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## Effect of physalins on the modulation of NF- $\kappa$ B and its possible implications for glucose homeostasis

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### Abstract

Physalins are steroidal lactone constituents of physalis and other closely related genera that belong to the Solanaceae family. These secondary metabolites have attracted much attention in recent years due to their various biological effects: they are anticarcinogenic, anti-inflammatory, immunomodulating, antibacterial and anti-diabetic. Researchers have shown that physalins are potential inhibitors of NF- $\kappa$ B activation via inhibition of phosphorylation and degradation of I $\kappa$ B $\alpha$ . Moreover, studies performed in a variety of cell and animal-based experimental systems suggest that NF- $\kappa$ B activation is a key event in the early pathobiology of diabetes. Therefore, these results indicate that physalins can be considered as a novel class of NF- $\kappa$ B inhibitors, which are promising as innovative anti-inflammatory agents for the treatment of various inflammatory disorders and diabetes. This review discusses current knowledge about physalins, and evidence of its effects on the modulation of NF- $\kappa$ B, as well as its implications for glucose homeostasis and the prevention and treatment of diabetes.

**Keywords:** Diabetes mellitus, medicinal plants, physalins, glucose homeostasis, NF- $\kappa$ B

### 1. Introduction

Diabetes mellitus (DM) is undoubtedly the major health and development challenge of the 21<sup>st</sup> century [1]. Diabetes is an important public health problem, one of four priority noncommunicable diseases (NCDs) targeted for action by world leaders [2]. In 2014, the International Diabetes Federation (IDF) estimated that 8.2% of adults aged 20–79 (387 million people) were living with diabetes, a considerable increase from the 382 million adults living with the condition reported by the same organization in 2013. The number of people with the disease was projected to rise beyond 592 million in 2035 [3]. Despite the existence of several oral agents and insulin which are widely used in the treatment of DM, glycemic control of patients continues to be frequently poor [4], increasing the possibilities of complications such as nephropathy, retinopathy, diabetic neuropathy, sexual dysfunction and risk of cardiovascular and cerebrovascular disease. Moreover, the financial resources involved in the treatment, recovery and maintenance of patients with the disease are too high for health care systems in many countries [4, 5].

Researchers from around the world have therefore agreed that there is a need to find drugs that provide stable, durable and safe blood glucose control through appropriate control of glucose metabolism [6, 7].

In order to meet the requirements established for the production of new anti-diabetic drugs, surveys have indicated new pharmaceutical compositions based on natural products [8–11]. These studies have shown that physalis plants such as *Physalis angulata*, *Physalis pruinosa* and other herbal medicinal plants that belong to the Solanaceae family, such as *Whiteningia Solanaceae*, have positive hypoglycemic and antihyperglycemic effects, as well as antioxidant and immunomodulatory effects through the inhibition of NF- $\kappa$ B activation [12–14].

Studies reveal that oxidative stress, hyperglycemia insulin resistance, and activation of the NF- $\kappa$ B factor play an essential role in the pathogenesis of diabetes and its complications [15–20].

Based on these encouraging observations, in recent years a great number of efforts have been aimed at discovering substances that act as hypoglycemic agents, antioxidants and inhibitors of NF- $\kappa$ B activation [16, 19, 21]. These properties are found in physalins such as physalins B, D and F [22, 23], and Physagulin-F, indicating that these molecules could represent new therapeutic targets to be explored for the treatment of diabetes mellitus [24].

This review focuses on the sources of physalin compounds, their chemical structure, and their beneficial effects on glucose homeostasis, with special attention paid to the treatment of diabetes.

## 2. Physalins

### 2.1. Sources and chemical structure of physalins

Physalins are steroidal lactone constituents of *Physalis* and other closely related genera that belong to the Solanaceae family. A total of 50 physalins are currently known, which have been isolated from the *Physalis* species *P. alkekengi* var. *franchetii*, *Physalis angulata*, *Physalis lancifolia* and *Physalis minima*. They are biogenetically related to the withanolides, from which they are formally derived by oxidative bond cleavage between C-13 and C-14, to yield a nine-membered ring, formation of a new six-membered carbocycle between C-16 and C-24, oxidation of the CH<sub>3</sub> group at C-13 to a COOH group, which results in 18,20-lactonization, and formation of an oxo bridge between C-14 and C-17, resulting in an oxygen heterocyclic system across rings C and D. Thus, physalins are commonly referred to as 16, 24-cycle-13, 14-secosteroids [25, 26].

Based on their structural skeletons, physalins can be divided into two basic types: the physalin skeleton type with a keto carbonyl group at C-15 along with an oxygen bridge at C-14/C-17, and the neophysalin skeleton type with a lactone carbonyl group at C-15, along with a carbon-carbon bond between C-14 and C-16. A neophysalin skeleton is considered to be derived from the physalin skeleton by a benzylic acid rearrangement. Until now, all neophysalins have been isolated exclusively from *P. alkekengi* var. *franchetii*. A wide variety of physalins are differentiated by the number and position of the carbon-carbon double bond and substituent groups in the skeleton [27].

Pharmacological investigations of these compounds have provided scientific support for traditional uses of many plants that produce physalins. Their biological effects include cytotoxicity and hepatotoxicity, immunomodulatory, antinociceptive, analgesic, antimycobacterial, antileishmanial, antitrypanosomal, antitumor and antidiabetic activities.

### 2.2. Benefits of physalins plants for glucose homeostasis and treatment of diabetes

Glucose is the first and main metabolic substrate required for normal activity of all mammalian cells. Most tissues and organs, such as the brain, need glucose constantly as an important source of energy. The process of maintaining blood glucose at a steady-state level is called glucose homeostasis. In the normal physiological state, glucose homeostasis is maintained by hormonal regulation of peripheral uptake and endogenous glucose production, primarily by muscle, adipose tissue and liver, as well as insulin secretion by the pancreas [28].

The body's inability to maintain glucose homeostasis over a long period of time leads to the onset of clinical manifestations of diabetes. One of the results of impaired glucose homeostasis is hyperglycemia. Prolonged elevation of blood glucose concentrations causes "microvascular disease" (due to damage to small blood vessels), and "macrovascular disease" (due to arterial damage) [29-31]. Microvascular complications include retinopathy, nephropathy and neuropathy, while major macrovascular complications include accelerated cardiovascular disease and cerebrovascular disease in the form of strokes [32]. Vascular complications represent the leading cause of mortality and morbidity in diabetic patients [29, 33].

Furthermore, failures in glucose metabolism may also lead to hypoglycemia – low blood sugar levels which interfere with the functioning of organ systems [34]. A person with hypoglycemia may feel weak, drowsy, confused, hungry, and dizzy. Other signs of low blood sugar are: paleness, headache,

irritability, trembling, sweating, rapid heartbeat, and chills. Hypoglycemia is a common consequence of diabetes treatment: low blood glucose levels occur most often in people who use insulin to lower their blood sugar [32, 35-38].

Several drugs have been used to improve glucose homeostasis, but none of them is able to provide stable, durable and safe blood glucose control, maintain the normal functioning of pancreatic beta cells, and promote or at least not harm patients' cardiovascular function [7, 39-41]. The search for the ideal drug for the treatment of diabetes has encouraged researchers to investigate medicinal plants, many of which are often used in traditional medicine [42-46].

Plants of the Solanaceae family have been reported to show hypoglycemic, antihyperglycemic or antidiabetic effects, especially those that belong to the genera *Physalis* and *Witheringia* [12, 42, 47-49], both of which have bioactive physalin compounds [25].

Herrera *et al.* (2011) demonstrated the hypoglycemic and antihyperglycemic effects of *Witheringia Solanaceae* in normal and alloxan-induced hyperglycemic rats. This plant is also able to inhibit activation of NF- $\kappa$ B. This effect was attributed to the action of physalins B and F, present in crude extracts of *Witheringia Solanaceae* leaves [13].

In the case of the *Physalis* plant, Oladele *et al.* (2013) [50] showed the potential anti-diabetic effect of ethanol extract of the roots of *Physalis angulata*. In another experiment, Sateesh and his co-workers reported anti-diabetic activity (*in vitro*) of the *P. angulata* fruit [48]. Surveys have also indicated that *Physalis angulata* Linneu has powerful anti-inflammatory and immunomodulatory effects, interfering with the cyclooxygenase pathway, lymphocyte proliferation, NO, and TGF- $\beta$  production [51, 52]. Other studies have revealed the anti-inflammatory and immunomodulatory effects of plant-derived physalins B, D, F, G and E. Studies suggest that physalin compounds may be a potent and effective anti-inflammatory agent [13, 53-60].

## 3. Conclusion

Despite the great variety of oral antidiabetics available, there is still no drug able to provide stable, durable and safe glycemic control, to maintain the normal functioning of pancreatic beta cells, and to reduce or prevent the onset of macrovascular and microvascular complications. Some studies have showed the relationship between oxidative stress, hyperglycemia and activation of the NF- $\kappa$ B factor on the pathogenesis of diabetes and its complications. Therefore, considering that some physalin compounds from medicinal plants have showed antidiabetic, antioxidant activity, and have the ability to inhibit NF- $\kappa$ B activation, we suggest that physalins should be considered as a logical solution for the treatment of diabetes and its associated complications.

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