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Review

Perspective on Quantitative Structure–Toxicity Relationship (QSTR) Models to Predict Hepatic Biotransformation of Xenobiotics

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Abstract: Biotransformation refers to the metabolic conversion of endogenous and xenobiotic chemicals into more hydrophilic substances. Xenobiotic biotransformation is accomplished by a restricted number of enzymes with broad substrate specificities. The biotransformation of xenobiotics is catalyzed by various enzyme systems that can be divided into four categories based on the reaction they catalyze. The primary concentration is in cytochrome P450, while the CYP enzymes responsible for xenobiotic biotransformation are located within the hepatic endoplasmic reticulum (microsomes). Cytochrome P450 (CYP450) enzymes are also present in extrahepatic tissues. Enzymes catalyzing biotransformation reactions often determine the intensity and duration of the action of drugs and play a key role in chemical toxicity and chemical tumorigenesis. The structure of a given biotransforming enzyme may differ among individuals, which can cause differences in the rates of xenobiotic biotransformation. The study of the molecular mechanisms underlying chemical liver injury is fundamental for preventing or devising new modalities of treatment for liver injury using chemicals. Active metabolites arise from the biotransformation of a parent drug compound using one or more xenobiotic-processing enzymes to generate metabolites with different pharmacological or toxicological properties. Understanding how exogenous chemicals (xenobiotics) are metabolized, distributed, and eliminated is critical to determining the impact of these compounds on human health. Computational tools such as Biotransformer have been developed to predict all the possible metabolites of xenobiotic and enzymatic profiles that are linked to the production of metabolites. The construction of xenobiotic metabolism maps can predict enzymes catalyzing metabolites capable of binding to DNA.

Keywords: hepatic biotransformation; metabolites; computational prediction; enzymes; xenobiotics

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1. Introduction

The liver plays a crucial role in the metabolism and detoxification of a wide range of foreign compounds known as xenobiotics. These compounds include medications, chemicals, contaminants, and dietary components. Xenobiotics, which are foreign compounds

that enter the body through multiple pathways, are mostly biotransformed in the liver [1]. These chemicals are transformed throughout the biotransformation process into more excretable metabolites that are hydrophilic [2]. Some of these metabolites, meanwhile, can be poisonous and have negative consequences. To determine xenobiotic safety and possible toxicity, it is, therefore, critical to anticipate the hepatic biotransformation of these substances [3]. Cytochrome P450 (CYP450) enzymes are particularly significant among the major enzymes involved in this process, as shown in Figure 1. These enzymes convert xenobiotics into more water-soluble molecules that can be readily removed from the body. However, genetic differences in CYP450 enzymes, notably the p-cytochrome P450 variants, can alter xenobiotic detoxification efficiency and efficacy. Cytochrome P450 enzymes are a subfamily of heme-containing enzymes found mostly in the liver but also in other organs. They participate in the oxidative metabolism of several endogenous molecules, such as steroids, fatty acids, and bile acids. In addition, they participate in the metabolism of exogenous substances, such as medicines, environmental pollutants, and carcinogens. The CYP450 enzyme system is made up of many isoforms, including CYP1A2, CYP2C9, CYP2D6, CYP2E1, and CYP3A4. Genetic variations in CYP450 enzyme genes can result in altered enzyme activity, altering xenobiotic metabolism.

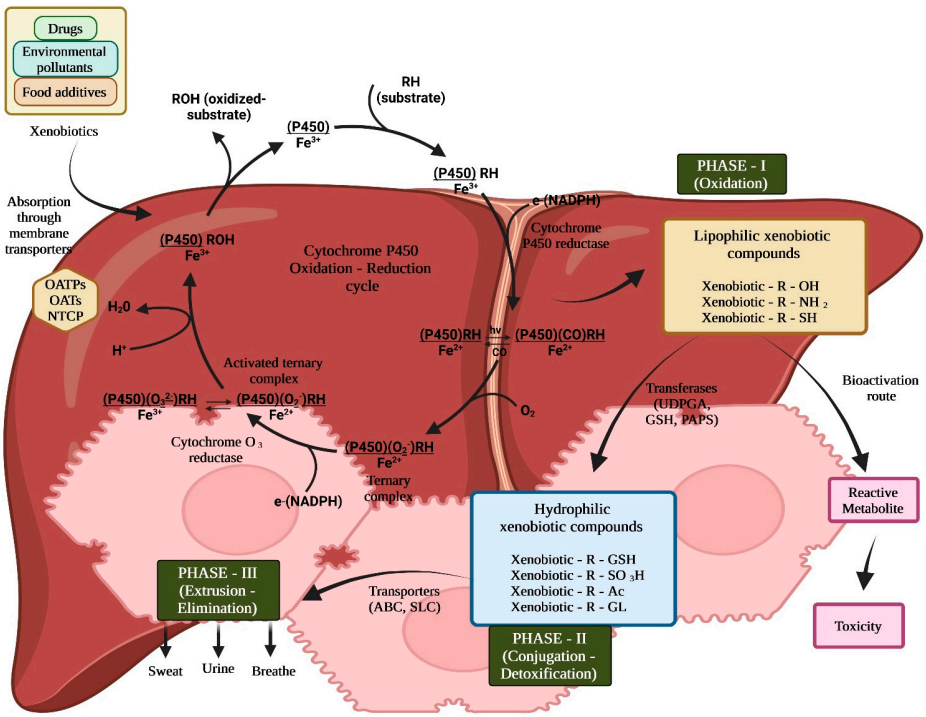

Figure 1. Role of liver enzyme cytochrome P450 variants (CYP1A2 (caffeine and other aromatic compounds), CYP2C9 (non-steroidal anti-inflammatory drugs (NSAIDs) and anticoagulants), CYP2D6 (antidepressants and antipsychotics), CYP2E1 (alcohol and some volatile organic compounds), and CYP3A4 (statins, antivirals, and immunosuppressants)) [4] in detoxification of xenobiotic substances, facilitating oxidation and increasing water solubility of various substances for subsequent excretion.

It is possible to forecast xenobiotic toxicity using methods called quantitative structure–toxicity relationship (QSTR) models to forecast their toxicity [5]. QSTR models predict the toxicity of numerous chemicals, such as pesticides, herbicides, and medications. The use of QSTR models to predict the hepatic biotransformation of xenobiotics has gained popularity in recent years.

1.1. Exploring the Enigma of Xenobiotic Hepatic Biotransformation

It is possible to forecast xenobiotic toxicity using methods called quantitative structure–toxicity relationship (QSTR) models to forecast their toxicity [6]. QSTR models predict the toxi-

city of numerous chemicals, such as pesticides, herbicides, and medications. The use of QSTR models to predict the hepatic biotransformation of xenobiotics has gained popularity [7]. To assess the structure–toxicity link of xenobiotics, QSTR models employ a range of physical parameters such as molecular weight, lipophilicity, and electronic properties. Novel compounds may be identified mathematically using these descriptors based on their structural resemblance to established toxicants. QSTR models that can forecast the hepatic biotransformation of xenobiotics have been shown in several investigations. For instance, the acute oral toxicity of organophosphate pesticides to male rats was assessed using a QSTR model [8]. Hepatic biotransformation refers to the enzymatic and chemical changes that occur in the liver, converting xenobiotics (foreign chemicals) into more water-soluble molecules for excretion by the body. QSTR models play a pivotal role in drug development, toxicity testing, ADME prediction, and structure–activity relationship studies by providing valuable insights into the hepatic biotransformation of various substances [9]. They empower researchers to make well-informed choices regarding compound selection, optimization, and lead prioritization, leading to the effective design of safer and more efficient medications.

The study presented conclusive evidence of the QSTR model's efficacy in accurately estimating pesticide toxicity based on its structural characteristics. To predict the harmful effects of nitroaromatic compounds (NACs), another study employed a QSTR model [10]. The research demonstrated that using chemical characteristics, including molecular weight, polarizability, and hydrogen bond acceptor capability, the QSTR model could accurately predict NAC toxicity.

Additionally, xenobiotics' liver biotransformation routes may be predicted using QSTR models. For instance, the biotransformation of polychlorinated dibenzofurans (PCDFs) in the liver was investigated using a QSTR model [11].

Research demonstrated that using quantum chemical descriptors of PCDFs, the QSTR model could predict the biotransformation routes of these compounds [12]. In conclusion, QSTR models are effective resources for forecasting xenobiotic hepatic biotransformation. These models can aid in the development of safer compounds by offering useful information on substances' possible toxicities. To increase the precision and dependability of QSTR models in foretelling the hepatic biotransformation of xenobiotics, more study is necessary.

1.2. Progress in QSTR Models for Anticipating Hepatic Biotransformation Pathways

In several in vitro and in vivo models, QSTR models have been utilized to predict the hepatic biotransformation of xenobiotics [13]. QSTR models have been used to forecast hepatic biotransformation in a variety of animal models, including those of rodents and non-human primates. These models take into account changes across species in enzyme expression, activity, and metabolic pathways.

The illustration in Figure 2 depicts a detailed flowchart detailing the step-by-step method of constructing QSTR models that are intended to forecast xenobiotic hepatic biotransformation. The use of molecular descriptors, model validation procedures, and subsequent application to in silico predictions are all used in the construction of these models. The flowchart is intended to serve as a reference for scholars and practitioners working on the subject. It highlights the critical phases and factors required for accurate predictions.

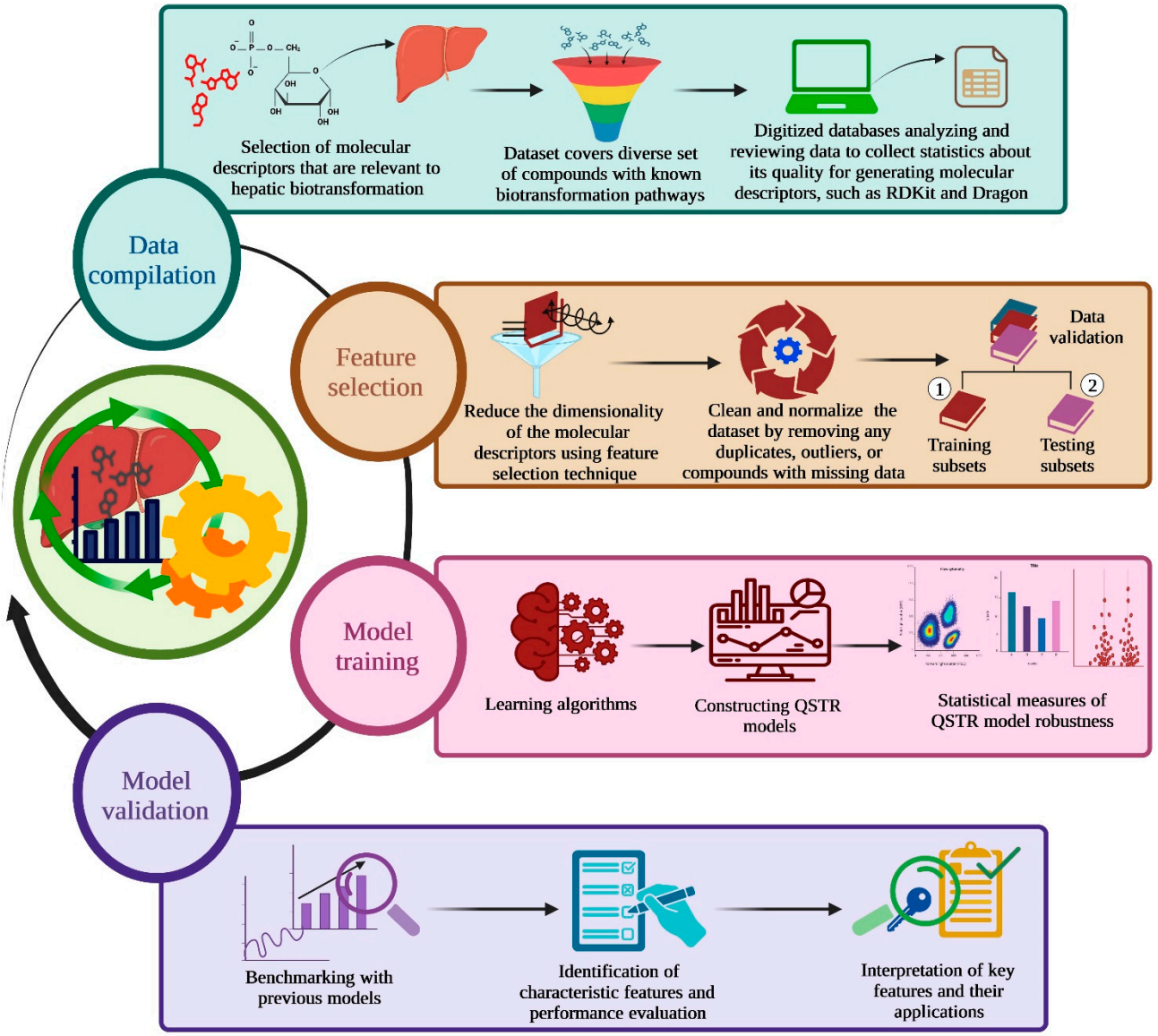

Figure 2. A flowchart illustrating the process of developing QSTR models for predicting hepatic biotransformation of xenobiotics, including the selection of molecular descriptors, model validation, and application to in silico predictions.

QSTR models extend metabolic data from animal models to humans, enabling medication development and safety assessment. This is achieved by merging the structural characteristics of xenobiotics with pharmacokinetic factors. Here are some recent changes in this area:

- A method was devised that uses measures of in vitro hepatic biotransformation in animals to predict in vivo hepatic clearance [14]. This method has been applied to chemical risk assessment, evaluating medication candidates, and looking at idiosyncratic drug reactions. Hepatic clearance estimates may be included successfully in compartmental clearance-volume models.
- Understanding the trajectory of a medication necessitates awareness of the extent of hepatic metabolism and the capability to predict hepatic clearance [15]. Translation of preclinical pharmacokinetic and pharmacodynamic data has improved because of recent advancements in in vitro and in vivo models.

- To parameterize 1-CoTK models, QSARs were created and validated for forecasting in vivo whole-body biotransformation half-lives [16]. These models can be used to forecast chemical toxicity and aid in safer compound development.
- To evaluate possible herb–drug interactions, clearance tests are frequently performed in in vitro hepatic models [17]. These models can aid in the development of safer compounds by offering useful information on substances' possible toxicities.
- Quantitative structure–pharmacokinetic relationships (QSPRs) that link biological activity to epithelial and hepatic first-pass biotransformation may also be created using QSTR models [18]. These models can be used to forecast drug pharmacokinetics and aid in the creation of more powerful pharmaceuticals.

In conclusion, in several in vitro and in vivo models, hepatic biotransformation of xenobiotics has been predicted using QSTR models. Both in vitro and in vivo models of xenobiotic hepatic biotransformation have shown the value of QSTR models. These models establish links between structure and activity, aid in toxicity evaluation and ADME prediction, and enable virtual screening. They also shed light on metabolic pathways. Our understanding of hepatic biotransformation is improved by combining QSTR models with experimental research, which helps with medication development and safety evaluation. These models can aid in the development of safer chemicals and more powerful medications by offering useful information on substances' possible toxicities. To increase the precision and dependability of QSTR models for foretelling the hepatic biotransformation of xenobiotics, more study is necessary.

2. Molecular Descriptors Used in QSTR Models for Hepatic Biotransformation

In quantitative structure–activity relationship (*QSAR*) models for liver metabolism predictions, molecular descriptors play a crucial role in determining the rate of metabolism and clearance of a drug [19]. Lipophilicity determines the rate of passive diffusion of a drug across the cell membrane and its distribution in the body [20]. Molecular weight affects drug metabolism and clearance. Polarizability and hydrogen bonding influence the interaction of a drug with an enzyme and its metabolism rate [21]. Topological indices account for a molecule's structural complexity and its effect on metabolism. Molecular surface area affects drug metabolism and clearance rates. However, it is important to note that each molecular descriptor comes with its own set of limitations [22]. For instance, lipophilicity alone cannot provide insights into the metabolism of compounds that are highly lipophilic. Similarly, while molecular weight is a useful descriptor, it does not consider the structural complexity of molecules. Polarizability, on the other hand, may not accurately predict the metabolism of highly polar compounds. Additionally, the predictive ability of hydrogen bonding is limited when it comes to compounds with weak hydrogen-bonding interactions [23]. Topological indices cannot assess compound metabolism. Molecular surface area has a limited ability to estimate the metabolism of highly lipophilic compounds [23]. To overcome these limitations, other molecular descriptors can be used in combination with the ones mentioned above. For example, if lipophilicity has a limited ability to predict the metabolism of highly lipophilic compounds, other molecular descriptors, such as polarizability and hydrogen bonding, can be considered. Similarly, if molecular weight does not account for a molecule's structural complexity, other molecular descriptors, such as topological indices and molecular surface area, can be used [24].

The graphic in Figure 3 depicts a heatmap of the relationship between numerous molecular descriptors and the rate of xenobiotic hepatic biotransformation. A color gradient is used in the heatmap, with different hues or colors representing the intensity and direction of the association. Positive correlations are often represented by warmer colors (e.g., red and orange), whereas negative correlations are typically represented by cooler colors (e.g., blue and green). On both axes, molecular descriptors are presented, with their names describing their unique qualities and characteristics. The correlation heatmap gives an in-depth look at the link between molecular descriptors and the rate of xenobiotic biotransformation in the liver. To enhance drug discovery, toxicology investigations, and risk assessment of

xenobiotics, it is crucial to identify the fundamental predictors of xenobiotic metabolism. This study focuses on pinpointing these essential factors, enabling the development of more precise prediction models. The quantification of the structure–toxicity relationship of xenobiotics involves the utilization of QSTR models, which rely on physicochemical descriptors [25]. Several of the molecular characteristics frequently employed in QSTR models to forecast hepatic biotransformation are listed below:

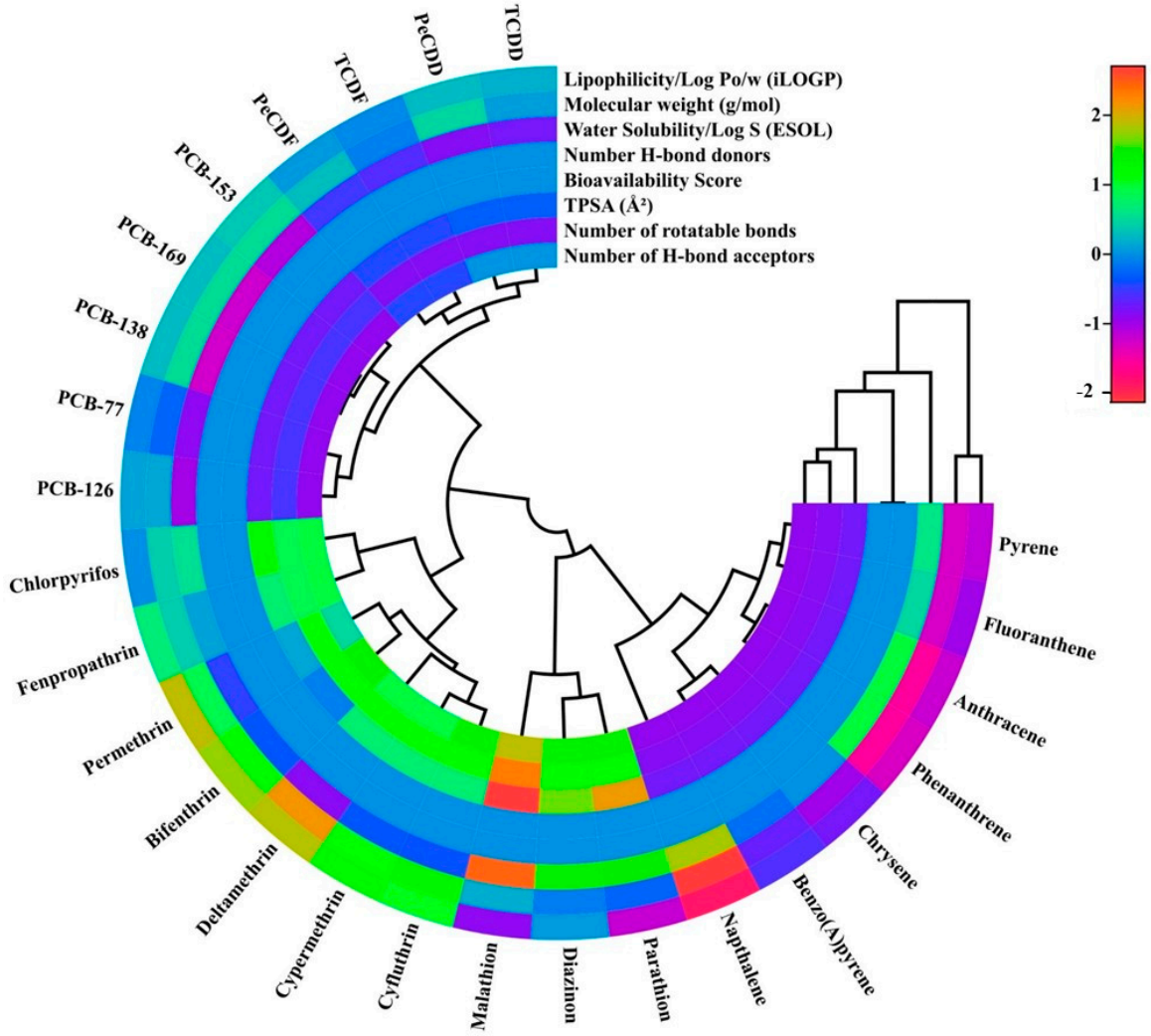

Figure 3. A heatmap showing the correlation between molecular descriptors and the rate of hepatic biotransformation of xenobiotics, highlighting the most important descriptors for predicting metabolism.

- **Lipophilicity:** Lipophilicity plays a pivotal role and is commonly considered in quantitative structure-toxicity relationship (QSTR) models. It describes a molecule's capacity to partition or dissolve into lipid-based environments, such as cell membranes or lipid bilayers. To accurately represent a compound's hydrophobic properties, lipophilicity is frequently measured experimentally or with a variety of molecular descriptors in QSTR modeling [26]. This term describes a substance's propensity to dissolve in lipids or fats. Lipophilicity significantly influences the ADME (absorption, distribution, metabolism, and excretion) of xenobiotics. High lipophilicity substances have longer half-lives in the body and accumulate in adipose tissue. In order to anticipate the hepatic biotransformation of xenobiotics, lipophilicity is a crucial molecular descriptor [18].
- **Molecular weight:** The term "molecular weight" describes how much mass a molecule has. In QSTR modeling, molecular weight is frequently employed as a descriptor

to characterize the size and mass of a drug. This might affect its biological activity, pharmacokinetics, and other aspects. Xenobiotics' physicochemical characteristics, such as solubility, permeability, and bioavailability, are significantly influenced by their molecular weights. High molecular weight substances often have reduced solubility and permeability, which might affect how they are absorbed and distributed by the body. As a result, molecular weight is a crucial molecule descriptor for determining how xenobiotics will be metabolized in the liver [27].

- **Polarizability:** Polarizability is frequently employed as a descriptor in QSTR modeling to describe compound electrical and structural features. This can influence how it interacts with biological targets and exhibits certain qualities. When exposed to an external electric field, a molecule's capacity to instantly create dipoles is measured by a property called polarizability. Polarizability is a crucial factor in determining how a molecule interacts with its surroundings, including whether or not it can pass through biological membranes. The capacity to anticipate the hepatic biotransformation of xenobiotics using polarizability is crucial [28].
- **Hydrogen bonding:** The term "hydrogen bonding" describes how well a molecule creates hydrogen bonds with other molecules. A key factor in determining solubility and reactivity is hydrogen bonding. As a result, hydrogen bonding is a crucial molecular descriptor for determining how xenobiotics will be transformed in the liver [29].
- **Topological indices:** These are mathematical descriptors that rate the branching, connectedness, and symmetry of molecules as well as other aspects of their topology. The physicochemical characteristics of xenobiotics, such as their solubility, permeability, and bioavailability, are significantly influenced by topological indices. Topological indicators are crucial molecular descriptors for foretelling xenobiotic hepatic biotransformation as a result [30].
- **Molecular surface area:** This term describes a molecule's surface area. A key factor in determining how a molecule interacts with its surroundings, such as whether it can pass through biological membranes, is its molecular surface area. In order to anticipate the hepatic biotransformation of xenobiotics, molecular surface area is a crucial molecular descriptor [31].

It is clear that using physicochemical descriptors, QSTR models are essential for measuring xenobiotic structure–toxicity links. For predicting the hepatic biotransformation of xenobiotics, lipophilicity and molecular weight are significant molecular descriptors [32]. These models have a huge potential for revealing significant details about chemical toxicity and assisting in the creation of safer compounds. It is imperative to recognize that further study is required to improve the precision and dependability of QSTR models in foretelling the hepatic biotransformation of xenobiotics [33].

QSARs also predict the intrinsic hepatic clearance of organic compounds in humans. These QSARs utilize multiple linear models and microsomes to forecast the in vitro clearance (CLINT) of xenobiotics metabolized in human hepatocytes. These models choose up to 6 predictors from a pool of over 2000 possible molecular descriptors. The explained variance (Radj(2)) and predictive power (Rext(2)) of the hepatocyte QSAR were 67% and 62%, respectively. The microsomes QSAR, on the other hand, showed a Radj(2) of 50% and Rext(2) of 30% [27]. In conclusion, QSARs make it easier to forecast intrinsic hepatic clearance, whereas QSTR models help quantify the link between structure and toxicity. Both of these models provide insightful information on chemical toxicity [34]. They facilitate chemical risk assessment, screen potential therapeutic candidates, and help create safer chemicals. To improve the precision and dependability of QSTR models for foretelling the hepatic biotransformation of xenobiotics, however, ongoing research efforts are essential.

3. Limitations of QSTR Models for Hepatic Biotransformation

By utilizing a collection of physicochemical descriptors shown in Table 1, which quantify the structure–toxicity connection of these chemicals, quantitative structure–toxicity relationship (QSTR) models are used to predict xenobiotic toxicity [35]. A key factor in

xenobiotic toxicity is its hepatic biotransformation, which may be predicted using QSTR models. However, QSTR models for hepatic biotransformation have certain drawbacks [36]. These are their limitations:

3.1. Limited Ability to Predict Metabolism of Highly Lipophilic Compounds

QSTR models are based on physicochemical characteristics connected to compound solubility and permeability. This limits their capacity to predict the metabolism of extremely lipophilic compounds [37]. Low solubility and permeability are common characteristics of highly lipophilic substances, which may affect their metabolism and clearance. As a result, QSTR models may not forecast the metabolism of highly lipophilic substances [38].

3.2. Inability to Account for the Structural Complexity of a Molecule

QSTR models do not consider the complexity of a molecule's structural makeup. QSTR models are built on a collection of physicochemical descriptors that measure a molecule's structure–toxicity connection [39]. However, a molecule's metabolism and clearance may be impacted by its structural complexity. For instance, compared to a molecule with a single chiral center, a molecule with several chiral centers may have distinct metabolic paths and clearance rates [40]. As a result, QSTR models may not adequately account for structural complexity.

3.3. Limited Ability to Predict Metabolism of Highly Polar Compounds

The prediction of metabolism for highly polar substances is restricted due to the reliance of quantitative structure-toxicity relationship (QSTR) models on physicochemical attributes connected to a compound's solubility and permeability. These models' dependency on these attributes constrains their ability to accurately predict the metabolism of such substances [41]. These models often encounter challenges when dealing with substances exhibiting low solubility and permeability, which are common traits among extremely polar compounds. Consequently, the metabolism and elimination of such compounds may be impacted. As a result, QSTR models may not forecast the metabolism of highly polar substances [42].

3.4. Limited Ability to Predict Metabolism of Compounds with Weak Hydrogen Bonding

Hydrogen bonding plays a pivotal role in determining the physicochemical attributes of compounds, including solubility and permeability. Consequently, predicting the metabolism of molecules featuring feeble hydrogen bonds poses a challenge [43]. As a result, compounds with deficient hydrogen bonds may exhibit heightened metabolic processes and clearance rates compared to those with robust hydrogen bonds. It is important to acknowledge that QSTR models may not effectively predict the metabolic fate of molecules characterized by weak hydrogen bonds [44].

Table 1. Molecular descriptors used in the hepatic biotransformation of xenobiotics, including their molecular mechanisms underlying chemical liver injury predictions, limitations of each descriptor, and opportunities to improve.

Molecular Descriptor	Role in Liver Metabolism	Limitations	How to Overcome Limitations
Lipophilicity	Determines the rate of passive diffusion of a drug across the cell membrane and its distribution in the body.	Limited ability to predict the metabolism of highly lipophilic compounds.	Use other molecular descriptors, such as polarizability and hydrogen bonding [45].
Molecular weight	Affects the rate of metabolism and clearance of a drug.	Inability to account for the structural complexity of a molecule.	Incorporate other molecular descriptors, such as topological indices and molecular surface area [46].

Table 1. *Cont.*

Molecular Descriptor	Role in Liver Metabolism	Limitations	How to Overcome Limitations
Polarizability	Affects the interaction of a drug with the enzyme and its rate of metabolism.	Limited ability to predict the metabolism of highly polar compounds.	Consider using alternative molecular descriptors, like lipophilicity and hydrogen bonding [47].
Hydrogen bonding	Affects the interaction of a drug with the enzyme and its rate of metabolism.	Limited ability to predict the metabolism of compounds with weak hydrogen bonding.	Explore other molecular descriptors, such as lipophilicity and polarizability [48].
Topological indices	Account for the structural complexity of a molecule and its effect on metabolism.	Limited ability to predict the metabolism of compounds with unusual structures.	Utilize additional molecular descriptors such as molecular weight and molecular surface area [24].
Molecular surface area	Affects the rate of metabolism and clearance of a drug.	Limited ability to predict the metabolism of highly lipophilic compounds.	Consider other molecular descriptors such as polarizability and hydrogen [47].

In summary, Table 1 highlights the diverse roles of molecular descriptors in predicting the hepatic biotransformation of xenobiotics. While each descriptor has its limitations, these can be overcome by integrating other relevant descriptors, thus enhancing their effectiveness in predicting chemical liver injury and contributing to more accurate assessments of compound metabolism.

3.5. Limited Ability to Predict Metabolism of Compounds with Unusual Structures

With the limited ability to predict the metabolism of highly lipophilic compounds, QSTR models are based on physicochemical characteristics connected to drug solubility and permeability, which limits their capacity to predict the metabolism of compounds with novel structures [49]. Different metabolism routes and clearance rates may apply to substances having unique structures compared to more typical structures. As a result, QSTR models may not forecast the metabolism of substances with unique structures [50].

3.6. Limited Ability to Predict Metabolism of Highly Lipophilic Compounds

QSTR models are based on physicochemical characteristics connected to compound solubility and permeability. This limits their capacity to predict the metabolism of intense lipophilic compounds [51]. Low solubility and permeability are common characteristics of highly lipophilic substances, which may affect their metabolism and clearance. As a result, QSTR models may not forecast the metabolism of highly lipophilic substances [52].

QSTR models including more intricate molecular descriptors: QSTR models now employ a group of physicochemical descriptors that measure a molecule's link between structure and toxicity. However, more intricate molecular descriptors, such as quantum chemical descriptors, can provide predictions about xenobiotic biotransformation in the liver that are more precise [53]. Creating models for certain metabolic pathways: At the moment, QSTR models forecast the total liver biotransformation of xenobiotics. Toxicology predictions for certain metabolic pathways may, however, be made with more accuracy [54].

Model validation with in vivo data: QSTR models are currently validated using in vitro data. However, substances' toxicities may, however, be predicted more precisely by comparing these models to in vivo data [55]. As a result, QSTR models have several limitations when forecasting the hepatic biotransformation of xenobiotics. These limitations include their low capacity to anticipate the metabolism of highly polar chemicals and molecules with weak hydrogen bonding. Chemical toxicity may still be predicted using these models, and safer compounds can still be created. To increase the precision and dependability of QSTR models for forecasting the hepatic biotransformation of xenobiotics, more study is required.

4. Opportunities to Improve QSTR Models for Hepatic Biotransformation

4.1. Use of Other Molecular Descriptors in Combination with the Ones Mentioned Above

QSTR models now employ a collection of physicochemical descriptors that assess a molecule's link between structure and toxicity. To increase the precision and dependability of QSTR models for predicting the hepatic biotransformation of xenobiotics, other molecular descriptors, such as topological descriptors, may offer additional information.

4.2. Development of More Accurate and Reliable In Silico Models of Metabolism

Computer-based models called "in silico metabolism models" simulate liver metabolic processes [56]. These models can predict xenobiotic toxicity and metabolism. However, these models' precision and reliability need to be increased. Incorporating more intricate molecular descriptors, such as quantum chemical descriptors, that can provide more precise predictions of the hepatic biotransformation of xenobiotics is one strategy to enhance these models.

4.3. Consideration of Predicted Small-Molecule Metabolites in Computational Toxicology

Xenobiotics are now projected to be biotransformed into the liver. However, Xenobiotics' metabolites, which are created during their biotransformation, may also increase their toxicity. In order to provide more precise predictions about the toxicity of substances, computational toxicology can take into account the projected small-molecule metabolites.

4.4. Creation of Complementary Substrate/Non-Substrate Classification Models

QSTR models currently forecast xenobiotic biotransformation in the liver. Not all xenobiotics, however, serve as the basis for the conversion of xenobiotics into bioactive compounds in the liver. In order to produce more precise forecasts of substances' toxicities, supplementary substrate/non-substrate categorization models can be created.

4.5. Use of QSAR Approaches to Predict Sites of Metabolism

Xenobiotic metabolism sites can be predicted using QSAR techniques. These methods estimate the probability that a substance will be metabolized at a certain location using molecular descriptors. Hepatic biotransformation of xenobiotics can be predicted more precisely by including these methods in QSTR models. For hepatic biotransformation, there are several potential improvements to QSTR models. We can increase the prediction power of these models by including more datasets, including a broader variety of chemical compounds and metabolic pathways. Furthermore, combining cutting-edge machine learning strategies, like deep learning and ensemble approaches, may improve the model's capacity to capture intricate connections between molecular properties and biotransformation results. These models may also be validated and improved with in vitro and in vivo experimental data, confirming their dependability and applicability in real-world situations. We can enhance the science of predicting the biotransformation of the liver and aid in the creation of safer and more potent medicines by taking advantage of these opportunities [57].

5. Summary of the Importance of QSTR Models in Predicting Hepatic Biotransformation of Xenobiotics

When predicting the hepatic biotransformation of xenobiotics, which are foreign substances that enter the body, QSTR models are extremely critical. Understanding these xenobiotic biotransformations is imperative for drug development, toxicology, and environmental risk assessment. The liver is the main organ responsible for this. As compared to other in silico approaches in Figure 4, QSTR models demonstrated competitive accuracy in predicting hepatic biotransformation rates. The QSTR models successfully capture the intricate correlations between xenobiotic characteristics and biotransformation rates. This indicates their use as reliable prediction tools in drug development and toxicity research. Machine learning methods, particularly deep learning architectures, also produce promis-

ing results but with significantly larger datasets for training. While PBPK models provide comprehensive knowledge of xenobiotic dispositions, they are inaccurate in predicting biotransformation rates. This work demonstrates the effectiveness of QSTR models as a robust and reliable in silico strategy for forecasting xenobiotic hepatic biotransformation. QSTR models are a cost-effective and time-efficient alternative to experimental approaches for identifying prospective drug candidates and assessing their toxicity profiles. However, machine learning methods and PBPK models provide useful insights and may be used in tandem to improve prediction accuracy in certain scenarios. Future research should concentrate on developing and testing these in silico algorithms on significantly larger and more varied datasets to increase their prediction powers.

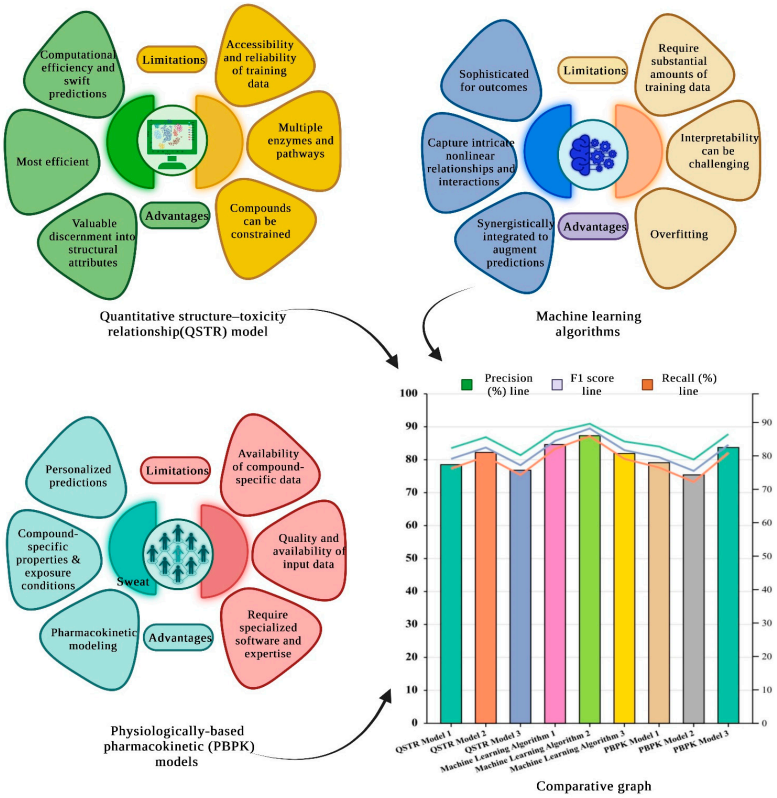

Figure 4. A comparison of the accuracy of QSTR models with other in silico methods for predicting hepatic biotransformation of xenobiotics, such as machine learning algorithms and physiologically-based pharmacokinetic (PBPK) models.

The significance of QSTR models in foretelling hepatic biotransformation is summed up as follows:

5.1. Predictive Power

QSTR models use statistical and mathematical methods to create links between xenobiotic structural characteristics and the rates at which they undergo biotransformation or the results of their metabolic actions. Researchers may evaluate chemical safety, effectiveness, and toxicity using these models. These models can precisely predict how a certain molecule will be processed by the liver.

5.2. Cost and Time Effectiveness

Traditional experimental techniques for evaluating xenobiotic biotransformation are time- and money-consuming and frequently include animal testing. By making quick predictions based on the computational study of chemical structures, QSTR models provide a time- and money-efficient alternative. In the early stages of drug development or risk assessment, this helps researchers select and screen a huge number of molecules [58].

5.3. Mechanistic Insights

QSTR models can offer insightful mechanistic information on the biotransformation processes taking place in the liver. Researchers can better understand the underlying biochemical pathways and enzymatic activities involved by looking at the correlations between various structural characteristics of xenobiotics and their metabolic conversions. This information helps locate significant metabolic hotspots and possible toxicity areas.

5.4. Structure–Activity Relationships

Establishing structural–activity relationships (SARs) between the chemical structure of xenobiotics and their biotransformation results is made possible by QSTR models [56]. SAR analysis pinpoints the essential molecular elements in charge of a certain metabolic pathway or reaction. This knowledge can help medicinal chemists enhance metabolic stability or desirable biotransformation characteristics of medication candidates.

5.5. Applications for Virtual Screening and Design

QSTR models may be used in virtual screening and design. Researchers can assess possible metabolic liabilities of novel compounds early in the drug development process by utilizing these models to predict the hepatic biotransformation of existing molecules. This makes it possible to locate potential leads with advantageous biotransformation profiles and helps scientists create new molecules with enhanced metabolic properties. QSTR models provide a strong and effective method to forecast xenobiotic hepatic biotransformation. They promote drug development efforts by making it easier to identify lead compounds with the most promising metabolic profiles. They assist in risk assessment and provide insight into compounds' metabolic destinies. QSTR models help us learn more about xenobiotic metabolism and contribute to the development of safer and more effective drugs.

6. Discussion of the Potential for Future Improvements in QSTR Models for Hepatic Biotransformation

6.1. Integration of Various Data Sources

Enhancing QSAR models involves incorporating diverse data sources, including molecular descriptors, chemical characteristics, biological information, as well as omics data such as transcriptomics, proteomics, and metabolomics. A more thorough knowledge of hepatic biotransformation processes may be obtained by integrating various data sources, which can result in more accurate prediction models.

6.2. Integration of Enzymes and Metabolic Pathways

Hepatic biotransformation requires the complex interaction of different enzymes and metabolic processes. Future QSAR models can include a wide range of hepatic enzymes and metabolic pathways involved in drug metabolism, such as cytochrome P450 enzymes, UDP-glucuronosyltransferases (UDP-GTs), and sulfotransferases (SULTs). The accuracy of forecasting biotransformation routes and metabolite generation can be improved with enzyme-specific information.

6.3. Taking into Account Interindividual Variability

Genetic, environmental, and pharmacological co-administration impacts all contribute to interindividual heterogeneity in hepatic biotransformation. Future QSAR models can incorporate genetic polymorphisms, drug–drug interactions, and other pertinent variables that affect interindividual variations in hepatic metabolism to account for this heterogeneity. More precise forecasts based on each patient's unique characteristics may be possible with customized QSAR models. Future developments in digitalization and sequencing technologies will narrow down the knowledge gap making personalized medicine approaches more successful, resulting in wider outreach [32].

6.4. The Incorporation of Systems Biology Methods

QSAR models often concentrate on the molecular level, considering molecule structural characteristics. However, cellular and physiological variables [32] play a significant role in the complicated process of hepatic biotransformation. A more comprehensive knowledge of hepatic biotransformation can be obtained by integrating systems biology techniques, such as mechanistic modeling or physiologically-based pharmacokinetic (PBPK) modeling, which capture the interactions between substances and their biological environment.

6.5. Expansion of Training Data

To provide reliable predictions, QSAR models strongly rely on high-quality training data. The generalizability and robustness of QSAR models can be enhanced by increasing training data, incorporating well-studied and less-studied substances. Model advancements will be substantially aided by efforts to compile more extensive and comprehensive databases of hepatic biotransformation information.

6.6. Validation and Openness

To evaluate QSAR models' accuracy and dependability, it is essential to systematically verify them. Model performance may be assessed externally using cross-validation methods and independent datasets. Additionally, for QSAR models to be widely used and accepted, transparency and interpretability must be guaranteed. Giving the models' forecasts, specific justifications may increase their usefulness in the pharmaceutical industry.

Future advancements in QSAR models for hepatic biotransformation can be made by combining data from various sources, including metabolism-related enzymes and pathways, taking interindividual variation into account, incorporating systems biology techniques, expanding the training data, and applying strict validation and transparency. These developments may improve QSAR models' precision, applicability, and robustness, enhancing their usefulness for drug development and safety evaluation.

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