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ORIGINAL ARTICLE

Predictive Toxicology and Toxicogenomics of Potassium Sorbate-Gene-Diseases Association

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KEYWORDS

Potassium sorbate; PreADMET; Predictive toxicology; comparative Toxicogenomics database; Endocrine disruptor chemical

ABSTRACT: In this century, exposure to numerous chemical from different sources became common in human life. Conversely, the toxicological data for a large portion of chemicals for its risk assessment are unknown. Potassium sorbate (PS) is preservative used in wide variety of food, cosmetic and pharmaceutical products and there many authors reported about the effect of PS. This investigation is to integrate computational TGx and predictive toxicology and first report of potassium sorbate on this aspect. It was aimed in order to understand the potential adverse health effects of PS by ADMET prediction and their curated interactions between PS-gene–disease relationships. PreADMET and Comparative Toxicogenomics Database were used for the computational study. PreADMET revealed prediction data for ADME via physic-chemical parameter along with Caco-2 cell, MDCK cell and BBB (blood-brain barrier), HIA (human intestinal absorption), skin permeability and plasma protein binding and toxicological prediction using chemical structures, such as mutagenicity and carcinogenicity. CTD results established curated and inferred interactions between PS-gene–disease relationships. The CTD outcomes exposed that PS may possess endocrine disruption potency and have impact on endocrine system diseases etiology. It is concluded, that computational prediction approach offers both a better understanding of the potential risks of chemical exposure to humans and a direction for future toxicological investigation.

INTRODUCTION

Exposure to several chemicals from various sources became ubiquitous in human life over the twentieth century. Conversely, the toxicological data for a large portion of chemicals for its risk assessment are unknown. Toxicogenomics (TGx) is a swiftly growing discipline that promises to aid researchers to understand the molecular and cellular effects of chemicals in biological systems. To comprehend chemicals, available experimental data from the scientific literature can be used. Toxicity, mechanisms, and mode of action, as well as exposure, may be determined using a predictive research model that also referred as *In silico*. No definitive definition for *In silico* study method or preparation to evaluate the safety of a chemical. Irrespective of the methodology employed, to figure out the risks and safety of the chemical by using available data and data findings from *In silico* [1].

The data such as existing knowledge on toxicology of the chemical, the process of read-across (similar chemicals), results from *in vitro* testing and high-throughput methods that reveals chemical's action and mechanisms and the impacts at the cellular or molecular level [2]**.** *In silico* toxicity prediction uses computational methodologies and technologies to analyse, model, simulate, and predict the toxicity of chemical to offer precedent for extending toxicological studies [3]. To construct pipelines for systems toxicology applications by utilizing abundantly

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available publicly accessible knowledge about chemical, gene/protein, disease and biological networks [4].

Potassium sorbate is preservative used in wide variety of food, cosmetic and pharmaceutical products and there many authors reported about the effect of PS. Molecular docking study conducted by [5] to understand the interaction with Human serum albumin (HSA) and PS. PS interacted with HAS subdomains IA and IB via physical connection with a non-covalent. Advanced glycation end products (AGEs), an agent of oxidative stress and clinical complications of diabetes mellitus and PS activated and increased the levels of AGE on HSA in the presence and absence of glucose. The results of that study confirmed PS could aggravate complication of diabetes and provides information on risk impact by PS. Computational studies on PS would be most appropriate to initiate the process before performing any time-consuming and tedious *In vitro* and *In vivo* studies. Hence, this leads to recognise the demand to study further to find effect of PS safety and on other public health issues.

The physicochemical properties, reactivity and toxicological parameters could be certainly characterised using conventional QSAR models. Challenging to model as a result of insufficiency data and the complicated of biological systems and toxicological mechanisms. Generally based on the hypothesis of a single binding mode QSAR models were developed. At the same time, diverse binding modes have been discovered in X-ray examination and this need attention. Toxicogenomic evidence from vast diverse chemical sets added a whole new approach of scientific information that could be valuable for chemical safety assessment [6].

For that reason, this investigation is to integrate computational TGx and predictive toxicology. Therefore, it was aimed in order to understand the potential adverse health effects of Potassium Sorbate (PS) by ADMET prediction using PreADMET and Comparative Toxicogenomics Database for their curated and inferred interactions between PS-gene–disease relationships. This could potentially aid with future risk assessment findings on PS, as different data inputs from the prediction outcome of this study could be recorded and analysed to gain insights from all resources and to recognize PS influence on human health.

MATERIALS AND METHODS

Computational tools

For the computational study, two tools were used that including (i) PreADMET (http://preadmet.bmdrc.org/) a web-based application for predicting ADME (Absorption, Distribution, Metabolism and Excretion) and toxicological data [7] and (ii) Comparative Toxicogenomics Database (CTD; http://ctd.mdibl.org/) is another valuable resource which includes more than 30.5 million toxicogenomic connections relating chemicals/drugs, genes/proteins, diseases, Gene Ontology (GO) annotations and gene interaction modules [8].

PreADMET

ADME prediction

Under ADME menu tab, the mol file format of PS was uploaded using “Open” option that converts into the chemical structure of PS. The given input was submitted for the prediction the resulting ADME data were exported in PDF format.

Toxicological prediction

In Toxicity menu tab, the mol file of PS was uploaded using “Open” option that converts into the chemical structure of PS. The given input was submitted for the prediction the resulting toxicological data were exported in PDF format.

Comparative Toxicogenomics Database (CTD)

Data Curation Process

In CTD simple search can be done using keyword query method by giving MeSH (Medical Subject Headings) name, synonym, MESH accession ID, CAS Registry Number or using the “name:” prefix. Here by giving “name: Potassium Sorbate” in the keyword Search for curation in CTD.

Gene Interaction

CTD manually curate the genes that interacting with PS, which were reported in available scientific literature.

Disease analysis

In CTD to analysis the direct disease relationship by the following two sources: curation of PS–disease and gene/protein–disease relationships from the literature and inferred data by integration of gene–disease relationships from the Online Mendelian Inheritance in Man (OMIM; http://www.ncbi.nlm.nih.gov/omim) database.

Gene Ontology (GO)

GO terms of PS-interacting gene based on the curated interaction gene data was analysed. GO annotations that provide information about their associated biological processes, molecular functions, and cellular components of the gene/protein interact with PS.

PS genes to genes association with disease and chemical

To compare Curated and inferred genes to genes association with specified diseases MyGeneVenn tool was used. The comparison between Curated and inferred genes to genes association with Endocrine system disease (ESD), Bisphenol A (BPA) and Estradiol (E2) using Venn diagram.

RESULTS

PreADMET analysis of PS

The ADME property is significant parameter in order to evaluate the action of mechanism of chemicals. ADMET predications can assist us in ensuring that our chemical evaluation is unbiased and accurate. Substantial progress has been made in the domain of structure-based in silico modelling of ADME characteristics in recent years [9]. With reference to this, attempt made to analyse absorption, distribution, metabolism, excretion and toxicity (ADMET) property prediction of PS using Pre ADMET server. The obtained results for ADME of PS listed in Table 1 and toxicological prediction for PS was tabulated in Table 2.

Table 1. Toxicity Prediction of PS from PreADMET

Toxicity	Values
Acute algae toxicity (mg L^{-1})	0.297792
Ames test	Mutagen
Carcinogenicity(Mouse)	Out of range
Carcinogenicity(Rat)	Out of range
Acute daphnia toxicity (mg L^{-1})	0.974548
hERG inhibition	Medium risk
Acute fish toxicity (medaka) (mg L^{-1})	1.03716
Acute fish toxicity (minnow) (mg L^{-1})	1.70179
TA100 10RLI	Positive
TA100 NA	Positive
TA1535 10RLI	Negative
TA1535 NA	Negative

CTD

The datasets retrieved from CTD capable to discover the relationships and to produce novel, testable hypotheses about chemical-gene-disease pathways and predictive inferences that are statistically ranked [10]. This curated data set for PS was analysed to demonstrate the possibility of CTD and to emphasize its prospective applications for understanding the mechanisms of chemical actions and potential links to human diseases.

Potassium sorbate-gene interaction

Manually curated data for PS–gene interactions contains interacting gene, the explanation about the interaction (increases, decreases, and affects (degree unspecified)), the number of references and organisms in which the interaction was reported. PS–gene and protein interactions of 10 were retrieved from CTD and tabulated in Table 3.

Table 3. Potassium Sorbate–Gene interactions.

S.No.	Interacting genes	Names of genes
1	CYP2E1	Cytochrome P450 family 2 subfamily E member 1
2	EPHX1	Epoxide hydrolase 1
3	FOSL1	FOS like 1, AP-1 transcription factor subunit
4	GSTM1	Glutathione S-transferase mu 1
5	GSTT1	Glutathione S-transferase theta 1
6	NQO1	NAD(P)H quinone dehydrogenase 1
7	ORM1	Orosomucoid 1
8	PHEX	Phosphate regulating endopeptidase homolog X-linked
9	RAD51AP1	RAD51 associated protein 1
10	VEGFA	Vascular endothelial growth factor A

Disease analysis

The curated data of PS–disease and gene/protein–disease relationships shows the following diseases are associated with PS which includes Pathology (process), Immune system disease, Skin disease, Genetic disease (inborn) and Occupational disease of 20% score based on the literature evidences. Urogenital disease (female), Urogenital disease (male), Metabolic disease, Digestive system disease and Endocrine system disease. Notably, Cancer with 57 inferred association of 21.1% inferred score, Urogenital disease (female) with 17 inferred association of 6.3% inferred score, Endocrine system disease with 9 inferred association of 3.3% inferred score and Pregnancy complication with 1 inferred association of 0.4% inferred score (Figure 1).

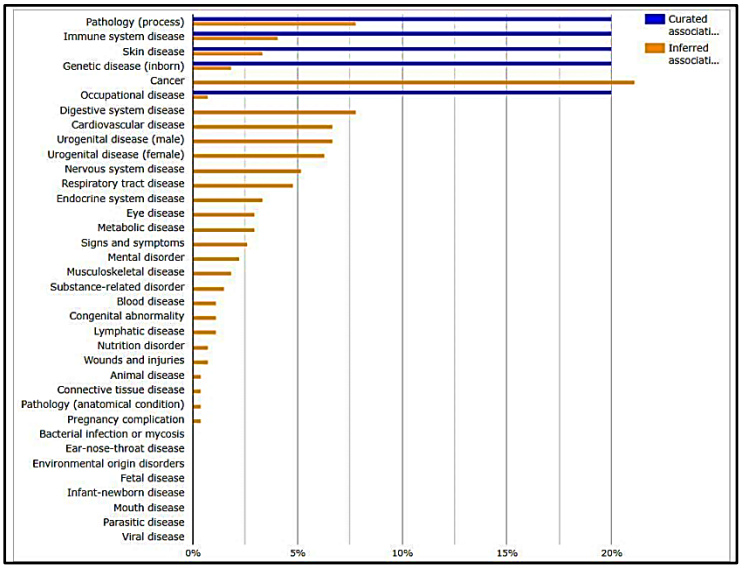

Figure 1. Potassium sorbate–curated and inferred disease association

Gene Ontology for PS

GeneOntology (GO) terms are enriched significantly among genes/proteins that interact with PS with a corrected p-value *<0.01* (Table 4). The significance of enrichment was calculated by the hypergeometric distribution and adjusted for multiple testing using the Bonferroni method [11].

Table 2. Gene Ontology (GO) annotations of potassium sorbate–interacting genes\proteins.

GO term	Corrected P-value	Annotated genes
Biological processes		
Response to toxic substance	4.00E-07	6
Xenobiotic metabolic process	1.08E-05	4
Cellular response to xenobiotic stimulus	4.68E-05	4
Response to stimulus	1.26E-04	10
Response to xenobiotic stimulus	3.10E-04	4
Response to chemical	4.86E-04	8
Cellular response to stimulus	7.16E-04	9
Cellular response to chemical stimulus	9.54E-04	7
Response to nitrogen compound	0.00162	5
Long-chain fatty acid metabolic process	0.00197	3
Cellular detoxification	0.00245	3
Detoxification	0.00272	3
Response to inorganic substance	0.00419	4
Response to stress	0.00469	7
Cellular Components		
Cytoplasmic part	0.00949	9

PS genes to genes association with disease and chemicals

From 10 genes interacting with PS was curated from CTD. The curated genes were compared with curated and inferred genes to genes diseases association. In the comparison of PS curated genes (10 genes) with ESD for curated association (1,188 genes) and inferred association (43,592 genes). It was clear for curated association and inferred association found 4 genes and 10 genes interacting with PS associated with ESD respectively (Figure 2A & B).

The interacting genes of PS (10) were compared with curated genes to genes interact with BPA (23,565) and E2 (8,672). The results revealed that all 10 genes of PS shares interaction with bisphenol A and 9 genes of PS interact with estradiol (Figure 3A &B).

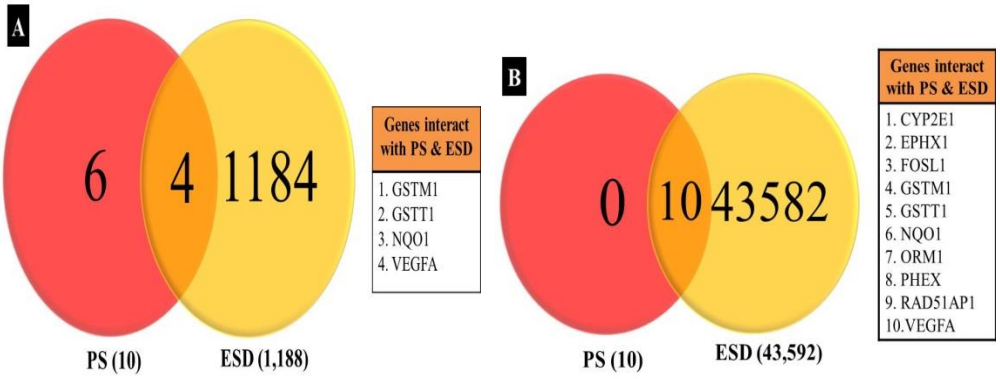

Figure 1. Genes Interact with PS that Associate with Disease A) curated genes and B) inferred genes associated with ESD.

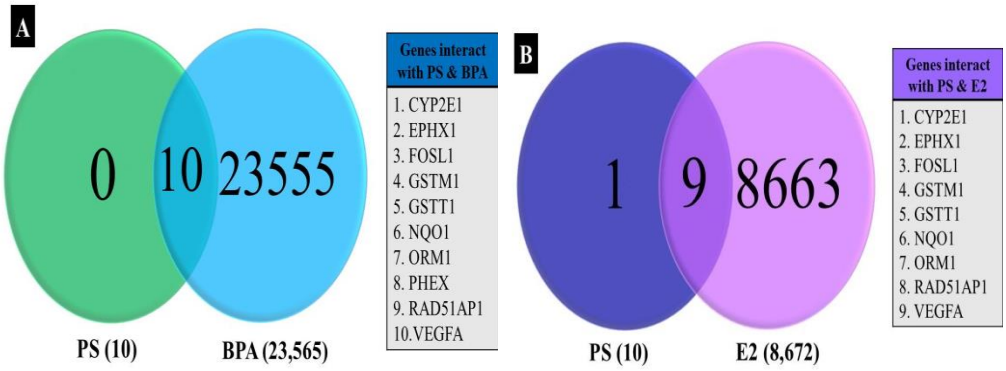

Figure 2. PS-Gene Interact with Chemicals A) Bisphenol A B) Estradiol.

DISCUSSION

Currently, computational tools are possibly used in prediction or assessing the absorption, distribution, metabolism, excretion and toxicity (ADMET) of chemicals PreADMET is one such tool. ADMET outcomes obtained from PreADMET in Table 1 shows that PS has ability to cross the blood-brain barrier (BBB). Metals, pesticides, herbicides and bacterial toxins studied for BBB penetration likely to evoke neurotoxicity [12]**.** The evidence from animal studies expose that the level of damage and dysfunction to BBB induced by chemical toxicity varies on immature brain as they are delicate than the adult brain [13]**.** This seems substantially for PS induced toxicity and influence to the etiology of central nervous system diseases. The human colon carcinoma cell line (Caco-2) for prediction of intestinal permeability leads to absorption [14]. The finding from this study showing PS has permeability in Caco-2; this prediction confirms the oral absorption in humans.

Inhibition of any isoform of Cytochrome P (CYP) directs to the failing of chemical metabolism and intensification of toxicity. PreADMET results revealed that PS strongly inhibits CYP2C19 and CYP2C9 enzymes this suggests the enhanced plasma concentrations might end up in harmful impact. In case of CYP2D6 and CYP3A4 enzymes are recognized for the involving in metabolism and oxidation of xenobiotics respectively but PS had not exhibits inhibitory effect. PS established weak action on CYP2D6 and CYP3A4 substrates [15]**.** HIA result of PS has 94.62% absorption and predicted measures established high intestinal absorption efficiency of PS. Madin–Darby Canine Kidney cells (MDCK) prediction allows studying cell membrane permeation and interaction of chemical with the membrane. The cell permeability less than 25 is considered as low diffusion, PreADMET prediction for PS is 4.89nm/sec. and this suggests it has less MDCK cell permeability. P-glycoprotein (P-gp) server as an efflux transporter of xenobiotic from the cells and found in blood brain barrier, blood placenta-barrier, gastrointestinal tract, kidney, liver etc. It plays major role in ADME process that prevent the accumulation of toxic, carcinogenic chemicals and thus inhibit carcinogenesis [16]. Predication results shows that PS inhibits P-gp thereby it can perceive PS interfere with detoxification process. Plasma protein binding (PPB) is percentage of chemical bound to the plasma protein. PS has 64.34% of PPB and a study by [17] has been hypothesised that elevated plasma protein binding not implies that chemical is more toxic but it is linked with high toxicity tendency for the reason that of its relationship with lipophilicity property. The chemical diffusion into and absorption through the skin is essential to predicting toxicological effects and its related health hazardous are typically underestimated [18]. The prediction of the rate of skin permeability of PS is -3.52 cm/hour. The reference logP values for skin permeability of chemicals ranging from -3 to +6, establish an effective absorption via the skin [19]**.** The chemical compound's physical-chemical factors associated with its lipophilicity nature were estimated with SKlogD, SKlogP and SKlogS values.

According PreADMET prediction results for toxicity of PS were summarised in Tables 2 and 3 The prediction of

acute toxicity in algae, daphnia, medaka and minnow fish revealed aquatic and environmental toxicity induced by PS. The study conducted by [20] to identify the toxic effect of PS to *Dunaliella tertiolecta* and had obvious toxicity effects on these algae. The records of PS from Databook of Preservatives [21] mention aquatic toxicity study on daphnia for 96-h LC50 750 mg L^{-1}. The above studies evident for aquatic toxicity of PS in different study models and these findings well agreed with prediction. The Ames test is *Salmonella typhimurium* reverse mutation assay and prediction declares PS as mutagenic agent. Alongside positive mutagenic activity results for TA100 10RLI and TA100 NA strains and negative mutagenic activity results for TA1535 10RLI and TA1535 NA strains. The prediction results for Ames test were well agreed with the investigation by [22] disclosed the Ames test results that 4,5-oxohexenoate an oxidation product of PS was mutagenic nature.

Biocurators like CTD never manipulate, standardize, or normalize data curated based on the query from publications. The data integrated in CTD includes (1) published literature on PS; (2) curating genes that interacting with the chemical; (3) a hierarchical vocabulary of organisms; (4) a hierarchical vocabulary of chemicals; and (5) the Gene Ontology (GO; hierarchical vocabulary of biological processes, cellular components, and molecular functions). In the process of integrated cross-references, CTD as well consolidate approach for further data associated with molecular and toxicology, including microarray data and articles related to environmental chemicals impact on health from the popular press [23]**.**

By integration of gene–disease relationships from the Online Mendelian Inheritance in Man database the diseases are inferred. Many of these genes/proteins have Gene Ontology (GO) annotations, which furnish information regarding their related biological processes, and cellular components [24]. To offer insight into the three domains of GO: biological process infers that the changes at the level of cell or organism which are mediated by gene products and cellular component provide details about the location of the gene products in the part of cell or its extracellular environment all of these actions may be influenced by PS.

Curated gene–disease and chemical associations are found by both CTD and OMIM curation. This helps to determine the genes associated with diseases along with the genes interacted with PS that extracted from previously proven results retrieved from the literature. Inferred gene–disease associations are recognized via CTD–curated chemical–gene interactions [25]**.** PS is associated with Endocrine System Diseases this is because of curated interaction with few genes hence exhibits the association. BPA is renowned endocrine disruption chemical (EDC) and explored for its endocrine disruption potency that interfere with the function of endocrine systems. The trans-generational effect, infertility and reproductive pathologies were witnessed due to the exposure of BPA [26]. E2 is dominant estrogen hormone found in human that activates with estrogen receptor-α (ERα) and many other signalling pathways [27]. Many studies confirmed BPA mimic like estrogen interact with ERα identified as reproductive, developmental and systemic toxicant also increase breast cancer risk and reproductive health related diseases [28, 29]. As PS shares interaction genes with BPA and E2 and this could be considered as a prominent evidence for EDCs potency of PS.

Although studies of individual genes are valuable for understanding function in a toxicological context, it is well accepted that genes and their proteins do not function in isolation, but rather as components of larger networks [30]**.** Similarly, chemicals affect larger networks and not just individual genes or proteins. The richest sources of information about chemical interactions are biomedical literature and high-throughput technologies such as microarrays [31].

The predication study by PreADMET and CTD results provides great insights on PS toxicity and gene-disease association. EDC potency of PS not been reported before and this findings would lead for extending the investigation to seek further knowledge on the same.

CONCLUSIONS

The etiology of most chronic diseases engaged with interactions between Chemical exposure and genes that alters vital physiological processes. This hypothesis was agreed by the numerous diseases caused by reversible actions or unnecessary exposures and the comparatively

rare number of diseases credited to single gene mutations. *In silico* and information-centred tools for via in advance risk assessment prediction aid leading to proper designing the experimental in the near future.

In summary, ADMET results from PreADMET that provides the information needed to establish assessment of PS to identify and predict a variety of toxicities outcomes. It is concluded, that computational toxicogenomics approach offers both a better understanding of the potential risks of chemical exposure to humans and a direction for future toxicological investigation for validation of PS–gene interactions and PS influenced diseases. In light of these data, extracted information from the computational approach on various toxicological endpoints and experimental attempts needed for further clarification on this aspect.

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Conflict of Interests

The authors declare that they have no conflict of interests.

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