



Review article

The potential benefits of plant cyclitols in the treatment of psoriasis

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ABSTRACT

Introduction: Cyclitols, the hydroxylated cycloalkanes biosynthetically derived from glucose, occur in all living cells and express a broad spectrum of biological activity and participate in many cellular processes including membrane biogenesis, signal transduction, ion channel physiology, osmoregulation, and antioxidation. They have several health-promoting and therapeutic properties such as: improving lipid profile in decreasing of serum triglycerides and total cholesterol, as well as having an insulin-mimetic effect. Moreover, they have antioxidative, anti-inflammatory and anti-cancer properties.

Aim: Revision the literature and analysis of available studies on the potential beneficial effects of cyclitols on inflammatory processes in psoriasis.

Results and discussion: This article discusses the potential anti-inflammatory properties of cyclitols affecting the individual elements of the pathophysiology of psoriatic inflammation: inhibits the expression of MHC class I and MHC class II of mature dendritic cells, resulting in a decrease of IL-12, IL-23, which are necessary to differentiation of naive lymphocytes in Th1 and Th17 line; inhibits NF- κ B, a major signaling pathway activated by TNF- α with reducing of inflammation; inhibits the angiogenic factor VEGF, with reducing epidermal hyperproliferation and enhance of the activity of antioxidants.

Conclusions: The anti-inflammatory effects of cyclitols suggest that they can be used for treatment of psoriasis.

1. INTRODUCTION

Cyclitols, the hydroxylated cycloalkanes, biosynthetically derived from glucose, occur in all living cells and express a broad spectrum of biological activity. They participate in many cellular processes including membrane biogenesis, signal transduction, ion channel physiology, osmoregulation, and antioxidation.¹ They are responsible for the tolerance to abiotic stresses such as salinity, cold or high temperature.^{1,2} Cyclitols are converted in plants via methylation of myo-Inositol, the major and ubiquitous inositol among all live organisms.³ The most common cyclitols are: D-chiro-inositol, D-ononitol, D-pinitol and D-sequoitol.⁴ They are present in seeds of many plant species (legumes, buckwheat, Cucurbitaceae), mostly in legumes and therefore are common constituents of human diet and feed for livestock.⁵ Moreover, free cyclitols present in food or released during degradation of galactosyl cyclitols by bacteria (in digestive tract) can be absorb by endothelial cells indicating some physiological benefits.^{6,7}

Myo-Inositol and other cyclitols indicate several health-promoting and therapeutic properties.⁸ They can improve lipid profile in decreasing of serum triglycerides and total cholesterol after oral using pinitol⁹ and myo-inositol.¹⁰ The mostly studied and well documented is the insulin-mimetic effect of D-pinitol,¹¹ D-chiro-inositol – isomer of myo-inositol¹² and sequoitol.¹³ Myo-Inositol indicates antioxi-

dative,⁶ anti-inflammatory¹⁴ and anti-cancer properties.¹⁵ Cyclitols can improve osteogenesis with bone mineral density, together with D-chiro-inositol, which inhibits osteoclastogenesis.¹⁶ Antioxidant properties have protective effects on the nervous system and developing of Alzheimer's disease.¹⁷ Furthermore myo-inositol has the effect of supporting normal ovulatory activity and sperm motility (Figure 1).¹⁸ The immunomodulatory effects of D-pinitol^{14,19} lead us to suggestion that some cyclitols can be used for treatment of psoriasis. Moreover, plant-derived food containing cyclitols can play an additional role in prevention of development of this disease.

Because of the unsatisfactory efficacy of psoriasis treatment, patients are constantly looking for new formulations, often turning to alternative medicine. Moreover, psoriasis is a systemic disease. Studies indicate its association with metabolic disorders: obesity, diabetes and cardiovascular disease compared with the general population. Psoriasis is an independent risk factor for atherosclerosis.^{20,21} Severe psoriasis can shortens life expectancy about 3–4 years.²² The appropriate treatment of psoriatic patients can prevent the development of comorbidities. The prevalence of the disease and its consequences should be treated as a serious social and economic problem. Cyclitols have anti-inflammatory effect and may be an effective alternative treatment for psoriasis, both topically and systemically, also reducing the risk of developing metabolic disorders in patients.

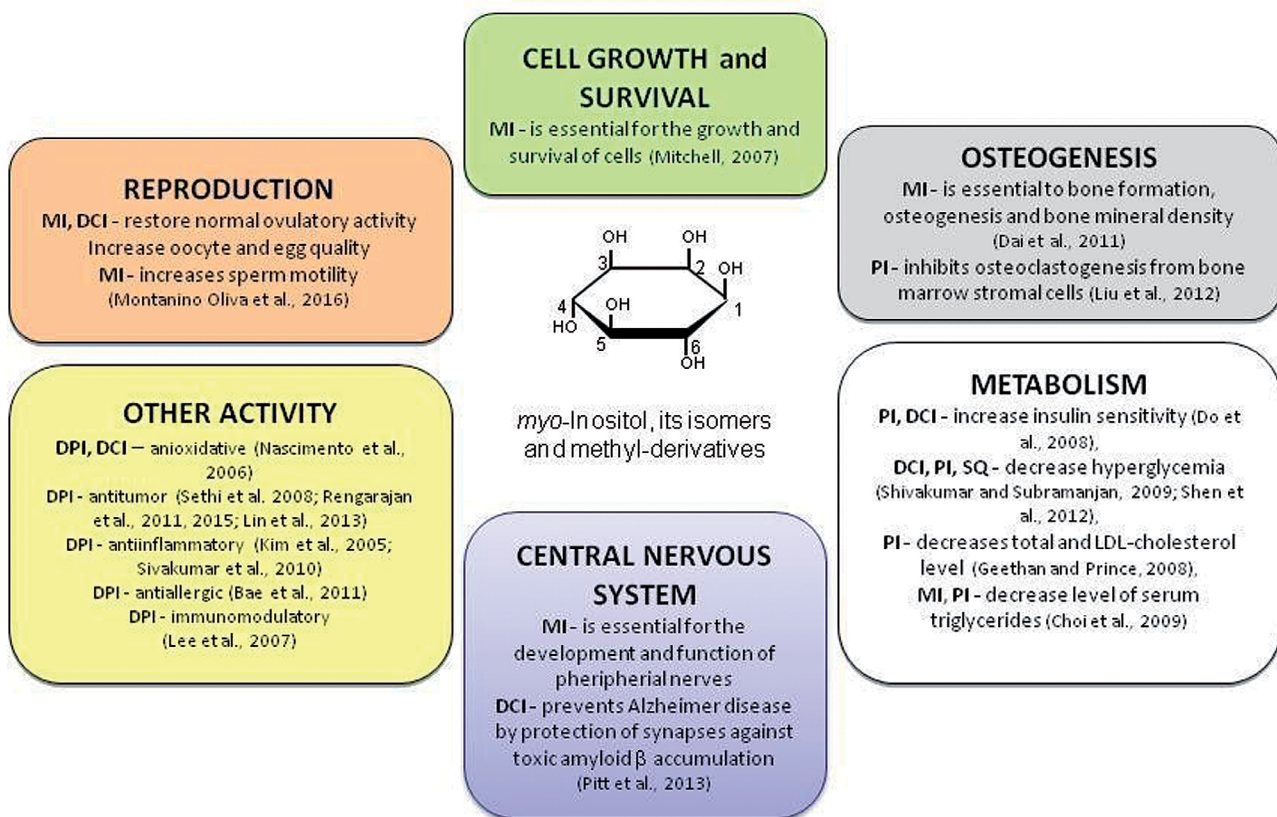


Figure 1. Biological and therapeutic activity of myo-inositol, its isomers and methyl-derivatives. Comments: MI – myo-inositol, PI – D-pinitol, DCI – D-chiro-inositol, SQ – D-sequoitol (by Croze MJ and Soulage CO, ⁸ modified).

2. AIM

The aim of this paper is to review the literature and analyze the data about cyclitols, taking into account their properties hypothetically affecting inflammatory processes of psoriasis.

3. RESULTS AND DISCUSSION

3.1. Cyclitols and Th1, Th17

Psoriasis is a disease mediated by Th1 and Th17. Lymphocytes Th1 secrete IL-2, IL-3, IFN- γ , TNF- α , and Th17 IL-17A, IL-17F, IL-21, IL-22, IL-25, IL-26, TNF- α . These cytokines drive and sustain inflammation, stimulate keratinocytes to excessive 'vicious circle' proliferation mechanism.^{23–25}

D-pinitol inhibits the expression of MHC class I and MHC class II of mature dendritic cells (DCs), resulting in a decrease of IL-12, IL-23, which are necessary to differentiation of naive lymphocytes in Th1 and Th17 line.^{25,26} The scientific results of Lee et al., suggest that the D-pinitol is a potent inhibitor of dendritic cell maturation, thereby blocking activation of IL-12/Th1/IFN- γ and Th17/IL-23 axes – the most important keys in the development of psoriatic inflammation.^{26,27} By weakening the activity of Th1 decreasing production of pro-inflammatory cytokines TNF- α , IL-1 and IL-6 is observed¹⁴. Moreover, D-pinitol affects the growth of expression of the GATA transcription protein 3, which regulates the Th1/Th2 balance.¹⁹

3.2. Cyclitols and proinflammatory cytokines

The main inflammatory cytokine in psoriasis is TNF- α , which stimulates endothelial cells to express adhesion molecules, resulting in the migration of neutrophils to the skin and to produce microabscesses and formation of elongated, dilated blood vessels (loops) in the dermal papillae in psoriasis lesions.²⁴

Nuclear factor κ B (NF- κ B) is responsible for the activation of Th1 and transcription of a numerous genes, which are involved in the pathogenesis of psoriasis, for the production of the proinflammatory cytokines (TNF- α , IL-6, IL-8, IL-12, cyclin D). It is believed that dysfunction of NF- κ B may contribute to the worsening of psoriasis.^{26,28}

Lee et al. observed that D-pinitol inhibits NF- κ B, a major signaling pathway activated by TNF- α with reducing of inflammation.²⁶ Geller et al., noted a significant reduction of TNF- α production by human monocytes, stimulated with bacterial lipopolysaccharide with the ethanolic extract of *Hancornia speciosa*, comprising bornesitol.²⁹

Inhibition of TNF- α by pinitol has a great importance in suppressing the insulin resistance.^{10,30} This is very important because the hyperinsulinemia accompanying insulin resistance, leading to faster development of atherosclerosis, destruct the endothelial cells and macrophages.³¹ Insulin regulates

gene expression of TNF- α in macrophages, exacerbating the inflammatory process, favoring the formation of oxidized low density lipoprotein (ox-LDL). This leads to excessive ox-LDL accumulation as lipid droplets in macrophages, thereby contributing to the formation of foam cells.³² Pinitol, in a dose-dependent manner, inhibits the formation of foam cells and the lipid storage processes in atherosclerotic plaques.^{33,34} Choi et al., demonstrated a significant reduction in TNF- α production, monocyte chemotactic protein-1, IL-1, IL-8 and the metalloproteinase-9 expression, during administration of pinitol into human macrophages.¹⁰ Summarizing, pinitol can inhibit the formation of foam cells, and thus the formation of atherosclerotic plaques. Atherosclerosis is observed in patients with psoriasis because of the common pathogenic mechanism.^{10,30,35}

Chauhan et al., showed immunosuppressive properties of D-pinitol, which inhibits the expression of CD3, CD19, CD4 and CD8 of splenocytes and secretion of proinflammatory cytokines Th1 and Th2, without toxic effect in vitro and in vivo. The immunosuppressive properties of D-pinitol were better in comparison to cyclophosphamide.³⁶

3.3. Cyclitols and apoptosis

Psoriasis is characterized by excessive proliferation and abnormal differentiation of epidermal keratinocytes, leading to parakeratosis. One of the factors responsible for this phenomenon are abnormal apoptosis. The index of apoptotic keratinocytes in the basal layer of epidermis is 0.12% in the normal epidermis, 0.035% in psoriatic papules and 0.31% in the outgoing lesions.³⁷ This confirms the observation that psoriatic keratinocytes are particularly resistant to apoptosis, in psoriatic lesions where overexpressed Bcl-XL, stimulated by TNF- α were found.³⁸ NF- κ B plays an important role in the growth, differentiation and apoptosis of epidermal cells. Its activation is one of the mechanisms of anti-apoptotic, initiated during the differentiation of keratinocytes.³⁹

D-pinitol inhibits NF- κ B, a major signaling pathway activated by TNF- α and reduce inflammation.²⁸ TNF- α effect on keratinocyte proliferation, reducing their sensitivity to apoptosis, stimulates T-cell activity, stimulates the expression of adhesion molecules and other proinflammatory cytokines.⁴⁰ Inhibition of NF- κ B reduces expression of antiapoptotic proteins (Bcl-2 and Bcl-XL).²⁶ Sethi et al., demonstrated that pinitol completely inhibits TNF-induced activation pathway of NF- κ B in various cell types cancer and embryonic.²⁸

3.4. Cyclitols and angiogenesis

An important element supporting the inflammation and hyperproliferation of the epidermis in psoriatic plaque is angiogenesis. Immune cells and activated keratinocytes produce angiogenic factor – VEGF, which maintains the activity of angiogenesis and endothelial cells. Its concentration correlates with the severity of psoriasis.⁴¹ VEGF stimulates mitosis of endothelial cells, vascular permeability, and also contributes to the chemotaxis of neutrophils and activation of monocytes. It is synthesized in keratinocytes, and its in-

creased concentrations in plasma and psoriatic lesions, correlating with disease activity.⁴²

Elevated levels of VEGF which are the main source of adipocytes can be noted in hyperinsulinemia accompanying obesity and metabolic syndrome.⁴³ Therefore, it is possible that hyperinsulinemia can provoke psoriasis or aggravate existing lesions not only by promoting inflammation, but also by stimulation of VEGF secretion.⁴⁴

It has been proven in Sethi et al. research, that D-pinitol inhibits the angiogenic factor VEGF, with reducing epidermal hyperproliferation.²⁸ Inositol has similar properties.⁶

3.5. Cyclitols and oxidative stress

Chronic inflammation in psoriatic lesions affects the formation of reactive oxygen species (ROS) leading to 'oxidative stress'.⁴⁵ They cause damage to endothelial cells, increase permeability of small blood and allow the migration of inflammatory cells. Oxidative stress increases the production of eicosanoids (by activation of phospholipase A) which have proinflammatory and chemoattractant properties.

In psoriasis during the penetration of the neutrophils to the epidermis and for microabscesses formation, the production of large amounts of ROS observed, which cause damage of proteins and lipids and disrupt the integrity of the epidermal barrier.²⁰

Oxidative stress plays a key role in the development of diabetes and its complications due to hyperinsulinemia. ROS production leads to endothelial dysfunction, observed already in the early stages of the disease and atherosclerosis.²¹ Hyperglycemia leads to increased ROS production in mitochondria of endothelial cells. It causes an activation of protein kinase C, increased production of glycation finish products, an increase in the concentration of glucose via activation pathway of the aldose reductase, enhanced activity of fructose-6-phosphate, which contributes to insulin resistance and NF- κ B pathway activation resulting in transcription of pro-inflammatory cytokines. In addition, it decreases the production of vasodilative NO.^{6,46}

In the study of Sivakumar et al., rats with streptozotocin-induced diabetes and secondary renal failure got orally d-pinitol for 30 days with improvements in the laboratory tests (lower the concentration of urea, uric acid, creatinine, glycation finish products and pro-inflammatory cytokines – TNF- α , IL-1, IL-6, NF- κ B).¹⁴ Furthermore, D-pinitol produce substantial weakening of the activity of antioxidants as superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase, with concomitantly decreased oxidation products in the kidneys (lipid peroxides, hydroperoxides and carbonyls protein), which proves its nephroprotective character.^{14,47}

3.6. Clinical experience of cyclitols use in patients with psoriasis

Only inositol is mentioned in the literature to have the beneficial effect in psoriasis. There is only one described case of

the effectiveness of inositol in the treatment of a patient with bipolar disorder and severe psoriasis provoked by lithium.⁴⁸ Interestingly, it is reported that the appearance of psoriasis during the lithium treatment is associated with decreased levels of inositol in the skin.⁴⁹ In addition, besides mood stabilization, relief of psoriasis was achieved, which did not occur after the withdrawal of lithium and using immunosuppressive systemic treatment.⁴⁸ Allan et al., applied the supplementation of inositol in 15 patients with bipolar disorder, who also suffered from psoriasis. Supplementation resulted in a reduction in PASI, despite lithium therapy, including patients who did not use lithium. Therefore it can be concluded that inositol has positive influence on the psoriatic process.⁵⁰

4. CONCLUSIONS

Anti-inflammatory properties of cyclitols may be a good therapeutic options for topical and systemic treatment of psoriasis, as well as reduce metabolically induced inflammation – metaflammation, which leads to more frequent development of metabolic disorders and atherosclerosis in patients with severe psoriasis. However, clinical studies are needed to confirm their beneficial effect on psoriasis.

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