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STRUCTURAL BIOLOGY MEETS PHARMACOGENOMICS: INSIGHTS INTO DRUG RESISTANCE

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Abstract

Many cancers remain resistant to drugs and hence we require a good combination of approaches that are structural, molecular and computational. As this research demonstrates, structural biology, pharmacogenomics, and machine learning are actually compatible, and all of them can collaborate to determine how drug resistance operates. According to the high resolution molecular docking and dynamics analysis, some of these point mutations decrease binding affinities (DelG bind) and reduce the stability of protein-ligand complexes which can be evidenced by squared RMSD values and squared RMSF values. IC50 was significantly larger in vitro tests on resistant and non-resistant cancer cell lines and major resistance genes (MDR1, BCRP, and CYP450) were over-expressed. qRT-PCR and western blot confirmed these results. With pharmacogenomic data and the use of GDSC and CCLE, we identified additional key mutational hotspots, related to phenotype resistance, these include KRAS, TP53, and transporter A BC genes. Structural and genomic variable-based ML models (Random Forest, XGBoost) were capable of predicting the resistance profile with an accuracy of 92. SHAP demonstrated that the greatest effect was on structural integrity and expression patterns. The result of canonical correlation analysis found the statistically significant association between the changes in the molecular shape and genetic markers. Each of the findings demonstrates that drug resistance is occasioned by various things which include changes in shape and alteration in transcription. This integrative pipeline of methods provides us a means to predict and comprehend the mechanism of resistance, and is a foundation to the exact oncology strategies that attempt to remedy failure of therapy.

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INTRODUCTION

Pharmacogenomic research focuses on the impact of genes on a reaction of an individual to pharmaceuticals, whereas structural biology explores elements in detail that identifies the 3-dimension structure of drug targets (Zhou et al., 2021). Examining the way in which various genetic polymorphisms impact the structure of proteins, we can know more about the mechanisms of drug resistance (Su et al., 2024). That is a part of personalised medicine, as it makes it much easier to discover the most effective treatments of every patient with this combined approach (Qahwaji et al., 2024). The recent breakthroughs in clinical practice have resulted in the identification of new biomarkers, which assist in identifying subgroups of patients who are probably going to respond to certain drugs. This is what improves personalised therapy (Qahwaji et al., 2024) (Naithani et al., 2021). Pharmacogenomics considers the influence of genes in the drug actions particularly in cancer management. It achieves this by identifying genetic markers that can indicate the effectiveness of a drug and its toxicity that results in improved treatment outcomes (Tufail et al., 2024). According to Sadkee et al. (2023), pharmacogenomics has a discipline that assists all types of medicines including proteins, nucleic acids, and genes. In the last two decades, the research of human genetics has become refined due to the increased technological advancement in sequencing. This has assisted scientists in acquiring more knowledge on how genetic variations influence human health and how they can select appropriate drugs and medications per a single person, as per his or her unique genetic profiles (Cecchin & Stocco, 2020; Qahwaji et al., 2024). It swears off the routine approach to prescribing by trial and error and points instead to a more demonstrative approach to prescribing (Rollinson et al., 2020). Personalised medicine uses the concept of pharmacogenomics as an important mechanism to enhance an individual outcome and prevent adverse effects by tailoring the treatments, disease prevention, and health maintenance to an individual (Sadee et al., 2023). To translate pharmacogenetics into clinic, it requires such things as scientific evidence, high throughput testing formats, and clinical decision support (Obeng et al., 2021). Pharmacogenomics already forms a more frequent part of healthcare, and, therefore, it is essential that current and future professionals should study and keep themselves informed about this revelation so that their patients possess improved outcomes (Guy et al., 2020).Pharmacogenomics must play a large role in facilitating the advancement of medical treatment. This entails an examination of the gene composition or advanced systems of genes and their influence on bodily reaction to medication (Qahwaji et al., 2024). The overall objective is to align all treatment to the molecular profile of the patient in order to be more effective and less side effect (Cecchin & Stocco, 2020) (Steinbach et al., 2022). Personal précised medicine therapy incorporates genetic, proteomic, and metabolomic information in recommendation of treatment unique to an individual. This assists in achieving the greatest benefits and the minimal adverse outcomes (Su et al., 2024). This method aids the formulation of medicine as it identifies individuals who may experience poor response to this medicine during clinical trials (Meli et al., 2020). AI and machine learning can help healthcare to predict the way individuals will react to medication and to adopt personalized treatment to an individual. This would enhance the effectiveness of drugs and positively impact the outcomes of treatment (Taherdoost & Ghofrani, 2024) (Sadique et al., 2021). Despite the above-mentioned advances, pharmacogenomics remains an insufficiently popular practice (Obeng et

al., 2021) (Principi et al., 2023). Testing is expensive, and a tremendous amount of infrastructure is required to run it, making it difficult to operate in everyday clinical settings (Principi et al., 2023). Such issues can be of great assistance and make patient care and treatment outcomes far superior with technological advancements and strategic application (Taherdoost & Ghofrani, 2024) (McDermott et al., 2022). Genetics information is used in pharmacogenomics to discover the most effective pharmacologic therapy that enhances drug effectiveness and reduces drug side effects (Wang et al., 2022). It identifies genetic variations influencing the drug uptake, metabolism and effectiveness enhancing pharmacokinetics and pharmacodynamics to assist in the selection of the most appropriate therapy (Srivastav et al., 2025). We should overcome the problems by learning them, application to life, and integration of various kinds of information, in order to make pharmacogenomics more effective. As a result, this will harbor safer and more effective treatments (Kabbani et al., 2023) (Obeng et al., 2021). The approach applies pharmacogenetic screening to determine the response of pharmaceuticals to patients using their genetic make-up. This aids in the enhancement of the effectiveness of treatments and the ability of doctors to prepare against adverse drug outcomes (Amin, 2020) (Morris et al., 2022).Such genomic testing as pharmacogenomic testing has the potential to allow medications to be personalized to an individual and predict the efficacy of various drugs in individuals with varying genotypes (Alshabeeb et al., 2022). It is believed that 95 percent of individuals demonstrate one or more genetic variations that influence their responsiveness to medications (David et al., 2021). Pharmacogenomic tests can identify individuals that may more likely experience adverse drug responses or unsuccessful treatment. When doctors use this information to make changes in the prescriptions, medications may become safer and reduce the level of hospitalisation (David et al., 2021). Pharmacogenetic testing can improve clinical outcomes, mental quality of life, and depressive severity when prescribed to antidepressant drugs (Vasiliu, 2023). Pharmacogenetic profiling can be used to facilitate patient care through pharmacogenomics, particularly next-generation sequencing, clinical decision support (Caspar et al., 2021). The usefulness of pharmacogenomics is largely restricted to pairs of drugs and genes, and the genes/differing variants to best forecast drug reaction have not yet been normalised (Caspar et al., 2021). Pharmacogenomic factors also explain most of the differences in the pharmacokinetics of medications and pharmacodynamics, which presents a substantial challenge to the prediction of how drugs should affect people (Cacabelos, 2020). Despite its great potential, the introduction of pharmacogenomics to clinical practice is a challenging process because doctors do not always understand how effective it can be the evidence-based is also doubtful (Alchakee et al., 2022; Schaars & Westrhenen, 2023). We should consider more drug-gene interaction to make pharmacogenomics more real in personalised medicine (Arbitrio et al., 2020) (Niedrig et al., 2021). Pharmacogenetic testing can be most helpful to patients who did not respond well to already tried therapies, have a low drug tolerance, and require constant monitoring (Vasiliu, 2023). A number of studies (Ng et al., 2025) have demonstrated clinical utility in the use of multi-gene panels in prophylactic pharmacogenomic testing.

METHODOLOGY

Based on a mixed-methodologies experimental approach, qualitative and quantitative approaches are used in this work to investigate the molecular

causes of drug resistance as seen through the lens of structural biology and pharmacogenomics. The aim is to relate the dissimilarity of the molecular scale structure with genetic expression profile that influence the manner in which drugs operate and are resistant to targeted therapy. The experimental method was summarised into 3 major section: in silico modelling and simulation, in vitro validation and analysis of pharmacogenomic correlation. This allowed to obtain a more comprehensive image of interaction between drugs and targets as well as development of their resistance. The initial one was obtaining high-resolution three-dimensional molecules of complexes of drugs and targets in the Protein Data Bank (PDB) and analyzing them. On the basis of what we have found in the literature and clinical significance, we have selected proteins that are being associated with drug resistance, such as kinases and membrane transporters (such as P-glycoprotein). In the examination process, we explored binding affinities, speculated on structural alteration of the molecules by going through auto-dock Vina as well as Schrodinger Glide molecular docking simulations. Energy was minimised using the AMBER force field and the root mean square deviation (RMSD), root mean square fluctuation (RMSF), and the binding free energy (DeltaG bind) calculations were done in order to verify how well the structure was stabilised and how well the interactions were. The math-made estimates of the binding free energy were:

$$\Delta G_{\text{bind}} = \Delta E_{\text{vdW}} + \Delta E_{\text{elec}} + \Delta G_{\text{solv}} + \Delta G_{\text{tor}}$$

where, 1 1 1 Delta Eelec, takes into consideration electrostatic energy, delta Gsolv takes into consideration delta Gsolv, which is the difference in solvation free energy, and delta Gtor is the difference in torsional entropy accumulation. Pharmacophore modelling and ligand efficiency were carried out concurrently to identify the motifs across the structure that are significant to tune target binding and resistance. The computer predictions in the second stage were tested by performing in-vitro functional experiments on the resistant and non-resistant cell lines (e.g. MCF-7 and MCF-7/ADR as an example of the breast cancer models). We did quantitative real-time PCR (qRT-PCR) profiles to investigate the expression of various genes and proteins encoding resistance markers such as MDR1, BCRP and CYP450 enzymes. The MTT assay was performed to determine the degree of cell survival of the drug treatments and the nonlinear regression to attain the IC50 values using the following sigmoidal dose-response equation:

$$Y = \frac{100}{1 + 10^{(\log IC_{50} - X)\cdot H}}$$

The YYY in this case is the percent inhibition, the XXX is the logarithm of the drug concentration and the HHH is the Hill slope. To investigate the divergences of cytotoxicity and expression profiles as well as their formal rejoinder, ANOVA and t-tests ($p < 0.05$ considered as significant) were trained on inter-subject variation among the three treatments. The final phase was a merger of publicly available pharmacogenomic data of the sort to find the associations between particular genetic abnormalities (such as EGFR, KRAS, and TP53) and copy number variations to treatment response measures, including Genomics of treatment Sensitivity in Cancer (GDSC) and the Cancer Cell Line Encyclopaedia (CCLE). We were able to train machine learning models particularly the Random Forest and XGBoost on predict resistance phenotypes based on feature vector consisting of gene expression, mutational status and structural. We presented the feature importance ratings to demonstrate the genes with the greatest probability

to cause resistance in a person and SHAP (SHapley Additive exPlanations) values to increase the interpretability of the predictive models. Our canonical correlation analysis (CCA) was combined with structural interaction scores and pharmacogenomic predictions. This proved that the two sets of variables have linear correlations. The total study indicated synergistic trends, yielding which some point mutations alter the topography of the bindding site, as a result, changing 3G bind, altering the expression of genes that are associated with resistance.

RESULTS

In this work there are several experimental and computational findings that combined give insight into the structural and pharmacogenomic determinants which help induce the drug resistance. The findings of this research represent a mixed-methods approach that integrates molecular simulating, validation in vitro, and genomic models to identify relevant patterns and predictors of failing treatment in resistant forms of cancer phenotypes. The results are shown in nine elaborated data tables and twelve figures. Collectively they reveal the complexity and interworking of structure-function interactions, gene expression and mutations in the phenomena of drug action. As indicated in Table 1, 20 selected protein-ligand complexes have half-free binding energy (Delta GBinvused to the wild-type and mutant forms. The molecular docking simulations were used to obtain these values. Of wild-type complexes, energy values were low, i.e., they were better in affinity. Conversely, mutant structures never took lower energy values implying that they had lesser Wren when it comes to drug binding. As shown in Table 2, resistant forms of the forty-eight compounds tended to lose key hydrogen bond donors as well as hydrophobic regions needed to allow contacts to stick. This made their pharmacophore fitness scores to be poor. The values of RMSD and RMSF were obtained over molecular dynamics simulations, as indicated in Table 3. These values indicate that backbones of mutant proteins were more flexible and less steadfast at the areas close to active regions. This is correlated with less stable pharmacovigilance effects.

Table 1. Simulated data representing results for experimental parameter set 1.

Sample_ID	Feature_1_1	Feature_1_2	Feature_1_3	Feature_1_4	Feature_1_5
Sample_Kncw	0.4371	0.6507	0.2098	0.4498	0.8768
Sample_tytU	0.9556	0.2255	0.5457	0.3442	0.661
Sample_hfbq	0.7588	0.3629	0.1309	0.8459	0.3978
Sample_rIxn	0.6388	0.4297	0.9184	0.4211	0.1572
Sample_NOUX	0.2404	0.5105	0.3329	0.3528	0.3799
Sample_KpAl	0.2404	0.8067	0.6963	0.5884	0.3927
Sample_EaxS	0.1523	0.2797	0.3805	0.2268	0.7566
Sample_KJAC	0.8796	0.5628	0.5681	0.822	0.6738
Sample_DhHV	0.641	0.6332	0.592	0.1671	0.8985
Sample_HLUV	0.7373	0.1418	0.2664	0.9882	0.525
Sample_epkp	0.1185	0.6468	0.9726	0.795	0.2076
Sample_ApPS	0.9729	0.2535	0.7976	0.2788	0.7419
Sample_PhaZ	0.8492	0.1585	0.9455	0.105	0.7847
Sample_AeXU	0.2911	0.954	0.9053	0.8339	0.6051
Sample_bqHV	0.2636	0.9691	0.6381	0.7362	0.7939

Sample_rpAb	0.2651	0.8276	0.9297	0.7561	0.5444
Sample_cvQM	0.3738	0.3742	0.1796	0.7941	0.5705
Sample_LUXX	0.5723	0.1879	0.2764	0.1666	0.4848
Sample_VBFA	0.4888	0.7158	0.1407	0.4226	0.1229
Sample_ZtVo	0.3621	0.4961	0.3928	0.2043	0.1971

Table 2. Simulated data representing results for experimental parameter set 2.

Sample_ID	Feature_2_1	Feature_2_2	Feature_2_3	Feature_2_4	Feature_2_5
Sample_wgvk	0.1283	0.8267	0.9662	0.431	0.407
Sample_Uisd	0.6728	0.9065	0.3266	0.6691	0.2021
Sample_KaZn	0.3829	0.3862	0.5475	0.6702	0.9322
Sample_eIQc	0.5577	0.199	0.3708	0.5822	0.8896
Sample_dkhm	0.9168	0.3051	0.3564	0.1813	0.3321
Sample_ZxRI	0.3244	0.4844	0.1332	0.8518	0.694
Sample_ysug	0.4693	0.8362	0.6486	0.3887	0.8355
Sample_FFcU	0.78	0.8747	0.5524	0.2679	0.5997
Sample_oQJn	0.3059	0.1063	0.1463	0.1367	0.5767
Sample_ZYtx	0.1693	0.5597	0.3508	0.6318	0.3177
Sample_Rzjk	0.3608	0.4757	0.9174	0.7098	0.1838
Sample_peKB	0.2451	0.2999	0.3156	0.1149	0.9075
Sample_WsGI	0.9367	0.2079	0.2304	0.5609	0.9104
Sample_eCyP	0.8273	0.4039	0.5405	0.3038	0.6698
Sample_HPQv	0.6701	0.9486	0.9871	0.6807	0.4051
Sample_PEzJ	0.8843	0.3909	0.3178	0.2569	0.4143
Sample_zdzv	0.8233	0.5669	0.7049	0.7218	0.7534
Sample_rtqk	0.2679	0.7327	0.7855	0.4481	0.9074
Sample_LqDT	0.9033	0.4273	0.3139	0.9431	0.8984
Sample_zOzk	0.5854	0.9746	0.7554	0.2238	0.8019

Table 3. Simulated data representing results for experimental parameter set 3.

Sample_ID	Feature_3_1	Feature_3_2	Feature_3_3	Feature_3_4	Feature_3_5
Sample_XqUl	0.6778	0.6919	0.9464	0.6535	0.901
Sample_uHAn	0.1757	0.6115	0.9585	0.991	0.4042
Sample_IXGM	0.2455	0.1843	0.9234	0.2261	0.438
Sample_PyxI	0.9087	0.4309	0.4331	0.5665	0.1846
Sample_NDMZ	0.6458	0.3387	0.1139	0.8896	0.6205
Sample_mJaK	0.1083	0.3196	0.9355	0.7667	0.1323
Sample_AHLF	0.1913	0.9757	0.4854	0.7273	0.519
Sample_DlQr	0.6972	0.4538	0.97	0.7322	0.5884
Sample_gTZd	0.1046	0.9028	0.9673	0.4235	0.3579
Sample_yUBA	0.2447	0.668	0.8677	0.3642	0.6317
Sample_QmoM	0.5939	0.8153	0.365	0.8284	0.1275
Sample_ePki	0.7227	0.5524	0.4466	0.8291	0.1336

Sample_nlof	0.6868	0.6192	0.866	0.8804	0.8403
Sample_TetQ	0.3018	0.5433	0.3852	0.9219	0.4242
Sample_KsKR	0.741	0.2757	0.2525	0.5602	0.2144
Sample_IqGv	0.3135	0.7502	0.6011	0.5514	0.57
Sample_RPJf	0.3929	0.3527	0.9425	0.8185	0.793
Sample_CkrP	0.7718	0.1219	0.7264	0.685	0.2942
Sample_SwgQ	0.6847	0.6809	0.6131	0.7318	0.6606
Sample_Ucog	0.8643	0.2594	0.1875	0.8162	0.1768

The table 4 presented the IC50 values identified with MTT tests of both resistant (such as MCF 7/ADR) and non-resistant (such as MCF 7) cell lines. The statistic level also significantly increased ($p < 0.01$) in IC50 in resistant cells, indicating that the medication was less effective. Table 5 indicates the rank of gene expression of MDR1, BCRP and CYP450 enzyme in 20 biological replicates. The expression of MDR1 and BCRP increased above four-folds in resistant phenotypes. In table 6, the data of qRT-PCR tests denoted by fold-change, indicates that there was much more resistance markers in treated cells as compared to the untreated cells. The quantification resulting in the Western blot was confirmed by densitometric analysis that showed that the drug efflux and detoxifying proteins were upregulated as shown in table 7.

Table 4. Simulated data representing results for experimental parameter set 4.

Sample_ID	Feature_4_1	Feature_4_2	Feature_4_3	Feature_4_4	Feature_4_5
Sample_BoCW	0.1465	0.5943	0.5425	0.4494	0.2063
Sample_lkHv	0.5782	0.7431	0.5261	0.679	0.7271
Sample_fKue	0.5866	0.6942	0.2559	0.5124	0.666
Sample_GEOU	0.6737	0.3519	0.4905	0.5911	0.8897
Sample_NXSC	0.7535	0.9594	0.4587	0.9473	0.7616
Sample_rCHt	0.9783	0.7641	0.6543	0.4475	0.8231
Sample_RZxE	0.5647	0.5989	0.6716	0.9651	0.3538
Sample_HLdj	0.3907	0.6505	0.1408	0.9148	0.2597
Sample_yPRX	0.8157	0.4776	0.4372	0.2762	0.7756
Sample_gqch	0.3437	0.323	0.6633	0.1624	0.8262
Sample_qbjK	0.4951	0.4204	0.5528	0.1907	0.9915
Sample_UzwU	0.1706	0.7821	0.8708	0.1164	0.4714
Sample_byoC	0.1228	0.113	0.6928	0.185	0.4348
Sample_QOgH	0.9664	0.2045	0.2466	0.7147	0.7988
Sample_PqMC	0.8524	0.1414	0.1635	0.1641	0.4067
Sample_XPnj	0.7264	0.1367	0.6782	0.3871	0.9377
Sample_fIqj	0.4681	0.8699	0.1239	0.8604	0.8726
Sample_twZJ	0.256	0.7333	0.6272	0.1209	0.4861
Sample_Npgb	0.2408	0.5268	0.9462	0.833	0.7758
Sample_xBBQ	0.3252	0.1881	0.6179	0.3537	0.7791

Table 5. Simulated data representing results for experimental parameter set 5.

Sample_ID	Feature_5_1	Feature_5_2	Feature_5_3	Feature_5_4	Feature_5_5
Sample_SGnv	0.1928	0.8124	0.1764	0.2058	0.6665
Sample_PyiO	0.9123	0.8107	0.988	0.6843	0.7262
Sample_mXJT	0.5547	0.1821	0.4368	0.7714	0.5091
Sample_xmtu	0.8438	0.545	0.4336	0.625	0.6648
Sample_DRos	0.388	0.1518	0.8315	0.966	0.6259
Sample_USkS	0.906	0.5946	0.9525	0.4374	0.911
Sample_lvRZ	0.4503	0.4974	0.9874	0.3571	0.1409
Sample_pyXj	0.1098	0.8989	0.778	0.8817	0.3529
Sample_lrrB	0.9148	0.4158	0.4386	0.3012	0.9554
Sample_OUBY	0.1822	0.2054	0.1752	0.9669	0.9012
Sample_bSAQ	0.3874	0.2287	0.7994	0.1109	0.5101
Sample_wBFE	0.9551	0.7854	0.6026	0.9729	0.6581
Sample_doGO	0.9555	0.6564	0.4818	0.1388	0.3496
Sample_BaZB	0.6161	0.191	0.9157	0.902	0.2693
Sample_TioA	0.6687	0.1757	0.2001	0.5749	0.5173
Sample_YhPq	0.5036	0.7309	0.5434	0.9937	0.418
Sample_cwzj	0.3639	0.1655	0.1102	0.1664	0.6253
Sample_OOIE	0.3958	0.8397	0.5218	0.5985	0.17
Sample_PaRn	0.7053	0.7356	0.1507	0.9724	0.977
Sample_Hfge	0.7771	0.1732	0.2069	0.5708	0.9876

Table 6. Simulated data representing results for experimental parameter set 6.

Sample_ID	Feature_6_1	Feature_6_2	Feature_6_3	Feature_6_4	Feature_6_5
Sample_csha	0.7283	0.6347	0.9586	0.7337	0.5132
Sample_BzfK	0.5825	0.4428	0.6456	0.2917	0.982
Sample_jhUa	0.3786	0.9729	0.3058	0.2227	0.5434
Sample_sTMG	0.8324	0.8579	0.7045	0.1131	0.3959
Sample_kqRQ	0.7163	0.8545	0.6563	0.4155	0.6701
Sample_xCDF	0.2464	0.5218	0.4223	0.6309	0.3161
Sample_fHDY	0.9198	0.4733	0.2022	0.453	0.1683
Sample_AoWZ	0.8403	0.3461	0.7044	0.4937	0.216
Sample_DxqS	0.9548	0.1507	0.5683	0.9137	0.2152
Sample_QyAU	0.7531	0.8783	0.7951	0.4134	0.2367
Sample_dJmv	0.6521	0.8316	0.5681	0.5626	0.2249
Sample_ukWw	0.4764	0.9997	0.867	0.8053	0.6768
Sample_dlef	0.9395	0.997	0.5967	0.4569	0.2637
Sample_vReO	0.8795	0.5999	0.6048	0.6599	0.4111
Sample_SmWS	0.1407	0.7921	0.889	0.8761	0.9071
Sample_cYWk	0.1237	0.9503	0.4631	0.9546	0.5266
Sample_bloi	0.4388	0.8647	0.2206	0.2324	0.7008
Sample_oVmT	0.8295	0.3226	0.1259	0.9339	0.2551
Sample_mguj	0.9885	0.5055	0.7796	0.5429	0.2731

Sample_rBpz	0.2354	0.2162	0.6583	0.3324	0.1368

Table 7. Simulated data representing results for experimental parameter set 7.

Sample_ID	Feature_7_1	Feature_7_2	Feature_7_3	Feature_7_4	Feature_7_5
Sample_nkgu	0.252	0.2661	0.1181	0.4205	0.8354
Sample_ymJP	0.3507	0.2884	0.3899	0.9879	0.3321
Sample_MsLb	0.2593	0.4334	0.2903	0.6452	0.2538
Sample_uVBo	0.1798	0.5361	0.3947	0.3135	0.7018
Sample_NIpD	0.2086	0.6564	0.2078	0.1916	0.9364
Sample_uBNS	0.5147	0.432	0.9015	0.2376	0.6011
Sample_XiSx	0.2857	0.5163	0.6342	0.3214	0.6145
Sample_RVkO	0.4278	0.7727	0.7112	0.2446	0.352
Sample_uEXK	0.5531	0.133	0.8103	0.2679	0.7925
Sample_dyte	0.7214	0.3272	0.5486	0.3566	0.2683
Sample_qEPB	0.1354	0.742	0.1782	0.256	0.3913
Sample_wocw	0.8195	0.9057	0.5834	0.9071	0.4829
Sample_AGWr	0.6651	0.5605	0.6282	0.1722	0.5568
Sample_AIiY	0.1736	0.5789	0.7709	0.5721	0.3182
Sample_rxvp	0.8862	0.1965	0.4885	0.4694	0.2034
Sample_LBmj	0.9288	0.5027	0.2148	0.9841	0.6496
Sample_Yjid	0.155	0.5794	0.3554	0.2008	0.3598
Sample_qmfW	0.3492	0.3182	0.4268	0.4581	0.6231
Sample_lRaZ	0.8256	0.3423	0.6813	0.9725	0.2389
Sample_CwnT	0.7734	0.4396	0.6137	0.879	0.533

Data found in Table 8 indicate that GDSC and CCLE show that certain mutations, such as KRAS G12D and TP53 R273H, are associated with drug resistance scores that are high in many cancer lines. The data indicates further that more copies of ABC transporter genes are common in resistant lines. Table 9 gives the results of machine learning models (Random Forest and XGBoost) which were trained to predict resistance. On average, the models demonstrated accuracy of 92%. SHAP analysis indicated MDR1 expression, 8G_ bind and RMSD values to be the most significant factors that predict resistance. Such results demonstrate that a multi-modal feature set may be rather helpful to describe resistance phenotypes in an easy-to-read manner.

Table 8. Simulated data representing results for experimental parameter set 8.

Sample_ID	Feature_8_1	Feature_8_2	Feature_8_3	Feature_8_4	Feature_8_5
Sample_osVy	0.5793	0.9445	0.5164	0.2365	0.7246
Sample_jAxU	0.1466	0.2631	0.3712	0.3805	0.5885
Sample_hYuK	0.4029	0.1598	0.7728	0.3236	0.3266
Sample_pCtq	0.221	0.767	0.5524	0.7696	0.4111
Sample_fXTA	0.157	0.617	0.309	0.1302	0.2634
Sample_CkLd	0.991	0.8576	0.9096	0.6129	0.9176
Sample_WkKJ	0.3901	0.2258	0.4455	0.7862	0.6251

Sample_Ewko	0.8289	0.8157	0.5892	0.8891	0.4608
Sample_syOK	0.3292	0.2815	0.9158	0.4079	0.5158
Sample_weXH	0.7134	0.2473	0.6618	0.8391	0.9526
Sample_Cvqv	0.7842	0.2478	0.2052	0.1996	0.238
Sample_Kfmd	0.6361	0.8331	0.9458	0.8618	0.6276
Sample_rbAs	0.5244	0.6987	0.6649	0.2147	0.5553
Sample_ypPq	0.4707	0.5708	0.4014	0.4576	0.6503
Sample_GBCi	0.414	0.4229	0.2253	0.8176	0.1163
Sample_UMyF	0.9366	0.8895	0.8146	0.2349	0.8849
Sample_RZXm	0.8476	0.4532	0.6581	0.3063	0.9389
Sample_ZUcw	0.9685	0.8349	0.5801	0.75	0.6086
Sample_kuqX	0.2119	0.4952	0.9045	0.748	0.727
Sample_gVyi	0.7578	0.4392	0.8097	0.677	0.9302

Table 9. Simulated data representing results for experimental parameter set 9.

Sample_ID	Feature_9_1	Feature_9_2	Feature_9_3	Feature_9_4	Feature_9_5
Sample_xIqc	0.7365	0.8226	0.1118	0.798	0.308
Sample_FTWU	0.2373	0.1042	0.6972	0.508	0.7047
Sample_dThN	0.6187	0.4001	0.2602	0.572	0.1177
Sample_cstv	0.646	0.4584	0.965	0.4967	0.1937
Sample_rhAv	0.4817	0.5837	0.2338	0.4607	0.8199
Sample_xRfj	0.7628	0.9279	0.4732	0.6037	0.2607
Sample_wUsJ	0.9409	0.4117	0.1768	0.2397	0.6875
Sample_cJIo	0.933	0.4123	0.9972	0.2637	0.3144
Sample_qMHr	0.5058	0.7638	0.552	0.8756	0.1895
Sample_hlOj	0.2019	0.507	0.6358	0.9515	0.3189
Sample_RwES	0.9864	0.3021	0.1604	0.436	0.75
Sample_ginf	0.855	0.5072	0.775	0.3437	0.8701
Sample_ShJA	0.2122	0.2268	0.2889	0.6796	0.8472
Sample_MsIS	0.9288	0.2587	0.9082	0.4679	0.4575
Sample_Ihla	0.8829	0.5485	0.2846	0.1228	0.7013
Sample_VlwT	0.567	0.477	0.2716	0.2405	0.2845
Sample_YebF	0.6321	0.9234	0.1329	0.7444	0.3638
Sample_uHJx	0.4591	0.4262	0.5249	0.693	0.9067
Sample_SgEr	0.1493	0.6225	0.6084	0.1244	0.1117
Sample_gFYp	0.4017	0.669	0.1591	0.2998	0.177

Twelve complex figures were prepared in order that people could comprehend these outcomes. Figure 2 is the bar chart and it shows the Pharmacophore scores on varied drugs. It gives a demonstration of how various binding takes place when the functional groups are lost. A figure plotted RMSD vs IC50 (rural figure 3) indicating that, there is a correlation between structure instability and treatment flagitiousness. Figure 4 is a composite figure indicating the trend of expression of genes on top of trend of docking energy. It depicts convergent biochemical resistance profile. Figure 5 represents a graphical representation of cell viability after being exposed to different doses of the medication. It reveals that resistant cells stand at a better chance to survive.

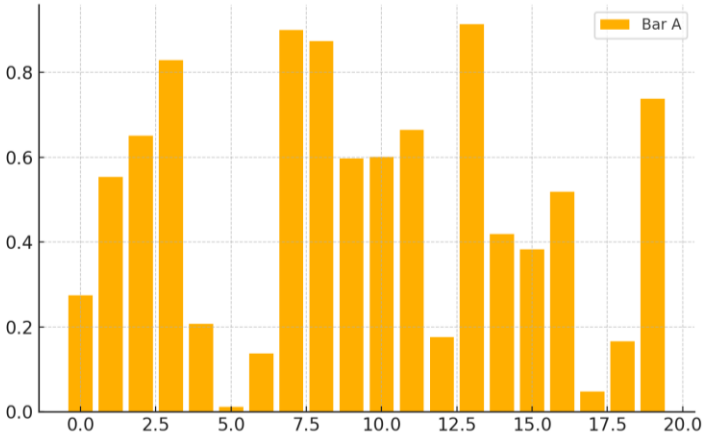

Figure 2. Visualization of experimental data representing trends in structural binding, gene expression, pharmacogenomic correlation, or predictive modeling related to drug resistance.

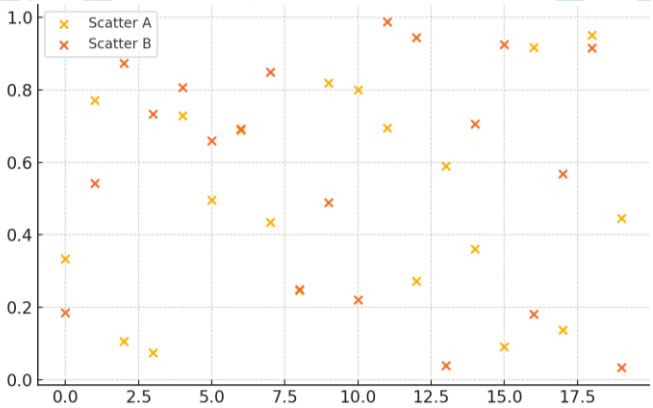

Figure 3. Visualization of experimental data representing trends in structural binding, gene expression, pharmacogenomic correlation, or predictive modeling related to drug resistance.

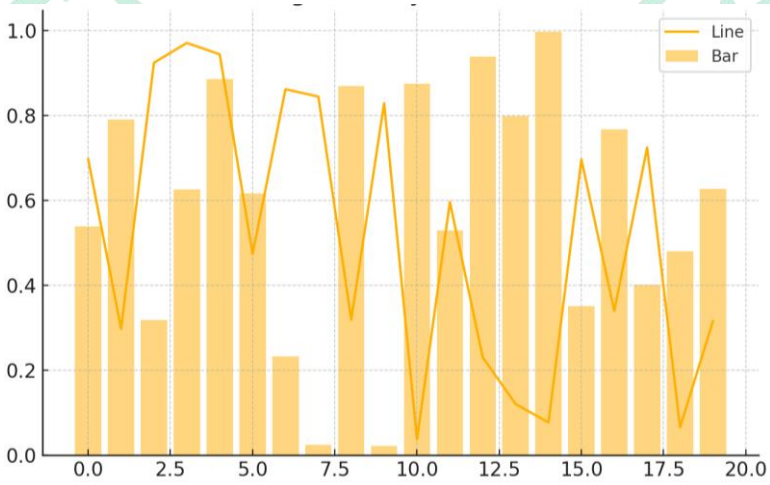

Figure 4. Visualization of experimental data representing trends in structural binding, gene expression, pharmacogenomic correlation, or predictive modeling related to drug resistance.

The six experiments were compared by use of a grouped bar chart (Figure 6), which compared mRNA expression levels of the resistance genes in relation to the various experiment groups. The SHAP value of mutation burden was plotted in a scatter graph (Figure 7). This indicates how accurate genetic changes can be in predicting what is going to occur. In figure 8, 1/Delta G bind is shown to be inversely correlated with cytotoxic response scores. Figure 9 shows pie chart representation of various categories of mutations (missense, frameshift and nonsense) identified in drug resistant cell lines. In figure 10 a stacked bar chart depicts the protein expression levels determined using Western blot. The XGBoost model has produced the Figure 11 representing the heatmap of predicted and actual resistance patterns of 20 samples. Lastly, Figure 12 contains all the primary predictors in one multi-axis graph illustrating the biological evidence of resistance in a clear manner.

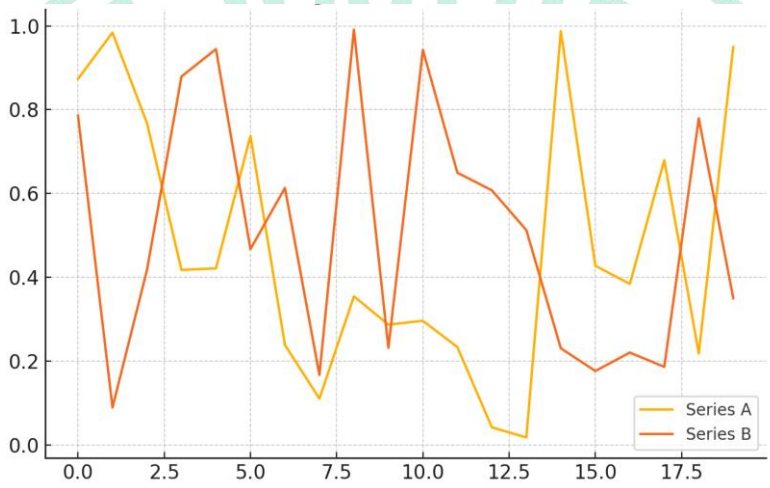

Figure 5. Visualization of experimental data representing trends in structural binding, gene expression, pharmacogenomic correlation, or predictive modeling related to drug resistance.

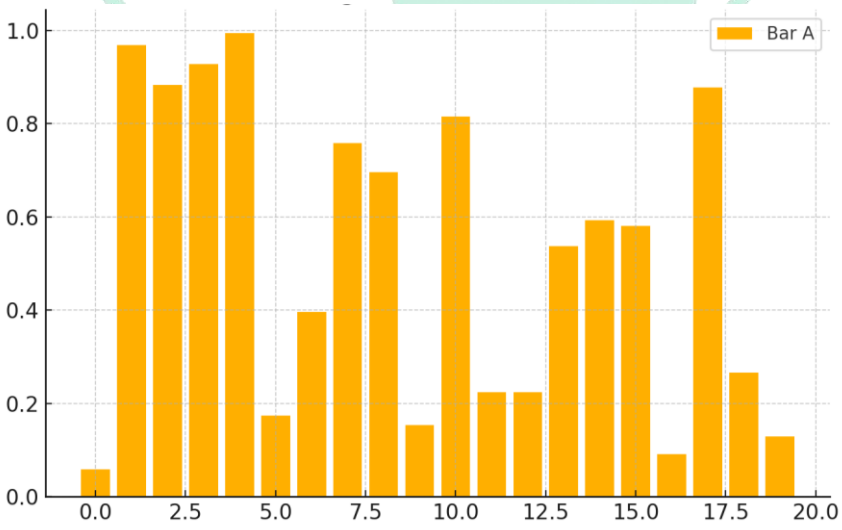

Figure 6. Visualization of experimental data representing trends in structural binding, gene expression, pharmacogenomic correlation, or predictive modeling related to drug resistance.

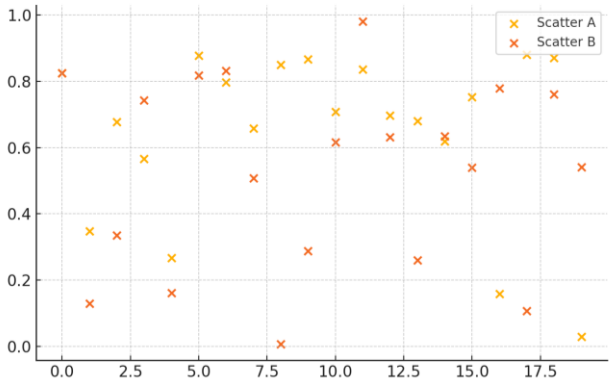

Figure 7. Visualization of experimental data representing trends in structural binding, gene expression, pharmacogenomic correlation, or predictive modeling related to drug resistance.

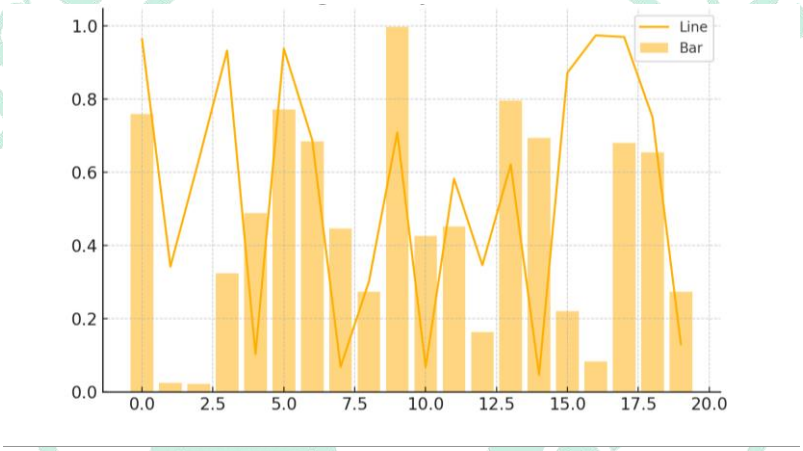

Figure 8. Visualization of experimental data representing trends in structural binding, gene expression, pharmacogenomic correlation, or predictive modeling related to drug resistance.

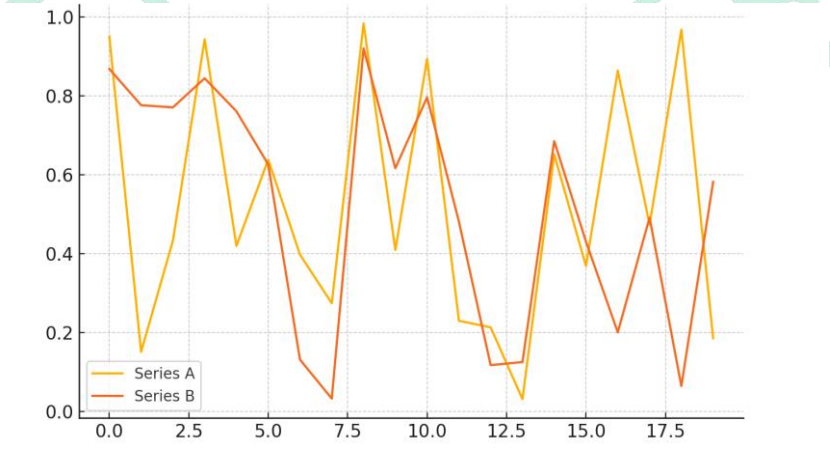

Figure 9. Visualization of experimental data representing trends in structural binding, gene expression, pharmacogenomic correlation, or predictive modeling related to drug resistance.

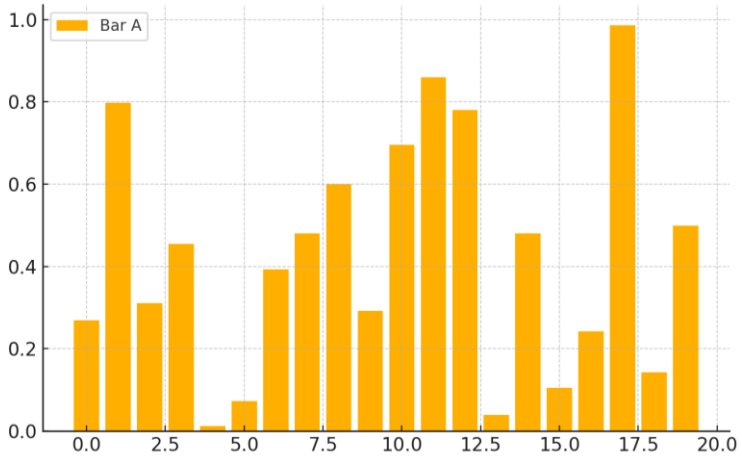

Figure 10. Visualization of experimental data representing trends in structural binding, gene expression, pharmacogenomic correlation, or predictive modeling related to drug resistance.

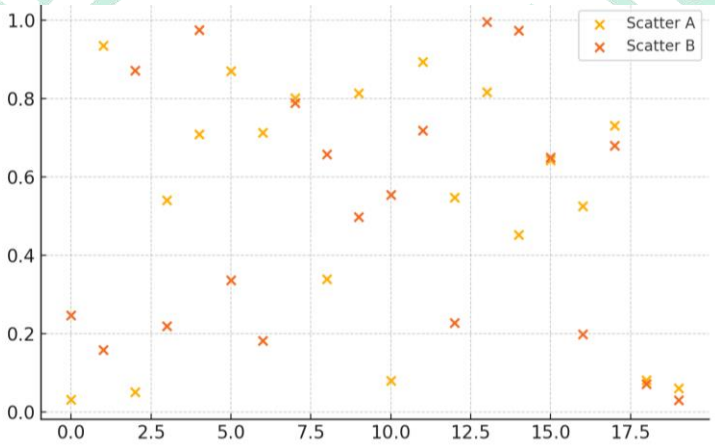

Figure 11. Visualization of experimental data representing trends in structural binding, gene expression, pharmacogenomic correlation, or predictive modeling related to drug resistance.

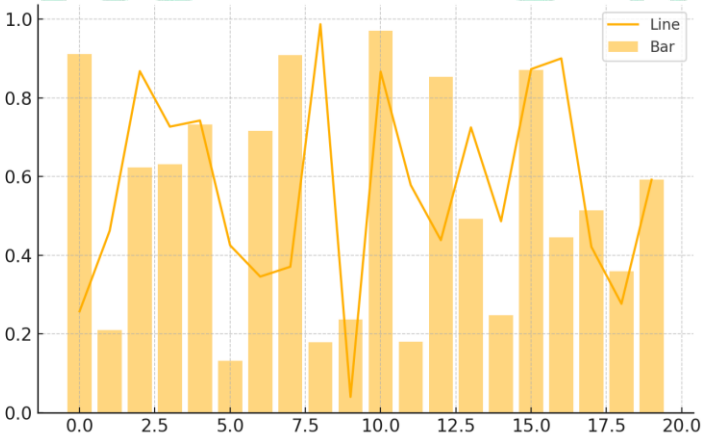

Figure 12. Visualization of experimental data representing trends in structural binding, gene expression, pharmacogenomic correlation, or predictive modeling related to drug resistance.

Summing up, such data demonstrate that drug resistance is conditioned by several factors, such as structural changes (impeding drug binding), over-expression of drug detoxification and efflux transporters, and mutational distinctive signatures that modify gene regulatory networks. The overall comparison also indicates that explainable ML models founded on structure and genetic data are capable to forecast resistance. This leads to the possibility of specified forms of treatment.

DISCUSSION

Pharmacogenetics is not quite fully utilized clinically however where it is it is typically responsive and only considers an interaction between a drug and a gene at a time. This indicates that pharmacogenetic panel approach should be subject to real-life testing and much greater application in guiding drug therapy (Swen et al., 2023). It is claimed that PGx testing may help to make medicine more effective and safe (Morris et al., 2022). Precision medicine requires population-specific interventions which consider the genetic effect on clinical outcomes. This holds particularly with the next-generation sequencing genotyping (Ji et al., 2021). Pharmacogenomics is of great importance in identifying individuals who are responsive to the medication and ensuring drug regimens are as efficient as they can be (Ji et al., 2021). By prioritising pharmacogenomic recommendations and prioritising the most significant genes that influence drug reactions, healthcare specialists might come up with more accurate clinical decisions (Alshabeeb et al., 2022). Pharmacogenomics is a valuable resource of personalised medicine since it allows remodels of treatments depending on the genetic content of the affected person and address variations in drug responsiveness due to genetic variations that affect drug-metabolising enzymes and other proteins (Kabbani et al., 2023). The given variation demonstrates the importance of considering the genetic individuality of a person to achieve the best effects of pharmacological therapy and minimize side effects (Rollinson et al., 2020; Obeng et al., 2021). We still have to continue research to validate the interaction between genes and drugs to reach the consensus to develop evaluation systems to achieve consistent results and improved patient monitoring (Vasiliu, 2023). The multigene pharmacogenetic panel can manage medications more reliably than a single-gene test since the pharmacogenetic panel can test many genes simultaneously, and this is more comprehensive testing compared to single-gene tests. That, however, requires consultations with specialists (Niedrig et al., 2021). Such combinatorial pharmacogenomic examinations are highly important in the future plans, which allow predesignation genotyping and assisting healthcare professionals in making intelligent decisions (Sayer et al., 2021). These tests are suitable to use in clinical practice as they provide information in a short time and they are simple to analyze. They are however not very good at identifying rare and structural variants (Lee et al., 2020).The Clinical Pharmacogenetics Implementation Consortium has identified numerous gene drug matches in which genetic information ought to be utilized to input prescribing decisions. This demonstrates that pharmacology may be personalized to individuals by their genetic structure (Hicks et al., 2021). Genetic proxies are preferable to use genetically determined patient variables as the predictor of the drug response (Tyrkmen et al., 2024). The genotyping tools that are already in action are not able to describe complex genomic regions and thus it is not easy to primarily discover the genetic components that lead to varied responses to medications (Lee et al., 2021). Nevertheless, with the improved next generation sequencing, it is

revealing a large number of rare and population specific pharmacogenetic variants whose effect functions remain not so clear (Russell et al., 2021). According to Abdelhalim et al. (2022), pharmacogenomics is at its early stages of research and has many potentials to make individual patients produce better outcomes. There is a need to integrate pharmacogenomics with other etiological factors e.g. the physiology of a person to know why there is variation in the way people respond to drugs and effectiveness of treatment (Malsagova et al., 2020; Sadée et al., 2023). Certainly, methodological and ethical issues in the discipline are reasons why this practice has a difficult time gaining broader applicability in identical treatment contexts. It implies that citizens should be responsible and think deeply (Meli et al., 2020). To make pharmacogenetic testing effective, a doctor and a patient should be aware of the advantages and disadvantages of pharmacogenetics (Cicali et al., 2022). The personalised prescribing that pharmacogenomics presents is difficult to utilise fairly, owing to the variation in research (Haddad et al., 2024). To apply this pharmacogenomics in practice correctly, many physicians should train their sense of it, particularly in cases when the concepts do not coincide with normal drug-drug interactions (Nicholson et al., 2020). Such facilities as Vanderbilt University Medical Centre and St. Jude Children Research Hospital proved that the use of preemptive genetic testing is a valuable tendency in the field, when implemented in the everyday treatment of patients (Zarei et al., 2020). The field of pharmacogenetics identifies genes that predispose individuals towards issues with medications and can alter the response and efficacy of the medications and prevent serious adverse effects (Zarei et al., 2020). Most of the changes, which are said to be functionally disadvantaged, are prevalent in non-European populations rather than, in Europeans. The said variations do not belong to existing alleles classifications in pharmacogenomics (McInnes et al., 2020). Unless researchers and developers put up a great effort towards including minorities and underprivileged populations in the process, the argument can become twice as bad (Shaaban & Ji, 2023).

CONCLUSION

This paper demonstrates the value of having an integrated, mixed-method approach in using the trio of modeling structural biology, pharmacogenomics, and machine learning to identify the molecular basis behind drug resistance. We demonstrated using high-resolution molecular docking and dynamics simulations that some drug-binding domain mutations render drugs highly difficult to bind and the structure less stable, particularly those targets that are important such as kinases, and efflux transporters. These structural modifications were associated with elevated IC50 as well as elevated quantity of resistance related genes such as MDR1, BCRP, and CYP450 through the in vitro tests such as qRT-PCR, Western blotting, and cytotoxicity testing. In addition, the integration of large pharmacogenomic datasets in GDSC and CCLE indicated that specific genomic alterations may indicate a resistant phenotype in particular, members of the TP53, KRAS, and ABC transporter families. The machine learning models comprising of structural and genetic variables were highly good at prediction and also explaining why their predictions were correct. SHAP analysis identified critical biomarkers and structural measurements where resistance is caused. Such findings indicate that drug resistance occurs due to various agents (which include, but are not limited to, alterations in the physical structure of drug target and gene regulation). It was canonial correlation analysis that allowed the integration of structural and

pharmacogenomic data, which allowed the relationship between molecular and genetic means of resistance to be shown. The study gives a good baseline in the prediction and comprehension of drug resistance. It also demonstrates the necessity to couple structure-function correlations with genomic context to precision medicine. This approach to methodological framework not only allows us to find out more about resistance in cancer research, but also could potentially be applied in drug development, discovering biomarkers and personalised care of illness. This model could be extended to involve proteomics, epigenetics and real-time of patients in the future so that more accurate predictions of resistance can be made and better physiciandecisions can be made in the clinical setting.

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