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Review

Dietary Soy Impact on Host Transcriptome Profile—A Review

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Abstract: Whether eaten, drank, or taken in the form of supplements, soybean has been a part of the human diet for centuries. The dietary use of soybean has been extensively proven to be beneficial for human health, protecting against a wide range of chronic diseases. However, our knowledge regarding the impact of soy intake on global gene expression is still incomplete. The present review summarizes and compares data describing the transcriptional changes in several tissues from two different phyla (fish and mammals) upon soybean diet supplementation. We performed comparative STRING-based pathway enrichment analysis of both individual and aggregated soy-induced transcriptome data in fish and mammals and identified the signaling pathways common between the two datasets. We hypothesize that these pathways represent a conserved transcriptome response to the soy-enriched dietary challenge.

Keywords: soy diet; transcriptome; nutrigenomics; gene expression

Citation: Anghel, A.; Sala-Cirtog, M.; Marian, C.; Samoila, C.; Sirbu, I.O. Dietary Soy Impact on Host Transcriptome Profile—A Review. *Appl. Sci.* **2021**, *11*, 7905. https://doi.org/10.3390/app11177905

Academic Editor: Veronica Mocanu

Received: 9 July 2021
Accepted: 23 August 2021
Published: 27 August 2021

1. Introduction

Known as a wonder food, wonder crop, or meat without bone, soybean has been a matter of intense debate regarding its diet-induced health effects. Soybean is not only a notoriously rich source of proteins and essential amino acids but also of folate, riboflavin and vitamin K, minerals (calcium, magnesium, iron, copper, manganese, molybdenum), and fibers [1,2]. Replacing meat with soy has beneficial health effects such as lowering cholesterol and saturated fat while increasing folate, calcium, magnesium, iron, vitamin K and fiber intake [3]. In addition, soybean contains unique nutrients such as isoflavonoids (ISO), phenolic acids, phytoalexins, phytosterols, and saponins, the roles of which are not yet fully understood [4]. These bioactive compounds may act through synergic or independent mechanisms to confer positive effects on human health [5].

Global soybean consumption varies from one country to another and even within the same country. For example, the average daily intake of soybean in China, Japan or Taiwan is around 36 g [6], while in Europe and the US is only 4 g [7]. There are also significant changes in dietary habits in Asians living in the US, and even in Asians living in urban vs. rural areas [6]. Furthermore, soy consumption varies according to age. In Japan, as the diet of young adults becomes more and more westernized, soy foods have begun to be replaced, such that older Japanese consume almost twice as much soy as the young ones [8]. These outstanding variations in diet habits might explain the divergent results of the health benefits analyses.

Most of the beneficial health effects of a soy diet have been attributed to isoflavones, generally known as phytoestrogens [9], while data on other soy phytochemicals are more limited [10]. After being metabolized by gut microbiota, their active compounds, genistein and daidzein, are either absorbed in the small intestine or delivered into the large intestine for further metabolism via intestinal microflora [11]. It is well known that among day-to-day dietary products, only soybean provides a relevant amount of isoflavones: 3.5 mg per gram of protein [12]. The concentration of isoflavones highly depends on the processing method: whole soy products such as edamame or soy flour have the highest dose of

isoflavones, while soy milk, soy sauce or other highly processed soy foods have up to 80% lower content of isoflavones [13].

The cardiovascular benefits of the soy diet are mainly linked to HDL cholesterol elevation and lowering LDL cholesterol/total cholesterol/triglycerides [14,15]. This effect is directly linked to soy proteins and saponins, which, due to their amphiphilic nature, form insoluble complexes that reduce the absorption of LDL cholesterol in the intestine [16,17]. Furthermore, the ISO, as well as genistein and daidzein, has an antioxidant effect by lowering LDL cholesterol oxidation [18], stimulating the production of superoxide dismutase [19], activating the Nrf2 pathway [20], and inhibiting nitric oxide synthesis in macrophages [21–23]. Of note, the combination of active soy principles was found to have an additive hypocholesterolemic effect compared to soy protein ingestion alone [24]. Furthermore, a high intake soy has been shown to promote vascular dilation in the periphery, while the data on cerebrovascular area are not conclusive [25]. However, a possible connection between soy diet and the development and management of vascular cerebral lesions including cerebral cavernous malformations (possibly mediated by gut lining bacteria) has not been explored so far [26,27].

Although supported by many ex vivo and in vivo data, the cancer prevention benefit of a soy enriched diet is still one of the most controversial, mainly due to the modest, inconsistent, and sometimes even controversial epidemiological data [28]. It is unanimously accepted that soy isoflavones, in general, and genistein, in particular, are the main cancer-preventing compounds. Genistein might exert its chemo-preventive properties through a combination of epigenetic (histone acetylation, DNA methylation), antiproliferative, proapoptotic, as well as anti-inflammatory, antioxidant, and antiangiogenic mechanisms [29–32]. Soy ISOs could bind to estrogen receptors (with significantly higher affinities for ER-β) [33] and androgen receptors [34] and thus impact the evolution of hormone-dependent cancers [35,36]. Although both ex vivo and clinical experiments show that soy ISOs might also promote the proliferation of malignant cells [37], the epidemiological data suggest an inverse correlation between soy food intake and the risk of cancer [38,39].

In women, ISOs might exert both estrogenic and antiestrogenic effects: in postmenopausal women, the phytoestrogens act as estrogens, while in premenopausal women, the estrogen levels are high, and exert the opposite effect [29].

Dietary soy could also have a protective effect against yet another chronic disorder, diabetes mellitus. Isoflavones, especially genistein, have a beneficial impact on the homeostasis of carbohydrate metabolism by lowering glucose uptake [34]. In addition, due to their high content in glycine and arginine, soy proteins might directly influence the secretion of insulin and glucagon [40]. Overall, soy diet intake is associated with a reduced risk of diabetes, although differences in sex and ethnicity might apply [41,42].

Overall, soy consumption has been demonstrated to provide health benefits, most notably regarding chronic diseases. Nevertheless, the components that seem to be responsible and their mechanisms of action are still debated. This review will focus on the transcriptional changes in several tissues from different species after whole soybean and soy protein/derivate dietary interventions.

2. Materials and Methods

In order to retrieve the current data on transcriptomic changes upon whole soybean (+/− soy protein) diet supplementation, we searched PubMed [43] using the keywords "soy diet", "transcriptome", "nutrigenomics", and gene expression regulation". Exclusion criteria were as follows: experiments using only soy components (proteins, genistein, saponins, etc.) instead of whole soybean/soybean + soy proteins, lack of high throughput methods (microarray or next-generation sequencing), and written in a language other than English. At the end of the selection process, only eight studies were included in the analysis. The details regarding the animal species used, the characteristics of the dietary

intervention (composition, duration), tissues analyzed, and the analytical platform used are presented in Table 1.

Table 1. Experimental conditions of studies reporting transcriptomic changes upon soy ingestion.

Species	Soy Diet	Duration of Feeding	Tissue	Analytical Platform	Ref.
Male rats (*Rattus norvegicus*)	Regular chow diet containing 20% soybean meal	18 months	Anterior pituitary and hypothalamus	Microarray	[44]
Male rats (*Rattus norvegicus*)	Regular chow containing 20% soy protein + 7% soybean oil	7 days	Liver	RNA-seq	[45]
Male mice (*Mus musculus*)	Regular chow containing 25% soybean meal	28 days	Liver	RNA-seq/Microarray	[46]
Human (*Homo sapiens*) breast cancer patients	Different soy foods	12 months	Tumor Tissue	NanoString nCounter	[47]
Atlantic salmon (*Salmo salar*)	Regular chow containing 20% soy protein + 10% soybean meal + 2% soy saponin	36 days	Distal intestine	RNA-seq	[48]
Atlantic salmon (*Salmo salar*)	Regular chow containing 45% soy protein/Regular chow containing 36% soybean meal	8 weeks	Distal intestine	Microarray	[49]
Yellow perch (*Perca flavescens*)	Regular chow containing 75% soybean meal	61 days	Mid intestine	RNA-seq	[50]
Zebrafish (*Danio Rerio*)	Regular chow containing 50% soybean meal + 2% soy saponin	53 days	Intestine	RNA-seq	[51]

We retrieved the sets of differentially expressed genes (as communicated by the authors) and subjected them to gene ontology/KEGG pathway overrepresentation analysis using the STRING platform, version 11.0 (http://string-db.org/), accessed on 21 May 2021). (using FDR = 0.05 as cutoff). The flowchart of our research work is presented in Figure 1. This represents Method 1.

To identify which soy-induced pathways changes are conserved in evolution, we aggregated the transcriptome data based on their phyla source: fish (Atlantic salmon, zebrafish, yellow perch) and mammals (rats, mice, humans). After removing the duplicates, we performed a novel STRING analysis (FDR < 0.05) of differentially expressed genes and compared the significant KEGG pathways from the fish group with those in the mammal group. This represents Method 2.

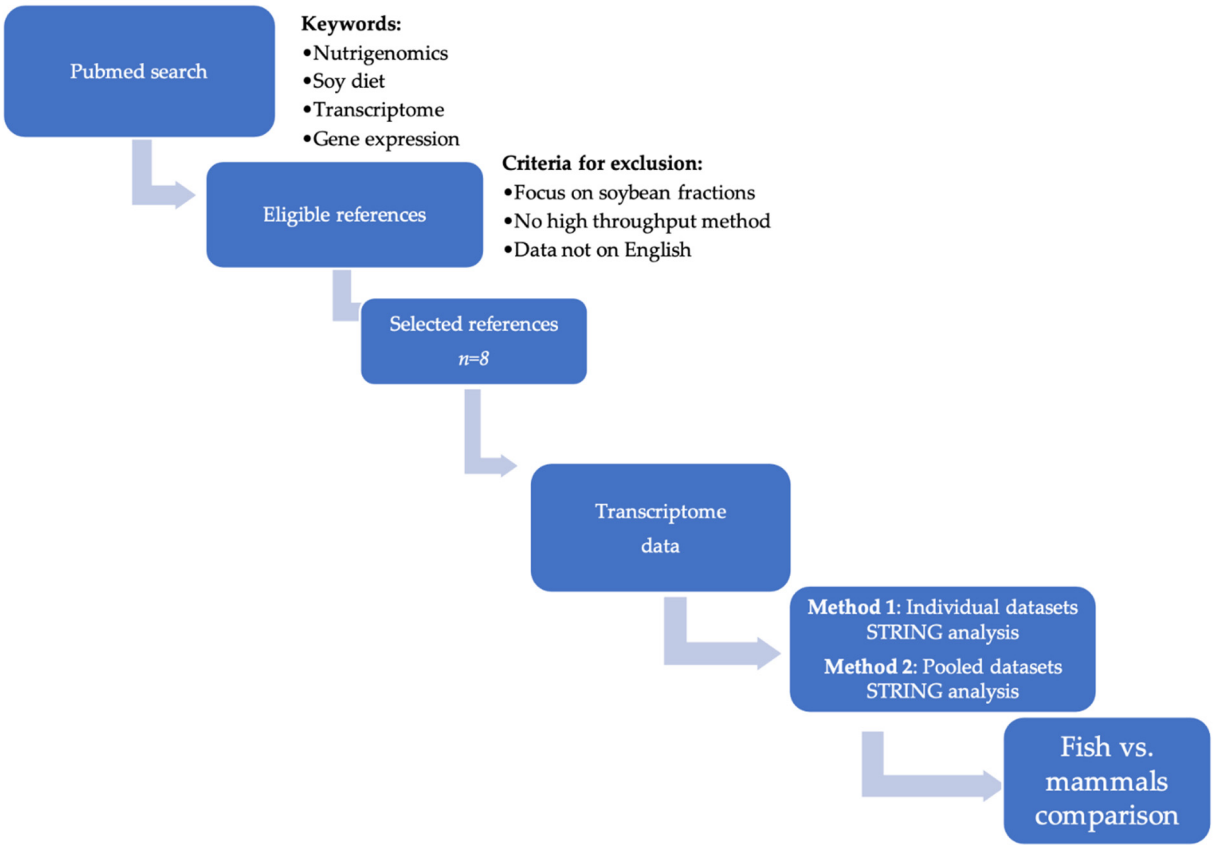

Figure 1. Flowchart displaying the process of our systematic review study.

3. Results

To our surprise, only eight reports matched our selection criteria and could be roughly divided into fish (four studies) and mammals (four studies). After removing the duplicates and the low confidence transcripts, the expression of 1.779 genes were reported as significantly altered in mammals, of which 838 (47.1%) were downregulated and 941 were upregulated. In the fish group, the expression of 1.524 genes was reported as significantly changed, of which 932 (61.1%) were downregulated and 592 were upregulated. The ratios between upregulated and downregulated genes in the two phyla are significantly different (p-value for the Z test < 0.00001). After combining fish and mammal data, 1770 (53.6%) genes were downregulated, and 1533 were upregulated upon soy diet intervention. All the upregulated and downregulated genes for both phyla groups and the commonly altered ones are shown in Supplementary Table S1. To better understand the biological significance of these changes, we decided to use two methods of analysis.

We submitted each set of reported data to STRING analysis (using a medium confidence interaction score of 0.400), focusing on retrieving the enriched KEGG pathways (FDR < 0.05). We have chosen STRING, since it builds gene interaction networks based on experimental and co-expression data, thus reducing the noise inherent to expression data from multiple cell/tissue types. The gene networks obtained are of relatively low complexity, with statistically significant protein–protein interaction (PPI) enrichment obtained for only six datasets. Overall, 67 KEGG pathways in mammals and 72 KEGG pathways in fish are potentially altered by soy enriched diet, of which 22 are common to both phyla (Table 2). These common pathways might represent a response to the soy diet conserved between fish and mammals and include metabolic pathways, biosynthesis of unsaturated fatty acids, steroid biosynthesis, fatty acid metabolism, fatty acid elongation, retinol, and xenobiotic metabolism. These pathways include most of the candidate genes for diabetes, atherosclerosis, regulation of lipid metabolism. Of note, the shared, potentially conserved pathways

are composed of different sets of altered genes, suggesting that distinct transcriptome changes mediate these common metabolic effects.

Table 2. STRING analysis of individual datasets (Method 1).

Common Pathways for Downregulated Genes	Common Pathways for Upregulated Genes	Common Pathways in Fish vs. Mammals (Up and Down DEGs)
Drug metabolism-other enzymes	Biosynthesis of unsaturated fatty acids	PPAR signaling pathway
Peroxisome	Phagosome	Steroid biosynthesis
Retinol metabolism	Proteasome	Drug metabolism-other enzymes
Biosynthesis of amino acids	Metabolic pathways	Arginine and proline metabolism
Metabolism of xenobiotics by cytochrome P450		Peroxisome
Drug metabolism-cytochrome P450		Metabolic pathways
PPAR signaling pathway		Biosynthesis of unsaturated fatty acids
ABC transporters		Retinol metabolism
Arginine biosynthesis		Metabolism of xenobiotics by cytochrome P450
Metabolic pathways		Fatty acid elongation
Steroid hormone biosynthesis		Pentose and glucuronate interconversions
Arginine and proline metabolism		Glutathione metabolism
Alanine, aspartate and glutamate metabolism		Phagosome
Pentose and glucuronate interconversions		Apoptosis
Glutathione metabolism		Carbon metabolism
Carbon metabolism		Glycine, serine and threonine metabolism
Ascorbate and aldarate metabolism		ABC transporters
		Drug metabolism-cytochrome P450
		Proteasome
		Arginine biosynthesis
		Alanine, aspartate and glutamate metabolism
		Biosynthesis of amino acids

Given that due to their size not all datasets allowed a successful STRING analysis, we performed a STRING/KEGG pathway enrichment analysis on pooled transcriptome data from fish, respectively, mammal samples. The gene interaction networks were of higher complexity, with significantly higher PPI probabilities, thus richer information. Nevertheless, the KEGG pathway analysis results were similar: 61 KEGG pathways in fish, 55 pathways in mammals, of which 23 are common to both phyla (Table 3). The two analysis methods (Method 1 and Method 2) lead to 16 KEGG pathways that are common between fish and mammals (Figure 2). See Supplementary Table S2 for all the DEGs corresponding to each Common KEGG pathways of individual and pooled datasets (Method 1 and Method 2).

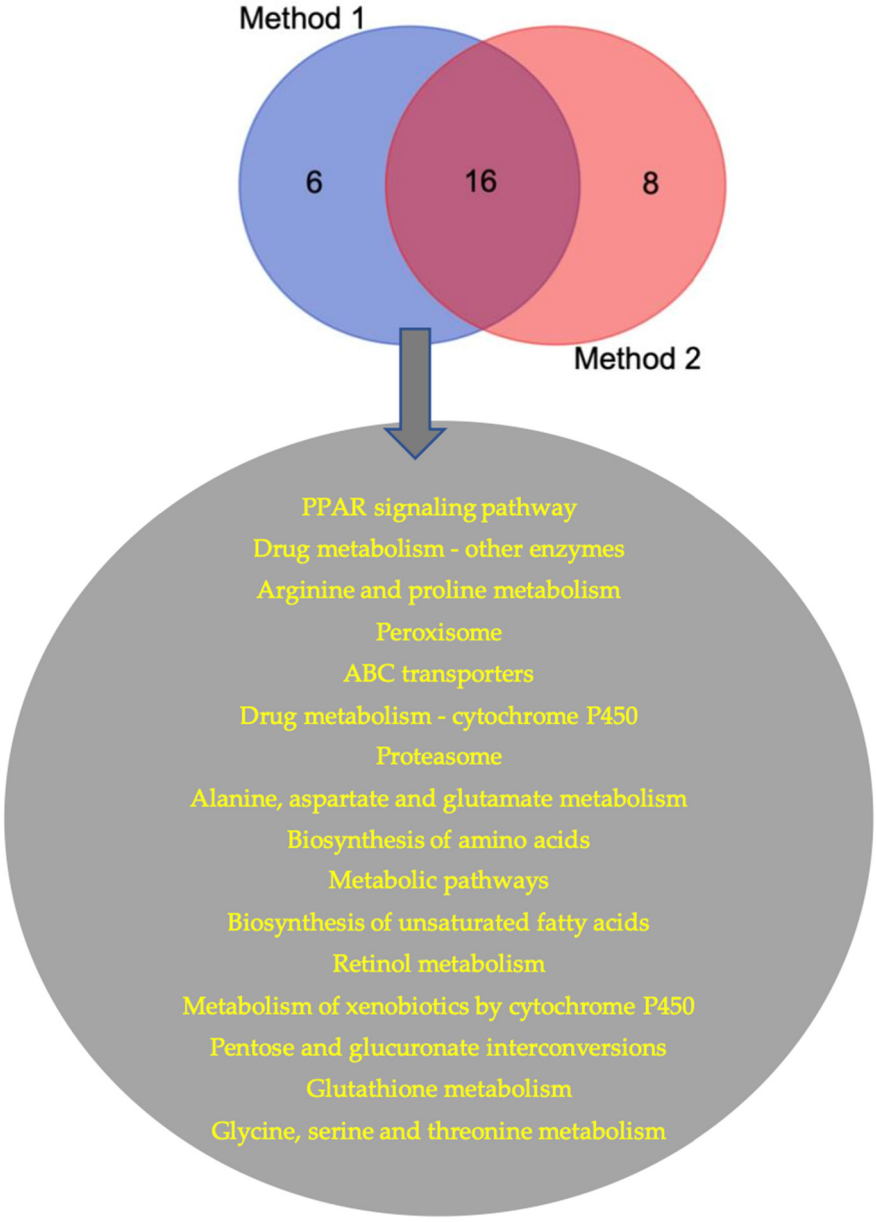

Figure 2. Venn diagram showing common KEGG pathways between mammals and fish (Method 1: blue circle; Method 2: red circle).

Table 3. STRING analysis of pooled datasets (Method 2).

Common Pathways for Downregulated Genes	Common Pathways for Upregulated Genes	Common Pathways in Fish vs. Mammals (Up and Down DEGs)
Drug metabolism-other enzymes	Biosynthesis of unsaturated fatty acids	PPAR signaling pathway
Peroxisome	Protein export	Steroid biosynthesis
Retinol metabolism	Proteasome	Drug metabolism-other enzymes
Biosynthesis of amino acids	Metabolic pathways	Metabolic pathways
Metabolism of xenobiotics by cytochrome P450		Biosynthesis of unsaturated fatty acids
Drug metabolism-cytochrome P450		Retinol metabolism
PPAR signaling pathway		Metabolism of xenobiotics by cytochrome P450

Table 3. *Cont.*

Common Pathways for Downregulated Genes	Common Pathways for Upregulated Genes	Common Pathways in Fish vs. Mammals (Up and Down DEGs)
ABC transporters		Fatty acid metabolism
Porphyrin and chlorophyll metabolism		ABC transporters
Metabolic pathways		Drug metabolism-cytochrome P450
Steroid hormone biosynthesis		Pentose and glucuronate interconversions
Arginine and proline metabolism		Glutathione metabolism
Alanine, aspartate and glutamate metabolism		Peroxisome
Pentose and glucuronate interconversions		Glycine, serine and threonine metabolism
Glutathione metabolism		Proteasome
Carbon metabolism		Alanine, aspartate and glutamate metabolism
Ascorbate and aldarate metabolism		Ascorbate and aldarate metabolism
Glycolysis/Gluconeogenesis		Glycolysis/Gluconeogenesis
Ferroptosis		Ferroptosis
		Protein export
		Biosynthesis of amino acids
		Porphyrin and chlorophyll metabolism
		Arginine and proline metabolism

Next, in order to find the pathways upon which the soy supplementation has an ambiguous effect in both fish and mammals, we stratified the data in upregulated and downregulated DEGs and performed separate STRING analyses. In fish, the up vs. down analysis found 10 pathways, while in mammals, only three pathways were found (of which, only the metabolic pathway is shared between the two phyla) (Table 4).

Table 4. Ambiguously changed KEGG pathways (found both up and downregulated in fish and mammals).

Up vs. Down Common Pathways in Mammals	Up vs. Down Common Pathways in Fish
Metabolic pathways	Metabolic pathways
Autophagy-animal Hepatocellular carcinoma	Protein processing in endoplasmic reticulum Carbon metabolism Citrate cycle (TCA cycle) Amino sugar and nucleotide sugar metabolism Fatty acid metabolism Glyoxylate and dicarboxylate metabolism Starch and sucrose metabolism Glycosaminoglycan degradation PPAR signaling pathway

4. Discussion

Nutrients can act as dietary signals detected by the cellular sensors and influence gene expression and metabolite production [52]. The health benefits of whole soybean diet include protection against chronic diseases, including heart diseases, diabetes, and osteoporosis [15,16]. The molecular mechanisms responsible for these effects are still intensely debated. Interventional studies focused only on soybeans components (proteins, genistein, saponins) attempted to shed on into how soy diet affects gene expression but fail in reproducing the natural changes induced by a regular (every day) soybean-supplemented diet. Since whole soybean and soy protein are among the most widely used soy diet supplements, and, in an attempt to make our analysis relevant to naturally occurring humans' feeding regimens, we chose to include in our analysis the transcriptome data only from this kind of interventional studies.

Our comparative analysis of fish and mammal transcriptome data identified multiple common pathways potentially impacted upon soy diet intervention.

As expected, the metabolic pathway was enriched in all species and tissues, irrespective of the dietary intervention regimen, reflecting soy's overall well-known metabolic impact. However, the enrichment was also common for both downregulated and upregulated genes datasets, suggesting that the overall metabolic effect results from balancing subclusters of metabolic gene networks. Previous studies indicated that soy might have a serum cholesterol-lowering effect in humans when consumed at levels of 1.5–2 g per day [53]. The hypocholesterolemic action of the soy diet relies on reducing associated risk factors for cardiovascular disease by lowering low-density lipoprotein (LDL) concentrations, increasing HDL (high-density lipoproteins), and by inhibiting lipid peroxidation [54].

Nevertheless, we also found several discrepancies between fish and mammals. In mammals, gene sets related to lipid catabolism were upregulated after soy dietary intervention. Both *Acacb* (Acetyl-CoA carboxylase 2), which is responsible for fatty acids oxidation [55], and *Ces1d* (Carboxylesterase 1D), whose function is to hydrolyze triacylglycerols and monoacylglycerols [56], were overexpressed. On the other hand, genes involved in cholesterol biosynthesis (such as *Cyp2c23* or *Cyp2c11*, members of cytochrome P450, subfamily 2) were repressed. *Cyp2c11* is an essential component of steroid hormones and fatty acid metabolism and a biomarker for hypertension [57]. We also noticed the downregulation of *Lipc* (Lipase C), involved in the conversion of very-low-density lipoproteins (VLDL) and intermediate-density lipoproteins (IDL) to low-density lipoproteins (LDL) [58]. Its repression is associated with a delay in atherosclerosis in mice [59].

While the hypocholesterolemic effect of the soy diet in mammals was expected, the impact in fish is puzzling, especially regarding cholesterol homeostasis. *Sc5d* (Sterol-C5-desaturase-like), *fdft1* (Farnesyl-diphosphate farnesyltransferase 1), *acat2* (Acetyl-CoA Acetyltransferase 2) are genes involved in cholesterol synthesis and absorption, and they were all upregulated with over 2-fold changes. Cytochrome P450 lanosterol 14α-demethylase (*cyp51*), a key enzyme responsible for an essential step in the biosynthesis of sterols, was increased [60] while *cyp7a1* (cholesterol 7-alpha-hydroxylase), an enzyme that oxidizes cholesterol, was decreased.

Rainbow trout subjected to plant-based diet interventions show enhanced hepatic cholesterol synthesis mediated by *srebp-2*, *lxr-α* (liver X receptor alpha), and miR-223 [61]. Physiologically, when dietary cholesterol level is low, *cyp7a1* is downregulated by Srebp (sterol regulatory element-binding protein) [62], which leads to an increase in the hepatocytes' cholesterol level [63]. It is possible that the soy-induced upregulation of cholesterol biosynthesis is meant to compensate for its dietary lack and thus maintains cholesterol homeostasis [50].

We also found that the biosynthesis of unsaturated fatty acids, fatty acid metabolism, and fatty acid elongation pathways were also highly enriched. In rodents, *acot1*, *acot2*, *acot3* (Acyl-CoA thioesterase), and *acaa1b* (Acetyl-Coenzyme A acyltransferase 1), enzymes responsible for acyl-Coa and acetyl-CoA hydrolysis were upregulated [64]. Although the role of Acot enzymes in fatty acid metabolism is not fully understood, they are considered a key element in maintaining an optimal level of fatty acids' beta-oxidation [65]. In fish, we noticed a possible activation of these lipids' pathways. *Fads2* (Fatty acid desaturase 2), known to catalyze the biosynthesis of fatty acids [66], is upregulated, while genes such as *hadha* and *hadhb* (hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex), essential for fatty acid oxidation, are downregulated. They are all essential components of the multistep process that breaks down fat molecules and converts them into energy [67]. The well-known impact of soy intake on lipid metabolism in mammals (reduction in hepatic lipotoxicity by preventing the transport of fatty acids to extra-adipose tissues) might thus be explained by these coordinated transcriptome changes [68]. One should nevertheless take into account that the response to soy diet is tissue-specific: reduced lipogenesis in the liver [69], increased unsaturated fatty acid biosynthesis (monounsaturated fatty acids, polyunsaturated fatty acids, C18:1 *trans*-11, C18:2 *trans*-10, *cis*-12, *omega*-3) in the mammary

gland [70]. As for the 240 fatty acid metabolism gene alterations in fish, we noticed changes that suggest an increase in fatty acid biosynthesis in the intestine. Since dietary fatty acids are taken up by enterocytes, resynthesized into triacylglycerol, and stored as lipid droplets, it is conceivable that the lipids-poor soy-rich diet increases intestinal fatty acid metabolism in an attempt to maintain lipid homeostasis [68].

Closely related to cholesterol metabolism, steroid hormone biosynthesis is another pathway common to fish and mammals. Rodent *Cyp4A14*, a member of the cytochrome P450 monooxygenases family, considered female-predominant [71], was overexpressed in the liver. Moreover, genes such as *Hsh17b* (hydroxysteroid 17-beta dehydrogenase family), involved in androgen and estrogen metabolism [72], were deregulated. In mammals, *Hsh17b6* (essential for dihydrotestosterone-DHT-biosynthesis and involved in the pathophysiology of Polycystic Ovary Syndrome) [73] was downregulated. In fish, *hsh17b7*, involved in the activation of estrogens (estrone to estradiol) and inactivation of androgens (dihydrotestosterone to androstanediol), was overexpressed [73]. Estradiol stimulates breast carcinogenesis while dihydrotestosterone (DHT) inhibits it [74]. Hence, the anti-carcinogenic effect of the soy diet might be explained by the modulation of *17β-HSD* (17β-hydroxysteroid dehydrogenases) gene activity in breast cancer cells through its phytoestrogenic effects, presumably mediated by Genistein's high affinity for the estrogen receptor [75,76].

Another expected fish-mammal common pathway targeted by the soy diet is retinol metabolism. Retinoids are obtained solely from the diet (and soybeans are rich in vitamin A), being required for maintaining normal growth, development, reproduction, vision, and a healthy immune system [77]. The clinical use of retinoids is known to induce hypertriglyceridemia [78], a side effect that could be counteracted by soy protein diet supplementation since soy is known to inhibit signaling through RAR-beta (Retinoic acid receptor beta) in the liver [78,79]. One should add that in the analysis of the fish dataset, we noticed a downregulation of *retsat* (retinoid saturase). *Retsat* has an important role in adipogenesis (promotes normal differentiation) and is downregulated in obese mice and humans [80].

Both phyla showed a downregulation of several UGT (UDP-Glucuronosyltransferases) superfamily genes. Based on current knowledge, xenobiotic metabolism (common among mammals and fish) is one of the main pathways altered by the soy diet [81]. UGT enzymes are essential members of phase I and II drug metabolism, which convert endogenous and exogenous lipophilic metabolites into more polar, less toxic, and easy to excrete compounds. They are often considered modulators for xenobiotics and steroids, thereby controlling their potency and availability [82]. We noticed downregulation of various genes from UGT1 and UGT2 families; since phytoestrogens' most important detoxification pathway is glucuronidation, this effect (most probably mediated by genistein) explains the pro-estrogenic role of soy diet supplementation [71]. Soy-induced diet inhibition of UDP-glucuronosyltransferases genes might increase the toxicity of anti-cancer drugs and contribute to drug resistance of cancer cells [83–85].

One of the fish-mammal common pathways, found enriched after STRING analysis of the pooled datasets (Method 2) is ferroptosis. Ferroptosis is a unique iron/ROS-dependent form of cell death driven by the accumulation of iron-dependent lipid peroxidation products [86]. Fe^{3+} is imported into the cell through TFR (transferrin receptor) and then reduced to Fe^{2+}, released in the cytoplasm by SLC11A2 (Solute Carrier Family 11 Member 2) metal transporter [87]. Ferroptosis is a natural tumor suppressor pathway and plays a significant anti-cancer role [88]. In our study, multiple inhibitors of ferroptosis, such as *Slc7a11* (Solute Carrier Family 7 Member 11), *Alox15* (15-lipoxygenase), and *Ftl* (Ferritin Light Chain) were found downregulated. Recent studies demonstrated that the overexpression of *Slc7a11* promotes tumor growth by suppressing ferroptosis [89]. By increasing iron uptake and reducing iron storage, the soy diet might promote ferroptosis; this could explain the reports linking soy diet to anti-tumoral effect and provides yet another strategy for cancer therapy. Moreover, the soy diet could counteract the age-related accumulation of iron stores, decreasing the risk for cardiovascular diseases [90].

An aspect that is often forgotten is that the soy diet has been shown to modulate the levels of specific mature microRNAs. Thus far, only two reports have assessed the relationship between soy intake and the changes in miRNA expression in mammals. Guo et al. evaluated the association of long-term (one year), pre-diagnosis soy consumption with the expression of miRNAs in patients diagnosed with triple-negative breast cancer (TNBC) [47]. A long-term soy diet was associated with strong upregulation of 13 microRNAs, including the well-known tumor suppressor miR-29a-3p. Seclaman et al. examined the liver of soy-fed male mice [46] and described the transcriptome impact of upregulated miR-145a-5p and miR-455-3p. Interestingly, the transcriptome analysis identified iron metabolism and xenobiotic/fatty acid metabolizing pathways as coordinately regulated by the two microRNAs. To the best of our knowledge, this is the first soy interventional study indicating that soy induced transcriptome changes might be due to post-transcriptional regulatory mechanisms. It is also worth noting that the conserved miR-150-5p was found to be upregulated in both studies, despite the differences in tissue analyzed (breast cancer cells vs. normal liver), duration of soy-diet (one year vs. one month), and species analyzed (humans vs. mice). This might suggest that miR-150-5p is part of mammals' common, evolutionary-conserved transcriptome response to soy-enriched diet. Of note, besides its role in lipid and iron metabolism, miR-150-5p is also known to be involved in carcinogenesis [91,92].

Taken together, these findings indicate that the soy diet induces significant gene expression responses in different experimental models, an effect that could be modulated at both transcriptional and post-transcriptional levels. The best-known transcriptional factors mediating soy transcriptional effects are RICTOR (rapamycin-insensitive companion of TOR, complex 2) and SREBF1 (sterol regulatory element-binding transcription factor 1) [45,46]. The soy-induced suppression of these two transcription factors protects against insulin resistance and fatty liver [93,94]. CEBPD (CCAAT/enhancer-binding protein delta), a transcriptional regulator that acts as a tumor suppressor, is strongly induced by soy-diet, which might explain the repression of multiple oncogene targets [39]. On the other hand, the impact on microRNA expression indicates that soy-induced gene regulation also involves post-transcriptional mechanisms [46,47].

Significant data show that diet might lead to epigenetic changes such as DNA methylation or histone modifications [95]. Genistein has been shown to induce specific DNA methylation changes in rodents by altering coat color and protecting mice offspring from obesity [96]. Additionally, epigenetic changes associated with the soy diet were observed in primates [97,98]. Howard et al. described an interesting pattern of DNA methylation for seven primate genes, among which, unexpectedly, the homeobox genes. These changes were then related to lipid and glucose metabolism modifications, suggesting increased insulin sensitivity [97]. Moreover, epigenetic changes in Hox genes can affect a variety of cancers [99].

By analyzing the similarities and differences of soy-related transcriptome impact in several experimental models and tissues, this review is an attempt to better understand the gene expression changes induced by soy diet. Taken together, the transcriptome data analyzed here fully support the already known benefits/risks associated with the soybean diet. On the one hand, the common responses of fish and mammals (such as retinol, xenobiotic or ferroptosis pathways) under different experimental conditions point towards a possibly conserved transcriptome response to soy diet. On the other hand, we found some evident discrepancies between the two phyla regarding cholesterol and fatty acid pathways. Some pathways, such as cancer-related pathways (bladder cancer, breast cancer, endometrial cancer) or thyroid hormone pathways, were enriched only in mammals, while others (glucose and amino acids metabolism), surprisingly, only in fish. Furthermore, it would be interesting to monitor miR-150p association with soy diet data in other, more complex experimental setups.

It should also be pointed out that, by restricting our analysis to transcriptome analyses upon whole soybean/soy proteins dietary interventions, only eight datasets were finally

included. Some of the datasets included did not support an enrichment analysis due to their small size. Although still more data are required to fully understand the link between soybean nutrients and gene expression changes, this review could be a helpful tool for further research.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/app11177905/s1, Table S1: Upregulated and downregulated genes for both phyla groups; Table S2: DEGs corresponding to Common KEGG pathways (Method 1 and Method 2).

Author Contributions: Conceptualization: M.S.-C., I.O.S., Investigation: A.A., C.S. and C.M.; Methodology: M.S.-C., I.O.S.; formal analysis: A.A., M.S.-C.; writing—original draft preparation: M.S.-C., I.O.S.; writing—review and editing: M.S.-C., I.O.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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