

The present study was conducted in the context of a debate about metformin may be discontinued at certain stage mainly due to lactic acidosis (Dell'Aglio, 2009) who reported that metformin use in patients with renal impairment is limited due to perceived risk of lactic acidosis. Furthermore, current National Institute for Health and Clinical Excellence guidelines recommend that the dose of metformin should be reviewed if the estimated glomerular filtration rate (eGFR) is <45 mL/min/1.73 m^2 and that metformin should be discontinued in patients in whom the eGFR falls to <30 mL/min/1.73 m^2 (Rocha et al., 2013). It is also reported by Kajbaf et al (2013) that there are criteria for withdrawing of metformin which are mainly qualitative (kidney failure), mainly quantitative in which a suggested threshold—mostly based on serum creatinine values—for withdrawing metformin, and quantitative with indication of a chronic kidney disease (CKD) threshold for withdrawal and/or adjustment of the metformin dose.

Accordingly, the need for investigating other alternatives to be used for diabetic treatment with less side effects exists. Among these alternatives is the *U. pilulifera* which has been used to treat diabetes by general public (Kavalali et al., 2003; Lopatkin et al., 2005; AlShuwayeb and Al-Khatib, 2013; Dina et al., 2013).

Our data showed significant increased concentration of urea, uric acid and creatinine in diabetic group compared with control group (P <0.05) . these findings are in line with other studies in which increased levels of serum blood urea nitrogen (BUN) and serum uric acid were observed (Piyachaturawat, Poprasit, Glinsukon, 1991; Asayama et al., 1994). It has also been reported that STZ displays nephrotoxic and necrosis of kidney tubules (Hasan et al., 1999).

The data of this study revealed that treatment using the extract of *U. pilulifera* and metformin for one month reversed the impacts of diabetes on kidneys of diabetic rats. Using either dose of *U. pilulifera or metformin* acted to to restore all kidney function tests under study urea, uric acid and creatinine to almost normal levels. These variations among treated groups and diabetic groups were statistically significant (P <0.05). Our findings were in agreement with other reported studies in literature in which various herbal treatments were used to treat diabetes and resulted in positive outcomes in improving kidney function tests. Gupta et al (2011) reported positive outcomes of kidney function tests by using *Momordica dioica*. Other researchers reported similar findings using *Olea europaea L*, *Gymnema montanum*, and *Annona squamosa* (Eidi et al., 2009; Ramkumar et al., 2009; Basha et al., 2011).

CONCLUSION

The present study showed that both metformin and *U. pilulifera* were successfully able to restore kidney parameters urea, uric acid and creatinine in diabetic group to almost levels of control group. In the context of debate that metformin may be discontinued or adjusted in cases of impaired kidney function, *U. pilulifera* may be a good alternative with less side effects. From this study, we invited pharmaceutical companies to consider pharmaceutical companies to prepare or formulate the extraction of *U. pilulifera* and to conduct more studies.

REFERENCES

1. Agrawal. V., Shah. A., Rice. C., Franklin. B.A., Mccullough. P.A., Impact of Treating the Metabolic Syndrome on Chronic Kidney Disease. Nat Rev Nephrol, 2009, 5(9):520-528.

2. Ali-Shtayeh., Yaniv. M. S., and Mahajna., J . Ethnobotanical survey in the Palestinian area: a classification of the healing potential of medicine. Journal of Ethnopharmacology, 2003, 2073, 221–232.

3. Ana. Rocha., Marta. Almeida., Josefina. Santos., and André. Carvalho., Metformin in patients with chronic kidney disease: strengths and weaknesses. JNEPHROL, 2013, 26(01): 55-60.

4. Asayama. K., Nakane. T., Uchida. N., Hayashihe. H., Dobashi. K., and Nakazawa. S., Serum antioxidant status in streptozotocin-induced Diabetic Rat. Horm. Metab. Res, 1994, 26: 313-315.

5. Basha. S.K.H., and Subramanian.S., Biochemical evaluation of anti-diabetic and antioxidant potentials of Annona squamosa leaves extracts studied in STZ induced diabetic rats. IJPSR, 2011, 2(3): 643-55.

6. Bodmer. M., Meier. C., Krahenbuhl. S., Jick. S.S., and Meier. C.R., Metformin, Sulfonylureas or other Antidiabetes Drugs and the Risk of Lactic Acidosis or Hypoglycemia. Diabetes Care, 2008, 31(11):2086-2091.

7. Chrubasik. Chrubasik. S., A comprehensive review on the stinging nettle effect and efficacy profiles. PartII: Urticae radix. Phytomedicine, 2007, 14,568–579.

8. Dell'Aglio. D.M., Perino. L.J., Kazzi. Z., Abramson. J., Schwartz. M.D., Morgan. B.W., Acute metformin overdose: examining serum pH, lactate level, and metformin concentrations in survivors versus nonsurvivors: a systematic review of the literature. Ann Emerg Med., 222009, 54(6):818-823.

9. Dina. M. Abo-elmatty., Soha. S., Essawy. Jihan., Badr. M., and Olov. Sterner., Antioxidant and anti-inflammatory effects of Urtica pilulifera extracts in type2 diabetic rats. Journal of Ethnopharmacology, 2013, 145, 269–277.

10. Eidi. A., Eidi. M., and Darzi. R., Antidiabetic effect of Olea europaea L. in normal and diabetic rats. Phytother Res, 2009, 23:347-350.

11. Ekstrom, N., Schioler, L., Svensson, AM et al . Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open, 2012, 2, (pii) e001076.

12. Frid A, Sterner GN, Löndahl M et al (2010). Novel assay of Metformin Levels in Patients with Type 2 Diabetes and Varying Levels of Renal Function: Clinical Recommendations. Diabetes Care, 33(6):1291-1293.

13. Fu, H.Y.,Chen, S. J., Chen, R. F., Ding,W.H.,Kuo-Huang, L.L.,Huang, R.N . Identification of oxalic acid and tartaric acid as major persistent pain-inducing toxins in the stinging hairs of the nettle, Urtica thunbergiana. Annals of Botany, 2006, 98, 57–65.

14. Gupta, R and Gupta, RS . Effect of Pterocarpus marsupium on streptozotocin-induced oxidative stress in kidney of diabetic Wistar rats. J Herbs Spices Med Plants, 2011, 17:169-182.

15. Hasan, V., Günes, Irfan Degirmenc.i, Miris, Aydin., Berrin,Bozan., Erinç, Aral., Zeynep, Tunalier., Cengiz, Üstüner., Murat, Erçakir., K. Hüsnü C. Baser and Ayse Basaran . The Effects of Rumex patientia L. and Urtica dioica L. on Some Blood and Urine Parameters, and Liver and Kidney Histology in Diabetic Rats. Tr. J. of Medical Sciences, 1999, 29, 227-232.

16. Holstein, A., Nahrwold, D., Hinze S et al. Contra-indications to metformin therapy are largely disregarded. Diabet Med, 1999, 16: 692–696.

17. Jean-Daniel, Lalau., Paul, Arnouts., Adnan, Sharif., Marc, E. De Broe. Metformin and other antidiabetic agents in renal failure patients. Kidney International advance online publication, 2014, 5, 1-15.

18. Jones, G., Macklin, J and Alexander W . Contraindications to the use of metformin. BMJ, 2003, 4: 4–5.

19. Kajbaf, K., Arnouts, P de Broe M et al. Metformin therapy and kidney disease: a review of guidelines and proposals for metformin withdrawal from around the world. Pharmacoepidemiol Drug Saf, 2013, 22: 1027–1035.

20. Kavalali, G., H. Tuncel., Goksel, S and Hatemi, H.H. Hypoglycemic activity of Urtica pilulifera in streptozotocin-diabetic rats. J. Ethnopharmacol, 2003, 84, 241-245.

21. Kovesdy, CP., Park, JC and Kalantar-Zadeh, K. Glycemic control and burnt-out diabetes in ESRD. Semin Dial, 2010, 23(2):148-156.

22. Lalau, JD and, Race, JM. Lactic Acidosis in Metformine Therapy: Searching for a Link with Metformin in Reports of Metformin Associated Lactic Acidosis. Diabetes Obes Metab, 2001, 3: 195-201.

23. Lopatkin, N., Sivkov, A., Walther, C.,Schlafke,S., Medvedev,A., Avdeichuk,J., Golubev,G., Melnik,K, Elenberger,N., and Engelmann,U. Long-term efficacy and safety of a combination of sabal and Urtica pilulifera extract for lower urinary tract symptoms: A placebo-controlled, double-blind multi-center trial. World J. Urol, 2005, 12: 742-749.

24. McCormack, J., Johns,K and Tildesley,H. Metformin's contraindications should be contraindicated. CAMJ, 2005, 173: 502–504.

25. Mousa, H., AlShuwayeb, Ahed J. Al-Khatib. Molecular and chemical therapeutic features of *Urtica* species. European Scientific Journal, 2013, 9 (24): 253-261.

26. Nye, HJ and Herrington, WG . Metformin: the safest hypoglycaemic agent in chronic kidney disease? Nephron Clin Pract, 2011, 118: c380–c383.

27. Pilmore,HL. Review: Metformin: Potential Benefits and Use in Chronic Kidney Disease. Nephrology (Carlton), 2010, 15(4): 412-418.

28. Piyachaturawat, P., Poprasit, J and Glinsukon, T. Gastric mucosal secretions and lesions by different doses of

streptozotocin in rats. Toxicology Letters, 1991, 55: 21-29.

29. Ramkumar, KM., Ponmanickam, P., Velayuthaprabhu, S., Archunan, G and Rajaguru P. Protective effect of Gymnema montanum against renal damage in experimental diabetic rats. Food Chem Toxicol, 2009, 47:2516-2521.

30. Sadki, G., Gafur,M.A., Bhyuiyan, M.S.A., Khurshid, A.H.M., Biswas, M.H.U., Hassan, M.O.F and Chowdhury, A.K.A. Antifertility activity of Pergularia daemia . Sciences, 2001, 1: 22-24.

31. Salpeter ,SR., Greyber, E., Pasternak, GA and Salpeter, EE. Risk of Fatal and Nonfatal Lactic Acidosis with Metformin Use in Type 2 Diabetes Mellitus. Arch Intern Med, 2003, 163(24):2594-2602.

32. Sharif,A . Should Metformin be our Antiglycemic Agent of Choice Post Transplantation? Am J Transplant, 2011, 11:1376-1381.

33. Stades,AME.,Heikens,JT.,Erkelens,DW., Holleman,F and Hoekstra, JBL. Metformin and Lactic Acidosis: Cause or Coincidence? A Review of Case Reports. J Intern Med, 2004, 255:179-187.

34. Tsuda, M., Terada, T., Ueba, M et al. Involvement of Human Multidrug and Toxin Extrusion 1 in the Drug Interaction between Cimetidine and Metformin in Renal Epithelial Cells. J Pharmacol Exp Ther, 2009, 329(1):185-191.

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