Advanced Glucose Discovery™ White Paper

This efficacious diabetic and cardiometabolic supplement is backed by strong clinical evidence. This nutraceutical formulation showed support for healthy blood sugar and hemoglobin A1c levels, healthy insulin function, healthy cholesterol and triglyceride levels, increased production of antioxidants, and numerous other improvements reported below. Formulation is NON-GMO and Halal certified †

As reported in the *European Journal of Biomedical and Pharmaceutical Sciences* in double-blind, placebo-controlled studies, *study results vs. baseline*

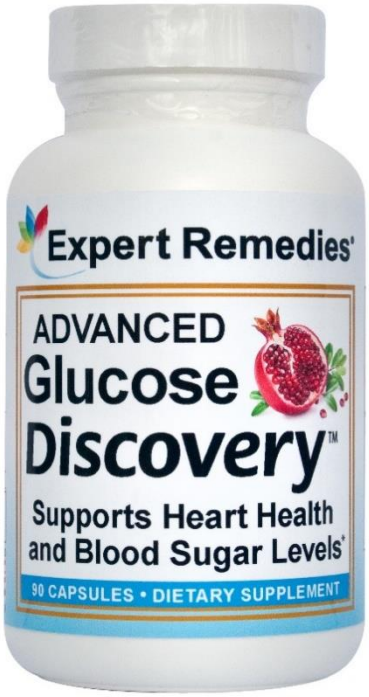
- 215% increase in HDLs (good cholesterol)
- 47% decrease in triglycerides
- 39% decrease in total cholesterol
- 21% decrease in low-density lipoprotein (bad cholesterol)
- 64% decrease in oxidized low-density lipoprotein
- 56% decrease in high sensitivity C-reactive protein
- 57% decrease in homocysteine

***Reference; Pomella® Study 1**

- 49% decrease in fasting blood glucose
- 60% decrease in postprandial blood glucose
- 40% decrease in HbA1c
- 379% increase total antioxidant activity
- 230% increase in GSH peroxidase
- 163% increase in GSH reductase
- 149% increase in SOD

***Reference; Pomella ® study 2**

Bottle Image:



Supplement Facts:

Supplement Facts

Serving Size: 3 Capsules
Servings Per Container: 30

	Amount Per Serving	% Daily Value*
Chromium (as Crominex® 3+)	400 mcg	333%
Proprietary Blend Pomegranate extract (fruit) (Pomella®, standardized to 30% punicalagins), Gymnema extract (leaf) (25% gymnemic acid)	1000 mg	*

* Daily Value not established.

Other ingredients: Bovine gelatin (capsule), rice flour and magnesium stearate.

***Note: Please view our Advanced Glucose Discovery™ promotional video. (Click Link: https://www.youtube.com/watch?v=8BERzgQf1Bc&t=0s)**

This video is available for use as an advertisement

1. Claims

Claim	Substantiation
• With ingredients that support healthy glucose levels already within normal ranges. †	Pomella® study 1, Chromium studies 1-2, Gymnema studies 1-2
• Pomella® supports healthy glucose levels already within normal ranges, after eating.†	Pomella® study 1
• With ingredients that promote healthy blood glucose metabolism.†	Chromium studies 1-2, Gymnema studies 1-2
• Chromium promotes healthy insulin levels already within normal ranges.†	Chromium studies 1-2
• With ingredients that promote healthy insulin function.†	Chromium studies 1-2, Gymnema studies 1 and 3
• Chromium supports healthy insulin-sensitivity.†	Chromium study 1
• Crominex® 3+ has been clinically tested to be more effective than chromium picolinate, chromium polynicotinate, and chromium dinicocysteinate.†	Crominex® study 3
• With ingredients clinically tested to help maintain long-term, healthy glucose metabolism.†	Pomella® study 1, Gymnema studies 1-2, Crominex® study 3-4
• With ingredients that promote healthy hemoglobin A1c levels already within normal ranges.†	Pomella® study 1, Gymnema studies 1-2, Crominex® study 3-4
• Pomella® and Crominex® 3+ have been clinically tested to help	Pomella® study 2, Crominex® study 1-2

maintain a healthy balance of total and HDL cholesterol already within normal ranges.†	
• Pomella® and Crominex® 3+ have been clinically tested to help support healthy triglyceride levels already within normal ranges.†	Pomella® study 2, Crominex® study 1-2
• Crominex® 3+ has been clinically tested to help support healthy blood vessel function.†	Crominex® study 1-2
• Crominex® 3+ has been clinically tested to help support healthy circulation.†	Crominex® study 1-2
• Pomella® has been clinically tested to help increase to increase total antioxidant activity in the body.†	Pomella® study 1
• Pomella® has been clinically tested to help increase levels of the antioxidants glutathione peroxidase, glutathione reductase, and super oxide dismutase.†	Pomella® study 1
• Pomella® supports healthy homocysteine levels already within normal ranges.†	Pomella® study 2
• Pomella® has been clinically tested to help reduce the oxidation of LDL cholesterol.†	Pomella® study 2
• Pomella® supports healthy levels of CRP (an inflammatory marker) already within normal ranges.†	Pomella® study 2

†These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

2. Claim Substantiation

Important Note: This white paper includes studies from European Journals referring to Pomegranate Extract Whole Fruit (PEWF) as a "Drug". This is simply a designation within the European Union where many botanicals are referred to as Drugs. **This product is not a Drug and is not to be marketed or sold as a Drug.**
Note: Pomegranate extracts are dietary ingredients that are exempt from U.S.F.D.A. approval under the October 15, 1994 DSHEA act (Dietary Supplement Health and Education Act). Pomegranate extracts are dietary ingredients and are not drugs.

<u>Pomella® Study 1</u>: Whole Fruit Extract of Pomegranate Resulted in Improvement in T2D and Antioxidative Status*

Diabetes Mellitus Type 2(T2D) is a heterogeneous metabolic disorder, which is characterized by hyperglycemia and cardiovascular complications. Pathogenesis of T2D is absolute or relative deficiency of insulin and insulin resistance. Patients with T2D are highly prone oxidative stress because hyperglycemia depletes natural antioxidants.

Pomegranate, usually consumed as fruit and containing significant antioxidant activity, is identified in Ayurvedic literature as a treatment for T2D. This prompted researchers to investigate whether a Whole Fruit Extract of Pomegranate (PEWF) would have any prognostic effects in patients with T2D.

A randomized, double-blind, placebo controlled, parallel trial[1] was conducted with 40 patients of either gender with T2D and a history of myocardial infarction (MI). All participants were assigned in two groups of 20 each.

One group was under "Add On" therapy of Active Drug which includes the pomegranate extract of the whole fruit PEWF (300 mg twice daily for One Month), matching Placebo of same color, shape and size was used as comparator agent for second group.

This was issued to the Patients initially for 15 days after which they were recalled for clinical valuation, compliance monitoring, adverse effect monitoring if any; and refill for next 15 days.

At the end of one month, the base line investigations were repeated. Patients were followed for next 3 months; on 4-month level of HbA1C was monitored to check the status of T2D.

Results were analyzed and statistically presentation shows that in Z test, the mean level of FSB and PP in both active and placebo shows statistically significance ($p<0.05$).

This indicates that Blood Glucose levels significantly reduced in post drug effects in patients with T2D. The level of TAA, GSH, GPX and SOD were increased, which shows that an antioxidants level in blood has been improved; which indicates the prognosis.

HbA1C level of active and placebo shows statistically significance ($p<0.05$) this indicates that prognostic effect has been seen in patients with T2D. In chi square test, post drug analysis of independent variables found statistically significant ($p<0.05$) in both active and placebo medications.

The present study indicates that the administration of PEWF as supplementation to participants with T2D for one month resulted in an improvement in T2D status and in antioxidative status.

Table number 2, 3 summarizes the Descriptive Statistics for active and placebo medication in both Pre and Post Drug effects. Mean and Standard Deviation of Pre and Post Drug analysis shows the reduction of Bio-chemical markers related to T2D and ROS after active medication. (See Page 6)

Table:2:- Descriptive statistics for PEWF (active) medication in Pre and Post Drug Analysis.

		Pre Dug analysis n=20		Post Drug Analysis n=20	
Sr.no	**Parameters**	**Mean**	**Std. Deviation**	**Mean**	**Std. Deviation**
1	Fasting Blood Glucose (mg/dl)	220.21	63.1	111.98	15.53
2	Postprandial Blood Glucose(mg/dl)	333.18	87.85	132.36	27.86
3	Total Antioxidant activity(mmmol/l)	0.61	0.18	2.92	0.65
4	Glutathion Peroxidase (U/l)	2929.88	1179.82	9673.40	1804.06
5	Glutathion Redctase(U/L)	24.79	4.98	65.30	8.05
6	Super oxide dismutase (U/L)	118.63	18.14	295.95	37.11
7	HbA1C	8.6	1.6	5.2	0.8

n=number of participants.

Table 3:- Descriptive statistics for Placebo medication in Pre and Post Drug Analysis.

		Pre Dug analysis n=20		Post Drug Analysis n=20	
Sr.no	**Parameters**	**Mean**	**Std. Deviation**	**Mean**	**Std. Deviation**
1	Fasting Blood Glucose (mg/dl)	191.85	59.89	129.01	24.10
2	Postprandial Blood Glucose (mg/dl)	226.23	69.44	151.47	32.30
3	Total Antioxidant activity (mmmol/l)	0.75	0.43	0.96	0.32
4	Glutathion Peroxidase (U/l)	2505.26	2084.88	2934.91	2567.07
5	Glutathion Redctase (U/L)	27.50	4.81	34.34	7.40
6	Super oxide dismutase (U/L)	111.33	23.97	130.52	17.55
7	HbA1C	7.8	1.6	6.9	1.3

n=number of participants.

Pomella® Study 2: Total Cholesterol, Serum Triglyceride, HDL, LDL, OX-LDL, hs-CRP and Serum Homocysteine Significantly Improved in PEWF Group*

A randomized, double-blind, placebo controlled, parallel trial[2] was conducted in 100 patients of either gender with myocardial infarction (MI). All participants were assigned in two groups (50 each). One group was under “Add On” therapy of active drug which included pomegranate extract of whole fruit (PEWF) (300 mg twice daily for one month), and the other group received a matching placebo of same color, shape and size.

The Drug was issued to the Patients initially for 15 days after which they were recalled for clinical evaluation, compliance monitoring, adverse effect monitoring if any; and drug refill for the next 15 days.

At the end of the month, the base line investigations were repeated for all participants. Demographic information, clinical and biochemical investigations related to oxidative stress and coronary artery disease (CAD) were done in 4 ml fasting venous blood.

Results were analyzed and showed that in Z test, the mean level of total cholesterol, triglyceride, HDL, LDL, Non-HDL cholesterol and OX-LDL after post drug analysis of PEWF (active) was highly significant ($p<0.05$). This indicated that risk markers for CHD and MI were reduced significantly.

Mean level of biomarkers for CHD and MI like hs-CRP and homocysteine were also significantly improved ($p<0.05$) after PEWF (active). In chi square test, when independent variables were tested, total cholesterol, serum triglyceride, HDL, LDL, OX-LDL, hs-CRP and serum homocysteine were also significantly improved ($p<0.05$) in PEWF group.

Table number 2, 3 summarizes the Descriptive Statistics for active and placebo medication in both Pre and Post Drug effects. Mean and Standard Deviation of Pre and Post Drug analysis shows the reduction in level of biochemical markers related to MI and CHD after active medication.

Table Number 2: Descriptive statistics for PEWF (active) medication in Pre and Post Drug Analysis

		Pre Dug analysis		Post Drug Analysis	
Sr.no	**Parameters**	**Mean**	**Std. Deviation**	**Mean**	**Std. Deviation**
1.	Total Cholesterol (mg/dl)	381.24	81.85	231.10	46.55
2.	Serum Triglyceride (mg/dl)	513.15	110.85	271.04	61.77
3.	HDL (mg/dl)	24.15	4.82	76.07	8.82
4.	Non-HDL cholesterol (mg/dl)	160.8611	10.70955	140.0556	2.82787
5.	LDL (mg/dl)	109.48	13.93	88.07	8.92
6.	OX-LDL (mg/dl)	2.31	0.70	0.84	0.21
7.	hs-CRP (mg/dl)	3.05	0.62	1.35	0.35
8.	Serum Homocystein(mg/dl)	49.35	12.91	21.46	5.47

Table No: 3: Descriptive statistics for Placebo in Pre and Post Drug Analysis

		Pre Dug analysis		Post Drug Analysis	
Sr.no	**Parameters**	**Mean**	**Std. Deviation**	**Mean**	**Std. Deviation**
1.	Total Cholesterol (mg/dl)	314.55	82.02	296.88	79.74
2.	Serum Triglyceride (mg/dl)	426.10	128.93	396.93	115.64
3.	HDL (mg/dl)	26.16	4.48	30.45	5.98
4.	Non-HD cholesterol (mg/dl)	163.83	15.33	156.55	11.43
5.	LDL (mg/dl)	108.3	11.00	101.02	10.64
6.	OX-LDL (mg/dl)	1.91	0.89	1.54	0.77
7.	hs-CRP (mg/dl)	1.94	0.82	1.60	0.68
8.	Serum Homocystein(mg/dl)	25.63	9.8	31.99	9.04

Crominex® 3+ Supports Healthy Glucose, Endothelial, and Cholesterol Levels

Crominex® 3+ is an advanced trivalent chromium complex that has been optimized with a standardized extract of Capros® and PrimaVie®. Crominex® 3+ has been clinically studied to be one of the most efficacious of all the branded Chromium III supplements on the market and, yet, the most economical. Research has shown it helps support healthy glucose levels, healthy endothelial function and healthy cholesterol levels.

Capros® is a super antioxidant (ORACFN of 47,000 µmoles TE/g) and an excellent cardiovascular support product, which is all natural, derived from the edible fruits of Phyllanthus emblica (Indian Gooseberry), organic and non-GMO.

Capros'® efficacy is backed by ten human clinical studies, which demonstrate its efficacy for healthy endothelial function, healthy cholesterol, healthy platelet aggregation and healthy glucose levels.

PrimaVie® is a high quality, clinically studied, purified Shilajit from the Himalayas, containing dibenzo-α-pyrones (DBPs), DBP-Chromoproteins (DCP), Fulvic Acid and over 40 different minerals. Its history of use goes back to The Indus Valley Civilization, 3,000 B.C., where British archaeologists have found evidence of use of Shilajit for anti-aging.

Research supports its use as a mitochondrial energy booster, to increase exercise endurance and overall fitness, upregulating genes for collagen synthesis and improving the bioavailability of coenzyme Q10.

Chromium Study 1

A biologically active form of chromium participates in glucose metabolism by enhancing the effects of insulin. Insulin is secreted by specialized cells in the pancreas in response to increased blood glucose levels, such as after a meal. Insulin binds to insulin receptors on the surface of cells, which activates the receptors and stimulates glucose uptake by cells.

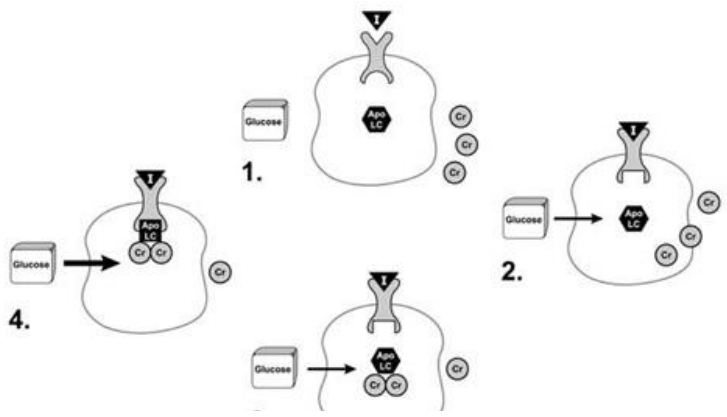
Through its interaction with insulin receptors, insulin provides cells with glucose for energy and prevents blood glucose levels from becoming elevated. In addition to its effects on carbohydrate (glucose) metabolism, insulin also influences the metabolism of fat and protein.

A decreased response to insulin or decreased insulin sensitivity may result in impaired glucose tolerance or type 2 diabetes, also known as non-insulin dependent diabetes mellitus (NIDDM). Type 2 diabetes is characterized by elevated blood glucose levels and insulin resistance.[3]

Chromium Study 2

The precise structure of the biologically active form of chromium is not known. Recent research suggests that a low-molecular-weight chromium-binding substance (LMWCr) may enhance the response of the insulin receptor to insulin. The following is a proposed model for the effect of chromium on insulin action.

A proposed model for the enhancing effects of chromium on insulin activity



First, the inactive form of the insulin receptor is converted to the active form by binding insulin.

The binding of insulin by the insulin receptor stimulates the movement of chromium into the cell and results in binding of chromium to apoLMWCr, a form of the LMWCr that lacks chromium.

Once it binds chromium, the LMWCr binds to the insulin receptor and enhances its tyrosine kinase activity. The ability of the LMWCr to activate the insulin receptor is dependent on its chromium content. When insulin levels drop due to normalization of blood glucose levels, the LMWCr may be released from the cell in order to terminate its effects.[4]

Crominex® Study 1: Statistically Significant Results

A prospective, randomized, double blind trial[5] was undertaken to evaluate the effect of chromium 200 mcg (group 1), chromium 400 mcg (group 2) and placebo (group 3) on endothelial function in 60 patients with type 2 diabetes mellitus (T2DM) and further study its probable mechanism of action.

The chromium was provided in the form of Crominex®, a proprietary combination of chromium chloride (CrCl3.6H2O), *Phyllanthus emblica* fruit extract, processed shilajit and microcrystalline cellulose in a proportion of 1:3:3:3.

Subjects were reviewed for follow up at 4 weeks, 8 and 12 weeks of therapy. At each visit they were evaluated for efficacy and safety. Pharmacodynamic evaluation for endothelial function was conducted at every visit.

Blood samples were collected for evaluation of biomarkers before and at end of treatment. Safety lab investigations for hematological, hepatic and renal biochemical parameters were conducted before and at the end of the study and also as and when required (in case of any adverse drug reaction (ADR)).

Subjects were enquired for the presence of ADR and the same was recorded in the case report form. Compliance to therapy was assessed by pill count method. Results demonstrated several statistically significant effects.

Treatment with Crominex® Showed Substantial Improvements in 6 Crucial Areas

1) significant reduction in reflection index (suggesting improvement in endothelial function) with 200 mcg ($p<0.001$ compared to baseline and placebo) and 400 mcg ($p<0.001$ compared to baseline and placebo, and $p<0.001$ compared to 200 mcg);

2) significant increase in nitric oxide (which promotes circulation) with 200 and 400 mcg ($p<0.001$ compared to baseline;

3) significant increases in glutathione (a critical antioxidant) with 200 and 400 mcg ($p<0.001$ compared to baseline);

4) significant reductions in MDA (a marker for oxidative stress) with 200 and 400 mcg ($p<0.001$ compared to baseline);

5) significant reductions in hs-CRP (an inflammatory marker) with 200 and 400 mcg ($p<0.001$ compared to baseline); and

6) significant reduction in glycosylated hemoglobin A1C with 200 mcg ($p<0.05$ compared to baseline) and 400 mcg ($p<0.001$ compared to baseline).

Table No 7: Effect of treatments on Glycosylated Hemoglobin A1c (HbA1c %)

Parameter	Crominex 200mcg (n=20)		Crominex 400mcg(n=20)		Placebo(n=20)	
	Pretreatment	Post treatment	Pretreatment	Post treatment	Pretreatment	Post treatment
HbA1c (%)	7.14±0.29	7.01±0.36 **$**	7.24±0.29	6.72±0.36 #	7.10±0.30	7.16±0.32

Baseline values between the three treatments were comparable

**$**=$p<0.05$ compared to baseline, # = $p<0.001$ compared to baseline

As seen from table 7, treatment with Crominex 200 mcg and Crominex 400 mcg showed significant reduction in HbA1c levels compared to baseline.

Table No 7A: Comparison of absolute change between the three treatments on Glycosylated Hemoglobin A1c (HbA1c %)

Parameter	Crominex 200mcg (n=20)	Crominex 400mcg (n=20)	Placebo (n=20)
HbA1c (%)	-0.13±0.21#	-0.52±0.20 **$**	0.06±0.18

#=$p<0.01$ Crominex 200 Vs Placebo, **$** $p<0.001$ Crominex 400 Vs Crominex 200 and Crominex 400 Vs Placebo

In addition, there were significant percentage changes in lipid profile after 12 weeks:

Parameter	Crominex 200mcg (n=20)	Crominex 400mcg (n=20)	Placebo (n=20)
Total Cholesterol (mg/dl)	-9.25±3.48	-18.05±6.86	2.95±4.81
HDL-C(mg/dl)	12.03±5.90	27.34±11.74	0.32±6.99
LDL-C(mg/dl)	-16.37±7.47	-27.70±7.85	3.59±4.91
Triglycerides(mg/dl)	-10.07±3.37	-25.41±8.16	0.48±3.60
VLDL-C(mg/dl)	-13.3±5.14	-22.42±6.02	1.04±8.71

1. **TC-** $p<0.001$ Crominex 200mcg Vs Crominex 400mcg, Crominex 200 mcg Vs placebo and Crominex 400mcgVs placebo
2. **HDL-C-** $p<0.001$ Crominex 200mcg Vs Crominex 400mcg, $p<0.001$ between Crominex 400 Vs placebo and Crominex 200mcg Vs Placebo
3. **LDL-** $p<0.001$ Crominex 200mcg Vs Crominex 400mcg, $p<0.001$ between Crominex 200mcg Vs placebo, $p<0.001$ TC 400mcg Vs placebo
4. **TG –** $p<0.001$ Crominex 200mcg Vs Crominex 400mcg, $p<0.001$ Crominex 200mcg Vs placebo and Crominex 400mcg Vs placebo
5. **VLDL-** $p<0.001$ Crominex 200mcg Vs Crominex 400mcg, $p<0.001$ Crominex 200mcg Vs Placebo and Crominex 400mcg Vs placebo

Furthermore, there were no significant changes in safety parameters, including vital, hematological, renal and hepatic functions with all treatments.

In Conclusion, Treatment with Crominex® Produced Significant Improvement in Mean RI Index Compared to Baseline and Placebo.

Reduction in the levels of markers of oxidative stress were observed suggesting improvement in endothelial function in diabetic patients. Both the active treatments showed significant improvement in the lipid parameters.

Treatment with Crominex® 200 mcg and Crominex® 400mcg significantly reduced glycosylated hemoglobin A1c levels compared to baseline and placebo. All the treatments were well tolerated and no patient discontinued the study because of side effects.

<u>Crominex® Study 2:</u> Measuring the Effect on Patients with Metabolic Syndrome

A prospective, randomized, double blind trial[6] was undertaken to evaluate the effect of chromium 200 mcg (group 1), chromium 400 mcg (group 2) and placebo (group 3) in 61 patients with metabolic syndrome.

The chromium was provided in the form of Crominex®, described in Crominex® study 1 above. Subjects were reviewed for follow up at 4 weeks, 8 and 12 weeks of therapy. At each visit they were evaluated for efficacy and safety. Pharmacodynamic evaluation for endothelial function was conducted at every visit.

Blood samples were collected for evaluation of biomarkers before and at end of treatment. Safety lab investigations for hematological, hepatic and renal biochemical parameters were conducted before and at the end of the study and also as and when required (in case of any adverse drug reaction (ADR)).

Subjects were enquired for the presence of ADR and the same was recorded in the case report form. Compliance to therapy was assessed by pill count method. Results demonstrated several statistically significant effects.

Further Treatment with Crominex® Showed 5 Areas of Marked Improvement

1) significant reduction in reflection index (suggesting improvement in endothelial function) with 400 mcg ($p<0.001$ compared to baseline and placebo);

2) significant increase in nitric oxide (which promotes circulation) with 400 mcg ($p<0.001$ compared to baseline;

3) significant increase in glutathione (a critical antioxidant) with 400 mcg ($p<0.001$ compared to baseline);

4) significant reduction in MDA (a marker for oxidative stress) with 400 mcg ($p<0.001$ compared to baseline); and

5) significant reduction in hs-CRP (an inflammatory marker) with 400 mcg ($p<0.001$ compared to baseline). In addition, there were significant percentage changes in lipid profile after 12 weeks:

Parameter	Crominex 200mcg (n=20)	Crominex 400mcg (n=21)	Placebo (n=20)
Total Cholesterol (mg/dl)	-1.39±2.71	-2.75±2.75	1.76±3.80
HDL-C(mg/dl)	0.57±5.63	3.41±5.67	-2.62±6.58
LDL-C(mg/dl)	-1.51±4.43	-12.86±6.41	1.98±3.20
Triglycerides(mg/dl)	-1.05±2.06	-2.92±4.48	-0.12±3.44

1. **TC-** Nonsignificant Crominex 200mcg Vs Crominex 400mcg,$p<0.01$ Crominex 200 mcg Vs placebo and Crominex 400mcgVs placebo
2. **HDL-C-** Nonsignificant Crominex 200mcg Vs Crominex 400mcg, Nonsignificant Crominex 200 Vs placebo and $p<0.01$ Crominex 400mcg Vs Placebo
3. **LDL-** $p<0.001$ Crominex 200mcg Vs Crominex 400mcg, $p<0.01$ between Crominex 200mcg Vs placebo, $p<0.001$ Crominex 400mcg Vs placebo
4. **TG –** Nonsignificant Crominex 200mcg Vs Crominex 400mcg and Crominex 200mcg Vs placebo, $p<0.05$ Crominex 400mcg Vs placebo

In Conclusion, Treatment with Crominex® 400 mcg Produced Significant Improvement in Mean Reflection Index Compared to Baseline.

Reduction in the levels of markers of oxidative stress was observed suggesting improvement in endothelial function in subjects with metabolic syndrome.

Treatment with Crominex® 400 mcg also showed significant improvement in the lipid parameters compared to baseline and placebo.

Note: The following summary discusses two studies, the first of which is "Crominex® study 1" described above. The second study in the summary

below demonstrates the efficacy of Crominex® over other forms of chromium.

<u>Crominex® Study 3</u>: Gauging Its Impact on Endothelial Function and Lipid Profile in Type 2 Diabetics

Crominex® 3+ is a proprietary chromium complex, designed to keep chromium in trivalent state under oxidative conditions and to improve bioavailability of chromium.

A randomized, placebo-controlled, double-blind clinical study[7] was conducted to evaluate the effect of Crominex® 3+ and its individual components in comparison to chromium picolinate, chromium polynicotinate and chromium dinicocysteinate on endothelial function, glycosylated hemoglobin and lipid profile in type 2 diabetics.

The study was done in two parts.

Part I: 60 type 2 diabetic patients of either sex, who are already stabilized on metformin treatment, have been given either 200 mcg or 400 mcg of the Crominex® 3+ per day with the third group receiving a matching placebo capsule for a duration of 12 weeks and patients visited the clinic at 4, 8 and 12 weeks after the first visit.

Pharmacodynamic evaluation for endothelial function was conducted at every visit. Blood samples were collected for evaluation of biomarkers before and at the end of the treatment period.

Part –II: When the results were highly significant, especially with the 400-mcg dose, more patients were included (n=96) to evaluate the individual components of Crominex® 3+ and other branded chromium salts available in the market, at 400 mcg dose level.

Results Showed Crominex® 3+ Significantly Improved Endothelial Function and Increased Levels of Nitric Oxide and Glutathione

It also significantly decreased the levels of malondialdehyde and highly sensitive C-reactive protein at both 200 mcg and 400 mcg per day dose levels, with the results being much more significant at the 400-mcg dose level.

Similarly, the effect on lipid profile was highly significant with improvement of lipid levels from 18-28% and a decrease of half a point in the glycosylated hemoglobin A1c level with the 400-mcg dose.

The results from the Crominex® 3+ group were much more significant than the sum of the results from the individual component arms, indicating that the proprietary chromium complex has significant synergistic activity.

Ranking with Respect to Efficacy—Crominex® 3+ Proved to be the Most Efficacious in the Parameters Tested Among All Chromium Products Studied

Crominex® 3+ was the best, followed by the combination of Phyllathus emblica and Shilajit extracts (the two other components in Crominex® 3+), chromium picolinate, chromium polynicotinate, chromium dinicocysteinate and the placebo, in that order.

In conclusion, Crominex® 3+ improves endothelial function, nitric oxide, glutathione and hs-CRP levels, lipid profile and glycosylated hemoglobin in type 2 diabetics and it appears to have a significant synergistic activity.

Table 8. Effect of Crominex 3+ and placebo on glycosylated hemoglobin (HbA1c)

Biomarker	200 mcg (n=20)		400 mcg (n=20)		Placebo (n=20)	
	Baseline	12 weeks	Baseline	12 weeks	Baseline	12 weeks
HbA1c, %	7.14±0.29	7.01±0.36 $	7.24±0.29	6.72±0.36 #	7.10±0.30	7.16±0.32

Table 9. Comparison of absolute change between the three treatments on glycosylated hemoglobin (HbA1c)

Parameter	200 mcg (n=20)	400 mcg (n=20)	Placebo (n=20)
HbA1c, %	-0.13±0.21#	-0.52±0.20 $	0.06±0.18

# p<0.01 200 mcg Vs Placebo,

$ p<0.001 400 mcg Vs 200 mcg and 400 mcg Vs placebo

Crominex® Study 4: OAD Helps Improve Diabetic Complications Within 2 Months

Chromium chelates/complexes are widely used as nutritional supplements to redress complications of type 2 diabetic mellitus (T2DM) patients.

However, most of these chelates could be susceptible to oxidation into toxic Cr(VI) state. Complexation of Cr (III) with gallo-ellagi tannoids produces a herbochromium supplement (HCrS) that maintains its Cr3+ oxidation state under oxidizing circumstances in vitro. It was tested with conventional oral hypoglycemic drugs [(oral antidiabetic drugs (OAD)] for its beneficial effects in T2DM patients.

A randomized clinical study[8] with three OADs with or without HCrS was carried out in 150 T2DM patients to evaluate the efficacy of the HCrS supplement. The patients were randomized into six treatment groups.

After 60 days of treatment, fasting blood glucose and post-prandial blood glucose (FBG and PPBG, respectively), HbA_{1C}, Hs-CRP, oxidized low density lipoprotein (LDL), and urinary microalbumin levels and other diabetic symptoms were evaluated.

Findings were compared using one-way analysis of variance (ANOVA) with post hoc pairwise comparisons of groups using the least significant difference method. Results showed better control of FBG and PPBG levels were observed in patients receiving HCrS (-12.4 to -16.6%) compared to placebo groups (-3.4 to -9.4%).

There was a 5.5–7.4% decrease in Hs-CRP and LDL levels in patients receiving HCrS, which is better than placebo treated groups. Significant decrease in urinary microalbumin level was observed in patients receiving HCrS (-20.0 to -22.5%) compared to placebo groups (-7.8 to -11.6%).

Significant decreases in diabetic symptoms were observed in patients receiving HCrS (-47.4 to -59.4%) compared to that observed in placebo groups (-18.0 to 34.0%). T2DM patients who took HCrS as an adjunct therapy experienced a better decrease in HbA1c (ranging from -5.2 to -6.7%; mean -6.1%) levels compared to that of only OAD treated groups (ranging from -2.1 to -6.2%; mean -4.1%).

In conclusion, the findings indicate that HCrS with OAD improves overall diabetic complications within 2 months and may be useful in long-term therapy.

<u>Gymnema Extract Study 1:</u> 22 Diabetic Patients Show a Range of Improvements

In an open-label study,[9] 22 type 2 diabetic patients received 400 mg Gymnema extract for 18-20 months, as a supplement to the conventional oral drugs. Subjects showed a significant reduction in blood glucose, HbA1c and other glycosylated blood proteins.

In addition, conventional drug dosage could be decreased.

Five of the 22 subjects were able to discontinue their conventional drug and maintain their blood glucose homeostasis with Gymnema extract alone. The researchers suggested that the results may have been due to beta cell regeneration/repair, as supported by the appearance of raised insulin levels in the serum of patients after supplementation.

<u>Gymnema Extract Study 2</u>: Insulin Requirements Go Down with Blood Glucose and Blood Protein Levels

In an open label study,[10] 400 mg/day Gymnema extract was administered to 27 patients with type 1 diabetes, who were also on insulin therapy.

The results were that insulin requirements came down together with blood glucose and glycosylated hemoglobin and glycosylated blood protein levels. Blood fats also returned to near normal levels with Gymnema therapy.

Type 1 diabetic patients who were on insulin therapy alone showed no significant reduction in serum lipids, glycosylated hemoglobin or glycosylated blood protein when followed up after 10-12 months.

<u>Gymnema Extract Study 3</u>: An Ancient Remedy Finds a Modern Application

Extracts of Gymnema sylvestre (GS) have been used for the treatment of Type 2 diabetes mellitus (T2DM) in India for centuries.

The effects of a novel high molecular weight GS extract, Om Santal Adivasi, (OSA(R)) on plasma insulin, C-peptide and glucose in a small cohort of patients with T2DM are reported here.[11] Oral administration of OSA(R) (1 g/day, 60 days) induced significant increases in circulating insulin and C-peptide, which were associated with significant reductions in fasting and post-prandial blood glucose.

In vitro measurements using isolated human islets of Langerhans demonstrated direct stimulatory effects of OSA(R) on insulin secretion from human ß-cells, consistent with an in vivo mode of action through enhancing insulin secretion.

These in vivo and in vitro observations suggest that OSA(R) may provide a potential alternative therapy for the hyperglycemia associated with T2DM.

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