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Administration of *Galega officinalis* in experimental and clinical investigations; a narrative review

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Abstract

Numerous remedies recently consumed in health system are obtained from natural plants. For instance metformin, one of the prevalent drugs for controlling diabetes mellitus with hypoglycemic activity, is derived from the plant, *Galega officinalis*. Type 2 diabetes mellitus is a frequent metabolic disorder characterized by persistent hyperglycemia. High blood sugar may give difficulties like renal and cardiovascular disorders, retinopathy, and poor blood flow for long-term. Its advance can be prohibited in patients with spoiled glucose tolerance by implementing lifestyle changes or the use of helpful agents such as medicinal herbs administered for many years because the presence of antioxidants like flavonoids in them can have a protective influence on various renal diseases and diabetic complications but since using of herbal medicine and also treatment of frequent chronic diseases such as diabetes mellitus, need a programmed management, so prevention and therapeutic process should be considered by healthcare system and also there is a need to develop a basis for standardization that ties the composition of herbs to efficacy. In absence of such standardization, the use of herbs in diabetes must be approached cautiously.

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Introduction

Recently, there has been an exponential growth in the area of medicinal plants and these herbs are gaining recognition both in developing and developed nations due to their natural origin and possibly less side effects (1). In fact, various traditional medicines in use are extracted from medicinal plants (1,2). A number of medicinal herbs conventionally administered for many years and their affectivity have been approved. As a matter of fact, the presence of antioxidants like flavonoids in diet can have a protective influence on various renal diseases and diabetic complications (1). The active phytochemicals and the mechanisms responsible for activities of numerous medicinal plants have been recognized that some of them have a positive effect on glucose homeostasis in diabetic patients (2). These plants have different and effective compounds to control diabetes mellitus or impaired glucose tolerance (1-3). Some plants lower blood pressure or improve the renal and cardiovascular functions, which are often seen in diabetic patients (2).

Materials and Methods

This review article discusses the antioxidant effects of *Galega officinalis* and it is derived from metformin to ameliorate diabetic kidney disease and acute renal failure. For this review, we used a variety of sources by searching through Web of Science, PubMed, EMBASE, Scopus and directory of open access journals (DOAJ). The search was performed using combinations of the following key words and or their equivalents such as *Galega officinalis*, antioxidants, metformin, diabetes mellitus, herbal drugs and medicinal plants.

Core tip

Medicinal herbs administered for many years because the presence of antioxidants like flavonoids in them can have a protective influence on various renal diseases and diabetic complications but since using of herbal medicine and also treatment of frequent chronic diseases such as diabetes mellitus, need a programmed management, so prevention and therapeutic process should be considered by healthcare system and also there is a need to develop a basis for standardization that ties the composition of herbs to efficacy. Numerous remedies recently consumed in health system are obtained from natural plants. For instance metformin, one of the prevalent drugs for controlling diabetes mellitus with hypoglycemic activity, is derived from the plant, *Galega officinalis*.

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Galega officinalis in experimental and clinical investigations

There are also some precious plants to treat a wide range of inflammatory diseases such as diabetes mellitus, and disturbed renal function (3). Of them, *Galega officinalis* can be considered as a worthy source of antioxidants in medicinal plants. *G. officinalis* is a herbaceous herb, derive from faboidae subfamily (2). According to the International Diabetes Federation warning in 2013 approximately 5 million patients died due to diabetes. So that, based on the latest estimation by this federation it is envisaged to involve 552 million people by 2030, that developing countries will allocate more than 75% of diabetic sufferer to themselves.

There are many studies about positive effects of one of the most outstanding drugs in the treatment of diabetes named ''Metformin" that is a miraculous tincture of *G. officinali*s.

In recent decades, metformin has been one of the major interesting research subjects due to its positive impacts on treatment and control of type 2 diabetes. Therefore, this paper aims to review the research conducted on the therapeutic potential of this precious plant for further use in the treatment of diabetes (3).

Toxicity; background, etiology

Before we talk about the healing properties of the plant we should also examine its toxicity. *G. officinalis* is vastly used for increasing lactation in alternative and complementary medicine due to anti-diabetic features. Unfortunately, the plant is toxic for widespread use, with the possibility to motivate tracheal foaming, pulmonic edema, hydrothorax, hypotension, paralysis and death and it is widely considered to represent a threat to grazing animals. Previous studies found this plant toxic to sheep and are capable of causing death. In some cases, sub-endocardial hemorrhage was reported and the highly steady microscopic alterations were discovered in the lungs with alveolar capillaries edema. A compared analysis of lung microscopic findings connote analogous toxicosis in breathing system. Puyt et al reported some cases of poisonings due to consumption of *Galega* herb in sheep. The contaminating was differentiated by an asphyxic syndrome which led to death within hours. Moreover, some other investigations endorsed deadly poisoning companioned by rigorous pulmonary problems. In another experiment, toxicity of *Verbesina encelioides* which has the same active substance as *G. officinalis*, galegine, was evaluated (4).

Microscopically, severe glomerulonephritis and liver cells congestion, cellular devastation and fatty alteration were indicated in sheep gained dehydrated substances of this herb (6.3 g/kg body weight). Besides, congestion in lymph nodes, and hemorrhagic and edematous lungs were noted. It is supposed that galegine is the main complex in the plant that causes damage (5,6).

Besides a study showed that the use of this herb could be safe, so that the oral LD50 value of *G. officinalis* was a relatively high. Several of these observations defend the deduction that liver and lung are possible target organs for both sexes, although the mechanism of venomous effect on liver is unknown. According to the results of a study conducted by Rasekh et al in 2007 it can be concluded that the risk of oral toxicity to mammals is not negligible. A dose-dependent significant increase in relative liver weight observed in animals. Reserving blood in sinusoidal area and congestion in liver may cause the relative liver weight elevation. On the other hand two key enzymes that have remarkable diagnostic value in skeletal muscle and myocardial injuries are creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)**.** Remarkable elevation in CPK and LDH, initial indicators of myopathy, in females represents potentials for muscular injury. Hence, it could be suggested that *G. officinalis* can lead to muscular injury in females. Despite all these findings about the toxicity of the *G. officinalis*, this plant also has antioxidant properties that make it particularly suitable for the treatment of many diseases (7).

Antioxidant activity

The use of natural products as anti-diabetic agents has a long history that began with traditional medicines. Several drugs in treatment of metabolic disorders were isolated from plant species or were derived from a natural prototype. Antioxidants are usually used to block the radical chain reactions of oxidation. They act through inhibiting the initiation and production, ending the reaction or delaying the oxidation process. Therefore, there has been an important concentration to realize biologic antioxidants to substitute the synthetic compounds in food applications and a growing interest in using natural antioxidants, all of which has given more impetus to explore the natural sources of antioxidants (8,9). In a study by Kahkeshani et al (10), they showed the presence of phenolic compounds like flavonol, triglycosides, kaempferol, galein, medicagol, quercetin, triterpenes like galegadiol, soyasapogenol, as well as saponins and phytosterols like beta-sitosterol, stigmasterol and campesterol in *G. officinalis*. They supposed that all therapeutic effects of this herb were mediated by its antioxidant compounds (10). Additionally**,** in another research by Lupak et al in 2015, they showed that alkaloid-free fraction from *G. officinalis* extract prevents oxidative stress development in rats with streptozotocin-induced diabetes, running mechanisms such as antiradical and antioxidant property to defend the blood system. In the case of extract application to animals in pathologic studies, can consider lowering effect of reactive oxygen species generation in leukocytes, preventing effect in protein and lipid oxidative modification activities and increased function of key enzymes of rat peripheral blood circulation and antioxidant system (catalase, superoxide dismutase and glutathione peroxidase). The revealed biological effect could be explained by the presence of naturally pure active constituents with antioxidant activities in the extract composition (phytol and flavonoids) (11). On one hand anti-oxidative properties of *G. officinalis* seem to be very important for different affected organs in diabetic patients such as kidney because of its damage is usually associated with an increase in oxidative stress and finally kidney injury. On the other hand antioxidants usually reduce kidney injury (3,11). Consequently, the antioxidant properties may be given special and valuable healing power to *G. officinalis* to treat different kinds of disorders.

Therapeutic potential

G. officinalis is a summer-flowering hardy perennial originated in southern parts of Europe and western regions of Asia, but, many other countries around the world have it now (12). It has long been cultivated as a garden plant, and has been used for diverse medicinal purposes because of its main components, guanidine. An antimalarial agent chloroguanidine hydrochloride was found in 1940s to have a weak glucose-lowering effect and in 1949 a preparation of dimethylbiguanide or flumamine was used for treatment of influenza in the Philippines and also for control of the polyuria associated with diabetes and for promotion of perspiration in people with the plague (13).

In a study by Pundarikakshudu et al in 2001, alcoholic extract (60%) of Goat's Rue (*Galega officinalis*) was tested on gram positive and gram negative bacteria, and finally this alcoholic extract exhibited significant inhibition on growth of both kinds of bacteria (14).

Moreover, the genus name, *Galega*, has been derived from "gala" (means milk) and "agein" (means production) because the other thing *G. officinalis* can affect is milk productive performance of domestic animals, especially milk yield, fat and protein percentage (10).

The last but not the least important therapeutic features of *G. officinalis* is belonging to the management of diabetes, defined in the first half of the twentieth century. *G. officinalis* is a prosperous resource of biological active components mentioned above, guanidine (1918) and related molecules. The toxicant potential of guanidine precludes its medical use, and investigates before the Great War identified by G. Tanret indicated galegine or isoamylene guanidine (1920) as a similar combination with a less noxious property than the guanidine which account for its effects such as potential anti-obesity effect (15).

Preliminary studies showed that galegine reduced gain weight, blood glucose and food intake in mice, suggesting that at least part of the effect of *G. officinalis* on body mass was intercede through galegine. In addition to above proven influences, this herb has weight cutting action, the mechanism of which is unclear but involves loss of body fat.

The exact structure of galegine was confirmed as isoamylene guanidine by a group in Edinburgh, UK, in 1923. Subsequently, in 1920s two synthetic diguanides, namely synthalin A (decamethylene diguanide) and synthalin B (dodecamethylene diguanide) were better tolerated and more effective, and these were used clinically. Until 1970, a lot of drugs such as insulin, buformin, phenformin were used medically but their connection with lactic acidosis resulted in stopping use of them in most countries by the end of 1970s. But increasing evidence confirmed the antihyperglycaemic ability of metformin without leading to overt weight gain or hypoglycemia (13,15).

Metformin a miraculous product from *G. officinalis*

The finding of the active hypoglycemic agent in *G. officinalis* led to the development of metformin, a biguanide drug which is used to treat type 2 diabetes mellitus. In fact, the only example of an approved anti-diabetic drug that was developed from an herbal source is metformin with a prolonged background of use for treatment diabetes (French lilac) (16).

The metformin's mechanism of action has not been clarified although considerable efforts have been made from 1950s. The main anti-diabetic effect of this drug is to decrease glucose generation by liver. A possible molecular mechanism of action can be control of energy homeostasis that emerges from recent breakthroughs. The mechanisms of metformin action are still being elucidated, however several studies put emphasis on its influence in the cellular energy balance. Metformin acts, mostly, via the activation of the AMP-activated protein kinase (AMPK). It seems metformin was disclosed to engender a slight and temporary deterrence of the mitochondrial respiratory chain complex 1. After that decrease in hepatic energy state activates the AMPK that plays a significant role as a cellular metabolic sensor, and subsequently provide a generally recognized mechanism for metformin operation on hepatic gluconeogenesis. In spite of this, AMPK activation in metformin action has recently been challenged. Although recent evidence has also suggested that the effects of this drug may be AMPK-independent (15,17).

Recent observations indicate that metformin-induced inhibition of hepatic glucose output is facilitated by falling cellular energy charge instead of direct inhibition of gluconeogenic gene expression. Furthermore, latest facts endorse a new process of metformin action involving antagonism of glucagon signaling pathways by inducing the repletion of AMP, which blocks adenylate cyclase and reduced levels of cAMP (17,18). Regarding to the earlier assumption metformin has been defined to raise the cellular AMP: ATP ratio inhibiting the complex I of mitochondrial respiratory chain. This change in AMP (ATP ratio and the consequence ATP depletion) is sensed via AMPK, the main controller of cellular energy homeostasis.

AMPK contain three subunits, α, β and γ, and each subunit has at least two isoforms.

Establishment of AMPK initiate with AMP binding to regulative locations on the γ subunits. This change in foundation leads to the activation of the enzyme and prohibits its dephosphorylation on Thr-172 within the activation loop of the catalytic α subunit. The AMP binding on the γ subunit is not enough to activate AMPK. Liver kinase B1 (LKB1) as a tumor suppressor gene, is needed to phosphorylate the α subunit of AMPK at Thr-172 to activate the enzyme. After activation, AMPK sets a tank of substrates which demonstrates the main enzymes in the catabolic ways and prevents ATP-consuming anabolic paths. AMPK also regulates enzymes implicated in cell cycle and protein metabolism. Numerous researches have revealed that loss of LKB1 ruins the potential of metformin in activation of AMPK and maintain plasma glucose and insulin homeostasis (19). Furthermore, patients affected by polycystic ovarian syndrome (PCOS) indicated a various ovulatory reaction once cured with metformin basing on their polymorphism in the LKB1 gene (20-22).

However, Foretz et al in 2010 found that metformin proscribes glucose production in the liver autonomously of LKB1 or AMPK status (22). In addition, Kalender et al in 2010 demonstrated that metformin may boost glucose uptake in skeletal muscle cells of rat and inhibit mTOR signaling independent of AMPK. These outcomes proposed that a metformin AMPK-independent mechanism of action may exist that interferes directly with the cellular energy output, and does not modify genes implicate in gluconeogenesis pathway (23).

Conclusion

G. officinalis (Galega, Goat's Rue, French Lilac) is well known for its hypoglycaemic action and has been used as part of a plant mixture in the treatment of diabetes mellitus (24). Regarding the mentioned traditional and folklor antecedent and previous veterinary study, the most obvious finding to emerge is that *G. officinalis* is one of the most outstanding herbal drug for prevention and treatment of diabetes mellitus due to its antioxidant and therapeutic properties. Additionally it is a proper and valuable plant as a source for producing metformin, the prolonged anti-diabetic drug (25). After over 50 years of using metformin for the treatment of type 2 diabetes we continue to learn about how this effective treatment works and interestingly we proposed more study about using *G. officinalis* instead of its derivative such as galegin and metformin. Since frequent chronic diseases such as diabetes mellitus, need a programmed management, so prevention and therapeutic process should be considered by healthcare system and also there is a need to develop a basis for standardization that ties the composition of herbs to efficacy. In absence of such standardization, the use of herbs in diabetes must be approached cautiously.

Author's contribution

SK is the single author of the manuscript.

Conflicts of interest

The author declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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