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Research Article

ANTIDEPRESSANT AND PRO-REPRODUCTIVE EFFECTS OF *MENTHA SPICATA* & *TERMINALIA CATAPPA* EXTRACTS IN STEROID-RESISTANT PCOS – A CASE REPORT AND LITERATURE REVIEW

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Abstract

Introduction: Polycystic ovary/ovarian syndrome (PCOS) is the commonest reproductive endocrinopathy in women. Amenorrhea/oligomenorrhea, hirsutism, and bilateral polycystic ovaries are its dominant symptoms. **Materials & Methods:** This study is both a consented report on the history, clinical, biochemical and radiological features of on a 25-year woman who presented to us and a literature review on PCOS. Her presenting features included moderate anaemia, amenorrhea/oligomenorrhea, dysmenorrhea, hirsutism, and bilateral polycystic ovaries. Other included prolonged/heavy menorrhagia which started after being placed on monthly oral contraceptive pills from her previous medical consultations before presenting to us. She volunteered that the latter features were often associated with mood swings and anxiety. Her overall profile indicated a diagnosis of PCOS with moderate depressive symptoms. The contraceptive pills were tailed off while she was immediately given haematinics and nutritional support. She was subsequently placed on a twice daily hot water decoctions of 2.5 g *Mentha spica* (MS) and teaspoonful of *Terminalia catappa* (TC) powders for several weeks/months. About 7 days of commencing the herbal treatment, clinical improvement was observed in menorrhagia, and 8 days later, the vaginal bleeding ceased. Although her hirsutism and dysmenorrhea did not improve very significantly, her moods, anxiety traits, menstrual cycles and flows progressively regularized until she achieved cyesis 9 months into the herbal treatment. In the meantime, Internet was also searched using several key words centered on PCOS treatments, aetiopathogenesis, and epidemiology. Full articles were selected, perused, and pcos-relevant information was included in the report. **Findings:** This study shows PCOS is a highly prevalent multi-endocrine, multi-genetic, and multifactorial gynaecological disorder with no streamlined standard drug treatments. The study further indicates the oral hormone contraceptive pills – the first/default and other synthetic anti-pcos drugs have efficacy and toxicity liabilities. This study suggests MS and TC extracts may have anti-pcos effect. **Conclusion:** This may justify the traditional use of extracts of these and other medicinal plants for the treatment of PCOS.

Keywords: PCOS, Spear mint, Tropical almond, Menorrhagia, Powder, Decoction

INTRODUCTION

Polycystic ovary syndrome (pcos) or Stein-Leventhal syndrome is a disorder having oligo/amenorrhea, hirsutism, and multiple cysts in both ovaries as its most prominent clinical features. From the original description by Irving Freiler Stein and Michael Leventhal in 1935, the syndrome is now recognized as a complex multi-endocrine disorder characterized by features of hyperandrogenism, insulin insensitivity, dysfunctional hypothalamus-pituitary-adrenal axis, and hypo-functioning multiple cysts-containing (polycystic) ovaries. Bilateral polycystic ovary morphology results from accumulated unruptured immature Graffian follicles, a fallout from recurrent anovulatory menstrual cycles (1–4)

The syndrome is currently regarded as the commonest gynaecology-related endocrinopathy in reproductive age. Currently, an estimated 10% or 200 million of the global women population reportedly suffer from pcos. The most frequent clinical features of this syndrome to date still include irregular, infrequent, anovulatory, or absent menstrual cycles (ovarian hypogonadism features), acne, male-type hirsutism and alopecia (hyperandrogenism features), dyslipidemia, hyperglycemia, and obesity (metabolic features) (5–7).

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METHODOLOGY

For the literature review component of this report, data bases such as Google, Google scholars, and Pubmed were searched for literature relevant to pcos and anti-pcos treatments, drugs, phytochemicals, medicinal plants and non-drug modalities validated for the management of pcos. The key search words for surfing the internet included but not limited to "polycystic ovary syndrome", "polycystic ovarian syndrome", "polycystic ovary disorder", "polycystic ovarian disorder", "PCOS', "PCOD", "medicinal plants for PCOS", "treatment of PCOS", "drug treatment of PCOD", "treatment of PCOD", "drug treatment of PCOS" "medicinal plants for PCOD", "phytochemicals used for PCOS", "phytochemicals used for PCOD", "herbs for PCOS", "herbs for PCOD", "herbal treatments for PCOS", "herbal treatments for PCOD", "*Mentha spicata* pcos", "spearmint pcos", "*Terminalia catappa* pcos", "tropical almond", "pcos treatments", "treatment of PCOD", "prevention of PCOS", and "prevention of PCOD". Journal/conference articles were searched for data/texts relevant to pcos, pcos treatments, *Mentha spicata*, spearmint, *Terminalia catappa*, tropical almond, were selected into the final write-up. For the Case Report component, personal, family, and past medical/drug treatment history as obtained from the client, clinical and laboratory examination findings, diagnosis and treatments as well as personal and clinical observations during treatments were all captured into the write-up. Relevant ethical clearance and full consent of the

client to the diagnosis, treatments, and this publication were duly obtained.

PCOS AETIOPATHOGENESIS

Although both external (epigenetics, environmental toxicants, diets, stress, etc.) and internal (oxidative stress, insulin resistance, inflammation, obesity, and genetic) factors are frequently linked to the emergence of this disorder, so far, its complete aetiopathogenesis is not yet known (6–8). However, hyperandrogenism appears to be central to the pathogenesis of this disorder and to be at the convergence of most of the above-listed pcos contributory factors – particularly hyperinsulinemia and inflammation. Other factors not included in the list of pcos factors above, like high body gonadotropin-releasing hormone (GnRH) level, and high luteinizing hormone (LH) to follicle-stimulating hormone (FSH) ratio promote pcos emergence via hyperandrogenism resulting from increased steroidogenesis (6–8).

Scientific reports indicate pcosis an inherited polygenic trait whose phenotypic expression essentially requires exposure to any of the requisite afore-listed environmental risk factors – with genetics contribution to its inheritability currently estimated to be only around 10 percent(6,9–12). Genome-wide association studies (GWAS) imply over-expression of or polymorphisms in the promoter genes associated with the coding of certain proteins i.e., sex hormone binding globulin (SHBG), Thyroid Adenoma-Associated Protein (THADA); Variable Number Tandem Repeats Insulin ((VNTR); Fat Mass/Obesity (FTO); Insulin Receptor (INSR); Luteinizing Hormone/Chorionic Gonadotropin Receptor (LHCGR); DENN Domain-containing Protein 1 (DENND1A); and Peroxisome Proliferator-Activated Receptor (PPAR) are some of the genetic predispositions to pcos pathogenesis via enhanced ovarian android steroidogenesis, insulin dysregulation, lipogenesis, and inflammation (13–15). Research has also shown defects in the mitochondrial transfer RNA and increased genetic polymorphisms in pcos victims are associated with altered electron transfer and exaggerated reactive oxygen species generation, inflammation, and insulin resistance, compared to their non-pcos counterparts, Additional evidence suggests the 100% mitochondrial DNA heritability exclusively from mothers may be the genetic reason behind why pcos tends to run in families and siblings tend to share similar metabolic, androgenic, and menstrual features(15–17).

Epigenetics, non-DNA sequence-based modifications in genetic expression, is also thought to play a significant role in pcos pathophysiology. Both animal and human studies indicate that in-utero exposure of fetuses to high maternal levels of insulin resistance, insulin, androgens, and anti-mullerian hormone (AMH), independent of diets, is significantly linked to the emergence of pcos in adult life (16,17). Research indicates these fetal environmental factors are associated with increased fetal androgenesis resulting from hypomethylation and the resultant over-expression of fetal genes concerned with androgen and insulin metabolic up-regulation on one hand, and with reduced placental aromatase activity-linked testosterone breakdown, on the other (17–19). These effects collectively result in increased fetal androgen steroidogenesis. Another important epigenetic contribution to this disorder is viewed to come from the hypomethylation of certain genes involved in mitochondrial metabolism i.e., Parkinson disease associated (PARK2), estradiol/estrogen receptor1 (ESR1), and insulin (INS) genes, all of which are partly involved in mitochondrial metabolism. The altered methylation of the latter genes has been associated with exaggerated rates of mitochondrial injury and death, accumulation of reactive species, lipogenesis, and apoptosis activation (20,21). Additionally, epigenetic re-programming of fetal DNA for adult life pcos emergence is suspected to come from the fetal DNA modulation by some micro RNAs. DNA modulatory activities of these micro RNAs (mi-155, mi-146a, mi-122, mi-132, mi-93, mi103, etc.,) are thought to be linked to pcos pathologic processes i.e., altered inflammation, insulin, androgen and lipid metabolism and regulation (22, 23).

Studies have shown chronic low-grade body systems-wide inflammation and cellular oxidative stress are ultimately pro-androgenic. Women with pcos are reported to exhibit greater rates of mitochondrial structural and metabolic anomalies with attendant greater risk of cellular oxidative stress, and reactive oxygen and nitrogen species generation from environmental stressors (e.g., psychological stress, infectious agents, apoptotic and senescent cells, chemicals, excessive energy intake, and accumulation of metabolic intermediates)(23–26). The increased rates of free reactive species are viewed to trigger diverse immune reactions that result in chronic systemic inflammatory processes (27,28). Systemic inflammation in pcos is also thought to arise from the activities of inflammasomes and other inflammatory propagators – cyclophilin A, adipokines, nuclear factor kappa B ($NF\text{-}K_B$), and vascular dysfunction mediators (27,29–32). This is in addition to the evidence showing chronic systemic inflammation resulting from cellular oxidative stress, alone, or in concert with insulin resistance/insulinemia promotes hyperandrogenism in pcos women by upscaling ovarian steroidogenic enzymatic activities (33–35).

Research further shows although Luteinising hormone (LH) and insulin exhibit some synergistic actions in the generation of the hyperandrogenism seen in pcos, nevertheless each hormone can contribute to this independently (36–39). For instance, Insulin contributes to pcos hyperandrogenism in several ways – including direct mechanisms by the promotion of chronic systemic low-grade inflammation and stimulation of PI3K and MAPK pathways-linked ovarian androgenesis. Insulin also exerts indirect androgenic effects via increased GnRH-LH and hypothalamic-pituitary-adrenal (HPA) axis activity with the resultant increased ovarian steroidogenesis and insulinemia-enhanced inhibition of SHBG hepatic synthesis – thus increasing free (biologically active) plasma testosterone(37–42).

On LH part, it contributes directly to pcos hyperandrogenism by stimulating increased production of ovarian and adrenal ketosteroid precursors by Cytochrome P450c17 (CYP17A1) enzyme – whose expression is regulated by LH – and for this effect, LH's role in pcos hyperandrogenism was thought to be primary (4,43,44). However, many of LH's indirect hyperandrogenic effects arising from exaggerated LH serum levels, pulse frequency and amplitude often occur only in about half of all pcos cases. Thus, LH dysregulation, just like insulin resistance, is no longer considered the primary pathology responsible for hyperandrogenism in this syndrome. However, evidence shows that in the face of co-existing hyperinsulinism, the normal ovarian theca cell desensitization to LH stimulation at submaximal serum androgen levels is lost and the ovarian tissues are often hypersensitive to the

increased steroidogenic stimulation by LH's exaggerated levels (45–47). Nutrition is another factor implicated in the pcos process. This is because human nutrition involves a lifelong intake of diverse chemical substances, many of which are pro-/anti-inflammatory and/or pro-/antioxidant in nature. Diets are therefore widely considered aninfluential factor to the emergence/progression of pcos – a disease process known to be significantly hinged on cellular inflammation and oxidation. Thus, chronic consumption of alcohol (with acetaldehyde as a byproduct), small molecule sugars (glucose, fructose), advanced glycation end-products (AGEs), and short-chain fatty acids have been implicated in pcos aetiopathogenesis (9,10,12,13) because of a pro-androgenic pressure they exert via their negative impact on the gut microbiota as well as on SHBG synthesis and plasma levels (48–50). Current evidence implies chronic dietary exposure to these substances results in a pro-inflammatory shift in the host immunity, gut microbiota and wall integrity – ultimately leading to the generation of a chronic low-grade systemic inflammation and increased androgenesis and the inhibition of the hepatocyte nuclear factor-4α (4HNF-4α)-mediated SHBG synthesis, which in turn results in increased plasma levels of biologically active androgens (10,12,47,51–54).

Dysregulation of an important enzymatic pathway - the CYP enzyme complex - involved in ovarian/adrenal steroidogenesis is a major source of hyperandrogenism in pcos. This genetically determined functional dysregulation implicates both cytochrome P450 CYP17 and cytochrome P450 CYP19 involved in the conversion of androgens to sex ketosteroid precursors and formation of estrogen from androgens, respectively. Both conversions which are the rate-limiting steps in ovarian and adrenal steroidogenesis are known to have their enzymatic activities upregulated in pcos (53–55). Specifically, scientific reports indicate the increased androgen biosynthesisby 17, 20-lyase of CYP17 is due to the following factors: firstly, abundant presence of hemoprotein cytochrome P450 oxidoreductase (POR), secondly, greater cytochrome b5-facilitated POR-17, 20-lyase CYP17 allosteric interactions, and lastly, greater phosphorylation of 17, 20-lyase CYP17 in ovarian tissues(56–58). Dysregulation of the androgen-oestrogen catalytic activity of the CYP19 (ovarian aromatase) in pcos is associated with hypo-oestrogenism, hyperandrogenism, and disruptions of several metabolic processes for which it is essential (59–61). Research also implies that most if not all pcos biochemical (hyperandrogenaemia, oestrogenaemia), histological/ radiological (impaired folliculosis. anovulation, pcos ovarian morphology), and clinical (hirsutism, male pattern of abdominal/chest hair distribution) features are reproducible with hyperandrogenism induced by aromatase dysfunction – suggesting ovarian aromatase dysregulation may be essential to pcos aetiopathogenesis(61–63).

Classification of pcos is as complex and un-unified as the clinical presentations of the disorder. However, certain diagnostic criteria – chief among which is hyperandrogenism - have been used to delineate the various disease forms into recognizable phenotypes (9,13,63). The Rotterdam classification – reputed to exhibit the most pcos-inclusive diagnostic yardstick due to the exclusion of only the presence of non-hyperandrogenic disorders to make a pcos diagnosis - describes four different variants. Phenotype 1, which corresponds to the classical (full blown) pcos phenotype, should have biochemical and/or clinical hyperandrogenism, oligo/anovulation, and radiological polycystic ovarian morphology. Phenotype 2 (non-polycystic ovary phenotype) consists of clinical and/or biochemical hyperandrogenism and oligo/anovulation. Phenotype 3 (non-androgenic phenotype) is made of oligo/anovulation and radiological polycystic ovarian morphology; and phenotype 4 (ovulatory phenotype) features comprise biochemical and/or clinical hyperandrogenism and radiological polycystic ovarian morphology (68,69). The National Institute of Health (1990) pcos-diagnostic criteria which require exclusion of hyperprolactinaemia in addition to hyperandrogenism invariably prescribe a pcos variant corresponding to Rotterdam's phenotype 2 for which polycystic ovarian morphology is non-essential. So far, the Androgen Excess Society (2006) diagnostic criteria remain the most stringent requiring the exclusion of concurrent hyperandrogenic disorders e.g., hyperprolactinemia, thyroid hormone imbalance and severe insulin resistance syndromes, and the presence of either clinical hyperandrogenism or hyperandrogenemia plus either oligo/anovulation or ultrasonographic polycystic ovarian morphology (64,66,67).

CASE REPORT

Our client is a 25-year-old married Nigerian woman who presented herself for a medical consultation September 2023 with a history of irregular and infrequent menstrual cycles which started way back to her menarche at the age of 13 years. Her menstrual cycles which often came once in 3 months and lasted about 5 days then, were with normal flow but associated with severe dysmenorrhea and heart palpitations. At the age of about sixteen years, due to worsening palpitations, she undertook a Cardiological/Gynaecological consultations from which a provisional diagnosis of polycystic ovary syndrome was made based on her personal and gynaecological history; clinical findings of male pattern of chest/abdominal hair distribution; biochemical findings of raised absolute luteinizing hormone (LH) values (about 20 0 mIU/microL) and increased LH/FSH ratio; and an ultrasonographic finding of polycystic ovaries. Consequently, she was placed on combined oral contraceptive pills (COCs).Following this,her heart palpitations abated and for the next 3 months her menses became more regularbut heavy due to COCs-induced syncronised menstrual cycles and withdrawal bleeding, even though her premenstrual and menstrual pains persisted. However, after this period, the heavy menstrual patterns took a twist; this time the COCs no longer achieved the expected withdrawal menstrual bleedings. Desiring to re-establish the lost cyclic withdrawal vaginal bleedings, different COCs were subsequently tried embarked by her doctors for about 3 years with little success. Then this period of nil or scanty menstruation was then followed by an episode of a very heavy thirteen-day-long blood clots-laden menstrual bleeding (menorrhagia). Following this, her subsequent menstrual flows would worsen - experiencing protracted menorrhagia and menstrual bleeding lasting periods longer than a month in several of her menstrual cycles. This phase of her pcos clinical course lasted for another 2-3 years till early 2020. Again, to curtail the protracted heavy menstrual bleeding, she was switched from the combined oral contraceptive pills she was all along placed on to a treatment regime alternating between oral and injectable progesterone-only steroid treatments. Again, there seemed to be a little initial clinical improvement in the heaviness and duration of her menstrual bleeding for the first three cycles of the new progestin-only hormonal therapy. However, after this initial improvement, her menstrual

bleeding got heavier and longer and would continue even while on steroid drugs. The bleedings were often associated with severe dysmenorrhea. The client also volunteered that due to the protracted nature of her menstrual symptoms she started having subjective mixed feelings of internal heat, tension, apprehension, unhappiness, and low moods over the past 2-3 years before her presentation to us. Other aspects of her social history reveal her meals during her teenage years consisted of the typical African diets with occasional indulgence in junk foods. Significantly, her mother does not but a maternal aunt of hers does have a history and features suggestive of pcos and/or infertility. This was her clinical state until she sought our medical consultation in August2023. At presentation, she was an anxious-looking, slim, averagely tall young woman with generally normal vital signs except for a moderate pallour and a rapid full radial pulse (a finding likely to have resulted from her protracted bleeding and the attendant anaemia). Significantly, there was a finding of a male pattern hair distribution on her chest and abdomen but there was no acne. There was also neither eye proptosis/exophthalmos or fidgetiness (to suggest hyperthyroidism) nor was there lactation from self-pressed breast nipples (to suggest hyperprolactinaemia).

Serum luteinizing hormone (LH) level was 29.75 mIU/mL (Normal range: 2.12-10.89mIU/mL) and Follicle stimulating hormone (FSH) level was: 3.4 mIU/mL(Normal range: 1.4-9.4 mIU/mL); LH/FSH ratio, 8.75 (normal ratio range1.00-2.00 ratio). Progesterone level, 0.39 ng/Mi (at the lowest end of the normal range: 0.0 - 12.8 ng/ml); serum insulin of 140.00 picomol/L (range: 12-150 ng/ml). Serum cortisol was 29.51 pmol/L (Normal range: 50-230). Serum testosterone level was slightly elevated to 0.93 ng/ml (Normal value <0.80 ng/ml). serum lipid and sugar levels were all within normal values. Serum triiodothyronine of 0.82 ng/ml (Normal range: 0.69-2.15 ng/ml).An ultrasonographic scan revealed multiple well-defined peripheral intraovarian cysts bilaterally. Her psychological score on Beck Depression Inventory (BDI) was 22 (68).

Based on the history, BDI score, clinical, biochemical, and radiological findings, a diagnosis of contraceptive hormones resistant-pcos (Rotterdam phenotype 1) with mild/moderate anaemia, clinical depression, and borderline hyperinsulinaemia was made. She was then placed on haematinics to correct the menorrhagia-induced anaemia. In addition to this, she was tailed off all steroid hormonal medications while she was advised to also continue feeding on locally sourced low table sugar/saturated fat, high fibre, protein, vegetable, and fruit diets she had been placed on from her previous medical consultations. This management was maintained for the following 6-8 weeks, with the haematological and nutritional status improving impressively, but the main pcos symptom, irregular and protracted menstrual bleeding not showing any alleviation. Owing to the severity of her symptoms and their seeming resistance to steroid contraceptive treatments coupled with the reported relative safety, nutritional uses, and anti-pcos potential of MS and TC extracts (69–73)she was then started by our team on a twice daily hot water decoctions of TC brown (fallen) leaves obtained from neighbourhood TC trees (dried and pulverized into fine powder) and MS (Spear mint) leaf tea obtained from nearby commercial stores. Specifically, the regime comprises 2. 5 g of MS and one (1) teaspoonful of TC dry leaf powder separately decocted in about 250 ml of hot water and allowed to cool off before being orally taken in the mornings and evenings for several weeks/months - so long as the symptoms remained. However, within a few days of initiating this herbal combination, the client notified the team she perceived a reduction in the volume (heaviness) of her vaginal bleeding. And about two weeks after the start of the herbal therapy she submitted the bleeding had eventually ceased. The observed clinical progress in her menstrual symptoms was sustained for the following several months – with the cycles becoming progressively more regular and the menstrual flow getting lighter and shorter with each successive menstrual cycle until her cycle lengths stabilized at 26 and 33 days and her monthly menstrual flows at 5-6 days. Over the same period, there was both subjective (self-reporting) and objective (observable) improvement in her moods – scoring less than 10 on a repeat BDI scoring within 3 months of being placed on the MS+TC leaf therapy. The client now felt happier, less tense, less worried, with little or no internal heat. This clinical progress was also mirrored by improvement in most of her biochemical indices. However, there was no commensurate improvement in her hirsutism and dysmenorrhea. This was her clinical picture until around mid-2024 when she informed us (her doctors) that her next menstrual period being expected around May ending 2024 was unusually delayed – even if the little residual fluctuations in her now largely nomalised menstrual cycles/flows were to be considered. This delay was also associated with bloating, fatigue, nausea and other symptoms suggestive of clinical malaria – for which she was treated. However, there was no improvement in this latest set of complaints despite adequate antimalaria treatment. This realization, coupled with the unexpected delay of her menses in view of the overall clinical improvement recorded in her reproductive symptoms, prompted a urine pregnancy test, which turned out positive, and a subsequent uterine ultrasonographic scan, which confirmed a six-week old intrauterine viable gestation. However, despite her impressive overall clinical progress, our client's hirsutism remained largely unresolved. To address this, a fresh study by our team to assess the specific anti-hirsutism efficacy of different oil extracts of MS and TC is already ongoing.

DISCUSSION

Both the case report and the reviewed literature in our study highlight the following facts. Firstly, pcos prevalence is high and under-reported. The high prevalence may be related to the increasing adoption of western-style diets (8–10). Secondly, despite the high prevalence and probability of it increasing further, there is still no streamlined drug treatment for pcos, making treatment approaches largely symptomatic (11,12). This therapeutic conundrum may be related to the fact that the disease aetiopathogenesis is still not completely deciphered (6–8). Thirdly, oral steroids and other synthetic drugs currently used as first/default treatment options have significant efficacy questions and intolerable adverse drug reactions – some of which are being reported in this study (74–77). Lastly, despite widespread anecdotal and scientific reports of the potential efficacy of phytotherapy in pcos management, medicinal plant extracts and natural products are still being both under-investigated and under-utilised for this syndrome (78–81). The foregoing is well illustrated by the impressive anti-pcos and even positive mood-modulatory effects MS and TC leaf extract decoctions exhibited in this report. The common pcos clinical indications for which combined oral contraceptives (COCs) are still considered first therapeutic option include menstrual

irregularity, acne, and hirsutism. COCs are believed to be efficacious for these hyperandrogenaemia-driven indications by a dual mechanism of coupling decreasing ovarian androgen production and plasma free androgen with increasing hepatic sex-hormone binding globulins (SHBGs) (82). Two other symptoms present in our case report for which COCs have been scheduled to be effective are menorrhagia and dysmenorrhea (82,83). However, this client claimed none of these symptoms recorded any clinical improvement in the 2- 4 years she was on oral contraceptives. Reports of complications arising from the use of COCs that are not different from the symptoms they are meant to cure are rampant in clinical practice. Apart from those stated in this presentation, there is a plethora of other potential long-term risks to which this and other pcos cases placed on COCs are exposed. These include obstetric (abortions, intrauterine fetal deaths, preeclampsia, macrosomia, increased fetal congenital anomalies, etc.), renal (failures, hypertension), cancers, metabolic (type 2 diabetes mellitus, obesity, hyperlipidemia, gestational diabetes mellitus), neuropsychiatric (anxiety, depression), and cardiovascular (hypertension, cardiomyopathies, coronary heart disease) complications (84–87). Other steroidal and non-steroidal anti-androgen drugs used in managing features of hyperandrogenism like hirsutism, acne, oligo/anovulation etc. such as metformin, spironolactone, cyproterone acetate, bicalutamide, and flutamide, apart from poor efficacy, are also saddled with intolerable adverse effects like hepatoxicity, ketoacidosis, nephrotoxicity, hyperkalaemia, cardiotoxicity, etc, (88–92).

Despite the above-stated attendant risks associated with their use, the fact that steroid hormones are still regarded as default prescriptions for hyperandrogenaemia symptoms is a clear indication of the unmet therapeutic gap existing in the management of pcos cases and a pointer to the urgent need to find alternative/complimentary therapeutic approaches that are natural, safer, and acceptable for both effective pcos case treatment and prevention of the highlighted potential long-term risks. Phytotherapy has always provided a promising alternative to synthetic drugs in the treatment of several disease classes: the ongoing achievement of progressive symptom relief by MS and TC leaf extracts over a short period compared to that of COCs in this presentation is an indication that pcos is not an exemption to the broad efficacy spectrum of phytotherapeutic agents(93,94). The wide therapeutic latitude of botanicals is viewed to derive from their inherent possession of diverse potent disease-fighting macromolecules, including particularly, antioxidant compounds(95). In respect to pcos, anecdotal, preclinical and clinical reports indicate several medicinal plant extracts e.g., *Cnidium officinale*(96,97), *Leonurus japonicus*(98,99), *Berberis vulgaris* L.(100) , *Angelica sinensis*(101), *Angelica gigantis*(102) and natural products e.g., berberine (103,104), folate (105), inositol (106–108), Luteolin and luteolin-7-methyl ether (109), paeoniflorin (110), apigenin (111,112), and catechins (113)have been effectively used to alleviate pcos symptoms -especially those related to cellular oxidative stress. As earlier highlighted, chronic systemic low-grade cellular oxidative stress is a hallmark of chronic inflammatory diseases including pcos (27,29). Relatedly, it is often viewed that their intrinsic antioxidant property to reverse/slow down cellular oxidative processes may explain why strategies involving the use of medicinal plant extracts and diets - which are inherently antioxidant, are being increasingly recognized as potential alternative treatment modalities for pcos (31,32). What more, antioxidant activity (34,35) is one of the best known biological properties of the two medicinal plant extracts being reported for their effective control of pcos menstrual symptoms in this study.

The first of the two medicinal plants in this report, *Mentha spicata* L. (MS) (Common name: spearmint), which has been investigated and reported for its ethnomedicinal and ethnopharmacological anti-pcos activities (70,114–116), is a creeping rhizomatous, strongly aromatous perennial hybrid herb native to Europe, the Americas, and Asia but now widely cultivated in virtually all cultures, often as a back garden flowery plant. This Lamiaceae family medicinal plant that can grow up to 100 cm high has over a hundred synonyms including *Mentha condensis* L., *Mentha viridis* (L.), *Mentha cordifolia*, *Mentha balsamea* Rchb., *Mentha aquatica* L., *Mentha laevigata* Willd., *Mentha spicata* L., *Mentha brevispicata* Lehm., and *Mentha piperita*., *Mentha crispa* var. *crispataf. reticulata*, and *Mentha glabra* Mill. (117,118). Essential oils, decoctions, infusions, and powders from different parts of spearmint have been traditionally administered to alleviate peptic ulcer disease, low libido, headache, fatigue, fevers, sore throat, diabetes mellitus, chest pain and infections, kidney ailments, asthma, colds, and flatulence (119,120). Oils and extracts from leaf, stem, flowers, and roots have been shown to be antifungal, insecticidal, antibacterial, antiparasitic, analgesic and antipyretic, anti-inflammatory, hypoglycemic, antioxidant, antiproliferative, and antidiuretic (121–125). As pointed out above, scientific reports on MS extracts indicate they are effective in managing female reproductive health diagnoses such as infertility, hyperandrogenaemia, menorrhagia, and dysmenorrhea in experimental animal studies and human clinical trials (78,79). Studies have further shown extracts of MS alone, or in combination, ameliorated ovarian follicular dysgenesis and hyperandrogenesis in rats (78,116), decreased significantly ovarian cystic folliculogenesis, adrogenaemia and oestrogaemia, and increased the number and quality of ovarian follicles across all stages of development in rats (116,126).

Human studies have also reported MS extracts orally or topically administered for various periods in pcos women caused significant free and total testosterone reduction, hirsutism severity reduction, and improved ovarian function and morphology (79,127). It is worth to note that in a study by Bahl, A. S. (2020)(128), topically administered MS extract was so effective in the MS-treatment group that over 36% of enlisted pcos women exposed to MS oil, compared to zero percent in the placebo-exposed group, overcame their existing infertility to achieve conception within six-month of post-trial follow up (127). It is our opinion that the impressive pro-conception report of MS oil application in pcos women appears to being surpassed by our finding whereby our client did achieve conception right while still on MS and TC therapy. The pro-conception inclination of MS oil, and MS+TC hot water decocts being highlighted in these studies may also be related to their potent antioxidant activity. In fact, the overall anti-pcos effect of MS extracts on the back of their antioxidant and anti-androgenic activity is viewed to be due to their rich possession of (116,129) of bioactive essential oils and terpenes made up of diverse phytochemicals including carvone, dihydrocarvone, trans-carveol, menthone, β-caryophyllene, carvacrol, germacrene D, limonene, menthol, etc.(130,131).

Terminalia catappa (TC), the second of the two medicinal plants combined in the herbal treatment in this report, is a tropical monoecious flowering plant of the Combretaceae family, initially native to Africa and Southeast Asia but now cultivated in most parts of the world (132,133). This medicinal and nutritional plant has several synonyms such as Terminalia catappa var. chlorocarpa Hassk., Terminalia catappa var. macrocarpa Hassk., Terminalia chebula, Terminalia catappa var. subcordata (Humb. & Bonpl. ex Willd.) DC., Terminalia bellirica, Terminalia burmanica King ex Prain., Terminalia badamia sensu Tul., Terminalia catappa var. pubescens Kurz, Terminalia catappa var. rhodocarpa Hassk, etc., and common names such as 'fruit', 'tropical almond', 'autaraa', 'kamani haole', 'kaukauariki', 'Indian almond', 'talie', 'talise', 'tavola', 'tivi ', in different cultures. This plant which can grow up to 35 metre tall has large 15-25 cm x 10-14 cm ovoid, dark green, and glossy/leathery leaves and 5-7 cm long x 3-5.5 cm green, yellow, or red (depending on degree of ripeness) succulent fruits – each containing a single shelled edible seed (134–137). Although TC extracts have been reported effective for diverse ethnobotanical and ethno pharmacological indications, our literature search revealed little or no scientific studies on the anti-pcos efficacy of extracts obtained from TC unlike those from MS, except for two of its synonyms – Terminalia chebula and Terminalia bellirica (138–140). The several therapeutic indications for which extracts of the kernel, leaves, stem bark, seed, fruits, roots, and flowers of TC have been ethnomedicinally used include male sexual disturbances (141), rheumatic arthritis, skin rashes/dermatitis, fevers (81,142,143), depression (80), hypertension (144), inflammatory and oxidative stress-related immune dysfunction (145), inflammatory and cancerous liver diseases (146), and to enhance longevity (147).

Similarly, the diverse pharmacological activities already reported for root, stembark, fruit, seed, and leaf extract of TC include antidepressant (72,80,148), anxiolytic (71,72,149), anti-hypertensive (150–153), aphrodisiac (154,155), antilipidaemic (156,157), and analgesic. antipyretic, and inflammatory (158–160).Other reported activities of TC extracts include hepatoprotective (161,162), interleukin-6 (IL-6) gene expression-suppressant (160), antihyperglcaemic (163,164), anti-parasitic and antimicrobial (165–169), immunomodulatory (170,171), wound-healing and anti-ageing (172,173), anticarcinogenic/antimutagenic (174–176), and neuroprotective (177). These biological activities of TC are believed to derive fromthe widely reported potent antioxidant property (137,178,179) of the large arrays of bioactive phytochemicals, such as flavonoids, beta-carotene, palmitoleic-acid, ursolic acid, castalagin, leucocyanidin, Linoleic-acid, eugenigrandin A, β-sitosterol, punicalagin, betulinic-acid, tannin, alkaloids, gallic-acid, corilagin, daucosterol, ellagic-acid, niacin, saponins, brevifolin-carboxylic-acid, steroids, oleic-acid, ellagic-acid, tercatain, oleanolic-acid, oxalic-acid, cardiac glycosides, grandinin,2, 3â, 23-trihydroxyurs-12-en-28-oic acid, myristic-acid, palmitic-acid, Corilagin, cyanidin-3-glucosideglucose, coumarins, riboflavin, pentosans, tannin. Magnesium, potassium, vitamin A, phosphorus, and many more, present in various parts of this medicinal plant (180–186). Taken together, our literature search implies antioxidant activity appears to be a key mechanism by which MS, TC, other medicinal plant extracts, and even some non-herbal treatments effective in pcos management exert their anti-pcos potency. This view is premised on the understanding of the central role systemic cellular inflammation and oxidative stress from diverse epigenetic, genetic, and environmental stimuli play in triggering systems-wide tissue steroidogenic activity of enzymes (dehydrogenases (3β-hydroxysteroid dehydrogenase type-1), reductases, hydroxylases) and other pro-androgenic proteins (steroidogenic acute regulatory proteins (StAR) and Steroidogenic Factor-1(SF-1)) towards hyperandrogenaemia and hyperandrogenism – the key biochemical features underpinning pcos (18–26,28,187–192). Indeed, antioxidant effect is likely the main factor behind the reported potential therapeutic benefits of vegetarian, organic or ketogenic dieting on one hand (193,194), and on the other, lack of antioxidant activity of high carbohydrate and low fibre dieting is behind the preponderant association of Advanced Glycation End-products (AGEs)-dominated dieting with pcos pathogenesis(195,196). Similar rationale lies behind the advisory to pcos victims and predisposed persons to scale down on AGEs -related foods and cultivate more pro-organic diets comprising fruits, vegetables, whole grains, and healthy plant and animal proteins (197–200). This is necessary because overweight resulting from habitual indulgence in AGEs, over fried/processed foods, cigarette smoking, refined sugar, and sedentary routines promotes cellular oxidative stress in the long term (195–200). Up taking antioxidant effect from herbal, dietary and/or kinetic interventions to mitigate or reverse oxidative stress and potentially, the pcos process and the associated insulin resistance is therefore recommended (201–203).

Preclinical studies suggest high-dose folate supplementation is a potential anti-pcos therapeutic intervention in foetuses of pcos mothers (204). It is of interest to note that the main mechanistic thrust of this epigenetic treatment is the electron (methyl group) donation-fuelled antioxidant potency of the natural folates, their physiological form, folic acid, and their basic antioxidant pharmacophore, 4-hydroxy-2,5,6-triaminopyrimidine (205–208). These therapeutic agents have been shown to possess potent free radical scavenging and ferric iron reducing activity (205,208). Research indicates the antioxidant activity of reduced folates and folic acid most likely accounts for their therapeutic efficacy for diverse therapeutic indications such as metabolic, neoplastic, neurodegenerative, cardiovascular, haematological, reproductive, etc. (49,209–211). Animal studies have shown the antioxidant activity of high-dose folate/folic acid supplementation ameliorated circulatory overload-induced left cardiac ventriculopathy and collagen loss in rat, mitigated negative foetal epigenetic impact, and reduced radiation-induced functional and morphological ovarian damage in mice (205, 207,212).

Similarly clinical studies indicate the antioxidant activity of high-dose folate/folic acid supplementation improved patients' clinical indices across a broad disease spectrum. For instance, chronic 10-mg daily folic acid supplementation ameliorated both carotid arteriosclerotic endothelial dysfunction and intima-media mitogenesis (213,214). Furthermore, randomised, double-blind, placebo-controlled studies in overweight and obese pcos women show a 5mg daily folate supplementation for various periods had positive impact on their inflammatory factors and oxidative stress biomarkers, improved glucose/lipid profiles/tissue insulin sensitivity, and ameliorated hyper homocysteinaemia (210–212,215,216). Evidence indicates the antioxidant activity of folates/folic acid is shared by most antioxidant compounds - herbal and natural products such as myo-inositol (217,218), alpha(α)-lipoic acid

(ALA, αLA) (219), and the sirtuins – a group of endogenous regulatory proteins that are pro-life nicotinamide adenine dinucleotides (NAD+)-dependent class III histone deacetylases (NHDACs) (220). Both myo-inositol/inositol derivatives (221–226) and α-lipoic acid/lipoate derivatives (219,227–229)have been implicated in the modulation of signal transduction, neuroinflammation, neuroendocrine signalling – including insulin sensitivity and lipogenesis, cellular reactive oxygen species generation, and regulation of ovarian cycle, folliculogenesis. and steroidogenesis. Thus, their individual and shared anti-inflammatory, antioxidant, insulin-mimicking, and ovarian function regulatory profiles – and knowing the important roles chronic inflammation, tissue insulin insensitivity, cellular oxidative, ovary dysfunction and dyssteroidogenesis play in pcos disease process make myo-inositol (217,222,230,231) and ALA (227–229,232–236) individually and synergistically (237–240) potentially effective in its management.

The sirtuins, of which the human homologous form is sirtuin1, SIRT1, are a group of stress- and calorie-sensitive proteins (genes) whose catalytic regulatory influence on cell metabolism is premised on acetylation-based posttranslational modification of other metabolic proteins (241–246). Acting as cellular calorie/energy sensors, these endogenous antioxidant proteins (247–249)are known to play key roles in diverse biological processes like calorie restriction response, cell cycle progression, transcription, chromatin remodelling, cell proliferation, ovarian granulosa cell and follicle growth, development and steroidogenesis, tumourigenesis, apoptosis, insulin signalling, DNA repair, senescence and ageing, cellular and mitochondrial inflammation, oxidative stress and reactive oxygen species scavenging, circadian rhythm, cell replication and cycle (242,250–257). Like myo-inositol and ALA, these highlighted activities appear to confer significant anti-pcos efficacy on sirtuins, as pcos amelioration in both animal and human studies has been reported for them (258–262). It is apt to mention that the fact that inositol and ALA and their derivatives are products of natural/botanical sources (263,264) like MS and TC on one hand, and the fact that phenolic phytochemicals (e.g., resveratrol, naringenin, etc.) have been shown to activate the sirtuin (SIRT1)-based anti-pcos activity (259,260,262,265,266) in previous studies on the other, may imply the observed anti-pcos effects of MS and TC hot water decoctions being reported in this study may be partly due to their possession of yet to be identified antioxidant inositol and ALA derivatives as well as modulation of the free radicals scavenging SIRT1-linked anti-pcos activity, Perhaps the lack of high antioxidant activity, unlike MS, TC, the folates, ALA, myo-inositol, and the sirtuin proteins, by the existing synthetic anti-pcos drugs like contraceptive hormones, metformin, spironolactone, cyproterone acetate, bicalutamide, and flutamide – may partly account for their perceived low anti-pcos efficacy and high toxicity (83,86–92). Additional advantage the use of phytotherapy may have over synthetic pharmacotherapy in the treatment of pcos is buttressed in our study by the subjective and objective aalleviation of our client's neuro-psychological symptoms within weeks following twice daily oral administration of MS and TC hot water decoctions. The mood lifting activity of these extracts, which may be closely related to their possession of potent antioxidant macromolecules such as ursolic acid, egallic acid, carvone, menthone, etc. (118,130,135,137,143,267),is a finding that should not be overlooked but further probed, developed and appropriated. Anxiety and depression are common features of pcos and related reproductive disorders. Already, findings from previous studies support the mood-alleviating activity of extracts from both MS and TC. This finding is supported by previous studies reporting significant antioxidant and antidepressant effects from MS essential oil, MS and TC phenolic compounds, and TC hydrolysable tannins (80,129,148,267–269). The inherent capacity of phytotherapeutic agents, unlike the synthetic drugs, to be effective across different body systems and pathophysiological pathways is well show-cased in the current report by the herbal extracts concurrently mitigating our client's mood and reproductive symptoms. This fact is yet another comparative strength of phytotherapy over synthetic pharmacotherapy. Does psychotherapy have a role in pcos treatment? Certainly yes, psychological counselling or behavioural therapy will be helpful in the clinical progress of these cases, especially when combined with the standard pharmacological treatment modalities. Many pcos women often are overweight or obese, prone to spells of low esteem, anxiety, depression, and sometimes, rejection – most of which psychotherapy will not only help to alleviate but also engender compliance to anti-pcos medications (270–272). Psychotherapy is also useful in the initiation and maintenance of positive lifestyle changes -including right kinetic, dietary, and psychosocial choicesthat will ultimately achieve and sustain the overall therapeutic goal (273–275).

CONCLUSION

This report highlights pcos high prevalence, existing anti-pcos therapeutic gap due to non-existent standard pcos treatments and the efficacy/toxicity challenges with the existing synthetic anti-pcos agents. The study also reports the effectiveness of a polyherbal treatment in alleviating pcos and associated mood symptoms. This outcome points to unexploited potential in phytotherapy and justifies the traditional uses of these medicinal plant extracts to remediate reproductive and neuropsychiatric symptoms. It is necessary to further develop phytomedicine to meet modern-day health needs.

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