

# Efficacy of Alimentary Components in an Oral Supplement for the Treatment of Insulin Resistance and Boosting Progesterone levels for Female Poly Cystic treatment.

**Rana Neha (Pharmacist)\*, Dr. Sharma Aman (Dermatologist)\*\*, Dr. Taneja Indu (Gynaecologist)\*\*\* with trial inputs from Eric Favre Laboratoire, France**

\* Pharmacist, Pure Natural Products Pvt. Ltd., Faridabad, India

\*\* Dermatologist, Sparsh The Skin Clinic, Gurgaon, India

\*\*\* Gynecologist, Fortis Escorts Hospital, India

DOI: 10.29322/IJSRP.8.8.2018.p80102

<http://dx.doi.org/10.29322/IJSRP.8.8.2018.p80102>

**Abstract-** Resveratrol is nutraceutical with many beneficial therapeutic effects. They're thought to act like antioxidants, protecting the body against damage that can put you at higher risk for things like cancer and heart disease. It has been found that for neurological disorders, cardiovascular diseases, and diabetes, the current clinical trials show that resveratrol is well tolerated and beneficially influenced disease biomarkers. Resveratrol and Alpha-lipoic Acid which appears to act on adiponectin, which is produced by our fat cells and helps us lose fat by improving our insulin sensitivity. Similarly Myo inositol and D-chiro inositol are potent insulin sensitizers which are especially used to treat PCOS. In this review we highlight the issues associated with increased fertility rate in females and symptoms like acne, pimples and aging related problems in PCOS that can be cured with oral supplementation of MI/DCI combination and systemic management of Resveratrol in Insulin resistance and other skin disorders.

Key Words: PCOS, Resveratrol, insulin sensitivity, fertilization, inflammation, Prediabetes, Overweight, AMPK

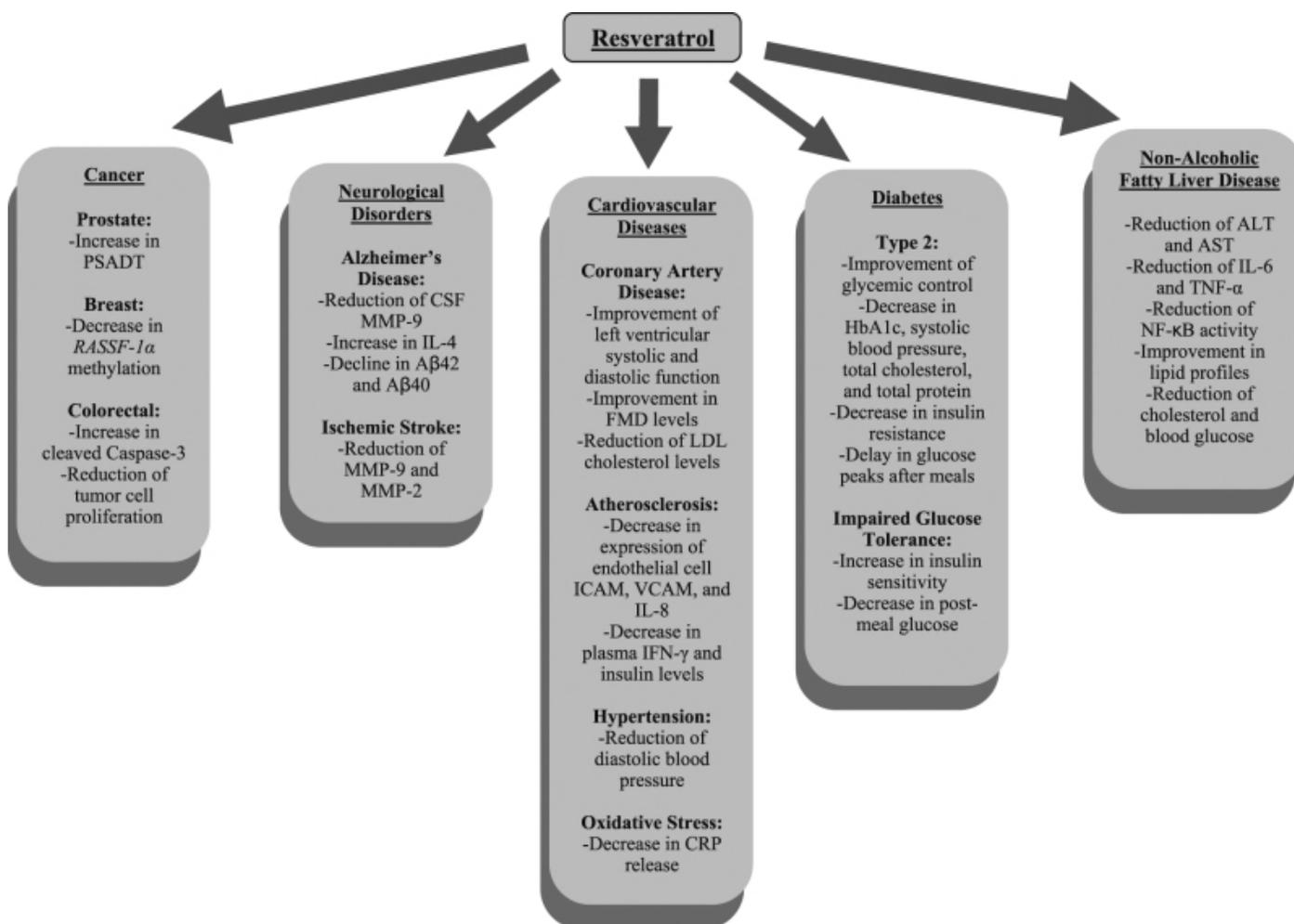
## INTRODUCTION

Resveratrol (trans-3,4',5-trihydroxystilbene), a natural polyphenolic, non-flavonoid antioxidant, is a phytoalexin found in many plants including grapes, nuts and berries, has recently attracted a lot of research attention due to its exciting pharmacological potential. Early research showed that resveratrol was present in large quantities in injured, infected, and ultraviolet-treated leaves. Processed plants products also contain a significant amount of resveratrol; its presence in red wine (concentrations of 0.1–14.3 mg/L) has been suggested as a solution to the “French paradox,” the observation of an unexpectedly low rate of heart disease among Southern French people who consume a lot of red wine, despite their diets being high in saturated fat.<sup>1</sup>

Resveratrol occurs in two isoforms cis and trans – resveratrol, but trans- resveratrol is more biologically active than its cis isoform.<sup>2</sup> Resveratrol alters gut microbiota and influences stem cell proliferation and differentiation. These pleiotropic actions of resveratrol may explain the multitude of its actions and benefits.<sup>3</sup>

Resveratrol is an activator of SIRT1, one of the mammalian forms of the sirtuin family of proteins. SIRT1 deacetylates histones and non-histone proteins including transcription factors. The SIRT1-regulated pathway affects metabolism, stress resistance, cell survival, cellular senescence, inflammation-immune function, endothelial functions, and circadian rhythms.<sup>1</sup>

A study by Bhatt et al. showed that daily resveratrol treatment for 3 months decreased HbA1c levels, systolic blood pressure, total cholesterol, and total protein, improving glycemic control. This suggests that resveratrol could be a possible adjuvant for diabetes treatment.



Dosage with biomarker changes due to resveratrol

Disease Type	Resveratrol dosage	Biomarker Changes
Multiple myeloma	5.0 g	Activate Sirtuin subtype 1 (SIRT-1)
Coronary Artery Disease	10 mg daily	Improved left ventricular function, Lowered LDL Level.
Hypertension	60 mg	Reduced diastolic pressure
Type 2 Diabetes	50 mg twice daily	Decrease insulin resistance, blood glucose, urinary ortho tyrosine excretion.

**Resveratrol in Insulin Resistance**

Diabetes affects 422 million people worldwide, with type 2 diabetes comprising 90% of those cases.<sup>4</sup> Despite increased understanding of this disease and advancements in treatment in recent years, its frequency continues to increase globally, with the WHO projecting that diabetes will be the seventh leading cause of death in 2030. Resveratrol consumption significantly reduced fasting glucose, insulin, glycated haemoglobin, and insulin resistance (measured by using the homeostatic model assessment) levels in individuals with diabetes.<sup>5</sup> A large body of evidence supports the beneficial effects of RSV in the management and treatment of IR, type 2 diabetes, and related complications through a multitude of mechanisms. This review article focuses on the mechanisms of action of RES, the mechanisms leading to improved insulin sensitivity, and its clinical role in the management and treatment of type 2 diabetes.<sup>6</sup>

RSV has anti-hyperglycemic effects in diabetic, which is associated with its stimulatory action on intracellular glucose transport.<sup>7</sup> Recently, it has been demonstrated that RSV enhances adiponectin cellular levels and multimolecularization by upregulation of DsbA-L, which in turn is mediated by the FOXO1 and AMPK signaling pathways.<sup>8</sup>

Study has been conducted among sixty-two patients with type 2 diabetes who received either oral hypoglycemic agents alone or oral hypoglycemic drugs plus RSV 250 mg/d for three months. Those receiving RSV showed an improvement in HbA1c after the completion of three months, suggesting an improvement of glycemic control among patients with type 2 diabetes after supplementation with RSV.<sup>9</sup> Another clinical trial enrolling nineteen patients with type 2 diabetes receiving RSV 2 x 5 mg for four weeks versus placebo, showed a decrease in insulin resistance via a RSV-induced amelioration of oxidative stress<sup>10</sup>

### **Resveratrol in anti-ageing**

Resveratrol has been a subject of intense interest in recent years due to range of unique anti-aging properties including lowered levels of oxidized low density lipoprotein, cyclooxygenase inhibition and most importantly sirtuin activation, which is believed to be involved in the caloric restriction-longevity effect. Several reports suggested that incorporation of resveratrol into dietary supplements or foods be a powerful therapeutic option for anti-aging. Recently, it has been demonstrated that resveratrol extends the lifespan through significantly increasing SIRT1 activity, resulting in the increase of SIRT1 affinity for both NAD<sup>+</sup> and the acetylated substrate<sup>11</sup>

Recently, it has been reported that resveratrol inhibits  $\alpha$ -melanocyte-stimulating hormone signaling, viability, and migration in melanoma cells. According to histological data by the study, resveratrol inhibits melanin synthesis via a reduction in tyrosinase-related protein 2 among the melanogenic enzymes. Notably, resveratrol inhibits mRNA expression of tyrosinase, TRP-1, MITF, and DCT in human melanocytes<sup>12</sup>. The anti-aging effect of CR (Calorie Restriction) has been strongly associated with an increased level and activation of members of the sirtuin family, and also related to other molecular signaling pathways, including peroxisome proliferator activated receptor G coactivator-1 $\alpha$  (PGC-1 $\alpha$ ), adenosine monophosphate activated protein kinase (AMPK), insulin/insulin growth factor-1.<sup>13</sup>

An instrumental study was performed in 50 subjects (25 treated with supplements and 25 with placebo) to identify clinical features induced by chronoaging or photoaging. Product efficacy was evaluated after 60 days of treatment in terms of in vivo and in situ skin hydration, elasticity, and skin roughness levels, systemic oxidative stress levels by plasmatic derivatives of reactive oxygen metabolites and oxyadsorbent tests, and extent of the skin antioxidant pool. After 60 days of treatment, values for systemic oxidative stress, plasmatic antioxidant capacity, and skin antioxidant power had increased significantly. Additionally, skin moisturization and elasticity had improved, while skin roughness and depth of wrinkles had diminished. Intensity of age spots had significantly decreased, as evidenced by improvement in the individual typological angle.<sup>14</sup>

### **EFFECTIVENESS OF MYO INOSITOL IN INSULIN RESISTANCE AND PCOD**

PCOS (Polycystic ovary syndrome) is a complex and debilitating disorder with several health complications including hirsutism, acne, infertility, miscarriage and menstrual dysfunction in which insulin resistance is another common feature of PCOS in both overweight and lean women, and it is often treated with insulin sensitizers like metformin. Currently 1 in 15 women are affected, however, numbers are expected to soar, alongside rising obesity rates.

#### **Natural support to PCOS**

- Weight management
- Blood sugar balance and insulin function normalization
- Hormone balance
- Ovarian health support

Over the last decade, low levels of Myo-inositol, an isomerized and dephosphorylated precursor of glucose-6-phosphate, found in the patients suffering with PCOS which can further led to PMDD (severe form of PMS) has been used more and more as a natural insulin sensitizer.

### Clinical evidence

In a 2009 double blind clinical trial, 42 women with PCOS received Myo-inositol (4 grams daily plus 400mcg folic acid) or placebo (folic acid alone). Results showed that Myo-inositol increased insulin sensitivity, improved glucose tolerance and decreased glucose-stimulated insulin release. In addition, the researchers noted a positive effect on ovulation - 16 out of 23 women in the Myo-inositol group ovulated, compared to 4 out of 19 women in the placebo group. In these women, there was also a 66% reduction of serum total testosterone and a 73% reduction of serum free testosterone concentrations. Cardiovascular markers, systolic and diastolic blood pressures, plasma triglycerides and total cholesterol concentrations also decreased in the myo-inositol group.<sup>15</sup>

Metformin resulted to be the most used and studied drug, even if this molecule is predominantly associated with gastrointestinal discomforts consisting of bloating, nausea, and diarrhea. Interesting and promising results have been obtained focusing on two inositol stereoisomers, such as Myo-inositol (MI) and D-chiro-inositol (DCI), acting like insulin mediators.<sup>16</sup>

### Chromium Polynicotinate in skin pigmentation: Promises and Prospects

Food	Chromium (mcg)
Broccoli, ½ cup	11
Grape juice, 1 cup	8
English muffin, whole wheat, 1	4
Potatoes, mashed, 1 cup	3
Garlic, dried, 1 teaspoon	3
Basil, dried, 1 tablespoon	2
Orange juice, 1 cup	2
Banana, 1 medium	1

Several studies have now demonstrated that chromium supplements enhance the metabolic action of insulin and lower some of the risk factors for cardiovascular disease, particularly in overweight individuals. Chromium picolinate, specifically, has been shown to reduce insulin resistance and to help reduce the risk of cardiovascular disease and type 2 diabetes.<sup>17</sup> Recent study that has been reported (which was presented in 1995 at the annual meeting of the American College of Nutrition) showed dramatic improvements in blood sugar using less than one milligram of supplemental chromium picolinate in a group of women who developed gestational diabetes (that is, they showed symptoms and signs of diabetes only during their pregnancies).

### Conclusion

Our understanding of the pathogenesis of insulin resistance has grown significantly over the past decade. The long-term ability of an association of Resveratrol, a polyphenolic non- flavonoid, tested to significantly improve the undesirable symptoms reported by people with insulin resistance and other skin disorders. We can now hope to reduce the use of metformin and also for the metformin intolerant patients, Resveratrol & its availability in various combinations is proved to be safe & well tolerated option. Initial use for 15 days, in doses of 1 tablet twice a day after that for next 15 days 1 tablet once a day has shown Within 30 days a reduction in serum insulin levels especially PP insulin levels. If combined with other dietary precautions then the response is even better.

Finding also suggests when Resveratrol is combined with other ingredients like ALA, Vitamin B1,B6, B12, folic acid & Chromium Polynicotinate , it works even better at the level of insulin resistance, metabolic balance and bringing homocysteine level in check , whereas Myo-inositol and D chiro inositol on the other hand balances excess androgen prolactin and sex hormone binding globulins(SHBG), it's found both these molecules are very effective in treating PCOD and for both, insulin dependent and non-insulin dependent patients. The benefits demonstrated by clinical research so far have involved myo-inositol in supplemental form rather than from food sources; it is also unlikely that food sources can supply high enough levels to achieve a therapeutic effect.

### References:

1. The therapeutic potential of resveratrol: a review of clinical trials Adi Y. Berman,Rachel A. Motechin, Maia Y. Wiesenfeld and Marina K. Holz <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5630227/>

2. Dose-Dependency of Resveratrol in Providing Health Benefits Subhendu Mukherjee, Jocelyn I. Dudley, and Dipak K. Das <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2990065/>
3. Beneficial action of resveratrol: How and why? Diaz-Gerevini GT, Repossi G, Dain A, Tarres MC, Das UN, Eynard AR <https://www.ncbi.nlm.nih.gov/pubmed/26706021>
4. World Health Organization. Diabetes <http://www.who.int/mediacentre/factsheets/fs312/en/> (2016).
5. Effect of resveratrol on glucose control and insulin sensitivity: a meta-analysis of 11 randomized controlled trials. Liu K, Zhou R, Wang B, Mi MT <https://www.ncbi.nlm.nih.gov/pubmed/24695890>
6. Role of resveratrol in the management of insulin resistance and related conditions: Mechanism of action. Abbasi Oshaghi E, Goodarzi MT, Higgins V, Adeli K <https://www.ncbi.nlm.nih.gov/pubmed/28704113>
7. Resveratrol and Diabetes Natalia G. Vallianou, Angelos Evangelopoulos, and Christos Kazazis <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4160010/>
8. Wang A, Liu M, Liu X, Dong LQ, Glickman RD, Slaga TJ, Zhou Z, Liu F. Up-regulation of adiponectin by resveratrol: the essential roles of the Akt/FOXO1 and AMP-activated protein kinase signaling pathways and DsbA-L. *J Biol Chem.* 2011-286:60–66.
9. Wang A, Liu M, Liu X, Dong LQ, Glickman RD, Slaga TJ, Zhou Z, Liu F. Up-regulation of adiponectin by resveratrol: the essential roles of the Akt/FOXO1 and AMP-activated protein kinase signaling pathways and DsbA-L. *J Biol Chem.* 2011-286:60–66.
10. Brasnyo P, Molnar GA, Mohas M, Marko L, Laczky B, Cseh J, Mikolas E, Szijarto IA, Merei A, Halmai R. et al. Resveratrol improves insulin sensitivity, reduces oxidative stress and activates the Akt pathway in type 2 diabetic patients. *Br J Nutr.* 2011; 106(3):383–389.
11. Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, Prabhu VV, Allard JS, Lopez-Lluch G, Lewis K, Pistell PJ, Poosala S, Becker KG, et al. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature.* 2006; 444: 337–42.
12. Inhibitory Effects of Resveratrol on Melanin Synthesis in Ultraviolet B-Induced Pigmentation in Guinea Pig Skin Taek Hwan Lee, Jae Ok Seo, So-Hyeon Baek, and Sun Yeou Kim <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3936427/>
13. A comparative study of anti-aging properties and mechanism: resveratrol and caloric restriction. Li J, Zhang CX, Liu YM, Chen KL, Chen G. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5630366/>
14. (Resveratrol-procyanidin blend: nutraceutical and antiaging efficacy evaluated in a placebocontrolled, double-blind study Daniela Buonocore, Angelo Lazzarretti, Pedro Tocabens, Vincenzo Nobile, Enza Cestone, Giada Santin, Maria G Bottone and Fulvio Marzatico <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3469214/>
15. Costantino D, Minozzi G et al Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a double-blind trial. *Eur Rev Med Pharmacol Sci.* 2009 Mar-Apr;13(2):105-10.  
<https://www.nutriadvanced.co.uk/news/benefits-of-myo-inositol-for-polycystic-ovary-syndrome-pcos/>
16. A Combined Therapy with Myo-Inositol and D-Chiro-Inositol Improves Endocrine Parameters and Insulin Resistance in PCOS Young Overweight Women Elena Benelli, Scilla Del Ghianda, Caterina Di Cosmo, and Massimo Tonacchera
17. <https://www.ncbi.nlm.nih.gov/pubmed/15208835>

#### Authors Information;

**Author** – Neha Rana, Pharmacist & Production Executive, Purenatural Products Pvt. Ltd., Faridabad, [neha@purenaturals.life](mailto:neha@purenaturals.life), 8586858837

#### Correspondence Author

Dr. Indu Taneja 9818590029, (MBBS, DGO, DNB) Fortis Escorts Hospital, [drindu.taneja@gmail.com](mailto:drindu.taneja@gmail.com),

Dr. Aman Sharma-9971974664 (MBBS, Master of Dermatology, Fellowship In Laser And Skin Surgeon) Sparsh The Skin Clinic, [amanforpeace@gmail.com](mailto:amanforpeace@gmail.com)