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From Anti-Inflammation To Anti-Spermatogenesis: Insights From Medicinal Plants

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Abstract:
Background*: Population explosion puts pressure on earth's resources, leading to environmental degradation and poverty in developing countries. Family planning remains the best solution to address overpopulation. However, family planning raises concerns about efficacy, cultural and religious perceptions, and side effects of contraceptives. Herbal male contraceptives could be a solution, as they are natural(with minimal side effects) and align with cultural beliefs and reduce the burden of chemical contraceptives on women.*
Methods*: Swiss Target Prediction tool was used to predict the targets of the individual compounds found on some selected and known anti- spermatogenic plants, patterns in their molecular targets were observed and their possible link to anti-inflammation were researched.*
Results*: The results of Swiss Target Predictions of the phytocompounds found in the selected medicinal plants with known anti-spermatogenic potentials churned out many molecular targets that mediate anti-inflammation. And the most common and recurrent molecular targets were Cyclooxygenase (COX)1 & 2, Peroxisome Proliferator Activated Receptor (PPAR) (gamma, delta and alpha), Cannabinoid receptor(CBR) 1 & 2, Fatty acid amide hydrolase (FAAH)/ Anandamide amido hydrolase, 5- lipoxygenase Inhibitors, 15- lipoxygenase inhibitors, 11-beta hydroxysteroid dehydrogenase (11B-HSD),(17-beta hydroxysteroid dehydrogenase)(17B-HSD), Protein tyrosine phosphatase(PTP) 1B& 1C, Protein Kinase C(PKC) and Androgen Receptor. These molecular targets, through NF-kB pathways, inhibit COX 2, leading to diminution of the levels of PGF_2 alpha and PGI_2 that regulates gonadotropin releasing hormone receptor (GnRHR) mRNA synthesis, resulting in diminished follicle stimulating hormone (FSH) levels and elevated level of luteinizing hormone (LH**).** The selected medicinal plants are rich in COX 2 inhibitors and androgen receptors blockers.*
Conclusion: *The induction of anti-inflammation with androgen receptors (AR) blockade in healthy physiological conditions may have fertility-regulatory effects, and could be exploited to enhance the efficacy of male chemical contraceptives.*
Key Word*:*
Phytocompounds; Contraceptives; Anti-inflammation;Spermatogenesis, Gonadotropins, Cyclooxygnease; Anti-oxidation Androgen receptors (AR);

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I. Introduction

Plants are like pots in which phytocompounds are cooked according to the recipe provided by nature. Many of these phytocompounds modulate the activities of enzymes and receptors in the living organisms[1], little wonder plants have been used as medicine since humans came into existence. The good thing about the use of plants as medicine is that the chemicals therein are natural and attuned to the human organ systems.The natural products are most important resources for developing new lead compounds and scaffolds[2]. With the recent demand for natural/organic products, which hinges on the fact that natural is better, the search for plants with huge medicinal and therapeutic value can never abate.

The search for reversible, safe, and organic contraceptives is still ongoing as the chemical contraceptives in use for females have numerous side effects[3]; and there is no one available for males, even though men are

willing to relieve the burden of chemical contraceptives from females. Therefore, search for safe, reversible, and organic contraceptives from a morass of plants cannot be overemphasized.

From our search through medicinal plants, we saw a pattern: a greater number of medicinal plants with strong anti-inflammatory properties also have anti-spermatogenic effects. Therefore, this preliminary research was undertaken to investigate the possible link between the anti-inflammatory activities of selected medicinal plants and there anti-spermatogenicity, with the aim of highlighting their putative molecular targets. Some of these plants with fertility-regulatory potentials and the phytocompounds replete in them are as follows:

Medicinal Plants With Fertilty-regulatory Activities With Their Respective Phytocompounds
Andrographis paniculata Prabha

Prabha *et al.,* 2019 showed that the major compounds present in *Andrographis paniculata* are Bis (2-ethylhexyl) phthalate (68.99%) and 9,12-Octadecadienoic acid (Z, Z)-2,3-dihydroxy Propyl ester (66.89%)[4]. This medicinal plant has been shown to have anti-spermatogenic activities[5].

Aristolochia indica

Aristolochia indica is replete with octadecanoic acid, 2,3-dihydroxypropyl ester, phosphoric acid, 2-chloroethenyl dimethyl ester (arachidonic acid inhibitor), pentanoic acid, 2-methylcyclohexyl ester, cis- (arachidonic acid inhibitor), O-Isobutyl methylphosphonothiolate (aldehyde oxidase inhibitor, downregulation of nuclear and cytosol androgen), 2-mthyl-3-methoxy-4H-pyran-4-one (11B-HSD-Inhibitor, 17-beta-hydroxysteroid dehydrogenase Inhibitor, 5-HETE-Inhibitor, 5-HT-Inhibitor, aryl-hydrocarbon-hydroxylase-Inhibitor), hexadecenoic acid, 2-hydroxy-1-(hydroxymethyl) ethyl ester (17beta hydroxysteroid dehydrogenase Inhibitor, testosterone-hydroxylase-inducer, acidifier, arachidonic acid inhibitor), pyrimidinedione, 5-iodo-5-methyl-iodothronine (deiodinase inhibitor, 11B-HSD- Inhibitor,12-lipoxygenase-Inhibitor,17-beta-hydroxysteroid dehydrogenase inhibitor,5-alpha-reductase-inhibitor,5-HT-Inhibitor,Aryl-Hydrocarbon-Hydroxylase-Inhibitor), ethyl-3,5-dimethylpyridine Smart Drug, (+)-Inotropic, (-)-Chronotropic (11B-HSD Inhibitor,12-lipoxygenaseinhibitor, 17-beta-hydroxysteroiddehydrogenase-Inhibitor, 5-alpha-reductase inhibitor, 5-HT-inhibitor, 8-HT Inhibitor, 5-lipoxygenase inhibitor), Kumar et al [2].. Both alcohol and aqueous extract of *Aristolochia indica* leaf has been shown to have antispermatogenic effect [5]

Plumbago zeylanica

Plumbago zeylanica Ajayi et al showed that the *Plumabago zeylancia* extract contains the following phytocompounds: phenol,2,4-bis(1,1-dimethylethyl) (54.623 %) , cyclopentadecane (3.748 %), hexadecanoic acid, methyl ester (0.942 %), 9-octadecenoic acid, methyl ester (1.9092 %), H-Indo-2-one,] 1-(2,6-dichlorophenyl)-1,3-dihydro- (0.653 %), heneicosanoic acid, methyl ester (2.095 %), 13-Docosenoic acid, methyl ester (2.369 %) [6] Ethanol extract of Plumbago zeylanica root has been shown to have antispermatogenic effect [5]

Imperata cylindrica

Imperata cylindrica is replete with -18-octadec-9-enolide (76.3%) octadecanoic acid (65.7%) bisnorphane, 13 octadecenoic acid [7] Results showed that the administration of the *Imperata cylindrica L.*root ethanol extract disrupted the testis interstitial area and seminiferous tubules, resulting in decreased epididymal sperm quality as well as serum testosterone levels in a dose-dependent pattern[24].

Phyllanthus amarus

Phyllanthus amarus: The phytocompounds present in the *Phyllanthus amarus* extract are : 9,12,15-octadecatrienoic acid (57.05 %), hexadecanoic acid, methyl ester (1.25 %), hexadecanoic acid, 1-methylethyl ester (5.39) [8] and 2, 13-octadecadiene-1-ol [9].Feeding an alcohol extract of *Phyllanthus* at a dose of 500 mg/kg for 45 days induced gradual inhibition of fertility potential in male albino mice with a decline in epididymal sperm profiles. [19]

Euphorbia hirta:

Euphorbia hirta: Igwe *et al* showed the presence of the following compounds - Hexadecanoic acid (4.12%), 2,3,5-trimethyl-1H-pyrrole(3.65%), 4-amino-4-oxobut-2-enoic acid(4.02%), Niacin or nicotinic acid (22.7%)- in the extract of *Euphorbia hirta* [10] The extract of *Euphorbia hirta* leaves have been shown to cause a reduction of sperm motility from 80% in the control to 47.5% in the experimental groups and live-dead ratio from 90.75% in the control to 32.5% in the experimental groups in rams [20].

Chromoleana odorata

Otuokere *et al*., showed the presence of the following compounds in the extract of Chromoleana odorata leaf**:** histamine (1.37%), 2-ethyl-2-hexen-1-al (3.91%), 1H-indole-4- carboxaldehyde (11.38%), p-cresidine (4.71%), hexadecanoic acid (17.37%), hexadecanoic acid, ethyl ester (14.17%), 9,12-octadecadienoic acid, methyl ester (13.53%), 2-ethylhex-3-enal (9.35%), 9,12,15- octadecatrien-1-ol (19.52%) and sarcosine, N-(2-methoxybenzoyl)-,octyl ester (7.32%). histamine (1.37%), 2-ethyl-2-hexen-1-al (3.91%), 1H-indole-4-carboxaldehyde (11.38%), p-cresidine (4.71%), hexadecanoic acid (17.37%), hexadecanoic acid, ethyl ester (14.17%), 9,12-octadecadienoic acid, methyl ester (13.53%), 2-ethylhex-3-enal (9.35%), 9,12,15-octadecatrien-1-ol (19.52%) and sarcosine, N-(2- methoxybenzoyl)-, octyl ester (7.32%) [11]. The crude alkaloid extract of *Chromoleana odorata* leaf has been shown to be antispermatogenic in rats [21].

Bryophyllum pinnatum:

Asiwe et al., showed that the major constituents present in Bryophylum pinnatum are hexadecanoic acid, methyl ester (24.88%), 10,13-Octadecadienoic acid, methyl ester (29.69%), tetracosanoic acid, methyl ester (7.84%), methyl stearate (6.97%), cis-Methyl 11-eicosenoate (6.26%), methyl 18- methylnonadecanoate (4.99%), docosanoic acid, methyl ester (3.71%) and 4,7-Methano-1H indene, octahydro- (2.43%) [12].The leaf extract of *Brophyllum pinnatum* possesses antifertility effects due to its suppressive effects on spermatogenesis in male wistar rats [22]

Carica papaya

Carica papaya is replete with 9-octadecenoic (28.86%), octadecanoic acid ethyl ester (14.22%)[13]. Both alcohol and aqueous extract of *Carica papaya* leaf has been shown to have antispermatogenic effects [5].

Azadirachta indica

The phytocomponds replete in this plant are phytol, linolenic acid, homo-γ-linolenic acid, palmitic acid and tridecylic acid.[14] The aqueous and alcohol extract of *Azadirachta indica* leaf induced decrease in the weight of seminal vesicles, ventral prostate, reduction in epithelial height, nuclear diameter, and the secretory materials in the lumen.

Justicia gendarusa

The phytocompounds replete in *Justicia gendarusa* are hexadecanoic acid, teradecamethyl-cyclohetasiloxane, 9, 12- octadecadienoic acid, octadecanoic acid[15]. The extract from this plant have beeen used as male contraceptive in Indonessia [23]

Justicia carnea

GC – MS analysis of ethanol leaf extracts of *J. carnea* showed the presence of six phytocompounds – isonicotinic acid N- oxide (2.55 %), phosphoinodithioc acid, diphenyl (1.73 %), hexadecanoic acid (10.5 %), 2,2,3,3,5,5,5 – nonafuoro – pentanoic acid methyl ester (73.19 %), 9,12,15 – octadecatrien- 1 – ol (9.33%), and 7H – purine, 7 – benzyl – 2,6 dichloro (2.45 %) [17] The ethanol extract of Justicia carnea leaf has been shown to have antispermatogenic potentials [18]

Cannabis sativa

Cannabis sativa is replete with three isomeric cannabinoids: cannabidiol (CBD), Δ9-tetrahydrocannabinol (Δ9-THC), and Δ8-tetrahydrocannabinol (Δ8-THC). [16] *Cannabis sativa* has been shown to induce testicular lessions in rats [5]

II. Methods

Swiss Target Prediction and Literature Review: The medicinal plants were sampled through browsing by using the keywords such as: antifertility, contraceptive, antispermatogenic, and fertility-regulation of medicnal plants**.** Only search results from known journals were used. In addition the phytocompounds present in the sampled medicinal plants were gotten from published journals. Then, SWISS target prediction of the individual compounds found in each of the afore-mentioned anti-spermatogenic plants were carried out to see if there are any commonalities in their molecular targets [34].

Study Design: This research employed a lot literature reviews and Swiss targets prediction of phytocompounds resident in known anti-spermatogenic plants to generate a range of molecular targets modulated by the compounds, and also to identify those targets that are most recurrent. The physiological effects/outputs of the identified targets were researched to identify their relevance in answering the questions raised by our previous research, which is the plausible link between anti-inflammatory events and induction of anti-spermatognesis.

Study Location: Prof. S. C. Udedi's Research and Development Laboratory, Nnamdi Azikiwe University, Akwa, Nigeria.

III. Result And Discussion

From Swiss Target Prediction, the most common molecular targets modulated by the phytocompounds (Table 1) replete in the selected anti-spermatogenic plants were fatty acid amido hydrolase(FAAH), cycloxygenase (COX 1 & 2)), tyrosine protein phosphatase, 11-beta hydroxysteroid dehydrogenase, 17-beta hydroxysteroid dehydrogenase, androgen receptors, prostanoid receptors, testis-specific androgen-binding, prostanoid DP receptor, arachidonate 15-lipoxygenase, cytosolic phospholipase A2, prostanoid EP4 receptor, corticosteroid binding globulin, vanilloid receptor, glucocorticoid receptor, estrogen receptor alpha, phospholipase A2 group 1B, prostanoid EP1 receptor, steroid 5-alpha-reductase, phosphodiesterase, nitric oxide synthase, inducible, prostanoid EP2 receptor, receptor-type tyrosine-protein phosphatase F, estrogen receptor beta, prostaglandin E synthase, protein-tyrosine phosphatase 1B, peroxisome proliferator-activated receptor gamma, peroxisome proliferator-activated receptor alpha, peroxisome proliferator-activated receptor delta, cannabinoid receptor 1, cannabinoid receptor 2, pI3-kinase p110-delta subunit, metabotropic glutamate receptor, MAP kinase ERK2, protein kinase C gamma, protein kinase C alpha, cyclin-dependent kinase 2/cyclin, c-Jun N-terminal kinase 2, inhibitor of NF-kappa-B kinase, prostanoid IP receptor, trace amine-associated receptor 1, adenosine A1 receptor, adenosine A2a receptor, adenosine A3 receptor, and adenosine A2b receptor.

Table no 1: Molecular targets of some phytocompounds replete in the selected anti-spermatogenic plants

PHYTOCOMPOUNDS	SOURCES	TARGETS
3-Methyl-3,4-divinylcyclohexene	C. ODORATA	1.Peroxisome proliferator-activated receptor alpha 2.Cannabinoid receptor 2
Geijerene	C. ODORATA	Peroxisome proliferator-activated receptor alpha) 2. Cannabinoid receptor 2 3. LXR-alpha
Bis(2-ethylhexyl) phthalate	Andrographis paniculata Prabha	1. Androgen Receptor 2. T-cell protein-tyrosine phosphatase 3. Protein-tyrosine phosphatase 1B 4. Protein kinase C (delta & alpha) 5. Cathepsin (K,L, S AND B) 6. Phosphodiesterase 10A 7. Metabotropic glutamate receptor 2 8. Cyclin-dependent kinase 4/cyclin D1 9. Cyclin-dependent kinase 4/cyclin D1 10. Cyclin-dependent kinase 2/cyclin E1
9,12 Octadecadienoic acid	Andrographis paniculata Prabha, Justicia gendarusa, Chromoleana odorata	1. Peroxisome proliferator- activated receptor (gamma,alpha & delta) 2. Free fatty acid receptor 1 3. Fatty acid binding protein adipocyte 4. Cyclooxygenase-1 5. Anandamide amidohydrolase) 6. Cannabinoid receptor 1 7. Arachidonate 5-lipoxygenase 8. Protein-tyrosine phosphatase 1B
13 octadecenoic acid	Imperata cylindrica	1. Anandamide amidohydrolase 2. Peroxisome proliferator-activated receptor (delta & gamma) 3. Protein-tyrosine phosphatase 1B 4. T-cell protein-tyrosine phosphatase 5. Protein-tyrosine phosphatase 1C 6. Cyclooxygenase-2 7. 11-beta-hydroxysteroid dehydrogenase 1
Bisnorphane	Imperata cylindrica	1.Testis-specific androgen-binding protein
Z)-18-octadec-9-enolide	Imperata cylindrica	1. Protein-tyrosine phosphatase 1B 2. Anandamide amidohydrolase 3. 11-beta-hydroxysteroid dehydrogenase 1 4. Prostaglandin E synthase 5. Androgen Receptor 6. Cyclooxygenase-2 7. Protein kinase C theta & delta

Methyl heneicosanoate	**Plumbago zeylanica**	**1. Carbonic anhydrase I & II** **2. Estradiol 17-beta-dehydrogenase** **3. Peroxisome proliferator -activated receptor (alpha & delta)** **4. Androgen Receptor**
1-(2,6-Dichlorophenyl)-2-indolinone	**Plumbago zeylanica**	**1. Interleukin-8** **2. Intercellular adhesion molecule (ICAM-1), Integrin alpha-L/beta-2** **3. Estradiol 17-beta-dehydrogenase 3** **4. Cyclooxygenase- 1 and 2** **5. Interleukin-8 receptor A** **6. Androgen receptor**
Cyclopentadecane	**Plumbago zeylanica**	**1. Carbonic anhydrase I and II and V** **2. Androgen Receptor** **3. Melatonin receptor 1A and 1B** **4. Cannabinoid receptor 2** **5. Proteasome Macropain subunit MB1** **6. Poly [ADP-ribose] polymerase-1** **7. Quinone reductase 2** **8. Steroid 5-alpha-reductase 1**
2,4-bis-(1,1-dimethylethyl)	**Plumbago zeylanica**	**1. Cathepsin D** **2. 11-beta-hydroxysteroid dehydrogenase 1** **3. Cannabinoid receptor 1 and 2** **4. 11-beta-hydroxysteroid dehydrogenase 2** **5. N-arachidonyl glycine receptor** **6. Vascular endothelial growth factor receptor 2** **7. Glycine receptor subunit alpha-1**
Gendarusa2	**Justicia gendarusa**	**1. Carbonic anhydrase II, III and XIII** **2. Dopamine D4 receptor** **3. Dopamine D3 receptor** **4. Adenosine A1 receptor** **5. Adenosine A2a receptor** **6. Adenosine A2b receptor**
Gendarusa2	**Justicia gendarusa**	**1. Adenosine A1 receptor** **2. Adenosine A2a receptor** **3. P-selectin** **4. Galectin-3** **5. Splicing factor 3B subunit 3** **6. Proteasome Macropain subunit MB1** **7. Thymidylate synthase** **8. Sialidase 2** **9. Caspase-,3,6,7,8**
Cannabidiol	**Cannabis sativa**	**1. Cannabinoid receptor 1 and 2** **2. G-protein coupled receptor 55** **3. Arachidonate 5-lipoxygenase** **4. N-arachidonyl glycine receptor** **5. Glycine receptor subunit alpha-1** **6. Arachidonate 15-lipoxygenase** **7. Cathepsin D** **8. Vascular endothelial growth factor receptor 2** **9. Beta-secretase 1**
delta9-Tetrahydrocannabinol	**Cannabis sativa**	**1. Cannabinoid receptor 1 and 2** **2. G-protein coupled receptor 55** **3. Arachidonate 5-lipoxygenase** **4. N-arachidonyl glycine receptor** **5. Glycine receptor subunit alpha-1** **6. Arachidonate 15-lipoxygenase** **7. Cathepsin D** **8. Vascular endothelial growth factor receptor 2** **9. Serotonin 2b (5-HT2b) receptor** **10. Serotonin 2c (5-HT2c) receptor**
cannabinol.	**Cannabis sativa**	**1. Cannabinoid receptor 1 and 2** **2. N-arachidonyl glycine receptor** **3. Vascular endothelial growth factor receptor 2** **4. Receptor protein-tyrosine kinase erbB-2** **5. Epidermal growth factor receptor erbB1** **6. 11-beta-hydroxysteroid dehydrogenase 1** **7. Phosphodiesterase 4B**
9,12,15-octadecatrien-1-ol	**Chromoleana odorata** **Justicia carnea**	**1. Androgen Receptor** **2. Peroxisome proliferator-activated receptor**

		gamma and delta, gamma and delta 3. Protein-tyrosine phosphatase 1B 4. Cyclooxygenase-1
Methano-1-Hindene	**Bryophyllum pinnatum**	**1.Testis-specific androgen-binding protein**
Docosanoic acid	**Bryophyllum pinnatum**	**1. Carbonic anhydrase I and II 2. Estradiol 17-beta-dehydrogenase 3 3. Peroxisome proliferator-activated receptor (delta & alpha)**
Methyl -18- nonadecanoate	**Bryophyllum pinnatum**	**1. Carbonic anhydrase I and II 2. Androgen Receptor 3. Arachidonate 5-lipoxygenase 4. Vanilloid receptor**
10,13-Octadecadienoic acid, methyl ester	**Bryophyllum pinnatum**	**1. Peroxisome proliferator-activated receptor (gamma, delta, & alpha). 2. Cannabinoid receptor 1 and 2 3. Cyclooxygenase-1 4. 11-beta-hydroxysteroid dehydrogenase 1 5. Anandamide amidohydrolase 6. Arachidonate 5-lipoxygenase**
Tridecanoic acid methyl ester	**Aristolochia indica**	**1. Carbonic anhydrase I and II 2. Androgen Receptor 3. Estradiol 17-beta-dehydrogenase 4. Peroxisome proliferator-activated receptor (alpha & delta) 5. 11-beta-hydroxysteroid dehydrogenase 1**
Octadecanoic acid, 2,3-bis(acetyloxy)propyl ester	**Aristolochia indica**	**1. 11-beta-hydroxysteroid dehydrogenase 1 2. Protein kinase C (eta, epsilon, alpha, delta, theta)**
eicosatrienoic		**1. Cyclooxygenase-1 and 2 2. Cannabinoid receptor 1 3. Anandamide amidohydrolase 4. Peroxisome proliferator-activated receptor alpha,gamma & delta 5. Protein-tyrosine phosphatase 1B**
Phytol	**Azdiracta indica**	**1. 11-beta-hydroxysteroid dehydrogenase 2 2. Androgen Receptor 3. Protein kinase C (alpha, beta, delta, gamma. epsilon, eta and theta).**
9,12,15-octatrienoic acid	**Phyllanthus amarus, Chromoleana odorata**	**1. Peroxisome proliferator-activated receptor (alpha, gamma & delta) 2. Cyclooxygenase-1 3. Anandamide amidohydrolase 4. Cannabinoid receptor 1 5. Protein-tyrosine phosphatase 1B 6. Arachidonate 5-lipoxygenase**
9-octadecenoic	**Carica papaya, Plumbago zeylanica**	**1. Anandamide amidohydrolase 2. Peroxisome proliferator-activated receptor (alpha,gamma & delta) 3. Protein-tyrosine phosphatase 1B**

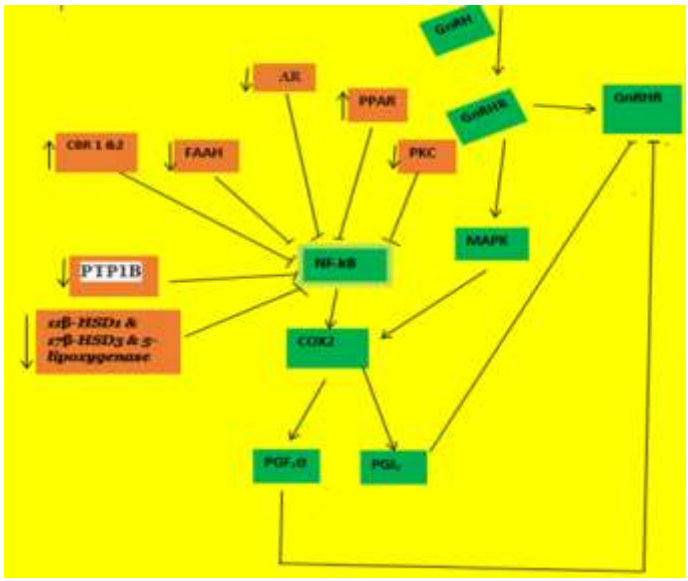

Figure 1: The crosstalk between anti-inflammatory pathways and hypothalamus-pituitary axis.

From figure 1, the inhibition of androgen receptor[26], fatty acid amide hydrolase [29], protein tyrosine phosphatase [30], 17beta-hydroxysteroid dehydrogenase [27], 11beta-hydroxysteroid dehydrogenase [28] ,5-lipoxygenase [33] abrogates nuclear factor-kappaB (NF-kB) activity, and hence the inhibition of cyclooxygenase 2 (COX2); whereas the activation of peroxisome proliferator activated receptor gamma [31] and cannabinoid receptor 1 & 2 [32] abrogates nuclear factor - kappaB and hence inhibition of cyclooxygenase 2 (COX2). Gonadotropin releasing hormone (GNRH) action activates cyclooxygenase activities, therefore any phytocompound that elicits the molecular targets that dampen cyclooxygenase activities (anti-inflammation) may rub off negatively on spermatogenesis. The phytocompounds listed above (Table 1) regulate molecular targets that dampen cyclooxygenase activities; this points to their anti- GnRHs pontentials/effects. Their actions mediate the diminution in the levels of prostaglandins that have roles in maintenance of the pulsatile secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) through the modulation of gonadotropin releasing hormone (GnRHR) mRNA synthesis.

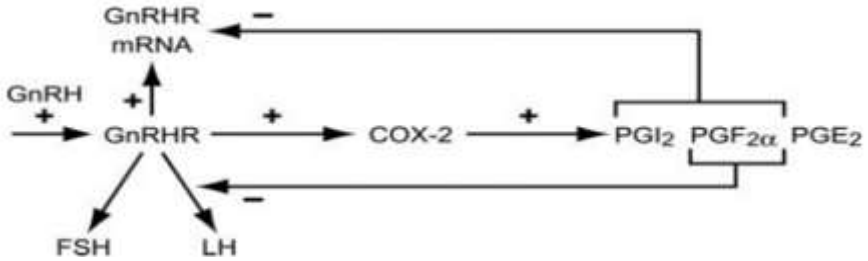

Figure 2: The crosstalks between GnRH actions and cyclooxygenase pathways (adapted from Naor *et al*.,2007)[25]

From figure 2, Pro- GnRH events would stimulate cyclooxygenase activities leading to production of prostaglandins that would mount feed- back inhibition of the pro-GnRH events. Therefore, the inhibition of cyclooxygenase activity by the phytocompounds found in the antispermatogenic plants would lead to diminution of the levels of PGI_2 and PGF_{2alpha} which mounts inhibtion on excessive secretion of GnRHR mRNA and LH.

PGI_2 and pGF2 alpha appear to play a role in pulsatile secretion of GnRHR, and any sustained diminution in their levels would abrogate the pulsatile secretion of GnRHR, leading to elevated GnRHR mRNA level, reduction in FSH levels and increased LH levels. Increased GnRHR number intensifies LHβ responses while diminishing the frequency selectivity of FSHβ activation[35 & 36.] The increase in LH levels would lead to increased testosterone levels and the reduction of FSH levels halts spermatogenic events. The increased testosterone levels would in turn tend to suppress LH levels through its action at the hypothalamus and through its aromatisation to estradiol at the pituitary site; but these actions would not proceed when the phytocompounds are rich in aromatase inhibitor(PPAR gamma inhibits aromatase activity)and androgen receptor inhibitors and androgen synthesis inhibitors. Therefore the resultant effect is antispermatogenesis due to reduced FSH levels and in part due to prolonged & sustained LH levels and testosterone levels (in the absence of testosterone synthesis inhibitors) in the plasma and androgen receptors blockade.

We therefore propose combination/synergistic therapy as the plausible strategy for effective male contraception which is the administration of cyclooxygenase (COX 2) inhibitors, aromatase inhibitors and androgen receptors inhibitors and testosterone synthesis inhibitors. This combination could lead to increase in efficacy of male contraception modalities.

The sustained administration of cyclooxygenase inhibitors (i.e mediation of anti-inflammation) would lead to decrease in levels of PGI_2 which inhibits the synthesis of GnRHR mRNA and decrease in the levels of $PGF_{2alpha,}$ which inhibits the synthesis of GnRHR mRNA and decreases LH levels. The diminution in the levels of these prostaglandins therefore lead to sustained increase in LH levels. Increasing LH levels triggers testosterone production which mounts feed-back inhibition on LH release at hypothalamus and pituitary gland. However, administration with testosterone synthesis inhibitors/ androgen receptor inhibitors would abrogate androgen-mediated suppression of LH. Similarly, administration with aromatase inhibitors would prevent the aromatisation of testosterone to estradiol which suppresses LH levels.

Within these medicinal plants is nature, providing a mix of cyclooxygenase inhibitors, aromatase inhibitors, and androgen receptors inhibitors and testosterone synthesis inhibitors which is the proposed synergistic strategy for effective male contraception. This would sustain elevated LH and reduced FSH with androgen recepors blockade, leading to antispermatogenic activities in normal and healthy states.

However, in abnormal states-which is infertility caused by oxidative stress, inflammation and elevated androgens, a pro-fertility effect can be achieved with this mix as inhibition of cyclooxygenase activity has been linked to anti-oxidation.

IV. Conclusion

Medicinal plants with high anti-inflammatory activities induced anti-spermatogenesis through the modulation of molecular targets that mediated inhibition of cyclooxgenase activities. Mediation of anti-inflammation in healthy/ normal conditions of mammals, seemed to downregulate the production of prostaglandins which play a role in regulation of gonadotropin releasing hormone receptor (GnRHR). The sustained and elevated increase in the number of GnRHR led to decrease in follicle stimulating hormone (FSH) levels and elevated Luteinizing hormones levels (LH). This could explain the reduction of spermatogenic events induced by strong anti-inflammatory medicinal plants. However, this study is allied to in silico prediction and literature review, therefore the proposed synergistic contraceptive strategy requires further experiments to confirm.

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