universität wien

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„Hepatotoxicity related target side effect association“

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1. INTRODUCTION

1.1 Aim of the thesis

Many scientific publications give the connection between adverse drug reaction and a specific substance or drug. Despite that, most of those publications and databases hold no information of the direct possible side effects connected to certain targets. Because the topic is widespread and adverse side effects are uncountable this study focusses on hepatotoxic side effects. Hepatotoxicity is of interest for pharma industries, medical staff, patients and researchers. Understanding the underlying mechanisms of toxicity better, could save thousands of lives. Many of them are not fully understood yet, but it is known by scientists that one substance is able to attack even multiple targets. If it is possible to bring the targets in direct connection with the adverse drug reaction it would save time, lives, and money. So, the aim of this study is to give an overview of proteins which are directly related with hepatotoxic side effects.

1.2. The role of the liver

The liver is an essential organ in a living organism and responsible for the biggest part of the metabolism. It lies in the upper abdomen in the human body, has a brown-reddish colour and consists of two main lobes. The liver is unique among our internal organs. It has the incredible ability to regenerate after a damage of two-thirds or even more of its volume. Furthermore, it has the astounding ability to regrow to its original size. [1] It has several functions like bile production and excretion, storage of glycogen and vitamins and many more to count. Detoxification of xenobiotics is one of the most important tasks.

Remarkable liver enzymes like the Cytochrome P450 (CYP) family are responsible for these detoxification mechanisms. Many of them catalyse the detoxification of xenobiotics, by forming hydrophilic metabolites. Those can be easily excreted from the body. [2]

Many chemicals undergo metabolism in the liver but are not hepatotoxic. Some exceptions can despite be harmful. CYPs can produce reactive toxic metabolite species in some cases. Those toxic metabolites can be formed and accumulated within hepatocytes as a result of oxidation, reduction, conjugation, and other processes which normally serve to remove or detoxify xenobiotics. [3] Instead of undergoing the normal detoxification pathway, they can act as

irreversible CYP inhibitors or metabolize the component in a more toxic one. [2] The formation of toxic or reactive substances such as electrophilic chemicals or free radicals lead to toxic effects. [4] The liver has several mechanisms for the metabolism of xenobiotics. If those mechanisms are unbalanced or disturbed and the clearance of xenobiotics is retarded the risk of toxic effects is increased.

1.3. Toxicity and Hepatotoxicity

Some medical agents may injure the organ. Therefore, drugs have to be carefully tested before being used in living beings to avoid severe side effects. However, in some cases the hepatotoxic effect is not predictable.

As most people know toxic effects are related with its dose. Even known as safe drugs can lead to toxic effects and be harmful when its dose is too high. Already Paracelsus stated that: "*Sola dosis facit venenum*"-Only the dose makes the poison. "Idiosyncratic drug-induced liver injury (DILI) is traditionally thought not to be dose-related. However, it has been pointed out that most medicines that were withdrawn from marketing or received a black-box warning because of hepatotoxicity were prescribed at daily doses greater than 50 mg/day." [5] The manifestations of DILI are highly variable, ranging from asymptomatic elevation of liver enzymes to fulminant hepatic failure.

DILI causes up to 40 percent of liver transplantation and hepatic failures. [6] In the worst case it can even lead to the death of the patient. It is the most frequent reason for withdrawal of an approved drug from the market. About 25 percent of the drugs are withdrawn from the market related to liver damage. [7] Moreover, it is a common reason for failure of drugs during preclinical and clinical development. [3] So, before a drug is registered and gets on the market a lot of clinical research is done.

Suzuki et al created a drug list from DILI and labelled categories based on the drugs withdrawn owing to hepatotoxicity, acute liver failure association and DILI association. [8] O'Brien et al classified drugs into four categories according to the severity of human hepatotoxicity based on the frequency of an observed increase in ALT and other evidence. [9] In clinical settings serum ALT, AST and bilirubin are associated with liver toxicity. Liver toxicity manifestations are generally accompanied by nonspecific symptoms such as abdominal pain, jaundice, fever, nausea, vomiting, diarrhea, pruritus and rash. [10]

There is a great number of risk factors including intrinsic drug properties like molecular weight and hydrophobicity. Furthermore drug-related impact on biological functions such as inhibition of transport proteins and mitochondria, and drug pharmacokinetic parameters such as daily dose and plasma concentration.

Hepatotoxicity is one of the most occurring and cited side effects of drugs. "Hepatotoxicity is a common finding for NRTIs, anticancer drugs, antibiotics, drugs used in various CNS applications, as well as biologics, immune-suppressants, and steroids." [11] The complexity of hepatotoxicity is related with its multifactorial underlying mechanisms. Most of them are not fully understood yet due to the lack of suitable in vivo and in vitro data. Such data could be used for prediction. Although, it is not only about structure of a compound but also environmental and genetic factors. "Evidence suggests, however, that there are four major modes of action: covalent modification of target proteins and oxidoreductive stress, immune-mediated reactions, interference with hepatobiliary export, and mitochondrial injury." [12]

The risk factors include idiosyncrasy, age, gender, alcohol consumption, concomitant use of other drugs, previous or underlying liver disease, genetic and environmental factors. Drugs, and natural products are alos associated with hepatotoxicity reactions. Some toxic effects are species specific. Fourches et al found out that the concordance of liver effects was low between different species and stated that different species could depend on specific features of chemical structure. [13] This states that animal studies are not completely predictive of human hepatotoxicity, because patient related risk factors like age, diseases, genetic predispositions can't be taken into account.

Hence the differentiation is intrinsic hepatotoxicity, which is dose related, and idiosyncratic hepatotoxicity, which seems to be unpredictable. Some molecular mechanisms are still remaining unclear, but others are well investigated. It is a complex phenomenon. Such mechanisms can directly result in damage to liver cells or they can initiate a cascade which will end also in damage to liver cells and toxic effects. It has to be taken into consideration that some side effects of drugs turn out to be beneficial but most of them are unwanted and injurious. However, some patients take drugs with well known side effects because the benefits outweigh the harm.

If its mechanisms could be understood in a better way, it would be easier to predict toxicity. Nowadays helpful tools to identify new and promising drugs are *in silico* methods which are used to predict hepatotoxicity. Structure-activity relationships (SAR, QSAR) have many advantages and are used to connect the structure of the molecule with its chemical and

biological activity to elucidate the toxicity of new and unknown substances. Structural alerts can thus be a powerful tool in helping to detect the toxic potential of a substance. It is hoped that the generation of predictive models for adverse drug reactions is able to help support early SAR to accelerate drug discovery and decrease late stage attrition in drug discovery projects. [14] It has to be acknowledged that there is no computer model which is absolute 100 percent predictive, but there are possible new ways to predetermine certain hazard substances.

However, in silico predictions of liver injuries needs trained personnel who will be able to build reasonable models. The computer program alone won't lead to success without human knowledge. Liver enzymes are an attractive biotechnological target in their use as biocatalysts for their ability to produce pharmaceuticals and drug metabolites. Since the initial discovery that covalent binding of acetaminophen to hepatic proteins was associated with hepatotoxicity, there has been a progression of techniques that have been used to identify the protein targets. [15]

If the underlying mechanisms could be understood, it would be easier to predict toxicity. Sometimes a certain drug initiates not one but multiple adverse outcome pathways leading to hepatotoxicity. It is a great advantage to know not only the drug, which causes the side effect, but also the targets of it. Those targets can then be avoided in the future and substances specifically tested against them.

1.4. Terminology of adverse drug reactions

Defined by the World Health Organization an "adverse drug reaction (ADR) is a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man." [16]

Liver disorders cover a wide spectrum of diseases of diverse terminology. Hepatotoxicity is an umbrella term for several other specific liver damages. The variety of terms concerning hepatic toxic effects are sometimes quite inextricable. For that purpose, detailed scientific vocabulary for adverse drug reaction terminology was assessed.

Some relevant databases for side effect vocabulary are MedDRA, WHO-ART, SIDER, ADRECS and MeSH.

1.4.1. MedDRA

The Medical Dictionary for Regulatory Activities Terminology (MedDRA) was established in 1990 because there was no standard international medical terminology. 1994 the ICH (=The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) adopted MedDRA Version 1.0 as basis for international terminology. Now it is available in different languages. It replaced the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART), which was a precursor for MedDRA.
MedDRA differentiates between thirteen types of DILI, including cirrhosis, acute hepatic failure, acute fatty liver with lactic acidosis, acute hepatic necrosis, nonalcoholic fatty liver, bland cholestasis, cholestatic hepatitis, acute viral hepatitis–like liver injury, autoimmune-like hepatitis, nodular regeneration, immunoallergic hepatitis, vanishing bile duct syndrome, and sinusoidal obstruction syndrome.
The terms are classified in 5 hierarchical ranks. They are named System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT), Preferred Term (PT) and Lowest Level Term (LLT).
MedDRA has in total 26 system organ classes in which the fifteenth class is related with all liver terms. It is used by drug authorization in some countries.

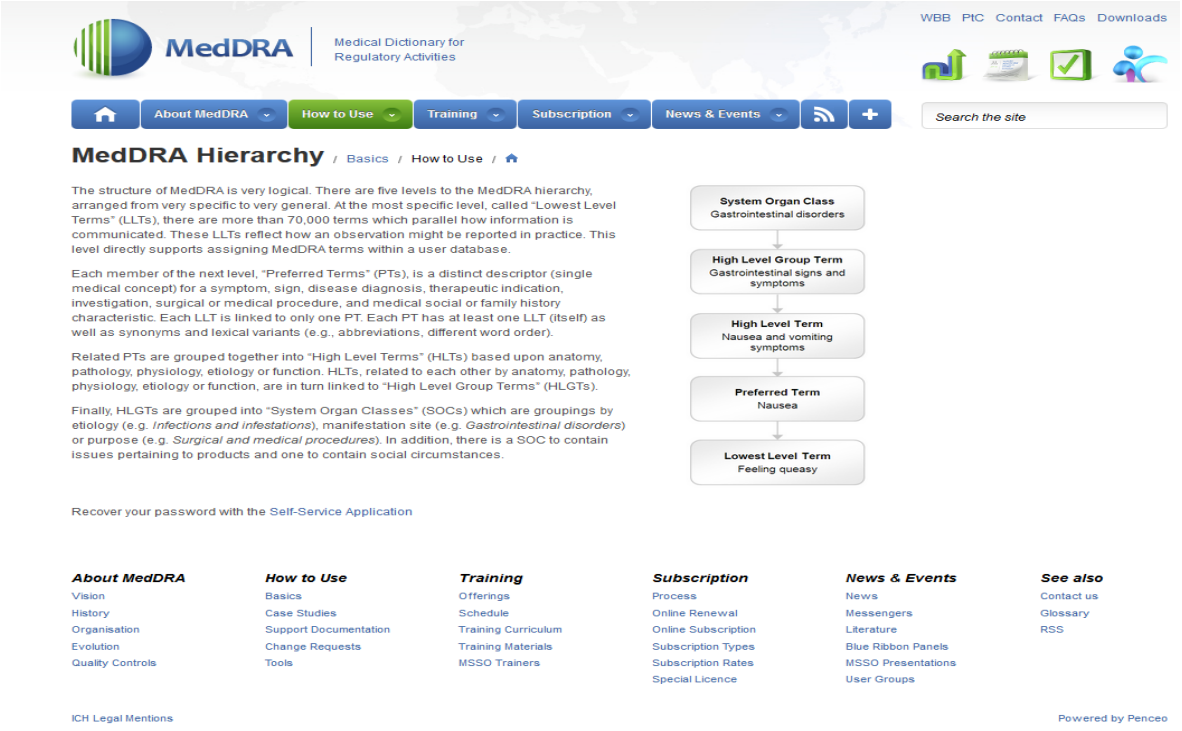

Figure 1: Screenshot of MedDRA homepage (29.08.2017)

1.4.2. WHO-ART

The World Health Organization's Adverse Reaction Terminology (WHO-ART) was developed over thirty years. The structure is divided in thirty organ classes with a code number system. Liver and biliary system disorders are encoded in number 0700. It was mainly superseded when MedDRA was established and is no longer actively maintained.

1.4.3. SIDER

Side Effect Resource which is better known as Sider is a database which contains free information of the connection of recorded side effects and the marketed drugs which cause that effects. Sider 4.1 is the latest version, which even holds information about some of the drug targets, but the direct connection between side effect and target is not given. Over a detour you get the information with the substance as a mediator. The adverse drug reactions are listed alphabetically.

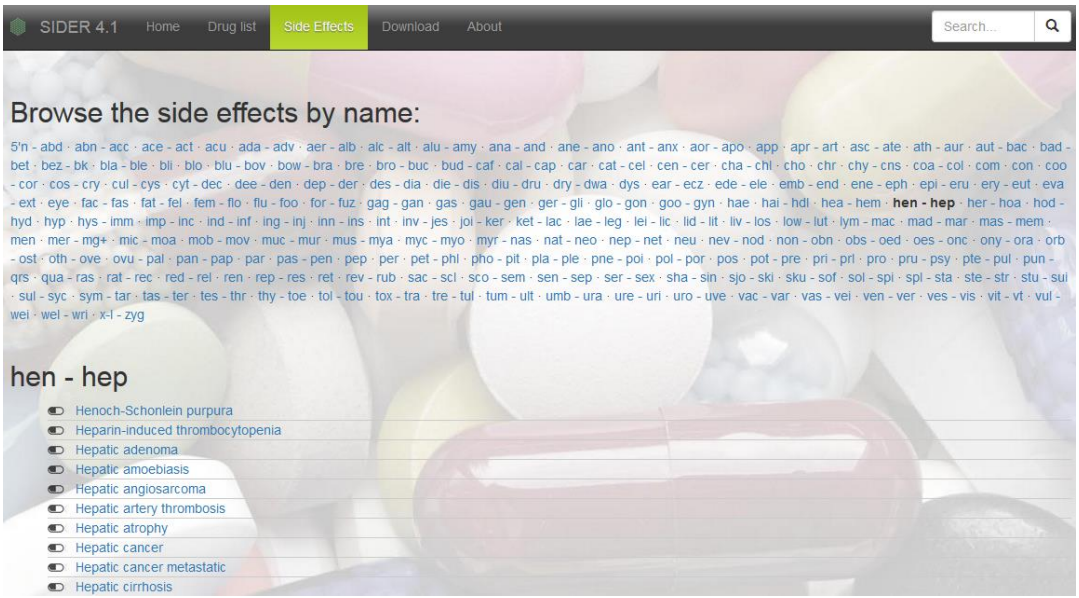

Figure 2: Screenshot of SIDER homepage (07.05.2019)

1.4.4. MeSH, UMLS, SNOMED CT

The Medical Subject Headings (MeSH), Unified Medical Language System (UMLS) and Unified Medical Language System (SNOMED CT) are Medical Terminologies of the US National Library of Medicine. (US NLM). MeSH is the vocabulary thesaurus of the US NLM. It has also a hierarchical structure of terms and is used for indexing articles in PubMED. It was not actively used during this diploma thesis but should be mentioned for consistency and completeness.

1.4.5. ADReCS

A very interesting and good structured database is the *Adverse Drug Reaction Classification System* of the Bioinformatics Research Group of the School of life sciences of the Xiamen Univesity Xiamen in China.

A unique ID of four digital combinations (xx.xx.xx.xxx) build the hierarchical sytem.

The formation is based on and integrates several other side effect databases like DailyMed up to 80 percent, MedDRA, SIDER2, DrugBank, PubChem and UMLS. It is an open source database and has a very user-friendly interface. It contains 6544 ADR terms and has several tools like structural search tool, drug search by complete or partial SMILES string, chemical structure can be drawn or uploaded. [16] This database uses their own classification system of terms of adverse drug reactions which is basically based on the World Health Organization (WHO) Classification of ADRs.

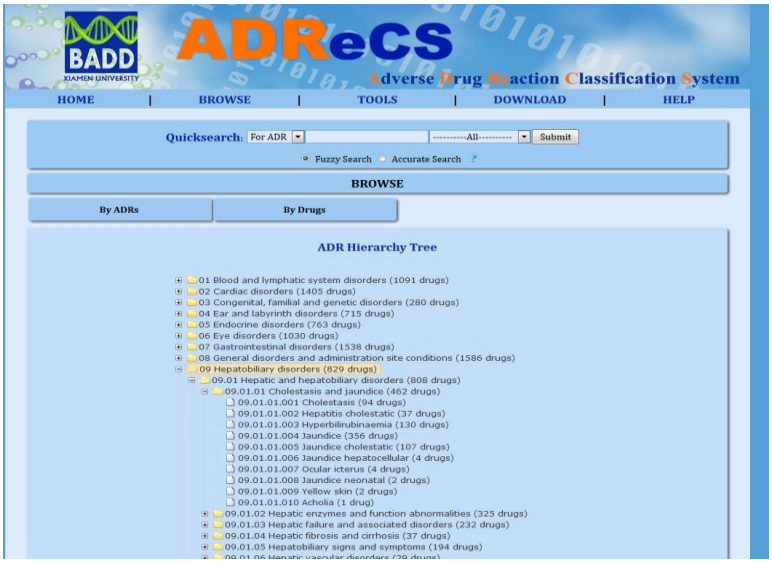

Figure 3: Screenshot of ADReCS homepage (15.08.2017)

2. METHODS

2.1. Databases

2.1.1. DART

Many databases already exist which relate drugs to adverse outcomes. Despite that, there are only a few which give the connection from the target to the toxic side effect. One of them is DART which stands for Drug Adverse Reaction Target Database. During the process of this thesis the database contains entries for 147 ADR targets and 89 potential targets and a total of 187 adverse reaction conditions. Furthermore, it holds information about 257 drugs, and 1080 ligands known to bind to each of these targets. Multiple search methods could be applied, so that target name, target physiological function, adverse effect, ligand name, and biological pathways can be extrapolated. [17] No information from DART was extracted for this thesis, but it is mentioned here for the sake of completeness of those databases specialised on adverse drug reaction and direct target connection.

2.1.2. DITOP

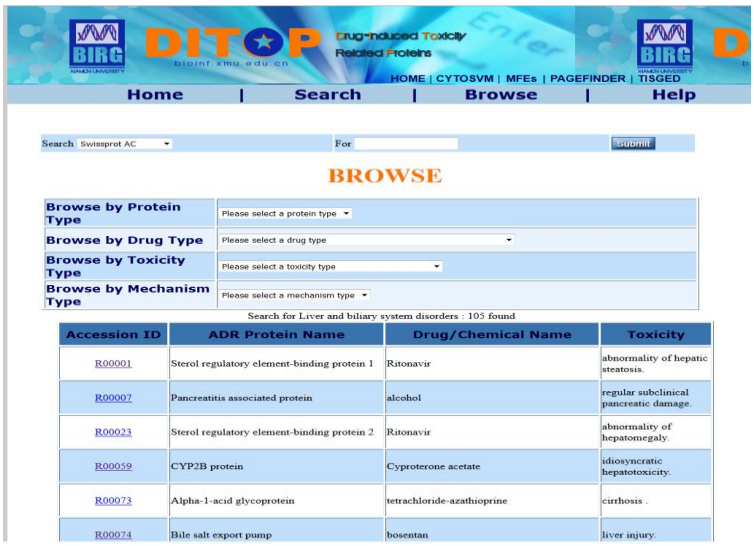

Figure 4: Screenshot of DITOPs searching function (14.07.2017)

Drug-Induced Toxicity Related Protein Database is another database connecting adverse outcome directly to the target. It was established from a research group of the Xiamen University in China. The database uses ADReCS adverse reaction terms because it was

established by the same University. On the 30th of March 2017 it was containing the following entries

Table A: List of targets in DITOP for ADRECS adverse reaction terms

Skin and appendages disorders :	21 found
Musculo-skeletal system disorders :	62 found
Autonomic nervous system disorders :	28 found
Central & peripheral nervous system disorders :	96 found
Autonomic nervous system disorders :	28 found
Vision disorders :	1 found
Hearing and vestibular disorders :	7 found
Special senses other, disorders :	1 found
Psychiatric disorders :	31 found
Gastro-intestinal system disorders :	67 found
Liver and biliary system disorders :	105 found
Metabolic and nutritional disorders :	59 found
Endocrine disorders :	15 found
Cardiovascular disorders, general :	108 found
Myo-, endo-, pericardial & valve disorders :	24 found
Heart rate and rhythm disorders :	27 found
Respiratory system disorders :	35 found
Vascular (extracardiac) disorders :	51 found
Red blood cell disorders :	6 found

In total there are 772 entries, but some targets are mentioned twice. Further, overdose toxicity, idiosyncratic toxicity, drug-drug interactions and genetic toxicity facts are provided. DITOP collects the literature-reported drug-induced toxicity related proteins and the information of adverse events. [18]

2.2. PubMed

PubMed is a United States database for medical and scientific articles. It has been established by the National Center for Biotechnology Information (NCBI). Every article has its own unique ID, which allows to search for articles very quickly. It contains 27 million records representing articles in the biomedical literature redirecting to full-length research articles, clinical trials databases, molecular biology data and links to publishers' Web sites. PubMed offers millions of abstracts for free. It acts as an intermediary and gives access to an enormous and steadily growing heap of information. As a huge meta-database it is undoubtedly a powerful source of gathered scientific information. [19] [20]

During the data mining for this work PubMed was used to collect information about hepatotoxicity. Therefore, vast amounts of publications were read, and information extracted into a list. The significant advantage lies in the fact that, because of the numerous articles, it is a source for a widespread search. Thence, it is possible to read a vast amount of articles. This means that in a fraction of time it was possible to get a good overview of the articles related to hepatotoxicity. This was one branch of how data for this work were rallied.

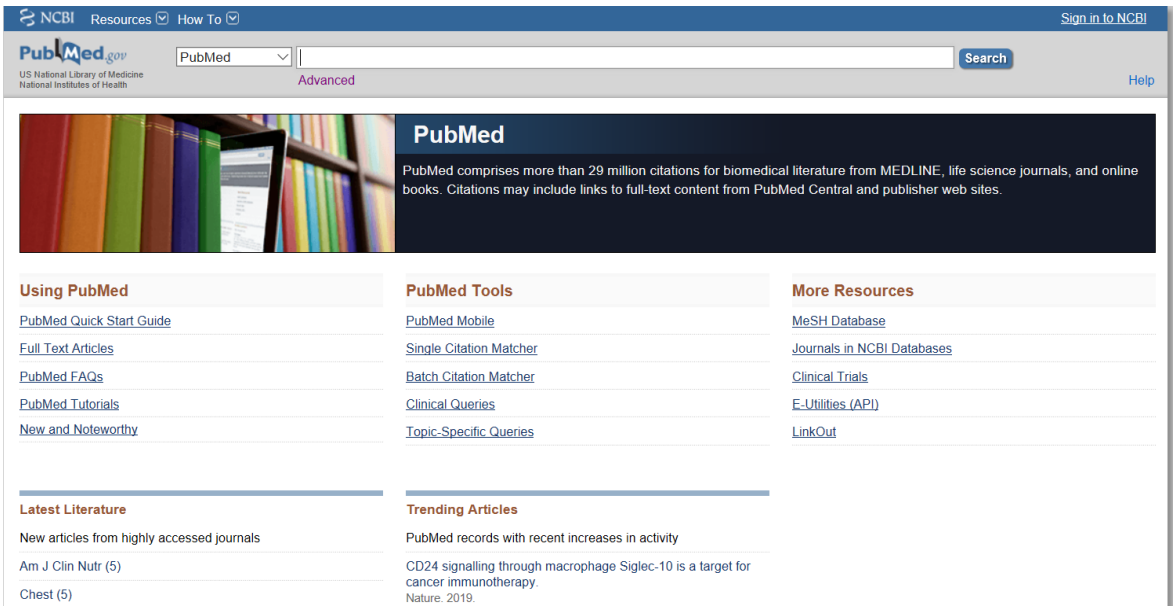

Figure 5: Screenshot of PubMed (15.06.2019)

2.3. KNIME®

KNIME® is an open source software. It can be used for every kind of statistic and is therefore suitable for all kind of different scientific tasks. The KNIME® Analytics platform allows to build multiple workflows. Huge data sets of information can be scanned, sorted, changed and practically used in short time. In the end there is the possibility to depict the result by modern graphics or diagrams.

The "Konstanz Information Miner" how it is called out spelled has its headquarters located in Zurich. Furthermore, they have offices in Konstanz, Berlin, and Austin. [21] It was outset in 2004 and at first not intentionally developed for chemo-informatics. Despite that, KNIME® has now a broad spectrum of contributors from software vendors, academia pharma and small biotechnical labs. [22]

KNIME® Analytics Platform offer workflow controls, mathematics & statistical functions, machine learning algorithms, advanced predictive algorithms, and other tasks. There is also the ability for image mining, text mining, and time series analysis. It has over 2000 modules and in addition, KNIME® Analytics Platform has numerous statistical functions and is capable of a variety of data types such as JSON, XML, documents, and images. Afterwards it is possible to analyse models and results easily. In the end the user can visualize the data with charts or other graphics. Besides that, it allows users to exchange workflows, build Web portals and create reusable workflows. During this research, KNIME® (version 4.3.2.) was used for different kinds of workflows.

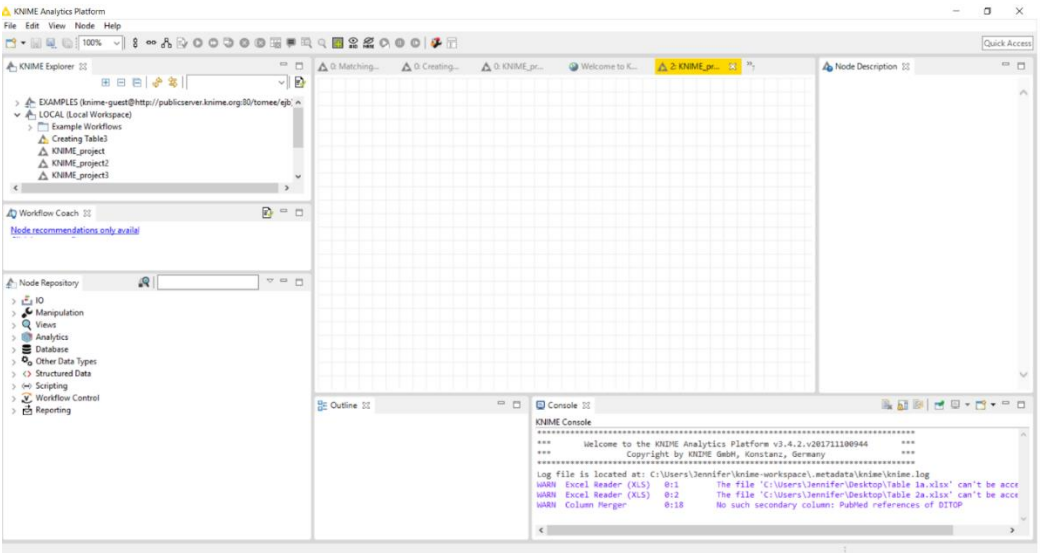

Figure 6: KNIME Analytics Platform working bench(17.07.2019)

At first all SIDER terms based on hepatotoxicity which were manually curated beforehand were uploaded by a file reader. The columns had to be renamed for further processing. Then the terms were grouped by its MedDRA numbers. A second branch of the workflow started with ADReCS terminology which was provided as an excel file. In the second node a row filter was used to receive all hepatotoxic terms and grouped them also by the MedDRA number. A "Joiner" matched the MedDRA numbers of those different start point branches. Then another filter was used to get the required terms. The output of the table was got by an excel writer and holds all terms related to liver damage.

The second workflow was used to create a detailed table of target proteins related to hepatotoxicity. The main project of this research is to get a better overview of all targets related to hepatotoxicity. The picture shows one of the workflows and its basic operational steps.

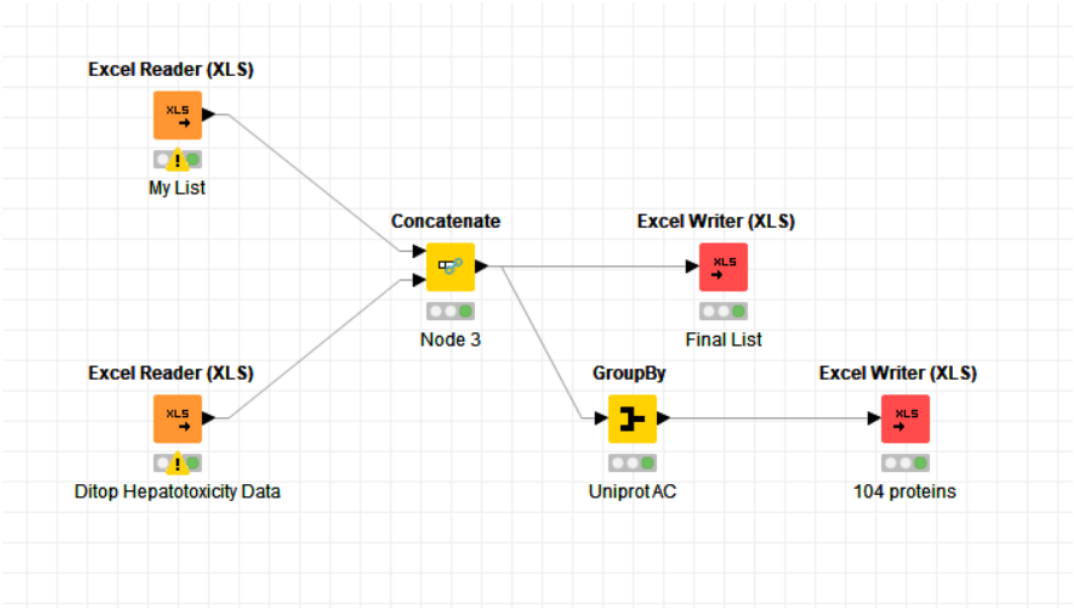

Figure 7: KNIME workflow Final Table overview

The first branch starts with DITOP data. The information was filtered by hepatotoxicity terms and then grouped by the Uniprot Accession numbers. This table was saved as an excel file per excel writer. The second branch starts with my list which is called "Table 1". It was grouped by the Uniprot Accession numbers and then joined with branch one. Now all targets are in one table, but a lot of colums were incomplete and difficult to work with. Via two more filter it was evident that there were 56 targets which were completely new and unique to DITOP. By means of a "table creator", "cross joiner", "manipulation", "column filter", "get request", "Xpath" and "Excel writer" it was possible to get the PubMed URL of every protein in one table. From that point it was necessary to manually curate the table. The result could be seen in picture 2.

After that another workflow with KNIME was made, "Table 1" was merged with "Table 2. The joined tables resume in a final table, which give enormous information. Those results will be discussed in the chapters below.

2.4. Creating the tables

At first scientific literature which is known for its antitarget- side effect content was the basis. The relevant information was extracted into a list. A lot of information was dragged from the two books "Antitargets" published by Roy J. Vaz and Thomas Klabunde [2] and "Antitargets and Drug Safety" edited by Urban, Patel and Vaz [3].

Starting from that point of view, most of the cited targets were directly searched for in PubMed. Most of them were collected from PubMed. Every article led to another one and so the mosaic of information was gained piece by piece. The citations of those publications lead also to more hepatotoxicity related articles. This method of collecting information was done until the list, which in the following is called Table 1, has 156 entries. An excel file was created and for every connection between a target and its adverse side effect a single entry was made. To make the list more useable for lateron additional information about the target was amended. Therefore, the abbreviation for every protein was given by the Uniprot Accession Number. Moreover, the Uniprot gene name was quoted. This information was manually extracted from Universal Protein Resource (UniProt). Uniprot is a database, which holds information about protein sequence and annotation data. Its codes for proteins are used worldwide. It holds over 120 million proteins and provide a global collection of protein sequences and annotations.

Every entry in Table 1 holds additional information like the organism in which this side effects was seen. The name of the publication, the publication year and the name of the journal in which it was published is also in the list. All entries in that list were labelled with S for STROBL, to distinguish those entries from the ones of DITOP in the following overlap.

It contains the most important headers for this target side effect information and some additional facts. To label the proteins with a relatively short number the Uniprot Identifyer was used. It is also called SwissProt and widely used worldwide.

The target and gene names are also adopted from Uniprot to make further edits easier. The header "organism" indicates the species at which the side effect was observed. In the column

"toxicity" the specific term which was used in the published text was used. Therefore, it can be compared. Because only targets with effects on the liver where used, most terms are related with hepatotoxicity. DITOP targets also have various terms.

Most of the referenced articles have a PubMed number, but some references refer to the previous mentioned books. To make sure an article can be found again the DOI number is mentioned. Some targets have other names in different publications and on this account, there is a column for other names of the target.

For a better understanding the circumstance in which a publication is embedded are essential. That is why in the list the Journal in which the article was published, the publishing date and the title is added also. The column "label" only refers to the proteins found by myself in literature to distinguish it from the DITOP data after merging the lists.

After creating the list (Table 1), it was combined with the DITOP list from Xiamen University to get a full overview of the targets related to hepatotoxicity.

The DITOP list is an EXCEL file received from professor Lihong Huang from Xiamen University. They do research on the topic of hepatotoxicity and bioinformatics for several years. The file contains information about 2202 listings of all kind of toxic side effects. This DITOP list has ten headers: RID, Drug name, Drug bank, Uniprot AC, ADReCS ID, ADR ID, ADR Term, Toxicity Detail, PMID, Species. Here a direct line can be drawn from the used drug to the side effect and further to the protein which is affected. from the DITOP data the hepatotoxicity related entries were extracted via KNIME. To work with the list KNIME was used to extract all the targets related to hepatotoxicity. 434 entries remained. This was achieved by manually curating the list. This could be done with the MedDRA codes for hepatotoxicity. An excel list remained with all those PubMed IDs. Via KNIME was the direct URL was connected to the ID. Afterwards each of this article was opened. The header and the publication date were extracted and formed a new list called Table 2. These entries all got the label D for DITOP because its origin was this database. With the help of the PubMed ID the list could be completed regarding the journal in which it was published, the title and the publishing year. Finally, those two tables were merged. Hence, KNIME was the medium of choice. The results are unfolded in the next chapter.

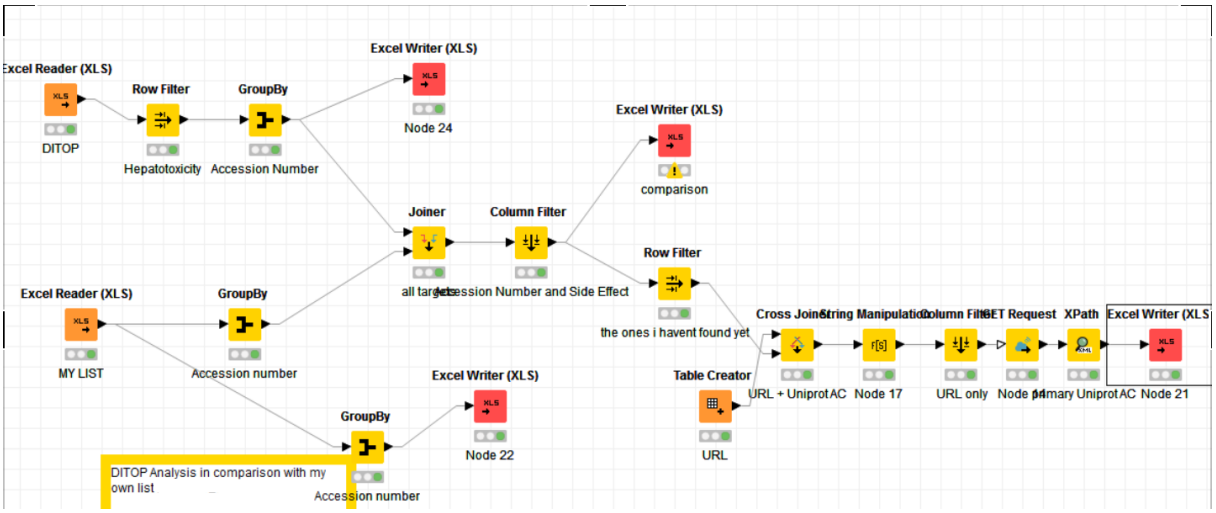

Figure 8: KNIME workflow to extract the hepatotoxicity related proteins out of the full DITOP list

3. RESULTS

3.1. Terminology of hepatotoxicity

Referring to nature.com hepatotoxicity is "damage or injury to the liver as a result of damaging or destructive agents such as drugs or industrial chemicals which are termed hepatotoxins" [24]. Hepatotoxicity is a term encompassing a wide variety of liver injuries. It stretches from acute to chronic damages like steatosis or necrosis up to elevation in serum enzymes, which can sometimes predict liver injury.

In the following table (Table B) is an excerpt of the terminology of adverse side effects mentioned in the final table. Therefore, all termes are sorted alphabetically. The table contains 42 terms. The number shows how often this term is counted in the final list. This gives an overview of the mostly used terminology of the mentioned published articles.

Table B: List of adverse side effect mentioned in terminal list of this work

Acute hepatic failure	7
Acute liver failure	1
Acute liver injuries	1
Adverse effects	1
Cardiac anaphylaxis	1
Cholestasis	37
Cholestasis and Jaundice	1
Cholestasis inPFIC1	1
Cholestasis of pregnancy	1
Cholestasis, DILI	1
Cholestatic liver disease	1
Could trigger intrahepatic cholestasis	4
DILI	8
Drug induced hepatitis	3
Dubin-Johnson-Syndrom	3
Expressed in liver , inducable, sensitive	1
Expressed in lung, placenta, lymphocytes	1
Hepatic cirrhosis	7
Hepatic encephalopathy	2
Hepatic failure	4
Hepatic function abnormal	36
Hepatic necrosis	7
Hepatic steatosis	36
Hepatitis	46
Hepatocyte necrosis	1
Hepatomegaly	4
Hepatotoxicity	233
Hyperbilirubinemia	1
Idiosyncratic liver toxicity	1
Jaundice	12
Liver disorder	22
Liver failure	1
Liver failure, fatal DILI	3
Liver injury	64
Lung injury	1
Metastases to liver	18
Porphyrin metabolism disorder	4
Prehepatic cholestasis	1
Progressive cholestatic liver injury	1
Progressive familial intrahepatic cholestasis	1
Progressive familial intrahepatic cholestasis type 1	1
Progressive familial intrahepatic cholestasis type 2	1

The most cited term is Hepatotoxicity, which is a widely used term and not very specific. Liver injury and Hepatic function abnormal are as well very unspecific terms. Cholestasis, steatosis ad hepatitis are listed often and are very specific.

Cholestasis is causes by various inbalanced physical ways resulting in accumulation of bile acids, bilirubin and cholesterol. It is a stagnation, or at least a reduction, in bile secretion and flow. There is the possibility of extrahepatic biliary obstruction (e.g. stones, tumors, biliary atresia) or on the other hand intrahepatic biliary obstruction (e.g. primary biliary cirrhosis, primary sclerosing cholangitis) or it can be intrahepatic cholestasis (e.g. drugs, genetic transporter defects, or infections). The physiological consequences of reduced intestinal bile acids include maldigestion of fat and malabsorption of fat-soluble vitamins. In the further process it can lead to apoptosis or necrosis of hepatocytes. hepatic fibrosis, cirrhosis and hepatic failure or the complications of portal hypertension.

Hepatic steatosis can be caused by nonalcoholic fatty liver disease (NAFLD), alcoholism, metabolic, toxic, and infectious causes like drugs or other diseases.

Jaundice, which is also known as icterus, describes a yellow discoloration of the skin and eyes. Mostly it is caused by increased serum bilirubin. Jaundice can happen to people of all ages. It normally indicates a problem with the liver or bile duct like inflammation, obstruction of bile flow or a handful of other diseases like for example Dubin-Johnson syndrome.

Acute liver failure can either happen by poisoning from toxins or drug overdose or viral infections, while at chronic liver failure inflammation progresses slowly and steadily. Often it is a result of former liver diseases like cirrhosis.

3.2.1. Hepatotoxicity related targets in manual curated list (Table 1)

Table 1 has in total 155 entries of targets. Every row in this table is referring to a protein mentioned in a certain publication. Only those proteins are collected which are connected to a hepatotoxic side effect. The adverse reaction terms used in this table rely on the terms of the publication from which they where extracted. Some terms are very specific, while others just use hepatotoxicity and not specialise. MedDRA encoded those terms in numbers, which makes it practicable to use and to compare. Different species are listed including human as well as rat or mouse. The terms used rely on the terms of the publication. The colour code tries to evaluate the meaningfulness of the found article. Green comments seem to be very reliable, yellow seem to be all right and red commented articles could be untrustworthy. This is mainly based on or influenced by the author's opinion. Therefore, it is not measurable and just a guideline to the reader. The MedDRA codes were manually curated to the terms in the list. "References" refer to the PubMED ID except that there is no PubMED ID. Then the PMCID or the book title was used. If a DOI number exists, it is mentioned in the same named column. The date and title of publication and the journal are also in the table

There are 52 different Uniprot AC in the table and 16 different terms of hepatotoxicity. The journals amount to 44 different ones and the date is ranking from 1988 to the youngest publication 2017.

The most cited protein is the "Bile salt export pump". It is counted 25 times. Progressive familial intrahepatic cholestasis type 2, cholestasis, DILI, progressive familial intrahepatic cholestasis and liver injury are related to that target when inhibited or mutated. The second most protein is "Canalicular multispecific organic anion transporter 1". It has 10 entries and is related with the Dubin-Johnson-Syndrom, Cholestasis, Liver injury, Cholestasis and Jaundice. The "Nuclear receptor subfamily 1 group I member 2" has 9 different entries. Hepatotoxicity, Cholestasis, Liver injury, Hepatic steatosis are related to this target.

Figure 9: A section of Table 1 (Full list in appendix; 22.02.2019)

	Uniprot AC	Target Uniprot protein name	Uniprot gene name	Organism	Toxicity	MEDdra	References	DOI	Comment	Other names	Dose	Drug	Journal	Date of Pu	Title	Label
2	Q14994	Nuclear receptor subfamily 1 group I member 3	NR1I3	Mus musculus (Mouse)	Hepatotoxicity	10019851	12376703	10.1126/science.1073502	green	Constitutive activator of retinoid res	Science		2002	Modulation	S
3	Q14994	Nuclear receptor subfamily 1 group I member 3	NR1I3	Homo sapiens (Human)	Hepatotoxicity	10019851	27293091	10.1134/S0006297916040040	green	Constitutive activator of retinoid res	Biochemist		2016	Role of Nu	S
4	Q14994	Nuclear receptor subfamily 1 group I member 3	NR1I3	Mus musculus (Mouse)	Hepatic steatosis	10019708	27180240	10.1016/j.taap.2016.05.006	green	Constitutive activator of retinoid res	Toxicology		2016	Activation	S
5	P35348	Alpha-1A adrenergic receptor	ADRA1A	Homo sapiens (Human)	Hepatotoxicity	10019851	9187524	10.3109/03602539709037587	red	Alpha-1A adrenoreceptor	Alpha-1C	Drug meta	1997	Adrenergic	S
6	P07550	Beta-2 adrenergic receptor	ADRB2			X	PMCID: PMC40992	10.1073/pnas.0401944101	red	Beta-2 adrenoreceptor		Proc Natl A	2004	Translocat	S
7	P08913	Alpha-2A adrenergic receptor	ADRA2A			X	7938249	10.1016/0031-9384(94)90206-2	red	Alpha-2 adrenergic receptor subtype	Physiology		1994	Alpha-adre	S
8	P10635	Cytochrome P450 2D6	CYP2D6	Homo sapiens (Human)	Hepatotoxicity	10019851	x	10.1002/ppr199828425 4	yellow	CYP11D6, Cholesterol 25-hydroxylase	Clinical cor		1998	Perhexiline	S
9	P10635	Cytochrome P450 2D6	CYP2D6	Homo sapiens (Human)	Hepatotoxicity	10019851	11089838	10.1016/S0140-6736(00)03167-6	yellow	CYP11D6, Cholesterol 25-hydroxylase	Lancet		2000	Pharmacog	S
10	P10635	Cytochrome P450 2D6	CYP2D6	Homo sapiens (Human)	Hepatotoxicity	10019851	8788564	10.1016/0163-7258(95)02013-6	green	CYP11D6, Cholesterol 25-hydroxylase	Pharmacol		1995	The role of	S
11	P08913	Alpha-2A adrenergic receptor	ADRA2A	Mus musculus (Mouse)	Hepatotoxicity	10019851	1957308	10.1016/0041-008X(91)90022-7	green			Toxicology	1991	Potentiatic	S
12	P03372	Estrogen receptor	ESR1	Homo sapiens (Human)	Hepatotoxicity	10019851	23875763	10.3109/10408444.2013.811215	green	ER-alpha, Estradiol receptor, Nuclea	Critical rev		2013	Hepatotox	S
13	P12821	Angiotensin-converting enzyme	ACE	Homo sapiens (Human)	Hepatotoxicity	10019851	23875763	10.3109/10408444.2013.811215	green	Dipeptidyl carboxypeptidase I, Kinin	Critical rev		2013	Hepatotox	S
14	P12821	Angiotensin-converting enzyme	ACE	Homo sapiens (Human)	Liver injury	10067125	20593053	X	yellow	Dipeptidyl carboxypeptidase I, Enalapril 20mg/day	Journal of g		2010	Acute hepa	S
15	P12821	Angiotensin-converting enzyme	ACE	Homo sapiens (Human)	Hepatitis	10019717	14651558	10.1111/j.1442-200X.2003.01817	green	Dipeptidyl carboxypeptidase I, Kinin	Pediatrics i		2003	Toxic hepa	S
16	Q14994	Nuclear receptor subfamily 1 group I member 3	NR1I3	Homo sapiens (Human)	Hepatotoxicity	10019851	14674787	10.2165/00003088-200342150-00	red	Constitutive activator of retinoid res	Clinical phic		2003	Role of orp	S
17	O75469	Nuclear receptor subfamily 1 group I member 2	NR1I2	Homo sapiens (Human)	Hepatotoxicity	10019851	14674787	10.2165/00003088-200342150-00	red	Orphan nuclear receptor PAR1, Orpl	Clinical phic		2003	Role of orp	S
18	Q96RI1	Farnesoid X receptor	NR1H4	Homo sapiens (Human)	Hepatotoxicity	10019851	14674787	10.2165/00003088-200342150-00	red			Clinical phic	2003	Role of orp	S
19	O75469	Nuclear receptor subfamily 1 group I member 2	NR1I2	Homo sapiens (Human)	Hepatotoxicity	10019851	11090943	10.1016/S0300-483X(00)00300-0	red			Toxicology	2000	Use of the	S
20	P14740	Dipeptidyl peptidase 4	Dpp4	Rattus norvegicus (Rat)	Hepatotoxicity	10019851	8603291	10.1021/tx00050a001	yellow			Chemical r	1995	Covalent m	S
21	P14740	Dipeptidyl peptidase 4	Dpp4	Rattus norvegicus (Rat)	Hepatotoxicity	10019851	15822174	10.1146/annurev.pharmtox.45.12	yellow			Annual rev	2005	The role of	S
22	P23219	Prostaglandin G/H synthase 1	PTGS1	Homo sapiens (Human)	Hepatotoxicity	10019851	15626590	10.1016/j.plefa.2004.10.005 and	10.1146/annure	Cyclooxygenase-1, Prosta	Diclofenac	Prostaglan	2005	COX-3 and	S
23	P31327	Carbamoyl-phosphate synthase [ammonia], mitochondrial	CPS1	Rattus norvegicus (Rat)	Hepatic encephal	10019660	3413798	10.1016/0300-483X(88)90085-6	yellow			Toxicology	1988	Hepatic AT	S
24	P00966	Argininosuccinate synthase	AS51	Rattus norvegicus (Rat)	Hepatic encephal	10019660	3413798	10.1016/0300-483X(88)90085-6	yellow			Toxicology	1988	Hepatic AT	S

3.2.2. Hepatotoxic side effect DITOP proteins (Table 2)

Table 2 contains all Uniprot Accession numbers from the DITOP databank, which are related to hepatotoxicity. Therefore, the whole data has been filtered by their MedDRA numbers related to hepatotoxicity in Knime. Then they were filtered by their Uniprot accession numbers. For every target and its own Pubmed ID were established a single row. For example, if a target were mentioned in five different articles five rows were created. As a result the table contains 434 single entries that are related to hepatotoxicity in DITOP. There are 68 different targets in connection with hepatotoxicity which are displayed in Table C. The Uniprot protein gene names are listed there in alphabetical order. Then additional information was added like the title and the date of the publication as well as the journal name, toxicity, MedDRA code, DOI, Uniprot gene name and the label. All those colums were added manually. The conclusion was that it is now compareable to the Table 1 which was created before. The most cited target of DITOP is Alanine aminotransferase 1, which has 40 entries. Transcription factor AP-1 and Cytochrome P450 1A1 are the ones with the fewest entries. This data of the Xiamen university is all labelled with D for DITOP and used lateron for comparison to Table 1. The figure below shows a section of Table 2.

	B	C	D	E	F	G	H	I	J	K	L	M
1	Uniprot AC	Target Uniprot protein name	Title	Date of Pub	Journal	Organism	Label	Toxicity	MEDdra	DOI	Uniprot gene name	
2	P00738	Haptoglobin	Ribavirin inhibits protein synthesis and cell prolif	1998	Hepatology	human anc	D	Hepatic function abnormal	10019670	10.1002/h	HP	
3	P00738	Haptoglobin	Ribavirin inhibits DNA, RNA, and protein synthesi	2003	Journal of Medical '	human anc	D	Hepatic function abnormal	10019670	10.1002/jn	HP	
4	P00738	Haptoglobin	Response of cultured fetal and adult rat hepatoc	1998	Cell Transplantatior	human anc	D	Hepatic function abnormal	10019670	x	HP	
5	P00738	Haptoglobin	Comitogenicity of eicosanoids and the peroxisor	1996	Journal of Cellular F	human anc	D	Hepatic function abnormal	10019670	10.1002/(S	HP	
6	P00738	Haptoglobin	Inhibition of DNA synthesis by somatostatin in ra	1992	The American Journ	human anc	D	Hepatic function abnormal	10019670	10.1016/0(	HP	
7	P00738	Haptoglobin	The hepatocyte growth factor regulates the synt	1996	Hepatology	human anc	D	Hepatic function abnormal	10019670	10.1002/h	HP	
8	P00738	Haptoglobin	Iron may induce both DNA synthesis and repair i	1997	Journal of Hepatolc	human anc	D	Hepatic function abnormal	10019670	10.1016/S(	HP	
9	P00738	Haptoglobin	Possible involvement of protein kinase C with inc	1993	Am J Vet Res	cow	D	Hepatic steatosis	10019708	x	HP	
10	P00738	Haptoglobin	Dexamethasone-induced haptoglobin release by	1994	Am J Vet Res	cow	D	Hepatic steatosis	10019708	x	HP	
11	P00738	Haptoglobin	Appearance of haptoglobin in serum from cows	1993	J Vet Med Sci	cow	D	Hepatic steatosis	10019708	x	HP	
12	P00738	Haptoglobin	Decreases of apolipoprotein B-100 and A-I conc	2002	Journal of Veterina	cow	D	Hepatic steatosis	10019708	10.1016/S(	HP	
13	P00738	Haptoglobin	Reduced protein kinase C activity and endogenou	1994	Veterinary research	cow	D	Hepatic steatosis	10019708	x	HP	
14	P00738	Haptoglobin	Purification of a protein from serum of cattle wi	1992	Am J Vet Res	cow	D	Hepatic steatosis	10019708	x	HP	
15	P00738	Haptoglobin	Protein kinase C and its endogenous substrate pr	1993	Am J Vet Res	cow	D	Hepatic steatosis	10019708	10.1292/jv	HP	
16	P02741	C-reactive protein	[Unknown fever and abnormal liver functions af	1994	Masui	human	D	Hepatitis	10019717	x	CRP	
17	P02741	C-reactive protein	[A case of using continuous double-tapped epidu	1995	Masui	human	D	Hepatitis	10019717	x	CRP	
18	P02741	C-reactive protein	Epidural clonidine relieves intractable neuropath	2003	Regional anesthesia	human	D	Hepatitis	10019717	x	CRP	
19	P02741	C-reactive protein	[The development of methicillin-resistant Staphy	2002	Masui	human	D	Hepatitis	10019717	x	CRP	
20	P02741	C-reactive protein	ransfusion-acquired AIDS in Taiwan.	1996	Journal of the Form	human	D	Hepatitis	10019717	x	CRP	
21	P02741	C-reactive protein	Patient-controlled epidural analgesia for posther	1998	Acta anaesthesiolo	human	D	Hepatitis	10019717	x	CRP	
22	P02741	C-reactive protein	[A complete relief of intractable postherpetic ne	1990	Masui	human	D	Hepatitis	10019717	x	CRP	
23	P02741	C-reactive protein	[Phenprocoumon-induced cholestatic hepatitis].	1995	Deutsche Medizinis	human	D	Hepatitis	10019717	10.1055/s-	CRP	
24	P02741	C-reactive protein	Drug-induced liver disease during continuous epi	2001	Anesthesiology	human	D	Hepatitis	10019717	10.1097/0(	CRP	
25	P23110	Albumin-8	Ribavirin inhibits protein synthesis and cell prolif	1998	Hepatology	human anc	D	Hepatic function abnormal	10019670	10.1002/h	N/A	
26	P23110	Albumin-8	Ribavirin inhibits DNA, RNA, and protein synthesi	2003	J Med Virol.	human anc	D	Hepatic function abnormal	10019670	10.1002/jn	N/A	
27	P23110	Albumin-8	Response of cultured fetal and adult rat hepatoc	1998	Cell Transplantatior	human anc	D	Hepatic function abnormal	10019670	10.1016/S(	N/A	
28	P23110	Albumin-8	Comitogenicity of eicosanoids and the peroxisor	1996	Journal of cellular F	human anc	D	Hepatic function abnormal	10019670	10.1002/(S	N/A	
29	P23110	Albumin-8	Inhibition of DNA synthesis by somatostatin in ra	1992	Am J Surg.	human anc	D	Hepatic function abnormal	10019670	10.1016/0(	N/A	

Figure 10: Screenshot of a section of Table 2 (17.06.2019)

Table C: List of Proteins extracted from DITOP in alphabetical order.

Alanine aminotransferase 1
Alanine aminotransferase 2
Albumin-8
Alkaline phosphatase, placental type
Alkaline phosphatase, tissue-nonspecific isozyme
Alpha-1-acid glycoprotein 1
Alpha-2A adrenergic receptor
Arylamine N-acetyltransferase 2
Aspartate aminotransferase, mitochondrial
Beta-2 adrenergic receptor
Bile salt export pump
Caspase recruitment domain-containing protein 10
Caspase recruitment domain-containing protein 10
Cholinesterase
C-reactive protein
CYP2B protein
Cytochrome P450 1A1
Cytochrome P450 1A2
Cytochrome P450 2A6
Cytochrome P450 2C19
Cytochrome P450 2C9
Cytochrome P450 2D6
Cytochrome P450 2E1
Cytochrome P450 3A4
Endothelin-1
Epidermal growth factor receptor
Fibroblast growth factor 4
Gamma-glutamyltranspeptidase 1
Glucocorticoid receptor
Glyceraldehyde-3-phosphate dehydrogenase
Glycogen [starch] synthase, muscle
Haptoglobin
Hepatic triacylglycerol lipase

Hepatocyte growth factor
Insulin receptor substrate 1
Insulin receptor substrate 2
Intercellular adhesion molecule 1
L-lactate dehydrogenase A chain
Low-density lipoprotein receptor-related protein 11
Lysosomal alpha-mannosidase
Lysosome-associated membrane glycoprotein 1
Metallothionein-1A
Mitogen-activated protein kinase 1
Myeloperoxidase
N-alpha-acetyltransferase 20
Nitric oxide synthase, endothelial
Ornithine decarboxylase
Phosphatidylinositol 4-phosphate 3-kinase C2 domain-containing subunit alpha
Proliferating cell nuclear antigen
Protein kinase C delta type
Solute carrier family 12 member 3
Solute carrier family 2, facilitated glucose transporter member 4
Sorbitol dehydrogenase
Sterol regulatory element-binding protein 1
Sterol regulatory element-binding protein 2
Sulfotransferase 1A3
Transcription factor AP-1
Transforming protein v-Fos/v-Fox
Tyrosine aminotransferase
Tyrosine-protein kinase ABL1
UDP-glucuronosyltransferase 1-1
UDP-glucuronosyltransferase 1-6
UDP-glucuronosyltransferase 1-9
UDP-glucuronosyltransferase 2B15
Uroporphyrinogen decarboxylase

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3.2.3. Merged list of hepatotoxic proteins (Final Table)

The final table of this work contains 104 different proteins and has 554 single entries. Those were created by matching my list (Table 1) with the DITOP data (Table 2). The interaction of these proteins is connected to a certain kind of hepatotoxicity in at least one publication. The full table can be found in the appendix.

After delimiting the huge data by grouping the double entries of several target proteins by their Uniprot AC number, only 54 remained which are not on my list and unique to DITOP. Furthermore, there are 28 targets found during this work which are not mentioned in DITOP.The table below gives the total overview over the hitherto known targets related to hepatotoxicity. The label shows in which of the two lists the protein is originated. The count shows how in how many articles the connection to adverse hepatic side effects is given.

Table D: Summary of the Proteins of the Final Table (Full list in appendix)

Uniprot AC	Uniprot Gene Name	Hepatotoxicity related to it	Label	Count
O00443	Phosphatidylinositol 4-phosphate 3-kinase C2 domain-containing subunit alpha	Liver injury	D	4
O00754	Lysosomal alpha-mannosidase	Metastases to liver	D	9
O15068	Guanine nucleotide exchange factor DBS	Could trigger intrahepatic cholestasis	S	1
O15438	Canalicular multispecific organic anion transporter 2	Cholestasis/ Could trigger intrahepatic cholestasis	S	2
O15439	Multidrug resistance-associated protein 4	Liver injury/ Could trigger intrahepatic cholestasis/ Cholestasis	S	3
O43520	Phospholipid-transporting ATPase IC	Cholestasis/ Progressive familial intrahepatic cholestasis type 1/ Cholestatic liver disease	S	3
O60656	UDP-glucuronosyltransferase 1-9	Hepatotoxicity/ Hepatic failure	D/ S	5
O70127	Bile salt export pump	Hepatotoxicity/ Cholestasis	S	2
O75469	Nuclear receptor subfamily 1 group I member 2	Cholestasis/ Hepatotoxicity/ Hepatic steatosis	S	5
O95342	Bile salt export pump	Liver injury/ Cholestasis/ Progressive familial intrahepatic cholestasis/ DILI/ Cholestasis, DILI	S/ D	25
P00338	L-lactate dehydrogenase A chain	Hepatotoxicity	D	7
P00505	Aspartate aminotransferase, mitochondrial	Acute hepatic failure	D	3
P00519	Tyrosine-protein kinase ABL1	Hepatomegaly	D	4
P00533	Epidermal growth factor receptor	Hepatic function abnormal	D	7
P00734	Prothrombin	DILI/ Hepatotoxicity	S	2

P00738	Haptoglobin	Hepatic steatosis/ Hepatic function abnormal	D	14
P00966	Argininosuccinate synthase	Hepatic encephalopathy	S	1
P02741	C-reactive protein	Hepatitis	D	9
P02763	Alpha-1-acid glycoprotein 1	Hepatic cirrhosis	D	4
P03372	Estrogen receptor	Hepatotoxicity/ Hepatic steatosis	S	2
P04035	3-hydroxy-3-methylglutaryl-coenzyme A reductase	Hepatotoxicity	S	1
P04150	Glucocorticoid receptor	Hepatotoxicity/ Hepatic steatosis	D/ S	5
P04406	Glyceraldehyde-3-phosphate dehydrogenase	Liver injury	D	4
P04731	Metallothionein-1A	Hepatotoxicity	D	3
P04798	Cytochrome P450 1A1	Hepatotoxicity	D	2
P05164	Myeloperoxidase	Hepatotoxicity	D	3
P05177	Cytochrome P450 1A2	Hepatotoxicity/ Drug induced hepatitis	D/ S	10
P05181	Cytochrome P450 2E1	Hepatotoxicity/ Hepatitis/ Drug induced hepatitis	D/ S	22
P05186	Alkaline phosphatase, tissue-nonspecific isozyme	Jaundice/ Hepatotoxicity	D	7
P05187	Alkaline phosphatase, placental type	Hepatitis/ Hepatotoxicity	D	12
P05305	Endothelin-1	Liver disorder	D	4
P05362	Intercellular adhesion molecule 1	Liver injury	D	7
P05412	Transcription factor AP-1	Hepatotoxicity	D	2
P06132	Uroporphyrinogen decarboxylase	Porphyrin metabolism disorder	D	4
P06276	Cholinesterase	Hepatotoxicity	D	2
P07550	Beta-2 adrenergic receptor	Hepatotoxicity/ Cardiac anaphylaxis	D/ S	8
P08183	Multidrug resistance protein 1	Cholestasis/ Hepatotoxicity	S	2
P08620	Fibroblast growth factor 4	Hepatotoxicity	D	3
P08684	Cytochrome P450 3A4	Hepatotoxicity	D/ S	34
P08913	Alpha-2A adrenergic receptor	Liver injury/ Adverse effects / Hepatotoxicity	D/ S	9
P0DMM9	Sulfotransferase 1A3	Hepatic necrosis	D	3
P10276	Retinoic acid receptor alpha	Hepatic steatosis	S	1
P10635	Cytochrome P450 2D6	Hepatotoxicity/ Liver failure, fatal DILI	D/ S	9
P10826	Retinoic acid receptor beta	Hepatic steatosis	S	1
P11245	Arylamine N-acetyltransferase 2	Liver injury	D	4
P11279	Lysosome-associated membrane glycoprotein 1	Liver injury	D	6
P11509	Cytochrome P450 2A6	Hepatotoxicity	D	6
P11712	Cytochrome P450 2C9	Hepatotoxicity/ Liver failure, fatal DILI/ Drug induced hepatitis	D/ S	15
P11926	Ornithine decarboxylase	Hepatotoxicity	D	3
P12235	ADP/ATP translocase 1	Acute hepatic failure	S	1
P12821	Angiotensin-converting enzyme	Liver injury/ Hepatotoxicity/ Hepatitis	S	3
P13631	Retinoic acid receptor gamma	Hepatic steatosis	S	1
P13807	Glycogen [starch] synthase, muscle	Hepatic function abnormal	D	8
P14210	Hepatocyte growth factor	Hepatic function abnormal	D	7
P14672	Solute carrier family 2, facilitated glucose transporter member 4	Liver disorder	D	3
P14740	Dipeptidyl peptidase 4	Hepatotoxicity	S	2

P17735	Tyrosine aminotransferase	Hepatotoxicity	D	4
P19224	UDP-glucuronosyltransferase 1-6	Hepatotoxicity	D	4
P19440	Gamma-glutamyltranspeptidase 1	Hepatitis	D	9
P21439	Phosphatidylcholine translocator ABCB4	Cholestasis/ Progressive cholestatic liver injury	S	6
P21447	Multidrug resistance protein 1A	Hepatocyte necrosis	S	1
P22309	UDP-glucuronosyltransferase 1-1	Idiosyncratic liver toxicity/ Hepatotoxicity	S/ D	5
P23110	Albumin-8	Hepatic function abnormal	D	7
P23219	Prostaglandin G/H synthase 1	Hepatotoxicity	S	1
P24298	Alanine aminotransferase 1	Liver injury/ Hepatotoxicity/ Jaundice/ Hepatic cirrhosis/ Hepatic necrosis/ Acute hepatic failure/ Hepatic steatosis	D	40
P27656	Hepatic triacylglycerol lipase	Metastases to liver	D	9
P28482	Mitogen-activated protein kinase 1	Liver injury	D	4
P29176	Transforming protein v-Fos/v-Fox	Hepatotoxicity	D	2
P29474	Nitric oxide synthase, endothelial	Liver disorder	D	4
P31327	Carbamoyl-phosphate synthase [ammonia], mitochondrial	Hepatic encephalopathy	S	1
P33261	Cytochrome P450 2C19	Hepatotoxicity/ Liver failure, fatal DILI	D/ S	5
P35348	Alpha-1A adrenergic receptor	Hepatotoxicity	S	1
P35568	Insulin receptor substrate 1	Liver injury	D	4
P35869	Aryl hydrocarbon receptor	Hepatic steatosis	S	1
P36956	Sterol regulatory element-binding protein 1	Hepatic steatosis	D	4
P37231	Peroxisome proliferator-activated receptor gamma	Acute liver injuries/ Hepatic steatosis	S	2
P54098	DNA polymerase subunit gamma-1	Hepatotoxicity/ Hepatic failure	S	2
P54855	UDP-glucuronosyltransferase 2B15	Hepatotoxicity	D	4
P55017	Solute carrier family 12 member 3	Hepatotoxicity	D	3
P61599	N-alpha-acetyltransferase 20	Hepatotoxicity	D	2
Q00268	Proliferating cell nuclear antigen	Liver injury	D	4
Q00796	Sorbitol dehydrogenase	Hepatotoxicity	D	9
Q05421	Cytochrome P450 2E1	Hepatotoxicity	S	1
Q05655	Protein kinase C delta type	Hepatic steatosis	D	7
Q07869	Peroxisome proliferator-activated receptor alpha	Hepatic steatosis	S	1
Q12772	Sterol regulatory element-binding protein 2	Hepatic steatosis	D	4
Q13133	Oxysterols receptor LXR-alpha	Hepatic steatosis	S	1
Q14032	Bile acid-CoA:amino acid N-acyltransferase	Cholestasis	S	1
Q14097	CYP2B protein	Hepatotoxicity	D	3
Q148W0	Phospholipid-transporting ATPase IC	Cholestasis	S	1
Q14973	Sodium/bile acid cotransporter	Hepatotoxicity/ Prehepatic cholestasis/ Cholestasis	S	3

Q14994	Nuclear receptor subfamily 1 group I member 3	Hepatic steatosis/ Hepatotoxicity/ Hepatoxicity	S	5
Q28DB5	Alanine aminotransferase 2	Hepatitis	D	9
Q86VZ4	Low-density lipoprotein receptor-related protein 11	Liver disorder	D	11
Q8QZR5	Alanine aminotransferase 1	Hepatotoxicity	D	7
Q91Y86	Mitogen-activated protein kinase 8	Protection	S	1
Q92887	Canalicular multispecific organic anion transporter 1	Liver injury/ Cholestasis/ Dubin-Johnson syndrome/ Cholestasis of pregnancy/ Could trigger intrahepatic cholestasis/ Cholestasis and Jaundice	S	8
Q96RI1	Bile acid receptor/ Farnesoid X receptor	Hepatotoxicity/ Cholestasis/ Cholestasis inPFIC1/ Hepatic steatosis	S	6
Q9BWT7	Caspase recruitment domain-containing protein 10	Hepatotoxicity	D	4
Q9NPD5	Solute carrier organic anion transporter family member 1B3	Hepatic failure	S	1
Q9UHN1	DNA polymerase subunit gamma-2, mitochondrial	Hepatotoxicity/ Hepatic failure	S	2
Q9UJ14	Caspase recruitment domain-containing protein 10	Jaundice	D	4
Q9Y4H2	Insulin receptor substrate 2	Liver injury	D	4
Q9Y6L6	Solute carrier organic anion transporter family member 1B1	Hepatotoxicity/ Hyperbilirubinemia	S	3

3.3. Journals

Different journals from around the world are considered, to get a diverse data set. The search for targets was not restricted to certain journals or parameters. As a result, 139 different journals are referred to in this work in the final table, which is in the appendix. Most of the articles can be found at PubMed with the specific PubMed ID and in addition, the DOI is mentioned if available.

The following table (Table E) should give a better overview of all journals and publications which were listed during this research. The journals are sorted alphabetically. The number of articles show how often this journal was mentioned in the final table. Furthermore, the publication dates of those articles are displayed in ascending order. This additional information indicates how long this hepatotoxic effect is already well known. In the third column the Impact Factor (IF) is mentioned if available. This impact factor calculation is based on the work of Dr. Zdrazil.

Table E: List of Journals mentioned in the final table

Journal	Number of articles	Date of Publication(Count)	Impact Factor in year of publication
AIDS	2	1998(1), 2000(1)	6.109/ 8.018
Acta Diabetologica	1	1994(1)	NA
Acta anaesthesiologica Sinica	1	1998(1)	NA
Acta pharmacologica et toxicologica	2	1983(2)	NA
Acta physiologica, pharmacologica et therapeutica latinoamericana	1	1992(1)	NA
Advances in experimental medicine and biology	1	1991(1)	NA
Alcoholism, clinical and experimental research	3	1995(1), 1998(1), 1999(1)	NA/ NA/ 2.013
American journal of surgery	1	1992(1)	NA
American journal of veterinary research	3	1992(1), 1993(1), 1994(1)	NA
Anesthesia and analgesia	1	1995(1)	NA
Anesthesiology	7	1979(1), 1981(1), 1983(1), 1988(1), 1993(1)1995(1), 2001(1),	NA/NA/ NA/NA/ NA/NA/ 3.381
Annals of emergency medicine	1	2004(1)	2.623
Annals of internal medicine	1	1982(1)	NA
Annals of oncology	1	1994(1)	NA
Annual review of pharmacology and toxicology	1	2005(1)	19.833
Archives of biochemistry and biophysics	1	1995(1)	NA
Archives of dermatological research	1	1982(1)	NA
Biochemical Society Symposium	1	1995(1)	NA

Biochemical and biophysical research communications	2	1983(1), 1987(1)	NA
Biochemical medicine and metabolic biology	1	1987(1)	NA
Biochemical pharmacology	3	1992(1), 1993(2)	NA
Biochemistry	1	2016(1)	NA
Biochimica et biophysica acta	1	2007(1)	2.371
Biomedicine and pharmacotherapy	1	1999(1)	0.852
Blood cells, molecules & diseases	1	1998(1)	3.026
British Journal of Clinical Pharmacology	3	1980(1), 1989(1), 2005(1)	NA/NA/ 2.777
British journal of anesthesia	1	1986(1)	NA
British journal of haematology	1	2002(1)	3.052
British medical Bulletin	1	1978(1)	NA
Canadian Journal of Gastroenterology	2	2000(2)	1.645
Cancer Research	3	1994(1), 1996(2)	NA/NA
Cardiology Journal	1	2017(1)	NA
Carcinogenesis	2	1995(1), 1999(1)	NA/ 4.118
Cell Transplantation	1	1998(1)	1.818
Chemical research in toxicology	17	1999(3), 1994(1), 1995(1), 1996(1), 1997(1), 2001(4), 2002(2), 2005(1), 2006(1), 2011(1) 2017(1),	NA/NA/ NA/NA/ NA/ 3.179/ 3.607/ 3.339/ 3.162/ 3.779/ NA
Chemico-Biological Interactions	3	2002(1), 2004(2)	1.261/ 2.789
Clinical Cancer Research	6	1997(1), 2001(1), 2002(2), 2003(2)	NA/ 5.076/ 5.991/ 6.511
Clinical Science	1	1980(1)	NA
Clinical chemistry	1	1994(1)	NA
Clinical communication	1	1998(1)	NA
Clinical infectious diseases	1	2000(1)	2.972
Clinical pharmacokinetics	2	1997(1), 2003(1)	3.899
Clinical pharmacology and therapeutics	3	1999(1), 2000(1), 2001(1)	4.394/ 4.846/ 5.275
Clinics and Research in Hepatology and Gastroenterology	1	2012(1)	1.348
Critical reviews in toxicology	2	2013(1), 2016(1)	NA
Current Opinion in Lipidology	1	2009(1)	6.133
Dermatology	1	1996(1)	NA
Deutsche Medizinische Wochenschrift	1	1995(1)	NA
Diabetes	1	1980(1)	NA
Drug and Chemical Toxicology	1	1988(1)	NA
Drug metabolism and disposition: the biological fate of chemicals	16	1981(1), 1984(1), 1987(1), 1991(1), 1996(2), 1998(1), 1999(1), 2000(1), 2002(1), 2004(1), 2006(1), 2012(1), 2014(3)	NA/NA/ NA/NA/ NA/2.271/ 2.519/ 2.513/ 3.277/ 3.836/ 3.638/ 3.361/ 3.252
Drug metabolism reviews	4	1992(1), 1997(1), 2007(1), 2010(1)	NA/NA/ 5.579/ 6.263
Drugs in R&D	1	2003(1)	NA
Endocrine practice	1	2001(1)	NA
Endocrinology	1	1983(1)	NA

European journal of clinical pharmacology	2	1987(1), 2006(1)	NA
European journal of drug metabolism and pharmacokinetics	1	1998(1)	0.556
European journal of gastroenterology and hepatology	1	1995(1)	NA
European journal of haemotology. Supplementum.	1	1996(1)	NA
European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology	1	2002(1)	NA
Free Radical Biology and Medicine	1	2001(1)	5.082
Gastroenterology	2	1988(1), 2002(1)	NA/ 13.44
Handbook of experimental pharmacology	3	2010(2), 2011(1)	NA
Hepatology	15	1985(1), 1996(3), 1997(1), 1998(1), 2000(1), 2001(3), 2003(1), 2004(1), 2006(1), 2007(1), 2010(1)	NA/ NA/ NA/ 5.621/ 7.304/ 8.096/ 9.503/ 10.416/ 10.446/ 10.734/ 10.885
Italian journal of gastroenterology and hepatology	1	1998(1)	0.589
Journal of Cellular Physiology	1	1996(1)	NA
Journal of Hepatology	6	1989(1), 1997(2), 2002(1), 2003(1), 2009(1)	NA/NA/ 4.974/ 5.283/ 7.818
Journal of Medical Virology	1	2003(1)	2.371
Journal of acquired immune deficiency syndromes	2	2000(1), 2003 (1)	NA
Journal of applied toxicology: JAT	1	1987(1)	NA
Journal of clinical gastroenterology	1	1998(1)	0.763
Journal of gastrointestinal and liver diseases	1	2010(1)	1.434
Journal of medicinal chemistry	1	2005(1)	NA
Journal of pharmacokinetics and biopharmaceutics	4	1992(1), 1995(1), 1998(2)	NA/ NA/ 1.477
Journal of the American Medical Association	1	2000(1)	NA
Journal of the American Veterinary Medical Association	3	1982(1), 1984(1), 1985(1)	NA
Journal of the Formosan Medical Association	1	1996(1)	NA
Journal of toxicology and environmental health	2	1995(1), 1996(1)	NA
Lancet	4	1998(1), 1999(1), 2000(1), 2001(1),	11.793/ 10.197/ 10.232/ 13.251
Leukemia	1	2005(1)	6.612
Life sciences	2	1994(1), 2001(1)	NA/ 1.758
Masui	4	1990(1), 1994(1), 1995(1), 2002(1)	NA
Medical Hypotheses	1	2001(1)	0.745
Medical Toxicology	1	1986(1)	NA
Methods and findings in experimental and clinical pharmacology	1	1998(1)	0.322
Molecular endocrinology	4	1998(1), 2000(2), 2005(1)	7.853/ 6.251/ 5.807

Molecular pharmacology	1	2001(1)	5.297
National Toxicology Program technical report series	1	1993(1)	NA
Onkologie	1	2000(1)	0.64
Pediatric infectious disease	1	1985(1)	NA
Pediatrics international: official journal of the Japan Pediatric Society	1	2003(1)	NA
Pharmacogenetics	1	1997(1)	NA
Pharmacology and Toxicology	2	1988(1), 1990(1)	NA
Pharmacology and therapeutics	1	1995(1)	NA
Physiological reviews	1	2003(1)	27.067
Physiology and behavior	1	1994(1)	NA
Presse medicale	1	2001(1)	0.398
Proceedings of the National Academy of Sciences of the United States of America	1	1996(1)	NA
Progress in lipid research	1	2003(1)	10
Prostaglandins, leukotrienes and essential fatty acids	1	2005(1)	1.807
Psychopharmacology	1	1999(1)	3.032
Recenti progressi in medicina	1	2000(1)	NA
Regional anesthesia and pain medicine	1	2003(1)	1.766
Research communication in chemical pathology and pharmacology	5	1984(1), 1986(1), 1987(2), 1996(1)	NA
Scandinavian journal of clinical and laboratory investigation	1	2001(1)	NA
Science	2	2002(2)	26.682
Seminars in liver disease	1	2010(1)	5.286
Sexually transmitted diseases	1	1983(1)	NA
Shock	1	2004(1)	3.122
The American Journal of Medicine	1	1992(1)	NA
The American Journal of Physiology	3	1997(1), 1999(1), 2000(1)	NA/ 3.077/ NA
The American Journal of Gastroenterology	4	1997(1), 2001(2), 2003(1)	NA/ 3.549/ 4.172
The American review of respiratory disease	2	1978(1), 1979(1)	NA
The Annals of pharmacotherapy	5	1992(1), 1994(1), 1998(1), 2002(1), 2004(1)	NA/ NA/ 1.276/ 1.796/ 1.739
The Biochemical journal	1	1995(1)	NA
The British Journal of dermatology	5	1995(1), 1996(2), 2005(2)	NA/ NA/ 2.978
The British Journal of venereal diseases	1	1984(1)	NA
The Journal of biological chemistry	5	1984(1), 2002(1), 2001(1), 2003(1), 2004(1)	NA
The Journal of clinical investigation	1	1988(1)	NA
The Journal of pharmacology and experimental therapeutics	2	1985(1), 1994(1)	NA
The Journal of the Association of Physicians of India	1	2000(1)	NA
The New England Journal of Medicine	1	1986(1)	NA
The international journal of biochemistry	1	1984(1)	NA
The journal of biological chemistry	1	1996(1)	NA
The journal of clinical investigation	1	1993(1)	NA

The journal of laboratory and clinical medicine	2	1975(1), 1985(1)	NA
The journal of pharmacology and experimental therapeutics	4	1986(1), 1989(1), 1997(2)	NA
The journal of steroid biochemistry and molecular biology	1	2012(1)	3.984
The journal of veterinary medicinal science	3	1993(2), 2002(1)	NA/ 0.496
Therapeutic drug monitoring	1	2000(1)	1.732
Toxicologic pathology	2	1987(1), 2005(1)	NA/ 1.962
Toxicological sciences	4	2003(1), 2005(1), 2013(2)	3.067/ 3.088/ 4.478
Toxicology	7	1976(1), 1988(1), 1995(1), 1996(1), 2000(1), 2001(1), 2010(1)	NA/ NA/ NA/ NA/ 1.427/ 1.752/ 3.641
Toxicology and applied pharmacology	10	1983(1), 1984(2), 1986(1), 1989(1), 1991(2), 1993(2), 2016(1)	NA
Toxicology letters	1	1991(1)	NA
Veterinary research communications	1	1994(1)	NA
World journal of gastroenterology	1	2012(1)	2.547
Xenobiotica	1	1988(1)	NA

4. DISCUSSION

4.1. Journals

The journals mentioned in this work, are based on different main focusses like biology, cancer research or chemistry. Despite that, they have all published articles united on the topic of hepatotoxicity. In response to growing health concerns, research on hepatotoxicity is continuously expanding in all sorts of fields.

The most cited journal here is "Drug metabolism and disposition: the biological fate of chemicals". It was founded 1973 by Kenneth C. Leibman and is published from the American Society for Pharmacology and Experimental Therapeutics.

An attempt to rank the credibility of scientific journals is the Impact Factor (IF). Therefore, the yearly average number of citations is considered. It was established by Eugene Garfield. This measurement is an attempt to show the importance of the journal on its scientific field. The IF has the aim to display that trustworthiness correlates with the height of the impact factor. The higher the impact factor, the more reliable the journal and its publications are. The factor is calculated yearly and therefore changing consequently throughout time. It is a method with which scientists can compare the liability of the published article. Although it is a help to evaluate the integrity of the journal or a certain article, there is also a lot of criticism regarding the impactor factor. [23] It can be used as a guideline but should not be seen as a dogma. This is because this system of citations can be also manipulated. Furthermore, it has to be taken into account, that small scientific fields are not cited that often, although their research is quite solid. Moreover, rarely spoken languages have less citations than others. A good example for that is the Japanese journal of anesthesiology "Masui" published by Nippon Masui Gakki. In 2002 when some of the mentioned articles were published it had an Impact Factor of 0.17 [24]. Despite that low IF the information published can be of great significance. Nevertheless, this method obviously does have some significant advantages, such as indicate a general direction which journals could offer the more reliable information.

4.2. Selected Proteins

In this chapter some of the most interesting targets are described more closely. The Alanine aminotransferase 1 was the one with the most entries in this work. Likewise, Cytochromes P450 3A4 is one with the second most entries and deserves a closer look. The Bile salt export pump has very specific hepatic adverse side effect terms and is therefore important to discuss. Nuclear receptor subfamily 1 group I member 2 and the Phosphatidylcholine translocator ABCB4 do not have a lot of entries but they all are unique in Table 1 and are not mentioned by DITOP.

4.2.1. Nuclear receptor subfamily 1 group I member 2

Nuclear receptor subfamily 1 group I member 2 with gene name NR1I2 has 5 entries in this works final table. It is also known as Pregnane X receptor or Orphan nuclear receptor PXR. It has a length of 434 aminoacids and a mass of 49,762 Da. [25] It is a member of the nuclear receptor superfamily of proteins and mapped to chromosome 13q11-13. [26] PXR is expressed mainly in the liver and just in small amounts in testis and embryonic tissues in humans. [27]

There are reports that this protein interacts with a huge amount of different endogenous and xenobiotic compounds. It is activated by variety of chemicals and xenobiotics like the antibiotic rifampicin and various plant metabolites, such as hyperforin, a hops β-bitter acid named colupulone, and isoflavones [30] [31]. Furthermore, it is activated by naturally occurring steroids, such as pregnenolone and progesterone. The structural diversity of the compounds that activate PXR is a broad range of ligands. As a key mediator in the transcriptional regulation of genes, it modulates the expression of those genes involved in the metabolism and clearance of structurally diverse compounds. It plays a physiological role in regulating metabolic pathways important for the elimination of cholesterol. It functions as a sensor of toxic byproducts of endogenous substances and of exogenous chemicals and enhance their elimination and in turn regulate aspects of the enterohepatic cycling and metabolism of bile acids. The accumulation of bile acid precursors leads to PXR activation. In that manner PXR offers hepatoprotection from the toxic accumulation of bile acids by inducing their clearance [28]. So the other way round, if there is a mutation or inhibition of this protein, it can lead to hepatotoxicity. Members of the nuclear receptor family are also involved in the adaptive response to cholestasis. They regulate bile acid and phospholipid transporter genes which are

important for hepatobiliary transport. Furthermore, they perform phases I and II metabolizing. A lack of therapeutic efficacy or an imbalance in mechanisms can lead to severe toxicity.

Recent findings show that the mouse and human pregnane X receptor transcriptionally activates cytochrome P4503A4 by compounds that induce CYP3A expression. PXR is remarkably divergent between species because it has diverged during evolution [29] Thirty-eight single nucleotide polymorphisms (SNPs) were identified. An upregulation of drug detoxification genes is of great interest in drug research. It will be promising to investigate the function of these common PXR SNPs to human variation in induction of other drug detoxification gene targets. PXR in a high throughput binding format provides a valuable tool for the rapid identification of compounds that will induce CYP3A expression and interact with other drugs.

Orphan' receptors like the PXR seem to have a major role in protection from bile acid toxicity. PXR is now widely viewed to be the mediator of xenobiotic regulation of CYP3A Several important physiological processes, such as cholesterol synthesis and bile acid metabolism, are also tightly controlled by other ligand-activated orphan nuclear receptors like the farnesoid X receptor (FXR) and liver X receptor (LXR). [30]

PXR-null mice showed a correlation between high mortality caused by hepatitis and hepatocellular injury and a cholesterol- and cholic acid-enriched diet in certain studies.

Pharmacological therapy for cholestasis is limited Therapeutic targeting of PXR have been shown to influence cholestatic liver injury. Many liver diseases could potentially benefit from pharmacological manipulation of these nuclear receptors.

4.2.2. Alanine aminotransferase 1

Alanine aminotransferase 1 or Glutamate pyruvate transaminase 1, how it is called with another name has a length of 496 amino acids. Its mass is 54,637Da. [31][1] It plays a key role in the intermediary metabolism of glucose and amino acids. Normally it catalyses the reversible transamination between alanine and 2-oxoglutarate to form pyruvate and glutamate. Other tasks are the participation in cellular nitrogen metabolism and also in liver gluconeogenesis.

Glutamate pyruvate transaminase has a lot of biochemical functions, for example, L-alanine:2-oxoglutarate aminotransferase activity, pyridoxal phosphate binding. GPT has many direct interactions with proteins and molecules

The protein is found mainly in the liver, but also in heart and skeletal muscles. GPT is a specific indicator of liver disease if the serum level raises. Serum activity levels of Alanine aminotransferase 1 are routinely used as a biomarker of liver injury caused by drug toxicity, alcohol and infection.

In this work this protein has 40 entries in the final list. It is connected to several terms of hepatotoxicity like jaundice, liver injury, acute hepatic failure hepatic cirrhosis, hepatic necrosis, hepatic steatosis. The interaction with this protein seems to have not a negative cause of side effects but only show that there is some kind of hepatotoxicity already going on when Alanine aminotransferase concentrations were marked as elevated.

Despite it is the protein with the most entries, it is only mentioned in the data sourced from DITOP. The reason for that is that it is more a kind of marker than a cause for hepatotoxicity and therefore has no entries in my list.

4.2.3. Bile salt export pump

The Bile salt export pump (BSEP) transporter belongs to the ATP-binding cassette (ABC) transporter protein family. It is encoded by the ABCB11 gene. BSEP contains 12 putative membrane-spanning helices. It has a length of 1,321AA and a mass of 146,407 Da. The Bile salt export pump is responsible for the secretion of conjugated bile salts across the canalicular membrane of hepatocytes followed by the export into the gastrointestinal tract. This is done in an ATP-dependent manner utilizing the energy from ATP hydrolysis against the concentration gradient. BSEP is almost exclusively expressed in the liver. There it is localized in the cholesterol-rich canalicular membrane of hepatocytes on the apical side of the bile canalicular membrane. A very low level can be found in kidney, testis, and choroid plexus. It is the major transporter for the secretion of bile acids from hepatocytes into bile in humans.

The Bile salt export pump translocates substrates including endogene ones such as taurocholate, estradiol-17 β-glucuronide, but also others like bosentan, cholic acid, muricholates and other mono-anionic bile salts. [32]. BSEP activity in the liver canalicular membrane is inhibited by a number of drugs or drug metabolites. It is the primary transporter responsible for excretion of monovalent bile acids into the bile, build-up of bile salts in the liver. This dysfunction of the transporter can lead to cholestasis and drug-induced liver injury (DILI). This is the reason why it has a high importance in drug development and why it is important that BSEP interactions should be considered.

A couple of mutations are detected in the human BSEP gene that led to progressive familial intrahepatic cholestasis type 2 (PFIC2). This is very likely caused by genetic mutation, suppression of gene expression, disturbed signaling, or steric BSEP inhibitors such as cyclosporine A, rifampicin, glibenclamide. [33]

Even the EMA recommends to screen compounds as inhibitors of BSEP during the research of new drugs. In this thesis BSEP can be linked to DILI, Cholestasis and liver injury.

15 different journals are found that give a connection between this protein and hepatotoxic effects. The final table holds 25 entries of the enzyme. The articles are all published after the millennial what states that those findings are relatively new.

4.2.4. CYP3A4

Cytochromes P450 are heme-thiolate monooxygenases found in all domains of life. It is named after the heme group, which absorbs light at the wave length of 450nm. The most prominent isoenzyme of this family is the CYP 3A4. It is mainly located in the liver and small intestine. Other names of the protein include Albendazole sulfoxidase, Nifedipine oxidase or Taurochenodeoxycholate 6-alpha-hydroxylase. It has a mass of 57,343Da and a length of 503 aminoacids (AA). CYP3A4 contributes to bile acid detoxification, the termination of action of steroid hormones, and elimination of phytochemicals in food and the majority of xenobiotics. Human liver cytochrome P450 3A4 is the main enzyme involved in drug metabolism and is responsible for the metabolism of about 50% of medicines. CYP3A4 is implicated in an NADPH-dependent electron transport pathway in liver microsomes and accomplishes a number of oxidation reactions for example caffeine 8-oxidation, omeprazole sulphoxidation and midazolam 4-hydroxylation. [34] Women seem to have higher CYP3A4 activity than men and CYP3A4 activity is absent in new-borns but reaches adult levels at around one year of age [39].

Potent inhibitors of CYP3A4 include clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, goldenseal and grapefruit. That effect is sometimes more than desirable. For example, Ritonavir is used to create higher levels of other HIV-Protease-Inhibitors while a HIV treatment and to spare the expensive Ciclosporin A. [35]

Inducers of CYP3A4 include phenobarbital, phenytoin, rifampicin, St. John's Wort and glucocorticoids. The induction of CYP3A is the basis for a multitude of common drug-drug interactions.

In our case CYP3A4 has 34 entries in the final list. The keyword always refers to hepatotoxicity. The connection to toxic effect is stated from 16 different journals in the years from 1991 until 2005. That shows that this toxic effect of this protein is already well known, but still of great value in research.

4.2.5. Phosphatidylcholine translocator ABCB4

Adenosine triphosphate (ATP)-binding cassette, sub-family B, member 4 (ABCB4) belongs to the ATP-binding cassette transporter superfamily. At the same time it is also called multidrug resistance 3 (MDR3). It has a mass of 141,523 Da and a length of 1,286 AA. ABCB4 is situated at the canalicular membrane of hepatocytes. It is responsible for the regulation of biliary lipid secretion and mediates the translocation of phosphatidylcholine into bile. This phospholipid efflux translocator works energy dependent. Phosphatidylcholine (PC) is transported from the inner to the outer leaflet of the canalicular membrane bilayer into the canaliculi of hepatocytes. ABCB4 encodes a flippase for PC. This makes the phospholipids available for extraction by bile salts and therefore protects from the activity of bile salts.

Genetic defects of ABCB4 can lead to progressive familial intrahepatic cholestasis type 3 (PFIC3). Evidence refers to a rare autosomic recessive disease arising early in childhood and other cholestatic or cholelithiasic diseases in heterozygous adults [36]

5. OUTLOOK

In this work, assuredly only a fraction of the existing hepatotoxicity related targets is mentioned. This is because on one hand, not all targets are yet identified which are related to hepatotoxicity and on the other hand, the underlying mechanisms of the hepatotoxic effect can't be so easily connected to one certain target. There are often even multiple pathways which are not so simple to detect. Moreover, every day findings in scientific research offer new opportunities to extend this list. Scientists are working worldwide on the field of hepatotoxicity and how to prevent it. Some of them haven't published their work yet and haven't shared their discoveries with the public. It would be eminently interesting to collect more data out of other data sources all over the world. Another approach would be to have a look at the withdrawals from the market and their affected targets. If some pharmaceutical companies would share their company secrets about failed compounds and test series, a more detailed picture of hepatotoxicity could be drawn. It is eligible to sort out the hepatotoxic components before patients will get harmed or too much time and money is invested in their research. This topic will be on many more minds in the near future. Improving drug safety and enhance people's lives will be a desirable goal to achieve.

6. ABSTRACT

The liver is an important organ in the human body and of immense significance to human health. Because the liver is often confronted with drugs and other xenobiotics hepatotoxicity remains a major reason for drug withdrawal from the market and the need for further pharmaceutical development.

At first the term hepatotoxicity and its related terms were looked at more closely. Therefore, different databases related to adverse drug reactions and their medical dictionaries were compared to and the results outlined. The different terminology of liver diseases is compared and the databases like MedDRA, ADReCS and SIDER are introduced.

The main aspect of this work however is to picture the connection of a hepatic adverse side effect and specific proteins. This early detection of such livertoxic components is important for saving time and lives within the search for new drugs.

On this account, a table was created which provides the connection of a certain target and its possible adverse outcome. The data mining was done manually by a literature search mainly based on PubMed. Then this list was matched with the list of the Chinese database called DITOP. A part of the work steps was done with the help of KNIME. The result of this final table is that some proteins were in both lists, but some were unique in each list. The outcome is a table containing 104 entries of proteins, which could possibly be related to hepatotoxic side effects.

Additional information like Uniprot accession number and gene name, journal, name and date of the publication is given. Furthermore, another table shows the journals and their Impact Factor, which tries to help to evaluate the credibility of the publications.

Examination reveals that there is a connection between certain proteins and toxic side effects, which could be predictable for some of them. In summary the subset of results shows that there is still a lot of research to do. The growing insight into mechanisms of hepatotoxicity is necessary for further approach of non-toxic drugs.

7. ZUSAMMENFASSUNG

Die Leber stellt eines der wichtigsten Organe des Körpers dar und ist für die Gesundheit des Menschen von außerordentlicher Bedeutung. Da die Leber oft mit toxischen Arzneimitteln und Xenobiotika konfrontiert ist, ist Hepatotoxizität einer der häufigsten Gründe ein Medikament vom Markt zu nehmen oder dessen weitere klinische Erprobung einzustellen.

Am Anfang dieser Diplomarbeit, war die Frage der Terminologie zu klären, welche im weiteren Verlauf verwendet werden würde. Sämtliche Datenbanken, die sich mit unerwünschten Nebenwirkungen auseinandersetzen, und einige medizinischen Lexika wie MedDRA, ADReCS, SIDER werden in dieser Arbeit kurz vorgestellt. Die unterschiedliche Terminologie der Lebererkrankungen wird verglichen.

Der Hauptaspekt der Arbeit betrifft jedoch die Frage, ob zwischen potentieller leberschädigender Nebenwirkung und spezifischen Proteinen ein Zusammenhang erkennbar ist. So wird versucht die Verbindung zwischen dem negativen Effekt und dem Protein zu erkennen. Diese frühzeitliche Erkennung von leberschädigenden Komponenten ist bei der Forschung nach neuen Medikamenten essentiell um Zeit und Leben zu sparen. Dazu wurden mit Hilfe einer Literaturrecherche Daten gesammelt und eine Tabelle erstellt, welche Proteine enthält, die im Verdacht stehen leberschädigend zu wirken. Das Datenmaterial wurde hauptsächlich über PubMed generiert. Im späteren Verlauf wird diese Liste mit einer chinesischen Datenbank namens DITOP zusammengeführt. Ein Teil der Arbeitsschritte wurde mit KNIME durchgeführt. Das Resultat dieser finalen Tabelle ist, dass einige Proteine in beiden Ursprungslisten zu finden sind, andere liefern jedoch keine Überschneidungen. Das Ergebnis ist eine Tabelle die insgesamt 104 Proteine umfasst, die potentiell mit verschiedenen lebertoxischen Nebenwirkungen in Verbindung gebracht werden können. Zusätzliche Informationen wie Uniprot accession number und gene name, sowie der Name der Publikation und deren Erscheinungsdatum, das Journal und der betroffene Organismus können aus der Tabelle abgelesen werden. Außerdem wurde eine Liste der verwendeten Journale und ihrer Impact Faktoren erstellt, um die Seriosität der Publikationen besser einschätzen zu können.

Die Untersuchung ergab, dass diese Korrelation zwischen Protein und toxischer Nebenwirkung für einige Proteine vorhersagbar ist. Zusammenfassend lässt sich sagen, dass noch viel Forschung auf diesem Gebiet betrieben werden sollte, um Hepatotoxizität frühzeitig auszuschließen.

8. APPENDIX

8.1. List of figures

8.2. List of tables

8.3 Table of hepatotoxicity related targets created by Strobl J.

No.	Uniprot AC	Target Uniprot protein name	Uniprot gene name	Organism	Toxicity	MedDRA	PubMED ID, Reference	Comment	Date of Publication	Journal	DOI
1	Q14994	Nuclear receptor subfamily 1 group I member 3	NR1I3	Mus musculus (Mouse)	Hepatotoxicity	10019851	12376703	green	2002	Science	10.1126/science.1073502
2	Q14994	Nuclear receptor subfamily 1 group I member 3	NR1I3	Homo sapiens (Human)	Hepatotoxicity	10019851	27293091	green	2016	Biochemistry	10.1134/S0006297916040040
3	Q14994	Nuclear receptor subfamily 1 group I member 3	NR1I3	Mus musculus (Mouse)	Hepatic steatosis	10019708	27180240	green	2016	Toxicology and applied pharmacology	10.1016/j.taap.2016.05.006
4	P35348	Alpha-1A adrenergic receptor	ADRA1A	Homo sapiens (Human)	Hepatotoxicity	10019851	9187524	red	1997	Drug metabolism review	10.3109/03602539709037587
5	P07550	Beta-2 adrenergic receptor	ADRB2	Wistar rat (Rat)	Cardiac anaphylaxis	N/A	28353311	green	2017	Cardiology Journal	10.5603/CJ.a2017.0034
6	P08913	Alpha-2A adrenergic receptor	ADRA2A	Rattus norvegicus (Rat)	Adverse effects	N/A	7938249	red	1994	Physiology and behavior	10.1016/0031-9384(94)90206-2
7	P10635	Cytochrome P450 2D6	CYP2D6	Homo sapiens (Human)	Hepatotoxicity	10019851	N/A	yellow	1998	Clinical communication	10.1002/jppr1998284254

8	P10635	Cytochrome P450 2D6	CYP2D6	Homo sapiens (Human)	Hepatotoxicity	10019851	11089838	yellow	2000	Lancet	10.1016/S0140-6736(00)03167-6
9	P10635	Cytochrome P450 2D6	CYP2D6	Homo sapiens (Human)	Hepatotoxicity	10019851	8788564	green	1995	Pharmacology and therapeutics	10.1016/0163-7258(95)02013-6
10	P08913	Alpha-2A adrenergic receptor	ADRA2A	Mus musculus (Mouse)	Hepatotoxicity	10019851	1957308	green	1991	Toxicology and applied pharmacology	10.1016/0041-008X(91)90022-7
11	P03372	Estrogen receptor	ESR1	Homo sapiens (Human)	Hepatotoxicity	10019851	23875763	green	2013	Critical reviews in toxicology	10.3109/10408444.2013.811215
12	P12821	Angiotensin-converting enzyme	ACE	Homo sapiens (Human)	Hepatotoxicity	10019851	23875763	green	2013	Critical reviews in toxicology	10.3109/10408444.2013.811215
13	P12821	Angiotensin-converting enzyme	ACE	Homo sapiens (Human)	Liver injury	10067125	20593053	yellow	2010	Journal of gastrointestinal and liver diseases	N/A
14	P12821	Angiotensin-converting enzyme	ACE	Homo sapiens (Human)	Hepatitis	10019717	14651558	green	2003	Pediatrics international: official journal of the Japan Pediatric Society	10.1111/j.1442-200X.2003.01817.x
15	Q14994	Nuclear receptor subfamily 1	NR1I3	Homo sapiens (Human)	Hepatotoxicity	10019851	14674787	red	2003	Clinical pharmacokinetics	10.2165/00003088-

		group I member 3									200342150-00003
16	O75469	Nuclear receptor subfamily 1 group I member 2	NR1I2	Homo sapiens (Human)	Hepatotoxicity	10019851	14674787	red	2003	Clinical pharmacokinetics	10.2165/00003088-200342150-00003
17	Q96RI1	Farnesoid X receptor	NR1H4	Homo sapiens (Human)	Hepatotoxicity	10019851	14674787	red	2003	Clinical pharmacokinetics	10.2165/00003088-200342150-00003
18	O75469	Nuclear receptor subfamily 1 group I member 2	NR1I2	Homo sapiens (Human)	Hepatotoxicity	10019851	11090943	red	2000	Toxicology	10.1016/S0300-483X(00)00300-0
19	P14740	Dipeptidyl peptidase 4	Dpp4	Rattus norvegicus (Rat)	Hepatotoxicity	10019851	8605291	yellow	1995	Chemical research in toxicology	10.1021/tx00050a001
20	P14740	Dipeptidyl peptidase 4	Dpp4	Rattus norvegicus (Rat)	Hepatotoxicity	10019851	15822174	yellow	2005	Annual review of pharmacology and toxicology	10.1146/annurev.pharmtox.45.120403.100058
21	P23219	Prostaglandin G/H synthase 1	PTGS1	Homo sapiens (Human)	Hepatotoxicity	10019851	15626590	green	2005	Prostaglandins, leukotrienes and essential fatty acids	10.1016/j.plefa.2004.10.005 and 10.1146/annurev.pharmtox.45.120403.100058

22	P31327	Carbamoyl-phosphate synthase [ammonia], mitochondrial	CPS1	Rattus norvegicus (Rat)	Hepatic encephalopathy	10019660	3413798	yellow	1988	Toxicology	10.1016/0300-483X(88)90085-6
23	P00966	Argininosuccinate synthase	ASS1	Rattus norvegicus (Rat)	Hepatic encephalopathy	10019660	3413798	yellow	1988	Toxicology	10.1016/0300-483X(88)90085-6
24	P00734	Prothrombin	F2	Homo sapiens (Human)	DILI	10072734	20020269	yellow	2010	Handbook of experimental pharmacology	10.1007/978-3-642-00663-0_13
25	P00734	Prothrombin	F2	Homo sapiens (Human)	Hepatotoxicity	10019851	15383641	yellow	2004	The Annals of pharmacotherapy	10.1345/aph.1E078
26	P00734	Prothrombin	F2	Homo sapiens (Human	Hepatotoxicity	10019851	Antitargets S.11	yellow	2008	N/A	N/A
27	P37231	Peroxisome proliferator-activated receptor gamma	PPARG	Homo sapiens (Human)	Acute liver failure	10049844	AntitargetsS.10f	yellow	2008	N/A	N/A
28	P23219	Prostaglandin G/H synthase 1	PTGS1	Homo sapiens (Human)	Hepatotoxicity	10019851	Antitargets	yellow	2008	N/A	N/A
29	P10635	Cytochrome P450 2D6	CYP2D6	Homo sapiens (Human)	Hepatotoxicity	10019851	AntitargetsS.9	green	2008	N/A	N/A
30	P08684	Cytochrome P450 3A4	CYP3A4	Homo sapiens (Human)	Hepatotoxicity	10019851	Antitargets S.9+11	green	2008	N/A	N/A

31	P37231	Peroxisome proliferator-activated receptor gamma	PPARG	Homo sapiens (Human	Acute liver injuries	10067970	12526954	yellow	2003	The American journal of gastroenterology	10.1111/j.1572-0241.2003.07175.x
32	P54098	DNA polymerase subunit gamma-1	POLG	Homo sapiens (Human)	Hepatic failure	10019663	9258627	green	1997	American journal of gastroenterology	10.2165/00002018-199717010-00001
33	Q9UHN1	DNA polymerase subunit gamma-2, mitochondrial	POLG2	Homo sapiens (Human)	Hepatic failure	10019663	9258627	green	1997	American journal of gastroenterology	10.2165/00002018-199717010-00001
34	P54098	DNA polymerase subunit gamma-1	POLG	Homo sapiens (Human)	Hepatotoxicity	10019851	8622980	green	1996	Proceedings of the National Academy of Sciences of the United States of America	N/A
35	Q9UHN1	DNA polymerase subunit gamma-2, mitochondrial	POLG2	Homo sapiens (Human)	Hepatotoxicity	10019851	8622980	green	1996	Proceedings of the National Academy of Sciences of the United States of America	N/A
36	P04798	Cytochrome P450 1A1	CYP1A1	Homo sapiens (Human)	Expressed in lung, placenta, lymphocytes,	N/A	Antitargets S.199	red	2008	N/A	N/A
37	P05177	Cytochrome P450 1A2	CYP1A2	Homo sapiens (Human)	Expressed in liver , inducable, sensitive	N/A	Antitargets S.199	red	2008	N/A	N/A

38	P05181	Cytochrome P450 2E1	CYP2E1	Homo sapiens (Human)	Hepatitis	10019717	Antitargets S.269	green	2008	N/A	N/A
39	P05177	Cytochrome P450 1A2	CYP1A2	Homo sapiens (Human)	Hepatitis	10019717	Antitargets S269	green	2008	N/A	N/A
40	P11712	Cytochrome P450 2C9	CYP2C9	Homo sapiens (Human)	Hepatitis	10019717	Antitargets S.269	green	2008	N/A	N/A
41	O75469	Nuclear receptor subfamily 1 group I member 2	NR1I2	Homo sapiens (Human)	Cholestasis	10008635	AntitargetsS .302	green	2008	N/A	N/A
42	Q92887	Canalicular multispecific organic anion transporter 1	ABCC2	Homo sapiens (Human)	Dubin-Johnson-Syndrom	10013800	Antitargets S.303	green	2008	N/A	N/A
43	O75469	Nuclear receptor subfamily 1 group I member 2	NR1I2	Homo sapiens (Human)	Hepatotoxicity	10019851	Antitargets S.323	green	2008	N/A	N/A
44	O75469	Nuclear receptor subfamily 1 group I member 2	NR1I2	Homo sapiens (Human)	Cholestasis	10008635	11248086	green	2001	N/A	10.1073/pnas. 051014398
45	Q14994	Nuclear receptor subfamily 1 group I member 3	NR1I3	Homo sapiens (Human)	Hepatotoxicity	10019851	Antitargets S.325	green	2008	N/A	N/A

46	Q96RI1	Bile acid receptor	NR1H4	Homo sapiens (Human)	Cholestasis	10008635	Antitargets S.327	green	2008	N/A	N/A
47	Q13133	Oxysterols receptor LXR-alpha	NR1H3	Homo sapiens (Human)	Hepatotoxicity	10019851	Antitargets S.328	yellow	2008	N/A	N/A
48	P55055	Oxysterols receptor LXR-beta	NR1H2	Homo sapiens (Human)	Hepatotoxicity	10019851	Antitargets S.328	yellow	2008	N/A	N/A
49	Q9Y6L6	Solute carrier organic anion transporter family member 1B1	SLCO1B1	Homo sapiens (Human	Hyperbilirubinemia	10020578	15535988	green	2004	Chemico-biological interactions	10.1016/j.cbi.2004.08.008
50	Q96RI1	Bile acid receptor	NR1H4	Homo sapiens (Human)	Hepatotoxicity	10019851	16107136	yellow	2005	Journal of medicinal chemistry	10.1021/jm0582221
51	P08684	Cytochrome P450 3A4	CYP3A4	Homo sapiens (Human)	Hepatotoxicity	10019851	11170509	yellow	2001	Chemical research in toxicology	10.1021/tx000180q
52	P08684	Cytochrome P450 3A4	CYP3A4	Homo sapiens (Human)	Hepatotoxicity	10019851	10628745	green	2000	Molecular endocrinology	10.1210/mend.14.1.0409
53	O75469	Nuclear receptor subfamily 1 group I member 2	NR1I2	Homo sapiens (Human)	Hepatotoxicity	10019851	10628745	green	2000	Molecular endocrinology	10.1210/mend.14.1.0409
54	P08684	Cytochrome P450 3A4	CYP3A4	Homo sapiens (Human)	Hepatotoxicity	10019851	Antitargets and Drug Safety S.136	yellow	2015	N/A	N/A

55	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	Progressive familial intrahepatic cholestasis type 2	10008635	Antitargets and Drug Safety S.160	green	2015	N/A	N/A
56	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	Cholestasis	10008635	Antitargets and Drug Safety S.160	green	2015	N/A	N/A
57	O75469	Nuclear receptor subfamily 1 group I member 2	NR1I2	Homo sapiens (Human)	Liver injury	10067125	Antitargets and Drug Safety S.160	yellow	2015	N/A	N/A
58	Q92887	Canalicular multispecific organic anion transporter 1	ABCC2	Homo sapiens (Human)	Cholestasis	10008635	Antitargets and Drug Safety S.162	green	2015	N/A	N/A
59	O15438	Canalicular multispecific organic anion transporter 2	ABCC3	Homo sapiens (Human)	Cholestasis	10008635	Antitargets and Drug Safety S.162	green	2015	N/A	N/A
60	O15439	Multidrug resistance-associated protein 4	ABCC4	Homo sapiens (Human)	Cholestasis	10008635	Antitargets and Drug Safety S.162	green	2015	N/A	N/A
61	O95342	Bile salt export pump	ABCB11	in vitro	DILI	10072734	Antitargets and Drug Safety S.181	yellow	2015	N/A	N/A
62	P00533	Epidermal growth factor receptor	EGFR	Homo sapiens (Human)	Skin toxicity	N/A	Antitargets and Drug	green	2015	N/A	N/A

							Safety S.371+381				
63	O60656	UDP-glucuronosyltransferase 1-9	UGT1A9	Homo sapiens (Human)	Liver failure	10024678	Antitargets and Drug Safety S.374	green	2015	N/A	N/A
64	P00533	Epidermal growth factor receptor	EGFR	Homo sapiens (Human)	Lung injury	N/A	Antitargets and Drug Safety S.388f	yellow	2015	N/A	N/A
65	P00519	Tyrosine-protein kinase ABL1	ABL1	Homo sapiens (Human)	Cardiotoxicity	N/A	Antitargets and Drug Safety S.405	yellow	2015	N/A	N/A
66	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	Cholestasis	10008635	21702456	green	2011	Chemical research in toxicology	10.1021/tx200168d
67	P11712	Cytochrome P450 2C9	CYP2C9	Homo sapiens (Human)	Hepatotoxicity	10019851	21702456	yellow	2011	Chemical research in toxicology	10.1021/tx200168d
68	O60656	UDP-glucuronosyltransferase 1-9	UGT1A9	Homo sapiens (Human)	Hepatic failure	10019663	21702456	green	2011	Chemical research in toxicology	10.1021/tx200168d
69	Q9Y6L6	Solute carrier organic anion transporter family member 1B1	SLCO1B1	Homo sapiens (Human)	Hepatotoxicity	10019851	2835398	yellow	1988	The Journal of clinical investigation	10.1124/pr.109.002014
70	Q14973	Sodium/bile acid cotransporter	SLC10A1	Homo sapiens (Human)	Hepatotoxicity	10019851	2835398	green	1988	The Journal of clinical investigation	10.1124/pr.109.002014
71	P21447	Multidrug resistance protein 1A	Abcb1a	Mus musculus (Mouse)	Hepatocyte necrosis	10019692	2835398	red	1988	The Journal of clinical investigation	10.1124/pr.109.002014

72	Q92887	Canalicular multispecific organic anion transporter 1	ABCC2	Homo sapiens (Human)	Cholestasis of pregnancy	10049055	2835398	red	1988	The Journal of clinical investigation	10.1124/pr.109.002014
73	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	Cholestasis	10008635	24115749	green	2014	Drug metabolism and disposition: the biological fate of chemicals	10.1124/dmd.113.054205
74	P21439	Phosphatidylcholine translocator ABCB4	ABCB4	Homo sapiens (Human)	Cholestasis	10008635	24115749	green	2014	Drug metabolism and disposition: the biological fate of chemicals	10.1124/dmd.113.054205
75	O43520	Phospholipid-transporting ATPase IC	ATP8B1	Homo sapiens (Human)	Progressive familial intrahepatic cholestasis type 1	10008635	24115749	green	2014	Drug metabolism and disposition: the biological fate of chemicals	10.1124/dmd.113.054205
76	O15068	Guanine nucleotide exchange factor DBS	MCF2L	Homo sapiens (Human)	Could trigger intrahepatic cholestasis	10008635	24115749	yellow	2014	Drug metabolism and disposition: the biological fate of chemicals	10.1124/dmd.113.054205

77	Q92887	Canalicular multispecific organic anion transporter 1	ABCC2	Homo sapiens (Human)	Could trigger intrahepatic cholestasis	10008635	24115749	yellow	2014	Drug metabolism and disposition: the biological fate of chemicals	10.1124/dmd.113.054205
78	O15438	Canalicular multispecific organic anion transporter 2	ABCC3	Homo sapiens (Human)	Could trigger intrahepatic cholestasis	10008635	24115749	yellow	2014	Drug metabolism and disposition: the biological fate of chemicals	10.1124/dmd.113.054205
79	O15439	Multidrug resistance-associated protein 4	ABCC4	Homo sapiens (Human)	Could trigger intrahepatic cholestasis	10008635	24115749	yellow	2014	Drug metabolism and disposition: the biological fate of chemicals	10.1124/dmd.113.054205
80	Q14973	Sodium/bile acid cotransporter	SLC10A1	Homo sapiens (Human)	Prehepatic cholestasis	10008635	24115749	yellow	2014	Drug metabolism and disposition: the biological fate of chemicals	10.1124/dmd.113.054205
81	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	DILI	10072734	24014644	green	2013	Toxicological sciences: an official journal of the Society of Toxicology	10.1093/toxsci/kft197

82	Q14032	Bile acid-CoA:amino acid N-acyltransferase	BAAT	Homo sapiens (Human)	Cholestasis	10008635	22783059	yellow	2012	World journal of gastroenterology	10.3748/wjg.v18.i25.3322
83	Q9NPD5	Solute carrier organic anion transporter family member 1B3	SLCO1B3	Homo sapiens (Human)	Hepatic failure	10019663	17006912	red	2006	Hepatology	10.1002/hep.21359
84	P08183	Multidrug resistance protein 1	ABCB1	Homo sapiens (Human)	Hepatotoxicity	10019851	17006912	yellow	2006	Hepatology	10.1002/hep.21359
85	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human	Cholestasis	10008635	20422497	yellow	2010	Seminars in liver disease	10.1055/s-0030-1253224
86	P21439	Phosphatidylcholine translocator ABCB4	ABCB4	Homo sapiens (Human	Cholestasis	10008635	20422497	yellow	2010	Seminars in liver disease	10.1055/s-0030-1253224
87	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	DILI	10072734	22961681	green	2012	Drug metabolism and disposition: the biological fate of chemicals	10.1124/dmd.112.047068
88	O70127	Bile salt export pump	Abcb11	Rattus norvegicus (Rat)	Hepatotoxicity	10019851	11179459	yellow	2001	Molecular pharmacology	10.1124/mol.59.3.627

89	Q91Y86	Mitogen-activated protein kinase 8	Mapk8	Mus musculus (Mouse)	Protection	N/A	17366662	yellow	2007	Hepatology	10.1002/hep.21475
90	P12235	ADP/ATP translocase 1	SLC25A4	Homo sapiens (Human)	Acute hepatic failure	10000804	11128230	red	2000	Therapeutic drug monitoring	10.1097/00007691-200012000-00001
91	Q9Y6L6	Solute carrier organic anion transporter family member 1B1	SLCO1B1	Homo sapiens (Human)	Hepatotoxicity	10019851	14977862	green	2004	Drug metabolism and disposition: the biological fate of chemicals	10.1124/dmd.32.3.291
92	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	Cholestasis	10008635	12404239	green	2002	Gastroenterology	10.1053/gast.2002.36591
93	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	DILI	10072734	11309550	green	2001	Clinical pharmacology and therapeutics	10.1067/mcp.2001.114667
94	Q92887	Canalicular multispecific organic anion transporter 1	ABCC2	Homo sapiens (Human)	Cholestasis	10008635	10869290	green	2000	Hepatology	10.1053/jhep.2000.8263
95	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	Cholestasis	10008635	15522265	green	2004	Chemico-biological interactions	10.1016/j.cbi.2004.09.011
96	P21439	Phosphatidylcholine	ABCB4	Homo sapiens (Human)	Cholestasis	10008635	15522265	green	2004	Chemico-biological interactions	10.1016/j.cbi.2004.09.011

		translocator ABCB4									
97	P08183	Multidrug resistance protein 1	ABCB1	Homo sapiens (Human)	Cholestasis	10008635	15522265	green	2004	Chemico-biological interactions	10.1016/j.cbi.2004.09.011
98	Q92887	Canalicular multispecific organic anion transporter 1	ABCC2	Homo sapiens (Human)	Cholestasis	10008635	15522265	green	2004	Chemico-biological interactions	10.1016/j.cbi.2004.09.011
99	P08684	Cytochrome P450 3A4	CYP3A4	Homo sapiens (Human)	Hepatotoxicity	10019851	15522265	green	2004	Chemico-biological interactions	10.1016/j.cbi.2004.09.011
100	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	DILI	10072734	19683031	green	2010	Toxicology	10.1016/j.tox.2009.08.007
101	P08684	Cytochrome P450 3A4	CYP3A4	Homo sapiens (Human)	Hepatotoxicity	10019851	15805052	green	2005	Toxicologic pathology	10.1080/01926230590522284
102	P04035	3-hydroxy-3-methylglutaryl-coenzyme A reductase	HMGCR	Guinea pig liver	Hepatotoxicity	10019851	2077527	red	1990	Pharmacology and toxicology	10.1111/j.1600-0773.1990.tb00840.x
103	Q05421	Cytochrome P450 2E1	Cyp2e1	Mus musculus (Mouse)	Hepatotoxicity	10019851	8662637	yellow	1996	The journal of biological chemistry	10.1074/jbc.271.20.12063
104	P05181	Cytochrome P450 2E1	CYP2E1	Homo sapiens (Human)	Hepatitis	10019717	12668988	yellow	2003	Hepatology	10.1053/jhep.2003.50144
105	O43520	Phospholipid-transporting ATPase IC	ATP8B1	Homo sapiens (Human)	Cholestasis	10008635	12663868	yellow	2003	Physiological reviews	10.1152/physrev.00027.2002

106	P21439	Phosphatidylcholine translocator ABCB4	ABCB4	Homo sapiens (Human)	Progressive cholestatic liver injury	N/A	12663868	yellow	2003	Physiological reviews	10.1152/physrev.00027.2002
107	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	Progressive familial intrahepatic cholestasis	N/A	12663868	yellow	2003	Physiological reviews	10.1152/physrev.00027.2002
108	Q92887	Canalicular multispecific organic anion transporter 1	ABCC2	Homo sapiens (Human)	Dubin-Johnson syndrome	10013800	12663868	yellow	2003	Physiological reviews	10.1152/physrev.00027.2002
109	O15438	Canalicular multispecific organic anion transporter 2	ABCC3	Homo sapiens (Human)	Cholestasis	10008635	12663868	red	2003	Physiological reviews	10.1152/physrev.00027.2002
110	O70127	Bile salt export pump	Abcb11	Rattus norvegicus (Rat)	Cholestasis	10008635	17364884	green	2007	Drug metabolism reviews	10.1080/03602530601093489
111	P22309	UDP-glucuronosyltransferase 1-1	UGT1A1	Homo sapiens (Human)	Idiosyncratic liver toxicity	N/A	N/A	green	2002	Chemico-Biological Interactions	10.1016/S0009-2797(02)00051-0
112	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	Cholestasis	10008635	20028269	green	2010	Drug metabolism reviews	10.3109/03602530903492004
113	P11712	Cytochrome P450 2C9	CYP2C9	Homo sapiens (Human)	Drug induced hepatitis	10019717	10851284	yellow	2000	Canadian journal of gastroenterology	N/A

114	P05177	Cytochrome P450 1A2	CYP1A2	Homo sapiens (Human)	Drug induced hepatitis	10019717	10851284	yellow	2000	Canadian journal of gastroenterology	N/A
115	P05181	Cytochrome P450 2E1	CYP2E1	Homo sapiens (Human)	Drug induced hepatitis	10019717	10851284	yellow	2000	Canadian journal of gastroenterology	N/A
116	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	Cholestasis	10008635	N/A	green	2001	Molecular Pharmacology	10.1124/mol.59.3.627
117	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	Cholestasis	10008635	24335466	green	2014	Drug metabolism and disposition: the biological fate of chemicals	10.1124/dmd.113.054189
118	Q92887	Canalicular multispecific organic anion transporter 1	ABCC2	Homo sapiens (Human)	Dubin-Johnson syndrome	10013800	21103974	green	2011	Handbook of experimental pharmacology	10.1007/978-3-642-14541-4_8
119	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	DILI	10072734	24154606	green	2014	Drug metabolism and disposition: the biological fate of chemicals	10.1124/dmd.113.054304
120	O15439	Multidrug resistance-	ABCC4	Homo sapiens (Human)	Cholestasis	10008635	24154606	green	2014	Drug metabolism and disposition:	10.1124/dmd.113.054304

		associated protein 4								the biological fate of chemicals	
121	Q96RI1	Bile acid receptor	NR1H4	Homo sapiens (Human)	Cholestasis inPFIC1	10008635	17291602	green	2007	Biochimica et biophysica acta	10.1016/j.bbamcr.2006.04.014
122	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	Liver injury	10067125	23956101	green	2013	Toxicological Sciences	10.1093/toxsci/kft176
123	O15439	Multidrug resistance-associated protein 4	ABCC4	Homo sapiens (Human)	Liver injury	10067125	23956101	green	2013	Toxicological Sciences	10.1093/toxsci/kft176
124	Q92887	Canalicular multispecific organic anion transporter 1	ABCC2	Homo sapiens (Human)	Liver injury	10067125	23956101	green	2013	Toxicological Sciences	10.1093/toxsci/kft176
125	P11712	Cytochrome P450 2C9	CYP2C9	Homo sapiens (Human)	Liver failure, fatal DILI	10024678	19839004	yellow	2010	Hepatology	10.1002/hep.23317
126	P33261	Cytochrome P450 2C19	CYP2C19	Homo sapiens (Human)	Liver failure, fatal DILI	10024678	19839004	yellow	2010	Hepatology	10.1002/hep.23317
127	P10635	Cytochrome P450 2D6	CYP2D6	Homo sapiens (Human)	Liver failure, fatal DILI	10024678	19839004	yellow	2010	Hepatology	10.1002/hep.23317
128	Q96RI1	Bile acid receptor	NR1H4	Homo sapiens (Human)	Cholestasis	10008635	19595470	yellow	2009	Journal of hepatology	10.1016/j.jhep.2009.05.012
129	P21439	Phosphatidylcholine translocator ABCB4	ABCB4	Homo sapiens (Human)	Cholestasis	10008635	19595470	yellow	2009	Journal of hepatology	10.1016/j.jhep.2009.05.012

130	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	DILI	10072734	19595470	green	2009	Journal of hepatology	10.1016/j.jhep.2009.05.012
131	O43520	Phospholipid-transporting ATPase IC	ATP8B1	Homo sapiens (Human)	Cholestatic liver disease	10008641	19595470	green	2009	Journal of hepatology	10.1016/j.jhep.2009.05.012
132	Q92887	Canalicular multispecific organic anion transporter 1	ABCC2	Homo sapiens (Human)	Cholestasis and Jaundice	10008636	19595470	green	2009	Journal of hepatology	10.1016/j.jhep.2009.05.012
133	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	Cholestasis	10008635	19684528	green	2009	Current Opinion in Lipidology	10.1097/MOL.0b013e32832b677c
134	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	Cholestasis	10008635	21103971	green	2010	Handbook of experimental pharmacology	10.1007/978-3-642-14541-4_5
135	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	Cholestasis	10008635	28437613	green	2017	Chemical research in toxicology	10.1021/acs.chemrestox.7b00048
136	P21439	Phosphatidylcholine translocator ABCB4	ABCB4	Homo sapiens (Human)	Cholestasis	10008635	28437613	green	2017	Chemical research in toxicology	10.1021/acs.chemrestox.7b00048
137	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	Cholestasis	10008635	16760228	green	2006	Drug metabolism and disposition: the biological fate of chemicals	10.1124/dmd.105.008748

138	Q14973	Sodium/bile acid cotransporter	SLC10A1	Homo sapiens (Human)	Cholestasis	10008635	16760228	yello w	2006	Drug metabolism and disposition: the biological fate of chemicals	10.1124/dmd.105.008748
139	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	Liver injury	10067125	21801835	green	2012	The journal of steroid biochemistry and molecular biology	10.1016/j.jsbmb.2011.06.012
140	O95342	Bile salt export pump	ABCB11	Homo sapiens (Human)	Cholestasis, DILI	10008635	22795478	green	2012	Clinics and Research in Hepatology and Gastroenterology	10.1016/j.clinre.2012.06.006
141	Q148W0	Phospholipid-transporting ATPase IC	Atp8b1	Mus musculus (Mouse)	Cholestasis	10008635	21801835	green	2012	The journal of steroid biochemistry and molecular biology	10.1016/j.jsbmb.2011.06.012
142	O75469	Nuclear receptor subfamily 1 group I member 2	NR1I2	Homo sapiens (Human)	Cholestasis	10008635	21801835	yello w	2012	The journal of steroid biochemistry and molecular biology	10.1016/j.jsbmb.2011.06.012
143	Q96RI1	Bile acid receptor	NR1H4	Homo sapiens (Human)	Cholestasis	10008635	21801835	yello w	2012	The journal of steroid biochemistry	10.1016/j.jsbmb.2011.06.012

										and molecular biology	
144	Q14994	Nuclear receptor subfamily 1 group I member 3	NR1I3	Homo sapiens (Human)	Hepatic steatosis	10019708	26451809	green	2016	Critical reviews in toxicology	10.3109/10408444.2015.1089471
145	P03372	Estrogen receptor	ESR1	Homo sapiens (Human)	Hepatic steatosis	10019708	26451809	green	2016	Critical reviews in toxicology	10.3109/10408444.2015.1089471
146	Q96RI1	Bile acid receptor	NR1H4	Homo sapiens (Human)	Hepatic steatosis	10019708	26451809	green	2016	Critical reviews in toxicology	10.3109/10408444.2015.1089471
147	P04150	Glucocorticoid receptor	NR3C1	Homo sapiens (Human)	Hepatic steatosis	10019708	26451809	green	2016	Critical reviews in toxicology	10.3109/10408444.2015.1089471
148	Q13133	Oxysterols receptor LXR-alpha	NR1H3	Homo sapiens (Human)	Hepatic steatosis	10019708	26451809	green	2016	Critical reviews in toxicology	10.3109/10408444.2015.1089471
149	Q07869	Peroxisome proliferator-activated receptor alpha	PPARA	Homo sapiens (Human)	Hepatic steatosis	10019708	26451809	green	2016	Critical reviews in toxicology	10.3109/10408444.2015.1089471
150	P37231	Peroxisome proliferator-activated receptor gamma	PPARG	Homo sapiens (Human)	Hepatic steatosis	10019708	26451809	green	2016	Critical reviews in toxicology	10.3109/10408444.2015.1089471
151	O75469	Nuclear receptor subfamily 1	NR1I2	Homo sapiens (Human)	Hepatic steatosis	10019708	26451809	green	2016	Critical reviews in toxicology	10.3109/10408444.2015.1089471

		group I member 2									
152	P10276	Retinoic acid receptor alpha	RARA	Homo sapiens (Human)	Hepatic steatosis	10019708	26451809	green	2016	Critical reviews in toxicology	10.3109/10408444.2015.1089471
153	P10826	Retinoic acid receptor beta	RARB	Homo sapiens (Human)	Hepatic steatosis	10019708	26451809	green	2016	Critical reviews in toxicology	10.3109/10408444.2015.1089471
154	P13631	Retinoic acid receptor gamma	RARG	Homo sapiens (Human)	Hepatic steatosis	10019708	26451809	green	2016	Critical reviews in toxicology	10.3109/10408444.2015.1089471
155	P35869	Aryl hydrocarbon receptor	AHR	Homo sapiens (Human)	Hepatic steatosis	10019708	26451809	green	2016	Critical reviews in toxicology	10.3109/10408444.2015.1089471

8.4 Final Table: Hepatotoxicity related targets from Strobl J. merged with DITOP targets

No.	Uniprot AC	Uniprot	Hepatotoxicity	MedDRA	DOI	Journal	Year of Publlication	Label
1	O00443	PIK3C2A	Liver injury	10067125	10.1111/j.1530-0277.1999.tb04182.x	Alcoholism, clinical and experimental research	1999	D
2	O00443	PIK3C2A	Liver injury	10067125	10.1111/j.1530-0277.1995.tb01528.x	Alcoholism, clinical and experimental research	1995	D
3	O00443	PIK3C2A	Liver injury	10067125	10.1111/j.1530-0277.1998.tb05921.x	Alcoholism, clinical and experimental research	1998	D
4	O00443	PIK3C2A	Liver injury	10067125	N/A	Cancer Research	1996	D
5	O00754	MAN2B1	Metastases to liver	10027457	10.1200/JCO.2001.19.5.1256	Clinical Cancer Research	2002	D
6	O00754	MAN2B1	Metastases to liver	10027457	N/A	Clinical Cancer Research	2001	D
7	O00754	MAN2B1	Metastases to liver	10027457	N/A	Cancer Research	1994	D
8	O00754	MAN2B1	Metastases to liver	10027457	10.1093/oxfordjournals.annonc.a058878	Annals of oncology	1994	D
9	O00754	MAN2B1	Metastases to liver	10027457	N/A	Clinical chemistry	1994	D
10	O00754	MAN2B1	Metastases to liver	10027457	N/A	Clincal Cancer Research	2003	D
11	O00754	MAN2B1	Metastases to liver	10027457	N/A	Clincal Cancer Research	2003	D
12	O00754	MAN2B1	Metastases to liver	10027457	10.1200/JCO.2006.08.6165	Clinical Cancer Research	2002	D
13	O00754	MAN2B1	Metastases to liver	10027457	N/A	Clincal Cancer Research	1997	D
14	O15068	MCF2L	Could trigger intrahepatic cholestasis	10008635	10.1124/dmd.113.054205	Drug metabolism and disposition: the biological fate of chemicals	2014	S

15	O15438	ABCC3	Cholestasis	10008635	10.1152/physrev.00027.2002	Physiological reviews	2003	S
16	O15438	ABCC3	Could trigger intrahepatic cholestasis	10008635	10.1124/dmd.113.054205	Drug metabolism and disposition: the biological fate of chemicals	2014	S
17	O15439	ABCC4	Liver injury	10067125	10.1093/toxsci/kft176	Toxicological Sciences	2013	S
18	O15439	ABCC4	Could trigger intrahepatic cholestasis	10008635	10.1124/dmd.113.054205	Drug metabolism and disposition: the biological fate of chemicals	2014	S
19	O15439	ABCC4	Cholestasis	10008635	10.1124/dmd.113.054304	Drug metabolism and disposition: the biological fate of chemicals	2014	S
20	O43520	ATP8B1	Cholestasis	10008635	10.1152/physrev.00027.2002	Physiological reviews	2003	S
21	O43520	ATP8B1	Progressive familial intrahepatic cholestasis type 1	10008635	10.1124/dmd.113.054205	Drug metabolism and disposition: the biological fate of chemicals	2014	S
22	O43520	ATP8B1	Cholestatic liver disease	10008641	10.1016/j.jhep.2009.05.012	Journal of hepatology	2009	S
23	O60656	UGT1A9	Hepatotoxicity	10019851	10.1124/dmd.30.3.324	Drug metabolism and disposition: the biological fate of chemicals	2002	D
24	O60656	UGT1A9	Hepatotoxicity	10019851	10.1021/tx050317i	Chemical research in toxicology	2006	D
25	O60656	UGT1A9	Hepatotoxicity	10019851	10.1093/toxsci/kfi211	Toxicological sciences: an official journal of the Society of Toxicology	2005	D

26	O60656	UGT1A9	Hepatotoxicity	10019851	10.1111/j.1365-2125.2005.02446.x	British journal of clinical pharmacology	2005	D
27	O60656	UGT1A9	Hepatic failure	10019663	10.1021/tx200168d	Chemical research in toxicology	2011	S
28	O70127	Abcb11	Hepatotoxicity	10019851	10.1124/mol.59.3.627	Molecular pharmacology	2001	S
29	O70127	Abcb11	Cholestasis	10008635	10.1080/03602530601093489	Drug metabolism reviews	2007	S
30	O75469	NR1I2	Cholestasis	10008635	10.1016/j.jsbmb.2011.06.012	The journal of steroid biochemistry and molecular biology	2012	S
31	O75469	NR1I2	Hepatotoxicity	10019851	10.2165/00003088-200342150-00003	Clinical pharmacokinetics	2003	S
32	O75469	NR1I2	Hepatic steatosis	10019708	10.3109/10408444.2015.1089471	Critical reviews in toxicology	2016	S
33	O75469	NR1I2	Hepatotoxicity	10019851	10.1210/mend.14.1.0409	Molecular endocrinology	2000	S
34	O75469	NR1I2	Hepatotoxicity	10019851	10.1016/S0300-483X(00)00300-0	Toxicology	2000	S
35	O95342	ABCB11	Liver injury	10067125	10.1093/toxsci/kft176	Toxicological Sciences	2013	S
36	O95342	ABCB11	Cholestasis	10008635	10.1016/j.cbi.2004.09.011	Chemico-biological interactions	2004	S
37	O95342	ABCB11	Progressive familial intrahepatic cholestasis		10.1152/physrev.00027.2002	Physiological reviews	2003	S
38	O95342	ABCB11	DILI	10072734	10.1016/j.tox.2009.08.007	Toxicology	2010	S

39	O95342	ABCB11	Cholestasis	10008635	10.1124/mol.59.3.627	Molecular Pharmacology	2001	S
40	O95342	ABCB11	Liver injury	10067125	10.1016/S0168-8278(02)00107-1	Journal of hepatology	2002	D
41	O95342	ABCB11	Cholestasis	10008635	10.1124/dmd.113.054205	Drug metabolism and disposition: the biological fate of chemicals	2014	S
42	O95342	ABCB11	DILI	10072734	10.1093/toxsci/kft197	Toxicological sciences: an official journal of the Society of Toxicology	2013	S
43	O95342	ABCB11	Cholestasis	10008635	10.1021/acs.chemrestox.7b00048	Chemical research in toxicology	2017	S
44	O95342	ABCB11	Liver injury	10067125	10.1016/j.jsbmb.2011.06.012	The journal of steroid biochemistry and molecular biology	2012	S
45	O95342	ABCB11	Cholestasis	10008635	10.1055/s-0030-1253224	Seminars in liver disease	2010	S
46	O95342	ABCB11	Cholestasis	10008635	10.1124/dmd.105.008748	Drug metabolism and disposition: the biological fate of chemicals	2006	S
47	O95342	ABCB11	DILI	10072734	10.1124/dmd.112.047068	Drug metabolism and disposition: the biological fate of chemicals	2012	S
48	O95342	ABCB11	DILI	10072734	10.1016/j.jhep.2009.05.012	Journal of hepatology	2009	S
49	O95342	ABCB11	Cholestasis	10008635	10.1097/MOL.0b013e32832b677c	Current Opinion in Lipidology	2009	S

50	O95342	ABCB11	DILI	10072734	10.1124/dmd.113.054304	Drug metabolism and disposition: the biological fate of chemicals	2014	S
51	O95342	ABCB11	Cholestasis	10008635	10.3109/03602530903492004	Drug metabolism reviews	2010	S
52	O95342	ABCB11	Cholestasis	10008635	10.1021/tx200168d	Chemical research in toxicology	2011	S
53	O95342	ABCB11	Cholestasis, DILI	10008635	10.1016/j.clinre.2012.06.006	Clinics and Research in Hepatology and Gastroenterology	2012	S
54	O95342	ABCB11	DILI	10072734	10.1067/mcp.2001.114667	Clinical pharmacology and therapeutics	2001	S
55	O95342	ABCB11	Liver injury	10067125	10.1067/mcp.2001.114667	Clinical pharmacology and therapeutics	2001	D
56	O95342	ABCB11	Cholestasis	10008635	10.1053/gast.2002.36591	Gastroenterology	2002	S
57	O95342	ABCB11	Cholestasis	10008635	10.1124/dmd.113.054189	Drug metabolism and disposition: the biological fate of chemicals	2014	S
58	O95342	ABCB11	Cholestasis	10008635	10.1007/978-3-642-14541-4_5	Handbook of experimental pharmacology	2010	S
59	O95342	ABCB11	Liver injury	10067125	10.1016/S0300-483X(01)00460-7	Toxicology	2001	D
60	P00338	LDHA	Hepatotoxicity	10019851	10.3109/01480548809017880	Drug and Chemical Toxicology	1988	D
61	P00338	LDHA	Hepatotoxicity	10019851	10.1016/0041-008X(84)90277-1	Toxicology and applied pharmacology	1984	D

62	P00338	LDHA	Hepatotoxicity	10019851	10.1016/0041-008X(84)90278-3	Toxicology and applied pharmacology	1984	D
63	P00338	LDHA	Hepatotoxicity	10019851	N/A	National Toxicology Program technical report series	1993	D
64	P00338	LDHA	Hepatotoxicity	10019851	10.1006/taap.1993.1021	Toxicology and applied pharmacology	1993	D
65	P00338	LDHA	Hepatotoxicity	10019851	10.1016/0041-008X(91)90179-I	Toxicology and applied pharmacology	1991	D
66	P00338	LDHA	Hepatotoxicity	10019851	10.1016/0300-483X(76)90003-2	Toxicology	1976	D
67	P00505	GOT2	Acute hepatic failure	10000804	10.1177/106002809202600504	The annals of pharmacotherapy	1992	D
68	P00505	GOT2	Acute hepatic failure	10000804	10.1177/106002809402801005	The annals of pharmacotherapy	1994	D
69	P00505	GOT2	Acute hepatic failure	10000804	10.1345/aph.1A414	The annals of pharmacotherapy	2002	D
70	P00519	ABL1	Hepatomegaly	10019842	10.1006/bcmd.1998.0166	Blood cells, molecules & diseases	1998	D
71	P00519	ABL1	Hepatomegaly	10019842	10.1038/sj.leu.2403556	Leukemia	2005	D
72	P00519	ABL1	Hepatomegaly	10019842	10.1046/j.1365-2141.2002.03241.x	British journal of haematology	2002	D
73	P00519	ABL1	Hepatomegaly	10019842	N/A	The Journal of the Association of Physicians of India	2000	D

74	P00533	EGFR	Hepatic function abnormal	10019670	10.1002/(SICI)1097-4652(199611)169:2<309::AID-JCP10>3.0.CO;2-4	Journal of cellular physiology	1996	D
75	P00533	EGFR	Hepatic function abnormal	10019670	10.1016/0002-9610(92)90271-R	American journal of surgery	1992	D
76	P00533	EGFR	Hepatic function abnormal	10019670	10.1016/S0168-8278(97)80432-1	Journal of hepatology	1997	D
77	P00533	EGFR	Hepatic function abnormal	10019670	10.1016/S0963-6897(98)00008-6	Cell transplantation	1998	D
78	P00533	EGFR	Hepatic function abnormal	10019670	10.1002/jmv.10264	Journal of Medical Virology	2003	D
79	P00533	EGFR	Hepatic function abnormal	10019670	10.1002/hep.510270630	Hepatology	1998	D
80	P00533	EGFR	Hepatic function abnormal	10019670	10.1002/hep.510230609	Hepatology	1996	D
81	P00734	F2	DILI	10072734	10.1007/978-3-642-00663-0_13	Handbook of experimental pharmacology	2010	S
82	P00734	F2	Hepatotoxicity	10019851	10.1345/aph.1E078	The Annals of pharmacotherapy	2004	S
83	P00738	HP	Hepatic steatosis	10019708	N/A	Journal of Veterinary Medical Science	1993	D
84	P00738	HP	Hepatic function abnormal	10019670	10.1002/(SICI)1097-4652(199611)169:2<309::AID-JCP10>3.0.CO;2-4	Journal of Cellular Physiology	1996	D

85	P00738	HP	Hepatic steatosis	10019708	10.1016/S0168-8278(97)80432-1	Journal of Veterinary Medical Science	2002	D
86	P00738	HP	Hepatic steatosis	10019708	N/A	American journal of veterinary research	1994	D
87	P00738	HP	Hepatic function abnormal	10019670	10.1016/0002-9610(92)90271-R	The American Journal of Surgery	1992	D
88	P00738	HP	Hepatic function abnormal	10019670	10.1016/S0168-8278(97)80432-1	Journal of Hepatology	1997	D
89	P00738	HP	Hepatic steatosis	10019708	N/A	American journal of veterinary research	1993	D
90	P00738	HP	Hepatic steatosis	10019708	10.1292/jvms.55.481	American journal of veterinary research	1993	D
91	P00738	HP	Hepatic steatosis	10019708	N/A	American journal of veterinary research	1992	D
92	P00738	HP	Hepatic steatosis	10019708	N/A	Veterinary research communications	1994	D
93	P00738	HP	Hepatic function abnormal	10019670	N/A	Cell Transplantation	1998	D
94	P00738	HP	Hepatic function abnormal	10019670	10.1002/jmv.10264	Journal of Medical Virology	2003	D
95	P00738	HP	Hepatic function abnormal	10019670	10.1002/hep.510270630	Hepatology	1998	D
96	P00738	HP	Hepatic function abnormal	10019670	10.1002/hep.510230609	Hepatology	1996	D
97	P00966	ASS1	Hepatic encephalopathy	10019660	10.1016/0300-483X(88)90085-6	Toxicology	1988	S

98	P02741	CRP	Hepatitis	10019717	N/A	Masui	1995	D
99	P02741	CRP	Hepatitis	10019717	N/A	Masui	1990	D
100	P02741	CRP	Hepatitis	10019717	10.1055/s-2008-1055506	Deutsche Medizinische Wochenschrift	1995	D
101	P02741	CRP	Hepatitis	10019717	N/A	Masui	2002	D
102	P02741	CRP	Hepatitis	10019717	N/A	Masui	1994	D
103	P02741	CRP	Hepatitis	10019717	10.1097/00000542-200107000-00038	Anesthesiology	2001	D
104	P02741	CRP	Hepatitis	10019717	N/A	Regional anesthesia and pain medicine	2003	D
105	P02741	CRP	Hepatitis	10019717	N/A	Acta anaesthesiologica Sinica	1998	D
106	P02741	CRP	Hepatitis	10019717	N/A	Journal of the Formosan Medical Association	1996	D
107	P02763	ORM1	Hepatic cirrhosis	10019641	10.1080/009841096161564	Journal of toxicology and environmental health	1996	D
108	P02763	ORM1	Hepatic cirrhosis	10019641	10.1080/15287399509532030	Journal of toxicology and environmental health	1995	D
109	P02763	ORM1	Hepatic cirrhosis	10019641	10.1054/mehy.2001.1354	Medical Hypotheses	2001	D
110	P02763	ORM1	Hepatic cirrhosis	10019641	10.1097/01.shk.0000126649.96850.36	Shock	2004	D
111	P03372	ESR1	Hepatotoxicity	10019851	10.3109/10408444.2013.811215	Critical reviews in toxicology	2013	S
112	P03372	ESR1	Hepatic steatosis	10019708	10.3109/10408444.2015.1089471	Critical reviews in toxicology	2016	S

113	P04035	HMGCR	Hepatotoxicity	10019851	10.1111/j.1600-0773.1990.tb00840.x	Pharmacology and toxicology	1990	S
114	P04150	NR3C1	Hepatotoxicity	10019851	N/A	Journal of pharmacokinetics and biopharmaceutics	1998	D
115	P04150	NR3C1	Hepatotoxicity	10019851	10.1023/A:1023233409550	Journal of pharmacokinetics and biopharmaceutics	1998	D
116	P04150	NR3C1	Hepatotoxicity	10019851	N/A	Journal of pharmacokinetics and biopharmaceutics	1992	D
117	P04150	NR3C1	Hepatic steatosis	10019708	10.3109/10408444.2015.1089471	Critical reviews in toxicology	2016	S
118	P04150	NR3C1	Hepatotoxicity	10019851	N/A	Journal of pharmacokinetics and biopharmaceutics	1995	D
119	P04406	GAPDH	Liver injury	10067125	10.1111/j.1530-0277.1999.tb04182.x	Alcoholism, clinical and experimental research	1999	D
120	P04406	GAPDH	Liver injury	10067125	10.1111/j.1530-0277.1995.tb01528.x	Alcoholism, clinical and experimental research	1995	D
121	P04406	GAPDH	Liver injury	10067125	10.1111/j.1530-0277.1998.tb05921.x	Alcoholism, clinical and experimental research	1998	D
122	P04406	GAPDH	Liver injury	10067125	N/A	Cancer Research	1996	D
123	P04731	MT1A	Hepatotoxicity	10019851	N/A	Research communication in chemical pathology and pharmacology	1987	D
124	P04731	MT1A	Hepatotoxicity	10019851	N/A	British medical Bulletin	1978	D
125	P04731	MT1A	Hepatotoxicity	10019851	N/A	Research communication in chemical pathology and pharmacology	1986	D

126	P04798	CYP1A1	Hepatotoxicity	10019851	N/A	Italian journal of gastroenterology and hepatology	1998	D
127	P04798	CYP1A1	Hepatotoxicity	10019851	N/A	The Journal of pharmacology and experimental therapeutics	1994	D
128	P05164	MPO	Hepatotoxicity	10019851	N/A	Advances in experimental medicine and biology	1991	D
129	P05164	MPO	Hepatotoxicity	10019851	10.1042/bss0610163	Biochemical Society Symposium	1995	D
130	P05164	MPO	Hepatotoxicity	10019851	10.3109/03602539208996297	Drug metabolism reviews	1992	D
131	P05177	CYP1A2	Hepatotoxicity	10019851	10.1111/j.1600-0609.1996.tb01652.x	European journal of haemotology. Supplementum.	1996	D
132	P05177	CYP1A2	Hepatotoxicity	10019851	10.1210/me.2005-0066	Molecular endocrinology	2005	D
133	P05177	CYP1A2	Hepatotoxicity	10019851	N/A	European journal of drug metabolism and pharmacokinetics	1998	D
134	P05177	CYP1A2	Hepatotoxicity	10019851	10.1016/S0168-8278(97)80495-3	Journal of hepatology	1997	D
135	P05177	CYP1A2	Hepatotoxicity	10019851	10.1126/science.1073502	Science	2002	D
136	P05177	CYP1A2	Hepatotoxicity	10019851	N/A	Journal of clinical gastroenterology	1998	D
137	P05177	CYP1A2	Drug induced hepatitis	10019717	N/A	Canadian journal of gastroenterology	2000	S

138	P05177	CYP1A2	Hepatotoxicity	10019851	10.1002/hep.510230619	Hepatology	1996	D
139	P05177	CYP1A2	Hepatotoxicity	10019851	10.1074/jbc.M409041200	The journal of biological chemistry	2004	D
140	P05177	CYP1A2	Hepatotoxicity	10019851	10.1126/science.298.5592.341a	Science	2002	D
141	P05181	CYP2E1	Hepatotoxicity	10019851	N/A	Anesthesia and analgesia	1995	D
142	P05181	CYP2E1	Hepatotoxicity	10019851	10.1210/me.2005-0066	Molecular endocrinology	2005	D
143	P05181	CYP2E1	Hepatotoxicity	10019851	N/A	Anesthesiology	1995	D
144	P05181	CYP2E1	Hepatotoxicity	10019851	10.1067/mcp.2000.104736	Clinical pharmacology and therapeutics	2000	D
145	P05181	CYP2E1	Hepatitis	10019717	N/A	European journal of gastroenterology and hepatology	1995	D
146	P05181	CYP2E1	Hepatitis	10019717	10.1007/s00228-006-0111-5	European journal of clinical pharmacology	2006	D
147	P05181	CYP2E1	Hepatitis	10019717	10.1053/jhep.2003.50144	Hepatology	2003	S
148	P05181	CYP2E1	Hepatotoxicity	10019851	N/A	The Journal of pharmacology and experimental therapeutics	1997	D
149	P05181	CYP2E1	Hepatotoxicity	10019851	N/A	The Journal of pharmacology and experimental therapeutics	1985	D
150	P05181	CYP2E1	Hepatotoxicity	10019851	N/A	The Journal of pharmacology and experimental therapeutics	1997	D

151	P05181	CYP2E1	Hepatotoxicity	10019851	N/A	Drug metabolism and disposition: the biological fate of chemicals	1996	D
152	P05181	CYP2E1	Hepatotoxicity	10019851	N/A	Drug metabolism and disposition: the biological fate of chemicals	1991	D
153	P05181	CYP2E1	Hepatotoxicity	10019851	N/A	Anesthesiology	1993	D
154	P05181	CYP2E1	Hepatotoxicity	10019851	N/A	Anesthesiology	1993	D
155	P05181	CYP2E1	Hepatotoxicity	10019851	10.1016/S0024-3205(01)01370-4	Life sciences	2001	D
156	P05181	CYP2E1	Hepatitis	10019717	10.1111/j.1572-0241.2001.05366.x	The American journal of gastroenterology	2001	D
157	P05181	CYP2E1	Hepatitis	10019717	10.1016/S0140-6736(00)04921-7	Lancet	2001	D
158	P05181	CYP2E1	Hepatotoxicity	10019851	10.1126/science.1073502	Science	2002	D
159	P05181	CYP2E1	Drug induced hepatitis	10019717	N/A	Canadian journal of gastroenterology	2000	S
160	P05181	CYP2E1	Hepatotoxicity	10019851	10.1074/jbc.M409041200	The journal of biological chemistry	2004	D
161	P05181	CYP2E1	Hepatitis	10019717	10.1111/j.1572-0241.2001.05368.x	The American journal of gastroenterology	2001	D
162	P05181	CYP2E1	Hepatotoxicity	10019851	10.1126/science.298.5592.341a	Science	2002	D
163	P05186	ALPL	Jaundice	10023126	N/A	Sexually transmitted diseases	1983	D

164	P05186	ALPL	Jaundice	10023126	N/A	The British Journal of venereal diseases	1984	D
165	P05186	ALPL	Jaundice	10023126	10.1056/NEJM198601303140503	The New England Journal of Medicine	1986	D
166	P05186	ALPL	Hepatotoxicity	10019851	10.1001/jama.283.1.74	Journal of the American Medical Association	2000	D
167	P05186	ALPL	Hepatotoxicity	10019851	10.1016/S0196064404005244	Annals of emergency medicine	2004	D
168	P05186	ALPL	Hepatotoxicity	10019851	10.1016/0002-9343(92)90687-7	The American Journal of Medicine	1992	D
169	P05186	ALPL	Jaundice	10023126	10.7326/0003-4819-97-2-216	Annals of internal medicine	1982	D
170	P05187	ALPP	Hepatitis	10019717	N/A	Masui	1995	D
171	P05187	ALPP	Hepatitis	10019717	N/A	Masui	1990	D
172	P05187	ALPP	Hepatitis	10019717	10.1055/s-2008-1055506	Deutsche Medizinische Wochenschrift	1995	D
173	P05187	ALPP	Hepatitis	10019717	N/A	Masui	2002	D
174	P05187	ALPP	Hepatitis	10019717	N/A	Masui	1994	D
175	P05187	ALPP	Hepatotoxicity	10019851	N/A	Clinical Cancer Research	2001	D
176	P05187	ALPP	Hepatitis	10019717	N/A	Anesthesiology	2001	D
177	P05187	ALPP	Hepatitis	10019717	10.1016/S1098-7339(03)00182-2	Regional anesthesia and pain medicine	2003	D
178	P05187	ALPP	Hepatitis	10019717	N/A	Acta anaesthesiologica Sinica	1998	D

179	P05187	ALPP	Hepatotoxicity	10019851	N/A	Clinical Cancer Research	2003	D
180	P05187	ALPP	Hepatotoxicity	10019851	10.1159/000055009	Onkologie	2000	D
181	P05187	ALPP	Hepatitis	10019717	N/A	Journal of the Formosan Medical Association	1996	D
182	P05305	EDN1	Liver disorder	10024670	10.1053/jhep.2001.22701	Hepatology	2001	D
183	P05305	EDN1	Liver disorder	10024670	N/A	The American Journal of Physiology	1999	D
184	P05305	EDN1	Liver disorder	10024670	10.1016/S0168-8278(03)00012-6	Journal of Hepatology	2003	D
185	P05305	EDN1	Liver disorder	10024670	10.1002/hep.20244	Hepatology	2004	D
186	P05362	ICAM1	Liver injury	10067125	10.1002/hep.510260621	Hepatology	1997	D
187	P05362	ICAM1	Liver injury	10067125	10.1016/S0891-5849(00)00490-1	Free Radical Biology and Medicine	2001	D
188	P05362	ICAM1	Liver injury	10067125	N/A	The American Journal of Physiology	1997	D
189	P05362	ICAM1	Liver injury	10067125	N/A	The American Journal of Physiology	2000	D
190	P05362	ICAM1	Liver injury	10067125	10.1002/hep.510240217	Hepatology	1996	D
191	P05362	ICAM1	Liver injury	10067125	10.1155/2000/735262	Canadian Journal of Gastroenterology	2000	D
192	P05362	ICAM1	Liver injury	10067125	10.1053/jhep.2001.25350	Hepatology	2001	D

193	P05412	JUN	Hepatotoxicity	10019851	N/A	Research communication in chemical pathology and pharmacology	1996	D
194	P05412	JUN	Hepatotoxicity	10019851	10.1016/0041-008X(84)90277-1	Toxicology and applied pharmacology	1984	D
195	P06132	UROD	Porphyrin metabolism disorder	10061356	10.1016/0020-711X(84)90134-4	The international journal of biochemistry	1984	D
196	P06132	UROD	Porphyrin metabolism disorder	10061356	10.1016/0016-5085(88)90191-6	Gastroenterology	1988	D
197	P06132	UROD	Porphyrin metabolism disorder	10061356	10.1042/cs0580477	Clinical Science	1980	D
198	P06132	UROD	Porphyrin metabolism disorder	10061356	N/A	Archives of dermatological research	1982	D
199	P06276	BCHE	Hepatotoxicity	10019851	10.1111/j.1365-2125.1980.tb01811.x	British Journal of Clinical Pharmacology	1980	D
200	P06276	BCHE	Hepatotoxicity	10019851	N/A	Medical Toxicology	1986	D
201	P07550	ADRB2	Hepatotoxicity	10019851	N/A	Drug metabolism reviews	1997	D
202	P07550	ADRB2	Hepatotoxicity	10019851	N/A	Research communications in chemical pathology and pharmacology	1984	D
203	P07550	ADRB2	Hepatotoxicity	10019851	10.1016/0300-483X(94)02924-J	Toxicology	1995	D

204	P07550	ADRB2	Hepatotoxicity	10019851	10.1016/0024-3205(94)00729-2	Life sciences	1994	D
205	P07550	ADRB2	Hepatotoxicity	10019851	N/A	National Toxicology Program technical report series	1993	D
206	P07550	ADRB2	Hepatotoxicity	10019851	10.1006/taap.1993.1021	Toxicology and applied pharmacology	1993	D
207	P07550	ADRB2	Hepatotoxicity	10019851	N/A	Toxicology and applied pharmacology	1991	D
208	P07550	ADRB2	Cardiac anaphylaxis	N/A	10.5603/CJ.a2017.0034	Cardiology Journal	2017	S
209	P08183	ABCB1	Cholestasis	10008635	10.1016/j.cbi.2004.09.011	Chemico-biological interactions	2004	S
210	P08183	ABCB1	Hepatotoxicity	10019851	10.1002/hep.21359	Hepatology	2006	S
211	P08620	FGF4	Hepatotoxicity	10019851	10.1093/carcin/16.8.1835	Carginogenesis	1995	D
212	P08620	FGF4	Hepatotoxicity	10019851	10.1093/carcin/20.11.2185	Carginogenesis	1999	D
213	P08620	FGF4	Hepatotoxicity	10019851	N/A	Cancer Research	1996	D
214	P08684	CYP3A4	Hepatotoxicity	10019851	10.1345/aph.17332	The Annals of pharmacotherapy	1998	D
215	P08684	CYP3A4	Hepatotoxicity	10019851	10.1016/0006-2952(93)90342-T	Biochemical pharmacology	1993	D
216	P08684	CYP3A4	Hepatotoxicity	10019851	10.1016/0006-2952(92)90696-G	Biochemical pharmacology	1992	D

217	P08684	CYP3A4	Hepatotoxicity	10019851	10.1016/j.cbi.2004.09.011	Chemico-biological interactions	2004	S
218	P08684	CYP3A4	Hepatotoxicity	10019851	10.1021/tx9700836	Chemical research in toxicology	1997	D
219	P08684	CYP3A4	Hepatotoxicity	10019851	10.1021/tx0100439	Chemical research in toxicology	2002	D
220	P08684	CYP3A4	Hepatotoxicity	10019851	10.1210/me.2005-0066	Molecular endocrinology	2005	D
221	P08684	CYP3A4	Hepatotoxicity	10019851	10.1016/0006-2952(93)90605-V	Biochemical pharmacology	1993	D
222	P08684	CYP3A4	Hepatotoxicity	10019851	10.1016/0300-483X(96)03352-5	Toxicology	1996	D
223	P08684	CYP3A4	Hepatotoxicity	10019851	10.1016/0378-4274(91)90037-7	Toxicology letters	1991	D
224	P08684	CYP3A4	Hepatotoxicity	10019851	10.1124/mol.54.6.1113	Molecular endocrinology	1998	D
225	P08684	CYP3A4	Hepatotoxicity	10019851	10.1021/tx0001981	Chemical research in toxicology	2001	D
226	P08684	CYP3A4	Hepatotoxicity	10019851	N/A	Italian journal of gastroenterology and hepatology	1998	D
227	P08684	CYP3A4	Hepatotoxicity	10019851	10.1016/S0924-977X(02)00005-6	European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology	2002	D

228	P08684	CYP3A4	Hepatotoxicity	10019851	10.1016/S0009-2797(02)00056-X	Chemical research in toxicology	2002	D
229	P08684	CYP3A4	Hepatotoxicity	10019851	10.1021/tx9802365	Chemical research in toxicology	1999	D
230	P08684	CYP3A4	Hepatotoxicity	10019851	10.1126/science.1073502	Science	2002	D
231	P08684	CYP3A4	Hepatotoxicity	10019851	N/A	Psychopharmacology	1999	D
232	P08684	CYP3A4	Hepatotoxicity	10019851	10.1080/01926230590522284	Toxicologic pathology	2005	S
233	P08684	CYP3A4	Hepatotoxicity	10019851	10.1021/tx050181o	Chemical research in toxicology	2005	D
234	P08684	CYP3A4	Hepatotoxicity	10019851	10.2165/00003088-199733030-00004	Clinical pharmacokinetics	1997	D
235	P08684	CYP3A4	Hepatotoxicity	10019851	N/A	Drug metabolism and disposition: the biological fate of chemicals	2000	D
236	P08684	CYP3A4	Hepatotoxicity	10019851	10.1016/S0009-2797(01)00163-6	Chemical research in toxicology	2001	D
237	P08684	CYP3A4	Hepatotoxicity	10019851	N/A	Drug metabolism and disposition: the biological fate of chemicals	1996	D
238	P08684	CYP3A4	Hepatotoxicity	10019851	10.1021/tx9802217	Chemical research in toxicology	1999	D
239	P08684	CYP3A4	Hepatotoxicity	10019851	N/A	Drug metabolism and disposition: the biological fate of chemicals	1999	D

240	P08684	CYP3A4	Hepatotoxicity	10019851	10.1021/tx000180q	Chemical research in toxicology	2001	S
241	P08684	CYP3A4	Hepatotoxicity	10019851	10.1021/tx000180q	Chemical research in toxicology	2001	D
242	P08684	CYP3A4	Hepatotoxicity	10019851	10.1074/jbc.M409041200	The journal of biological chemistry	2004	D
243	P08684	CYP3A4	Hepatotoxicity	10019851	10.1210/mend.14.1.0409	Molecular endocrinology	2000	S
244	P08684	CYP3A4	Hepatotoxicity	10019851	N/A	The Journal of pharmacology and experimental therapeutics	1994	D
245	P08684	CYP3A4	Hepatotoxicity	10019851	10.1126/science.298.5592.341a	Science	2002	D
246	P08684	CYP3A4	Hepatotoxicity	10019851	N/A	Drug metabolism and disposition: the biological fate of chemicals	1998	D
247	P08684	CYP3A4	Hepatotoxicity	10019851	10.1124/mol.58.1.48	Molecular endocrinology	2000	D
248	P08913	ADRA2A	Liver injury	10067125	10.3109/03602539709037587	Drug metabolism reviews	1997	D
249	P08913	ADRA2A	Adverse effects	N/A	10.1016/0031-9384(94)90206-2	Physiology and behavior	1994	S
250	P08913	ADRA2A	Liver injury	10067125	N/A	Research communications in chemical pathology and pharmacology	1984	D
251	P08913	ADRA2A	Liver injury	10067125	10.1016/0300-483X(94)02924-J	Toxicology	1995	D

252	P08913	ADRA2A	Liver injury	10067125	10.1016/0024-3205(94)00729-2	Life sciences	1994	D
253	P08913	ADRA2A	Liver injury	10067125	N/A	National Toxicology Program technical report series	1993	D
254	P08913	ADRA2A	Liver injury	10067125	10.1006/taap.1993.1021	Toxicology and applied pharmacology	1993	D
255	P08913	ADRA2A	Hepatotoxicity	10019851	10.1016/0041-008X(91)90022-7	Toxicology and applied pharmacology	1991	S
256	P08913	ADRA2A	Liver injury	10067125	N/A	Toxicology and applied pharmacology	1991	D
257	P0DMM9	SULT1A3	Hepatic necrosis	10019692	10.1016/0041-008X(86)90329-7	Toxicology and applied pharmacology	1986	D
258	P0DMM9	SULT1A3	Hepatic necrosis	10019692	10.1006/taap.1993.1178	Toxicology and applied pharmacology	1993	D
259	P0DMM9	SULT1A3	Hepatic necrosis	10019692	N/A	Drug metabolism and disposition: the biological fate of chemicals	1987	D
260	P10276	RARA	Hepatic steatosis	10019708	10.3109/10408444.2015.1089471	Critical reviews in toxicology	2016	S
261	P10635	CYP2D6	Hepatotoxicity	10019851	N/A	Drug metabolism and disposition: the biological fate of chemicals	1981	D
262	P10635	CYP2D6	Hepatotoxicity	10019851	10.1111/j.1365-2125.1989.tb05430.x	British journal of clinical pharmacology	1989	D

263	P10635	CYP2D6	Hepatotoxicity	10019851	10.1016/0168-8278(89)90003-2	Journal of hepatology	1989	D
264	P10635	CYP2D6	Liver failure, fatal DILI	10024678	10.1002/hep.23317	Hepatology	2010	S
265	P10635	CYP2D6	Hepatotoxicity	10019851	10.1002/jppr1998284254	Clinical communication	1998	S
266	P10635	CYP2D6	Hepatotoxicity	10019851	10.1016/S0140-6736(00)03167-6	Lancet	2000	S
267	P10635	CYP2D6	Hepatotoxicity	10019851	10.1053/cp.1999.v66.99989	Clinical pharmacology and therapeutics	1999	D
268	P10635	CYP2D6	Hepatotoxicity	10019851	10.1097/00008571-199710000-00007	Pharmacogenetics	1997	D
269	P10635	CYP2D6	Hepatotoxicity	10019851	10.1016/0163-7258(95)02013-6	Pharmacology and therapeutics	1995	S
270	P10826	RARB	Hepatic steatosis	10019708	10.3109/10408444.2015.1089471	Critical reviews in toxicology	2016	S
271	P11245	NAT2	Liver injury	10067125	10.1080/009841096161564	Journal of toxicology and environmental health	1996	D
272	P11245	NAT2	Liver injury	10067125	10.1080/15287399509532030	Journal of toxicology and environmental health	1995	D
273	P11245	NAT2	Liver injury	10067125	10.1054/mehy.2001.1354	Medical Hypotheses	2001	D
274	P11245	NAT2	Liver injury	10067125	10.1097/01.shk.0000126649.96850.36	Shock	2004	D

275	P11279	LAMP1	Liver injury	10067125	10.1111/j.1365-2133.1995.tb02697.x	The British Journal of dermatology	1995	D
276	P11279	LAMP1	Liver injury	10067125	N/A	Dermatology	1996	D
277	P11279	LAMP1	Liver injury	10067125	N/A	The British Journal of dermatology	2005	D
278	P11279	LAMP1	Liver injury	10067125	10.1111/j.1365-2133.2005.06422.x	The British Journal of dermatology	2005	D
279	P11279	LAMP1	Liver injury	10067125	10.1046/j.1365-2133.1996.d01-1036.x	The British Journal of dermatology	1996	D
280	P11279	LAMP1	Liver injury	10067125	10.1046/j.1365-2133.1996.35790.x	The British Journal of dermatology	1996	D
281	P11509	CYP2A6	Hepatotoxicity	10019851	N/A	The journal of pharmacology and experimental therapeutics	1997	D
282	P11509	CYP2A6	Hepatotoxicity	10019851	N/A	The journal of pharmacology and experimental therapeutics	1997	D
283	P11509	CYP2A6	Hepatotoxicity	10019851	N/A	Drug metabolism and disposition: the biological fate of chemicals	1996	D
284	P11509	CYP2A6	Hepatotoxicity	10019851	N/A	Drug metabolism and disposition: the biological fate of chemicals	1991	D
285	P11509	CYP2A6	Hepatotoxicity	10019851	N/A	Anesthesiology	1993	D

286	P11509	CYP2A6	Hepatotoxicity	10019851	10.1016/S0024-3205(01)01370-4	Life sciences	2001	D
287	P11712	CYP2C9	Hepatotoxicity	10019851	10.1021/tx9700836	Chemical research in toxicology	1997	D
288	P11712	CYP2C9	Hepatotoxicity	10019851	10.1021/tx0100439	Chemical research in toxicology	2002	D
289	P11712	CYP2C9	Hepatotoxicity	10019851	N/A	The Journal of pharmacology and experimental therapeutics	1997	D
290	P11712	CYP2C9	Hepatotoxicity	10019851	N/A	Drug metabolism and disposition: the biological fate of chemicals	1991	D
291	P11712	CYP2C9	Hepatotoxicity	10019851	10.1016/S0024-3205(01)01370-4	Life sciences	2001	D
292	P11712	CYP2C9	Hepatotoxicity	10019851	10.1021/tx9802365	Chemical research in toxicology	1999	D
293	P11712	CYP2C9	Hepatotoxicity	10019851	10.1021/tx980136z	Chemical research in toxicology	1999	D
294	P11712	CYP2C9	Liver failure, fatal DILI	10024678	10.1002/hep.23317	Hepatology	2010	S
295	P11712	CYP2C9	Hepatotoxicity	10019851	10.1021/tx050181o	Chemical research in toxicology	2005	D
296	P11712	CYP2C9	Hepatotoxicity	10019851	N/A	Drug metabolism and disposition: the biological fate of chemicals	2000	D

297	P11712	CYP2C9	Hepatotoxicity	10019851	10.1021/tx9802217	Chemical research in toxicology	1999	D
298	P11712	CYP2C9	Hepatotoxicity	10019851	10.1021/tx00039a023	Chemical research in toxicology	1994	D
299	P11712	CYP2C9	Hepatotoxicity	10019851	10.1021/tx200168d	Chemical research in toxicology	2011	S
300	P11712	CYP2C9	Hepatotoxicity	10019851	N/A	Drug metabolism and disposition: the biological fate of chemicals	1999	D
301	P11712	CYP2C9	Drug induced hepatitis	10019717	N/A	Canadian journal of gastroenterology	2000	S
302	P11926	ODC1	Hepatotoxicity	10019851	N/A	The journal of laboratory and clinical medicine	1985	D
303	P11926	ODC1	Hepatotoxicity	10019851	10.1002/jat.2550070206	Journal of applied toxicology: JAT	1987	D
304	P11926	ODC1	Hepatotoxicity	10019851	10.1177/019262338701500407	Toxicologic pathology	1987	D
305	P12235	SLC25A4	Acute hepatic failure	10000804	10.1097/00007691-200012000-00001	Therapeutic drug monitoring	2000	S
306	P12821	ACE	Liver injury	10067125	N/A	Journal of gastrointestinal and liver diseases	2010	S
307	P12821	ACE	Hepatotoxicity	10019851	10.3109/10408444.2013.811215	Critical reviews in toxicology	2013	S

308	P12821	ACE	Hepatitis	10019717	10.1111/j.1442-200X.2003.01817.x	Pediatrics international: official journal of the Japan Pediatric Society	2003	S
309	P13631	RARG	Hepatic steatosis	10019708	10.3109/10408444.2015.1089471	Critical reviews in toxicology	2016	S
310	P13807	GYS1	Hepatic function abnormal	10019670	10.2337/diab.29.4.266	Diabetes	1980	D
311	P13807	GYS1	Hepatic function abnormal	10019670	10.1042/bj3100819	The Biochemical journal	1995	D
312	P13807	GYS1	Hepatic function abnormal	10019670	10.1016/0885-4505(87)90008-9	Biochemical medicine and metabolic biology	1987	D
313	P13807	GYS1	Hepatic function abnormal	10019670	N/A	The Journal of biological chemistry	1984	D
314	P13807	GYS1	Hepatic function abnormal	10019670	10.1006/abbi.1995.1230	Archives of biochemistry and biophysics	1995	D
315	P13807	GYS1	Hepatic function abnormal	10019670	N/A	Acta physiologica, pharmacologica et therapeutica latinoamericana	1992	D
316	P13807	GYS1	Hepatic function abnormal	10019670	N/A	The journal of laboratory and clinical medicine	1975	D
317	P13807	GYS1	Hepatic function abnormal	10019670	10.1210/endo-113-6-2113	Endocrinology	1983	D
318	P14210	HGF	Hepatic function abnormal	10019670	10.1002/(SICI)1097-4652(199611)169:2<309:	Journal of cellular Physiology	1996	D

					:AID-JCP10>3.0.CO;2-4			
319	P14210	HGF	Hepatic function abnormal	10019670	10.1016/0002-9610(92)90271-R	American journal of surgery	1992	D
320	P14210	HGF	Hepatic function abnormal	10019670	10.1016/S0168-8278(97)80432-1	Journal of hepatology	1997	D
321	P14210	HGF	Hepatic function abnormal	10019670	10.1016/S0963-6897(98)00008-6	Cell Transplantation	1998	D
322	P14210	HGF	Hepatic function abnormal	10019670	10.1002/jmv.10264	Journal of Medical Virology	2003	D
323	P14210	HGF	Hepatic function abnormal	10019670	10.1002/hep.510270630	Hepatology	1998	D
324	P14210	HGF	Hepatic function abnormal	10019670	10.1002/hep.510230609	Hepatology	1996	D
325	P14672	SLC2A4	Liver disorder	10024670	10.1007/BF00580757	Acta Diabetologica	1994	D
326	P14672	SLC2A4	Liver disorder	10024670	10.1172/JCI116747	The journal of clinical investigation	1993	D
327	P14672	SLC2A4	Liver disorder	10024670	10.1080/00365510121046	Scandinavian journal of clinical and laboratory investigation	2001	D
328	P14740	Dpp4	Hepatotoxicity	10019851	10.1021/tx00050a001	Chemical research in toxicology	1995	S
329	P14740	Dpp4	Hepatotoxicity	10019851	10.1146/annurev.pharmtox.45.120403.100058	Annual review of pharmacology and toxicology	2005	S

330	P17735	TAT	Hepatotoxicity	10019851	N/A	Journal of pharmacokinetics and biopharmaceutics	1998	D
331	P17735	TAT	Hepatotoxicity	10019851	N/A	Journal of pharmacokinetics and biopharmaceutics	1998	D
332	P17735	TAT	Hepatotoxicity	10019851	N/A	Journal of pharmacokinetics and biopharmaceutics	1992	D
333	P17735	TAT	Hepatotoxicity	10019851	N/A	Journal of pharmacokinetics and biopharmaceutics	1995	D
334	P19224	UGT1A6	Hepatotoxicity	10019851	10.1124/dmd.30.3.324	Drug metabolism and disposition: the biological fate of chemicals	2002	D
335	P19224	UGT1A6	Hepatotoxicity	10019851	10.1021/tx050317i	Chemical research in toxicology	2006	D
336	P19224	UGT1A6	Hepatotoxicity	10019851	10.1093/toxsci/kfi211	Toxicological sciences: an official journal of the Society of Toxicology	2005	D
337	P19224	UGT1A6	Hepatotoxicity	10019851	10.1111/j.1365-2125.2005.02446.x	British jounal of clinical pharmacology	2005	D
338	P19440	GGT1	Hepatitis	10019717	N/A	Masui	1995	D
339	P19440	GGT1	Hepatitis	10019717	N/A	Masui	1990	D
340	P19440	GGT1	Hepatitis	10019717	10.1055/s-2008-1055506	Deutsche Medizinische Wochenschrift	1995	D
341	P19440	GGT1	Hepatitis	10019717	N/A	Masui	2002	D
342	P19440	GGT1	Hepatitis	10019717	N/A	Masui	1994	D

343	P19440	GGT1	Hepatitis	10019717	N/A	Anesthesiology	2001	D
344	P19440	GGT1	Hepatitis	10019717	10.1097/00115550-200307000-00016	Regional anesthesia and pain medicine	2003	D
345	P19440	GGT1	Hepatitis	10019717	N/A	Acta anaesthesiologica Sinica	1998	D
346	P19440	GGT1	Hepatitis	10019717	N/A	Journal of Formosan Medical Association	1996	D
347	P21439	ABCB4	Cholestasis	10008635	10.1016/j.cbi.2004.09.011	Chemico-biological interactions	2004	S
348	P21439	ABCB4	Progressive cholestatic liver injury		10.1152/physrev.00027.2002	Physiological reviews	2003	S
349	P21439	ABCB4	Cholestasis	10008635	10.1124/dmd.113.054205	Drug metabolism and disposition: the biological fate of chemicals	2014	S
350	P21439	ABCB4	Cholestasis	10008635	10.1021/acs.chemrestox.7b00048	Chemical research in toxicology	2017	S
351	P21439	ABCB4	Cholestasis	10008635	10.1055/s-0030-1253224	Seminars in liver disease	2010	S
352	P21439	ABCB4	Cholestasis	10008635	10.1016/j.jhep.2009.05.012	Journal of hepatology	2009	S
353	P21447	Abcb1a	Hepatocyte necrosis	10019692	10.1124/pr.109.002014	The Journal of clinical investigation	1988	S
354	P22309	UGT1A1	Idiosyncratic liver toxicity	N/A	10.1016/S0009-2797(02)00051-0	Chemico-Biological Interactions	2002	S

355	P22309	UGT1A1	Hepatotoxicity	10019851	10.1124/dmd.30.3.324	Drug metabolism and disposition: the biological fate of chemicals	2002	D
356	P22309	UGT1A1	Hepatotoxicity	10019851	10.1021/tx050317i	Chemical research in toxicology	2006	D
357	P22309	UGT1A1	Hepatotoxicity	10019851	10.1093/toxsci/kfi211	Toxicological sciences: an official journal of the Society of Toxicology	2005	D
358	P22309	UGT1A1	Hepatotoxicity	10019851	10.1111/j.1365-2125.2005.02446.x	British Journal of Clinical Pharmacology	2005	D
359	P23110	N/A	Hepatic function abnormal	10019670	10.1002/(SICI)1097-4652(199611)169:2<309::AID-JCP10>3.0.CO;2-4	Journal of cellular Physiology	1996	D
360	P23110	N/A	Hepatic function abnormal	10019670	10.1016/0002-9610(92)90271-R	The American Journal of Surgery	1992	D
361	P23110	N/A	Hepatic function abnormal	10019670	10.1016/S0168-8278(97)80432-1	Journal of Hepatology	1997	D
362	P23110	N/A	Hepatic function abnormal	10019670	10.1016/S0963-6897(98)00008-6	Cell Transplantation	1998	D
363	P23110	N/A	Hepatic function abnormal	10019670	10.1002/jmv.10264	Journal of Medical Virology	2003	D
364	P23110	N/A	Hepatic function abnormal	10019670	10.1002/hep.510270630	Hepatology	1998	D

365	P23110	N/A	Hepatic function abnormal	10019670	10.1002/hep.510230609	Hepatology	1996	D
366	P23219	PTGS1	Hepatotoxicity	10019851	10.1016/j.plefa.2004.10.005 and 10.1146/annurev.pharmtox.45.120403.100058	Prostaglandins, leukotrienes and essential fatty acids	2005	S
367	P24298	GPT	Liver injury	10067125	N/A	Drug metabolism reviews	1997	D
368	P24298	GPT	Hepatotoxicity	10019851	N/A	Anesthesiology	1979	D
369	P24298	GPT	Hepatotoxicity	10019851	10.1111/j.1600-0773.1990.tb00840.x	Pharmacology amd Toxicology	1990	D
370	P24298	GPT	Hepatotoxicity	10019851	N/A	Anesthesiology	1988	D
371	P24298	GPT	Hepatotoxicity	10019851	10.3109/00498258809167523	Xenobiotica	1988	D
372	P24298	GPT	Jaundice	10023126	N/A	Sexually transmitted diseases	1983	D
373	P24298	GPT	Hepatotoxicity	10019851	N/A	Drugs in R&D	2003	D
374	P24298	GPT	Hepatic cirrhosis	10019641	N/A	Journal of the American Veterinary Medical Association	1984	D
375	P24298	GPT	Hepatotoxicity	10019851	N/A	Anesthesiology	1983	D
376	P24298	GPT	Hepatic necrosis	10019692	N/A	British journal of anesthesia	1986	D

377	P24298	GPT	Hepatic necrosis	10019692	N/A	Drug metabolism and disposition: the biological fate of chemicals	1984	D
378	P24298	GPT	Hepatotoxicity	10019851	N/A	Research communication in chemical pathology and pharmacology	1987	D
379	P24298	GPT	Liver injury	10067125	N/A	Research communication in chemical pathology and pharmacology	1984	D
380	P24298	GPT	Hepatotoxicity	10019851	10.1111/j.1600-0773.1988.tb00909.x	Pharmacology amd Toxicology	1988	D
381	P24298	GPT	Jaundice	10023126	10.1136/sti.60.6.387	The British Journal of venereal diseases	1984	D
382	P24298	GPT	Jaundice	10023126	10.1056/NEJM198601303140503	The New England Journal of Medicine	1986	D
383	P24298	GPT	Acute hepatic failure	10000804	10.1177/106002809202600504	The annals of pharmacotherapy	1992	D
384	P24298	GPT	Hepatotoxicity	10019851	N/A	Anesthesiology	1981	D
385	P24298	GPT	Hepatotoxicity	10019851	10.1016/0041-008X(83)90306-X	Toxicology and applied pharmacology	1983	D
386	P24298	GPT	Hepatic cirrhosis	10019641	N/A	Journal of the American Veterinary Medical Association	1982	D
387	P24298	GPT	Hepatic cirrhosis	10019641	N/A	Journal of the American Veterinary Medical Association	1985	D
388	P24298	GPT	Hepatic necrosis	10019692	10.1111/j.1600-0773.1983.tb01861.x	Acta pharmacologica et toxicologica	1983	D
389	P24298	GPT	Hepatic steatosis	10019708	10.1111/j.1600-0773.1983.tb01861.x	Acta pharmacologica et toxicologica	1983	D
390	P24298	GPT	Hepatotoxicity	10019851	N/A	Pediatric infectious disease	1985	D
391	P24298	GPT	Hepatotoxicity	10019851	N/A	Acta pharmacologica et toxicologica	1983	D
392	P24298	GPT	Hepatotoxicity	10019851	10.1021/tx950153d	Chemical research in toxicology	1996	D
393	P24298	GPT	Liver injury	10067125	10.1016/0300-483X(94)02924-J	Toxicology	1995	D

394	P24298	GPT	Liver injury	10067125	10.1016/0024-3205(94)00729-2	Life sciences	1994	D
395	P24298	GPT	Liver injury	10067125	N/A	National Toxicology Program technical report series	1993	D
396	P24298	GPT	Liver injury	10067125	10.1006/taap.1993.1021	Toxicology and applied pharmacology	1993	D
397	P24298	GPT	Acute hepatic failure	10000804	10.1177/106002809402801005	The annals of pharmacotherapy	1994	D
398	P24298	GPT	Acute hepatic failure	10000804	10.1345/aph.1A414	The annals of pharmacotherapy	2002	D
399	P24298	GPT	Liver injury	10067125	10.1016/0041-008X(91)90022-7	Toxicology and applied pharmacology	1991	D
400	P24298	GPT	Hepatotoxicity	10019851	10.1164/arrd.1978.118.3.461	The American review of respiratory disease	1978	D
401	P24298	GPT	Hepatotoxicity	10019851	10.1002/hep.1840050214	Hepatology	1985	D
402	P24298	GPT	Hepatotoxicity	10019851	N/A	The journal of pharmacology and experimental therapeutics	1986	D
403	P24298	GPT	Jaundice	10023126	10.7326/0003-4819-97-2-216	Annals of internal medicine	1982	D
404	P24298	GPT	Hepatic necrosis	10019692	10.1093/toxsci/kfg033	Toxicological sciences: an official journal of the Society of Toxicology	2003	D
405	P24298	GPT	Hepatotoxicity	10019851	N/A	The journal of pharmacology and experimental therapeutics	1989	D
406	P24298	GPT	Hepatotoxicity	10019851	10.1164/arrd.1979.119.6.879	The American review of respiratory disease	1979	D
407	P27656	Lipc	Metastases to liver	10027457	N/A	Clinical Cancer Research	2002	D
408	P27656	Lipc	Metastases to liver	10027457	N/A	Clinical Cancer Research	2001	D
409	P27656	Lipc	Metastases to liver	10027457	N/A	Cancer Research	1994	D
410	P27656	Lipc	Metastases to liver	10027457	N/A	Annals of oncology	1994	D
411	P27656	Lipc	Metastases to liver	10027457	N/A	Clinical chemistry	1994	D
412	P27656	Lipc	Metastases to liver	10027457	N/A	Clinical Cancer Research	2003	D
413	P27656	Lipc	Metastases to liver	10027457	N/A	Clinical Cancer Research	2003	D
414	P27656	Lipc	Metastases to liver	10027457	N/A	Clinical Cancer Research	2002	D

415	P27656	Lipc	Metastases to liver	10027457	N/A	Clinical Cancer Research	1997	D
416	P28482	MAPK1	Liver injury	10067125	10.1111/j.1530-0277.1999.tb04182.x	Alcoholism, clinical and experimental research	1999	D
417	P28482	MAPK1	Liver injury	10067125	10.1111/j.1530-0277.1995.tb01528.x	Alcoholism, clinical and experimental research	1995	D
418	P28482	MAPK1	Liver injury	10067125	10.1111/j.1530-0277.1998.tb05921.x	Alcoholism, clinical and experimental research	1998	D
419	P28482	MAPK1	Liver injury	10067125	N/A	Cancer Research	1996	D
420	P29176	FOS-FOX	Hepatotoxicity	10019851	N/A	Research communication in chemical pathology and pharmacology	1996	D
421	P29176	FOS-FOX	Hepatotoxicity	10019851	10.1016/0041-008X(84)90277-1	Toxicology and applied pharmacology	1984	D
422	P29474	NOS3	Liver disorder	10024670	10.1053/jhep.2001.22701	Hepatology	2001	D
423	P29474	NOS3	Liver disorder	10024670	N/A	The American Journal of Physiology	1999	D
424	P29474	NOS3	Liver disorder	10024670	10.1016/S0168-8278(03)00012-6	Journal of hepatology	2003	D
425	P29474	NOS3	Liver disorder	10024670	10.1002/hep.20244	Hepatology	2004	D
426	P31327	CPS1	Hepatic encephalopathy	10019660	10.1016/0300-483X(88)90085-6	Toxicology	1988	S
427	P33261	CYP2C19	Hepatotoxicity	10019851	10.1021/tx9700836	Chemical research in toxicology	1997	D
428	P33261	CYP2C19	Hepatotoxicity	10019851	10.1021/tx0100439	Chemical research in toxicology	2002	D
429	P33261	CYP2C19	Liver failure, fatal DILI	10024678	10.1002/hep.23317	Hepatology	2010	S
430	P33261	CYP2C19	Hepatotoxicity	10019851	10.1021/tx050181o	Chemical research in toxicology	2005	D
431	P33261	CYP2C19	Hepatotoxicity	10019851	N/A	Drug metabolism and disposition: the biological fate of chemicals	2000	D
432	P35348	ADRA1A	Hepatotoxicity	10019851	10.3109/03602539709037587	Drug metabolism review	1997	S
433	P35568	IRS1	Liver injury	10067125	10.1111/j.1530-0277.1999.tb04182.x	Alcoholism, clinical and experimental research	1999	D

434	P35568	IRS1	Liver injury	10067125	10.1111/j.1530-0277.1995.tb01528.x	Alcoholism, clinical and experimental research	1995	D
435	P35568	IRS1	Liver injury	10067125	10.1111/j.1530-0277.1998.tb05921.x	Alcoholism, clinical and experimental research	1998	D
436	P35568	IRS1	Liver injury	10067125	N/A	Cancer Research	1996	D
437	P35869	AHR	Hepatic steatosis	10019708	10.3109/10408444.2015.1089471	Critical reviews in toxicology	2016	S
438	P36956	SREBF1	Hepatic steatosis	10019708	10.1074/jbc.M202411200	The Journal of biological chemistry	2002	D
439	P36956	SREBF1	Hepatic steatosis	10019708	10.1074/jbc.M104557200	The Journal of biological chemistry	2001	D
440	P36956	SREBF1	Hepatic steatosis	10019708	N/A	Journal of aquired immune deficiency syndromes	2003	D
441	P36956	SREBF1	Hepatic steatosis	10019708	10.1074/jbc.M306540200	The Journal of biological chemistry	2003	D
442	P37231	PPARG	Acute liver injuries	10067970	10.1111/j.1572-0241.2003.07175.x	The American journal of gastroenterology	2003	S
443	P37231	PPARG	Hepatic steatosis	10019708	10.3109/10408444.2015.1089471	Critical reviews in toxicology	2016	S
444	P54098	POLG	Hepatotoxicity	10019851	N/A	Proceedings of the National Academy of Sciences of the United States of America	1996	S
445	P54098	POLG	Hepatic failure	10019663	10.2165/00002018-199717010-00001	American journal of gastroenterology	1997	S
446	P54855	UGT2B15	Hepatotoxicity	10019851	10.1124/dmd.30.3.324	Drug metabolism and disposition: the biological fate of chemicals	2002	D
447	P54855	UGT2B15	Hepatotoxicity	10019851	10.1021/tx050317i	Chemical research in toxicology	2006	D
448	P54855	UGT2B15	Hepatotoxicity	10019851	10.1093/toxsci/kfi211	Toxicological sciences: an official journal of the Society of Toxicology	2005	D
449	P54855	UGT2B15	Hepatotoxicity	10019851	10.1111/j.1365-2125.2005.02446.x	British Journal of Clinical Pharmacology	2005	D
450	P55017	SLC12A3	Hepatotoxicity	10019851	10.1016/0006-291X(87)91624-X	Biochemical and biophysical research communications	1987	D
451	P55017	SLC12A3	Hepatotoxicity	10019851	10.1016/0006-2952(83)90116-8	Biochemical and biophysical research communications	1983	D

452	P55017	SLC12A3	Hepatotoxicity	10019851	10.1016/0041-008X(89)90327-X	Toxicology and applied pharmacology	1989	D
453	P61599	NAA20	Hepatotoxicity	10019851	N/A	European journal of clinical pharmacology	1987	D
454	P61599	NAA20	Hepatotoxicity	10019851	10.1358/mf.1998.20.8.487491	Methods and findings in experimental and clinical pharmacology	1998	D
455	Q00268	N/A	Liver injury	10067125	10.1111/j.1530-0277.1999.tb04182.x	Alcoholism, clinical and experimental research	1999	D
456	Q00268	N/A	Liver injury	10067125	10.1111/j.1530-0277.1995.tb01528.x	Alcoholism, clinical and experimental research	1995	D
457	Q00268	N/A	Liver injury	10067125	10.1111/j.1530-0277.1998.tb05921.x	Alcoholism, clinical and experimental research	1998	D
458	Q00268	N/A	Liver injury	10067125	N/A	Cancer Research	1996	D
459	Q00796	SORD	Hepatotoxicity	10019851	N/A	Anesthesiology	1979	D
460	Q00796	SORD	Hepatotoxicity	10019851	N/A	Anesthesiology	1988	D
461	Q00796	SORD	Hepatotoxicity	10019851	10.3109/00498258809167523	Xenobiotica	1988	D
462	Q00796	SORD	Hepatotoxicity	10019851	N/A	Anesthesiology	1983	D
463	Q00796	SORD	Hepatotoxicity	10019851	10.1111/j.1600-0773.1988.tb00909.x	Pharmacology amd Toxicology	1988	D
464	Q00796	SORD	Hepatotoxicity	10019851	N/A	Anesthesiology	1981	D
465	Q00796	SORD	Hepatotoxicity	10019851	10.1016/0041-008X(83)90306-X	Toxicology and applied pharmacology	1983	D
466	Q00796	SORD	Hepatotoxicity	10019851	N/A	Acta pharmacologica et toxicologica	1983	D
467	Q00796	SORD	Hepatotoxicity	10019851	10.1002/hep.1840050214	Hepatology	1985	D
468	Q05421	Cyp2e1	Hepatotoxicity	10019851	10.1074/jbc.271.20.12063	The journal of biological chemistry	1996	S
469	Q05655	PRKCD	Hepatic steatosis	10019708	10.1292/jvms.55.893	The journal of veterinary medicinal science	1993	D
470	Q05655	PRKCD	Hepatic steatosis	10019708	10.1292/jvms.64.51	The journal of veterinary medicinal science	2002	D

471	Q05655	PRKCD	Hepatic steatosis	10019708	N/A	American journal of veterinary research	1994	D
472	Q05655	PRKCD	Hepatic steatosis	10019708	N/A	American journal of veterinary research	1993	D
473	Q05655	PRKCD	Hepatic steatosis	10019708	10.1292/jvms.55.481	The journal of veterinary medicinal science	1993	D
474	Q05655	PRKCD	Hepatic steatosis	10019708	N/A	American journal of veterinary research	1992	D
475	Q05655	PRKCD	Hepatic steatosis	10019708	N/A	Veterinary research communications	1994	D
476	Q07869	PPARA	Hepatic steatosis	10019708	10.3109/10408444.2015.1089471	Critical reviews in toxicology	2016	S
477	Q12772	SREBF2	Hepatic steatosis	10019708	10.1074/jbc.M202411200	The Journal of biological chemistry	2002	D
478	Q12772	SREBF2	Hepatic steatosis	10019708	10.1074/jbc.M104557200	The Journal of biological chemistry	2001	D
479	Q12772	SREBF2	Hepatic steatosis	10019708	N/A	Journal of aquired immune deficiency syndromes	2003	D
480	Q12772	SREBF2	Hepatic steatosis	10019708	10.1074/jbc.M306540200	The Journal of biological chemistry	2003	D
481	Q13133	NR1H3	Hepatic steatosis	10019708	10.3109/10408444.2015.1089471	Critical reviews in toxicology	2016	S
482	Q14032	BAAT	Cholestasis	10008635	10.3748/wjg.v18.i25.3322	World journal of gastroenterology	2012	S
483	Q14097	CYP2B	Hepatotoxicity	10019851	10.1124/mol.54.6.1113	Molecular pharmacology	1998	D
484	Q14097	CYP2B	Hepatotoxicity	10019851	10.1016/S0009-2797(01)00163-6	Chemico-biological interactions	2001	D
485	Q14097	CYP2B	Hepatotoxicity	10019851	10.1124/mol.58.1.48	Molecular pharmacology	2000	D
486	Q148W0	Atp8b1	Cholestasis	10008635	10.1016/j.jsbmb.2011.06.012	The journal of steroid biochemistry and molecular biology	2012	S
487	Q14973	SLC10A1	Hepatotoxicity	10019851	10.1124/pr.109.002014	The Journal of clinical investigation	1988	S
488	Q14973	SLC10A1	Prehepatic cholestasis	10008635	10.1124/dmd.113.054205	Drug metabolism and disposition: the biological fate of chemicals	2014	S
489	Q14973	SLC10A1	Cholestasis	10008635	10.1124/dmd.105.008748	Drug metabolism and disposition: the biological fate of chemicals	2006	S

490	Q14994	NR1I3	Hepatic steatosis	10019708	10.1016/j.taap.2016.05.006	Toxicology and applied pharmacology	2016	S
491	Q14994	NR1I3	Hepatotoxicity	10019851	10.1126/science.1073502	Science	2002	S
492	Q14994	NR1I3	Hepatoxicity	10019851	10.1134/S0006297916040040	Biochemistry	2016	S
493	Q14994	NR1I3	Hepatotoxicity	10019851	10.2165/00003088-200342150-00003	Clinical pharmacokinetics	2003	S
494	Q14994	NR1I3	Hepatic steatosis	10019708	10.3109/10408444.2015.1089471	Critical reviews in toxicology	2016	S
495	Q28DB5	gpt2	Hepatitis	10019717	N/A	Masui	1995	D
496	Q28DB5	gpt2	Hepatitis	10019717	N/A	Masui	1990	D
497	Q28DB5	gpt2	Hepatitis	10019717	10.1055/s-2008-1055506	Deutsche Medizinische Wochenschrift	1995	D
498	Q28DB5	gpt2	Hepatitis	10019717	N/A	Masui	2002	D
499	Q28DB5	gpt2	Hepatitis	10019717	N/A	Masui	1994	D
500	Q28DB5	gpt2	Hepatitis	10019717	N/A	Anesthesiology	2001	D
501	Q28DB5	gpt2	Hepatitis	10019717	10.1016/S1098-7339(03)00182-2	Regional anesthesia and pain medicine	2003	D
502	Q28DB5	gpt2	Hepatitis	10019717	N/A	Acta anaesthesiologica Sinica	1998	D
503	Q28DB5	gpt2	Hepatitis	10019717	N/A	Journal of Formosan Medical Association	1996	D
504	Q86VZ4	LRP11	Liver disorder	10024670	N/A	Presse medicale	2001	D
505	Q86VZ4	LRP11	Liver disorder	10024670	N/A	Recenti progressi in medicina	2000	D
506	Q86VZ4	LRP11	Liver disorder	10024670	N/A	AIDS	2000	D
507	Q86VZ4	LRP11	Liver disorder	10024670	N/A	AIDS	1998	D
508	Q86VZ4	LRP11	Liver disorder	10024670	10.1016/S0140-6736(98)08468-2	Lancet	1999	D
509	Q86VZ4	LRP11	Liver disorder	10024670	10.1016/S0163-7827(02)00046-2	Progress in lipid research	2003	D
510	Q86VZ4	LRP11	Liver disorder	10024670	10.1086/313854	Clinical infectious diseases	2000	D
511	Q86VZ4	LRP11	Liver disorder	10024670	N/A	Biomedicine and pharmacotherapy	1999	D
512	Q86VZ4	LRP11	Liver disorder	10024670	N/A	Journal of acquired immune deficiency syndromes	2000	D

513	Q86VZ4	LRP11	Liver disorder	10024670	10.1016/S0140-6736(98)03391-1	Lancet	1998	D
514	Q86VZ4	LRP11	Liver disorder	10024670	10.4158/EP.7.6.430	Endocrine practice	2001	D
515	Q8QZR5	Gpt	Hepatotoxicity	10019851	10.3109/01480548809017880	Drug and Chemical Toxicology	1988	D
516	Q8QZR5	Gpt	Hepatotoxicity	10019851	10.1016/0041-008X(84)90277-1	Toxicology and applied pharmacology	1984	D
517	Q8QZR5	Gpt	Hepatotoxicity	10019851	10.1016/0041-008X(84)90278-3	Toxicology and applied pharmacology	1984	D
518	Q8QZR5	Gpt	Hepatotoxicity	10019851	N/A	National Toxicology Program technical report series	1993	D
519	Q8QZR5	Gpt	Hepatotoxicity	10019851	10.1006/taap.1993.1021	Toxicology and applied pharmacology	1993	D
520	Q8QZR5	Gpt	Hepatotoxicity	10019851	10.1016/0041-008X(91)90179-I10.1016/0041-008X(91)90179-I	Toxicology and applied pharmacology	1991	D
521	Q8QZR5	Gpt	Hepatotoxicity	10019851	10.1016/0300-483X(76)90003-2	Toxicology	1976	D
522	Q91Y86	Mapk8	Protection	N/A	10.1002/hep.21475	Hepatology	2007	S
523	Q92887	ABCC2	Liver injury	10067125	10.1093/toxsci/kft176	Toxicological Sciences	2013	S
524	Q92887	ABCC2	Cholestasis	10008635	10.1016/j.cbi.2004.09.011	Chemico-biological interactions	2004	S
525	Q92887	ABCC2	Dubin-Johnson syndrome	10013800	10.1152/physrev.00027.2002	Physiological reviews	2003	S
526	Q92887	ABCC2	Cholestasis of pregnancy	10049055	10.1124/pr.109.002014	The Journal of clinical investigation	1988	S
527	Q92887	ABCC2	Could trigger intrahepatic cholestasis	10008635	10.1124/dmd.113.054205	Drug metabolism and disposition: the biological fate of chemicals	2014	S
528	Q92887	ABCC2	Cholestasis	10008635	10.1053/jhep.2000.8263	Hepatology	2000	S
529	Q92887	ABCC2	Dubin-Johnson syndrome	10013800	10.1007/978-3-642-14541-4_8	Handbook of experimental pharmacology	2011	S
530	Q92887	ABCC2	Cholestasis and Jaundice	10008636	10.1016/j.jhep.2009.05.012	Journal of hepatology	2009	S

531	Q96RI1	NR1H4	Hepatotoxicity	10019851	10.1021/jm0582221	Journal of medicinal chemistry	2005	S
532	Q96RI1	NR1H4	Cholestasis	10008635	10.1016/j.jsbmb.2011.06.012	The journal of steroid biochemistry and molecular biology	2012	S
533	Q96RI1	NR1H4	Cholestasis	10008635	10.1016/j.jhep.2009.05.012	Journal of hepatology	2009	S
534	Q96RI1	NR1H4	Cholestasis inPFIC1	10008635	10.1016/j.bbamcr.2006.04.014	Biochimica et biophysica acta	2007	S
535	Q96RI1	NR1H4	Hepatotoxicity	10019851	10.2165/00003088-200342150-00003	Clinical pharmacokinetics	2003	S
536	Q96RI1	NR1H4	Hepatic steatosis	10019708	10.3109/10408444.2015.1089471	Critical reviews in toxicology	2016	S
537	Q9BWT7	CARD10	Hepatotoxicity	10019851	10.1210/me.2005-0066	Molecular endocrinology	2005	D
538	Q9BWT7	CARD10	Hepatotoxicity	10019851	10.1126/science.1073502	Science	2002	D
539	Q9BWT7	CARD10	Hepatotoxicity	10019851	10.1074/jbc.M409041200	The Journal of biological chemistry	2004	D
540	Q9BWT7	CARD10	Hepatotoxicity	10019851	10.1126/science.298.5592.341a	Science	2002	D
541	Q9NPD5	SLCO1B3	Hepatic failure	10019663	10.1002/hep.21359	Hepatology	2006	S
542	Q9UHN1	POLG2	Hepatotoxicity	10019851	N/A	Proceedings of the National Academy of Sciences of the United States of America	1996	S
543	Q9UHN1	POLG2	Hepatic failure	10019663	10.2165/00002018-199717010-00001	American journal of gastroenterology	1997	S
544	Q9UJ14	GGT7	Jaundice	10023126	N/A	Sexually transmitted diseases	1983	D
545	Q9UJ14	GGT7	Jaundice	10023126	10.1136/sti.60.6.387	The British Journal of venereal diseases	1984	D
546	Q9UJ14	GGT7	Jaundice	10023126	10.1056/NEJM198601303140503	The New England Journal of Medicine	1986	D
547	Q9UJ14	GGT7	Jaundice	10023126	10.7326/0003-4819-97-2-216	Annals of internal medicine	1982	D
548	Q9Y4H2	IRS2	Liver injury	10067125	10.1111/j.1530-0277.1999.tb04182.x	Alcoholism, clinical and experimental research	1999	D
549	Q9Y4H2	IRS2	Liver injury	10067125	10.1111/j.1530-0277.1995.tb01528.x	Alcoholism, clinical and experimental research	1995	D

550	Q9Y4H2	IRS2	Liver injury	10067125	10.1111/j.1530-0277.1998.tb05921.x	Alcoholism, clinical and experimental research	1998	D
551	Q9Y4H2	IRS2	Liver injury	10067125	N/A	Cancer Research	1996	D
552	Q9Y6L6	SLCO1B1	Hepatotoxicity	10019851	10.1124/pr.109.002014	The Journal of clinical investigation	1988	S
553	Q9Y6L6	SLCO1B1	Hyperbilirubinemia	10020578	10.1016/j.cbi.2004.08.008	Chemico-biological interactions	2004	S
554	Q9Y6L6	SLCO1B1	Hepatotoxicity	10019851	10.1124/dmd.32.3.291	Drug metabolism and disposition: the biological fate of chemicals	2004	S

9. REFERENCES

[1] *Nancy L. R. Bucher, „Experimental Aspects of Hepatic Regeneration“, New England Journal of Medicine 277, Nr. 14 (5. Oktober 1967): 738–46,.*

[2] *Antitargets, ISBN-13: 9783527318216 ed., Vaz, Roy J.; Klabunde, Thomas, Januar 2008.*

[3] *Antitargets and Drug Safety, ISBN: 978-3-527-33511-4 ed., Laszlo Urban, Vinod Patel, Roy J. Vaz, June 2015.*

[4] *Neil Kaplowitz, Drug-Induced Liver Injury, Clinical Infectious Diseases, Volume 38, Issue Supplement_2, 1 March 2004, Pages S44–S48, https://doi.org/10.1086/381446.*

[5] *Craig Lammert u. a., „Relationship between Daily Dose of Oral Medications and Idiosyncratic Drug-Induced Liver Injury: Search for Signals“, Hepatology 47, Nr. 6 (1. Juni 2008): 2003–9, https://doi.org/10.1002/hep.22272..*

[6] *„In Vitro Drug-Induced Liver Injury Prediction: Criteria Optimization of Efflux Transporter IC50 and Physicochemical Properties | Toxicological Sciences | Oxford Academic“, https://academic.oup.com/toxsci/article/157/2/487/309.*

[7] *„THE ROLE OF METABOLIC ACTIVATION IN DRUG-INDUCED HEPATOTOXICITY | Annual Review of Pharmacology and Toxicology“, https://www.annualreviews.org/doi/abs/10.1146/annurev.pharmtox.45.120403.100058?rfr_dat=cr_pub%3Dpubmed&url_ver=.*

[8] *Ayako Suzuki u. a., „Drugs Associated with Hepatotoxicity and Their Reporting Frequency of Liver Adverse Events in VigiBaseTM“, Drug Safety 33, Nr. 6 (1. Juni 2010): 503–22, https://doi.org/10.2165/11535340-000000000-00000..*

[9] *P. J. O'Brien u. a., „High Concordance of Drug-Induced Human Hepatotoxicity with in Vitro Cytotoxicity Measured in a Novel Cell-Based Model Using High Content Screening“, Archives of Toxicology 80, Nr. 9 (1. September 2006): 580–604, https://doi.org/10.10.*

[10] *Alejandra Cano Paniagua and Pedro Amariles (December 20th 2017). Hepatotoxicity by Drugs, Pharmacokinetics and Adverse Effects of Drugs - Mechanisms and Risks Factors, Ntambwe Malangu, IntechOpen, DOI: 10.5772/intechopen.72005..*

[11] *James A. Dykens und Yvonne Will, „The significance of mitochondrial toxicity testing in drug development“, Drug Discovery Today 12, Nr. 17 (1. September 2007): 777–85, https://doi.org/10.1016/j.drudis.2007.07.013..*

[12] Urs A. Boelsterli, „Idiosyncratic Drug Hepatotoxicity Revisited: New Insights from Mechanistic Toxicology“, Toxicology Mechanisms and Methods 13, Nr. 1 (1. Januar 2003): 3–20, https://doi.org/10.1080/15376510309824..

[13] Denis Fourches u. a., „Cheminformatics Analysis of Assertions Mined from Literature That Describe Drug-Induced Liver Injury in Different Species“, Chemical Research in Toxicology 23, Nr. 1 (18. Januar 2010): 171–83, https://doi.org/10.1021/tx900326k..

[14] „Analysis of Pharmacology Data and the Prediction of Adverse Drug Reactions and Off-Target Effects from Chemical Structure - Bender - 2007 - ChemMedChem - Wiley Online Library“, https://onlinelibrary.wiley.com/doi/abs/10.1002/.

[15] „THE ROLE OF METABOLIC ACTIVATION IN DRUG-INDUCED HEPATOTOXICITY | Annual Review of Pharmacology and Toxicology“..

[16] Mei-Chun Cai, Quan Xu, Yan-Jing Pan, Wen Pan, Nan Ji, Yin-Bo Li, Hai-Jing Jin, Ke Liu, Zhi-Liang Ji, ADReCS: an ontology database for aiding standardization and hierarchical classification of adverse drug reaction terms, Nucleic Acids Research, Volume 43,.

[17] Zhi Liang Ji u. a., „Drug Adverse Reaction Target Database (DART) : Proteins Related to Adverse Drug Reactions“, Drug Safety 26, Nr. 10 (2003): 685–90..

[18] Jing-Xian Zhang u. a., „DITOP: Drug-Induced Toxicity Related Protein Database“, Bioinformatics 23, Nr. 13 (1. Juli 2007): 1710–12, https://doi.org/10.1093/bioinformatics/btm139..

[19] McEntyre, J, and D Lipman. "PubMed: bridging the information gap." CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne vol. 164,9 (2001): 1317-9..

[20] https://www.ncbi.nlm.nih.gov/pubmed/ (24.06.2019).

[21] https://www.knime.com/about vom 26.07.2019.

[22] Warr, W.A. J Comput Aided Mol Des (2012) 26: 801. https://doi.org/10.1007/s10822-012-9577-7.

[23] Zupanc, G.K.H. J Comp Physiol A (2014) 200: 113. https://doi.org/10.1007/s00359-013-0863-1.

[24] https://www.researchgate.net/journal/0021-4892_Masui_The_Japanese_journal_of_anesthesiology (19.02.2019).

[25] https://www.uniprot.org/uniprot/O75469 (20.08.2019).

[26] Stacey A. Jones, Linda B. Moore, Jennifer L. Shenk, G. Bruce Wisely, Geraldine A. Hamilton, David D. McKee, Nicholas C. O. Tomkinson, Edward L. LeCluyse, Millard H. Lambert, Timothy M. Willson, Steven A. Kliewer, John T. Moore, The Pregnane X Receptor: A.

[27] Timsit, Yoav E, and Masahiko Negishi. "CAR and PXR: the xenobiotic-sensing receptors." Steroids vol. 72,3 (2007): 231-46. doi:10.1016/j.steroids.2006.12.006.

[28] *Teotico DG, Bischof JJ, Peng L, Kliewer SA, Redinbo MR. Structural basis of human pregnane X receptor activation by the hops constituent colupulone. Mol Pharmacol. 2008;74(6):1512–1520. doi:10.1124/mol.108.050732.*

[29] *Stacey A. Jones, Linda B. Moore, Jennifer L. Shenk, G. Bruce Wisely, Geraldine A. Hamilton, David D. McKee, Nicholas C. O. Tomkinson, Edward L. LeCluyse, Millard H. Lambert, Timothy M. Willson, Steven A. Kliewer, John T. Moore, The Pregnane X Receptor: A.*

[30] *Wang, Hongbing & Lecluyse, Edward. (2003). Role of Orphan Nuclear Receptors in the Regulation of Drug-Metabolising Enzymes. Clinical pharmacokinetics. 42. 1331-57. 10.2165/00003088-200342150-00003..*

[31] *https://www.uniprot.org/uniprot/P24298 (15.08.2019).*

[32] *"https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/abcb11 (16.08.2019)".*

[33] *Soroka CJ, Boyer JL. Biosynthesis and trafficking of the bile salt export pump, BSEP: therapeutic implications of BSEP mutations. Mol Aspects Med. 2014;37:3–14. doi:10.1016/j.mam.2013.05.001.*

[34] *https://www.uniprot.org/uniprot/P08684 (15.08.2019).*

[35] *https://www.deutsche-apotheker-zeitung.de/daz-az/2012/daz-40-2012/interaktionen-mit-cyp3a4 (20.08.2019).*

[36] *T. A.-S. C. H. M. M. Thomas Falguières, "ABCB4: Insights from pathobiology into therapy," Clinics and Research in Hepatology and Gastroenterology, pp. 557-563, October 2014.*

[37] *„THE ROLE OF METABOLIC ACTIVATION IN DRUG-INDUCED HEPATOTOXICITY | Annual Review of Pharmacology and Toxicology", zugegriffen 8. Oktober 2018, https://www.annualreviews.org/doi/abs/10.1146/annurev.pharmtox.45.120403.100058?rfr_dat=cr_pub%3Dpubmed&url_ver=.*

[38] *https://www.uniprot.org/uniprot/O75469 (20.08.2019).*