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Table 2: Substances Contraindicated and Synergistic with Hormone-Modifying Medication

Tamoxifen (TAM) selective estrogen-receptor modulator	
Avoid	Powerful inhibitors of CYP2D6 pathway such as SSRIs, moderate inhibitors such as OTC antihistamines, berberines, less concern with mild inhibitors like Panax ginseng.[1–5]
	Agents metabolized by the CYP3A4 pathway such as St. John's wort, especially in the elderly; moderate inhibitors (rhodiola, gaultheria, uva ursi), echinacea, and other mild 3A4 inhibitors appear to be safer.[6–9]
Synergistic	**Indole-3-carbinole** enhances TAM effect; may also increase toxic metabolites (caution: hepatotoxicity).[10] DIM has no effect on TAM metabolism.[11]
	Green tea, omega-6 (gamma linolenic acid), and **melatonin** may enhance effect of TAM in vitro.[12–15]
	Diet high in **vegetables** associated with reduced risk of recurrence among TAM users.[16]
	Flax seeds enhanced the tumor-inhibiting effect of TAM-resistant breast cancer cells in mice.[17]
	Quercetin enhances the effect of TAM in vitro and may reduce acquired TAM resistance.[18,19]
	Black cohosh reduces hot flashes among TAM users, enhances the inhibition of proliferation of TAM in vitro; possible concern for 2D6 and 3A4 inhibition, caution: may increase hepatotoxicity of TAM. NB: Black cohosh may increase the risk of lung metastasis in those with HER2+ breast cancer. [20–23]
	Vitamin E enhances the tumor inhibition of TAM in vitro and tocotrienols were found to increase survivorship by as much as 60% among TAM users; the result was not statistically significant.[24,25]
	Dietary intake of **soy isoflavones** combined with TAM (in postmenopausal American women) resulted in 60% reduction in breast cancer recurrence comparing highest with lowest intake; "appears not to interfere with tamoxifen efficacy."[26]
	Silymarin, grapeseed extract, and **curcumin** reduced hepatotoxicity in TAM-intoxicated rats.[27] Taurine appears to do the same.[28]
Notes	Consider CYP2D6 and CYP 3A4 polymorphism testing to ensure proper drug metabolism. See notes below.
Aromatase Inhibitors (AI)	
Avoid	Inducers of the CYP3A4 drug metabolism pathway may lower plasma concentrations of AIs (see notes) such as St. John's wort (especially in the elderly) and berberine-rich plants like goldenseal, which may interfere with efficacy of these medications.[29,30]
	Caution is recommended when taking with other 3A4 substrates and inhibitors (such as SSRIs, antifungals, antibiotics, opiates, ginkgo, milk thistle, grapefruit juice, gaultheria, rhodiola, uva ursi) as plasma concentrations of AIs may increase resulting in toxicity. For a list of substrates and inhibitors, consider: http://ctep.cancer.gov/protocolDevelopment/docs/cyp3a4.doc[31,32]
	A study to evaluate the safety of flaxseed consumption by those taking anastrozole is under way.[33]
Synergistic	Women eating the most **soy** with anastrozole had 33% lower recurrence vs. those who ate the least.[34]
	Curcumin enhances the effect of letrozole in mice endometrial cancer model.[35]
	Vitamin D: Achieving a 40 ng/mL concentration of 25OHD may prevent AI-induced arthralgia. Routine pre-AI vitamin D testing recommended due to risk of bone loss with AIs.[36,37]
Notes	Consider CYP3A4 polymorphism testing to identify errors in drug metabolism and inform selection.

SERM: selective estrogen receptor modulator such as tamoxifen (TAM) commonly used in premenopausal survivors
AI: aromatase inhibitor such as anastrozole (Arimidex), exemestane (Aromasin), and letrozole (Femara) used only in postmenopausal survivors to block the conversion of adrenal testosterone to estrogen
SSRI: selective serotonin reuptake inhibitor

Notes: Tamoxifen-treated patients carrying CYP2D6 variants that impaired formation of 4-hydroxytamoxifen, had more than double the risk of recurrence of breast cancer, shorter relapse-free periods, and worse event-free survival rates compared with patients with functional CYP2D6.[38] Those with CYP3A41b variants are at higher risk of endometrial cancer.[39] Femara only mildly inhibits 3A4; Arimidex moderately inhibits 3A4; Aromasin is metabolized by 3A4 and has the greatest risk of interactions with other 3A4-metabolised drugs.[40]

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