

# World Journal of *Diabetes*

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## Potential therapeutic targets for the prevention of diabetic nephropathy: Glycyrrhetic acid

Lu Cai, Michael Horowitz, Md Shahidul Islam

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### Abstract

Uncontrolled hyperglycemia or poorly managed disease increases the propensity for a number of diabetes-related complications targeting major organs including the heart, eyes, and kidney. Although the mechanisms by which diabetes induces cardiovascular diseases include oxidative stress and inflammation, when insulin resistance remains the key to the pathogenesis, as implicated in the two reviews in this issue. This editorial mainly comments on the potential preventive application of glycyrrhetic acid (or 18 $\beta$ -GA) in relation to diabetic nephropathy. The therapeutic or preventive effects of 18 $\beta$ -GA, as a hydrolytic product of glycyrrhizic acid that is a component of licorice, have been appreciated in other disorders, but have received much less attention in relation to diabetic complications. A study in this issue has identified 18 $\beta$ -GA as a therapeutic for preventing diabetic nephropathy and provides evidence to support efficacy in cultured human renal tubule cells *in vitro*. Although it represents a pilot study, the observations support a new therapeutic approach that warrants further exploration.

**Key Words:** Insulin resistance; Diabetic cardiomyopathy; Diabetic nephropathy; Glycyrrhetic acid; Licorice; Chinese herbal remedy

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**Core Tip:** Uncontrolled hyperglycemia or poorly managed disease increases the propensity for a number of diabetes-related complications targeting major organs including the heart, eyes, and kidney. Although the mechanisms by which diabetes induces cardiovascular diseases include oxidative stress and inflammation, when insulin resistance remains the key to the pathogenesis, as implicated in the two reviews in this issue. This editorial mainly comments on the potential preventive application of glycyrrhetic acid (or 18 $\beta$ -GA) in relation to diabetic nephropathy (DN). The therapeutic or preventive effects of 18 $\beta$ -GA, as a hydrolytic product of glycyrrhizic acid that is a component of licorice, have been appreciated in other disorders, but have received much less attention in relation to diabetic complications. A study in this issue has identified 18 $\beta$ -GA as a therapeutic for preventing DN and provides evidence to support efficacy in cultured human renal tubule cells *in vitro*. Although it represents a pilot study, the observations support a new therapeutic approach that warrants further exploration.

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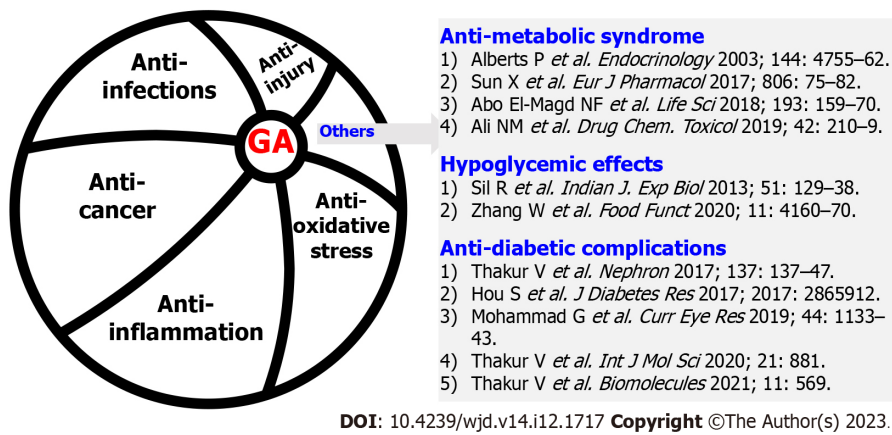
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## INTRODUCTION

Diabetes is well known as a chronic, metabolic disease that over time often leads to serious damage to the heart, blood vessels, eyes, kidneys and nerves. More than 95% of people with diabetes have type 2 diabetes mellitus (T2DM). T2DM occurs when the body becomes resistant to insulin or doesn't make sufficient insulin due to partial pancreatic  $\beta$ -cell damage. T2DM usually occurs in adults but a number of recent studies have demonstrated its disturbing increasing prevalence in children and adolescents[1,2]. Uncontrolled hyperglycemia or poorly managed diabetes leads to a number of diabetes-related complications targeting major organs, including heart, kidney, brain and eyes. Although these potentially life-threatening complications can be reduced or delayed by following healthy lifestyle, awareness of warning signs, regular visits to a health care provider, and effective therapeutic interventions are urgently needed, as discussed in two reviews in this or recent issue[3,4]. The mechanisms by which diabetes induces cardiovascular diseases include oxidative stress and inflammation[1-4]. However, insulin resistance remains key to the pathogenesis, underpinning the increases in oxidative stress and inflammation, particularly in individuals with T2DM[1-4]. Insulin resistance is often accompanied by hyperlipidemia, therefore, atorvastatin as one of the statins, HMG-CoA reductase inhibitors, are used widely as a class of lipid-lowering medications. Song *et al*[5] reported their efficacy in preventing diabetic cardiomyopathy in db/db T2DM mice, which may also be associated with anti-oxidative and anti-inflammatory effects through modulating the polarization of macrophages. This information provides an additional rationale for statins in the management of diabetic complications. However, these drugs may also exhibit adverse effects on other organs. Accordingly, the importance of natural compounds for the management of diabetic complications cannot be underestimated due to their minimal adverse effects. These natural compounds include, but not limited to, polyphenols, flavonoids, phenolic acids and zinc that have been shown to have substantial beneficial effects in the management of hyperglycemia, diabetes and its associated complications[6]. In line of this notion, a study by Meng *et al*[7] in a recent issue proposed the potential preventive effect of glycyrrhetic acid (also called 18 $\beta$ -Glycyrrhetic acid, 18 $\beta$ -GA) for the management of diabetic nephropathy (DN).

18 $\beta$ -GA, as a hydrolytic product of glycyrrhizic acid, is a component of licorice. Licorice (sometimes spelled liquorice) has been used as an herbal remedy and sweetening agent across cultures for centuries. Chinese licorice (or liquorice) root is the rhizome (the underground stem) of the plant *Glycyrrhiza glabra*, which is native to Asia, Turkey, and Greece. Glycyrrhizic acid is structurally composed of two molecules of glucuronic acid and 18 $\beta$ -GA. Glycyrrhizic acid is metabolized by gut bacteria to 18 $\beta$ -GA[8-10]. Therefore, 18 $\beta$ -GA is an *in vivo* metabolic component of glycyrrhizic acid. It is considered widely as one of the main active substances of licorice. Although a number of recent studies have focused on the biological activities of 18 $\beta$ -GA, this has related primarily to its anti-inflammatory, immunoregulatory, anti-tumor, anti-injury, and antioxidative properties. A number of comprehensive reviews have summarized the protective effects of licorice-derived 18 $\beta$ -GA against liver injury[8] and its potential immunomodulatory and anti-inflammatory properties[9], and efficacy in cancer therapy[10], as summarized in Figure 1. However, less work has been done in relation to its potential in the management of diabetic complications.

Although many studies have shown the beneficial effects of 18 $\beta$ -GA on other conditions, its application, and associated mechanisms for the preventive and therapeutic effects on diabetic complications are poorly understood[11,12]. The study by Meng *et al*[7] in this issue, explored the therapeutic targets and molecular mechanisms of 18 $\beta$ -GA against DN based on network pharmacology and molecular docking, and found that 18 $\beta$ -GA has a therapeutic effect on DN with a potential 186 targets. Molecular docking studies demonstrated strong binding of 18 $\beta$ -GA to mitogen-activated protein kinase (MAPK)-1, SRC, PIK3R1, HSP90AA1, CASPASE9, HARS, KRAS, and MAPK14. It was revealed that 18 $\beta$ -GA inhibits HK-2 cell viability, induces cell cycle arrest at the G2/M phase, and reduces apoptosis with 18 $\beta$ -GA in a dose-dependent manner after the treatment of an immortalized proximal tubule epithelial cell line from normal adult human kidney cells or HK-2 cells with high level of glucose with and without 18 $\beta$ -GA. Further analysis showed that 18 $\beta$ -GA differentially up-regulated key insulin signaling pathway members including PI3K, AKT and GSK3. These innovative and important



**Figure 1 Summary of the beneficial effects of glycyrrhetic acid family members.** The left panel summarizes the well-known beneficial effects based on several reviews cited in this editorial publication[8–10]. The right panel of this figure as a small part of total research on provides the limited publications that showed the certain protective effects on metabolic syndrome, hyperglycemia, and potential diabetic complications. GA: Glycyrrhetic acid.

observations have provided the evidence to support the concept of therapeutic efficacy as published previously[11,12].

## CONCLUSION

In conclusion, as a main component of licorice, 18 $\beta$ -GA-mediated beneficial effects in several pathogenic conditions have been widely appreciated; however, its application to the management of diabetes and diabetic complications remains elusive. Although the outcomes of this pilot study have raised many questions that should be further addressed, as the authors propose, it also provides a new direction in relation to its potential clinical application for the prevention and management of DN, which is likely to be safe, inexpensive and with no or lower adverse effects.

## FOOTNOTES

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