Polycystic Ovarian Syndrome – PCOS SUPPORT: A Systems-Based Nutraceutical Protocol for Polycystic Ovary Syndrome 2020.

'PCOS Support' including 'Metabolic Balance' and 'Hormone Balance'
–Developed by Life Source

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Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women affecting about 5-6% of women according to a systematic review of meta-analysis of PCOS prevalence, however some studies report up to 10% or more women affected (Ding 2017). PCOS is a not only a dysfunctional ovarian condition of irregular long cycles with scanty periods in the majority (80-90%) or no periods (30-75%) and infertility (40%), and hyperandrogonism (10-75%), but a systemic heterogeneous condition with an extensive landscape of clinical signs and symptoms including weight gain, Metabolic Syndrome and insulin resistance with the risk of type 2 diabetes and cardiovascular disease. 30-70% of women have weight gain/obesity and the more overweight a woman is, the more severe the condition is likely to be. However, non-obese women can also suffer from PCOS. On diagnostic scanning the vast majority of women have polycystic ovaries (90%), but by no means all (Hifsa 2016).

PCOS is life-long condition starting around puberty and continuing post-menopause with no exact cause identified. However, there appears to be a combination of genetic and epigenetic events including the gestational environment and lifestyle factors (Norman 2017). Formal diagnosis is according to the Rotterdam Criteria of 2003 and the Amsterdam Consensus Criteria of 2010, where two out of three criteria are necessary for a diagnosis of PCOS: (a), hyperandrogenism (unwanted hair growth, possible loss of scalp hair and acne), (b), oligomenorrhoea or amenorrhoea (scanty or no menstruation) and polycystic ovaries on ultrasound and (c), excluding other causes of hyperandrogenism). However, systemic mechanisms (auto-immunity and inflammation) may be at play as the drivers of this condition and the ovaries possibly targets of endocrine, immumnological (with inflammatory consequences), as well as molecular mechanisms driven by gene polymorphisms and mutations, may be the systemic mediators of this condition.

Many PCOS sufferers will have insulin resistance. It is thought to be due to increased insulin production, but also reduced insulin clearance by the liver which appears exacerbated by the pro-inflammatory mediators released by fat cells (adipocytes). One such cytokine mediator, tumour necrosis factor alpha (TNFa), has been found to induce insulin resistance through inhibition of intracellular insulin signaling at insulin receptor substrate-1 (IRS-1) which is serine phosphorylated (Hotamisligil 1996). This action causes the tyrosine kinase enzyme which promotes insulin signaling through IRS-1 to be suppressed resulting in insulin resistance. Furthermore, 'the Gatekeeper' the glucose transporters (GLUT-4) are less abundant resulting less optimal glucose uptake by fat cells (Rosenbaum 1993).

The consequences of Insulin resistance are multifold: poor clearance of glucose and a risk of impaired glucose tolerance (IGT) by the age of 40 in PCOS. This is a 'green light' for type 2 diabetes

which occurs in about 15%. High insulin also increases fat deposition and is a growth factor and have cancer causing potential.

The Standard of Care as per the Australian Family Physician 2012 PCOS update, includes the combined oral contraceptive pill (COCP), but this is limited by personal risk factors like smoking, age, weight, metabolic and thromboembolic events. Metformin is offered for insulin resistance and second messenger effects. If a PCOS patient cannot fall pregnant, six cycles of Clomiphene have a 50% chance of success. If clomiphene citrate, metformin or a combination of the two are unsuccessful in achieving pregnancy then gonadotrophin ovulation induction or laparoscopy with ovarian surgery/drilling (LOS) is second line treatment. The pregnancy rate with LOS is as effective as 3–6 cycles of gonadotrophin ovulation induction. Third line treatment is IVF or intra-cytoplasmic sperm injection. (Boyle 2012).
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'The glass half empty' approach is that COCP will worsen insulin resistance, 'ground zero' for PCOS. Where the Pill may establish a regular cycle, it cannot enhance conception, as it is a contraceptive after all. Furthermore, a number of PCOS patients do not tolerate the Pill. Metformin is limited by gastrointestinal symptoms: stomach pain, nausea and vomiting, cramps, bloating, diarrhea, constipation, dizziness, fatigue and long –term vitamin B12 deficiency and possible lactic acidosis. If you have reacted to COCPs or COCPs are contra-indicated and you are intolerant of Metformin the Standard of Care has little to offer. Even if Clomiphene or gonadotrophin ovulation induction or LOS or IVF results in pregnancy, is the biological terrain healthy enough to carry the pregnancy to term and deliver a healthy baby? When clomiphene and metformin have resulted in pregnancy, there is a 15%-20% chance (1 in 5- 6.7) chance of abortion (Dasari 2009).

Whatever success is achieved from the Standard of care approach, appears to occur without any attention directed to the drivers of chronic low grade inflammation in PCOS, being a plethora of cytokines, chemokines and other mediators being elevated and whose parent genes are polymorphic. In an illuminating research study Deligeorgoglou and colleagues found C-reactive protein levels are 96% higher in PCOS patients. Patients with the -308A SNP of the TNFa gene have elevated androgens in comparison with carriers of the -308G. Interleukin 18 (IL-18) is elevated in lean patients, with a further rise in the presence of obesity and insulin resistance. SNPs of IL-1a, IL-1b and IL-6 genes are also associated with PCOS. 4G allele of the PAI-1 4G/5G SNP are at risk of developing PCOS. Other mediators include adhesion molecules, osteoprotegerin, asymmetric dimethylarginine (ADMA), homocysteine and advanced glycation end-products (Deligeoroglou 2012).

This level of penetrance into the machinery of inflammation creates more targets to test for and treat. By understanding the inflammatory mechanisms, we can plan individualised treatments.

Chen et al have found similar single nucleotide polymorphisms in PCOS describing raised pro-inflammatory cytokines, white blood cells, chemokines and multiple endothelial inflammation marker found in PCOS pts. IL-1β is a member of the IL-1 family pro-inflammatory cytokines, crucial moderating element in ovulation, fertilization, embryo implantation and tissue restructuring. IL-1RA minimizes the inflammatory response, but when polymorphic increases inflammation. 6 different SNPs of IL-1Ra are associated with PCOS. In a recent study involving 95 women with PCOS and 45 healthy women as controls analyzed the connection between *IL-1β* and *IL-1Ra* gene polymorphisms and the risk of PCOS. SNPs in these cytokines genes were found in PCOS sufferers and hence may contribute to the risk of PCOS (Chen 2018).

StAR SNPs
However, Chen et al investigates beyond inflammatory SNPs. Is there a signature of genes SNPs, that is unique to PCOS? Chen discusses the following gene SNPs: Steroidogenic acute regulatory (*StAR*),C218T Gonadotropin-releasing hormone receptor (*GnRHR*), Follicle-stimulating hormone receptor (*FSHR*), Fat mass and obesity-associated (*FTO*), Insulin receptor (*IR*) and IR substrate (*IRS*),

Vitamin D receptor (*VDR*), Methylenetetrahydrofolate reductase (*MTHFR*) C677T, Peroxisome proliferator-activated receptor gamma (*PPAR-γ*) nterleukin-1beta/IL-1 receptor antagonist (*IL-1β/ IL-1Ra*).

The StAR (Steroid Acute Regulatory) gene encodes the StAR protein which regulates Cholesterol through the mitochondria of hormonal glandular tissue in the biosynthesis of androgens. StAR has a critical role in transporting cholesterol and in steroidogenesis, changes in the active site of this gene might affect steroidogenesis and causes hyperandrogenemia which is one of the most important PCOS stigmata. In a study of 7 StAR candidates gene SNP only the StAR C218T(Ala218Val) revealed 8/45 PCOS patients were heterozygous as opposed to 1/45 healthy fertile adults. While these are not statistically significant there is a tendency for the heterozygous genotype to be more likely present in PCOS patients with the implications of higher steroidogenesis. However larger studies are needed (Nazouri 2015).

GnRHR SNPs

Another gene of interest described by Chen et al is GnRHR: PCOS patients have high LH; lower FSH compared to the normal range. These changes might be due in part to the dysfunction of the GnRH pulse generator that displays decreased sensitivity to the inhibition of ovarian steroids. GnRHR is expressed on anterior pituitary & many extra-pituitary tissues, including ovary, placenta, breast and cancer tissue.

A study of the relationship between gonadotropin-releasing hormone receptor (GnRHR) gene polymorphisms and outcome of patients with polycystic ovary syndrome (PCOS) undergoing in vitro fertilization and embryo transfer (IVF-ET) was performed. The PCOS group showed more patients with CC+CT genotypes of rs12644822, rs3756159 and rs13138607 than the control group, and CC+CT genotypes and C alleles from three positions enhanced the risk of PCOS. Patients with CC+CT genotypes from three positions exhibited increased serum LH, LH/FSH, testosterone and follicles than those with TT genotypes. The CCC, CCT and TCC haplotypes increased the risk of PCOS, while TCT, TTC and TTT haplotypes lowered the risk. After IVF-ET treatment, patients with CC+CT genotypes of three positions in the GnRHR gene had a lower pregnancy rate than patients with TT genotypes. Logistic regression analysis indicated that CC+CT genotypes rs12644822, rs3756159 and rs13138607 were risk factor for patients undergoing IVF-ET.

The authors demonstrated that CC+CT genotypes rs12644822C>T, rs3756159C>T and rs13138607C>T in the GnRHR gene may contribute to a decreased pregnancy rate for PCOS patients after IVF and embryo transfer (Chen 2017).

FSHR SNPs

Follicle Stimulting Hormone Receptor (FSHR) SNPs and PCOS:

FSH participates in the processes of steroidogenesis, oocyte maturation and follicle development via the FSHR on the surface of granulosa cells in ovary tissue.

The FSHR Asn680Ser variant allele, results in longer menstrual cycles, poor ovulation, reflecting receptor resistance. The *FSHR* gene, which is located on chromosome 2p21, has 10 exons and 9 introns. Only two FSHR SNPs Thr307Ala (919 A > G; rs6165) & Asn680Ser (c.2039A > G; rs6166), on exon 10 which exist in linkage disequilibrium likely associated with risk PCOS.

The Asn680Ser variant allele is associated with a higher basal FSH level, longer menstrual cycles and higher ovarian threshold to ovulation induction, reflecting the difference of receptor sensitivity. Based on the knowledge that PCOS is characterized by follicular growth failure, several studies broadly investigated the association between Thr307Ala and Asn680Ser for FSHR genetic variations with PCOS. Kim *et al*. performed genotyping in 377 women with PCOS and 388 women without PCOS by TaqMan allelic discrimination assay and found that both Thr307Ala and Asn680Ser had a significant association with PCOS (Kim 2017).

FTO gene SNPs

Since up to 70% of PCOS patients suffer from being overweight, s genome-wide association study (GWAS) in 2007 associated the *FTO* gene with body mass index (BMI) and obesity The FTO (FaT mass and Obesity associated protein) gene encodes the FTO protein which alpha-keto-glutarate dependent dioxygenase, a demethylase enzyme and participates in energy metabolism. Hence if the FTO gene is polymorphic and its encoded gene product produces dysfunctional metabolism, then the *FTO* gene might take part in the pathogenesis of PCOS through BMI and/or obesity. Recent studies identified a common SNP (rs9939609) in the first intron of the *FTO* gene with a nucleotide switch where T (thymine) is replaced by A (Adenine) change in PCOS cases. A meta-analysis that included five studies comprising 5010 PCOS cases and 5300 controls indicated the relevance of the rs9939609 A/T polymorphism of the *FTO* gene with PCOS risk and that an allele might be a risk factor for pathology of PCOS. The results of meta-analysis showed that the FTO gene rs9939609 A/T polymorphism was significantly different between PCOS group and control group with the odds ratio for the homozygous variant AA vs the non-variant ('wild-type') OR = 1.74, suggesting that A allele was a risk factor for PCOS susceptibility (Lin 2017).

Insulin Receptor Substrate (IRS) SNPs

Since insulin resistance and raised insulin levels are linked to ovarian dysfunction in PCOS, understanding insulin receptor and insulin receptor substrate (IRS) SNPs may shed etiological insights. A recent meta-analysis to evaluate the relevance between *IR* and *IRS* gene polymorphisms analysed 28 articles comprising 2975 PCOS cases and 3011 controls suggested an association between the Gly972Arg polymorphism of IRS-1 and PCOS in Caucasians. The higher risk of PCOS was related to 972Arg with an OR of 1.74 and between the Gly1057Asp polymorphism of *IRS-2* an OR of 2.14 for PCOS in Asians. However, INSR His 1058 C/T polymorphism may not be implicated in PCOS (Shi 2016).

Vitamin D Receptor VDR SNPs

Vitamin D Receptor (VDR) might be a causal factor for characteristics associated with PCOS such as obesity and type 2 diabetes. 4 SNPs on the VDR gene BsmI A/G (rs1544410), ApaI A/C (rs7975232) and TaqI T/C (rs731236) revealed a higher risk of PCOS in South Indian women. Haplotype frequencies including loci in linkage disequilibrium showed significantly increased frequencies of BsmI G/G (p = .0197), ApaI C/C (p = .048), TaqI C/C (p = .044) genotypes and BsmI G (p = .0181), ApaI C (p = .0092), TaqI C (p = .0066) alleles in patients compared to controls. In addition, the frequency of the 'BsmI G, ApaI C, TaqI C' haplotype was also significantly elevated in patients (p = .0087). Hence BsmI A/G ApaI A/C TaqI T/C of the VDR gene and haplotype may be a risk factor for PCOS in South Indian women.

A 2019 meta-analysis by Shi et al on 1922 PCOS patients and 1665 from 13 studies revealed a statistically significant association between VDR ApaI (rs7975232) polymorphism and PCOS susceptibility (C vs. A: OR = 1.19, 95%CI = 1.06~1.34, P = 0.004) there is a significant association between VDR ApaI (rs7975232) polymorphism and susceptibility to PCOS in the Asian (C vs. A: OR = 1.21, 95%CI = 1.04~1.42, P = 0.016) population, but this association was not found in the Caucasian population. Additionally, a significant relationship between VDR BsmI (rs1544410) variates with PCOS susceptibility in the Asian (G vs. A: OR = 1.27, 95%CI = 1.06~1.53, P = 0.011) population, but this association was not found in the Caucasian population. No association between VDR FokI (rs2228570), VDR TaqI (rs731236), VDR Tru9I (rs757343) and PCOS susceptibility was found (Shi 2019).

MTHFR (Methylene tetrahydrofolate reductase) SNP

MTHFR is the critical enzyme in the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which can donate methyl groups for the re-methylation of homocysteine to methionine. A raised homocysteine levels suggests a MTHFR SNP resulting in inadequate MTHFR

enzyme. Since folate is so important to follicle maturation, assessing MTHFR in PCOS, is important, as there is a relationship of raised homocysteine to PCOS and to insulin resistance (Diwaker 2018).

A Jan 2020 meta-analysis of the MTHFR C677T SNP of 22 studies of 2405 PCOS cases and 2419 controls. Meta-analysis results showed a significant association between the MTHFR C677T polymorphism in Asians with PCOS.

3 genetic models were used: allele model-(whether the nucleotide C or T in the MTHFR C677T SNP were at risk markers for PCOS): OR = 1.40, 95% CI = 1.27–1.53; the dominant model (TT+CT vs CC,); OR = 1.47, 95% CI = 1.17–1.85); the homozygous model (TT vs CC.) OR = 1.90, 95% CI = 1.55–2.32. No associations were found with Caucasians (Li 2020).

Review of homocysteine and folate may be a significant diagnostic marker especially in Asian PCOS patients.

PPARG (Peroxisome Proliferator Activated Receptor Gamma) SNP

The *PPAR-γ* (*PPARG*) gene participates in the management of insulin sensitivity and in lipid metabolism. Obesity and insulin resistance are very common features in PCOS The *PPARG* Pro12Ala polymorphism where Pro is the Proline amino acid from the G allele and Alanine is the amino of the C allele, was examined in 2017 Macedonian study of 100 women and similar matched controls for its potential effect on obesity in PCOS.

The carriers of Ala allele had statistically significant higher values of BMI waist circumference, waist to hip ratio and sum of skin folds than on- carriers in PCOS group. They also had higher fasting glucose, insulin, triglycerides and cholesterol. Hence the *PPARG* Pro12Ala polymorphism might contribute to the risk of PCOS (Zaki 2017).

IL-1β (Interleukin-1beta) and IL-1R*α* (Interleukin 1receptor alpha) SNPs

Up to 70% of PCOS sufferers are overweight and obese. Systemic levels of free fatty acids are elevated in obesity, and these FFAs are primary ligands for Toll-like receptors, central regulators of the innate immune response . Free fatty acids and Toll-like receptors therefore act as a direct link between the systems that regulate obesity and inflammation (Sathapalan 2010).

PCOS is a recognized pro-inflammatory condition, with elevations of circulating inflammatory mediators white blood cells, chemokines and multiple endothelial inflammation markers: CRP, and cytokines (TNF alpha, IL-6 and IL-18) are more likely raised in obese PCOS sufferers. In patients with PCOS circulating levels of tumour necrosis factor *α* (TNF *α*), interleukin (IL)-6, hs-CRP, as well as white blood count (WBC) and neutrophil count have been found to be elevated compared with age- and / body mass index- (BMI-) matched control. However lean persons with PCOS who have visceral obesity may also express higher pro-inflammatory cytokines. This inflammatory process could be the underlying cause of obesity-related comorbidities, including atherosclerosis, diabetes and fatty liver disease (steatohepatosis) (Sathapalan 2010).

IL-1β is a member of the IL-1 family; it is a valid pro-inflammatory cytokine that has a great impact on the physiology of reproduction. IL-1β has also been reported as a crucial moderating element in ovulation, fertilization, embryo implantation and tissue restructuring (93, 94). Another important member of the IL-1 family is IL-1RA; it may be able to minimize the inflammatory response.

In a study of 95 PCOS patients and 45 age matched healthy control subjects were genotyped for IL-1β C-511T, IL-1Ra intron 2 and FABP1A/G. Hormonal and lipid profiles were evaluated for all the

subjects. The IL-1β511 T allele, allele II in intron 2of IL-Ra and the A allele of FABP1 showed significant association with many metabolic features associated with PCOS.

Hormonal and lipid profiles showed significant differences between PCOS and control subjects. Allele and genotype frequencies of IL-1β, IL-1Ra and FABP1 gene polymorphisms did not vary between the control and PCOS group. However, T allele of C[-511]T variant of IL-1β, allele II in intron 2 of IL-1Ra and A allele of A/G variant of FABP1 (rs2197076) showed significant association with many metabolic features associated with PCOS (Rashid 2017).

Since IL-1β plays a role in ovarian development, fertilization and implantation and since IL-1Ra quells an immune response, polymorphisms of these genes and encoded dysfunctions proteins may be in part responsible for anovulation and infertility.

Knowledge of this mechanism, suggests addressing immune dysfunction and inflammation as a target of PCOS management.

From an immunological perspective, auto-immune antibodies are directed to beta cells of the pancreas more than any other organ (islet cell antibodies 56% patients, GAD antibodies 44% and the next closest organ targeted being the thyroid gland with anti-TPO antibodies 27% and the ovaries and Anti-ovarian antibody 27%). Furthermore, insulin resistance drives hyperandrogenism (70%) via second messenger effects, meaning that high serum levels of insulin will be recognized by hypothalamic mechanisms and drive hyeperandroginsim as evidenced by low SHBG (sex hormone binding globulin or testosterone binding protein).

Large amounts of precursor androgens (Androstenedione and DHEAS) driven by central hypothalamic and pituitary mechanisms, result in high testosterone with low SHBG availing more testosterone to be in its active 'free state'. This then drives the symptoms of unwanted hair growth and loss of hair and to a lesser extent acne but from a more sinister perspective high androgens, will further suppress progesterone. Also excess androgens can exacerbate oestrogen excess as the aromatase enzyme which is increased in obesity, inflammation, hyperinsulinemia and in the presence of alcohol and zinc deficiency, will further drive up oestrogens.

Hence expediting the removal of oestrogens may offer a multitude of benefits by downgrading auto-antibodies, reducing the hyperoestrogenic stimulus on ovarian follicles and possibly lowering the potential of endometrial cancer. PCOS patients are proven at risk of suffering from endometrial cancer with a 3 fold increase risk (Barry 2014), but not breast or ovarian cancer.

To date the 'gold standard' of treatment has been treatment with Metformin to manage the insulin resistance component of PCOS and prevent further sinister slide towards Metabolic Syndrome, Type 2 diabetes and cardiovascular disease.

However, a 2016 PCOS review article published in Scientifica suggests, the PCOS mosaic of conditions is far more complex than initially understood. The laboratory stigmata of PCOS includes increased luteinizing hormone (LH) and increased LH/FSH (Follicle Stimulating Hormone) ratio, and increase in amplitude and frequency of pulsatile LH secretion (Hifsa 2016). This is reflected in the deficiency of progesterone, a seldom mentioned feature of PCOS.

Progesterone deficiency and increased estrogen secretion as reflected in low FSH which may lead to secretion of autoantibodies (Azziz 2009). The presence of auto-antibodies signals an immune system dysfunction facet in PCOS -. Some auto-antibodies like ANA (anti-nuclear antibodies) anti-thyroid antibodies-(thyroglobulin antibodies Anti-thyroperoxidase antibodies), beta cell of the pancreas cell antibodies (anti- Islet cell antibodies, GAD antibodies and insulin auto antibodies) and many others are raised in PCOS.

A cardinal feature of auto-immune disease is inflammation, hence inflammation as a consequence of 'unseen auto-immune dysfunction' and further contributed to by the inflammatory cytokines secreted by fat cells, enables the inflammatory process. There are common markers of inflammation which may be marginally raised in PCOS patients like CRP (C reactive protein), IL-18, Monocyte chemoattractant protein-1 [MCP-1], raised lipid peroxidation marker malondialdehyde and reduced glutathione with overall reduced antioxidant capacity suggesting this condition also reflects oxidative stress experienced by target organs. The increase in lipid peroxidation correlates positively with increased BMI, insulin level and blood pressure in PCOS (Duleba 2013).

Other inflammatory markers like Neopterin is raised in PCOS patients. Neopterin is a marker of cellular immunity and oxidative stress, suggesting a low grade chronic inflammatory state (Allenbay 2012).

What is auto-immunity? The inability of the body to adopt self-tolerance and the activation of the auto-reactive system (T cells and B cells) which drive antibodies to attack specific organs (auto-immune thyroiditis) or a multitude of organs (Lupus erythematosus). Trauma, surgery environmental substances including foods or drugs could activate these auto-immune processes.

PCOS patients are 3x more likely to have auto-immune thyroiditis which if unchecked can result in hypothyroidism and further weight gain (Janssen 2004).

So what is the relationship between hormones and auto-immunity? It has been established that oestrogen excess promotes autoantibodies (Angstwurm 1997). Oestrogen increases the production of pro-inflammatory cytokines (IL-1, IL-4, IL-6, and interferon gamma). Endothelial markers may be deranged like PAI-1 and adhesion molecules these could increase the risk of heart disease.

There appears to be specific gene polymorphisms peculiar to PCOS like PAI 4G allele.

From a hormonal perspective, there are more hormonal derangements then just high androgens and high insulin as part of insulin resistance. This may explain why Metformin treatment by itself is often reported anecdotally as not helping patients resolve the full complex symptomatology this syndrome presents.

Hence with this updated understanding, the condition offers more targets for treatment. Testing for and lowering oestrogens raising progesterone provides an opportunity to balance auto-immune drivers as well as reduce unopposed oestrogen effects on tissues (uterus, breast, ovaries and cervix). Since this condition has a large inflammatory component, targeting inflammation by upstream modulation of cytokines may also reduce the pro-inflammatory signals which drive further hormone and tissue dysregulation.

At Life Source, we have searched for nutraceuticals acting on different targets of the HPO axis, while also supporting insulin sensitivity through multiple mechanisms, which through second messenger mechanisms, or directly support healthy ovarian function, regulate ovulation and facilitate pregnancy. Research on these individual ingredients, is suggesting correction of hormonal and metabolic imbalances.

The combination of ingredients in the Metabolic and Hormonal Balance bottle with The PCOS SUPPORT creation, are geared to start the restoration of immune, hormone, inflammatory and anti-oxidative balance.

Many of our clients, have consulted with GPs and endocrinologists and either have noticed no benefit from Metformin or react to Metformin. Others on the Pill, cannot tolerate the Pill (weight

gain, mastalgia, headaches, anxiety, poor sleep). Some women on the Pill, have no improvement, approach us for additional support,

At Life Source, we support whatever conventional program has been prescribed. We also encourage a robust change to a person's diet favouring a ketogenic or Banting style approach. Studies including a recent 2019 review have shown reduction in medications in type 1 and Type 2 diabetes on a controlled ketogenic diet (Bolla 2019). This review highlighted that even Type 1 and Type 2 Diabetic patients with major metabolic dysfunction can not only reduce medications which is remarkable in itself, but also lost weight and fat mass. The vast majority of PCOS sufferers are not diabetic, however, poor attention to diet and exercise and being overweight can promote unfavourables outcomes.

Results of a pilot study of a low carbohydrate ketogenic diet (LCKD) investigated the 6 month metabolic and endocrine effects on overweight and obese women with PCOS. As low carb diets have been shown to reduce insulin resistance (IR), this pilot study assessed women whose BMI >27 kg/m2 and a clinical diagnosis of PCOS were recruited from the community. They were instructed to limit their carbohydrate intake to 20 grams or less per day for 24 weeks. Participants returned every two weeks to an outpatient research clinic for measurements and reinforcement of dietary instruction. There were significant reductions in 24 weeks in body weight (-12%), free testosterone (-22%), LH/FSH ratio (-36%), and fasting insulin (-54%). There were non- significant decreases in insulin, glucose, testosterone, HgbA1c, triglyceride, and perceived body hair.Two women became pregnant despite previous infertility problem (Mayropoulos 2005).

As little as 7% weight loss can restore fertility in obese PCOS patients. Weight loss is well known to reduce androgen levels. Weight loss lowers insulin levels. Lower insulin improves ovarian function (Kiddy 1992).

We encourage a rigorous exercise program from multiple perspectives- Exercise lowers insulin and blood sugar, helps burn fat, creates endorphins, improves sleeps, increases muscles mass, improves mood.

Emotional symptoms are rarely discussed as PCOS symptoms, but for a PCOS sufferer, the emotional vortex that envelops them due to their altered cosmetic appearance, their loss of cycles, inability to have children, but most importantly dealing with inappropriate androgens (and oestrogens) raging through their body, are very common in my experience consulting with hundreds of PCOS sufferers. Symptoms of anxiety, panic attacks, fear, isolationism, loss of self-worth and depression are 'mainstream'.

A number of the ingredients support emotional quiescence.

Action of ingredients:

PCOS SUPPORT Metabolic Balance

PCOS SUPPORT Metabolic Balance uses high quality certified ingredients which have insulin sensitising effects across all ingredients (Myo-Inositol/d-chiro Inositol/Gynostemma and chromium hexanicotinate).

GYNOSTEMMA has been found to lower blood sugar (haemoglobin A1C) by about 20% of its value. It lowers blood sugar and insulin resistance likely through raising AMPK without the potential side-effects of Metformin. AMPK acts as a moderator of liver glucose production and release into the circulation. Less glucose evokes less insulin and less insulin is less fat producing. Less insulin also

lowers male hormone effects through central feedback mechanisms. This assists with less androgenic symptoms. So Gynostemma also known as Southern Ginseng may assist in reducing insulin resistance, lowering blood insulin levels, lowering blood sugar levels, lowering fat mass and indirectly reducing androgenic signs and symptoms.

MYO-INOSITOL (MI) and D-CHIRO INOSITOL (DCI) also have insulin sensitising effects.
In a study of 50 PCOS patients consuming 2g MI, concentrations of luteinizing hormone (LH), prolactin, androstenedione, insulin, and LH/FSH (follicle stimulating hormone) ratio were reduced significantly. Insulin sensitivity improved as well. The duration of ovulation induction was significantly shorter with MI therapy. Treatment with MI had a greater proportion of quality oocytes, which resulted in more PCOS women falling pregnant on MI (10 Vs 4) compared to untreated controls (Artini 2013).

Both forms of Inositol appear to produce better effects than MI alone. Via the enzyme epimerase, MI is converted to DCI. If Epimerase function is defective, then poor DCI production results. DCI may have better insulin receptor sensitizing than MI, whereas MI appear to improve ovarian function better. Their dual use in their unique physiological ratio appears to provide best outcome with weight loss lowering Metabolic Syndrome, improving insulin sensitivity lowering androgens and improving ovarian function. This translates to improving the stigmata of PCOS complex of signs and symptoms.

In a randomized controlled trial of 50 obese PCOS women, MI and DCI (550mg/13.6mg), was found better than 2 g powdered MI, at lowering insulin resistance and weight improving ovarian function and reducing hyperandrogenism. (Minossi 2013).

It is a common held principle to use MI/DCI ratio in a strictly 40:1 ratio as this is the reputed physiological ratio (Benneli 2013). However, the relative concentrations of MI and DCI vary in health and disease and are organ specific. Deficiency of DCI has been found in women with PCOS, pre-eclampsia and Type 2 Diabetes patients. The deficiency of DCI appears related a defect of the epimerase enzyme responsible for converting MI to DCI (Larner 2002, Sun 2002). Epimerase is a NAD, NADH dependent enzyme stimulated by insulin to work but this stimulus is lost in insulin resistance. Hence replacing MI/DCI in a 40:1 'physiological ratio may not be the only ratio that is effective, based on the inability of epimerase to function effectively during insulin resistance and a slightly higher level of DCI may support better DCI induced insulin sensitivity. Furthermore, DCI has beneficial effects on the ovary separate from MI. In a study of PCOS patients pretreated before ovarian stimulation with 500mg DCI bd, or Metformin 850mg bd. DCI improved maturity and quality of oocytes significantly while reducing oxidative stress. Most importantly, there were no associated adverse effects of DCI treatment (Piomboni 2014)

A 2019 study by Marcin Januszewski et al, found women with PCOS treated with MI/DCI 10:1 ratio, had significant body weight reduction and decreases in free testosterone, FSH, LH and insulin levels, and a significant increase of serum SHBG concentrations. Skin conditions improved after 3 months and blood sugar decreased during OGTT after 6 months of treatment. The authors concluded that MI/DCI 10:1 was efficient in improving hormonal and metabolic parameters in PCOS patients.

DCI has been used as the inositol of choice in a number of studies at 600mg per day in lean PCOS patients, reduced insulin and free testosterone and a higher rate of ovulation was noted in spite of the fact that a high concentration of MI is required to ensure healthy oocyte maturation in the ovary (Iuorno 2002).

In a 2016 paper by Bharti Kalra et al the authors discuss that the current evidence is inadequate to provide a definite answer regarding the optimal MI/DCI ratio. They state that: "While MI is necessary for metabolic management, DCI is equally important for menstrual, ovulatory, and cutaneous

hyperandrogenic resolution. Therefore, the ratio may be less important than the absolute concentrations of both inositols. It is clear, therefore, that a high concentration of DCI is necessary to circumvent epimerase deficiency and ensure adequate levels in the ovary. Most pharmaceutical preparations provide very low amounts of DCI, which are insufficient to achieve adequate levels in the ovary. Hence, formulations with relatively higher levels of DCI are preferred." (Kalra 2016)

Following this context, PCOS SUPPORT has slightly higher DCI to accommodate poor epimerase activity in insulin resistance and the likely overall low DCI in PCOS patients as described by Bharti et al.

GYNOSTEMMA PENTAPHYLLUM

A Vietnamese tea leaf 'Giao-Co-Lam Tea' Gynostemma pentaphyllum has been used traditionally for the treatment of diabetes. Gynostemma performs similar functions to Metformin, possibly better and without unwanted side-effects. In a 2012 publication **'**Antidiabetic Effects of Add-On *Gynostemma pentaphyllum* Extract Therapy with Sulfonylureas (SU) in Type 2 Diabetic Patients**',** the author Huyen and colleagues found improved glycemic control in patients treated with SU who received the addition of GP extract, as compared to patients on SU therapy alone. The decrease of HbA_{1C} was approximately 2%-units and of FPG nearly 3 mmol/L over 8 weeks (Huyen. Thus, the glycemic control effect of the combination therapy with SU and GP extract was comparable with that of SU combined with metformin (Hanefeld 2004). However, in the Hanefeld study, Type 2 diabetic patients treated with a sunphonyl urea agent and metformin only reduced HbA1C by 1.36% and fasting glucose by 2.3mmol/L

Huyen et al performed a separate study assessing the effect of Gynostemma pentaphyllum tea against placebo tea and treatment naïve Type 2 diabetes patients. After 12-week treatment, fasting plasma glucose levels totally decreased to an extent of 3.0+/-1.8 mmol/l in the Gynostemma pentaphyllum tea group as compared to a decrease of 0.6+/-2.2 mmol/l in the control group ($p<0.01$). HbA(1C) levels after 12 weeks decreased approximately 2% units in the Gynostemma pentaphyllum group compared to 0.2% unit in the controls ($p<0.001$). Change in Homeostasis Model Assessment-Insulin Resistance between baseline and twelfth week indicated that insulin resistance decreased significantly in the Gynostemma pentaphyllum group (-2.1+/-3.0) compared with that (+1.1+/-3.3) in the control group ($p<0.05$) (Huyen 2010).

In her PhD thesis Vu Thi Thank Huyen found significant anti-diabetic effects & improved insulin sensitivity after 12 weeks treatment with Gynostemma pentaphyllum tea.
Fasting glucose was greater than 3.0 ± 1.8 mmol/l versus 0.6 ± 2.2 mmol/l in control group ($p < 0.01$).
HbA1C levels decreased approx. 2%-units vs 0.2%-unit Controls ($p< 0.001$).
HOMA-IR (baseline -12th week) Insulin resistance was reduced in Gynostemma group (-2.1 ± 3.0) compared with that (+1.1 ± 3.3) in the control group ($p < 0.05$).
As add-on therapy to antidiabetic drug, Gynostemma tea further improved glycemic control and this improvement was sustained over 12 weeks (Huyen 2011).

Gynostemma's ability to lower blood glucose appears multi-targeted. Studies have reported triterpene compounds especially dammaranes which specifically inhibit Protein Tyrosine phosphatase -1B (PTP-1B) (Hung 2009); (Zhang 2012). PTP-1B is negative modulator of the insulin receptor between the trans-membraneous domain and the insulin receptor substrate 1 (IRS-1a). PTP-1B is regarded as a possible therapeutic target against metabolic syndrome, obesity and diabetes (Thiebaut 2016).

Gynostemma also promotes AMPK (5' adenosine monophosphate activated protein kinase), a key regulator of insulin sensitivity, glucose control, energy and lipid metabolism. Activation of AMPK

improves metabolic abnormalities associated with metabolic diseases including obesity and type-2 diabetes. Type 2 diabetics has been found to have low AMPK levels. PCOS patients also have low AMPK. Gold standard treatment for PCOS uses Metformin which increases AMPK and lowers insulin resistance and through second messenger effects should regulate hyperandrogenism. However, the drug can cause a host of side-effects most commonly gastro-intestinal symptoms but also mineral and specific vitamin malabsorption.

Gynostemma pentaphyllum has been shown to activate AMPK via two dammarane saponins within its leaf, Damulin A and Damulin Bi, which increased beta oxidation of fat and improved blood glucose uptake by enhancing GLUT-4 translocation to the plasma membrane. (Nguyen 2011).

A recent 2019 study reported on the anti-obesity effects of Gynostemma pentaphyllum. Rats fed a high fat diet as well as an extract of Gynostemma pentaphyllum were able to produce more AMPK than rats fed a normal diet, down regulating many fat promoting co-factors and activated SIRT-1 (Lee 2019). SIRT-1a has multiple biological regulatory functions and a key longevity factor.
Hence Gynostemma as a single player, can improve energy, metabolism, burn fat, improve blood sugar, improve insulin resistance, reduce Metabolic Syndrome severity through a few mechanisms including increased AMPK, and through second messenger effects on the GLUT-4 transporter enhancing glucose uptake, the burning of fat and the inhibition of PTP-1B.

CHROMIUM

Chromium is an essential mineral having a beneficial role in the regulation of insulin action and its effects on carbohydrate, protein and lipid metabolism. Chromium is an important factor for enhancing insulin activity. Studies show that people with type 2 diabetes have lower blood levels of chromium than those without the disease. Chromium lower insulin and lowers some of the risk factors for cardiovascular disease, particularly in overweight individuals. 200-1000 mcg/day lowers blood sugar (Diab Educ 2004).

Chromium supports AMPK which in turn promotes the translocation of the GLUT-4 transporter to the cell surface. Chromium also decreases the activity of PTP-1B (protein tyrosine phosphatase 1-B) which down regulates insulin signaling. By blocking PTP-1B, chromium supports insulin signaling. Chromium also acts as an antioxidant reducing the oxidation of fats (lipid peroxidation) as well as reducing glycosylation of proteins (oxidative damage through exposure of proteins to toxic levels of glucose). Chromium increases glutathione the body's principle antioxidant as well as glutathione peroxidase.

Chromium works at the beginning and the end of insulin signaling-at the beta sub-unit of the Insulin Receptor, blocking JNK at IRS-1 and PTP-1B trying to stop insulin signaling, and at the 'last piece in the puzzle', promoting GLUT-4 transposition to the cell surface to allow glucose into the cell (Hua 2011).

In a study of chromium supplementation in a group of PCOS adolescents, there was a 85% (29/35) reduction in oligo/amenorrhea simply taking 1000mcg chromium picolinate a day. versus 11/35 (31%) in controls. There was a significant reduction in mean ovarian volume, total follicular count and free testosterone was observed. No significant improvement in acne or hirsutism was noted. The authors considered supplementation with chromium to adolescents with PCOS a promising treatment option (Amr 2014).

A 2017 systematic review and meta-analysis of 7 RCTs shows that using chromium picolinate supplementation has beneficial effects on decreasing BMI, fasting insulin and free testosterone in

PCOS patients. The results indicated that chromium supplementation had a beneficial effect on BMI with effect size: -2.37 (kg/m^2), and free testosterone concentration with effect size=-0.52 (pg/mL. Chromium reduced fasting insulin: -0.86mIU/ml, No beneficial effects on reducing total testosterone, FG score, DHEA, FSH and LH (Fazelian 2017).

In a prospective, randomized, double-blind, placebo-controlled trial, eight weeks of chromium supplementation among PCOS women had favorable effects on markers of insulin metabolism markers of insulin metabolism and lipid concentrations. Chromium supplementation in women with PCOS resulted in significant decreases in serum insulin levels (-3.6 ± 7.4 vs. +3.6 ± 6.2 µIU/ml, $p < 0.001$), homeostasis model of assessment-insulin resistance (HOMA-IR; -0.8 ± 1.6 vs. +0.9 ± 1.5, $p < 0.001$), homeostatic model assessment-beta cell function (HOMA-B; -15.5 ± 32.3 vs. +13.6 ± 23.1, $p < 0.001$), and a significant increase in quantitative insulin sensitivity check index (QUICKI) score (+0.02 ± 0.03 vs. -0.008 ± 0.02, $p = 0.001$) compared with the placebo. In addition, a trend toward a significant effect of chromium supplementation on decreasing serum triglycerides (-12.4 ± 74.4 vs. +15.2 ± 32.4 mg/dl, $p = 0.05$), very low-density lipoprotein-cholesterol (-2.5 ± 14.9 vs. +3.0 ± 6.5 mg/dl, $p = 0.05$), and cholesterol concentrations (-8.6 ± 21.9 vs. +0.7 ± 22.4 mg/dl, $p = 0.09$) was seen (Jamilian 2015).

Chromium has also been studied in the management of depression in PCOS sufferers. The mechanism of antidepressant activity of Chromium involves noradrenergic, dopaminergic and serotonin signaling (Piotrowska 2019). The potential anti-depressant mood altering effect of chromium adds another facet of accomplishment to this 'talented' mineral in the management of PCOS.

Our formula uses the polyniconinate carrier, rather than the picolinate form. There was concern in the past that picolinates may cause chromosomal abnormalities. In spite of that seemingly not proven correct, industry uses the other carriers like hexanicotinate or polynicotinate which maybe superior to picolinates with regard to insulin sensitivity.

PCOS SUPPORT-Hormone Balance

CHASTE TREE

Women with PCOS often have intermittent or no ovulation, irregular cycles and poor fertility. Anovulatory PCOS women are unlikely to produce adequate progesterone. Progesterone deficiency is often 'overlooked' in PCOS patients. Progesterone deficiency, with oestrogen, androgen, insulin and glucose excess can induce a sustained hypothalamic signal (Gonadotrophin Releasing Hormone [GnRH]) level to the pituitary causing disturbed pituitary signaling to ovaries resulting in a disturbed cycle, with poor ovulation, irregular length of cycle and a risk of infertility.

Supporting progesterone production may assist in increasing fertility. Progesterone is made from the corpus luteum with small contributions from the adrenals. Is it possible to increase progesterone levels?

Interestingly progesterone deficiency is rarely directly discussed in PCOS but implied. A hormonal marker of PCOS is the FSH/LH ratio. Chronic Low FSH/LH implies disturbed hypothalamic signaling to the pituitary, with raised quantity (amplitude) and frequency of the signal (Gonadotrophin Releasing Hormone [GnRH]) from the hypothalamus to the pituitary (Roland 2014). Studies have repeatedly shown increases in LH levels, LH/FSH ratio, and LH pulse frequency and amplitude in women with PCOS (Waldstreicher 1988).

A high LH surge in healthy women releases the egg from the mature follicle with subsequent increase in progesterone. However, this does not occur in PCOS, as the follicle do not mature through suppressed FSH and the sustained high LH causes the production of androgens by the theca cells of the ovaries (Gilling-Smith 1994). High androgens drive further GnRH.

To assist with ovarian regulation, the complimentary PCOS Metabolic Balance contains Myo-inositol (MI) and D-Chiro Inositol (DCI) complex. MI and DCI have been shown to support ovarian function. PCOS SUPPORT Hormone Balance also contains Chaste Tree (Chaste Berry) to assist the production of progesterone.

This imbalance of high oestrogen, low progesterone and high androgens are the effect and also cause of ongoing endocrine dysfunction in PCOS.

A chronic low FSH/LH ratio suggests a more disorganized hormonal balance with low progesterone and high oestrogen, a toxic combination for the ovaries, uterus, weight management with resultant weight gain, worsening insulin resistance, thyroid dysfunction and auto-immune dysfunction.

A monograph on chasteberry found increased progesterone levels in blood, the lining of the uterus and vaginal secretions. (Brown 1994.)

A double blind, placebo-controlled study of the effects of Chaste Tree, green tea, L-arginine, vitamins (including folate) and minerals, on progesterone levels, basal body temperature, menstrual cycle length, pregnancy rate and side-effects, found Chaste Tree improved all parameters and significantly increased fertility. Chaste Tree is thought to increase luteinizing hormone which is the stimulus to the ovaries to release progesterone (Westphal 2005).

Positive effects for V*itex agnus-castus* in oligo/amenorrhoea and infertility was demonstrated in three placebo controlled RCTs reported in a 2014 research article report by Susan Arentz et al.

An extract of Chaste Tree was as effective as the pharmaceutical drug Bromocriptine in lowering prolactin on one study and all three and showed a longer luteal phase improved regularity of cycles (Arentz 2014). In a randomized comparative effectiveness trial 80 women (40 with hyper-prolactinaemia and 40 with cyclical mastalgia were given 40mg commercial Vitex agnus castus or bromocriptine on day 5-8 of cycle. Mean prolactin before vitex was 946mIU/L and 526mIU/L after treatment. Bromocriptine group dropped from 885mIU/L to 472mIU/L. The Vitex treatment reduced prolactin as much as Bromocriptine (56% vs 53%) and was slightly superior. There were no adverse reactions in the vitex group. There were adverse reactions (nausea and vomiting in 12.5% in the Bromocriptine group (Kilicdag 2004)

In a study including of 96 women with menstrual irregularity and infertility, menstrual cyclicity was significantly improved for women treated with *Vitex agnus-castus* (Mastodynon® 32.4mg per day for three months) compared to placebo In a subgroup of women with luteal insufficiency (n = 21) there were significant improvements in clinical parameters in the treatment group compared to placebo (p = 0.023). 15 women conceived in the treatment group compared to 8 in placebo group in the first 3 months of treatment. After 2 years there were 21 more pregnancies with 2 miscarriages – evenly spread over active and placebo group (Gerhard 1998).

Another study, including 67 women with poor fertility showed improved menstrual cyclicity for a sub-group of women with oligomenorrhoea following treatment with *Vitex agnus-castus* (Phyto-Hypophyson® 7.5 ml per day) compared to placebo, (p = 0.023) (Bergmann 2000).

A third study including 52 women with hyperprolactinaemia demonstrated improved menstrual cyclicity by an increased average number of luteal days from 3.4 days (±5.0) to 10.5 days (±4.3) (p <

0.005) following treatment with *Vitex agnus-castus* (Strotan® 20 mg per day) for three months (Milewicz. 1993)

Addressing progesterone therefore becomes an interesting and supportive factor in attempting to organize hormone function to improve symptoms in PCOS sufferers. Positive effects for Chaste Tree (Vitex agnus-castus) in women with prolonged cycles (oligomenorrhoea) and also no cycles (amenorrhoea) and infertility have been alluded to in the above reports By improving progesterone in a PCOS sufferer there appear to be benefits as every point of the hypothalamic /pituitary/gonadal axis, with opportunities for improved cyclicity, improved fertility, improved mood, downregulation of oestrogens and androgens..

CYPERUS ROTUNDUS

Cyperus rotundus known as Nut Grass has been found to exhibit anti-oestrogenic properties from its tuber, by inhibiting the enzyme aromatase which converts the androgenic hormones Androstenedione and Testosterone to Oestrone and Oestradiol respectively. The active ingredient is thought to be a sesquiterpene isoflavone isocyperol, but also other sesquiterpenes isolated revealed anti-oestrogenic activity through aromatase inhibition. Sesqueterpenes anti-oestrogenic action may also be related to competitive binding to the oestrogen receptor excluding oestradiol (competitive inhibition) hence downgrading oestrogen signaling.

Cyperus has been used in traditional medicine for menstrual disorders and dymenorrhoea which may well be due to oestrogen dominant hormonal effects. Cyperus rhizome isoflavones may have benefit in oestrogen driven illnesses including cancer (Minsun Nat Prod Chem & Res 2014).

Beyond its anti-oestrogenic effect, an extract of the cyperus rotundus rhizome has been recorded as having anti-inflammatory properties. α-Cyperone isolated from the n-hexane fraction significantly inhibited prostaglandin E2 (PGE2) production by suppressing the lipopolysacchyaride (LPS)-induced expression of inducible COX-2 at both the mRNA and the protein levels. Additionally, α-cyperone downregulated the production and mRNA expression of the inflammatory cytokine IL-6. Moreover, treatment with α-cyperone suppressed the transcriptional activity of NFκB and the nuclear translocation of the p65 NFκB subunit in LPS-induced RAW 264.7 cells.

Cyperus rotundus has displayed an anti-proliferative effect in triple negative breast cancer (TNBC) cells (MDA-MB-231 and MDA-MB-468). An alcohol extract of Cyperus rotundus inhibits the proliferation of MDA-MB-231 and MDA-MB-468 in a dose-dependent manner, which may be related to the arrest of cell cycle in G_0/G_1 phase. It induces apoptosis by promoting the expression of BAX and inhibiting the expression of BCL-2. In addition, autophagy inhibitor 3-Methyladenine (3-MA) inhibited TNBC cells pro-survival autophagy and increased the sensitivity of Ethanolic extract of Cyperus rotundus (EECR). The results demonstrated that cyperus rotundus EECR has potential effects on induction of apoptosis and inhibiting the proliferation of triple negative breast cancer cells (Wang 2019).

Cyperus rotundus rhizome has been used traditionally for inflammatory conditions. In an investigation of alpha-cyperone (α-cyperone) The authors comment that the anti-inflammatory activity of α-cyperone isolated from the N-hexane fraction of cyperus rotundus is associated with the down-regulation of COX-2 and IL-6 via the negative regulation of the NFκB pathway in LPS-stimulated RAW 264.7 cells. (Jung 2013).

Hence cyperus is yet another multi-functional nutraceutical in PCOS SUPPORT Hormone Balance having anti-oestrogenic, anti-proliferative and anti-inflammatory properties

CALCIUM-D-GLUCARATE (C-D-G)
CDG is the calcium salts of a naturally occurring D-Glucaric Acid which is found in oranges, apples, carrots, grapefruit and brassicas. Calcium dissociates from the D-glucaric acid in the stomach. D-glucaric acid, is further partially be further into the active D-glucaro-1,4-lactone or and the less active D-glucaro-6,3-lactone in approximately equal amounts.

The metabolites of D-Glucaric acid especially glucaro-1,4,lactone perform phase 2 detoxification reactions which is the attachment of a fat soluble hydrophobic molecule to glucaro-1,4,lactone for conjugation forming an complex which can be eliminated through the bile (Alt Med Rev 2003).

Glucuronidation reactions involve the metabolism of hormones testosterone and oestrogens, polycyclic aromatic hydrocarbons (PAH), benzo(a)pyrene in burnt meat and some pharmaceutical drugs.

Animal studies have found D-glucaric acid and its metabolites reduced the breast cancer carcinogen 7,12 DMBA with reduced tumour recurrance (Walaszek Z,1986)

The process of glucuronidation is modulated by the presence of beta glucuronidase an enzyme naturally excreted by the gut microbiota. However, dysbiosis of the microbiome may result in over-expansion of some genus populations like Bacteroides and specifically the bacteroides vulgatus species have been shown to increase beta glucuronidase. Other microbiota which can increase beta glucuronidase include the E Coli Shigella genus of the proteobacteria phylum.

High levels of beta-glucuronidase will cause the glucuronidation of the toxic moiety or hormone to D-glucaro-1,4-lactone to disassociate in the bowel and become reabsorbed via the liver into the systemic circulation.

Hormone receptor cancers like breast and prostate but also colon cancer have been positively correlated with raised beta-glucuronidase levels reflective of activity (Zółtaszek 2008).

However, by supplementing with Calcium-D-Glucarate an independent suppression of beta glucuronidase occurs facilitating appropriate gluronide conjugation and elimination

Calcium D-Glucarate has been found to have an anti-inflammatory effect through the promotion of the anti-inflammatory cytokine IL-10 which modulates pro-inflammatory cytokines.

Pro-inflammatory cytokines promoting tumour progression through the transformation of pre-malignant cells to malignant cells. (Zoltaszek 2011).

Hence in a PCOS setting of hyperoestrogens, inflammation, and obesity, Calcium-D-Glucarate is well placed to facilitate enhanced elimination of oestrogens reducing the potential risk of cancer, weight gain, ovarian dysfunction. Glucuronidation also eliminates testosterone one of many androgens which are major markers of PCOS.

From a PMS standpoint, CDG can effectively remove anxiety, breast tenderness and headaches from oestrogen dominance.

Animal studies have shown that calcium D-glucarate lowers serum oestrogen levels and increases its urinary excretion. This appears to be due to the inhibition of beta-glucuronidase causing reduced oestrogen reabsorption and lower circulating oestrogen levels.

CURCUMIN

Turmeric, a spice that has long been recognized for its medicinal properties medical/scientific world and from culinary enthusiasts, is the major source of the polyphenol curcumin one of a few curcuminoids within turmeric. Most of these benefits of curcumin can be attributed to its antioxidant boosting SOD, catalase, glutathione peroxidase and its potent anti-inflammatory effects. Curcumin is also anti-mitogenic.

Curcumin suppresses reactive oxygen species (ROS) and reactive nitrogen species (RNS), which promote pro-inflammatory gene expression and anti-inflammatory effects.
Curcumin lowers: TNF alpha, IL-1b, IL-4, VEGF, IL-6, TGFb, MCP-1, and malondialdehyde MDA.
Curcumin aids in the management of oxidative and inflammatory conditions, Metabolic Syndrome, arthritis, anxiety, and hyperlipidemia. It may also help in the management of exercise-induced inflammation and muscle soreness, thus enhancing recovery.
Curcumin has been shown to block Nf-κB activation increased by several different inflammatory stimuli, thus reducing TNF alpha. (Hewlings 2017).

Curcumin has been shown to attenuate several aspects of Metabolic Syndrome by improving insulin sensitivity as was shown in a paediatric study of pre-diabetic children given 9-month curcumin intervention in a prediabetic population. The treated group significantly lowered the number of pre-diabetic individuals who eventually developed T2DM. In addition, the curcumin treatment appeared to improve overall function of β-cells, with very minor adverse effects. After 9 months of treatment, 16.4% of subjects in the placebo group were diagnosed with T2DM, whereas none of the curcumin treated patients were diagnosed with T2DM In addition, the curcumin-treated group showed a better overall function of β-cells, with higher HOMA-β (61.58 vs. 48.72; $P < 0.01$) and lower C-peptide (1.7 vs. 2.17; $P < 0.05$). The curcumin-treated group showed a lower level of HOMA-IR (3.22 vs. 4.04; $P < 0.001$) and higher adiponectin (22.46 vs. 18.45; $P < 0.05$) when compared with the placebo group (Chuengsamarn 2012)

Cytokines are involved in the development of metabolic abnormalities that may result in metabolic syndrome (MetS). PCOS sufferers are at risk of MetS. Can curcumin improve improve MetS (hyperglycaemia, hyperinsulinemia, visceral obesity, high cholesterol, hypertriglyceridemia)?

In a randomized controlled trial in which males and females with diagnosis of MetS, according to the criteria defined by the National Cholesterol Education Program Adult Treatment Panel III guidelines, were randomly assigned to either curcumin (daily dose of 1g/day) or a matched placebo for a period of 8 weeks.

One hundred and seventeen subjects were assigned to either curcumin (n=59) or placebo (n=58) groups. Within-group analysis revealed significant reductions in serum concentrations of TNF-α, IL-6, TGF-β and MCP-1 following curcumin supplementation ($p<0.001$). Between-group comparison suggested significantly greater reductions in serum concentrations of TNF-α, IL-6, TGF-β and MCP-1 in the curcumin versus placebo group ($p<0.001$). Apart from IL-6, changes in other parameters remained statistically significant after adjustment for potential confounders including changes in serum lipids and glucose levels, and baseline serum concentration of the cytokines (Panahi 2016).

The importance of this study, is that it highlights the inflammatory nature of MetS and MetS in a PCOS sufferer. As described above and as shown by Duleba et al, PCOS is an inflammatory process, with raised inflammatory cytokines whose origin is likely genetic and possibly epigenetic (lifestyle, diet, stressors). This study highlights that to treat Metabolic Syndrome by standard care, misses the underlying inflammatory mechanism.

Curcumin has been shown to attenuate several aspects of MetS by not only improving insulin sensitivity but also suppressing adipogenesis. Curcumin directly interacts with white adipose tissue to suppress chronic inflammation. In adipose tissue, curcumin inhibits macrophage infiltration and nuclear factor κB (NF-κB) activation induced by inflammatory agents. Curcumin reduces the expression of the potent pro-inflammatory adipokines tumor necrosis factor-α (TNFα), monocyte chemoattractant protein-1 (MCP-1), and plasminogen activator inhibitor type-1 (PAI-1), and it induces the expression of adiponectin, the principal anti-inflammatory agent secreted by adipocytes. Curcumin also has effects to inhibit adipocyte differentiation and to promote antioxidant activities. Through these diverse mechanisms curcumin reduces obesity and curtails the adverse health effects of obesity (Bradford 2013).

One facet of Metabolic Syndrome is hypertriglyceridemia and hypercholesterolemia and is a risk factor of not only cardiovascular disease but but the former for fatty liver disease as well.

In a RCT 100 MetS patients 50 were assigned curcuminoids (C3 complex(®); 1000 mg/day; and 50 received a placebo for 8 weeks. The curcuminoid group achieved lower LDL-C non-HDL-C, total cholesterol, triglycerides and Lp(a), and elevating HDL-C. The authors commented that curcuminoid therapy is an 'efficacious adjunctive therapy in patients with Metabolic Syndrome and can modify serum lipid concentrations beyond what is achieved with standard of care' (Panahi 2014).

Curcumin has been found to independently lower blood yet another tentacle of Metabolic Syndrome. Animas given L-NAME (N-nitro-L-arginine-methylester) a nonspecific inhibitor of all three NO synthase (NOS) isoforms (neuronal - nNOS; inducible - iNOS; endothelial - eNOS), causes an increase of blood pressure in a dose-dependent manner. Administration of piperine or curcumin, less their combination, is able to partially prevent the increase of blood pressure caused by chronic L-NAME administration. The spices modify the remodeling of the wall of the aorta induced by hypertension. The results show that independent administration of curcumin is more effective in preventing negative changes in blood vessel morphology accompanying hypertensive disease (Hlavackova 2011).

Since overweight and obesity is experienced by 30-70% of PCOS patients and since inflammation and dysfunctional immune activation is an up-stream mechanism in the inflammatory cascade which assails PCOS patients, a further study investigates cytokines involved in obesity more extensively.

A randomized crossover trial investigated the efficacy of curcumin, with established anti-inflammatory and immunomodulatory effects, on the serum levels of a panel of cytokines and mediators in obese individuals.

Thirty obese individuals received curcumin 1 g daily or a matched placebo for 4 weeks, followed by a 2-week wash-out period, and then the alternate treatment regimen for another 4 weeks. Serum levels of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, IFNγ, EGF, MCP-1, and TNF α were measured. L-1β (P = 0.042), IL-4 (P = 0.008), and VEGF (P = 0.01) were found to be significantly reduced by curcumin therapy. In contrast, no significant difference was observed in the concentrations of IL-2, IL-6, IL-8, IL-10, IFNγ, EGF, and MCP-1.

The findings of the present trial suggested that curcumin may exert immunomodulatory effects via altering the circulating concentrations of IL-1β, IL-4, and VEGF (Ganjali 2014).

Hence curcumin is a 'base' nutritional intervention across vast swathes of pathophysiology that besets a PCOS sufferer. It is an integral member of PCOS SUPPORT and champions many regulatory features, including inflammation which it targets both at the level of cytokines but also at a nuclear inflammatory promoter level downregulating Nf-KB, as well as at a tissue level reducing COX and LOX eicosanoids. Through this anti-inflammatory and antioxidant intervention many of the signs and symptoms of PCOS are addressed.

……CURCUMIN AND DEPRESSION

Several studies have demonstrated that curcumin, possesses antidepressant properties. Meta-analysis of six clinical trials revealed that curcumin administration showed a significantly higher reduction in depression symptoms. Sub-group analyses showed that curcumin had the highest effect when given to middle-aged patients for longer duration of administration, and at higher doses. The administration of of curcumin (BCM-95) had non-significantly higher effect on depression as compared with the conventional curcumin-piperine formula. The authors conclude that there is supporting evidence that curcumin administration reduces depressive symptoms in patients with major depression (Karawi 2015).

Genetic factors including hormone receptor polymorphisms, through the HPO/HPG axis, as as well gene polymorphisms of pancreas islet cells and insulin receptor genes, as well as thyroid auto-antibodies as a result of immunological gene SNP directed at the thyroid , suddenly expand the platform of complexity that PCOS involves.

At Life Source, the creation of PCOS SUPPORT Metabolic Balance and Hormone Balance addresses many (but by no means all) of the hidden nuances in this very complex condition.

The results speak for themselves…….

We have a number of testimonials of women, who in spite of multiple practitioner consultations and four failed IVF procedures remained without a period and anovular. Within 2-3 months of starting PCOS SUPPORT, a cycle occurred and pregnancy followed soon after. Not only has this lady delivered a healthy baby, but fell pregnant 4 months later and has just delivered her second baby.

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