

Hormone and Urinary Metabolites Assessment Profile

Clinical and Therapeutic Considerations



SCIENCE + INSIGHT



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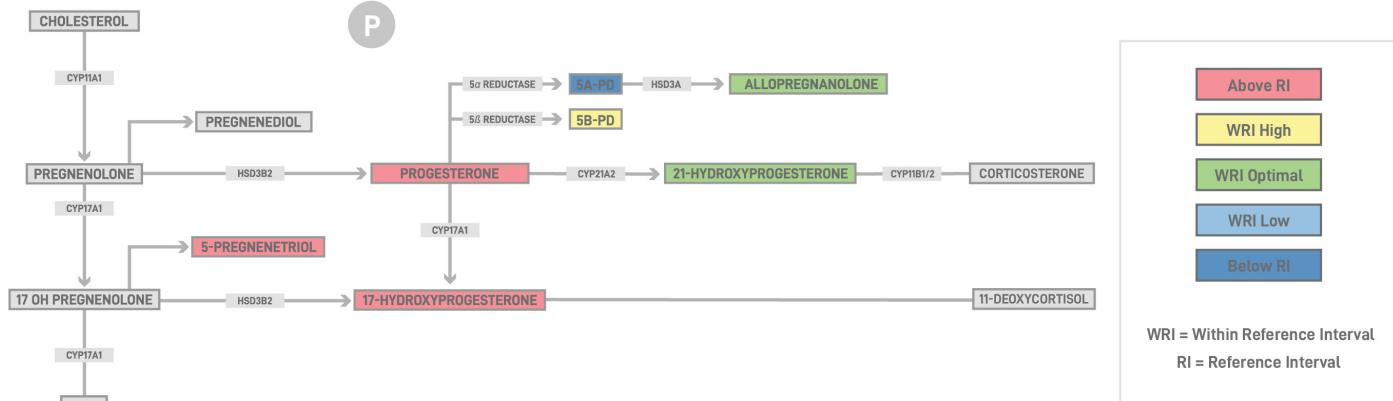
Health Disclaimer: All information given about treatments is not intended to be a substitute for professional medical advice, diagnosis or treatment. The information provided is based on scientific literature and the experience of Doctor's Data Scientific Support staff and guest experts; it is not a recommendation for the treatment of a specific patient. Treating physicians are responsible for determining proper treatment options based upon factors including, but not limited to, laboratory analysis, physical exams, symptoms, patient histories, diet and lifestyle evaluations, and most importantly, the physician's own judgment.





TARGETED TREATMENT CONSIDERATIONS AND INFLUENCES

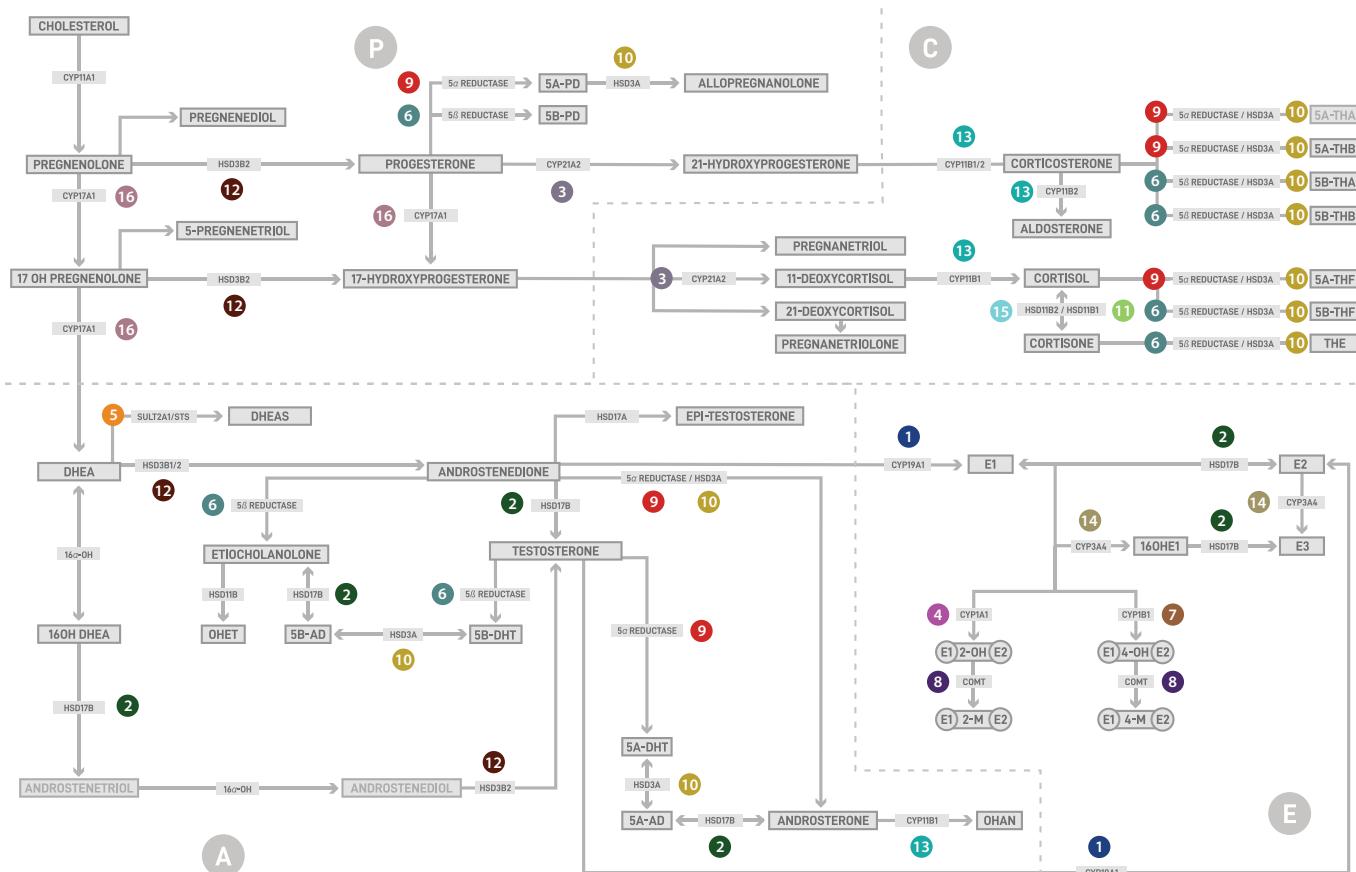
Your patient's HuMap results will dynamically illustrate areas of hormone metabolism that may require additional support. The pathways on your patient's HuMap results will be color coded to correspond with their test results, allowing for clear assessment of highs and lows.



*Example HuMap results, for illustrative purposes only

This document is designed to complement your patient's HuMap results and present evidence-based treatment considerations and influences in two ways. **On the top of page 5**, you will find a comprehensive and expanded view of potential influences, including treatments and lifestyle considerations. Organized by enzyme, these influences have been shown to slow down or speed up enzyme activity.

The chart on the bottom of page 5 provides a valuable reference for simplifying treatment considerations and understanding the potential effects of common, multi-functional treatments on hormone metabolism. Based on research findings, it identifies treatments that have been shown to influence multiple enzymes involved in hormone metabolism, serving as a handy tool to assess the potential benefits and unintended effects of different treatment strategies.



1 CYP19A1	(-) Chrysin, Zn, nettles, damiana, grape seed, ECGC, resveratrol, licorice, flavonoids, anti-inflammatories (+) Coleus forskohlii, inflammation, stress, Zn deficiency, excess adipose, high insulin, alcohol	7 CYP1B1	(-) Apiaceae family, grapefruit, resveratrol, rosemary, St John's wort, quercetin, flavonoids, curcumin, ECGC, rooibos (+) THC, UV exposure, PAHs, PCBs, diesel exhaust, inflammation, insulin resistance, leptin resistance	12 HSD3B1/2	(-) Resveratrol, isoflavonoids, progestins, phytoestrogens, trilostane, troglitazone, ketoconazole, metformin, chronic EtOH use, CAH (+) Fenugreek, pregnenolone, PCOS, high insulin, hyperadrenalinism, hyperthyroid, inflammation, coleus forskohlii
2 HSD17B	(-) Licorice, quercetin, apigenin, phytoestrogen, flax, tamoxifen (+) Grape seed, propolis, DHEA, coleus forskohlii, rutin, flavonoids, alcohol, inflammation, abdominal adiposity	8 COMT	(-) High sucrose diet, leptin resistance, inflammation, bisphenol and PCBs (+) B12, folate, Mg, methionine, SAMe, betaine, TMG, resveratrol, citrus, rosemary, DIM, rooibos, curcumin	13 CYP11B1/2	(-) Flavonoids, isoflavones, DHEA, azoles (+) Vit D, Korean red ginseng, coleus forskohlii, heme, dexamethasone, progestins, tizanidine
3 CYP21A2	(-) Vit D, resveratrol, curcumin, rooibos, apigenin, isoflavonoids, DHEA, omeprazole, valproic acid, PDE inhibitors (+) Coleus forskohlii	9 5α Reductase	(-) Saw palmetto, nettles, pygeum, ECGC, progesterone, Zn, berberine, polyunsaturated fatty acids (+) DHEA, insulin resistance, obesity, PCOS, essential HTN, high carb diet, sodium restriction	14 CYP3A4	(-) Grapefruit, aloe, polyphenols (i.e. resveratrol), flavonoids, ECGC, coffee, fennel, black pepper, licorice, chrysanthemum, quercetin (+) St. John's wort, capsaicin, valerian, gingko biloba, fatty acids, Vit D
4 CYP1A1	(-) Resveratrol, ECGC, berries, St. John's wort, lycopene, propolis, grapefruit (+) DIM, rosemary, fish oil, tea, coffee, hops	10 HSD3A	(-) Coumestrol, taxifolin, mirtazapine (+) Sulforaphane, oral progesterone, coleus forskohlii	15 HSD11B2	(-) Intense exercise, grapefruit, progesterone, licorice, fluoxymesterone, azoles (+) Glucocorticoids, NAD
5 SULT2A1/STS	(-) Quercetin, licorice, spironolactone, testosterone, clomiphene, inflammation (+) Genistein	11 HSD11B1	(-) Physical activity, rooibos, holy basil, curcumin, bitter melon, ECGC, progesterone, coffee, hyperthyroid, estrogen excess (+) Glucocorticoids, inflammation, hypothyroid, impaired glucose tolerance, insulin resistance, visceral adiposity	16 CYP17A1	(-) Resveratrol, curcumin, licorice, apigenin, isoflavones, spironolactone, azoles, metformin, nicotine, dioxins (+) Vit D, DHEA, coleus forskohlii, hyperglycemia, stress, alcohol, antiepileptics (high dose), PCBs
6 5β Reductase	(-) Licorice, budesonide (+) NAD				

	coleus forskohlii	curcumin	DIM	ECGC	grape seed	licorice	quercetin	resveratrol	rooibos	rosemary
1 CYP19A1	+			-	-	-		-		
2 HSD17B	+				+	-	-			
3 CYP21A2	+	-						-	-	
4 CYP1A1			+	-				-		+
5 SULT2A1/STS						-	-			
6 5β Reductase						-				
7 CYP1B1		-		-			-	-	-	-
8 COMT		+	+					+	+	+
9 5α Reductase				-						
10 HSD3A	+									
11 HSD11B1		-		-					-	
12 HSD3B1/2	+							-		
13 CYP11B1/2	+									
14 CYP3A4				-		-	-	-		
15 HSD11B2						-				
16 CYP17A1	+	-				-		-		



EXPANDED CONSIDERATIONS AND REFERENCES

Hormone metabolism is complex. Focusing on individual enzymes can be helpful, but improving lifestyle and diet is an appropriate way to impact overall balance. Consider high fiber, brightly colored fruits and veggies, herbs and spices, stress management, exercise, reducing environmental exposures, improving gastrointestinal health, etc.

Note: Bioavailable unconjugated hormones (i.e. estradiol, progesterone, etc) are not well represented in urine. When utilizing hormone therapy, confirming low or elevated values via salivary testing is a consideration.

Progesterones

Progesterone Low	Progesterone High
<p>Upregulate HSD3B2:</p> <ul style="list-style-type: none"> Forskolin (found in coleus plant) HCG FSH <p>Address contributing factors:</p> <ul style="list-style-type: none"> Stress, hyperinsulinemia, opioids, high prolactin, underweight, hypothyroid, low cholesterol <p>Avoid (if possible):</p> <ul style="list-style-type: none"> Inhibitors of HSD3B2: endocrine disruptors, including industrial compounds (phthalates, bisphenols, and perfluoroalkyl substances), insecticides and biocides (organochlorine insecticides and organotins), food additives (butylated hydroxyanisole), and drugs (etomidate, troglitazone, medroxyprogesterone acetate, and ketoconazole) inhibit testicular HSD3B2 4th generation progestins – NoMAC, drospirenone, nestorone; azastene, cyanoketone, epostane, trilostane THC Gossypol (cotton seed) 	<p>Downregulate HSD3B2:</p> <ul style="list-style-type: none"> Resveratrol Flavones, isoflavones Androstenedione Medication: metformin <p>To support appropriate metabolism, refer to:</p> <ul style="list-style-type: none"> Low 21-Hydroxyprogesterone (Upregulate CYP21A2) Low 17-Hydroxyprogesterone (Upregulate CYP17A1) Low 5A-PD Low 5B-PD
5A-PD Low	5A-PD High
<ul style="list-style-type: none"> Progesterone supplementation Vitex tincture Avoid gossypol, which downregulates HSD3B2 	<p>Downregulate 5α reductase:</p> <ul style="list-style-type: none"> Polyunsaturated fatty acids Berberine Saw palmetto Nettles Pygeum Green tea, EGCG Progesterone Zinc 5α reductase inhibitors such as finasteride <p>Downregulate HSD3B2:</p> <ul style="list-style-type: none"> Resveratrol Flavones, isoflavones Androstenedione Medication: metformin

5B-PD Low	5B-PD High
<ul style="list-style-type: none"> Progesterone supplementation Vitex tincture Avoid gossypol, which downregulates HSD3B2 	<p>Downregulate 5β reductase:</p> <ul style="list-style-type: none"> Licorice Medication: budesonide <p>Downregulate HSD3B2 (if progesterone is elevated):</p> <ul style="list-style-type: none"> Resveratrol Flavones, isoflavones Androstenedione Medication: metformin
Allopregnanolone Low	Allopregnanolone High
<p>Upregulate HSD3A:</p> <ul style="list-style-type: none"> Oral progesterone Sulforaphane Forskolin (found in coleus plant) Medications: paroxetine and fluoxetine raise allopregnanolone in rodents without affecting pregnenolone or progesterone levels <p>Avoid inhibitors of HSD3A:</p> <ul style="list-style-type: none"> Methoxychlor (pesticide) and its metabolite HPTE, gossypol, Ziram (fungicide) 	<p>Downregulate HSD3A:</p> <ul style="list-style-type: none"> Genistein Daidzen Coumestrol Taxifolin Medications: sepranolone, mirtazapine <p>Address:</p> <ul style="list-style-type: none"> Visceral adipose tissue which increases HSD3A activity Hyperinsulinemia, obesity, PCOS increase 5α reductase activity <p>Downregulate 5α reductase (to decrease the precursor):</p> <ul style="list-style-type: none"> Polyunsaturated fatty acids Berberine Saw palmetto Nettles Pygeum Green tea, EGCG Progesterone Zinc 5α reductase inhibitors such as finasteride
21-OH Progesterone Low	21-OH Progesterone High
<p>Upregulate CYP21A2:</p> <ul style="list-style-type: none"> Calforsin (Coleus Forskoli) <p>Downregulate CYP11B1/2:</p> <ul style="list-style-type: none"> Medications for Cushing Syndrome: metapyrone Osilodrostat (inhibitor of both the CYP enzymes 11β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2)) <p>Address/avoid:</p> <ul style="list-style-type: none"> Chronic exposure to ACTH, Cushing's disease, type 2 diabetes, congenital adrenal hyperplasia and adrenocortical carcinoma Sodium depletion, High prolactin, Stress, Inflammation, Obesity Galaxolide (common synthetic musk scent in perfumes and household cleaners) 	<p>Downregulate CYP21A2:</p> <ul style="list-style-type: none"> Vitamin D Resveratrol Curcumin Flavonoids (rooibos, apigenin) Isoflavones (daidzein) Medications: PDE inhibitors, valproic acid <p>Upregulate CYP11B1/2:</p> <ul style="list-style-type: none"> Heme iron (cofactor) Dexamethasone, medroxyprogesterone, pemirolast, clobenpropit, desogestrel, dexmedetomidine, tizanidine Vitamin D Korean red ginseng <p>Avoid:</p> <ul style="list-style-type: none"> Insecticides (fipronil) which upregulate CYP21A2

17-OH Progesterone Low	17-OH Progesterone High
<p>Upregulate CYP17A1:</p> <ul style="list-style-type: none"> Vitamin D <p>Upregulate HSD3B2:</p> <ul style="list-style-type: none"> Calforsin (Coleus Forskoli) HCG FSH <p>The most frequent cause of a low 17-OHP concentration is suppression of the pituitary–adrenal axis by synthetic glucocorticoids given therapeutically.</p> <p>Avoid:</p> <ul style="list-style-type: none"> Insecticides (fipronil) which upregulate 21 hydroxylase Gossypol which downregulates HSD3B2 	<p>Address possible contributing factors:</p> <ul style="list-style-type: none"> Hyperinsulinemia promotes 17 hydroxylase Alcohol and stress increase 17α-hydroxylase activity PCOS, idiopathic hirsutism, congenital adrenal hyperplasia, 11β-hydroxylase deficiency, adult onset virilizing adrenal hyperplasia, and men with cytochrome P450c17 deficiency. Efavirenz (HIV medication) <p>Downregulate CYP17A1:</p> <ul style="list-style-type: none"> Medications: spironolactone, azole antifungals <p>Downregulate HSD3B2:</p> <ul style="list-style-type: none"> Resveratrol Flavones, Isoflavones Androstenedione Medication: metformin <p>Upregulate CYP21A2 (21 hydroxylase):</p> <ul style="list-style-type: none"> Calforsin (Coleus Forskoli)
5-Pregnenetriol Low	5-Pregnenetriol High
<p>Pregnenolone supplementation</p> <p>Upregulate CYP17A1:</p> <ul style="list-style-type: none"> Vitamin D <p>Downregulate HSD3B2:</p> <ul style="list-style-type: none"> Resveratrol Flavones, isoflavones Androstenedione Medication: metformin 	<p>Downregulate CYP17A1:</p> <ul style="list-style-type: none"> Medications: spironolactone, azole antifungals <p>Address PCOS, Cushing's Syndrome, congenital adrenal hyperplasia, and adrenocortical carcinoma</p> <p>Avoid gossypol, which downregulates HSD3B2</p> <p>Upregulate HSD3B2:</p> <ul style="list-style-type: none"> Forskolin (found in coleus plant) HCG FSH

Progesterones References

- Zhang S, Mo J, Wang Y, et al. Endocrine disruptors of inhibiting testicular 3 β -hydroxysteroid dehydrogenase. *Chem Biol Interact.* 2019;303:90-97. doi:10.1016/j.cbi.2019.02.027
- Louw-du Toit R, Perkins MS, Snoep JL, Storbeck KH, Africander D. Fourth-Generation Progestins Inhibit 3 β -Hydroxysteroid Dehydrogenase Type 2 and Modulate the Biosynthesis of Endogenous Steroids. *PLoS One.* 2016;11(10):e0164170. Published 2016 Oct 5. doi:10.1371/journal.pone.0164170
- Cooke GM. Differential effects of trilostane and cyanoketone on the 3 beta-hydroxysteroid dehydrogenase-isomerase reactions in androgen and 16-androstene biosynthetic pathways in the pig testis. *J Steroid Biochem Mol Biol.* 1996;58(1):95-101. doi:10.1016/0960-0760(96)00002-7
- Mast N, Linger M, Pikuleva IA. Inhibition and stimulation of activity of purified recombinant CYP11A1 by therapeutic agents. *Mol Cell Endocrinol.* 2013;371(1-2):100-106. doi:10.1016/j.mce.2012.10.013
- Lundqvist J, Norlin M, Wikvall K. 1alpha,25-Dihydroxyvitamin D3 affects hormone production and expression of steroidogenic enzymes in human adrenocortical NCI-H295R cells. *Biochim Biophys Acta.* 2010;1801(9):1056-1062. doi:10.1016/j.bbala.2010.04.009
- Kim IH, Kim SK, Kim EH, et al. Korean Red Ginseng Up-regulates C21-Steroid Hormone Metabolism via Cyp11a1 Gene in Senescent Rat Testes. *J Ginseng Res.* 2011;35(3):272-282. doi:10.5142/jgr.2011.35.3.272
- Bird IM, Imaishi K, Pasquarette MM, Rainey WE, Mason JI. Regulation of 3 beta-hydroxysteroid dehydrogenase expression in human adrenocortical H295R cells. *J Endocrinol.* 1996;150 Suppl:S165-S173.
- Hirsch A, Hahn D, Kempná P, et al. Metformin inhibits human androgen production by regulating steroidogenic enzymes HSD3B2 and CYP17A1 and complex I activity of the respiratory chain. *Endocrinology.* 2012;153(9):4354-4366. doi:10.1210/en.2012-1145
- Zoller LC. Effects of tetrahydrocannabinol on rat preovulatory follicles: a quantitative cytochemical analysis. *Histochem J.* 1985;17(12):1347-1358. doi:10.1007/BF01002531
- Asif AR, Ljubojevic M, Sabolic I, et al. Regulation of steroid hormone biosynthesis enzymes and organic anion transporters by forskolin and DHEA-S treatment in adrenocortical cells. *Am J Physiol Endocrinol Metab.* 2006;291(6):E1351-E1359. doi:10.1152/ajpendo.00653.2005
- Rasmussen MK, Ekstrand B, Zamaratskaia G. Regulation of 3 β -hydroxysteroid dehydrogenase/ Δ^5 - Δ^4 isomerase: a review. *Int J Mol Sci.* 2013;14(9):17926-17942. Published 2013 Sep 2. doi:10.3390/ijms140917926
- Havelock JC, Smith AL, Seely JB, et al. The NGFI-B family of transcription factors regulates expression of 3beta-hydroxysteroid dehydrogenase type 2 in the human ovary. *Mol Hum Reprod.* 2005;11(2):79-85. doi:10.1093/molehr/gah139

Thomas JL, Rajapaksha M, Mack VL, DeMars GA, Majzoub JA, Bose HS. Regulation of human 3 β -hydroxysteroid dehydrogenase type 2 by adrenal corticosteroids and product-feedback by androstenedione in human adrenarche. *J Pharmacol Exp Ther.* 2015;352(1):67-76. doi:10.1124/jpet.114.219550

Nicolaides NC, Pavlaki AN, Maria Alexandra MA, et al. Glucocorticoid Therapy and Adrenal Suppression. [Updated 2018 Oct 19]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK279156/>

Malikova J, Zingg T, Fingerhut R, et al. HIV Drug Efavirenz Inhibits CYP21A2 Activity with Possible Clinical Implications. *Horm Res Paediatr.* 2019;91(4):262-270. doi:10.1159/000500522

Ueshiba H, Shimizu Y, Hiroi N, et al. Decreased steroidogenic enzyme 17,20-lyase and increased 17-hydroxylase activities in type 2 diabetes mellitus. *Eur J Endocrinol.* 2002;146(3):375-380. doi:10.1530/eje.0.1460375

Serafini P, Lobo RA. The effects of spironolactone on adrenal steroidogenesis in hirsute women. *Fertil Steril.* 1985;44(5):595-599. doi:10.1016/s0015-0282(16)48972-7

Pignatelli D. Non-classic adrenal hyperplasia due to the deficiency of 21-hydroxylase and its relation to polycystic ovarian syndrome. *Front Horm Res.* 2013;40:158-170. doi:10.1159/000342179

Paton DP. Osilodrostat: 11 β -hydroxylase inhibitor for treatment of Cushing's disease. *Drugs Today (Barc).* 2020;56(10):643-654. doi:10.1358/dot.2020.56.10.3182908

Schüle C, Romeo E, Uzunov DP, et al. Influence of mirtazapine on plasma concentrations of neuroactive steroids in major depression and on 3alpha-hydroxysteroid dehydrogenase activity. *Mol Psychiatry.* 2006;11(3):261-272. doi:10.1038/sj.mp.4001782

Mao B, Wu C, Zheng W, et al. Methoxychlor and its metabolite HPTE inhibit rat neurosteroidogenic 3 α -hydroxysteroid dehydrogenase and retinol dehydrogenase 2. *Neurosci Lett.* 2018;684:169-174. doi:10.1016/j.neulet.2018.08.008

Su Y, Li H, Chen X, et al. Ziram inhibits rat neurosteroidogenic 5 α -reductase 1 and 3 α -hydroxysteroid dehydrogenase. *Toxicol Mech Methods.* 2018;28(1):38-44. doi:10.1080/15376516.2017.1355950

Sasaki M, Shinozaki S, Shimokado K. Sulforaphane promotes murine hair growth by accelerating the degradation of dihydrotestosterone. *Biochem Biophys Res Commun.* 2016;472(1):250-254. doi:10.1016/j.bbrc.2016.02.099

Blouin K, Richard C, Bélanger C, et al. Local androgen inactivation in abdominal visceral adipose tissue. *J Clin Endocrinol Metab.* 2003;88(12):5944-5950. doi:10.1210/jc.2003-030535

Vassiliadi DA, Barber TM, Hughes BA, et al. Increased 5 alpha-reductase activity and adrenocortical drive in women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2009;94(9):3558-3566. doi:10.1210/jc.2009-0837

Blomquist CH, Lima PH, Hotchkiss JR. Inhibition of 3alpha-hydroxysteroid dehydrogenase (3alpha-HSD) activity of human lung microsomes by genistein, daidzein, coumestrol and C(18)-, C(19)- and C(21)-hydroxysteroids and ketosteroids. *Steroids.* 2005;70(8):507-514. doi:10.1016/j.steroids.2005.01.004

Su Y, Zhu Q, Hong X, Ge RS. Taxifolin Inhibits Neurosteroidogenic Rat Steroid 5 α -Reductase 1 and 3 α -Hydroxysteroid Dehydrogenase. *Pharmacology.* 2020;105(7-8):397-404. doi:10.1159/000504057

Cao S, Wang G, Ge F, et al. Gossypol inhibits 5 α -reductase 1 and 3 α -hydroxysteroid dehydrogenase: Its possible use for the treatment of prostate cancer. *Fitoterapia.* 2019;133:102-108. doi:10.1016/j.fitote.2018.12.024

Bäckström T, Ekberg K, Hirschberg AL, et al. A randomized, double-blind study on efficacy and safety of sepranolone in premenstrual dysphoric disorder. *Psychoneuroendocrinology.* 2021;133:105426. doi:10.1016/j.psyneuen.2021.105426

Stansbury J. Saw Palmetto May Reduce Elevated Androgens and Prolactin in Women with PCOS. *Restorative Medicine Digest.* Aug 4 2016. Available at <https://restorativemedicine.org/digest/saw-palmetto-may-reduce-elevated-androgens-and-prolactin-in-women-with-pcos/>. Access confirmed 3/10/2022.

Nahata A, Dixit VK. Evaluation of 5 α -reductase inhibitory activity of certain herbs useful as antiandrogens. *Andrologia.* 2014;46(6):592-601. doi:10.1111/and.12115

Jena AK, Vasishth K, Sharma N, Kaur R, Dhingra MS, Karan M. Amelioration of testosterone induced benign prostatic hyperplasia by Prunus species. *J Ethnopharmacol.* 2016;190:33-45. doi:10.1016/j.jep.2016.05.052

Hu, D. Webster, J. Cao, A. Shao. The safety of green tea and green tea extract consumption in adults - results of a systematic review. *Regul. Toxicol. Pharmacol.*, 95 (2018), pp. 412-433, 10.1016/j.yrtph.2018.03.019

Stamatiadis D, Bulteau-Portois MC, Mowszowicz I. Inhibition of 5 alpha-reductase activity in human skin by zinc and azelaic acid. *Br J Dermatol.* 1988;119(5):627-632. doi:10.1111/j.1365-2133.1988.tb03474.x

Bethany Montgomery Hays MD, Tori Hudson ND, in *Textbook of Natural Medicine (Fifth Edition)*, 2020

<https://www.sciencedirect.com/topics/medicine-and-dentistry/steroid-5beta-reductase>. Access verified 4/11/2022.

<https://selfdecode.com/gene/cyp21a2/#all-ways-to-decrease-gene>. Access verified 4/11/2022.

Omar HR, Komarova I, El-Ghonemi M, et al. Licorice abuse: time to send a warning message. *Ther Adv Endocrinol Metab.* 2012;3(4):125-138. doi:10.1177/2042018812454322

Corticoids

Cortisol Low	Cortisol High
<p>Upregulate CYP11B1:</p> <ul style="list-style-type: none"> • Heme iron (cofactor) • Vitamin D • Korean red ginseng • Medications: dexamethasone, medroxyprogesterone, pemirolast, clobenpropit, desogestrel, dexmedetomidine, tizanidine 	<p>Downregulate CYP11B1:</p> <ul style="list-style-type: none"> • Flavonoids • Isoflavones • Medications: ketoconazole, metyrapone, etomidate
<p>Upregulate HSD11B1:</p> <ul style="list-style-type: none"> • Glucocorticoids • Influences: inflammation (NFκB), Hypothyroid, impaired glucose tolerance/insulin resistance, belly fat 	<p>Downregulate HSD11B1:</p> <ul style="list-style-type: none"> • Reduce inflammation • Reduce insulin resistance/insulin • Reduce central adiposity • Physical activity • Hyperthyroid • Estrogen excess • Rooibos • Holy Basil • Curcumin • Bitter melon • EGCG • Progesterone • Coffee
<p>Downregulate HSD11B2:</p> <ul style="list-style-type: none"> • Intense exercise • Grapefruit juice • Progesterone • Abietic acid • Licorice • Fluoxymesterone • Itraconazole and posaconazole 	<p>Upregulate HSD11B2:</p> <ul style="list-style-type: none"> • Hydrocortisone, dexamethasone, fludrocortisone • NADH
<p>Downregulate 5α reductase:</p> <ul style="list-style-type: none"> • Polyunsaturated fatty acids • Berberine • Saw palmetto • Nettles • Pygeum • Green tea, EGCG • Progesterone • Zinc • 5α reductase inhibitors such as finasteride 	<p>Upregulate 5α reductase:</p> <ul style="list-style-type: none"> • DHEA • PCOS • Cadmium <p>Upregulate 5β reductase:</p> <ul style="list-style-type: none"> • NAD+ <p>Upregulate HSD3A:</p> <ul style="list-style-type: none"> • Oral progesterone • Sulforaphane • Forskolin (found in coleus plant)
<p>Downregulate HSD3A:</p> <ul style="list-style-type: none"> • Medications: mirtazapine, ziram noncompetitively inhibits • Coumestrol • Taxifolin <p>Address/avoid:</p> <ul style="list-style-type: none"> • Female abdominal adiposity which upregulates HSD3A • PCOS, hyperinsulinemia, obesity, and cadmium which upregulate 5α reductase 	<p>Avoid:</p> <ul style="list-style-type: none"> • Potassium chloride, perfluorooctane sulfonic acid (Scotch Guard), benidipine, BPA, walrycin, ACTH, water pollutants, mycotoxins which upregulate CYP11B1 • Methoxychlor and its metabolite HPTE, gossypol acetate, which inhibit HSD3A • Diethylstilbestrol, gossypol, alkylphenols, organotins, phthalates which downregulate HSD11B2

Cortisone Low	Cortisone High
<p>Upregulate HSD11B2:</p> <ul style="list-style-type: none"> • Hydrocortisone, dexamethasone, fludrocortisone • NADH <p>Downregulate HSD11B1:</p> <ul style="list-style-type: none"> • Intense exercise • Grapefruit juice • Progesterone • Abietic acid • Licorice • Fluoxymesterone • Diethylstilbestrol • Itraconazole and posaconazole <p>Downregulate 5β reductase:</p> <ul style="list-style-type: none"> • Licorice • Budesonide 	<p>Upregulate HSD11B1:</p> <ul style="list-style-type: none"> • Glucocorticoids • Influences: Inflammation (NFkappaBeta), Hypothyroid, impaired glucose tolerance/insulin resistance, belly fat <p>Downregulate HSD11B2:</p> <ul style="list-style-type: none"> • Intense exercise • Grapefruit juice • Progesterone • Abietic acid • Licorice • Fluoxymesterone • Diethylstilbestrol • Itraconazole and posaconazole <p>Upregulate 5β reductase:</p> <ul style="list-style-type: none"> • NAD+ <p>Upregulate HSD3A:</p> <ul style="list-style-type: none"> • Oral progesterone • Sulforaphane • Forskolin (found in coleus plant)
Corticosterone Low	Corticosterone High
<p>Upregulate CYP11B1/2:</p> <ul style="list-style-type: none"> • Heme iron (cofactor) • Vitamin D • Korean red ginseng • Medications: dexamethasone, medroxyprogesterone, pemirolast, clobenpropit, desogestrel, dexmedetomidine, tizanidine <p>Downregulate 5α reductase:</p> <ul style="list-style-type: none"> • Polyunsaturated fatty acids • Berberine • Saw palmetto • Nettles • Pygeum • Green tea, EGCG • Progesterone • Zinc • 5α reductase inhibitors such as finasteride <p>Downregulate 5β reductase:</p> <ul style="list-style-type: none"> • Licorice • Budesonide <p>Downregulate HSD3A:</p> <ul style="list-style-type: none"> • Medications: mirtazapine, ziram noncompetitively inhibits • Coumestrol • Taxifolin 	<p>Upregulate CYP11B2:</p> <ul style="list-style-type: none"> • Heme iron (cofactor) • Vitamin D • Korean red ginseng • Potassium • Medications: dexamethasone, medroxyprogesterone, pemirolast, clobenpropit, desogestrel, dexmedetomidine, tizanidine <p>Upregulate 5α reductase:</p> <ul style="list-style-type: none"> • DHEA • PCOS • Cadmium <p>Upregulate 5β reductase:</p> <ul style="list-style-type: none"> • NAD+ <p>Upregulate HSD3A:</p> <ul style="list-style-type: none"> • Oral progesterone • Sulforaphane • Forskolin (found in coleus plant) <p>Avoid:</p> <ul style="list-style-type: none"> • Methoxychlor and its metabolite HPTE, gossypol acetate which inhibit HSD3A
5B-THA Low	5B-THA High
<p>Upregulate 5β reductase:</p> <ul style="list-style-type: none"> • NAD+ <p>Upregulate HSD3A:</p> <ul style="list-style-type: none"> • Oral progesterone • Sulforaphane • Forskolin (found in coleus plant) 	<p>Downregulate 5β reductase:</p> <ul style="list-style-type: none"> • Licorice • Budesonide <p>Downregulate HSD3A:</p> <ul style="list-style-type: none"> • Medications: mirtazapine, ziram noncompetitively inhibits • Coumestrol • Taxifolin

5B-THB Low	5B-THB High
<p>Upregulate 5β reductase:</p> <ul style="list-style-type: none"> • NAD+ <p>Upregulate HSD3A:</p> <ul style="list-style-type: none"> • Oral progesterone • Sulforaphane • Forskolin (found in coleus plant) 	<p>Downregulate 5β reductase:</p> <ul style="list-style-type: none"> • Licorice • Budesonide <p>Downregulate HSD3A:</p> <ul style="list-style-type: none"> • Medications: mirtazapine, ziram noncompetitively inhibits • Coumestrol • Taxifolin
5A-THB Low	5A-THB High
<p>Upregulate 5α reductase:</p> <ul style="list-style-type: none"> • DHEA <p>Upregulate HSD3A:</p> <ul style="list-style-type: none"> • Oral progesterone • Sulforaphane • Forskolin (found in coleus plant) 	<p>Downregulate 5α reductase:</p> <ul style="list-style-type: none"> • Polyunsaturated fatty acids • Berberine • Saw palmetto • Nettles • Pygeum • Green tea, EGCG • Progesterone • Zinc • 5α reductase inhibitors such as finasteride <p>Downregulate HSD3A:</p> <ul style="list-style-type: none"> • Medications: mirtazapine, ziram noncompetitively inhibits • Coumestrol • Taxifolin <p>Address/avoid:</p> <ul style="list-style-type: none"> • PCOS and cadmium which upregulate 5α reductase • Female abdominal adiposity which upregulates HSD3A
11-Deoxycortisol Low	11-Deoxycortisol High
<p>Upregulate CYP21A2:</p> <ul style="list-style-type: none"> • Calforsin (Coleus Forskoli) <p>Downregulate CYP11B1 (this will lower cortisol):</p> <ul style="list-style-type: none"> • Flavonoids • Isoflavones • Meds: ketoconazole, metyrapone, etomidate <p>Avoid:</p> <ul style="list-style-type: none"> • Galaxolide (common synthetic musk scent in perfumes and household cleaners) downregulates CYP21A2 • Potassium chloride, perfluorooctane sulfonic acid (Scotch Guard), benidipine, BPA, walrycin, ACTH, water pollutants, mycotoxins which upregulate CYP11B1 	<p>Downregulate CYP21A2:</p> <ul style="list-style-type: none"> • Vitamin D • Resveratrol • Curcumin • Flavonoids (rooibos, apigenin) • Isoflavones (daidzein) • Medications: PDE inhibitors, valproic acid, sildenafil, vardenafil, tadalafil <p>Upregulate CYP11B1:</p> <ul style="list-style-type: none"> • Heme iron (cofactor) • Vitamin D • Korean red ginseng • Medications: dexamethasone, medroxyprogesterone, pemirolast, clobenpropit, desogestrel, dexmedetomidine, tizanidine <p>Avoid:</p> <ul style="list-style-type: none"> • Insecticides: fipronil

5A-THF Low	5A-THF High
<p>Upregulate 5α reductase:</p> <ul style="list-style-type: none"> • DHEA • PCOS • Cadmium <p>Upregulate HSD3A:</p> <ul style="list-style-type: none"> • Oral progesterone • Sulforaphane • Forskolin (found in coleus plant) <p>Avoid:</p> <ul style="list-style-type: none"> • Methoxychlor and its metabolite HPTE, gossypol acetate, which inhibit HSD3A 	<p>Downregulate 5α reductase:</p> <ul style="list-style-type: none"> • Polyunsaturated fatty acids • Berberine • Saw palmetto • Nettles • Pygeum • Green tea, EGCG • Progesterone • Zinc • 5α-reductase inhibitors such as finasteride <p>Downregulate HSD3A:</p> <ul style="list-style-type: none"> • Medications: mirtazapine, ziram noncompetitively inhibits • Coumestrol • Taxifolin <p>Address/avoid:</p> <ul style="list-style-type: none"> • PCOS and cadmium which upregulate 5α reductase • Female abdominal adiposity which upregulates HSD3A
5B-THF Low	5B-THF High
<p>Upregulate 5β reductase:</p> <ul style="list-style-type: none"> • NAD+ <p>Upregulate HSD3A:</p> <ul style="list-style-type: none"> • Oral progesterone • Sulforaphane • Forskolin (found in coleus plant) 	<p>Downregulate 5β reductase:</p> <ul style="list-style-type: none"> • Licorice • Budesonide <p>Downregulate HSD3A:</p> <ul style="list-style-type: none"> • Medications: mirtazapine, ziram noncompetitively inhibits • Coumestrol • Taxifolin
THE Low	THE High
<p>Upregulate 5β reductase:</p> <ul style="list-style-type: none"> • NAD+ <p>Upregulate HSD3A:</p> <ul style="list-style-type: none"> • Oral progesterone • Sulforaphane • Forskolin (found in coleus plant) 	<p>Downregulate 5β reductase:</p> <ul style="list-style-type: none"> • Licorice • Budesonide <p>Downregulate HSD3A:</p> <ul style="list-style-type: none"> • Medications: mirtazapine, ziram noncompetitively inhibits • Coumestrol • Taxifolin

Corticoids References

<https://selfdecode.com/gene/cyp21a2/#all-ways-to-decrease-gene>. Access verified 4/11/2022.

<https://selfdecode.com/gene/cyp11b1/#all-ways-to-increase-gene>. Access verified 4/11/2022.

Cheng LC, Li LA. Flavonoids exhibit diverse effects on CYP11B1 expression and cortisol synthesis. *Toxicol Appl Pharmacol*. 2012;258(3):343-350. doi:10.1016/j.taap.2011.11.017

Loose DS, Kan PB, Hirst MA, Marcus RA, Feldman D. Ketoconazole blocks adrenal steroidogenesis by inhibiting cytochrome P450-dependent enzymes. *J Clin Invest*. 1983;71(5):1495-1499. doi:10.1172/jci110903

LIDDLE GW, ISLAND D, LANCE EM, HARRIS AP. Alterations of adrenal steroid patterns in man resulting from treatment with a chemical inhibitor of 11 beta-hydroxylation. *J Clin Endocrinol Metab*. 1958;18(8):906-912. doi:10.1210/jcem-18-8-906

NELSON AA, WOODARD G. Severe adrenal cortical atrophy (cytotoxic) and hepatic damage produced in dogs by feeding 2,2-bis(parachlorophenyl)-1,1-dichloroethane (DDD or TDE). *Arch Pathol (Chic)*. 1949;48(5):387-394.

CUETO C, BROWN JH, RICHARDSON AP Jr. Biological studies on an adrenocorticolytic agent and the isolation of the active components. *Endocrinology*. 1958;62(3):334-339. doi:10.1210/endo-62-3-334

Wagner RL, White PF, Kan PB, Rosenthal MH, Feldman D. Inhibition of adrenal steroidogenesis by the anesthetic etomidate. *N Engl J Med*. 1984;310(22):1415-1421. doi:10.1056/NEJM198405313102202

- Fry DE, Griffiths H. The inhibition by etomidate of the 11 beta-hydroxylation of cortisol. *Clin Endocrinol (Oxf)*. 1984;20(5):625-629. doi:10.1111/j.1365-2265.1984.tb00112.x
- de Jong FH, Mallios C, Jansen C, Scheck PA, Lamberts SW. Etomidate suppresses adrenocortical function by inhibition of 11 beta-hydroxylation. *J Clin Endocrinol Metab*. 1984;59(6):1143-1147. doi:10.1210/jcem-59-6-1143
- Azzouni F, Godoy A, Li Y, Mohler J. The 5 alpha-reductase isozyme family: a review of basic biology and their role in human diseases. *Adv Urol*. 2012;2012:530121. doi:10.1155/2012/530121
- Youn DH, Park J, Kim HL, et al. Berberine Improves Benign Prostatic Hyperplasia via Suppression of 5 Alpha Reductase and Extracellular Signal-Regulated Kinase in Vivo and in Vitro [published correction appears in Front Pharmacol. 2019 May 22;10:541]. *Front Pharmacol*. 2018;9:773. Published 2018 Jul 16. doi:10.3389/fphar.2018.00773
- Stomati M, Monteleone P, Casarosa E, et al. Six-month oral dehydroepiandrosterone supplementation in early and late postmenopause. *Gynecol Endocrinol*. 2000;14(5):342-363. doi:10.3109/09513590009167703
- Fassnacht M, Schlenz N, Schneider SB, Wudy SA, Allolio B, Arlt W. Beyond adrenal and ovarian androgen generation: Increased peripheral 5 alpha-reductase activity in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2003;88(6):2760-2766. doi:10.1210/jc.2002-021875
- Garrett SH, Somji S, Sens MA, Zhang K, Sens DA. Microarray analysis of gene expression patterns in human proximal tubule cells over a short and long time course of cadmium exposure. *J Toxicol Environ Health A*. 2011;74(1):24-42. doi:10.1080/15287394.2010.514230
- Schüle C, Romeo E, Uzunov DP, et al. Influence of mirtazapine on plasma concentrations of neuroactive steroids in major depression and on 3alpha-hydroxysteroid dehydrogenase activity. *Mol Psychiatry*. 2006;11(3):261-272. doi:10.1038/sj.mp.4001782
- Su Y, Zhu Q, Hong X, Ge RS. Taxifolin Inhibits Neurosteroidogenic Rat Steroid 5α-Reductase 1 and 3α-Hydroxysteroid Dehydrogenase. *Pharmacology*. 2020;105(7-8):397-404. doi:10.1159/000504057
- Mao B, Wu C, Zheng W, et al. Methoxychlor and its metabolite HPTE inhibit rat neurosteroidogenic 3α-hydroxysteroid dehydrogenase and retinol dehydrogenase 2. *Neurosci Lett*. 2018;684:169-174. doi:10.1016/j.neulet.2018.08.008
- Cao S, Wang G, Ge F, et al. Gossypol inhibits 5α-reductase 1 and 3α-hydroxysteroid dehydrogenase: Its possible use for the treatment of prostate cancer. *Fitoterapia*. 2019;133:102-108. doi:10.1016/j.fitote.2018.12.024

CYP21A2

- Hasegawa E, Nakagawa S, Sato M, Tachikawa E, Yamato S. Effect of polyphenols on production of steroid hormones from human adrenocortical NCI-H295R cells. *Biol Pharm Bull*. 2013;36(2):228-37. doi: 10.1248/bpb.b12-00627.
- Lundqvist J, Norlin M, Wikvall K. 1alpha,25-Dihydroxyvitamin D3 affects hormone production and expression of steroidogenic enzymes in human adrenocortical NCI-H295R cells. *Biochim Biophys Acta*. 2010 Sep;1801(9):1056-62. doi: 10.1016/j.bbalaip.2010.04.009. Epub 2010 Apr 24.
- Marti N, Bouchoucha N, Sauter KS, Flück CE. Resveratrol inhibits androgen production of human adrenocortical H295R cells by lowering CYP17 and CYP21 expression and activities. *PLoS One*. 2017 Mar 21;12(3):e0174224. doi: 10.1371/journal.pone.0174224.
- Schloms L, Swart AC. Rooibos Flavonoids Inhibit the Activity of Key Adrenal Steroidogenic Enzymes, Modulating Steroid Hormone Levels in H295R Cells. *Molecules*. 2014; 19(3):3681-3695. https://doi.org/10.3390/molecules19033681
- Castaño PR, Parween S, Pandey AV. Bioactivity of Curcumin on the Cytochrome P450 Enzymes of the Steroidogenic Pathway. *International Journal of Molecular Sciences*. 2019; 20(18):4606. https://doi.org/10.3390/ijms20184606
- Ohno S, Shinoda S, Toyoshima S, Nakazawa H, Makino T, Nakajin S. Effects of flavonoid phytochemicals on cortisol production and on activities of steroidogenic enzymes in human adrenocortical H295R cells. *J Steroid Biochem Mol Biol*. 2002;80(3):355-363. doi:10.1016/s0960-0760(02)00021-3
- Sheweita SA, Meftah AA, Sheweita MS, Balbaa ME. Erectile dysfunction drugs altered the activities of antioxidant enzymes, oxidative stress and the protein expressions of some cytochrome P450 isozymes involved in the steroidogenesis of steroid hormones. *PLoS One*. 2020;15(11):e0241509. Published 2020 Nov 9. doi:10.1371/journal.pone.0241509

- Hasegawa E, Nakagawa S, Sato M, Tachikawa E, Yamato S. Effect of polyphenols on production of steroid hormones from human adrenocortical nci-h295r cells. *Biological & Pharmaceutical Bulletin*. 2013;36(2):228-237.

HSD11B1

- Guilliams T. The Role of Stress and the HPA Axis in Chronic Disease Management. Point Institute; 2015.
- Chapman K, Holmes M, Seckl J. 11β-hydroxysteroid dehydrogenases: intracellular gate-keepers of tissue glucocorticoid action. *Physiol Rev*. 2013;93(3):1139-1206. doi:10.1152/physrev.00020.2012
- Schloms L, Smith C, Storbeck KH, Marnewick JL, Swart P, Swart AC. Rooibos influences glucocorticoid levels and steroid ratios in vivo and in vitro: a natural approach in the management of stress and metabolic disorders?. *Mol Nutr Food Res*. 2014;58(3):537-549. doi:10.1002/mnfr.201300463
- Jothie Richard E, Illuri R, Bethapudi B, et al. Anti-stress Activity of Ocimum sanctum: Possible Effects on Hypothalamic-Pituitary-Adrenal Axis. *Phytother Res*. 2016;30(5):805-814. doi:10.1002/ptr.5584
- Hu GX, Lin H, Lian QQ, et al. Curcumin as a potent and selective inhibitor of 11β-hydroxysteroid dehydrogenase 1: improving lipid profiles in high-fat-diet-treated rats. *PLoS One*. 2013;8(3):e49976. doi:10.1371/journal.pone.0049976
- Blum A, Loerz C, Martin HJ, Staab-Weijnitz CA, Maser E. Momordica charantia extract, a herbal remedy for type 2 diabetes, contains a specific 11β-hydroxysteroid dehydrogenase type 1 inhibitor. *J Steroid Biochem Mol Biol*. 2012;128(1-2):51-55. doi:10.1016/j.jsbmb.2011.09.003
- Hintz Peter J, Stapelfeld C, Loerz C, Martin HJ, Maser E. Green tea and one of its constituents, Epigallocatechine-3-gallate, are potent inhibitors of human 11β-hydroxysteroid dehydrogenase type 1. *PLoS One*. 2014;9(1):e84468. Published 2014 Jan 3. doi:10.1371/journal.pone.0084468
- Atanasov AG, Dzyakanchuk AA, Schweizer RA, Nashev LG, Maurer EM, Odermatt A. Coffee inhibits the reactivation of glucocorticoids by 11beta-hydroxysteroid dehydrogenase type 1: a glucocorticoid connection in the anti-diabetic action of coffee?. *FEBS Lett*. 2006;580(17):4081-4085. doi:10.1016/j.febslet.2006.06.046

Hoshiro M, Ohno Y, Masaki H, Iwase H, Aoki N. Comprehensive study of urinary cortisol metabolites in hyperthyroid and hypothyroid patients. *Clin Endocrinol (Oxf)*. 2006;64(1):37-45. doi:10.1111/j.1365-2265.2005.02412.

Zhou Y, Xu F, Deng H, et al. PEDF expression is inhibited by insulin treatment in adipose tissue via suppressing 11 β -HSD1. *PLoS One*. 2013;8(12):e84016. Published 2013 Dec 18. doi:10.1371/journal.pone.0084016

Diederich S, Quinkler M, Mai K, et al. In vivo activity of 11 β -hydroxysteroid dehydrogenase type 1 in man: effects of prednisolone and chenodesoxycholic acid. *Horm Metab Res*. 2011;43(1):66-71. doi:10.1055/s-0030-1267170

Tomlinson, J.W., et al., Impaired glucose tolerance and insulin resistance are associated with increased adipose 11 β -hydroxysteroid dehydrogenase type 1 expression and elevated hepatic 5alpha-reductase activity. *Diabetes*, 2008. 57(10): p. 2652-60.

Dube, S., et al., 11 β -hydroxysteroid dehydrogenase types 1 and 2 activity in subcutaneous adipose tissue in humans: implications in obesity and diabetes. *J Clin Endocrinol Metab*, 2015. 100(1): p. E70-6

Esteves CL, Kelly V, Breton A, et al. Proinflammatory cytokine induction of 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) in human adipocytes is mediated by MEK, C/EBP β , and NF- κ B/RelA. *J Clin Endocrinol Metab*. 2014;99(1):E160-E168. doi:10.1210/jc.2013-1708

Kargl C, Arshad M, Salman F, Schurman RC, Del Corral P. 11 β -hydroxysteroid dehydrogenase type-II activity is affected by grapefruit juice and intense muscular work. *Arch Endocrinol Metab*. 2017;61(6):556-561. doi:10.1590/2359-3997000000296

Schweizer RA, Atanasov AG, Frey BM, Odermatt A. A rapid screening assay for inhibitors of 11 β -hydroxysteroid dehydrogenases (11 β -HSD): flavanone selectively inhibits 11 β -HSD1 reductase activity. *Mol Cell Endocrinol*. 2003;212(1-2):41-49. doi:10.1016/j.mce.2003.09.027

Classen-Houben D, Schuster D, Da Cunha T, et al. Selective inhibition of 11 β -hydroxysteroid dehydrogenase 1 by 18 α -glycyrrhetic acid but not 18 β -glycyrrhetic acid. *J Steroid Biochem Mol Biol*. 2009;113(3-5):248-252. doi:10.1016/j.jsbmb.2009.01.009

Quinkler, M., Johanssen, S., Grossmann, C., Bahr, V., Muller, M., Oelkers, W., Diederich, S. Progesterone metabolism in the human kidney and inhibition of 11 β -hydroxysteroid dehydrogenase type 2 by progesterone and its metabolites. *J. Clin. Endocr. Metab.* 84: 4165-4171, 1999.[PubMed: 10566667]

Wang Y, Dong Y, Fang Y, et al. Diethylstilbestrol inhibits human and rat 11 β -hydroxysteroid dehydrogenase 2. *Endocr Connect*. 2019;8(7):1061-1069. doi:10.1530/EC-19-0288

Inderbinen SG, Zogg M, Kley M, Smieško M, Odermatt A. Species-specific differences in the inhibition of 11 β -hydroxysteroid dehydrogenase 2 by itraconazole and posaconazole. *Toxicol Appl Pharmacol*. 2021;412:115387. doi:10.1016/j.taap.2020.115387

5 α reductase

Stomati M, Monteleone P, Casarosa E, et al. Six-month oral dehydroepiandrosterone supplementation in early and late postmenopause. *Gynecol Endocrinol*. 2000;14(5):342-363.

Fassnacht M, Schlenz N, Schneider SB, Wudy SA, Allolio B, Arlt W. Beyond adrenal and ovarian androgen generation: increased peripheral 5 α -reductase activity in women with polycystic ovary syndrome. *The Journal of Clinical Endocrinology & Metabolism*. 2003;88(6):2760-2766.

Garrett SH, Somji S, Sens MA, Zhang K, Sens DA. Microarray analysis of gene expression patterns in human proximal tubule cells over a short and long time course of cadmium exposure. *J Toxicol Environ Health A*. 2011;74(1):24-42.

CYP11B2

LIDDLE GW, ISLAND D, LANCE EM, HARRIS AP. Alterations of adrenal steroid patterns in man resulting from treatment with a chemical inhibitor of 11 beta-hydroxylation. *J Clin Endocrinol Metab*. 1958 Aug;18(8):906-12. doi: 10.1210/jcem-18-8-906.

NELSON AA, WOODARD G. Severe adrenal cortical atrophy (cytotoxic) and hepatic damage produced in dogs by feeding 2,2-bis(parachlorophenyl)-1,1-dichloroethane (DDD or TDE). *Arch Pathol (Chic)*. 1949 Nov;48(5):387-94.

CUETO C, BROWN JH, RICHARDSON AP Jr. Biological studies on an adrenocorticolytic agent and the isolation of the active components. *Endocrinology*. 1958 Mar;62(3):334-9. doi: 10.1210/endo-62-3-334.

Takeda Y, Demura M, Wang F, et al. Effect of potassium on DNA methylation of aldosterone synthase gene. *J Hypertens*. 2021;39(5):1018-1024. doi:10.1097/HJH.0000000000002742

5 β Reductase

Chen M, Jin Y, Penning TM. The rate-determining steps of aldo-keto reductases (AKRs), a study on human steroid 5 β -reductase (AKR1D1). *Chem Biol Interact*. 2015;234:360-365. doi:10.1016/j.cbi.2014.12.004

HSD3A

Sasaki M, Shinozaki S, Shimokado K. Sulforaphane promotes murine hair growth by accelerating the degradation of dihydrotestosterone. *Biochem Biophys Res Commun*. 2016;472(1):250-254.

Androgens

Androstenedione Low	Androstenedione High
<p>Upregulate HSD3B:</p> <ul style="list-style-type: none"> • Fenugreek steroids • Pregnenolone • Progesterone activates HSD3B1 • ACTH <p>Avoid:</p> <ul style="list-style-type: none"> • Phthalates, organochlorines, BPA, ketoconazole; many endocrine disruptors, including industrial compounds (phthalates, bisphenols, and perfluoroalkyl substances), insecticides and biocides (organochlorine insecticides and organotins), food additives (butylated hydroxyanisole, which inhibit testicular HSD3B2) • Gossypol which downregulates HSD3B <p>To support appropriate metabolism, refer to:</p> <ul style="list-style-type: none"> • Downregulate HSD17A • Downregulate HSD17B • Downregulate 5α reductase • Downregulate 5β reductase 	<p>Downregulate HSD3B:</p> <ul style="list-style-type: none"> • Resveratrol, flavones, and isoflavones • Medications: etomidate, troglitazone, medroxyprogesterone acetate, ketoconazole, trilostane, finasteride • HSD3B1 downregulated by glucocorticoids • HSD3B2 downregulated by 4th generation progestins – NoMAC, drospirenone, nestorone and azastene, cyanoketone, epostane, trilostane • Coumestrol, isoflavones – genistein which contains daidzen • Phytoestrogens <p>Address conditions that promote HSD3B:</p> <ul style="list-style-type: none"> • PCOS • High ACTH, hyperadrenalinism <p>Upregulate 5β reductase:</p> <ul style="list-style-type: none"> • NAD+ <p>Upregulate HSD17B:</p> <ul style="list-style-type: none"> • Meditation • Bioflavonoids (I.e. rutin) • Sacred fig • Grapeseed extract • Malaysian propolis • Medication: promethazine <p>Upregulate 5α reductase:</p> <ul style="list-style-type: none"> • DHEA <p>Upregulate CYP19A1 (aromatase):</p> <ul style="list-style-type: none"> • Forskolin (found in coleus plant) • SSRIs: <ul style="list-style-type: none"> • Paroxetine • Sertraline (both upregulates and downregulates aromatase)
Epitestosterone Low	Epitestosterone High
<i>Research is needed</i>	<i>Research is needed</i>
Testosterone Low	Testosterone High
<p>Upregulate HSD17B:</p> <ul style="list-style-type: none"> • Meditation • Bioflavonoids (I.e. rutin) • Sacred fig • Grapeseed extract • Malaysian propolis • Medication: promethazine <p>Upregulate HSD3A:</p> <ul style="list-style-type: none"> • Abdominal adiposity in females <p>Downregulate 5α reductase:</p> <ul style="list-style-type: none"> • Polyunsaturated fatty acids • Berberine • Saw palmetto • Nettles • Pygeum • Green tea, EGCG • Progesterone 	<p>Downregulate HSD17B:</p> <ul style="list-style-type: none"> • Licorice • Quercetin <p>Upregulate CYP19A1 (aromatase):</p> <ul style="list-style-type: none"> • Forskolin (found in coleus plant) • SSRIs: <ul style="list-style-type: none"> • Paroxetine • Sertraline (both upregulates and downregulates aromatase) <p>Upregulate 5β reductase:</p> <ul style="list-style-type: none"> • NAD+ <p>Upregulate 5α reductase:</p> <ul style="list-style-type: none"> • DHEA (Note: DHEA can convert to testosterone) <p>Upregulate HSD3A:</p> <ul style="list-style-type: none"> • Sulforaphane • Oral progesterone • Forskolin (found in coleus plant)

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<ul style="list-style-type: none"> Zinc 5α reductase inhibitors such as finasteride <p>Address conditions that upregulate 5α reductase:</p> <ul style="list-style-type: none"> PCOS Cadmium exposure <p>Downregulate 5β reductase:</p> <ul style="list-style-type: none"> Licorice Medication: budesonide <p>Downregulate HSD3A:</p> <ul style="list-style-type: none"> Coumestrol Medications: mirtazapine, ziram noncompetitively inhibits Taxifolin 	Avoid methoxychlor and its metabolite HPTE, Gossypol acetate, which inhibit HSD3A
Androsterone Low	Androsterone high
<p>Upregulate 5α reductase:</p> <ul style="list-style-type: none"> DHEA <p>Upregulate HSD17B:</p> <ul style="list-style-type: none"> Meditation Bioflavonoids (I.e. rutin) Sacred fig Grapeseed extract Malaysian propolis Medication: promethazine <p>Upregulate HSD3A:</p> <ul style="list-style-type: none"> Sulforaphane Oral progesterone Forskolin (found in coleus plant) <p>Avoid methoxychlor and its metabolite HPTE, gossypol acetate, which inhibit HSD3A</p>	<p>Downregulate 5α reductase:</p> <ul style="list-style-type: none"> Polyunsaturated fatty acids Berberine Saw palmetto Nettles Pygeum Green tea, EGCG Progesterone Zinc 5α reductase inhibitors such as finasteride <p>Address:</p> <ul style="list-style-type: none"> Female abdominal adiposity which upregulates HSD3A PCOS, which upregulates 5α reductase <p>Downregulate HSD3A:</p> <ul style="list-style-type: none"> Ziram Mirtazapine Coumestrol Taxifolin <p>Downregulate HSD17B:</p> <ul style="list-style-type: none"> Licorice Quercetin <p>Upregulate CYP11B1:</p> <ul style="list-style-type: none"> Heme (cofactor) Vitamin D Korean red ginseng Medications: dexamethasone, medroxyprogesterone, pemirolast, clobenpropit, desogestrel, dexmedetomidine, tizanidine
OHAN Low	OHAN High
<p>Upregulate CYP 11B1:</p> <ul style="list-style-type: none"> Heme (cofactor) Vitamin D Korean red ginseng Medications: dexamethasone, medroxyprogesterone, pemirolast, clobenpropit, desogestrel, dexmedetomidine, tizanidine 	<p>Downregulate CYP11B1:</p> <ul style="list-style-type: none"> Flavonoids Isoflavones Meds: ketoconazole, metyrapone, etomidate
5A-AD Low	5A-AD High
Refer to low androstenedione	Refer to high androstenedione

5A-DHT Low	5A-DHT High
<p>Upregulate 5α reductase:</p> <ul style="list-style-type: none"> • DHEA <p>Upregulate HSD17B:</p> <ul style="list-style-type: none"> • Meditation • Bioflavonoids (I.e. rutin) • Sacred fig • Grapeseed extract • Malaysian propolis • Medication: promethazine 	<p>Downregulate 5α reductase:</p> <ul style="list-style-type: none"> • Polyunsaturated fatty acids • Berberine • Saw palmetto • Nettles • Pygeum • Green tea, EGCG • Progesterone • Zinc • 5α reductase inhibitors such as finasteride <p>Address conditions that upregulate 5α reductase:</p> <ul style="list-style-type: none"> • PCOS • Cadmium exposure <p>Downregulate HSD17B:</p> <ul style="list-style-type: none"> • Licorice • Quercetin
Etiocholanolone Low	Etiocholanolone High
<p>Upregulate 5β reductase:</p> <ul style="list-style-type: none"> • NAD+ <p>Downregulate HSD11B:</p> <ul style="list-style-type: none"> • HSD11B1 inhibited by: <ul style="list-style-type: none"> • Rooibos • Experimental Alzheimer's drug Xanamem • Flavanone • Licorice, holy basil, curcumin, bitter melon, ECGC, coffee • 7-keto-DHEA, progesterone • HSD11B2 inhibited by: <ul style="list-style-type: none"> • Grapefruit juice • Licorice • Progesterone • Diethylstilbestrol (carcinogen and teratogen) • Itraconazole and posaconazole <p>Downregulate HSD17B:</p> <ul style="list-style-type: none"> • Licorice • Quercetin 	<p>Downregulate 5β reductase:</p> <ul style="list-style-type: none"> • Budesonide • Licorice <p>Upregulate HSD11B:</p> <ul style="list-style-type: none"> • Glucocorticoids <p>Upregulate HSD17B:</p> <ul style="list-style-type: none"> • Meditation • Bioflavonoids (I.e. rutin) • Sacred fig • Grapeseed extract • Malaysian propolis • Medication: promethazine
OHET Low	OHET High
<p>Upregulate HSD11B:</p> <ul style="list-style-type: none"> • Glucocorticoids 	<p>Downregulate HSD11B:</p> <ul style="list-style-type: none"> • HSD11B1 inhibited by: <ul style="list-style-type: none"> • Rooibos • Experimental Alzheimer's drug Xanamem • Flavanone • Licorice, holy basil, curcumin, bitter melon, ECGC, coffee • 7-keto-DHEA, progesterone • HSD11B2 inhibited by: <ul style="list-style-type: none"> • Grapefruit juice • 18β - glycyrrhetic acid • Progesterone • Diethylstilbestrol (carcinogen and teratogen) • Itraconazole and posaconazole <p>Address obesity</p>

5B-AD Low	5B-AD High
<p>Upregulate HSD17B:</p> <ul style="list-style-type: none"> Meditation Bioflavonoids (I.e. rutin) Sacred fig Grapeseed extract Malaysian propolis Medication: promethazine <p>Avoid sodium benzoate</p>	<p>Downregulate HSD17B:</p> <ul style="list-style-type: none"> Licorice Quercetin
DHEA Low	DHEA High
<p>Upregulate CYP17A1:</p> <ul style="list-style-type: none"> Vitamin D <p>Downregulate SULT2A1:</p> <ul style="list-style-type: none"> Quercetin Licorice Medications: spironolactone, danazol, clomiphene, testosterone. <p>Downregulate HSD3B:</p> <ul style="list-style-type: none"> Resveratrol, flavones, and isoflavones Medications: etomidate, troglitazone, medroxyprogesterone acetate, ketoconazole, trilostane, finasteride HSD3B1 downregulated by glucocorticoids HSD3B2 downregulated by 4th generation progestins – NoMAC, drospirenone, nestorone and azastene, cyanoketone, epostane, trilostane Coumestrol, isoflavones – genistein which contains daidzen Phytoestrogens 	<p>Downregulate CYP17A1:</p> <ul style="list-style-type: none"> Resveratrol Daidzen Curcumin Apigenin Isoflavones Medications: spironolactone, azole antifungals, metformin <p>Address alcoholic cirrhosis, acute phase reaction if applicable which downregulate SULT2A1</p> <p>Upregulate SULT2A1:</p> <ul style="list-style-type: none"> Genistein <p>Upregulate HSD3B:</p> <ul style="list-style-type: none"> Fenugreek steroids Pregnenolone Progesterone activates HSD3B1 ACTH
DHEAs Low	DHEAs High
<p>Address alcoholic cirrhosis, acute phase reaction if applicable which downregulate SULT2A1</p> <p>Upregulate SULT2A1:</p> <ul style="list-style-type: none"> Genistein 	<p>Downregulate SULT2A1:</p> <ul style="list-style-type: none"> Quercetin Licorice Medications: spironolactone, danazol, clomiphene, testosterone.
Androsterone (5α) / Etiocholanolone (5β) Low	Androsterone (5α) / Etiocholanolone (5β) High
<p>Upregulate 5α reductase:</p> <ul style="list-style-type: none"> DHEA <p>Downregulate 5β reductase:</p> <ul style="list-style-type: none"> Budesonide Licorice 	<p>Downregulate 5α reductase:</p> <ul style="list-style-type: none"> Polyunsaturated fatty acids Berberine Saw palmetto Nettles Pygeum Green tea, EGCG Progesterone Zinc 5α reductase inhibitors such as finasteride <p>Address PCOS, which upregulates 5α reductase</p> <p>Upregulate 5β reductase:</p> <ul style="list-style-type: none"> NAD+

T/Epi-T (HSD17A vs HSD17B) Low	T/Epi-T (HSD17A vs HSD17B) High
<p>Upregulate HSD17A:</p> <ul style="list-style-type: none"> • Unknown <p>Downregulate HSD17B:</p> <ul style="list-style-type: none"> • Licorice • Quercetin 	<p>Upregulate HSD17B:</p> <ul style="list-style-type: none"> • Meditation • Bioflavonoids (i.e. rutin) • Sacred fig • Grapeseed extract • Malaysian propolis • Medication: promethazine <p>Downregulate HSD17A:</p> <ul style="list-style-type: none"> • Unknown <p>Avoid sodium benzoate</p>
Aromatase activity High (CYP19A1)	Aromatase activity Low (CYP19A1)
<p>Downregulate with:</p> <ul style="list-style-type: none"> • Anti-Mullerian hormone • Chrysin (honey and propolis) • Zinc • Damiana • Grape seed extract • Nettle root • Ketoconazole • Prolactin • Metformin • Plant flavonoids • Apigenin • Catechins (EGCG in green tea) • Eriodictyol (Yerba santa) • Hesperetin (citrus) • Plant phenols: • Chalcones (i.e. hesperidin methylchalcone) • Isoliquiritigenin (licorice) • Mangostin • Myosime (alkaloid from tobacco and other plants/ related to nicotine) • Nicotine • Resveratrol • Vitamin E • White button mushrooms • Aromatase inhibitors – (both steroidal and nonsteroidal) i.e. Formestane, Anastrozole • Things that reduce inflammation: • Paclitaxel – breast cancer treatment, downregulates TNF-receptors stimulated by aromatase • 2-MOE2- downregulates TNF-receptors stimulated by aromatase <p>Both paclitaxel and 2-MOE2 also inhibited stimulation of aromatase activity by IL-6 plus its soluble receptor and PGE(2)</p> <p>Avoid/address conditions and substances that upregulate aromatase:</p> <ul style="list-style-type: none"> • Reactive toxins up-regulate aromatase • Poor dietary choices/high glycemic foods • Major illness • Brain injury • High insulin • Excess adipose tissue/Obesity/Leptin resistance • Inflammatory cytokines • IL-6, TNFalpha, prostaglandin PGE(2) 	<p>Upregulate with:</p> <ul style="list-style-type: none"> • Heme iron (CYP enzymes are heme dependent) • Forskolin (found in coleus plant) • Estrogen • Stress/cortisol (animal studies, acts in a protective manner for brain health) • Alcohol/Red wine • Xeno-estrogens/endocrine disruptors (pesticides, herbicides, benzene, plastic by-products, some pharmaceuticals and cosmetics, petroleum, UV filters) • Free-fatty acids (increased in metabolic syndrome)

Androgens References

- Wang LQ, James MO. Inhibition of sulfotransferases by xenobiotics. *Curr Drug Metab.* 2006;7(1):83-104. doi:10.2174/138920006774832596
- Al-Dujaili EA, Kenyon CJ, Nicol MR, Mason JI. Liquorice and glycyrrhetic acid increase DHEA and deoxycorticosterone levels in vivo and in vitro by inhibiting adrenal SULT2A1 activity. *Mol Cell Endocrinol.* 2011;336(1-2):102-109. doi:10.1016/j.mce.2010.12.011
- Chen Y, Zhang S, Zhou T, Huang C, McLaughlin A, Chen G. Liver X receptor alpha mediated genistein induction of human dehydroepiandrosterone sulfotransferase (HSULT2A1) in Hep G2 cells. *Toxicology and Applied Pharmacology.* 2013;268(2):106–112. doi:10.1016/j.taap.2013.01.006
- Yalcin EB, More V, Neira KL, et al. Downregulation of sulfotransferase expression and activity in diseased human livers. *Drug Metab Dispos.* 2013;41(9):1642-1650. doi:10.1124/dmd.113.050930
- Kim MS, Shigenaga J, Moser A, Grunfeld C, Feingold KR. Suppression of DHEA sulfotransferase (Sult2A1) during the acute-phase response. *Am J Physiol Endocrinol Metab.* 2004;287(4):E731-E738. doi:10.1152/ajpendo.00130.2004
- Serafini P, Lobo RA. The effects of spironolactone on adrenal steroidogenesis in hirsute women. *Fertil Steril.* 1985;44(5):595-599. doi:10.1016/s0015-0282(16)48972-7
- Hamden K, Jaouadi B, Carreau S, et al. Potential protective effect on key steroidogenesis and metabolic enzymes and sperm abnormalities by fenugreek steroids in testis and epididymis of surviving diabetic rats. *Arch Physiol Biochem.* 2010;116(3):146-155. doi:10.3109/13813455.2010.486405
- Bar-Ami S, Gitay-Goren H. Increased progesterone secretion and 3 beta-hydroxysteroid dehydrogenase activity in human cumulus cells by pregnenolone is limited to the high steroidogenic active cumuli. *J Assist Reprod Genet.* 2000;17(8):437-444. doi:10.1023/a:1009465218688
- <https://www.genecards.org/cgi-bin/carddisp.pl?gene=HSD3B1>. Access verified 4/11/2022.
- Simonian MH. ACTH and thyroid hormone regulation of 3 beta-hydroxysteroid dehydrogenase activity in human fetal adrenocortical cells. *J Steroid Biochem.* 1986;25(6):1001-1006. doi:10.1016/0022-4731(86)90336-5
- Zhang S, Mo J, Wang Y, et al. Endocrine disruptors of inhibiting testicular 3 β -hydroxysteroid dehydrogenase. *Chem Biol Interact.* 2019;303:90-97. doi:10.1016/j.cbi.2019.02.027
- de Gier J, Wolthers CH, Galac S, Okkens AC, Kooistra HS. Effects of the 3 β -hydroxysteroid dehydrogenase inhibitor trilostane on luteal progesterone production in the dog. *Theriogenology.* 2011;75(7):1271-1279. doi:10.1016/j.theriogenology.2010.11.041
- Zein J, Gaston B, Bazeley P, et al. HSD3B1 genotype identifies glucocorticoid responsiveness in severe asthma. *Proc Natl Acad Sci U S A.* 2020;117(4):2187-2193. doi:10.1073/pnas.1918819117
- Cooke GM. Differential effects of trilostane and cyanoketone on the 3 beta-hydroxysteroid dehydrogenase-isomerase reactions in androgen and 16-androstene biosynthetic pathways in the pig testis. *J Steroid Biochem Mol Biol.* 1996;58(1):95-101. doi:10.1016/0960-0760(96)00002-7
- Blomquist CH, Lima PH, Hotchkiss JR. Inhibition of 3alpha-hydroxysteroid dehydrogenase (3alpha-HSD) activity of human lung microsomes by genistein, daidzein, coumestrol and C(18)-, C(19)- and C(21)-hydroxysteroids and ketosteroids. *Steroids.* 2005;70(8):507-514. doi:10.1016/j.steroids.2005.01.004
- Deluca D, Krazeisen A, Breitling R, Prehn C, Möller G, Adamski J. Inhibition of 17beta-hydroxysteroid dehydrogenases by phytoestrogens: comparison with other steroid metabolizing enzymes. *J Steroid Biochem Mol Biol.* 2005;93(2-5):285-292. doi:10.1016/j.jsbmb.2004.12.035
- Fassnacht M, Schlenz N, Schneider SB, Wudy SA, Allolio B, Arlt W. Beyond adrenal and ovarian androgen generation: Increased peripheral 5 alpha-reductase activity in women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2003;88(6):2760-2766. doi:10.1210/jc.2002-021875
- Garrett SH, Somji S, Sens MA, Zhang K, Sens DA. Microarray analysis of gene expression patterns in human proximal tubule cells over a short and long time course of cadmium exposure. *J Toxicol Environ Health A.* 2011;74(1):24-42. doi:10.1080/15287394.2010.514230
- Krazeisen A, Breitling R, Möller G, Adamski J. Human 17beta-hydroxysteroid dehydrogenase type 5 is inhibited by dietary flavonoids. *Adv Exp Med Biol.* 2002;505:151-161. doi:10.1007/978-1-4757-5235-9_14
- Chen M, Jin Y, Penning TM. The rate-determining steps of aldo-keto reductases (AKRs), a study on human steroid 5 β -reductase (AKR1D1). *Chem Biol Interact.* 2015;234:360-365. doi:10.1016/j.cbi.2014.12.004
- Blouin K, Richard C, Bélanger C, et al. Local androgen inactivation in abdominal visceral adipose tissue. *J Clin Endocrinol Metab.* 2003;88(12):5944-5950. doi:10.1210/jc.2003-030535
- Suriyakalaa U, Ramachandran R, Doulathunnisa JA, et al. Upregulation of Cyp19a1 and PPAR- γ in ovarian steroidogenic pathway by Ficus religiosa: A potential cure for polycystic ovary syndrome. *J Ethnopharmacol.* 2021;267:113540. doi:10.1016/j.jep.2020.113540
- Tian M, Liu F, Liu H, et al. Grape seed procyanidins extract attenuates Cisplatin-induced oxidative stress and testosterone synthase inhibition in rat testes. *Syst Biol Reprod Med.* 2018;64(4):246-259. doi:10.1080/19396368.2018.1450460
- Munkboel CH, Hasselstrøm SB, Kristensen DM, Styrlhave B. Effects of antihistamines on the H295R steroidogenesis - Autocrine up-regulation following 3 β -HSD inhibition. *Toxicol In Vitro.* 2018;48:302-309. doi:10.1016/j.tiv.2018.01.026
- Nna VU, Bakar ABA, Ahmad A, et al. Malaysian propolis and metformin mitigate subfertility in streptozotocin-induced diabetic male rats by targeting steroidogenesis, testicular lactate transport, spermatogenesis and mating behaviour. *Andrology.* 2020;8(3):731-746. doi:10.1111/andr.12739
- Su Y, Li H, Chen X, et al. Ziram inhibits rat neurosteroidogenic 5 α -reductase 1 and 3 α -hydroxysteroid dehydrogenase. *Toxicol Mech Methods.* 2018;28(1):38-44. doi:10.1080/15376516.2017.1355950
- Schüle C, Romeo E, Uzunov DP, et al. Influence of mirtazapine on plasma concentrations of neuroactive steroids in major depression and on 3alpha-hydroxysteroid dehydrogenase activity. *Mol Psychiatry.* 2006;11(3):261-272. doi:10.1038/sj.mp.4001782
- Cao S, Wang G, Ge F, et al. Gossypol inhibits 5 α -reductase 1 and 3 α -hydroxysteroid dehydrogenase: Its possible use for the treatment of prostate cancer. *Fitoterapia.* 2019;133:102-108. doi:10.1016/j.fitote.2018.12.024
- Su Y, Zhu Q, Hong X, Ge RS. Taxifolin Inhibits Neurosteroidogenic Rat Steroid 5 α -Reductase 1 and 3 α -Hydroxysteroid Dehydrogenase. *Pharmacology.* 2020;105(7-8):397-404. doi:10.1159/000504057

Stomati M, Monteleone P, Casarosa E, et al. Six-month oral dehydroepiandrosterone supplementation in early and late postmenopause. *Gynecol Endocrinol.* 2000;14(5):342-363. doi:10.3109/09513590009167703

Sasaki M, Shinozaki S, Shimokado K. Sulforaphane promotes murine hair growth by accelerating the degradation of dihydrotestosterone. *Biochem Biophys Res Commun.* 2016;472(1):250-254. doi:10.1016/j.bbrc.2016.02.099

Fassnacht M, Schlenz N, Schneider SB, Wudy SA, Allolio B, Arlt W. Beyond adrenal and ovarian androgen generation: Increased peripheral 5 alpha-reductase activity in women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2003;88(6):2760-2766. doi:10.1210/jc.2002-021875

Garrett SH, Somji S, Sens MA, Zhang K, Sens DA. Microarray analysis of gene expression patterns in human proximal tubule cells over a short and long time course of cadmium exposure. *J Toxicol Environ Health A.* 2011;74(1):24-42. doi:10.1080/15287394.2010.514230

Azzouni F, Godoy A, Li Y, Mohler J. The 5 alpha-reductase isozyme family: a review of basic biology and their role in human diseases. *Adv Urol.* 2012;2012:530121. doi:10.1155/2012/530121

Youn DH, Park J, Kim HL, et al. Berberine Improves Benign Prostatic Hyperplasia via Suppression of 5 Alpha Reductase and Extracellular Signal-Regulated Kinase in Vivo and in Vitro [published correction appears in *Front Pharmacol.* 2019 May 22;10:541]. *Front Pharmacol.* 2018;9:773. Published 2018 Jul 16. doi:10.3389/fphar.2018.00773

Krazeisen A, Breitling R, Möller G, Adamski J. Human 17beta-hydroxysteroid dehydrogenase type 5 is inhibited by dietary flavonoids. *Adv Exp Med Biol.* 2002;505:151-161. doi:10.1007/978-1-4757-5235-9_14

Chen M, Jin Y, Penning TM. The rate-determining steps of aldo-keto reductases (AKRs), a study on human steroid 5 β -reductase (AKR1D1). *Chem Biol Interact.* 2015;234:360-365. doi:10.1016/j.cbi.2014.12.004

Jin Y. Activities of aldo-keto reductase 1 enzymes on two inhaled corticosteroids: implications for the pharmacological effects of inhaled corticosteroids. *Chem Biol Interact.* 2011;191(1-3):234-238. doi:10.1016/j.cbi.2011.01.019

Latif SA, Conca TJ, Morris DJ. The effects of the licorice derivative, glycyrrhetic acid, on hepatic 3 alpha- and 3 beta-hydroxysteroid dehydrogenases and 5 alpha- and 5 beta-reductase pathways of metabolism of aldosterone in male rats. *Steroids.* 1990;55(2):52-58. doi:10.1016/0039-128x(90)90024-6

Mast N, Linger M, Pikuleva IA. Inhibition and stimulation of activity of purified recombinant CYP11A1 by therapeutic agents. *Mol Cell Endocrinol.* 2013;371(1-2):100-106. doi:10.1016/j.mce.2012.10.013

Lundqvist J, Norlin M, Wikvall K. 1alpha,25-Dihydroxyvitamin D3 affects hormone production and expression of steroidogenic enzymes in human adrenocortical NCI-H295R cells. *Biochim Biophys Acta.* 2010;1801(9):1056-1062. doi:10.1016/j.bbapap.2010.04.009

Kim IH, Kim SK, Kim EH, et al. Korean Red Ginseng Up-regulates C21-Steroid Hormone Metabolism via Cyp11a1 Gene in Senescent Rat Testes. *J Ginseng Res.* 2011;35(3):272-282. doi:10.5142/jgr.2011.35.3.272

Diederich S, Quinkler M, Mai K, et al. In vivo activity of 11 β -hydroxysteroid dehydrogenase type 1 in man: effects of prednisolone and chenodesoxycholic acid. *Horm Metab Res.* 2011;43(1):66-71. doi:10.1055/s-0030-1267170

Schloms L, Smith C, Storbeck KH, Marnewick JL, Swart P, Swart AC. Rooibos influences glucocorticoid levels and steroid ratios in vivo and in vitro: a natural approach in the management of stress and metabolic disorders?. *Mol Nutr Food Res.* 2014;58(3):537-549. doi:10.1002/mnfr.201300463

Webster SP, McBride A, Binnie M, et al. Selection and early clinical evaluation of the brain-penetrant 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) inhibitor UE2343 (Xanamem™). *Br J Pharmacol.* 2017;174(5):396-408. doi:10.1111/bph.13699

Deluca D, Krazeisen A, Breitling R, Prehn C, Möller G, Adamski J. Inhibition of 17beta-hydroxysteroid dehydrogenases by phytoestrogens: comparison with other steroid metabolizing enzymes. *J Steroid Biochem Mol Biol.* 2005;93(2-5):285-292. doi:10.1016/j.jsbmb.2004.12.035

Classen-Houben D, Schuster D, Da Cunha T, et al. Selective inhibition of 11beta-hydroxysteroid dehydrogenase 1 by 18alpha-glycyrrhetic acid but not 18beta-glycyrrhetic acid. *J Steroid Biochem Mol Biol.* 2009;113(3-5):248-252. doi:10.1016/j.jsbmb.2009.01.009

Jothie Richard E, Illuri R, Bethapudi B, et al. Anti-stress Activity of Ocimum sanctum: Possible Effects on Hypothalamic-Pituitary-Adrenal Axis. *Phytother Res.* 2016;30(5):805-814. doi:10.1002/ptr.5584

Hu GX, Lin H, Lian QQ, et al. Curcumin as a potent and selective inhibitor of 11 β -hydroxysteroid dehydrogenase 1: improving lipid profiles in high-fat-diet-treated rats. *PLoS One.* 2013;8(3):e49976. doi:10.1371/journal.pone.0049976

Blum A, Loerz C, Martin HJ, Staab-Weijnitz CA, Maser E. Momordica charantia extract, a herbal remedy for type 2 diabetes, contains a specific 11 β -hydroxysteroid dehydrogenase type 1 inhibitor. *J Steroid Biochem Mol Biol.* 2012;128(1-2):51-55. doi:10.1016/j.jsbmb.2011.09.003

Hintzpter J, Stapelfeld C, Loerz C, Martin HJ, Maser E. Green tea and one of its constituents, Epigallocatechine-3-gallate, are potent inhibitors of human 11 β -hydroxysteroid dehydrogenase type 1. *PLoS One.* 2014;9(1):e84468. Published 2014 Jan 3. doi:10.1371/journal.pone.0084468

Chapman K, Holmes M, Seckl J. 11 β -hydroxysteroid dehydrogenases: intracellular gate-keepers of tissue glucocorticoid action. *Physiol Rev.* 2013;93(3):1139-1206. doi:10.1152/physrev.00020.2012

Atanasov AG, Dzyakanchuk AA, Schweizer RA, Nashev LG, Maurer EM, Odermatt A. Coffee inhibits the reactivation of glucocorticoids by 11beta-hydroxysteroid dehydrogenase type 1: a glucocorticoid connection in the anti-diabetic action of coffee?. *FEBS Lett.* 2006;580(17):4081-4085. doi:10.1016/j.febslet.2006.06.046

Kargl C, Arshad M, Salman F, Schurman RC, Del Corral P. 11 β -hydroxysteroid dehydrogenase type-II activity is affected by grapefruit juice and intense muscular work. *Arch Endocrinol Metab.* 2017;61(6):556-561. doi:10.1590/2359-3997000000296

Classen-Houben D, Schuster D, Da Cunha T, et al. Selective inhibition of 11beta-hydroxysteroid dehydrogenase 1 by 18alpha-glycyrrhetic acid but not 18beta-glycyrrhetic acid. *J Steroid Biochem Mol Biol.* 2009;113(3-5):248-252. doi:10.1016/j.jsbmb.2009.01.009

Quinkler M, Johanssen S, Grossmann C, et al. Progesterone metabolism in the human kidney and inhibition of 11beta-hydroxysteroid dehydrogenase type 2 by progesterone and its metabolites. *J Clin Endocrinol Metab.* 1999;84(11):4165-4171. doi:10.1210/jcem.84.11.61613

Wang Y, Dong Y, Fang Y, et al. Diethylstilbestrol inhibits human and rat 11 β -hydroxysteroid dehydrogenase 2. *Endocr Connect.* 2019;8(7):1061-1069. doi:10.1530/EC-19-0288

Inderbinen SG, Zogg M, Kley M, Smieško M, Odermatt A. Species-specific differences in the inhibition of 11 β -hydroxysteroid dehydrogenase 2 by itraconazole and posaconazole. *Toxicol Appl Pharmacol.* 2021;412:115387. doi:10.1016/j.taap.2020.115387

El-Shennawy L, Kamel MAE, Khalaf AHY, Yousef MI. Dose-dependent reproductive toxicity of sodium benzoate in male rats: Inflammation, oxidative stress and apoptosis. *Reprod Toxicol.* 2020;98:92-98. doi:10.1016/j.reprotox.2020.08.014

Mao B, Wu C, Zheng W, et al. Methoxychlor and its metabolite HPTE inhibit rat neurosteroidogenic 3 α -hydroxysteroid dehydrogenase and retinol dehydrogenase 2. *Neurosci Lett.* 2018;684:169-174. doi:10.1016/j.neulet.2018.08.008

Aromatase

Sisti JS, Hankinson SE, Caporaso NE, et al. Caffeine, coffee, and tea intake and urinary estrogens and estrogen metabolites in premenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2015;24(8):1174-1183. doi:10.1158/1055-9965.EPI-15-0246

Chow HH, Garland LL, Hsu CH, et al. Resveratrol modulates drug- and carcinogen-metabolizing enzymes in a healthy volunteer study. *Cancer Prev Res (Phila).* 2010;3(9):1168-1175. doi:10.1158/1940-6207.CAPR-09-0155

Jaruchotikamol A, Jarukamjorn K, Sirisangtrakul W, Sakuma T, Kawasaki Y, Nemoto N. Strong synergistic induction of CYP1A1 expression by andrographolide plus typical CYP1A inducers in mouse hepatocytes. *Toxicol Appl Pharmacol.* 2007;224(2):156-162. doi:10.1016/j.taap.2007.07.008

Chen HW, Tsai CW, Yang JJ, Liu CT, Kuo WW, Lii CK. The combined effects of garlic oil and fish oil on the hepatic antioxidant and drug-metabolizing enzymes of rats. *Br J Nutr.* 2003;89(2):189-200. doi:10.1079/BJN2002766

Yao HT, Hsu YR, Lii CK, Lin AH, Chang KH, Yang HT. Effect of commercially available green and black tea beverages on drug-metabolizing enzymes and oxidative stress in Wistar rats. *Food Chem Toxicol.* 2014;70:120-127. doi:10.1016/j.fct.2014.04.043

Hitzman RT, Dunlap TL, Howell CE, et al. 6-Prenylnaringenin from Hops Disrupts ER α -Mediated Downregulation of CYP1A1 to Facilitate Estrogen Detoxification. *Chem Res Toxicol.* 2020;33(11):2793-2803. doi:10.1021/acs.chemrestox.0c00194

Thomson CA, Ho E, Strom MB. Chemopreventive properties of 3,3'-diindolylmethane in breast cancer: evidence from experimental and human studies. *Nutr Rev.* 2016;74(7):432-443. doi:10.1093/nutrit/nuw010

Vigier B, Forest MG, Eychenne B, et al. Anti-Müllerian hormone produces endocrine sex reversal of fetal ovaries. *Proc Natl Acad Sci U S A.* 1989;86(10):3684-3688. doi:10.1073/pnas.86.10.3684

Balam FH, Ahmadi ZS, Ghorbani A. Inhibitory effect of chrysin on estrogen biosynthesis by suppression of enzyme aromatase (CYP19): A systematic review. *Helijon.* 2020;6(3):e03557. Published 2020 Mar 7. doi:10.1016/j.heliyon.2020.e03557

Om AS, Chung KW. Dietary zinc deficiency alters 5 alpha-reduction and aromatization of testosterone and androgen and estrogen receptors in rat liver. *J Nutr.* 1996;126(4):842-848. doi:10.1093/jn/126.4.842

Zhao J, Dasmahapatra AK, Khan SI, Khan IA. Anti-aromatase activity of the constituents from damiana (*Turnera diffusa*). *J Ethnopharmacol.* 2008;120(3):387-393. doi:10.1016/j.jep.2008.09.016

Kijima I, Phung S, Hur G, Kwok SL, Chen S. Grape seed extract is an aromatase inhibitor and a suppressor of aromatase expression. *Cancer Res.* 2006;66(11):5960-5967. doi:10.1158/0008-5472.CAN-06-0053

Chrubasik JE, Roufogalis BD, Wagner H, Chrubasik S. A comprehensive review on the stinging nettle effect and efficacy profiles. Part II: urticae radix. *Phytomedicine.* 2007;14(7-8):568-579. doi:10.1016/j.phymed.2007.03.014

Watanabe M, Nakajin S. Forskolin up-regulates aromatase (CYP19) activity and gene transcripts in the human adrenocortical carcinoma cell line H295R. *J Endocrinol.* 2004;180(1):125-133. doi:10.1677/joe.0.1800125

Scheller MS, Nakakimura K, Fleischer JE, Zornow MH. Cerebral effects of sevoflurane in the dog: comparison with isoflurane and enflurane. *Br J Anaesth.* 1990;65(3):388-392. doi:10.1093/bja/65.3.388

Dickens MJ, Cornil CA, Balthazart J. Acute stress differentially affects aromatase activity in specific brain nuclei of adult male and female quail. *Endocrinology.* 2011;152(11):4242-4251. doi:10.1210/en.2011-1341

Wei J, Yuen EY, Liu W, et al. Estrogen protects against the detrimental effects of repeated stress on glutamatergic transmission and cognition. *Mol Psychiatry.* 2014;19(5):588-598. doi:10.1038/mp.2013.83

Weber MM, Will A, Adelmann B, Engelhardt D. Effect of ketoconazole on human ovarian C17,20-desmolase and aromatase. *J Steroid Biochem Mol Biol.* 1991;38(2):213-218. doi:10.1016/0960-0760(91)90128-r

Brown KA, Hunger NI, Docanto M, Simpson ER. Metformin inhibits aromatase expression in human breast adipose stromal cells via stimulation of AMP-activated protein kinase. *Breast Cancer Res Treat.* 2010;123(2):591-596. doi:10.1007/s10549-010-0834-y

Balunas MJ, Su B, Brueggemeier RW, Kinghorn AD. Natural products as aromatase inhibitors. *Anticancer Agents Med Chem.* 2008;8(6):646-682.

Satoh K, Sakamoto Y, Ogata A, et al. Inhibition of aromatase activity by green tea extract catechins and their endocrinological effects of oral administration in rats. *Food Chem Toxicol.* 2002;40(7):925-933. doi:10.1016/s0278-6915(02)00066-2

Ye L, Chan FL, Chen S, Leung LK. The citrus flavonone hesperetin inhibits growth of aromatase-expressing MCF-7 tumor in ovariectomized athymic mice. *J Nutr Biochem.* 2012;23(10):1230-1237. doi:10.1016/j.jnutbio.2011.07.003

Le Bail JC, Pouget C, Fagnere C, Basly JP, Chulia AJ, Habrioux G. Chalcones are potent inhibitors of aromatase and 17 β -hydroxysteroid dehydrogenase activities. *Life Sci.* 2001;68(7):751-761. doi:10.1016/s0024-3205(00)00974-7

Biegan A, Kim SW, Logan J, Hooker JM, Muench L, Fowler JS. Nicotine blocks brain estrogen synthase (aromatase): in vivo positron emission tomography studies in female baboons. *Biol Psychiatry.* 2010;67(8):774-777. doi:10.1016/j.biopsych.2010.01.004

Wang Y, Lee KW, Chan FL, Chen S, Leung LK. The red wine polyphenol resveratrol displays bilevel inhibition on aromatase in breast cancer cells. *Toxicol Sci.* 2006;92(1):71-77. doi:10.1093/toxsci/kfj190

Siler U, Barella L, Spitzer V, et al. Lycopene and vitamin E interfere with autocrine/paracrine loops in the Dunning prostate cancer model. *FASEB J.* 2004;18(9):1019-1021. doi:10.1096/fj.03-1116fje

Chen S, Oh SR, Phung S, et al. Anti-aromatase activity of phytochemicals in white button mushrooms (*Agaricus bisporus*). *Cancer Res.* 2006;66(24):12026-12034. doi:10.1158/0008-5472.CAN-06-2206

Purohit A, Singh A, Ghilchik MW, Reed MJ. Inhibition of tumor necrosis factor alpha-stimulated aromatase activity by microtubule-stabilizing agents, paclitaxel and 2-methoxyestradiol. *Biochem Biophys Res Commun.* 1999;261(1):214-217. doi:10.1006/bbrc.1999.1010

Scheller MS, Nakakimura K, Fleischer JE, Zornow MH. Cerebral effects of sevoflurane in the dog: comparison with isoflurane and enflurane. *Br J Anaesth.* 1990;65(3):388-392. doi:10.1093/bja/65.3.388

Spratt DL, Morton JR, Kramer RS, Mayo SW, Longcope C, Vary CP. Increases in serum estrogen levels during major illness are caused by increased peripheral aromatization. *Am J Physiol Endocrinol Metab.* 2006;291(3):E631-E638. doi:10.1152/ajpendo.00467.2005

Hiltunen M, Iivonen S, Soininen H. Aromatase enzyme and Alzheimer's disease. *Minerva Endocrinol.* 2006;31(1):61-73.

Monteiro R, Soares R, Guerreiro S, Pestana D, Calhau C, Azevedo I. Red wine increases adipose tissue aromatase expression and regulates body weight and adipocyte size. *Nutrition.* 2009;25(6):699-705. doi:10.1016/j.nut.2009.01.001

Randolph JF Jr, Kipersztok S, Ayers JW, Ansbacher R, Peegel H, Menon KM. The effect of insulin on aromatase activity in isolated human endometrial glands and stroma. *Am J Obstet Gynecol.* 1987;157(6):1534-1539. doi:10.1016/0002-9378(87)80258-2

Magoffin DA, Weitsman SR, Aagarwal SK, Jakimiuk AJ. Leptin regulation of aromatase activity in adipose stromal cells from regularly cycling women. *Ginekol Pol.* 1999;70(1):1-7.

Gelsomino L, Giordano C, Camera G, et al. Leptin Signaling Contributes to Aromatase Inhibitor Resistant Breast Cancer Cell Growth and Activation of Macrophages. *Biomolecules.* 2020;10(4):543. Published 2020 Apr 3. doi:10.3390/biom10040543

Purohit A, Singh A, Ghilchik MW, Reed MJ. Inhibition of tumor necrosis factor alpha-stimulated aromatase activity by microtubule-stabilizing agents, paclitaxel and 2-methoxyestradiol. *Biochem Biophys Res Commun.* 1999;261(1):214-217. doi:10.1006/bbrc.1999.1010

Estrogens

Estrone Low	Estrone High
<p>Upregulate HSD17B (bidirectional):</p> <ul style="list-style-type: none"> Meditation Bioflavonoids (i.e. rutin) Abdominal obesity Sacred fig Grapeseed extract Malaysian propolis Promethazine <p>Upregulate CYP19A1 (aromatase):</p> <ul style="list-style-type: none"> Forskolin (found in coleus plant) SSRIs: <ul style="list-style-type: none"> Paroxetine Sertraline (both upregulates and downregulates aromatase) <p>Address possible contributing factors:</p> <ul style="list-style-type: none"> Visceral abdominal adiposity Stress High glycemic diet Insulin elevations, leptin resistance, metabolic syndrome Alcohol/red wine Inflammatory cytokines: IL-6, TNFalpha, prostaglandin, PGE (2) Xeno-estrogens / endocrine disruptors / toxins (pesticides, herbicides, benzene, plastic by-products, petroleum, UV) 	<p>Upregulate CYP3A4:</p> <ul style="list-style-type: none"> CYP3A4 medication inducers: <ul style="list-style-type: none"> Carbamazepine Dexamethasone Modafinil Phenobarbital Phenytoin St. John's wort Capsaicin Valerian Ginkgo biloba Vitamin D/UV exposure Fatty acids Heme iron (CYP enzymes are heme dependent) <p>Downregulate HSD17B:</p> <ul style="list-style-type: none"> Licorice Quercetin Flavonoids of phytoestrogens: <ul style="list-style-type: none"> Zearalenone Coumestrol Quercetin Biochanin A <p>Downregulate CYP19A1 (aromatase):</p> <ul style="list-style-type: none"> Chrysin Zinc Damiana Grapeseed extract Nettles Flavonoids Mangostin Resveratrol Vitamin E White button mushrooms Aromatase Inhibitors SSRIs: <ul style="list-style-type: none"> Venlafaxine, fluoxetine, paroxetine and sertraline (both upregulates and downregulates aromatase) Stress reduction Low glycemic diet Address insulin elevations, obesity, leptin resistance, metabolic syndrome <p>Reduce alcohol/red wine</p> <p>Reduce inflammatory cytokines: IL-6, TNFalpha, prostaglandin, PGE (2)</p> <p>Reduce xeno-estrogens / endocrine disruptors / toxins (pesticides, herbicides, benzene, plastic by-products, petroleum, UV)</p>

Estradiol Low	Estradiol High
<p>Upregulate HSD17B:</p> <ul style="list-style-type: none"> Meditation Bioflavonoids (I.e. rutin) Sacred fig Grapeseed extract Malaysian propolis Medication: Promethazine <p>Upregulate CYP19A1 (aromatase):</p> <ul style="list-style-type: none"> Forskolin (found in coleus plant) SSRIs: <ul style="list-style-type: none"> Paroxetine Sertraline (both upregulates and downregulates aromatase) 	<p>Address abdominal adiposity, which upregulates HSD17B</p> <p>Upregulate CYP3A4:</p> <ul style="list-style-type: none"> St. John's wort Capsaicin Valerian Ginkgo biloba Vitamin D/UV exposure Fatty acids Heme iron (CYP enzymes are heme dependent) CYP3A4 medication inducers: <ul style="list-style-type: none"> Carbamazepine Dexamethasone Modafinil Phenobarbital Phenytoin
2-OH E1/E2 Low	2-OH E1/E2 High
<p>Upregulate CYP1A1:</p> <ul style="list-style-type: none"> DIM/cruciferous veggies I3C (requires stomach acid to convert to DIM) Coffee Resveratrol Rosemary Andrographolide, from the Andrographis paniculata plant Astaxanthin (shrimps and some algae) Fish oil and garlic oil Green and black tea Hops Heme iron <p>Avoid CYP1A1 down regulators:</p> <ul style="list-style-type: none"> PAHs, PCBs, xenoestrogens, phthalates BPA Smoking Charred meats 	<p>Downregulate CYP1A1:</p> <ul style="list-style-type: none"> Grapefruit juice (bergamottin) Berries (ellagic acid) can reduce overactivity Green tea extracts Sulforaphane found in broccoli St. John's Wort Lycopene, a red pigment found in tomatoes, carrots, and watermelon Naringenin and 6'7'-dihydroxybergamottin (from grapefruit juice) Galangin, found in some plants (<i>Alpinia officinarum</i>, <i>Alpinia galanga</i>, and <i>Helichrysum aureonitens</i>) and propolis A widely used herbal formulation produced from the extracts of ten common herbs (rosemary, turmeric, ginger, holy basil, green tea, hu zhang, Chinese goldthread, barberry, oregano, and Baikal skullcap) <p>Upregulate COMT:</p> <ul style="list-style-type: none"> Cruciferous vegetables, soy foods (ex. genistein), resveratrol, citrus foods, teas (rooibos, dandelion), and spices (rosemary, curcumin). Support for methylation consists of nutrient cofactors and methyl donors, such as methionine, vitamin B12, vitamin B6, betaine, folate, and magnesium <p>Antioxidants to address free radicals:</p> <ul style="list-style-type: none"> Vitamins A, C, E Selenium, copper, Zinc, manganese CoQ10 Thiols (garlic, onions, cruciferous vegetables) Bioflavonoids, silymarin Oligomeric, proanthocyanidins NAC

4-OH E2 Low	4-OH E1/E2 High
<p>Upregulate CYP1B1:</p> <ul style="list-style-type: none"> • Estrogen • Tetrahydrocannabinol (THC) • UV exposure • Biotin supplementation 	<p>Downregulate CYP1B1:</p> <ul style="list-style-type: none"> • Apiaceae family: carrots, cumin, anise, celery, caraway • Grapefruit • Resveratrol • Rosemary • Apigenin and amentoflavone (St. John's wort) • Ginseng • Lycopene, a red pigment found in tomatoes, carrots, and watermelon • Chrysoeriol, present in rooibos tea and celery • Naringenin (grapefruit juice) • A polyherbal formulation produced from the extracts of ten common herbs (rosemary, turmeric, ginger, holy basil, green tea, hu zhang, Chinese goldthread, barberry, oregano, and Baikal skullcap) • Quercetin • Many natural flavonoids and synthetic stilbenes show inhibitory activity toward CYP1B1 expression and function, notably isorhamnetin and 2,4,3',5'-tetramethoxystilbene. • Genetics: 150 gene polymorphisms have been reported <p>Avoid/address: PAHs, PCBs, Diesel exhaust particles (DEP), Leptin resistance /inflammation/insulin resistance which upregulate CYP1B1</p> <p>Upregulate COMT:</p> <ul style="list-style-type: none"> • Cruciferous vegetables, soy foods (ex. genestein), resveratrol, citrus foods, teas (rooibos, dandelion), and spices (rosemary, curcumin). • Support for methylation consists of nutrient cofactors and methyl donors, such as methionine, vitamin B12, vitamin B6, betaine, folate, and magnesium
16-OH E1 Low	16-OH E1 High
<p>Upregulate CYP3A4:</p> <ul style="list-style-type: none"> • St. John's wort • Capsaicin • Valerian • Gingko biloba • Vitamin D/UV exposure • Fatty acids • Heme iron (CYP enzymes are heme dependent) • CYP3A4 medication inducers: <ul style="list-style-type: none"> • Carbamazepine • Dexamethasone • Modafinil • Phenobarbital • Phenytoin 	<p>Upregulate HSD17B:</p> <ul style="list-style-type: none"> • Meditation • Bioflavonoids (i.e. rutin) • Sacred fig • Grapeseed extract • Malaysian propolis • Promethazine <p>Avoid/address:</p> <ul style="list-style-type: none"> • Diabetes, polycyclic aromatic hydrocarbons (PAH) found in cigarettes, Aflatoxin B1 which upregulate CYP3A4 <p>Downregulate CYP3A4 (this could also bring down estriol)</p> <ul style="list-style-type: none"> • Grapefruit juice • Starfruit juice • Aloe vera juice • Polyphenols • Flavonoids: <ul style="list-style-type: none"> • Kaempferol (kale, beans, tea, spinach, broccoli) • Quercetin • Apigenin • Chrysanthemum • Luteolin • Genistein • Green tea flavonols EGCG and epicatechin gallate

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- Phytoestrogen: coumestrol (soybeans, brussels sprouts, spinach and a variety of legumes)
- Phenolic acids: caffeic acid
- Mixed vegetable juices
- Kale (animal study)
- Garden cress
- Fennel
- Black pepper (piperine)
- Horsetail
- Goldenseal
- Raspberry leaf
- Milk thistle (silybin and isosilybin)
- Echinacea
- Sage
- Horse chestnut
- Tannins
 - Tannic acid
 - Gallic acid
- Other Polyphenols
 - Licochalcone A from licorice
 - Sesamin in sesame seeds (*Sesamum indicum*)
 - Resveratrol
 - Sulforaphane
 - Berberine
 - Allyl isothiocyanate (creates the pungent taste of mustard, radish, horseradish, and wasabi)
 - Ginsenoside Rd derived from Ginseng
 - Gomisin C and gomisin G found in *Schisandra Chinensis*
- CYP3A4 medication inhibitors
 - Amiodarone
 - Cyclosporine
 - Cimetidine
 - Erythromycin
 - Fluconazole
 - Diltiazem
 - Delavirdine
 - Amprenavir
 - Osamprenavir
 - Conivaptan
 - Fluconazole
 - Diltiazem
 - Delavirdine
 - Amprenavir
 - Osamprenavir
 - Conivaptan
 - Fluoxetine
 - Ketoconazole
 - Atazanavir
 - Darunavir
 - Indinavir
 - lopinavir
 - Nelfinavir
 - Saquinavir
 - Tipranavir
 - Tamoxifen
 - Ritonavir

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	<ul style="list-style-type: none"> • Itraconazole • Azole antifungals: miconazole, ketoconazole • Verapamil • Sertraline • Metformin • Nefazodone • Clarithromycin • Telithromycin <p>*It is important to note that not all drugs within a class of medications are known to be inhibitors of CYP3A4</p> <p>*Drugs metabolized by CYP3A4 are called CYP3A4 substrates. Many CYP3A4 substrates have substantial toxicity, especially when CYP3A4 inhibitors are taken concurrently.</p>
2-M E1/E2 Low	2-M E1/E2 High
<p>Upregulate COMT:</p> <ul style="list-style-type: none"> • Cruciferous vegetables, soy foods (ex. genestein), resveratrol, citrus foods, teas (rooibos, dandelion), and spices (rosemary, curcumin) • Support for methylation consists of nutrient cofactors and methyl donors, such as methionine, vitamin B12, vitamin B6, betaine, folate, and magnesium 	<p>Address high 2-OH E1/E2 if applicable</p> <p>Support phase 3 detoxification:</p> <ul style="list-style-type: none"> • Optimize digestive health • Hydration • Fiber • Herbs to prevent/treat constipation (aloe, ginger, avipatakar, triphala) • Magnesium • Physical activity <p>Ongoing support of COMT:</p> <ul style="list-style-type: none"> • Cruciferous vegetables, soy foods (ex. genestein), resveratrol, citrus foods, teas (rooibos, dandelion), and spices (rosemary, curcumin). • Support for methylation consists of nutrient cofactors and methyl donors, such as methionine, vitamin B12, vitamin B6, betaine, folate, and magnesium
4-M E1/E2 Low	4-M E1/E2 High
<p>Upregulate COMT:</p> <ul style="list-style-type: none"> • Cruciferous vegetables, soy foods (ex. genestein), resveratrol, citrus foods, teas (rooibos, dandelion), and spices (rosemary, curcumin). • Support for methylation consists of nutrient cofactors and methyl donors, such as methionine, vitamin B12, vitamin B6, betaine, folate, and magnesium <p>Address/avoid conditions that downregulate COMT:</p> <ul style="list-style-type: none"> • High sucrose diet may inhibit methylation • Leptin resistance • Bisphenol and PCBs • Having too little SAM (s-adenosylmethionine) and too much SAH (s-adenosylhomocysteine) from undermethylation • TNFalpha, present in inflammatory states • Anything that affects the methionine cycle (homocysteine to cysteine): B6 insufficiency 	<p>Address high 4-OH if applicable</p> <p>Support CYP 1A1 if 2-OH E1/E2 is low</p> <p>Support phase 3 detoxification:</p> <ul style="list-style-type: none"> • Optimize digestive health • Hydration • Fiber • Herbs to prevent/treat constipation (aloe, ginger, avipatakar, triphala) • Magnesium • Physical activity <p>Ongoing support of COMT:</p> <ul style="list-style-type: none"> • Cruciferous vegetables, soy foods (ex. genestein), resveratrol, citrus foods, teas (rooibos, dandelion), and spices (rosemary, curcumin). • Support for methylation consists of nutrient cofactors and methyl donors, such as methionine, vitamin B12, vitamin B6, betaine, folate, and magnesium

Estriol Low	Estriol High
<p>Upregulate HSD17B:</p> <ul style="list-style-type: none"> • Grapeseed extract • Malaysian propolis • Meditation • Bioflavonoids (I.e. rutin) • Sacred fig • Medication: Promethazine <p>Upregulate CYP3A4:</p> <ul style="list-style-type: none"> • St. John's wort • Capsaicin • Valerian • Gingko biloba • Vitamin D/UV exposure • Fatty acids • Heme iron (CYP enzymes are heme dependent) • CYP3A4 medication inducers: <ul style="list-style-type: none"> • Carbamazepine • Dexamethasone • Modafinil • Phenobarbital • Phenytoin 	<p>Downregulate HSD17B:</p> <ul style="list-style-type: none"> • Licorice • Quercetin • Flavonoids of Phytoestrogens: zearalenone, coumestrol, quercetin and biochanin A <p>Address/avoid:</p> <ul style="list-style-type: none"> • Abdominal obesity which upregulates HSD17B • Polycyclic aromatic hydrocarbons (PAH) found in cigarettes and Aflatoxin B1, diabetes which upregulates CYP3A4 <p>Downregulate CYP3A4:</p> <ul style="list-style-type: none"> • Grapefruit juice • Starfruit juice • Aloe vera juice • Polyphenols • Flavonoids: <ul style="list-style-type: none"> • Kaempferol (kale, beans, tea, spinach, broccoli) • Quercetin • Apigenin • Chrysin • Luteolin • Genestein • Green tea flavonols EGCG and epicatechin gallate • Phytoestrogen: Coumestrol (soybeans, brussels sprouts, spinach and a variety of legumes) • Phenolic acids: Caffeic acid • Mixed vegetable juices • Kale • Garden cress • Fennel • Black pepper (piperine) • Horsetail • Goldenseal • Raspberry leaf • Milk thistle (silybin and isosilybin) • Echinacea • Sage • Horse chestnut • Tannins: <ul style="list-style-type: none"> • Tannic acid • Gallic acid • Other Polyphenols: <ul style="list-style-type: none"> • Licochalcone A from licorice • Sesamin in sesame seeds (<i>Sesamum indicum</i>) • Resveratrol • Sulforaphane • Berberine • Allyl isothiocyanate (creates the pungent taste of mustard, radish, horseradish, and wasabi) • Ginsenoside Rd derived from Ginseng • Gomisin C and gomisin G found in <i>Schisandra Chinensis</i> • CYP3A4 medication Inhibitors: <ul style="list-style-type: none"> • Amiodarone • Cyclosporine • Cimetidine • Erythromycin

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	<ul style="list-style-type: none"> • Fluconazole • Diltiazem • Delavirdine • Osamprenavir • Conivaptan • Fluoxetine • Ketoconazole • Atazanavir • Darunavir • Indinavir • lopinavir • Nelfinavir • Saquinavir • Tipranavir • Tamoxifen • Ritonavir, itraconazole • Azole antifungals: Miconazole, ketoconazole • Verapamil • Sertraline • Metformin • Nefazodone • Clarithromycin • Telithromycin <p>*It is important to note that not all drugs within a class of medications are known to be inhibitors of CYP3A4</p> <p>*Drugs metabolized by CYP3A4 are called CYP3A4 substrates. Many CYP3A4 substrates have substantial toxicity, especially when CYP3A4 inhibitors are taken concurrently.</p>
2-M E1&E2 / 2-OH E1&E2 Low	2-M E1&E2 / 2-OH E1&E2 High
<p>Upregulate COMT:</p> <ul style="list-style-type: none"> • Cruciferous vegetables, soy foods (ex. genestein), resveratrol, citrus foods, teas (rooibos, dandelion), and spices (rosemary, curcumin). • Support for methylation consists of nutrient cofactors and methyl donors, such as methionine, vitamin B12, vitamin B6, betaine, folate, and magnesium <p>Antioxidants to address free radicals:</p> <ul style="list-style-type: none"> • Vitamins A, C, E • Selenium, copper, zinc, manganese • CoQ10 • Thiols (garlic, onions, cruciferous vegetables) • Bioflavonoids, silymarin • Oligomeric, proanthocyanidins • NAC 	<p>Support phase 3 detoxification:</p> <ul style="list-style-type: none"> • Optimize digestive health • Hydration • Fiber • Herbs to prevent/treat constipation (aloe, ginger, avipatakar, triphala) • Magnesium • Physical activity <p>Ongoing support of COMT:</p> <ul style="list-style-type: none"> • Cruciferous vegetables, soy foods (ex. genestein), resveratrol, citrus foods, teas (rooibos, dandelion), and spices (rosemary, curcumin). • Support for methylation consists of nutrient cofactors and methyl donors, such as methionine, vitamin B12, vitamin B6, betaine, folate, and magnesium

8-OHdG Low	8-OHdG High
<p><i>There is no low range for this marker. It is within range or elevated.</i></p>	<p>Identify and address the cause of oxidative stress.</p> <p>Antioxidant and anti-inflammatory strategies:</p> <ul style="list-style-type: none"> • Colorful fruits and vegetables • Glutathione, NAC • Green tea • Oranges • Onion and garlic • Vitamins C and E • Folate • Melatonin • Berberine • Curcumin • Alpha lipoic acid • EPA/DHA • CoQ10 • Yoga

Estrogens References

CYP1A1

Thomson CA, Ho E, Strom MB. Chemopreventive properties of 3,3'-diindolylmethane in breast cancer: evidence from experimental and human studies. *Nutr Rev*. 2016;74(7):432-443. doi:10.1093/nutrit/nuw010

Horn TL, Reichert MA, Bliss RL, Malejka-Giganti D. Modulations of P450 mRNA in liver and mammary gland and P450 activities and metabolism of estrogen in liver by treatment of rats with indole-3-carbinol. *Biochem Pharmacol*. 2002;64(3):393-404. doi:10.1016/s0006-2952(02)01190-5

Sisti JS, Hankinson SE, Caporaso NE, et al. Caffeine, coffee, and tea intake and urinary estrogens and estrogen metabolites in premenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2015;24(8):1174-1183. doi:10.1158/1055-9965.EPI-15-0246

Chow HH, Garland LL, Hsu CH, et al. Resveratrol modulates drug- and carcinogen-metabolizing enzymes in a healthy volunteer study. *Cancer Prev Res (Phila)*. 2010;3(9):1168-1175. doi:10.1158/1940-6207.CAPR-09-0155

Jaruchotikamol A, Jarukamjorn K, Sirisangtrakul W, Sakuma T, Kawasaki Y, Nemoto N. Strong synergistic induction of CYP1A1 expression by andrographolide plus typical CYP1A inducers in mouse hepatocytes. *Toxicol Appl Pharmacol*. 2007;224(2):156-162. doi:10.1016/j.taap.2007.07.008

Ohno M, Darwish WS, Ikenaka Y, Miki W, Ishizuka M. Astaxanthin can alter CYP1A-dependent activities via two different mechanisms: induction of protein expression and inhibition of NADPH P450 reductase dependent electron transfer. *Food Chem Toxicol*. 2011;49(6):1285-1291. doi:10.1016/j.fct.2011.03.009

Chen HW, Tsai CW, Yang JJ, Liu CT, Kuo WW, Lii CK. The combined effects of garlic oil and fish oil on the hepatic antioxidant and drug-metabolizing enzymes of rats. *Br J Nutr*. 2003;89(2):189-200. doi:10.1079/BJN2002766

Yao HT, Hsu YR, Lii CK, Lin AH, Chang KH, Yang HT. Effect of commercially available green and black tea beverages on drug-metabolizing enzymes and oxidative stress in Wistar rats. *Food Chem Toxicol*. 2014;70:120-127. doi:10.1016/j.fct.2014.04.043

Hitzman RT, Dunlap TL, Howell CE, et al. 6-Prenylnaringenin from Hops Disrupts ERα-Mediated Downregulation of CYP1A1 to Facilitate Estrogen Detoxification. *Chem Res Toxicol*. 2020;33(11):2793-2803. doi:10.1021/acs.chemrestox.0c00194

Xu H, Zhang X, Ye Y, Li X. Bisphenol A affects estradiol metabolism by targeting CYP1A1 and CYP19A1 in human placental JEG-3 cells. *Toxicol In Vitro*. 2019;61:104615. doi:10.1016/j.tiv.2019.104615

Anderson GD, Chan LN. Pharmacokinetic Drug Interactions with Tobacco, Cannabinoids and Smoking Cessation Products. *Clin Pharmacokinet*. 2016;55(11):1353-1368. doi:10.1007/s40262-016-0400-9

Olgún-Reyes S, Camacho-Carranza R, Hernández-Ojeda S, Elinos-Baez M, Espinosa-Aguirre JJ. Bergamottin is a competitive inhibitor of CYP1A1 and is antimutagenic in the Ames test. *Food Chem Toxicol*. 2012;50(9):3094-3099. doi:10.1016/j.fct.2012.05.058

Hodges RE, Minich DM. Modulation of Metabolic Detoxification Pathways Using Foods and Food-Derived Components: A Scientific Review with Clinical Application. *J Nutr Metab*. 2015;2015:760689. doi:10.1155/2015/760689

Williams SN, Shih H, Guenette DK, et al. Comparative studies on the effects of green tea extracts and individual tea catechins on human CYP1A gene expression. *Chem Biol Interact*. 2000;128(3):211-229. doi:10.1016/s0009-2797(00)00204-0

Yang F, Zhuang S, Zhang C, Dai H, Liu W. Sulforaphane inhibits CYP1A1 activity and promotes genotoxicity induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin in vitro. *Toxicol Appl Pharmacol*. 2013;269(3):226-232. doi:10.1016/j.taap.2013.03.024

Chaudhary A, Willett KL. Inhibition of human cytochrome CYP 1 enzymes by flavonoids of St. John's wort. *Toxicology*. 2006;217(2-3):194-205. doi:10.1016/j.tox.2005.09.010

Wang H, Leung LK. The carotenoid lycopene differentially regulates phase I and II enzymes in dimethylbenz[a]anthracene-induced MCF-7 cells. *Nutrition*. 2010;26(11-12):1181-1187. doi:10.1016/j.nut.2009.11.013

Santes-Palacios R, Romo-Mancillas A, Camacho-Carranza R, Espinosa-Aguirre JJ. Inhibition of human and rat CYP1A1 enzyme by grapefruit juice compounds. *Toxicol Lett*. 2016;258:267-275. doi:10.1016/j.toxlet.2016.07.023

Ciolino HP, Yeh GC. The flavonoid galangin is an inhibitor of CYP1A1 activity and an agonist/antagonist of the aryl hydrocarbon receptor. *Br J Cancer*. 1999;79(9-10):1340-1346. doi:10.1038/sj.bjc.6690216

Mohebati A, Guttenplan JB, Kochhar A, et al. Carnosol, a constituent of Zyflamend, inhibits aryl hydrocarbon receptor-mediated activation of CYP1A1 and CYP1B1 transcription and mutagenesis. *Cancer Prev Res (Phila)*. 2012;5(4):593-602. doi:10.1158/1940-6207.CAPR-12-0002

Zhu BT, Loder DP, Cai MX, Ho CT, Huang MT, Conney AH. Dietary administration of an extract from rosemary leaves enhances the liver microsomal metabolism of endogenous estrogens and decreases their uterotrophic action in CD-1 mice. *Carcinogenesis*. 1998;19(10):1821-1827. doi:10.1093/carcin/19.10.1821

CYB1B1

Tsuchiya Y, Nakajima M, Kyo S, Kanaya T, Inoue M, Yokoi T. Human CYP1B1 is regulated by estradiol via estrogen receptor. *Cancer Res*. 2004;64(9):3119-3125. doi:10.1158/0008-5472.ca-04-0166

Li F, Zhu W, Gonzalez FJ. Potential role of CYP1B1 in the development and treatment of metabolic diseases. *Pharmacol Ther*. 2017;178:18-30. doi:10.1016/j.pharmthera.2017.03.007

Jacob A, Hartz AM, Potin S, et al. Aryl hydrocarbon receptor-dependent upregulation of Cyp1b1 by TCDD and diesel exhaust particles in rat brain microvessels. *Fluids Barriers CNS*. 2011;8:23. Published 2011 Aug 25. doi:10.1186/2045-8118-8-23

Villard PH, Sampol E, Elkaim JL, et al. Increase of CYP1B1 transcription in human keratinocytes and HaCaT cells after UV-B exposure. *Toxicol Appl Pharmacol*. 2002;178(3):137-143. doi:10.1006/taap.2001.9335

Rodriguez-Melendez R, Griffin JB, Zempleni J. Biotin supplementation increases expression of the cytochrome P450 1B1 gene in Jurkat cells, increasing the occurrence of single-stranded DNA breaks. *J Nutr*. 2004;134(9):2222-2228. doi:10.1093/jn/134.9.2222

Habib CN, Al-Abd AM, Tolba MF, et al. Leptin influences estrogen metabolism and accelerates prostate cell proliferation. *Life Sci*. 2015;121:10-15. doi:10.1016/j.lfs.2014.11.007

Shouman S, Wagih M, Kamel M. Leptin influences estrogen metabolism and increases DNA adduct formation in breast cancer cells. *Cancer Biol Med*. 2016;13(4):505-513. doi:10.20892/j.issn.2095-3941.2016.0079

Jeyabalan J, Aqil F, Soper L, Schultz DJ, Gupta RC. Potent Chemopreventive/Antioxidant Activity Detected in Common Spices of the Apiaceae Family. *Nutr Cancer*. 2015;67(7):1201-1207. doi:10.1080/01635581.2015.1075051

Girennavar B, Poulose SM, Jayaprakasha GK, Bhat NG, Patil BS. Furocoumarins from grapefruit juice and their effect on human CYP 3A4 and CYP 1B1 isoenzymes. *Bioorg Med Chem*. 2006;14(8):2606-2612. doi:10.1016/j.bmc.2005.11.039

Shoieb SM, El-Kadi AOS. Resveratrol attenuates angiotensin II-induced cellular hypertrophy through the inhibition of CYP1B1 and the cardiotoxic mid-chain HETE metabolites. *Mol Cell Biochem*. 2020;471(1-2):165-176. doi:10.1007/s11010-020-03777-9

Chaudhary A, Willett KL. Inhibition of human cytochrome CYP 1 enzymes by flavonoids of St. John's wort. *Toxicology*. 2006;217(2-3):194-205. doi:10.1016/j.tox.2005.09.010

Chang TK, Chen J, Benetton SA. In vitro effect of standardized ginseng extracts and individual ginsenosides on the catalytic activity of human CYP1A1, CYP1A2, and CYP1B1. *Drug Metab Dispos*. 2002;30(4):378-384. doi:10.1124/dmd.30.4.378

Wang H, Leung LK. The carotenoid lycopene differentially regulates phase I and II enzymes in dimethylbenz[a]anthracene-induced MCF-7 cells. *Nutrition*. 2010;26(11-12):1181-1187. doi:10.1016/j.nut.2009.11.013

Hodges RE, Minich DM. Modulation of Metabolic Detoxification Pathways Using Foods and Food-Derived Components: A Scientific Review with Clinical Application. *J Nutr Metab*. 2015;2015:760689. doi:10.1155/2015/760689

Poon CH, Wong TY, Wang Y, et al. The citrus flavanone naringenin suppresses CYP1B1 transactivation through antagonising xenobiotic-responsive element binding. *Br J Nutr*. 2013;109(9):1598-1605. doi:10.1017/S0007114512003595

Mohebati A, Guttenplan JB, Kochhar A, et al. Carnosol, a constituent of Zyflamend, inhibits aryl hydrocarbon receptor-mediated activation of CYP1A1 and CYP1B1 transcription and mutagenesis. *Cancer Prev Res (Phila)*. 2012;5(4):593-602. doi:10.1158/1940-6207.CAPR-12-0002

Choi EJ, Kim T, Kim GH. Quercetin acts as an antioxidant and downregulates CYP1A1 and CYP1B1 against DMBA-induced oxidative stress in mice. *Oncol Rep*. 2012;28(1):291-296. doi:10.3892/or.2012.1753

Chaudhary A, Willett KL. Inhibition of human cytochrome CYP 1 enzymes by flavonoids of St. John's wort. *Toxicology*. 2006;217(2-3):194-205. doi:10.1016/j.tox.2005.09.010

Li F, Zhu W, Gonzalez FJ. Potential role of CYP1B1 in the development and treatment of metabolic diseases. *Pharmacol Ther*. 2017;178:18-30. doi:10.1016/j.pharmthera.2017.03.007

CYP3A4

Teo YL, Saetaew M, Chanthawong S, et al. Effect of CYP3A4 inducer dexamethasone on hepatotoxicity of lapatinib: clinical and in vitro evidence. *Breast Cancer Res Treat*. 2012;133(2):703-711. doi:10.1007/s10549-012-1995-7

Cuttle L, Munns AJ, Hogg NA, et al. Phenytoin metabolism by human cytochrome P450: involvement of P450 3A and 2C forms in secondary metabolism and drug-protein adduct formation. *Drug Metab Dispos*. 2000;28(8):945-950.

Whitten DL, Myers SP, Hawrelak JA, Wohlmuth H. The effect of St John's wort extracts on CYP3A: a systematic review of prospective clinical trials. *Br J Clin Pharmacol*. 2006;62(5):512-526. doi:10.1111/j.1365-2125.2006.02755.x

Hellum BH, Hu Z, Nilsen OG. The induction of CYP1A2, CYP2D6 and CYP3A4 by six trade herbal products in cultured primary human hepatocytes. *Basic Clin Pharmacol Toxicol*. 2007;100(1):23-30. doi:10.1111/j.1742-7843.2007.00011.x

Han EH, Kim HG, Choi JH, et al. Capsaicin induces CYP3A4 expression via pregnane X receptor and CCAAT/enhancer-binding protein β activation. *Mol Nutr Food Res*. 2012;56(5):797-809. doi:10.1002/mnfr.201100697

Wang Z, Schuetz EG, Xu Y, Thummel KE. Interplay between vitamin D and the drug metabolizing enzyme CYP3A4. *J Steroid Biochem Mol Biol*. 2013;136:54-58. doi:10.1016/j.jsbmb.2012.09.012

Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Ther.* 2013;138(1):103-141. doi:10.1016/j.pharmthera.2012.12.007

Hu N, Hu M, Duan R, et al. Increased levels of fatty acids contributed to induction of hepatic CYP3A4 activity induced by diabetes - in vitro evidence from HepG2 cell and Fa2N-4 cell lines. *J Pharmacol Sci.* 2014;124(4):433-444. doi:10.1254/jphs.13212fp

Luckert C, Ehlers A, Bührke T, Seidel A, Lampen A, Hessel S. Polycyclic aromatic hydrocarbons stimulate human CYP3A4 promoter activity via PXR. *Toxicol Lett.* 2013;222(2):180-188. doi:10.1016/j.toxlet.2013.06.243

Ratajewski M, Walczak-Drzwińska A, Salkowska A, Dastych J. Aflatoxins upregulate CYP3A4 mRNA expression in a process that involves the PXR transcription factor. *Toxicol Lett.* 2011;205(2):146-153. doi:10.1016/j.toxlet.2011.05.1034

DeVane CL, Donovan JL, Liston HL, et al. Comparative CYP3A4 inhibitory effects of venlafaxine, fluoxetine, sertraline, and nefazodone in healthy volunteers. *J Clin Psychopharmacol.* 2004;24(1):4-10. doi:10.1097/00004568-200401000-00004

Diczfalusy U, Nylin H, Elander P, Bertilsson L. 4β-Hydroxycholesterol, an endogenous marker of CYP3A4/5 activity in humans. *Br J Clin Pharmacol.* 2011;71(2):183-189. doi:10.1111/j.1365-2125.2010.03773.x

Dvorak Z. Drug-drug interactions by azole antifungals: Beyond a dogma of CYP3A4 enzyme activity inhibition. *Toxicol Lett.* 2011;202(2):129-132. doi:10.1016/j.toxlet.2011.01.027

Martin P, Gillen M, Millson D, et al. Effects of CYP3A4 Inhibitors Ketoconazole and Verapamil and the CYP3A4 Inducer Rifampicin on the Pharmacokinetic Parameters of Fostamatinib: Results from In Vitro and Phase I Clinical Studies. *Drugs R D.* 2016;16(1):81-92. doi:10.1007/s40268-015-0118-4

Masubuchi Y, Kawaguchi Y. Time-dependent inhibition of CYP3A4 by sertraline, a selective serotonin reuptake inhibitor. *Biopharm Drug Dispos.* 2013;34(8):423-430. doi:10.1002/bdd.1857

Krausova L, Stejskalova L, Wang H, et al. Metformin suppresses pregnane X receptor (PXR)-regulated transactivation of CYP3A4 gene. *Biochem Pharmacol.* 2011;82(11):1771-1780. doi:10.1016/j.bcp.2011.08.023

DeVane CL, Donovan JL, Liston HL, et al. Comparative CYP3A4 inhibitory effects of venlafaxine, fluoxetine, sertraline, and nefazodone in healthy volunteers. *J Clin Psychopharmacol.* 2004;24(1):4-10. doi:10.1097/00004568-200401000-00004

Jenkins H, Jenkins R, Patat A. Effect of Multiple Oral Doses of the Potent CYP3A4 Inhibitor Clarithromycin on the Pharmacokinetics of a Single Oral Dose of Vonoprazan: A Phase I, Open-Label, Sequential Design Study. *Clin Drug Investig.* 2017;37(3):311-316. doi:10.1007/s40261-016-0488-6

Ho PC, Saville DJ, Wanwimolruk S. Inhibition of human CYP3A4 activity by grapefruit flavonoids, furanocoumarins and related compounds. *J Pharm Pharm Sci.* 2001;4(3):217-227.

Zhang JW, Liu Y, Cheng J, et al. Inhibition of human liver cytochrome P450 by star fruit juice. *J Pharm Pharm Sci.* 2007;10(4):496-503. doi:10.18433/j30593

Djuv A, Nilsen OG. Aloe vera juice: IC₅₀ and dual mechanistic inhibition of CYP3A4 and CYP2D6. *Phytother Res.* 2012;26(3):445-451. doi:10.1002/ptr.3564

Savai J, Varghese A, Pandita N, Chintamaneni M. Investigation of CYP3A4 and CYP2D6 Interactions of Withania somnifera and Centella asiatica in Human Liver Microsomes. *Phytother Res.* 2015;29(5):785-790. doi:10.1002/ptr.5308

Rastogi H, Jana S. Evaluation of inhibitory effects of caffeic acid and quercetin on human liver cytochrome p450 activities. *Phytother Res.* 2014;28(12):1873-1878. doi:10.1002/ptr.5220

Basheer L, Kerem Z. Interactions between CYP3A4 and Dietary Polyphenols. *Oxid Med Cell Longev.* 2015;2015:854015. doi:10.1155/2015/854015

Rastogi H, Jana S. Evaluation of inhibitory effects of caffeic acid and quercetin on human liver cytochrome p450 activities. *Phytother Res.* 2014;28(12):1873-1878. doi:10.1002/ptr.5220

Tsujiimoto M, Uchida T, Kozakai H, Yamamoto S, Minegaki T, Nishiguchi K. Inhibitory Effects of Vegetable Juices on CYP3A4 Activity in Recombinant CYP3A4 and LS180 Cells. *Biol Pharm Bull.* 2016;39(9):1482-1487. doi:10.1248/bpb.b16-00263

Yamasaki I, Yamada M, Uotsu N, Teramoto S, Takayanagi R, Yamada Y. Inhibitory effects of kale ingestion on metabolism by cytochrome P450 enzymes in rats. *Biomed Res.* 2012;33(4):235-242. doi:10.2220/biomedres.33.235

Al-Jenoobi FI, Al-Thukair AA, Alam MA, et al. Effect of Garden Cress Seeds Powder and Its Alcoholic Extract on the Metabolic Activity of CYP2D6 and CYP3A4. *Evid Based Complement Alternat Med.* 2014;2014:634592. doi:10.1155/2014/634592

Makhov P, Golovine K, Canter D, et al. Co-administration of piperine and docetaxel results in improved anti-tumor efficacy via inhibition of CYP3A4 activity. *Prostate.* 2012;72(6):661-667. doi:10.1002/pros.21469

Langhammer AJ, Nilsen OG. In vitro inhibition of human CYP1A2, CYP2D6, and CYP3A4 by six herbs commonly used in pregnancy. *Phytother Res.* 2014;28(4):603-610. doi:10.1002/ptr.5037

Chatterjee P, Franklin MR. Human cytochrome p450 inhibition and metabolic-intermediate complex formation by goldenseal extract and its methylenedioxymethyl components. *Drug Metab Dispos.* 2003;31(11):1391-1397. doi:10.1124/dmd.31.11.1391

Langhammer AJ, Nilsen OG. In vitro inhibition of human CYP1A2, CYP2D6, and CYP3A4 by six herbs commonly used in pregnancy. *Phytother Res.* 2014;28(4):603-610. doi:10.1002/ptr.5037

Mooiman KD, Maas-Bakker RF, Moret EE, Beijnen JH, Schellens JH, Meijerman I. Milk thistle's active components silybin and isosilybin: novel inhibitors of PXR-mediated CYP3A4 induction. *Drug Metab Dispos.* 2013;41(8):1494-1504. doi:10.1124/dmd.113.050971

Hellum BH, Hu Z, Nilsen OG. The induction of CYP1A2, CYP2D6 and CYP3A4 by six trade herbal products in cultured primary human hepatocytes. *Basic Clin Pharmacol Toxicol.* 2007;100(1):23-30. doi:10.1111/j.1742-7843.2007.00011.x

He W, Wu JJ, Ning J, et al. Inhibition of human cytochrome P450 enzymes by licochalcone A, a naturally occurring constituent of licorice. *Toxicol In Vitro.* 2015;29(7):1569-1576. doi:10.1016/j.tiv.2015.06.014

Lim YP, Ma CY, Liu CL, et al. Sesamin: A Naturally Occurring Lignan Inhibits CYP3A4 by Antagonizing the Pregnan X Receptor Activation. *Evid Based Complement Alternat Med.*

2012;2012:242810. doi:10.1155/2012/242810

Zhou C, Poulton EJ, Grün F, et al. The dietary isothiocyanate sulforaphane is an antagonist of the human steroid and xenobiotic nuclear receptor. *Mol Pharmacol.* 2007;71(1):220-229. doi:10.1124/mol.106.029264

Guo Y, Chen Y, Tan ZR, Klaassen CD, Zhou HH. Repeated administration of berberine inhibits cytochromes P450 in humans. *Eur J Clin Pharmacol.* 2012;68(2):213-217. doi:10.1007/s00228-011-1108-2

Lim YP, Cheng CH, Chen WC, et al. Allyl isothiocyanate (AITC) inhibits pregnane X receptor (PXR) and constitutive androstane receptor (CAR) activation and protects against acetaminophen- and amiodarone-induced cytotoxicity. *Arch Toxicol.* 2015;89(1):57-72. doi:10.1007/s00204-014-1230-x

He N, Edeki T. The inhibitory effects of herbal components on CYP2C9 and CYP3A4 catalytic activities in human liver microsomes. *Am J Ther.* 2004;11(3):206-212. doi:10.1097/00045391-200405000-00009

Zhao J, Sun T, Wu JJ, et al. Inhibition of human CYP3A4 and CYP3A5 enzymes by gomisin C and gomisin G, two lignan analogs derived from Schisandra chinensis. *Fitoterapia.* 2017;119:26-31. doi:10.1016/j.fitote.2017.03.010

CYP19A1

Hudon Thibeault AA, López de Los Santos Y, Doucet N, Sanderson JT, Vaillancourt C. Serotonin and serotonin reuptake inhibitors alter placental aromatase. *J Steroid Biochem Mol Biol.* 2019;195:105470. doi:10.1016/j.jsbmb.2019.105470

Dickens MJ, Cornil CA, Balthazard J. Acute stress differentially affects aromatase activity in specific brain nuclei of adult male and female quail. *Endocrinology.* 2011;152(11):4242-4251. doi:10.1210/en.2011-1341

Wei J, Yuen EY, Liu W, et al. Estrogen protects against the detrimental effects of repeated stress on glutamatergic transmission and cognition. *Mol Psychiatry.* 2014;19(5):588-598. doi:10.1038/mp.2013.83

Scheller MS, Nakakimura K, Fleischer JE, Zornow MH. Cerebral effects of sevoflurane in the dog: comparison with isoflurane and enflurane. *Br J Anaesth.* 1990;65(3):388-392. doi:10.1093/bja/65.3.388

Spratt DL, Morton JR, Kramer RS, Mayo SW, Longcope C, Vary CP. Increases in serum estrogen levels during major illness are caused by increased peripheral aromatization. *Am J Physiol Endocrinol Metab.* 2006;291(3):E631-E638. doi:10.1152/ajpendo.00467.2005

Hiltunen M, Iivonen S, Soininen H. Aromatase enzyme and Alzheimer's disease. *Minerva Endocrinol.* 2006;31(1):61-73.

Monteiro R, Soares R, Guerreiro S, Pestana D, Calhau C, Azevedo I. Red wine increases adipose tissue aromatase expression and regulates body weight and adipocyte size. *Nutrition.* 2009;25(6):699-705. doi:10.1016/j.nut.2009.01.001

Watanabe M, Nakajin S. Forskolin up-regulates aromatase (CYP19) activity and gene transcripts in the human adrenocortical carcinoma cell line H295R. *J Endocrinol.* 2004;180(1):125-133. doi:10.1677/joe.0.1800125

Randolph JF Jr, Kipersztok S, Ayers JW, Ansbacher R, Peegeel H, Menon KM. The effect of insulin on aromatase activity in isolated human endometrial glands and stroma. *Am J Obstet Gynecol.* 1987;157(6):1534-1539. doi:10.1016/s0002-9378(87)80258-2

Magoffin DA, Weitsman SR, Aagarwal SK, Jakimiuk AJ. Leptin regulation of aromatase activity in adipose stromal cells from regularly cycling women. *Ginekol Pol.* 1999;70(1):1-7.

Purohit A, Singh A, Ghilchik MW, Reed MJ. Inhibition of tumor necrosis factor alpha-stimulated aromatase activity by microtubule-stabilizing agents, paclitaxel and 2-methoxyestradiol. *Biochem Biophys Res Commun.* 1999;261(1):214-217. doi:10.1006/bbrc.1999.1010

Vigier B, Forest MG, Eychenne B, et al. Anti-Müllerian hormone produces endocrine sex reversal of fetal ovaries. *Proc Natl Acad Sci U S A.* 1989;86(10):3684-3688. doi:10.1073/pnas.86.10.3684

Gasnier C, Dumont C, Benachour N, Clair E, Chagnon MC, Séralini GE. Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines. *Toxicology.* 2009;262(3):184-191. doi:10.1016/j.tox.2009.06.006

Balam FH, Ahmadi ZS, Ghorbani A. Inhibitory effect of chrysin on estrogen biosynthesis by suppression of enzyme aromatase (CYP19): A systematic review. *Helijon.* 2020;6(3):e03557.

Published 2020 Mar 7. doi:10.1016/j.heliyon.2020.e03557

Om AS, Chung KW. Dietary zinc deficiency alters 5 alpha-reduction and aromatization of testosterone and androgen and estrogen receptors in rat liver. *J Nutr.* 1996;126(4):842-848. doi:10.1093/jn/126.4.842

Zhao J, Dasmahapatra AK, Khan SI, Khan IA. Anti-aromatase activity of the constituents from damiana (*Turnera diffusa*). *J Ethnopharmacol.* 2008;120(3):387-393. doi:10.1016/j.jep.2008.09.016

Kijima I, Phung S, Hur G, Kwok SL, Chen S. Grape seed extract is an aromatase inhibitor and a suppressor of aromatase expression. *Cancer Res.* 2006;66(11):5960-5967. doi:10.1158/0008-5472.CAN-06-0053

Chrubaśik JE, Roufogalis BD, Wagner H, Chrubaśik S. A comprehensive review on the stinging nettle effect and efficacy profiles. Part II: *urticae radix*. *Phytomedicine.* 2007;14(7-8):568-579. doi:10.1016/j.phymed.2007.03.014

Weber MM, Will A, Adelmann B, Engelhardt D. Effect of ketoconazole on human ovarian C17,20-desmolase and aromatase. *J Steroid Biochem Mol Biol.* 1991;38(2):213-218. doi:10.1016/0960-0760(91)90128-r

Balunas MJ, Su B, Brueggemeier RW, Kinghorn AD. Natural products as aromatase inhibitors. *Anticancer Agents Med Chem.* 2008;8(6):646-682.

Balunas MJ, Kinghorn AD. Natural compounds with aromatase inhibitory activity: an update. *Planta Med.* 2010;76(11):1087-1093. doi:10.1055/s-0030-1250169

Satoh K, Sakamoto Y, Ogata A, et al. Inhibition of aromatase activity by green tea extract catechins and their endocrinological effects of oral administration in rats. *Food Chem Toxicol.* 2002;40(7):925-933. doi:10.1016/s0278-6915(02)00066-2

Le Bail JC, Pouget C, Fagnere C, Basly JP, Chulia AJ, Habrioux G. Chalcones are potent inhibitors of aromatase and 17beta-hydroxysteroid dehydrogenase activities. *Life Sci.* 2001;68(7):751-761. doi:10.1016/s0024-3205(00)00974-7

Biegon A, Kim SW, Logan J, Hooker JM, Muench L, Fowler JS. Nicotine blocks brain estrogen synthase (aromatase): in vivo positron emission tomography studies in female baboons. *Biol Psychiatry.* 2010;67(8):774-777. doi:10.1016/j.biopsych.2010.01.004

Wang Y, Lee KW, Chan FL, Chen S, Leung LK. The red wine polyphenol resveratrol displays bilevel inhibition on aromatase in breast cancer cells. *Toxicol Sci.* 2006;92(1):71-77. doi:10.1093/toxsci/kfj190

Siler U, Barella L, Spitzer V, et al. Lycopene and vitamin E interfere with autocrine/paracrine loops in the Dunning prostate cancer model. *FASEB J.* 2004;18(9):1019-1021. doi:10.1096/fj.03-1116fje

Chen S, Oh SR, Phung S, et al. Anti-aromatase activity of phytochemicals in white button mushrooms (*Agaricus bisporus*). *Cancer Res.* 2006;66(24):12026-12034. doi:10.1158/0008-5472.CAN-06-2206

Purohit A, Singh A, Ghilchik MW, Reed MJ. Inhibition of tumor necrosis factor alpha-stimulated aromatase activity by microtubule-stabilizing agents, paclitaxel and 2-methoxyestradiol. *Biochem Biophys Res Commun.* 1999;261(1):214-217. doi:10.1006/bbrc.1999.1010

HSD17B

Suriyakalaa U, Ramachandran R, Doulathunnisa JA, et al. Upregulation of Cyp19a1 and PPAR- γ in ovarian steroidogenic pathway by *Ficus religiosa*: A potential cure for polycystic ovary syndrome. *J Ethnopharmacol.* 2021;267:113540. doi:10.1016/j.jep.2020.113540

Tian M, Liu F, Liu H, et al. Grape seed procyanidins extract attenuates Cisplatin-induced oxidative stress and testosterone synthase inhibition in rat testes. *Syst Biol Reprod Med.* 2018;64(4):246-259. doi:10.1080/19396368.2018.1450460

Munkboel CH, Hasselstrøm SB, Kristensen DM, Styrlhave B. Effects of antihistamines on the H295R steroidogenesis - Autocrine up-regulation following 3 β -HSD inhibition. *Toxicol In Vitro.* 2018;48:302-309. doi:10.1016/j.tiv.2018.01.026

Nna VU, Bakar ABA, Ahmad A, et al. Malaysian propolis and metformin mitigate subfertility in streptozotocin-induced diabetic male rats by targeting steroidogenesis, testicular lactate transport, spermatogenesis and mating behaviour. *Andrology.* 2020;8(3):731-746. doi:10.1111/andr.12739

Krazeisen A, Breitling R, Möller G, Adamski J. Human 17beta-hydroxysteroid dehydrogenase type 5 is inhibited by dietary flavonoids. *Adv Exp Med Biol.* 2002;505:151-161. doi:10.1007/978-1-4757-5235-9_14

Krazeisen A, Breitling R, Möller G, Adamski J. Phytoestrogens inhibit human 17beta-hydroxysteroid dehydrogenase type 5. *Mol Cell Endocrinol.* 2001;171(1-2):151-162. doi:10.1016/s0303-7207(00)00422-6

COMT

Hodges RE, Minich DM. Modulation of Metabolic Detoxification Pathways Using Foods and Food-Derived Components: A Scientific Review with Clinical Application. *J Nutr Metab.* 2015;2015:760689. doi:10.1155/2015/760689

Shouman S, Wagih M, Kamel M. Leptin influences estrogen metabolism and increases DNA adduct formation in breast cancer cells. *Cancer Biol Med.* 2016;13(4):505-513. doi:10.20892/j.issn.2095-3941.2016.0079

Xie T, Ho SL, Ramsden D. Characterization and implications of estrogenic down-regulation of human catechol-O-methyltransferase gene transcription. *Mol Pharmacol.* 1999;56(1):31-38. doi:10.1124/mol.56.1.31

Blum K, Chen TJ, Meshkin B, et al. Manipulation of catechol-O-methyl-transferase (COMT) activity to influence the attenuation of substance seeking behavior, a subtype of Reward Deficiency Syndrome (RDS), is dependent upon gene polymorphisms: a hypothesis. *Med Hypotheses.* 2007;69(5):1054-1060. doi:10.1016/j.mehy.2006.12.062

Wang P, Heber D, Henning SM. Quercetin increased bioavailability and decreased methylation of green tea polyphenols in vitro and in vivo. *Food Funct.* 2012;3(6):635-642. doi:10.1039/c2fo10254d

van Duursen MB, Sanderson JT, de Jong PC, Kraaij M, van den Berg M. Phytochemicals inhibit catechol-O-methyltransferase activity in cytosolic fractions from healthy human mammary tissues: implications for catechol estrogen-induced DNA damage. *Toxicol Sci.* 2004;81(2):316-324. doi:10.1093/toxsci/kfh216

Cavalieri EL, Rogan EG. Is bisphenol A a weak carcinogen like the natural estrogens and diethylstilbestrol?. *IUBMB Life.* 2010;62(10):746-751. doi:10.1002/iub.376

Woods JS, Heyer NJ, Russo JE, et al. Genetic polymorphisms of catechol-O-methyltransferase modify the neurobehavioral effects of mercury in children. *J Toxicol Environ Health A.* 2014;77(6):293-312. doi:10.1080/15287394.2014.867210

Hartung JE, Eskew O, Wong T, et al. Nuclear factor-kappa B regulates pain and COMT expression in a rodent model of inflammation. *Brain Behav Immun.* 2015;50:196-202. doi:10.1016/j.bbi.2015.07.014

Tsao D, Wieskopf JS, Rashid N, et al. Serotonin-induced hypersensitivity via inhibition of catechol O-methyltransferase activity. *Mol Pain.* 2012;8:25. Published 2012 Apr 13. doi:10.1186/1744-8069-8-25

Phase III Detoxification

Popkin BM, D'Anci KE, Rosenberg IH. Water, hydration, and health. *Nutr Rev.* 2010;68(8):439-458. doi:10.1111/j.1753-4887.2010.00304.x

Cline JC. Nutritional aspects of detoxification in clinical practice. *Altern Ther Health Med.* 2015;21(3):54-62.

Nikkhah Bodagh M, Maleki I, Hekmatdoost A. Ginger in gastrointestinal disorders: A systematic review of clinical trials. *Food Sci Nutr.* 2018;7(1):96-108. Published 2018 Nov 5. doi:10.1002/fsn3.807

Peterson CT, Denniston K, Chopra D. Therapeutic Uses of Triphala in Ayurvedic Medicine. *J Altern Complement Med.* 2017;23(8):607-614. doi:10.1089/acm.2017.0083

8-OHdG

Arab H, Mahjoub S, Hajian-Tilaki K, Moghadasi M. The effect of green tea consumption on oxidative stress markers and cognitive function in patients with Alzheimer's disease: A prospective intervention study. *Caspian J Intern Med.* 2016;7(3):188-194.

Biglan KM, Dorsey ER, Evans RV, et al. Plasma 8-hydroxy-2'-deoxyguanosine Levels in Huntington Disease and Healthy Controls Treated with Coenzyme Q10. *J Huntingtons Dis.* 2012;1(1):65-69. doi:10.3233/JHD-2012-120007

Boyle SP, Dobson VL, Duthie SJ, Kyle JA, Collins AR. Absorption and DNA protective effects of flavonoid glycosides from an onion meal. *Eur J Nutr.* 2000;39(5):213-223. doi:10.1007/s003940070014

Zalejska-Fiolka J, Wielkoszyński T, Rokicki W Jr, et al. The Influence of α-Lipoic Acid and Garlic Administration on Biomarkers of Oxidative Stress and Inflammation in Rabbits Exposed to Oxidized Nutrition Oils. *Biomed Res Int.* 2015;2015:827879. doi:10.1155/2015/827879

Guest J, Bilgin A, Hokin B, Mori TA, Croft KD, Grant R. Novel relationships between B12, folate and markers of inflammation, oxidative stress and NAD(H) levels, systemically and in the CNS of a healthy human cohort. *Nutr Neurosci.* 2015;18(8):355-364. doi:10.1179/1476830515Y.0000000041

Dai P, Wang J, Lin L, Zhang Y, Wang Z. Renoprotective effects of berberine as adjuvant therapy for hypertensive patients with type 2 diabetes mellitus: Evaluation via biochemical markers and color doppler ultrasonography. *Exp Ther Med* 2015, Sep;10(3):869-76.

Ghorbanihaghjo A, Safa J, Alizadeh S, et al. Protective effect of fish oil supplementation on DNA damage induced by cigarette smoking. *J Health Popul Nutr.* 2013;31(3):343-349. doi:10.3329/jhpn.v31i3.16826

Franke AA, Cooney RV, Henning SM, Custer LJ. Bioavailability and antioxidant effects of orange juice components in humans. *J Agric Food Chem.* 2005;53(13):5170-5178. doi:10.1021/jf050054y

Nirwan M, Halder K, Saha M, Pathak A, Balakrishnan R, Ganju L. Improvement in resilience and stress-related blood markers following ten months yoga practice in Antarctica. *J Complement Integr Med.* 2020;18(1):201-207. Published 2020 Jun 19. doi:10.1515/jcim-2019-0240



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3755 Illinois Avenue • St. Charles, IL 60174-2420

800.323.2784 (US AND CANADA)

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