Estrogen Sulfotransferase (SULT1E1): Its Molecular Regulation, Polymorphisms, and Clinical Perspectives

Myeong Jin Yi 1, Masahiko Negishi 1 and Su-Jun Lee 2,*

1 Pharmacogenetics Section, Reproductive and Developmental Biology Laboratory, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC 27709, USA; myeongjin.yi@nih.gov (M.Y.); negishi@niehs.nih.gov (M.N.) 2 Department of Pharmacology and Pharmacogenomics Research Center, Inje University College of Medicine, Inje University, Bokji-ro 75, Busanjin-gu, Busan 47392, Korea  
* Correspondence: 2sujun@inje.ac.kr; Tel.: +82-51-890-8665

Abstract: Estrogen sulfotransferase (SULT1E1) is a phase II enzyme that sulfates estrogens to inactivate them and regulate their homeostasis. This enzyme is also involved in the sulfation of thyroid hormones and several marketed medicines. Though the profound action of SULT1E1 in molecular/pathological biology has been extensively studied, its genetic variants and functional studies have been comparatively rarely studied. Genetic variants of this gene are associated with some diseases, especially sex-hormone-related cancers. Comprehending the role and polymorphisms of SULT1E1 is crucial to developing and integrating its clinical relevance; therefore, this study gathered and reviewed various literature studies to outline several aspects of the function, molecular regulation, and polymorphisms of SULT1E1.

Keywords: estrogen sulfotransferase; SULT1E1; estrogen; estrogen sulfate; thyroid hormones; breast cancer; endometrial cancer; polymorphism

1. Introduction

The metabolism of endogenous compounds and hormones is important in physiological homeostasis. Sulfation, which occurs in many metabolic pathways, generates sulfoconjugated forms that are typically regarded as inactive metabolites. Sulfation is one of the phase II metabolizing pathways that represent the inactivation of hormones, such as estrogens, and this reaction is usually performed by an enzyme from the cytosolic enzyme group referred to as sulfotransferases (SULTs) [1]. In various mammals, such as mice and rats, SULTs play the essential roles of sulfating estrogens, thyroid hormones, bile acids, and other xenobiotics [2–6].

Sulfotransferase isoforms sulfate not only xenobiotics (e.g., flavonoids and hydroxyl metabolites of anticancer drugs) but also endogenous compounds, such as steroid hormones. They have essential roles in the homeostasis of bile acids, thyroid hormone, androgens, and estrogens, and their expressions are influenced by substrates and pathological conditions as well [14].

Among the SULT isoforms, SULT1E1 has the lowest $K_m$ values for estrone (E1), estradiol (E2), and catecholestrogen sulfation [15–19]. This enzyme had been referred to as EST (estrogen sulfotransferase) due to its substantial role in estrogen inactivation. It was discovered and cloned in other mammalian species (Table 2), and its amino acid sequence
homologies regarding rabbit, horse, pig, mouse, cow, and rat EST compared with human EST are 82.6%, 79.2%, 77.8%, 77.5%, 73.7%, and 71.3%, respectively.

| Gene ID 1 | Locus 2 | Alias 1 | Number of Amino Acids 3 | Number of Exons 1 |
|-----------|---------|---------|------------------------|------------------|
| SULT1A1   | Chr 16p11.2 | HAST1/HAST2, PST, PST, ST1A1, ST1A3, STP, TSP1, TSPST1 | 295 (isoform a) | 13 |
| SULT1A2   | Chr 16p11.2 | HAST4, PST, PST, PST, ST1A2, TSPST2 | 217 (isoform b) | 8 |
| SULT1A3   | Chr 16p11.2 | HAST, HAST3, M-PST, ST1A3, ST1A4, ST1A4, ST1A5, STM, TL-PST | 295 | 8 |
| SULT1A4   |Chr 16p11.2 | HAST3, M-PST, ST1A3, ST1A4, ST1A4, ST1A5, TL-PST | 296 | 10 |
| SULT1B1   |Ch 4q13.3 | ST1B1, ST1B2, SULT1B2 | 296 | 10 |
| SULT1C2   | Ch 2q12.3 | ST1C1, ST1C2, SULT1C1, SULT1C2 | 296 (isoform a) | 9 |
| SULT1C3   | Ch 2q12.3 | ST1C3 | 307 (isoform b) | 9 |
| SULT1C4   | Ch 2q12.3 | SULT1C, SULT1C2 | 304 (isoform 1) | 10 |
| SULT1D1   | Ch 4q13.3 | EST, EST-1, STE1 | 304 (isoform 2) | 10 |
| SULT2A1   | Ch 19q13.33 | DHEA-ST, DHEA-ST8, DHEAS, HST, ST2, ST2A1, ST2A3, STD, SULT2A3, hSTa | 284 | 11 |
| SULT2B1   | Ch 19q13.33 | ARCI14, HSST2 | 304 (isoform 1) | 9 |
| SULT4A1   | Ch 22q13.31 | BR-STL-1, BRST1, DJ388M5.3, NST, SULTX3, hBR-STL-1 | 265 | 6 |
| SULT6B1   | Ch 2q22.2 | STE8B1 | 365 (isoform b) | 7 |
| SULT1C2P1 | Ch 2q12.3 | SULT1CIP | pseudogene | 4 |
| SULT1C2P2 | Ch 2q12.3 | pseudogene | pseudogene | 4 |
| SULT1D1P1 | Ch 4q13.3 | SULT1D1 | pseudogene | 4 |
| SULT6B2P1 | Ch 12p12.1 | pseudogene | pseudogene | 4 |

| Species | RefSeq 1 | RefSeq mRNA 2 | RefSeq Protein 3 | Number of Exons 1 |
|---------|---------|--------------|-----------------|------------------|
| Homo sapiens (human) | NC_000004.12 | NM_005420.3 | NP_005411.1 | 9 |
| Mus musculus (mouse) | NC_000071.7 | NM_023135.2 | NP_075624.2 | 8 |
| Rattus norvegicus (rat) | NC_005113.4 | NM_012883.2 | NP_037015.2 | 10 |
| Bos taurus (cow) | NC_037333.1 | NM_177488.3 | NP_803454.2 | 9 |
| Oryctolagus cuniculus (rabbit) | NC_013683.1 | XM_002717123.2 | XP_002717169.1 | 8 |
| Sus scrofa (pig) | NC_010450.4 | NM_213992.1 | NP_999157.1 | 9 |
| Equus caballus (horse) | NC_009146.3 | NM_001081919.1 | NP_001075387.1 | 8 |

1 Information is described according to NCBI Gene. 2 All reference loci were based on the GRCh38 assembly. 3 The way to divide genes into isoform a/b or 1/2 was described in accordance with the NCBI Protein database.

Although the SULT1A subfamily can sulfate estrogens, their affinity for endogenous estrogens is significantly lower than the affinity of SULT1E1 for those substrates. Moreover, SULT1E1 engages in the sulfation of thyroid hormones alongside the SULT1A subfamily. Though the important roles and regulation of SULT1E1 have been identified and stressed, functional studies related to genetic variants are relatively limited.

This review concentrates on the expression, functional characterization, regulation, associations with diseases, and genetic polymorphisms of SULT1E1.

2. Expression of SULT1E1

Human SULT1E1 cDNA was first isolated, cloned, and characterized from the liver, and its localization was mapped to human chromosome 4 [20]. SULT1E1 is expressed in the human embryo, and is also highly expressed in a wide range of fetal tissues, such as the liver, lung, kidney, and hormone-dependent tissues—such as the testis or endometrium—but its expression in adults with normal status is much lower than in the fetus and placenta [21,22]. The expression of SULT1E1 varies widely in the human population, although it is not known whether this is under genetic control or not [23]. Thus, it is possible that the variability in SULT1E1 expression results from different chemical influences.
Two agonists of peroxisome-proliferator-activated receptor α (PPARα), WY14643 and IGF-1, show different regulatory effects on the SULT1E1 promoter activity. While WY14643 suppressed SULT1E1 activity, IGF-1 upregulated it, as measured by estrogen levels in endothelial cells and smooth muscle cells [24]. Interestingly, SULT1E1 was attenuated by both transfection with PPARγ small interfering RNA (siRNA) and exposure to GW9662, the PPARγ antagonist [25].

SULT1E1 regulation was observed when hepatocyte nuclear factor 4α (HNF4α) was silenced. The significant suppression of both mRNA and protein levels of SULT1E1 occurred via Farnesoid X receptor (FXR) agonists in HepG2 cells [26]. This finding confirmed that the effect of FXR on E2 was SULT1E1-dependent. In patients with obstructive cholestasis, the accumulation of bile acids (activator of FXR) led to reduced mRNA and protein expression of hepatic SULT1E1, increased serum E2 levels, and decreased serum estrone sulfate concentration [27]. Phosphorylated RORα takes a regulatory signal to HNF4α, and then activates the SULT1E1 promoter in human liver cells [28].

Basal expression of SULT1E1 in the liver is relatively low [29], but its expression and role could be impacted in response to ligands/substrates for nuclear receptors, such as the liver X receptor (LXR) [29], the glucocorticoid receptor (GR) [30], the constitutive androstane receptor (CAR) [31], the estrogen receptor α (ERα) [32], the pregnane X receptor (PXR) [33], and the RAR-related orphan receptor α (RORα) [34] (Table 3).

Table 3. The nuclear receptors associated with Sult1e1 regulation.

| Gene ID | Nuclear Receptor | Species | Tissue | Reference |
|---------|------------------|---------|--------|-----------|
| NR3A1   | ERα              | Mouse   | Liver tissue | [32]       |
| NR3C1   | GR               | Mouse   | Liver tissue | [30]       |
| NR1C1   | PPARα            | Human   | Vascular endothelial cell | [24]       |
| NR1C3   | PPARγ            | Human   | Endothelial cell | [25]       |
| NR1H2, H3 | LXR          | Mouse   | Uterine | [29]       |
| NR1H4   | FXR              | Human   | Liver cell line | [26]       |
| NR1I2   | PXR              | Mouse   | Liver cell line | [33]       |
| NR1H3   | CAR              | Mouse   | Liver tissue | [31,32]   |
| NR2A1   | HNF4α            | Human   | Liver tissue | [27]       |
| NR1F1   | RORα             | Mouse   | Liver cell line | [28]       |

3. Sulfation of Estrogens and Thyroid Hormones by SULT1E1

3.1. Sulfation of Estrogens

Estrogens play fundamental roles in a variety of physiological systems. It has been widely established that estradiol (E2) exposure is one of the risk factors for breast carcinogenesis. One of the critical pathways for E2 inactivation is sulfation by SULT1E1. Estrone (E1) is synthesized by aromatization of androstenedione and is subsequently sulfated. After E1 is desulfated and subsequently turned into E2 by the 17β-hydroxysteroid dehydrogenases (17β-HSD), E2 can then be sulfated through SULT1E1 [35]. As previously mentioned, SULT1E1 is a cytosolic enzyme that catalyzes estrogen sulfation at the 3-hydroxyl site while using PAPS as a sulfate donor (Figure 1). Moreover, this enzyme has high affinity for its substrate E2, indicating its crucial role in modulating estrogen’s action and homeostasis [36].

SULT1E1 has shown the distinct characteristic of having a high sulfating affinity for not only E2, but also other estrogens, such as E1 and ethinylestradiol (EE2), with nanomolar K_m values (Table 4). Due to its high affinity for sulfate estrogens, SULT1E1 exhibits inhibition of substrate with increasing E2 and E1 concentrations. SULT1E1 is also used to sulfate other compounds, namely dehydroepiandrosterone (DHEA), pregnenolone, diethylstilbestrol (DES), and equilenin [37,38].
Table 4. Substrates of SULT1E1.

| Substrate        | Compound Characteristics            | $K_m$     | Reference |
|------------------|-------------------------------------|-----------|-----------|
| $E_1$            | Agonist of ER                       | ~0.17 μM  | [39]      |
| $E_2$            | Most active agonist of ER           | 5 ± 0.8 nM| [16]      |
| $EE_2$           | Agonist of GPER and ER              | 6.7 ± 0.1 nM| [40]      |
| DHEA             | Partial agonist of AR and ER        | ~0.85 μM  | [37]      |
| $T_4$            | Thyroid prohormone                  | 22.6 ± 1.0 μM| [40]      |
| $T_3$            | Receptor active iodothyronine       | 25.7 ± 10.4 μM| [41]      |
| rT3              | Receptor inactive iodothyronine     | 2.15 ± 1.45 μM| [41]      |
| $T_2$            | Breakdown metabolite of triiodothyronine | 4.75 ± 1.25 μM| [41]      |
| Apigenin         | Common dietary flavonoid            | 5.3 ± 0.65 μM| [41]      |
| Epicatechin      | Antioxidative flavonoid             | 0.96 ± 0.17 mM| [42]     |
| Resveratrol      | Antioxidative flavonoid             | 6.88 ± 1.12 μM| [42]     |
| Chrysin          | Flavonoid in bee pollen or propolis| 4.5 ± 0.65 μM| [42]     |
| Quercetin        | Flavonoid in plants or fruits       | 2.0 ± 0.34 μM| [42]     |
| Fulvestrant      | Steroidal ER antagonist             | 0.2 ± 0.02 μM| [43]     |
| 4-OH-TOR         | Hydroxy metabolite of TOR (nonsteroidal agonist-antagonist of ER) | 6.4 ± 0.09 μM| [44]     |
| Troglitazone     | PPAR agonist                        | 8.5 ± 0.44 μM| [45]     |
| Endoxifen        | Active metabolite of Tamoxifen (nonsteroidal antagonist of ER) | 24 ± 5 μM| [46]     |
| 4-OH TAM         | Hydroxy metabolite of Tamoxifen     | 24 ± 5 μM| [46]     |
| N-des TAM        | N-demethyl metabolite of Tamoxifen  | 96 ± 52 μM| [46]     |
| Tibolone         | Selective tissue estrogenic activity regulator | 19.5 ± 2.8 μM| [47]     |
| 3α-OH-TIB        | Hydroxy metabolite of TIB           | 6.6 ± 2.2 μM| [47]     |
| 3β-OH-TIB        | Hydroxy metabolite of TIB           | 2.1 ± 0.5 μM| [47]     |

$K_m$, the constant value of Michaelis-Menten equation which is numerically equal to the substrate concentration at the half reaction rate of enzyme $V_{max}$; $E_1$, estrone; $E_2$, estradiol; $EE_2$, ethinylestradiol; DHEA, dehydroepiandrosterone; $T_4$, thyroxine; $T_3$, 3,3',5'-triiodothyronine; $rT_3$, 3,5,3'-triiodothyronine; $T_2$, 3,3'-diiodothyronine; TOR, toremifene; ERs, estrogen receptors; GPER, G protein-coupled receptor; AR, androgen receptor; PPARs, peroxisome proliferator-activated receptors; 4-OH TAM, 4-hydroxy tamoxifen; N-des TAM, N-desmethyltamoxifen; TIB, tibolone.
SULT1E1 is also expressed in hormone-dependent tissues, such as endometrium [22,48] and placenta [21]. SULT1E1 is specifically expressed during the secretory phase of the menstrual cycle in human endometrium [49]. Upregulated SULT1E1 activity in the endometrium may result in sulfating E2 after ovulation [50]. In addition, SULT1E1 can be induced by progestins in human Ishikawa endometrial adenocarcinoma cells [51].

As an interesting effect, estrogens inhibit expression of the potent growth factor repressor transforming growth factor (TGF)-β1. In addition, it was observed that MCF-7 cells expressing SULT1E1 activity did not show a decrease in ERα levels, an increase in progesterone receptor, or a decrease in transforming growth factor-β expression, suggesting the rapid sulfoconjugation of E2 by SULT1E1.

It is possible that SULT1E1 contributes to EE2 sulfation during hepatic-mediated first-pass metabolism. SULT1E1 is the high-affinity enzyme responsible for EE2 sulfation at nanomolar concentrations, so SULT1E1 plays a predominant role in the sulfation of EE2 in the intestine and liver.

### 3.2. Sulfation of Thyroid Hormones

Many factors serve as regulators for the effectiveness and bioavailability of receptor active thyroid hormone (T3) [52,53]. The prohormone thyroxine (T4) is predominantly secreted to regulate metabolism [54,55]. Deiodination is one of the principal and major pathways to degrade active compounds, and there are three types of deiodinase selenoproteins—iodothyronine deiodinases (D1, D2, and D3) [56]. These deiodinases are promotive of the reductive T4 deiodination and its metabolites (Figure 2).

![A schematic metabolic pathway of thyroid hormones. T4, thyroxine (prohormone); T4S, thyroxine sulfate (sulfoconjugated metabolite); T3, 3,3′,5-triiodothyronine (receptor active iodothyronine); rT3, 3,3′,5′-triiodothyronine (receptor inactive iodothyronine); T2, 3,3′-diiodothyronine.](image)

Figure 2. A schematic metabolic pathway of thyroid hormones. T4, thyroxine (prohormone); T4S, thyroxine sulfate (sulfoconjugated metabolite); T3, 3,3′,5-triiodothyronine (receptor active iodothyronine); rT3, 3,3′,5′-triiodothyronine (receptor inactive iodothyronine); T2, 3,3′-diiodothyronine.

One major modification thyroid hormones receive is sulfation, which deactivates them. Thyroxine sulfate can be detected in human fetal blood and amniotic fluid, indicating that the production of sulfoconjugates is critical in utero [57]. Iodothyronine sulfates (T3S, T3S, rT3S, and T3S) are generated by SULT enzymes, which are located in a variety of different tissues, and catalyze the sulfation and substitution of the hydroxyl groups of various compounds using PAPS as the sulfate donor [58]. Interestingly, among the SULTs, most of the SULT1 enzymes catalyze the sulfation of iodothyronines [41,59–61]. SULT1E1 is
highly effective at catalyzing rT₃ sulfation and has sulfating activity for all iodothyronines (Table 4). For rT₃ sulfation especially, SULT1E1 has the highest activity among the SULT1 subfamily, even compared to SULT1A1 [59]. Moreover, SULT1E1 was reported as the most active enzyme that exhibited catalyzing activity for T₄ sulfation [62].

SULT1E1 can be detected in the human endometrium and in the mouse uterus, so it might be possible that the uterus could protect the fetus from excessive thyroid hormone by inactivating pathways via SULT1E1 or D3. It is notable that the metabolites derived from D3 (rT₃ and T₂) are also favorable substrates of SULT1E1, suggesting that T₄ and T₃ are metabolized in the uterus by consecutive sulfation. The physiological roles of each iodothyronine SULT still remain too complex to be comprehended in full. Although SULT1E1 has been proven to be a potent iodothyronine SULT along with SULT1A1, it is probable that the other SULT1 enzymes contribute to iodothyronine sulfation in a tissue- or growth-dependent way [63–65].

4. Sulfation of Other Substrates by SULT1E1

SULT1E1 has the role of sulfotransferase not only for endogenous substrates, such as estrogens or iodothyronines, but also for various other compounds (Table 4).

Flavonoids are a class of naturally occurring polyphenols in most plants, and they play diverse roles. Many of them have antioxidative influences in vitro and in vivo. Apigenin (4′, 5, 7-trihydroxyflavone) is one of the flavonoids that usually exists in chamomile flowers, and it is a yellow compound that can dye wool [66]. Catechin enantiomers are ubiquitous constituents of herbal medicines. The active isomer (−)-epicatechin is known for its anti-inflammatory effects by the activation of the NF-κB signaling pathway [67]. Resveratrol (3, 5, 4′-trihydroxy-trans-stilbene) is expressed in several plants in response to damage or attack by pathogens [68]. Chrysin (5, 7-dihydroxyflavone) is typically found in honey or propolis [69]. Quercetin (5, 7, 3′, 4′-flavon-3-ol) is distributed in naturally occurring polar auxin transport inhibitor, and it is one of the most common natural dietary flavonoids [70]. Though most polyphenols are sulfated by SULT1A isoforms, many sulfocojugated forms of polyphenols can be generated by SULT1E1 due to its phenotypic response at the cellular level [42].

Fulvestrant is a novel medicine for endocrine treatment; it is an antagonist of estrogen receptors (ERs) that provides no agonistic activity. This compound is an analog of E₂ that has a distinguishable structure from nonsteroidal medicines such as tamoxifen and other selective estrogen receptor modulators (SERMs). Fulvestrant performs as a competitive inhibitor and suppresses the binding of E₂ to the ERs, and SULT1E1 has exhibited clear sulfating activity towards fulvestrant [43].

Synthetic estrogens for oral administration are widely prescribed and given to fertile women. Various SERMs have been developed and administered to inhibit the activation of estrogen’s activity in the breast. It has been revealed that SULT1E1 sulfates 4-hydroxytoremifene (4-OH TOR), an active metabolite of toremifene, alongside SULT1A1 [44]. Among the SULT isoforms, SULT1E1 has a high affinity for the tamoxifen active metabolite 4-hydroxytamoxifen (4-OH TAM) and other active tamoxifen metabolites, including endoxifen and N-desmethyltamoxifen (N-des TAM), which are substrates of SULT1E1 as well [46]. These metabolites show weak inhibitory effects on SULT1E1, suggesting that they are unlikely to interfere with the sulfation of E₂ in SULT1E1-expressing tissues.

Troglitazone acts as an agonist of PPARα and has been used as an oral antidiabetic for the treatment of insulin-independent diabetes mellitus. SULT1E1 appropriately sulfates troglitazone and had greater activity than SULT1A1 when 10 uM of troglitazone was treated [45].

After tibolone binds to nuclear receptors, such as ERs, progesterone receptor (PG), and androgen receptor (AR), to activate them, it is dramatically metabolized into two active hydroxylated isomers, 3α-OH and 3β-OH-tibolone, which can be metabolized into Δ⁴-tibolone. SULT1E1 sulfates tibolone as well as its metabolites, 3α-OH and 3β-OH-tibolones [47].
5. SULT1E1 and Diseases

Due to SULT1E1 being highly activated in pathophysiological conditions, such as estrogen-related diseases, the quantification of the E\textsubscript{1}S form of estrogen during the menstrual cycle and in menopausal women has been widely used [71–73]. It has been reported that a strong association between breast cancer vulnerability and increased E\textsubscript{2} concentration exists [74]. Moreover, the concentrations of E\textsubscript{1}S and E\textsubscript{2}S are higher in patients with breast fibroadenoma [75] (Figure 3); however, in that same study, the expression of SULT1E1 decreased or was abolished in breast cancer tissues, though it was expressed in normal breast cells. In breast carcinoma cell lines, E\textsubscript{1} and E\textsubscript{2} can be sulfoconjugated by SULT1E, which appears to be expressed at low levels in breast cancer cells. The expression of SULT1E1 during the progression of tumorigenesis was characterized using an MCF-7 cell line transfected with SULT1E1, and it was observed that sulfation increased in the SULT1E1-transfected MCF-7 cells compared to the control cells [76]. A similar observation of the physiological implications of SULT1E1 expression was examined by the MCF-7 cell line as well; the response to physiological concentrations of E\textsubscript{2} was reduced, as determined in an estrogen-responsive reporter gene assay [77]. SULT1E1 has shown very strong affinity for the sulfation of E\textsubscript{2} and EE\textsubscript{2}, so the ability of SULT1E1 to be involved in estrogen concentrations is important for regulating estrogen receptor target tissues. Estrogen-dependent breast cells with high SULT1E1 levels grow more slowly, suggesting an inhibitory role in carcinogenesis, depending on the role of SULT1E1 in creating physiologically inactive estrogen via sulfoconjugation [51,76,78,79].

![Breast Carcinoma Tissue](image)

**Figure 3.** A schematic pathway for estrogen formation by SULT1E1 and STS in breast carcinoma tissue. E\textsubscript{1}S, estrone sulfate; E\textsubscript{1}, estrone; E\textsubscript{2}, estradiol.

Due to the high homology (77.5%) between humans and mice, mouse models have been developed and studied in various approaches. Many pathological mouse models that are related to SULT1E1 have been studied, such as sepsis and diabetes. Sepsis is a lethal condition caused by physiological reactions to infections. There was an in vivo mouse study where hepatic SULT1E1 was upregulated via the activation of the NF-\(\kappa\)B pathway’s associated inflammatory pathways [80].

The Akita mouse was derived from C57BL/6 and inherited the mutated insulin 2 gene, so it can be used as a model of diabetes mellitus (DM) type 1. Interestingly, hepatic SULT1E1 mRNA was highly upregulated in Akita, and this pathological situation acts as a stimulus to regulate SULT1E1 expression via phosphorylated-ER\textsubscript{α} and dephosphorylated-CAR [32]. Likewise, diabetes type 2 mouse models (\(db/db\) and \(ob/ob\)) also exhibited
the hepatic overproduction of SULT1E1, representing SULT1E1’s role in maintaining the balance of estrogen sulfation [81,82].

6. Functional Variants of SULT1E1 and Current Research Status

A total of 4760 single-nucleotide polymorphisms (SNPs) have been validated by frequency, cluster, and ALFA (allele frequency aggregator) out of the total of 5428 SNPs, including 214 missense variants in human SULT1E1, according to NCBI dbSNP. Most SNPs are intronic variants. Diverse studies have been conducted to identify SULT1E1 polymorphisms and their effects, especially based on association cohort studies (Table 5).

Six SNPs from the introns of SULT1E1 were associated with treatment failure of abiraterone acetate (AA) therapy in metastatic castration-resistant prostate cancer (mCRPC) patients [83]. Each DNA sample was isolated from patients with mCRPC who were treated with AA approximately three years previously, and the samples were analyzed for the study. In groups 1 (rs3775777, rs4149534, and rs10019305) and 2 (rs3775770, rs4149527, and rs3775768), it was observed that the patients carrying polymorphic alleles had the estimated hazard ratios of 3.58 and 3.12, respectively [83].

There was an association study using Korean females that included breast cancer patients and healthy subjects [84]. The patients carrying rs3775775 (TC or CC) had a hazard ratio of 3.2 (1.39–7.48) compared to that of TT carriers [84]. Regulating estrogen levels, which is especially related to SULT1E1’s sulfation capacity, could facilitate the development of breast cancer or its avoidance in Korean females [84].

The most popular and broadly studied polymorphism of SULT1E1 is rs3736599, which has a nucleotide alteration at c.–64G>A of the 5’UTR region. Though other variants were also involved, this variant influenced the DHEA sulfation, endometrial carcinogenesis risk, and bone mineral density in females [85–87]. There was a cohort study that enrolled equal numbers of African American (AA) and European-American (EA) women, and approximately 11 years after the study’s inception, complete data were collected from 301 women. In the EA women, SULT1E1 rs3736599 carriers had lower DHEA sulfate levels [85].

In a study in which 150 endometrial cancer patients in total and 165 age-matched healthy control individuals were enrolled [86], surprisingly, the odds ratios of AA and AA+GA were 3.50 and 1.76, respectively, reflecting the higher endometrial cancer risks [86].

In another study, 397 healthy Korean female subjects with menopause and without any cancer or thyroid-related disease history were genotyped to identify the differences in bone mineral density of the distal radius and calcaneus [87]. A variant of SULT1E1, rs3736599, was associated with bone mineral density of the distal radius and the calcaneus. Moreover, a combined effect between this polymorphism and altered estrogen consumption might exist in the calcaneus [87].

Three of the SULT1E1 SNPs—Asp22Tyr (rs11569705), Ala32Val (rs34547148), and Pro253His (rs11569712)—were discovered, and these variants were in the encoded amino acids [88]. These alleles were transfected and expressed in COS-1 cells to discover their functional impacts on stability and activity. Among them, rs11569705 indicated the most significant decrease in enzyme activity and protein level, and rs34547148 also displayed a 50% decrease in both the enzyme and the protein [88].

Table 5. Reported human SULT1E1 functional variants.

| Type     | Position 1 | SNP ID 2 | Effect                               | Reference |
|----------|------------|----------|--------------------------------------|-----------|
| Intron   | c.772+369T>C | rs3775777 | Treatment failure on abiraterone acetate with mCRPC | [83]      |
|          | c.369+1930A>C | rs4149534 |                                      |           |
|          | c.369+402T>C | rs10019305|                                      |           |
|          | c.-9-899G>A  | rs3775770 |                                      |           |
|          | c.-10+771C>A | rs4149527 |                                      |           |
|          | c.-10+655G>A  | rs3775768 |                                      |           |
|          | c.-9-469G>A  | rs3822172 | Lower survival rate in colorectal cancer | [89]      |
|          | c.772+856G>T,C,A | rs1238574 |                                      |           |
|          | c.369+1633T>C | rs3775775 | Decreased survival rate from breast cancer | [84]      |
Table 5. Cont.

| Type       | Position 1 | SNP ID 2 | Effect                                                                 | Reference |
|------------|------------|----------|------------------------------------------------------------------------|-----------|
| 5′UTR      | c.-64G>A   | rs3736599| Lower DHEA sulfate levels in the menopausal transition of European-American population [85] May strongly contribute to risk for endometrial carcinogenesis in Caucasians [86] Higher bone mineral density of distal radius and calcaneus in Korean women [87] |           |
| Missense   | 95C>T (Ala32Val) 64G>A (Asp22Tyr) | rs34547148, rs11569705 | Increased $K_m$ value for the sulfation of $E_2$ | [88] |

1 All reference sequences are described according to GRCh38.p12 chromosome 4, and the accession number is NM_005420.3. 2 Each single-nucleotide polymorphism (SNP) ID is described according to the NCBI dbSNP. UTR, untranslated region; mCRPC, metastatic castration-resistant prostate cancer; DHEA, dehydroepiandrosterone.

7. Future Directions for Clinical Integrations

SULT1E1 is responsible for the metabolism of active estrogens and plays crucial roles in their homeostasis. Therefore, this enzyme makes a variety of contributions to human health, including in regard to cancers and drug responses. However, the lack of genetic research on SULT1E1 needs to be enhanced by precisely designed studies in many respects. Several cohort-study-based analyses have been conducted regarding SULT1E1 genetic variants, but relatively few compared to the number of such studies for the SULT1A subfamily. Due to human SULT1E1’s high nucleotide homology with several animal SULT1E1s, and their similar substrate-binding structures, animal models and in vivo studies have provided useful clues for the genetic regulation and kinetics of humans. Thus, using transgenic animal models would aid in determining gene–gene or gene–xenobiotic interactions in the study of SULT1E1 activity.

Since the substrate-binding sites and neighboring amino acids are regarded as being involved prominently in enzyme activity and structure, we suggest candidate SNPs corresponding to adjacent substrate-binding sites be investigated in genetic association studies (Table 6).

Several cohort studies have developed SULT1E1 association models, such as Predictors of Breast Cancer Recurrence (ProBeCaRE) [90] and U-statistics-based tests for identifying the pathway-based candidate genes of breast cancer and hormone metabolism pathways [91]. In addition, an intronic polymorphism (rs3775779) was discovered as a marker for analyzing the ethnic difference in the fine-scale population structure of Malays in Peninsular Malaysia and Singapore [92]. These studies suggest diverse scientific approaches to figure out the role of SULT1E1.

Many studies of SULT1E1 have highlighted aspects of its impacts on biological systems. Therefore, we encourage such studies to elucidate the related pathophysiological perspectives of human SULT1E1.

Table 6. Amino acids near to substrate-binding sites of SULT1E1.

| Impacted Amino Acids | Substrate 1 | Alteration | SNP ID 2 |
|---------------------|-------------|------------|----------|
| Arg256              | PAPS        | Not reported | -        |
| Phe254              | $E_2$, 4-OH TCB | Phe254Cys | rs746067466 |
| Met247              | 4-OH TCB    | Met247Ile  | rs1188553969 |
| Ile246              | 4-OH TCB, TBBPA | Ile246Leu | rs1413235220 |
| Tyr239              | $E_2$, 4-OH TCB | Not reported | -        |
| Phe228              | PAPS        | Not reported | -        |
| Thr226              | PAPS        | Thr226Ser  | rs756363002 |
| Asn168              | 4-OH TCB, TBBPA | Asn168Ser | rs1265277815 |
| Val145              | 4-OH TCB    | Val145Leu  | rs200443686 |
| Phe141              | $E_2$, 4-OH TCB, TBBPA, 3-OH BDE47 | Phe141Leu | rs1220949195 |
Table 6. Cont.

| Impacted Amino Acids | Substrate 1 | Alteration | SNP ID 2 |
|----------------------|-------------|------------|----------|
| Phe138               | TBBPA       | Not reported | -        |
| Ser137               | PAPS, E2    | Ser137Pro  | rs1208507410 |
| Arg129               | PAPS        | Arg129Gln  | rs774700339 |
| His107               | PAPS, E2, 4-OH TCB, TBBPA | His107Arg | rs1316115370 |
| Lys105               | PAPS, E2, 4-OH TCB, TBBPA, 3-OH BDE47 | Not reported | - |
| Cys83                | 3-OH BDE47, E2, 4-OH TCB, TBBPA, 3-OH BDE47 | Cys83Phe | rs1431397129 |
| Phe80                | TBBPA, 3-OH BDE47 | Not reported | - |
| Trp52                | PAPS        | Not reported | -        |
| Thr51                | PAPS        | Thr51Ile   | rs1170826222 |
| Thr50                | PAPS        | Thr51Ala   | rs761632873 |
| Gly49                | PAP         | Gly49Val   | rs1460190031 |
| Ser48                | PAP         | Ser48Cys   | rs1336407598 |
| Lys47                | PAPS, E2    | Lys47Glu   | rs1361781887 |
| Pro46                | 4-OH TCB, TBBPA | Pro46Leu | rs771011878 |
| Phe23                | 4-OH TCB    | Phe23Cys   | rs1400776691 |
| Asp22                | 4-OH TCB    | Asp22Asn   | rs11569705 |
| Tyr20                | PAP-E2, 4-OH TCB, TBBPA | Tyr20Cys | rs778407495 |

1 The crystal structures and neighboring amino acids of SULT1E1 substrate-binding sites were described according to the RCSB protein data bank (PDBid: 1G3M, 1HY3, 4JVM, 4JVN, and 4JVL) [11,12,93]. 2 Each SNP ID was based on NCBI dbSNP. 4-OH TCB, 4′-OH-3,5,3′,5′-tetrachlorinated biphenyl; TBBPA, tetrabromobisphenol A; 3-OH BDE47, 3-hydroxyl bromodiphenyl ether.

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References
1. Gamage, N.; Barnett, A.; Hempel, N.; Duggleby, R.G.; Windmill, K.F.; Martin, J.L.; McManus, M.E. Human sulfotransferases and their role in chemical metabolism. Toxicol. Sci. 2006, 90, 5–22. [CrossRef]

2. Liu, L.; Klaassen, C.D. Regulation of hepatic sulfotransferases by steroidal chemicals in rats. Drug Metab. Dispos. 1996, 24, 854–858. [PubMed]

3. Sonoda, J.; Xie, W.; Rosenfeld, J.M.; Barwick, J.L.; Guzelian, P.S.; Evans, R.M. Regulation of a xenobiotic sulfonation cascade by nuclear pregnane X receptor (PXR). Proc. Natl. Acad. Sci. USA 2002, 99, 13801–13806. [CrossRef]

4. Song, C.S.; Echchgadda, I.; Baek, B.S.; Ahn, S.C.; Oh, T.; Roy, A.K.; Chatterjee, B. Dehydroepiandrosterone sulfotransferase gene induction by bile acid activated farnesoid X receptor. J. Biol. Chem. 2001, 276, 42549–42556. [CrossRef]

5. Qatanani, M.; Zhang, J.; Moore, D.D. Role of the constitutive androstane receptor in xenobiotic-induced thyroid hormone metabolism. Endocrinology 2005, 146, 995–1002. [CrossRef]
6. Tien, E.S.; Matsui, K.; Moore, R.; Negishi, M. The nuclear receptor constitutively active/androstane receptor regulates type 1 deiodinase and thyroid hormone activity in the regenerating mouse liver. *J. Pharmacol. Exp. Ther.* 2007, 320, 307–313. [CrossRef]

7. Falany, C.N. Enzymology of human cytosolic sulfotransferases. *FASEB J.* 1997, 11, 206–216. [CrossRef] [PubMed]

8. Kleessen, C.D.; Boles, J.W. Sulfation and sulfotransferases 5: The importance of 3'-phosphoadenosine 5'-phosphosulfate (PAPS) in the regulation of sulfation. *FASEB J.* 1997, 11, 404–418. [CrossRef] [PubMed]

9. Kakuta, Y.; Pedersen, L.G.; Carter, C.W.; Negishi, M.; Pedersen, L.C. Crystal structure of estrogen sulfotransferase. *Nat. Struct. Biol.* 1997, 4, 904–908. [CrossRef] [PubMed]

10. Kakuta, Y.; Petrotchenko, E.V.; Pedersen, L.C.; Negishi, M. The sulfuryl transfer mechanism. Crystal structure of a vanadate complex of estrogen sulfotransferase and mutational analysis. *J. Biol. Chem.* 1998, 273, 27325–27330. [CrossRef]

11. Pedersen, L.C.; Petrotchenko, E.; Shevtsov, S.; Negishi, M. Crystal structure of the human estrogen sulfotransferase-PAPS complex: Evidence for catalytic role of Ser137 in the sulfuryl transfer reaction. *J. Biol. Chem.* 2002, 277, 17928–17932. [CrossRef] [PubMed]

12. Shevtsov, S.; Petrotchenko, E.V.; Pedersen, L.C.; Negishi, M. Crystallographic analysis of a hydroxylated polychlorinated biphenyl (OH-PCB) bound to the catalytic estrogen binding site of human estrogen sulfotransferase. *Environ. Health Perspect.* 2003, 111, 884–888. [CrossRef] [PubMed]

13. Allali-Hassani, A.; Pan, P.W.; Dombrovski, L.; Najmanovich, R.; Tempel, W.; Dong, A.; Loppnau, P.; Martin, F.; Thornton, J.; Edwards, A.M.; et al. Structural and chemical profiling of the human cytosolic sulfotransferases. *PLoS Biol.* 2007, 5, e97.

14. Kodama, S.; Negishi, M. Sulfotransferase genes: Regulation by nuclear receptors in response to xeno/endobiotics. *Drug Metab. Rev.* 2013, 45, 441–449. [CrossRef]

15. Falany, C.N.; Krasnykh, V.; Falany, J.L. Bacterial expression and characterization of a cDNA for human liver estrogen sulfotransferase. *J. Steroid Biochem. Mol. Biol.* 1995, 52, 529–539. [CrossRef]

16. Zhang, H.; Varlamova, O.; Vargas, F.M. Sulfuryl transfer: The catalytic mechanism of human estrogen sulfotransferase. *J. Biol. Chem.* 1998, 273, 10888–10892. [CrossRef]

17. Faucher, F.; Lacoste, L.; Dufort, I.; Luu-The, V. High metabolism of catecholestrogens by type 1 estrogen sulfotransferase (hEST1). *J. Steroid Biochem. Mol. Biol.* 2001, 77, 83–86. [CrossRef]

18. Faucher, F.; Lacoste, L.; Luu-The, V. Human type 1 estrogen sulfotransferase: Catecholestrogen metabolism and potential involvement in cancer promotion. *Ann. N. Y. Acad. Sci.* 2002, 963, 221–228. [CrossRef]

19. Adjei, A.A.; Weinshilboum, R.M. Catecholestrogen sulfation: Possible role in carcinogenesis. *Biochem. Biophys. Res. Commun.* 2002, 292, 402–408. [CrossRef]

20. Her, C.; Aksoy, I.A.; Kimura, S.; Brandriff, B.F.; Wasmuth, J.J.; Weinshilboum, R.M. Human estrogen sulfotransferase gene (STE): Cloning, structure, and chromosomal localization. *Genomics* 1995, 29, 16–23. [CrossRef]

21. Stanley, E.L.; Hume, R.; Visser, T.J.; Coughtrie, M.W. Differential expression of sulfotransferase enzymes involved in thyroid hormone metabolism and mutational profiling of the human cytosolic sulfotransferases. *FASEB J.* 2001, 15, 441–450. [CrossRef] [PubMed]

22. Rubin, G.L.; Harrold, A.J.; Mills, J.A.; Falany, C.N.; Coughtrie, M.W. Regulation of sulfotransferase expression in the endometrium during the menstrual cycle, by oral contraceptives and during early pregnancy. *Mol. Hum. Reprod.* 1999, 5, 995–1002. [CrossRef]

23. Song, W.C.; Qian, Y.; Li, A.P. Estrogen sulfotransferase expression in the human liver: Marked interindividual variation and lack of gender specificity. *J. Pharmacol. Exp. Ther.* 1998, 284, 1197–1202. [CrossRef]

24. Li, Y.; Xu, Y.; Li, X.; Qin, Y.; Hu, R. Effects of PPAR-α agonist and IGF-1 on estrogen sulfotransferase in human vascular endothelial and smooth muscle cells. *Mol. Med. Rep.* 2013, 8, 133–139. [CrossRef]

25. Xu, Y.; Yang, X.; Wang, Z.; Li, M.; Ning, Y.; Chen, S.; Yin, L.; Li, X. Estrogen sulfotransferase (SULT1E1) regulates inflammatory response and lipid metabolism of human endothelial cells via PPARγ. *Mol. Cell. Endocrinol.* 2013, 369, 140–149. [CrossRef] [PubMed]

26. Wang, S.; Yuan, X.; Lu, D.; Guo, L.; Wu, B. Farnesoid X receptor regulates SULT1E1 expression through inhibition of PGC1α binding to HNF4α. *Biochem. Pharmacol.* 2017, 145, 202–209. [CrossRef]

27. Liu, X.; Xue, R.; Yang, C.; Gu, J.; Chen, S.; Zhang, S. Cholestasis-induced bile acid elevates estrogen level via farnesoid X receptor-mediated suppression of the estrogen sulfotransferase SULT1E1. *J. Biol. Chem.* 2018, 293, 12759–12769. [CrossRef] [PubMed]

28. Hu, H.; Negishi, M. RORα signaling by casein kinase 1α as glucose signal to regulate estrogen sulfation in human liver cells. *Biochem. J.* 2020, 477, 3583–3598. [CrossRef]

29. Gong, H.; Guo, P.; Zhai, Y.; Zhou, J.; Uppal, H.; Jarzynka, M.J.; Song, W.C.; Cheng, S.Y.; Xie, W. Estrogen deprivation and inhibition of breast cancer growth in vivo through activation of the orphan nuclear receptor liver X receptor. *Mol. Endocrinol.* 2007, 21, 1781–1790. [CrossRef] [PubMed]

30. Gong, H.; Jarzynka, M.J.; Cole, T.J.; Lee, J.H.; Wada, T.; Zhang, B.; Gao, J.; Song, W.C.; DeFranco, D.B.; Cheng, S.Y.; et al. Glucocorticoids antagonize estrogens by glucocorticoid receptor-mediated activation of estrogen sulfotransferase. *Cancer Res.* 2008, 68, 7386–7393. [CrossRef]

31. Sueyoshi, T.; Green, W.D.; Vinal, K.; Woodrum, T.S.; Moore, R.; Negishi, M. Garlic extract diallyl sulfide (DAS) activates nuclear receptor CAR to induce the Sult1e1 gene in mouse liver. *PLoS ONE* 2011, 6, e21229. [CrossRef]

32. Yi, M.; Fashe, M.; Arakawa, S.; Moore, R.; Sueyoshi, T.; Negishi, M. Nuclear receptor CAR-ERα signaling regulates the estrogen sulfotransferase gene in the liver. *Sci. Rep.* 2020, 10, 5001. [CrossRef] [PubMed]
33. Hu, H.; Yokobori, K.; Negishi, M. PXR phosphorylated at Ser350 transduces a glucose signal to repress the estrogen sulfotransferase gene in human liver cells and fasting signal in mouse livers. *Biochem. Pharmacol.* 2020, 180, 114197. [CrossRef]

34. Fashe, M.; Hashiguchi, T.; Yi, M.; Moore, R.; Negishi, M. Phenobarbital-induced phosphorylation converts nuclear receptor RORalpha from a repressor to an activator of the estrogen sulfotransferase gene Sult1e1 in mouse livers. *FEBS Lett.* 2018, 592, 2760–2768. [CrossRef] [PubMed]

35. Poisson Paré, D.; Song, D.; Luu-The, V.; Han, B.; Li, S.; Liu, G.; Labrie, F.; Pelletier, G. Expression of Estrogen Sulfotransferase 1E1 and Steroid Sulfatase in Breast Cancer: A Immunohistochemical Study. *Breast Cancer* 2009, 3, 9–21.

36. Song, W.C.; Melner, M.H. Steroid transformation enzymes as critical regulators of steroid action in vivo. *Endocrinology* 2000, 141, 1587–1589. [CrossRef]

37. Falany, C.N.; Wheeler, J.; Oh, T.S.; Falany, J.L. Steroid sulfation by expressed human cytosolic sulfotransferases. *J. Steroid Biochem. Mol. Biol.* 1994, 48, 369–375. [CrossRef]

38. Falany, C.N.; Comer, K.A.; Dooley, T.P.; Glatt, H. Human dehydroepiandrosterone sulfotransferase. Purification, molecular cloning, and characterization. *Ann. N. Y. Acad. Sci.* 1995, 774, 59–72. [CrossRef]

39. Aksoy, I.A.; Wood, T.C.; Weinshilboum, R. Human liver estrogen sulfotransferase: Identification by cDNA cloning and expression. *Biochim. Biophys. Res. Commun.* 1994, 200, 1621–1629. [CrossRef]

40. Schrag, M.L.; Cui, D.; Rushmore, T.H.; Shou, M.; Glatt, H.; Falany, C.N.; Coughtrie, M.W.; et al. Sulfation of thyroid hormone by sulfotransferase. *J. Clin. Endocrinol. Metab.* 1999, 84, 2577–2580. [CrossRef] [PubMed]

41. Kester, M.H.; van Dijk, C.H.; Tibboel, D.; Hood, A.M.; Meinl, W.; Pabel, U.; Glatt, H.; Falany, C.N.; Coughtrie, M.W.; et al. Regulation of estrogen activity by sulfation in human Ishikawa endometrial adenocarcinoma cells. *J. Steroid Biochem. Mol. Biol.* 2004, 88, 383–391. [CrossRef]

42. Ung, D.; Nagar, S. Variable sulfation of dietary polyphenols by recombinant human sulfotransferase (SULT) 1A1 genetic variants and SULT1E1. *Drug Metab. Dispos.* 2007, 35, 740–746. [CrossRef] [PubMed]

43. Edavana, V.K.; Yu, X.; Dhakal, I.B.; Williams, S.; Ning, B.; Cook, I.T.; Caldwell, D.; Falany, C.N.; Kadihar, S. Sulfation of fulvestrant by human liver cytosol and recombinant SULT1A1 and SULT1E1. *Pharmacogenom. Pers. Med.* 2011, 4, 137–145.

44. Hu, H.; Yokobori, K.; Negishi, M. Phenobarbital-induced phosphorylation converts nuclear receptor RORalpha from a repressor to an activator of the estrogen sulfotransferase gene Sult1e1 in mouse livers. *FEBS Lett.* 2018, 592, 2760–2768. [CrossRef] [PubMed]

45. Honma, W.; Shimada, M.; Sasano, H.; Ozawa, S.; Miyata, M.; Nagata, K.; Ikeda, T.; Yamazoe, Y. Phenol sulfotransferase, ST1A3, as the main enzyme catalyzing sulfoxidation of troglitazone in human liver. *Drug Metab. Dispos.* 2002, 30, 944–949. [CrossRef] [PubMed]

46. Squirewell, E.J.; Duffell, M.W. The effects of endoxifen and other major metabolites of tamoxifen on the sulfation of estradiol catalyzed by human cytosolic sulfotransferases hSULT1E1 and hSULT1A1*.1. *Drug Metab. Dispos.* 2015, 43, 843–850. [CrossRef]

47. Falany, J.L.; Macrina, N.; Falany, C.N. Sulfation of tibolone and tibolone metabolites by expressed human cytosolic sulfotransferases. *J. Steroid Biochem. Mol. Biol.* 2004, 88, 383–391. [CrossRef]

48. Buirchell, B.J.; Hahn, R. Metabolism of estradiol-17beta in human endometrium during the menstrual cycle. *J. Steroid Biochem.* 1975, 6, 1489–1494. [CrossRef]

49. Falany, J.L.; Azziz, R.; Falany, C.N. Identification and characterization of cytosolic sulfotransferases in normal human endometrium. *Chem. Biol. Interact.* 1998, 109, 329–339. [CrossRef]

50. Kotov, A.; Falany, J.L.; Wang, J.; Falany, C.N. Regulation of estrogen activity by sulfation in human Ishikawa endometrial adenocarcinoma cells. *J. Steroid Biochem. Mol. Biol.* 1999, 68, 137–144. [CrossRef]

51. Falany, J.L.; Falany, C.N. Regulation of estrogen sulfotransferase in human endometrial adenocarcinoma cells by progesterone. *Endocrinology* 1996, 137, 1395–1401. [CrossRef]

52. Moreau, X.; Lejeune, P.J.; Jeanninros, R. Kinetics of red blood cell T3 uptake in hypothyroidism with or without hormonal replacement, in the rat. *J. Endocrinol. Invest.* 1999, 22, 257–261. [CrossRef] [PubMed]

53. Kim, S.Y.; Woo, S.; Choi, K.H.; Yun, J. Evaluation of phototoxicity of tattoo pigments using the 3T3 neutral red uptake phototoxicity test and a 3D human reconstructed skin model. *Toxicol. In Vitro* 2020, 65, 104813. [CrossRef] [PubMed]

54. Leiner, K.A.; Mackenzie, D.S. Central regulation of thyroidal status in a teleost fish: Nutrient stimulation of T4 secretion and negative feedback of T3. *J. Exp. Zool. Comp. Exp. Biol.* 2003, 298, 32–43. [CrossRef]

55. Mihasan, M.; Brandsch, R. A predicted T4 secretion system and conserved DNA-repeats identified in a subset of related Arthrobacter plasmids. *Microbiol. Res.* 2016, 191, 32–37. [CrossRef]

56. St Germain, D.L.; Galton, V.A.; Hernandez, A. Minireview: Defining the roles of the iodothyronine deiodinases: Current concepts and challenges. *Endocrinology* 2009, 150, 1097–1107. [CrossRef]

57. Wu, S.Y.; Huang, W.S.; Polk, D.; Florsheim, W.H.; Green, W.L.; Fisher, D.A. Identification of thyroxine-sulfate (T4S) in human serum and amniotic fluid by a novel T4S radioimmunoassay. *Thyroid* 1992, 2, 101–105. [CrossRef]

58. Chatterjee, B.; Song, C.S.; Kim, J.M.; Roy, A.K. Androgen and estrogen sulfotransferases of the rat liver: Physiological function, molecular cloning, and in vitro expression. *Chem. Biol. Interact.* 1994, 92, 273–279. [CrossRef]

59. Kester, M.H.; Kaptein, E.; Roeijt, T.J.; van Dijk, C.H.; Tibboel, D.; Meinl, W.; Glatt, H.; Coughtrie, M.W.; Visser, T.J. Characterization of human iodothyronine sulfotransferases. *J. Clin. Endocrinol. Metab.* 1999, 84, 1357–1364. [CrossRef]

60. Wang, J.; Falany, J.L.; Falany, C.N. Expression and characterization of a novel thyroid hormone-sulfating form of cytosolic sulfotransferase from human liver. *Mol. Pharmacol.* 1998, 53, 274–282. [CrossRef]

61. Li, X.; Clemens, D.L.; Anderson, R.J. Sulfation of iodothyronines by human sulfotransferase 1C1 (SULT1C1). *Biochem. Pharmacol.* 2000, 60, 1713–1716. [CrossRef]
62. Kester, M.; Coughtrie, M.W.; Visser, T.J. Sulfation of Thyroid Hormones. In Human Cytosolic Sulfotransferases; Pacifici, G.M., Coughtrie, M.W., Eds.; CRC Press/Taylor & Francis Group: Boca Raton, FL, USA, 2005; pp. 121–134.

63. Glatt, H.; Boeing, H.; Engelke, C.E.; Ma, L.; Kuhlow, A.; Pabel, U.; Pomplun, D.; Teubner, W.; Meinl, W. Human cytosolic sulfotransferases: Genetics, characteristics, toxicological aspects. Mutat. Res. 2001, 482, 27–40. [CrossRef]

64. Weinshilboum, R.M.; Otterness, D.M.; Aksoy, I.A.; Wood, T.C.; Her, C.; Rafiqtagianis, R.B. Sulfation and sulfotransferases 1: Sulfotransferase molecular biology: cDNAs and genes. FASEB J. 1997, 11, 3–14. [CrossRef]

65. Kiehlbauch, C.C.; Lam, Y.F.; Ringer, D.P. Homodimeric and heterodimeric aryl sulfotransferases catalyze the sulfuric acid esterification of N-hydroxy-2-acetylaminoaniline. J. Biol. Chem. 1995, 270, 18941–18947. [CrossRef] [PubMed]

66. Salehi, B.; Venditti, A.; Sharifi-Rad, M.; Kregel, D.; Sharifi-Rad, J.; Durazzo, A.; Lucarini, M.; Santini, A.; Souto, E.B.; Novellino, E.; et al. The Therapeutic Potential of Apigenin. Int. J. Mol. Sci. 2019, 20, 1305. [CrossRef] [PubMed]

67. Tan, J.; de Bruin, W.J.C.; van Zadelhoff, A.; Lin, Z.; Vincken, J.P. Browning of Epicatechin (EC) and Epigallocatechin (EGC) by homodimeric and heterodimeric aryl sulfotransferases catalyze the sulfuric acid esterification of N-hydroxy-2-acetylaminoaniline. J. Biol. Chem. 1995, 270, 18941–18947. [CrossRef] [PubMed]

68. Jana, K.; Yin, X.; Schiffer, R.B.; Chen, J.J.; Pandey, A.K.; Stocco, D.M.; Grammas, P.; Wang, X. Chrysin, a natural flavonoid enhances steroidogenesis and steroidogenic acute regulatory protein gene expression in mouse Leydig cells. J. Endocrinol. 2008, 197, 315–323. [CrossRef]

69. Thomas, H.V.; Key, T.J.; Allen, D.S.; Moore, J.W.; Dowsett, M.; Fentiman, I.S.; Wang, D.Y. A prospective study of endogenous serum hormone concentrations and breast cancer risk in post-menopausal women. J. Clin. Invest. 1996, 98, 1460–1464.

70. Li, Y.; Yao, J.; Han, C.; Yang, J.; Chaudhry, M.T.; Wang, S.; Liu, H.; Yin, Y. Quercetin, Inflammation and Immunity. Nutrients 2016, 8, 167. [CrossRef]

71. Pasqualini, J.R.; Chetrite, G.; Blacker, C.; Feinstein, M.C.; Delalonde, L.; Talbi, M.; Maloche, C. Concentrations of estrone, estradiol, and estrone sulfate and evaluation of sulfatase and aromatase activities in pre- and postmenopausal breast cancer patients. J. Clin. Endocrinol. Metab. 1996, 81, 1460–1464.

72. Mady, E.A.; Ramadan, E.E.; Osman, A.A. Sex steroid hormones in serum and tissue of benign and malignant breast tumor patients. Dis. Markers 2000, 16, 151–157. [CrossRef] [PubMed]

73. Bonorden, M.J.; Greany, K.A.; Wangen, K.E.; Phipps, W.R.; Feirtag, J.; Adlercreutz, H.; Kurzer, M.S. Consumption of Lactobacillus acidophilus and Bifidobacterium longum do not alter urinary equol excretion and plasma reproductive hormones in premenopausal women. Eur. J. Clin. Nutr. 2012, 66, 151–157. [CrossRef] [PubMed]

74. Salehi, B.; Mishra, A.P.; Nigam, M.; Sener, B.; Kilic, M.; Sharifi-Rad, M.; Fokou, P.V.T.; Martins, N.; Sharifi-Rad, J. Resveratrol: A Double-Edged Sword in Health Benefits. Biomedicines 2018, 6, 91. [CrossRef]

75. Thomas, H.V.; Key, T.J.; Allen, D.S.; Moore, J.W.; Dowsett, M.; Fentiman, I.S.; Wang, D.Y. A prospective study of endogenous serum hormone concentrations and breast cancer risk in post-menopausal women on the island of Guernsey. Br. J. Cancer 1997, 76, 401–405. [CrossRef]

76. Pasqualini, J.R.; Cortes-Prieto, J.; Chetrite, G.; Talbi, M.; Ruiz, A. Concentrations of estrone, estradiol and their sulfates, and evaluation of sulfatase and aromatase activities in patients with breast fibroadenoma. Int. J. Cancer 1997, 70, 639–643. [CrossRef]

77. Falany, J.L.; Falany, C.N. Expression of cytosolic sulfotransferases in normal mammary epithelial cells and breast cancer cell lines. Cancer Res. 1996, 56, 1551–1555. [PubMed]

78. Chetrite, G.S.; Paris, J.; Shields-Botella, J.; Philippe, J.C.; Pasqualini, J.R. Effect of nomegestrol acetate on human estrogen sulfotransferase activity in the hormone-dependent MCF-7 and T-47D breast cancer cell lines. Anticancer Res. 2003, 23, 4651–4655.

79. Qian, Y.; Deng, C.; Song, W.C. Expression of estrogen sulfotransferase in MCF-7 cells by cDNA transfection suppresses the estradiol response: Potential role of the enzyme in regulating estrogen-dependent growth of breast epithelial cells. J. Pharmacol. Exp. Ther. 1998, 286, 555–560.

80. Qian, Y.M.; Sun, X.J.; Tong, M.H.; Li, X.P.; Richa, J.; Song, W.C. Targeted disruption of the mouse estrogen sulfotransferase gene reveals a role of estrogen metabolism in breast cancer risk in post-menopausal women. J. Biol. Chem. 2001, 142, 5342–5350. [CrossRef] [PubMed]

81. Chai, X.; Guo, Y.; Jiang, M.; Hu, B.; Li, Z.; Fan, J.; Deng, M.; Billiar, T.R.; Kucera, H.R.; Gaikwad, N.W.; et al. Oestrogen sulfotransferase ablation sensitizes mice to sepsis. Nat. Commun. 2015, 6, 7979. [CrossRef]

82. Leiter, E.H.; Chapman, H.D. Obesity-induced diabetes (diabesity) in C57BL/KsJ mice produces aberrant trans-regulation of sex steroid sulfotransferase genes. J. Clin. Invest. 1994, 93, 2007–2013. [CrossRef] [PubMed]

83. Gao, J.; He, J.; Shi, X.; Stefanovic-Racic, M.; Xu, M.; O’Doherty, R.M.; Garcia-Ocana, A.; Xie, W. Sex-specific effect of estrogen sulfotransferase on mouse models of type 2 diabetes. Diabetes 2012, 61, 1543–1551. [CrossRef]

84. Agarwal, N.; Alexander, S.; Farnham, J.M.; Patel, S.; Gill, D.; Buckley, T.H.; Stephenson, R.A.; Cannon-Albright, L. Inherited variants in SULT1E1 and response to abiraterone acetate by men with metastatic castration refractory prostate cancer. J. Urol. 2016, 196, 1112–1116. [CrossRef]

85. Choi, J.Y.; Lee, K.M.; Park, S.K.; Noh, D.Y.; Ahn, S.H.; Chung, H.W.; Han, W.; Kim, J.S.; Shin, S.G.; Jang, I.J.; et al. Genetic polymorphisms of SULT1A1 and SULT1E1 and the risk and survival of breast cancer. Cancer Epidemiol. Biomark. Prev. 2005, 14, 1090–1095. [CrossRef] [PubMed]

86. Rebbeck, T.R.; Su, H.I.; Sammel, M.D.; Lin, H.; Tran, T.V.; Gracia, C.R.; Freeman, E.W. Effect of hormone metabolism genotypes on steroid hormone levels and menopausal symptoms in a prospective population-based cohort of women experiencing the menopausal transition. Menopause 2010, 17, 1026–1034. [CrossRef]
86. Hirata, H.; Hinoda, Y.; Okayama, N.; Suehiro, Y.; Kawamoto, K.; Kikuno, N.; Rabban, J.T.; Chen, L.M.; Dahiy, R. CYP1A1, SULT1A1, and SULT1E1 polymorphisms are risk factors for endometrial cancer susceptibility. Cancer 2008, 112, 1964–1973. [CrossRef] [PubMed]

87. Lee, S.A.; Choi, J.Y.; Shin, C.S.; Hong, Y.C.; Chung, H.; Kang, D. SULT1E1 genetic polymorphisms modified the association between phytoestrogen consumption and bone mineral density in healthy Korean women. Calcif. Tissue Int. 2006, 79, 152–159. [CrossRef] [PubMed]

88. Adjei, A.A.; Thomae, B.A.; Prondzinski, J.L.; Eckloff, B.W.; Wieben, E.D.; Weinshilboum, R.M. Human estrogen sulfotransferase (SULT1E1) pharmacogenomics: Gene resequencing and functional genomics. Br. J. Pharmacol. 2003, 139, 1373–1382. [CrossRef]

89. Li, S.; Xie, L.; Du, M.; Xu, K.; Zhu, L.; Chu, H.; Chen, J.; Wang, M.; Zhang, Z.; Gu, D. Association study of genetic variants in estrogen metabolic pathway genes and colorectal cancer risk and survival. Arch. Toxicol. 2018, 92, 1991–1999. [CrossRef]

90. Collin, L.J.; Cronin-Fenton, D.P.; Ahern, T.P.; Christiansen, P.M.; Damkier, P.; Ejlersen, B.; Hamilton-Dutoit, S.; Kjærsgaard, A.; Silliman, R.A.; Sørensen, H.T.; et al. Cohort Profile: The Predictors of Breast Cancer Recurrence (ProBe CaRE) Premenopausal Breast Cancer Cohort Study in Denmark. BMJ Open 2018, 8, e021805. [CrossRef]

91. Wei, Z.; Li, M.; Rebbeck, T.; Li, H. U-statistics-based tests for multiple genes in genetic association studies. Ann. Hum. Genet. 2008, 72, 821–833. [CrossRef]

92. Hoh, B.P.; Deng, L.; Julia-Asnizila, M.J.; Zuraihan, Z.; Nur-Hasnah, M.; Nur-Shaawati, A.R.; Hatin, W.I.; Endom, I.; Zilfalil, B.A.; Khalid, Y.; et al. Fine-scale population structure of Malays in Peninsular Malaysia and Singapore and implications for association studies. Hum. Genom. 2015, 9, 16. [CrossRef] [PubMed]

93. Gosavi, R.A.; Knudsen, G.A.; Birnbaum, L.S.; Pedersen, L.C. Mimicking of estradiol binding by flame retardants and their metabolites: A crystallographic analysis. Environ. Health Perspect. 2013, 121, 1194–1199. [CrossRef] [PubMed]