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# Nutraceutical prospective: The synergetic mechanism of action of inositols and resveratrol on metabolic syndrome

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## Abstract

It has been known that inositols function as insulin second messengers and mediate different insulin-dependent processes and are a valid natural, non-pharmaceutical alternative to contrast insulin-resistance as well as associated metabolic syndrome in women with Polycystic ovarian disease (PCOS). Several studies also have shown positive effects of resveratrol in reducing glucose and lipid concentrations in patients. Recently, clinical evidence has proven that an D-chiro-inositol/resveratrol combination has a potential role to play in maintaining metabolic and endocrine health, however no large clinical trials have demonstrated the medical effectiveness of the combination, and the combined mode of action remains poorly discussed. Herein, we address the hypothesis of a synergistic mechanism adopted by D-chiro-inositol and resveratrol in reducing insulin resistance and hyperlipidemia and thus showing a greater therapeutic potential compared to treatment with inositol's alone.

**Keywords:** resveratrol, inositols, insulin and metabolic syndrome

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## Introduction

Metabolic Syndrome (MetS) is a series of symptoms and signs, that recur with singular characteristics (diabetes, obesity, hypertension, ovarian polycytosis, cardiovascular disease)(1, 2). When in MetS, type 2 diabetes predominates, prevalent therapy for glucose intolerance and diabetes is required (3). MetS may occur in pregnancy with prevalence of alterations in glucose metabolism and require proper treatment. Clinical aspects and health benefits of functional foods and nutraceuticals on several metabolic factors have been suggested, however, limited evidence does not allow to draw final conclusions on preventive health strategies and nutritional guidelines that should be encouraged during pregnancy (4). Several studies have shown the positive effects of inositols, D-chiro-inositol (DCI) and Myo-inositol (MI) in reducing glucose and lipid concentrations. In particular studies have demonstrated these effects in prediabetic and diabetic patients in late pregnancy (5-9). Recent research data also suggests the preventive effect of resveratrol supplementation for the prevention of diabetic embryopathologies (10). Other studies have reported that resveratrol in addition to the combination of inositols (DCI + MI) reduce extracellular glucose levels and extra and intra cellular lipid levels in obese pregnant women (11). Thus, the supplementation with resveratrol could be considered a valid treatment in patients with prediabetic and diabetic glucose intolerance (11, 12).

## The central role of insulin resistance in the metabolic syndrome

Insulin resistance (IR) is a pathological condition in which cells, tissues or a whole organism fail to respond normally to the hormone insulin. Consequently, beta cells in the pancreas increase the production of insulin thus leading to excess levels of insulin circulating in the blood. "Compensatory hyperinsulinemia", is the organism's response to low cellular

glucose, a condition that occurs even if the blood glucose levels remain in the normal range. IR plays a central role in 70–80% of obese women and in 15-30% of lean women diagnosed with PCOS, and portrays the pathogenic link between metabolic and reproductive disorders present in this syndrome (13). Clinical manifestations commonly associated with IR and present in PCOS are hyperandrogenism, menstrual irregularities, and other metabolic manifestations (14). Hyperandrogenism, is a condition in which IR increases the production of gonadotropins, especially luteinizing hormone (15). The elevated levels of circulating insulin in women with PCOS, together with high levels of LH, could determine follicular growth arrest. Follicular development and oocyte growth are indicative of oocyte immaturity, which contribute to the onset of an anovulatory phase (16), and poor oocyte quality (17). The compensatory hyperinsulinemia also leads to altered secretion of gonadotropin-releasing hormone (GnRH) and the inhibition of hepatic production of sex hormone-binding globulin (SHBG). This consecutively leads to an increased concentration of circulating free androgens (18). Consistent with these metabolic and hormonal findings associated with the complex metabolic disorders in PCOS, natural insulin-sensitising molecules, such as inositols could possess great therapeutic potential. These molecules could provide benefit by ameliorating reproductive and metabolic outcomes for women with PCOS.

## Inositols in metabolic syndrome

Inositols are a stereoisomeric family, comprised of 9 isomers, myo-, cis-, allo-, epi-, muco-, neo, scylloand, D and L chiro-inositols. Myo-inositol (MI) is found in nature, while D-chiro-inositol (DCI) is a product obtained through the epimerizing hydroxyl of myo-inositol (19). MI and DCI function as insulin second messengers. Thus, inositols can mediate insulin in various insulin-dependent processes (20). MI is converted to an inositolphosphoglycan (IPG) insulin second messenger (MI-IPG) involved in several cellular functions that control the glucose metabolism, such as glucose uptake. DCI is also converted to an IPG insulin second messenger (DCI-IPG), participates in the insulin signaling cascade and is involved in glycogen synthesis (21). Insulin-resistance also increases plasma concentrations of free fatty acid (FFA). The increased levels of FFA is due to increased production from liver and increased mobilization from adipose tissue. Excess of FFA or the reduction of glucose transport activity leads inactivation of pyruvate dehydrogenase (PDH) and other key enzymes. These effects may be a consequence of altered insulin signaling through decreased insulin receptor substrate-1 (IRS-1) associated PI3 kinase activity (22). In fact, restoring inositols levels, with oral supplementations of MI and DCI has been demonstrated to ameliorates insulin-resistance, hyperandrogenism, regularity of menstrual cycles, and oocyte quality in patients with PCOS (23, 24).

## Resveratrol in metabolic syndrome

Resveratrol (3, 5, 4′ trihydroxystilbene) a natural polyphenolic compound is found in and produced by several plants. The richest source of natural resveratrol is a plant known from traditional Chinese and Japanese medicine called Polygonum cuspidatum, (25). Lower quantities of resveratrol can be found in peanuts, grapes, red wine and mulberries (26). Resveratrol has emerged in recent years as a molecule conferring strong protection against metabolic, cardiovascular and other age-related complications, such as neurodegenerative disorders. Given its potential as a novel molecule for the development of drugs that treat metabolic disorders, understanding the molecular mechanisms underlying resveratrol's metabolic modulations is imperative. Resveratrol indirectly activates hepatocellular AMP-activated protein kinase (AMPK). AMPK is the central target for the metabolic effects dependent on resveratrol (27). The crucial mediator of cellular metabolism, AMPK is stimulated by conditions that increase AMP/ATP and ADP/ATP ratios such as physical exercise, ischemia, and glucose deprivation. AMPK is also involved in feeding behavior and entrains circadian rhythms of metabolism (28). Studies have demonstrated the activation of AMPK is depended upon the specific inhibition phosphodiesterase IV (29). In human HepG2 hepatocytes, polyphenols, including molecules such as resveratrol increased phosphorylation of AMPK and acetyl-CoA carboxylase (ACC), its downstream target. This particular activation has been demonstrated to lead to an amplified activity of AMPK with the effectiveness 200 times that of metformin. Metformin, in fact is a first-line medication for the treatment of type 2 diabetes and also a known activator of AMPK. Treatment with metformin improves lipids and macrovascular disease in diabetes (30). This indirectly points out to a novel mechanism of action of resveratrol towards lowering lipids through the activation of AMPK, and thus benefits hyperlipidemia and atherosclerosis specifically in diabetes via AMPK activation (30). It has been reported that resveratrol administration to DOCA-salt hypertensive rats decreased oxidative stress and lipid peroxidation. These effects determined the improvement of the cardiovascular function (31). Furthermore, hyperglycaemia in microvascular endothelial cells leads to mitochondrial dysfunction. Thus, resveratrol-mediated mitochondrial protection could be used to prevent long-term diabetic cardiovascular complications (32). Indeed, resveratrol's effect on metabolic health has received considerable attention in the last decade. Pre-clinical and clinical studies have acknowledged promising results regarding beneficial effects. Some of which have also focused on the capability of resveratrol in preventing and reducing obesity-induced metabolic disturbances. However, future research should focus on dose, efficacy and bioavailability of the molecule in order to guarantee and determine the therapeutic potential is still a necessity.

## The proposed synergetic mechanism of a nutraceutical association- Inositols/Resveratrol

Inositol's mediate different actions of insulin and act to partially restore insulin sensitivity and enhancing glucose availability (21) thus are considered a valid nutraceutical formulation

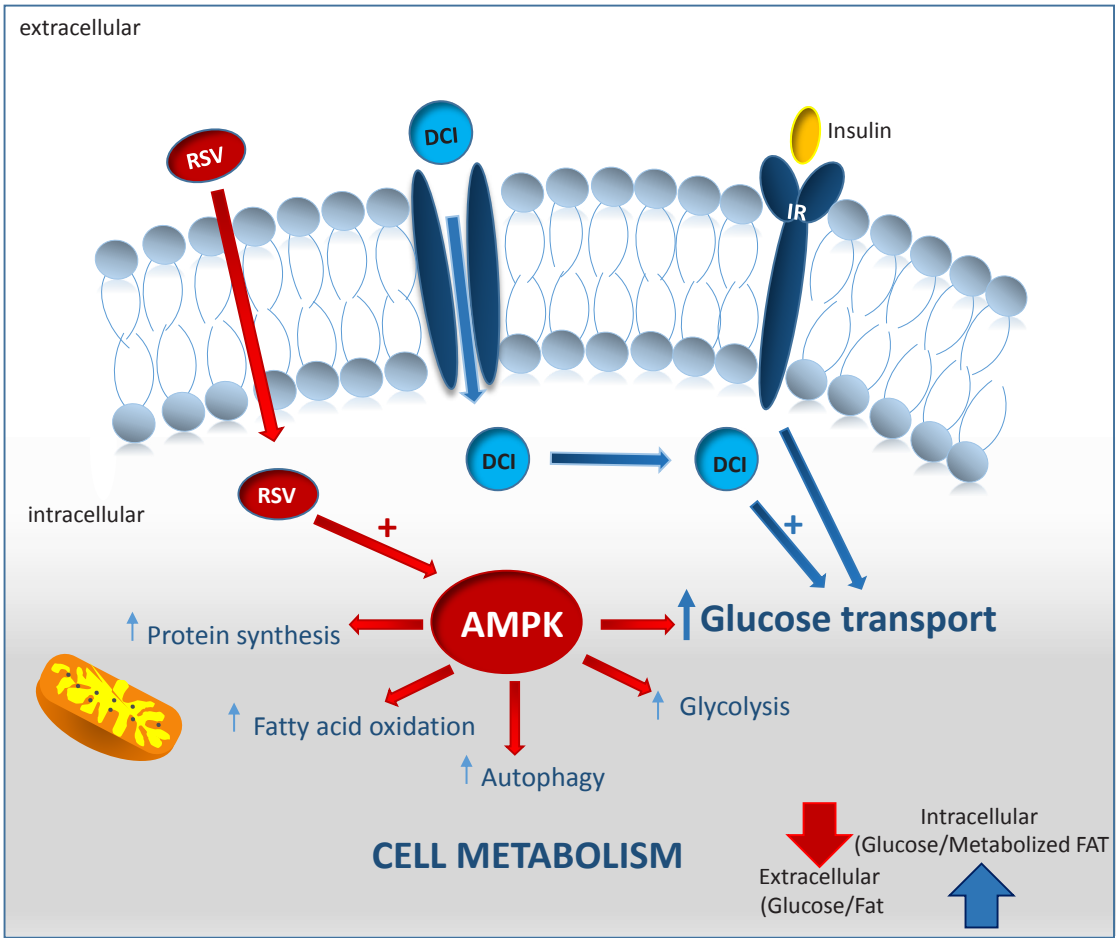


**Figure 1.** The proposed synergetic mechanism of a nutraceutical association- Inositols/Resveratrol.

to contrast insulin-resistance as well as associated metabolic syndrome in women with Polycystic ovarian disease (PCOS). DCI is involved insulin signal transduction pathway and in the stimulation of key enzymes that are sequentially involved in the regulation of glucose metabolism (20). Recently, clinical evidence has proven that an D-chiro-inositol/resveratrol combination has a potential role to play in maintaining metabolic and endocrine health (11). Specifically nutraceutical combination based on Inositols (DCI+ MI) and trans-resveratrol (RSV) was more effective than Inositols alone in reducing total cholesterol, HDL, LDL, triglycerides and glucose blood levels (11). Under these circumstances and given the significant amelioration of serum glucose levels with the association of resveratrol it appeared clear that both DCI and RSV acted upon related metabolic pathways and that the consequences would benefit diabetes and be useful to the patients with risk factors for metabolic syndrome. Herein, we propose a synergistic mechanism adopted by D-chiro-inositol and resveratrol in reducing insulin resistance and hyperlipidemia. Thus showing a greater therapeutic potential compared to treatment with inositols alone. This mechanism amplifies glucose uptake and its metabolism as well as inhibiting fatty acid synthesis and promoting mitochondrial β-oxidation. RSV could facilitate glucose uptake by the translocation of Glucose transporter type 4 (GLUT4) and glycolysis, both mechanisms dependent upon the activation and metabolic activity of AMPK (33). The activation of AMPK also inactivates ACC (acetyl-CoA carboxylase), leading to the inhibition of fatty acid synthesis and the promotion of mitochondrial β-oxidation (34) (**Fig. 1**). Thus, the final result would be less extracellular glucose concentration and fat and on the contrary increased intracellular glucose and metabolized fat in the respiratory chain. The association of inositols with resveratrol, represents a valid, alternative therapeutic approach for the treatment of insulin resistance. Given the central role of IR in the pathogenesis and related metabolic disorders in PCOS a therapy based on inositols and resveratrol could presently as discussed herein provide further benefit.

## Abbreviations

IR-Insulin Resistance
RSV-Resveratrol
DCI- D-Chiro-Inositol
MI – Myo-Inositol
PCO- Polycystic Ovarian Disease
AMPK- AMP-activated protein kinase
GLUT4- Glucose transporter type 4

## Conflict of interest statement

The authors declare that they have no conflicts of interest for the publication of this article.

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