



A new approach for treatment of type 1 diabetes: Phytotherapy and phytopharmacology of regulatory T cells

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ABSTRACT

Type 1 diabetes (T1D), which resulting in hyperglycemia, is an autoimmune disease. This disease characterized by destruction of the insulin-secreting cells of the islets of Langerhans. The CD4 T regulatory cells (Tregs) are important for prevention of disease. Treg cells (defined as CD4+CD25+Foxp3+) have been found to play a critical role in maintaining self-tolerance and preventing autoimmune diseases. Dysfunction and decreased numbers of Tregs may lead to the development of T1D. This review article aimed to report medicinal plants and their nature-based derivatives that are effective on regulation of Tregs activity in diabetes patients. The EndNote software, Web of Science and PubMed databases were searched from 2000 through 2016 for publications on role of Tregs in diabetes. It was found that *Uncaria tomentosa*, *Dioscorea alata*, *Cordyceps sinensis*, *Origanum vulgare*, TJ-48, compound K, azaspirane, lisofylline, and curcumin can promote the function of Tregs in T1D. The reported medicinal plants and their derivatives are rich resources for diabetes treatment. They can be used more extensively for diabetes patients if be evaluated in clinical trials.

Implication for health policy/practice/research/medical education:

The medicinal plants and their derivatives that are effective on regulation of Tregs activity can prevent and treat the diabetes. *Uncaria tomentosa*, *Dioscorea alata*, *Cordyceps sinensis*, *Origanum vulgare*, TJ-48, compound K, azaspirane, lisofylline, and curcumin have been reported to regulate the function of Tregs in type 1 diabetes (T1D). Therefore they can be used in discovering new drugs for prevention and treatment of T1D.

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Introduction

Type 1 diabetes (T1D) is a multifactorial disease associated with a combination of genetic and environmental factors resulting in the loss of insulin-producing β -cells in the pancreas. Numerous studies have reported a decreased T1D risk in the offspring of affected mothers compared to the offspring of fathers with T1D (1). Seroconversion to positivity for beta cell-specific autoantibodies, such

as IAA, GAD A, IA-2A and ZnT8 A, strongly predicts progression to overt type 1 (2). In fact, T1D that leading to hyperglycemia is an autoimmune disease and characterizes by destruction of the insulin-secreting cells of the islet of Langerhans. Although cytotoxic CD8 T cells destroy the insulin-secreting islets, CD4 T regulatory cells (Tregs) play a main role for prevention of the T1D. Voluminous evidence indicates that Tregs have more significant role



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in prevent or pause many forms of autoimmunity (3-5). Generally, patients with T1D have defective CD4+CD25+ Treg cells in their pancreatic lymph nodes, but not in peripheral blood (6). Tregs are essential for sustained immune homeostasis and preventing autoimmune diseases (7). For example, Treg prevention of dendritic cell (DC) activation in lymphoid organs has been used to maintain immune homeostasis and prevent self-reactive T cell priming (8,9).

There is a need to prevent and treat autoimmune diseases, particularly diabetes. Medicinal plants with their various roles for prevention and treatment of diseases can be an effective item in future. They have been frequently used in traditional medicine and studied in different research (10-20). They can be used in most diseases due to their antioxidant effects (21-24). This review article aimed to report medicinal plants and their nature-based derivatives that are effective on regulation of Treg activity in diabetes patients.

Materials and Methods

The EndNote software, Web of Science and PubMed databases were searched from 2000 through 2016 for publications on role of the Tregs in diabetes. The following subject heading terms/keywords and their combinations were used in the search: "diabetes, medicinal plant, herb/herbal medicine, natural compound, phytochemical/herbal drugs, and regulatory T cell/Treg. Each database was searched independently. The retrieved articles from the databases were then analyzed. Abstracts were reviewed based on predefined inclusion and/or exclusion criteria. When necessary, full texts were retrieved to assess study eligibility. Articles were excluded from the study if they were not accompanied with English abstracts. Thus, only the articles directly addressing the effect of the medicinal plants and their derivatives were selected and analyzed. Four articles from the Web of Science and 22 articles from PubMed, were retrieved. Overall, 26 articles were retrieved from both databases and included in the final analysis. After reviewing the abstracts, two articles were excluded from the analysis as they did not meet the inclusion criteria. Twenty-four remaining articles were used to determine the role of the medicinal plants and their derivatives in regulating Tregs. The medicinal plants and their derivatives, *Uncaria tomentosa*, *Dioscorea alata*, *Cordyceps sinensis*, *Origanum vulgare*, TJ-48, compound K, azaspirane, lisofylline, and curcumin have been reported to regulate the function of Tregs in T1D (Table 1).

Phytotherapy and phytopharmacology

Uncaria tomentosa

Uncaria tomentosa is a species native to the Amazon rainforest. It is endowed with immunomodulatory properties and has been widely used around the world (25).

In a study, C57BL/6 male mice were injected with multiple low-dose streptozotocin MLDS (40 mg/kg) and orally treated with *U. tomentosa* at 10-400 mg/kg. The results showed when the animals were treated with 50-400 mg/kg of *U. tomentosa*, a significant reduction in the glycemic levels of diabetic mice detected. Based on the phenotypic analysis the groups treated with higher doses (100-400 mg/kg) showed CD4(+) and CD8(+) T-cell values similar to those observed in healthy animals. The proportion of CD4(+)CD25(+)Foxp3(+) regulatory T-cells were also increased by these same higher doses (26).

Dioscorea alata

Yam or *Dioscorea alata* is a commonly used herb in Chinese medicine for the treatment of clinical diabetes mellitus (27). Following the inhibition of Smad2/3, pSmad2/3, and Smad4, Yam extract dose-dependently (50-200 µg/mL) suppressed beta-HB-induced expression of fibronectin in NRK-49F cells. Against, Smad7 expression was significantly increased. A decrease in alpha-SMA (alpha-smooth muscle actin) and MMP-2 levels but an increase in E-cadherin expression was developed by Yam extract. It appears that Yam extract acts pretty via down regulating the TGF-beta/smad signaling and modulating epithelial-mesenchymal transition expression pathway (28).

Cordyceps sinensis

Cordyceps sinensis as a parasitic fungus has been used widely in traditional Chinese medicines for centuries (29). Although the immunoregulatory effect of *C. sinensis* has been proved in various kinds of diseases, the underlying mechanism remains unclear. Orally-administered *C. sinensis* can reduce the overall incidence of diabetes which is due to an increase in the portion of Treg cells/Th17 in the spleen and pancreatic lymph nodes. In sum, these data imply that *C. sinensis* contributes to the inhibition of diabetes because it is able to modulate Treg to Th17 cell ratio *in vivo* (30). When non-obese diabetic (NOD) mice are treated with *C. sinensis* extract, the disease development slows down. However, in peripheral lymph nodes treatment with *C. sinensis* extract increases the frequency of IFN-gamma and Treg cells producing Th1 cells. On the other hand, *C. sinensis* has no any effects on the natural Treg cell differentiation in thymus (31).

Origanum vulgare

A native plant found to be rich in phenolic and ester compounds (especially rosmarinic acid) is *Origanum vulgare* L. ssp. *hirtum* (Greek oregano) (32). This plant is able to reduce diabetes incidence and preserve normal insulin secretion. In addition, it has been shown that *O. vulgare* by scavenging reactive oxygen and nitrogen species can alleviate the need for the up-regulation of antioxidant enzymes. *O. vulgare* treatment can attenuated

pro-inflammatory response mediated by T helper 17 (Th 17) cells. Also, through the influence on transcription factors and specific signalling pathways, *O. vulgare* enhances anti-inflammatory T helper 2 and (induced) Tregs (33).

TJ-48

TJ-48 is known as a common Japanese herbal medicine which able to decrease Treg population in cancer patients (34). TJ-48 (2.0 g/kg/d) was administered for NOD mice from three weeks to 20 weeks of age. Lymphocyte profiles were investigated every month with FACS. The results showed that lymphocyte infiltrations into islets were suppressed in the TJ-48 group when were compared to the age-matched NOD mice control group. In the NOD mice model, the effect of TJ-48 on decreasing Tregs was less apparent. Beginning T1D in NOD mice was prevented as TJ-48 had inhibited lymphocyte infiltrations into islets (35).

Compound K

Compound (Cpd) K, as a ginseng metabolite, is a synthesized analog of highly unsaturated fatty acids of *Isatis tinctoria* L. (27,36). The therapeutic effect of Cpd K in diabetic mice shows that Cpd K significantly prolongs islet allograft survival with minimal adverse effects after 10 days. Cpd K is also able to reduce the rate of CD4(+) T cells and CD8(+) T cells in spleen and lymph nodes, inhibit inflammatory cell infiltration in allografts, suppress serum interleukin-2 and interferon-gamma secretion, and increase transforming growth factor-beta (TGF-beta) and Foxp3 mRNA expression. Cpd K suppresses proliferation of naive T cells via inducing anergy of T-cell and promoting the generation of regulatory T cells. Moreover, nuclear factor-kappa B (NF-κB) signaling can be blocked by Cpd K. These findings suggest that Cpd K have a probable immunosuppressant effect on islet transplantation (37).

Azaspiranes

Immunosuppressive activity in various kinds of autoimmune diseases such as experimental autoimmune encephalomyelitis and adjuvant-induced arthritis is attributed to immunomodulatory azaspirane compounds (38). Induction of antigen non-specific (natural) suppressor cell activity is found to be the probable action mechanism of azaspiranes. The azaspirane, SK&F 106610 in an animal model of autoimmune (type 1) diabetes (the BB rat) was investigated in this research. A decrease in lymphocytic infiltration of the pancreatic islets (insulinitis) was found in orally-administered SK&F 106610 (15 mg/kg/d) to diabetes-prone BB rats, from age 30 days. There were no changes in splenic T cell, B cell or macrophage subsets, or in proliferative responses to the mitogens lipopolysaccharide and concanavalin A (Con-A). Due

to the relative depletion of T cells, B cells, macrophages and natural killer cells, the suppressor cell activity was enriched in a low density fraction of splenic cells. The results suggest that the SK&F 106610 is able to prevent insulinitis and autoimmune diabetes in BB rats and that these functions can be associated with activation of non-specific suppressor cells (39).

Lisofylline

Lisofylline, is known as a factor to decrease mortality during serious infections. It is a synthetic modified methylxanthine and associated with cancer chemotherapy (40). Lisofylline is able to block Th1 cell differentiation and reduce IL-1beta-induced dysfunction in rat islets. *In vitro*, lisofylline in the presence of IL-1beta inhibits DNA damage of islets and keeps secretion of beta-cell insulin active. *In vivo*, lisofylline suppresses IFN-gamma production, reduces the onset of insulinitis and diabetes, and inhibits diabetes after transfer of splenocytes from Lisofylline-treated donors to NOD mice. However, a simultaneous transfer of splenocytes from both lisofylline-treated and diabetic NOD donors may not prevent the development of diabetes in recipient mice. It appears that lisofylline through suppression of proinflammatory cytokines and reduction of cellular infiltration in islets averts the beginning of autoimmune diabetes in NOD mice, that does not appear to increase the function of Tregs. A therapeutic advantage of using lisofylline is that it can suppress the onset of T1D (41).

Curcumin

Curcumin is a natural polyphenolic antioxidant compound with well-known immunomodulatory and anti-inflammatory effects, can induce the activation of immune cells including T cells (42,43). Also curcumin can inhibit the expression of pro-inflammatory cytokines and chemokines through suppression of the NF-kappaB signaling pathway. When T cells are treated with curcumin initiated via the phosphorylation of PERK and IRE1 develops. In human CD4+ and Jurkat T cells, curcumin is able to increase the expression of the endoplasmic reticulum stress associated transcriptional factors XBP-1, cleaved ATF6alpha-p50 and C/EBP homologous protein (CHOP). Moreover, curcumin can enhance PHA-induced CHOP expression and reduce the expression of the anti-apoptotic protein Bcl-2 in PHA-activated T cells. Finally, the treatment of activated T cells with curcumin induces apoptotic cell death via eliciting an excessive endoplasmic reticulum stress response, reversed via transfection with CHOP-specific siRNA or the endoplasmic reticulum-stress inhibitor 4-phenylbutyric acid. The results suggest that curcumin has a strong effect on both ER stress and mitochondrial functional pathways. Consequently, as a promising therapy, curcumin can be used in the context of Th1-mediated autoimmune diseases (44).

Table 1. Effective medicinal plants on type 1 diabetes through regulatory T cells

Medicinal plants/ phytochemicals	Study design	Main results	Dosage	Ref
<i>Uncaria tomentosa</i> extract	<i>In vivo</i>	Increasing the number of CD4(+)CD25(+)Foxp3(+) regulatory T-cells.	MLDS (40 mg/kg) orally (10-400 mg/kg)	(26)
TJ-48	<i>In vivo</i>	Inhibiting lymphocyte infiltrations into islets	2.0 g/kg/d	(35)
Compound (Cpd) K	-	Reducing the proportion of CD4(+) and CD8(+) T cells in spleen and lymph nodes, inhibiting inflammatory cell infiltration in allografts, Suppressing serum interleukin-2 and interferon-gamma secretion, and increasing transforming growth factor-beta and Foxp3 mRNA expression	-	(37)
Azaspirane (SK&F 106610)	<i>In vivo</i>	Activation of non-specific (natural) suppressor cells	15 mg/kg/d	(39)
Curcumin	<i>In vivo</i> and <i>in vitro</i>	Increasing levels of proinflammatory cytokines (TNF-alpha, IL1-beta and IFN-gamma), reducing level of cellular defense proteins (Nrf-2 and HO-1) and glucose transporter (GLUT-2) along with enhanced levels of signaling molecules of ER stress dependent and independent apoptosis (cleaved Caspase-12/9/8/3)	65 mg/kg 100 mg/kg	(44)
<i>Cordyceps sinensis</i>	<i>In vivo</i>	Increasing in the ratio of Treg cells to Th17 in the spleen and pancreatic lymph nodes (PLNs).	-	(30)
<i>Cordyceps sinensis</i>	-	Increasing the frequency of Treg cells and IFN-gama producing	-	(31)
Lisofylline	-	-	-	(41)

-.: Articles without fulltext.

Implication

T1D is a chronic disorder which associated with generation and activation of autoreactive T cells (45). TGF- β induces the generation of CD4+CD25+FoxP3+Treg cells (46). But, TGF- β plus IL-6 can abolish the generation of induced Treg cells (47,48). Using substances that induce immune tolerance via Treg cells activation or deletion of lymphocyte subsets have been suggested as immunoregulatory strategies for the disease (49). However, the efficiency of some of these approaches have been proved in clinical trials, the risks such as abnormal cytokine release render difficult its adoption (50). In this regards, natural products especially medicinal plants and their derivatives are getting more attention. The immunological tests reveal that some medicinal plants and their derivatives can be used for expansion of Foxp3+ Treg cells. Therefore, a number of phytochemical compounds have been applied to the clinic with important roles in prevention and treatment of T1D.

Conclusion

The present report suggests that medicinal plants such as *U. tomentosa*, *D. alata*, *C. sinensis*, *O. vulgare*, and some of their derivatives such as TJ-48, compound K, azaspirane (SK&F 106610), lisofylline, and curcumin can promote the function of Tregs in T1D. The use of medicinal plants and their derivatives results in reduction in the overall prevalence of diabetes due to the increased ratio of Treg cells. Thus, the extract of aforementioned plants, or their purified derivatives, are valuable to be considered in diabetes treatment and should be used more extensively in clinical trials.

Authors' contribution

All authors contributed to the manuscript equally.

Conflicts of interest

Authors declare that they have no conflicts of interest.

Ethical considerations

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

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