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EXPLORING PHARMACOGENOMICS OF MEDICINAL PLANTS FOR OPTIMISING CANCER MANAGEMENT: A NARRATIVE REVIEW

Actuality. *Cancer remains the second leading cause of death worldwide. Various cancer treatments are associated with side effects and chemoresistance. Phytomedicines, rich in bioactive compounds, can target tumour cells with low toxicity. Pharmacogenetics plays a crucial role in the metabolism of phytochemicals and the response to medication. However, the interaction of medicinal plants with genes encoding membrane transporters and metabolising enzymes is still poorly understood.*

Purpose of the work. *This study aims to highlight the interactions of certain natural products used in cancer treatment with target sites or related genes that modulate their pharmacokinetics (PK) and pharmacological pathways.*

Material and methods. *A narrative review was conducted using PubMed, Google Scholar, and Scopus databases.*

Research results. *Specific genetic variations, including FBN2, ZFAND3, SPDYA, and others, have been reported to protect against vincristine-induced peripheral neuropathy, while the MCM3AP variant increases the risk. The role of CYP polymorphisms in the PK of this phytomedicine remains debated. Notably, CYP3A5*3/*3 has been associated with increased toxicity in Paediatric rhabdomyosarcoma patients. Additionally, the ABCB1 rs1045642 variant appears to impact event-free survival in acute lymphoblastic leukaemia, whereas the rs4728709 variant has been linked to a higher risk of neurotoxicity. No statistically significant associations were found between the CYP3A422 and CYP2C8*3/*4 genotypes and overall drug-related adverse reactions for Taxol and nab-paclitaxel. However, carriers of the ABCB1 3435TT genotype exhibited a higher treatment response and increased incidence of severe neutropenia. Additionally, the ABCB1 rs2032582 variant was associated with improved survival in ovarian cancer patients treated with carboplatin and paclitaxel. Gigantol significantly reduced the number of invaded cancer cells by inhibiting the RNA expression of Wnt target genes and epithelial-mesenchymal transition marker genes. Furthermore, it downregulated CD133 and ALDH1A1 – key cancer stem cell markers – by inhibiting AKT signalling in lung cancer cell lines.*

Conclusion. *While certain gene polymorphisms have been associated with the safety of vincristine, no specific polymorphism has been definitively identified as a predictor of its toxicities. The impact of single nucleotide polymorphisms in the CYP and ABCB1 genes on the safety and efficacy of paclitaxel remains uncertain. This review may contribute to evaluating both the safety and efficacy of phytomedicines, as well as their potential for drug-drug interactions, particularly in the context of combined herbal and conventional therapies.*

Key words: *pharmacogenomics, pharmacogenetics, cancer, vincristine, paclitaxel, gigantol.*

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ДОСЛІДЖЕННЯ ФАРМАКОГЕНОМІКИ ЛІКАРСЬКИХ РОСЛИН ДЛЯ ОПТИМІЗАЦІЇ ЛІКУВАННЯ РАКУ: НАРАТИВНИЙ ОГЛЯД

Актуальність. *Рак залишається другою провідною причиною смертності в усьому світі. Різноманітні підходи до лікування раку пов'язані з побічними ефектами та хіміорезистентністю. Фітопрепарати багаті на біологічно активні сполуки, які можуть впливати на пухлинні клітини з низькою токсичністю, тому фармакогенетика відіграє важливу роль у фітохімічному метаболізмі та відповіді на лікування. Однак взаємодія лікарських рослин із генами, що кодують мембранні транспортери та метаболізуючі ферменти, залишається недостатньо вивченою.*

Мета дослідження *– висвітлення взаємодії деяких природних препаратів, що використовуються в лікуванні раку, із сайтами-мішенями або пов'язаними з ними генами, які модулюють їх фармакокінетику (ФК) та фармакологічні шляхи.*

Матеріали та методи. *Проведено наративний огляд з використанням баз даних PubMed, Google Scholar та Scopus.*

Результати дослідження та їх обговорення. *Повідомлялося, що певні генетичні варіації, включаючи FBN2, ZFAND3, SPDYA та інші, захищають від периферичної нейропатії, спричиненої вінкристином, тоді як варіант MCM3AP підвищує ризик. Роль поліморфізмів CYP на ФК цього фітопрепарату залишається дискусійною. Зокрема, CYP3A5*3/*3 асоціюється з підвищеною токсичністю в пацієнтів з дитячою рабдоміосаркомою. Крім того, варіант ABCB1 rs1045642 впливає на виживаність без подій за гострого лімфобластного лейкозу, тоді як варіант rs4728709 пов'язаний з підвищеним ризиком нейротоксичності. Не було виявлено статистично значущих асоціацій між генотипами CYP3A422 і CYP2C8*3/*4 та загальними побічними реакціями, пов'язаними з прийомом таксолу і наб-паклітакселу. Однак у носіїв генотипу ABCB1 3435TT спостерігалася вища відповідь на лікування та тяжка нейтропенія. Крім того, ABCB1 rs2032582 був пов'язаний з кращою виживаністю у пацієнток з раком яєчників, які отримували карбоплатин і паклітаксел. Гігантол значно зменшував кількість уражених ракових клітин, пригнічуючи експресію РНК генів-мішеней Wnt та генів-маркерів епітеліально-мезенхімального переходу. Крім того, він знижував рівень CD133 та ALDH1A1 – ключових маркерів стовбурових клітин раку – шляхом пригнічення сигналізації AKT у клітинних лініях раку легенів.*

Висновки. *Хоча певні генні поліморфізми асоціюються з безпекою вінкристину, жоден конкретний поліморфізм не був остаточно ідентифікований як предиктор його токсичності. Вплив однонуклеотидних поліморфізмів у генах CYP та ABCB1 на безпеку та ефективність паклітакселу залишається невизначеним. Цей огляд може сприяти оцінюванню як безпеки та ефективності фітопрепаратів, так і їх потенціалу щодо взаємодії між лікарськими засобами, особливо в контексті комбінованої фітотерапії та традиційної терапії.*

Ключові слова: *фармакогеноміка, фармакогенетика, рак, вінкристин, паклітаксел, гігантом.*

Actuality. According to the World Health Organization (WHO), cancer (also known as neoplasm or malignant tumour) is the second leading cause of death worldwide, placing substantial physical, emotional, and financial burdens on individuals, families, communities, and public health systems (World Health Organization, 2022). In 2024, the total number of new invasive cancer cases in the United States, categorised by sex and cancer type, is estimated at approximately 2,001,140, with a higher prevalence among men and middle-aged adults (50–64 years) (Siegel, 2024, pp. 12–49). However, according to a report by the World Cancer Research Fund, cancer cases in women increased by 3.7% from 2019 to 2021, while cases in men remained stable (The WCRF team, 2024). In 2022, lung cancer was the most commonly diagnosed cancer worldwide, followed by prostate cancer in men. In women, breast cancer was the most commonly diagnosed, followed by lung and cervical cancers (Filho, 2024, pp. 1336–1346). There are various approaches to treating different types of cancer, including surgery, radiotherapy, stem cell transplantation, and systemic therapies such as chemotherapy, immunotherapy, targeted therapy, and hormone therapy. Information on these treatments is available in the National Cancer Database (NCDB) registry (American College of Surgeons; American Cancer Society). However, clinical trial results have revealed that these treatments can cause side effects, which may impact patients' quality of life and slow down the treatment process. For instance, Altun and Sonkaya (2018, pp. 1218–1219) reported symptoms such as nausea, vomiting, fatigue, decreased appetite, changes in taste, hair loss, dry mouth, and constipation as the most common chemotherapy-induced side effects. Results from the multicentre observational study by Ruhlmann et al. (2015, pp. 333–337) demonstrated a greater severity of chemo-radiotherapy-induced side effects compared to those experienced by patients receiving chemotherapy alone. Moreover, chemoresistance poses a significant obstacle to successful cancer therapy (Garg, 2024, pp. 2478). Hence, modern oncology must explore innovative therapeutic interventions to enhance patients' quality of life. Phytomedicines should be considered as sources of bioactive compounds capable of targeting tumour cells with low toxicity, thereby reducing the adverse effects of chemotherapy in cancer patients. The role of some of the most beneficial phytochemicals, including alkaloids, flavonoids, tannins, and essential oils used in cancer treatment, has been discussed in our previous work (Parchami Ghazaee, 2022, pp. 21–26). Now is the time to integrate strategies that improve the efficacy of medicinal plants while minimising their adverse reactions.

Pharmacogenetics/pharmacogenomics (PGx) is the science that studies the correlation between individual genetic variations and drug responses. Genomic testing identifies gene polymorphisms that contribute to the

encoding of membrane proteins and drug-metabolising enzymes, which play crucial roles in the pharmacokinetics (PK) and pharmacodynamics (PD) of both synthetic drugs and phytochemicals, leading to variability in medication response (Lampe, 2007; Kuo-Chen, 2019). Moreover, genomic testing assists healthcare providers in moving towards the application of personalised or precision medicine to improve treatment outcomes (Oates, 2018; Parchami Ghazaee, 2024). However, the impact of natural products from medicinal plants on the regulation of genes encoding membrane transporters and metabolising enzymes remains poorly understood.

Purpose of the work. Here, we aim to highlight the interactions of certain natural products used in cancer treatment with target sites or related genes that modulate their PK and pharmacological pathways. The findings of this review promise innovative approaches for achieving more effective personalised therapies tailored to patients' genetic variations.

Material and methods. A narrative review was conducted using the PubMed, Google Scholar, and Scopus databases from October 2024 to January 2025. Manual searches were performed independently by reviewers. To gather pertinent information, search terms such as "Pharmacogenetics", "Pharmacogenomics", "Phytotherapy", "Natural Products", "Pharmacokinetics", "Cancer Treatment", "Gene Expression", "Medicinal Plants" and "Phytochemicals" were used. The inclusion criteria were limited to original, high-quality papers in English that focused on the PGx assessment of phytochemicals and herbal drugs used in cancer management, based on *in vivo*, *in vitro* studies, clinical trials, case reports, observational studies, narrative reviews, and databases. Exclusion criteria were applied to items such as inappropriate topics, study protocols, and letters to the editor. Initially, 1325 papers were identified, with 948 unique ones subsequently screened. Around 377 articles were recorded for eligibility. After excluding 364 studies, 13 articles met the inclusion criteria for this review. Additional searches were carried out to support the findings of the included articles. Cited references from these papers were also considered.

Research results and discussion. The regulatory properties of plant secondary metabolites, including alkaloids, terpenes, flavonoids, lignans, steroids, curcumins, saponins, phenolics, and glucosides, on cellular metabolic and signalling pathways have been demonstrated. These metabolites highlight their protective roles against cancer through various lines of evidence (Sadiq, 2022, pp. 744–784).

Vincristine and related PGx. Vincristine (VCR), also known as leurocristine, is a Vinca alkaloid derived from the medicinal plant *Catharanthus roseus*. This bioactive phytochemical is commonly utilised, primarily in combination therapy, for the treatment of acute juvenile leukaemia, lymphocytic leukaemia, Hodgkin's disease, reticulum cell sarcoma, neuroblastoma, and Wilms tumour (Dhyani, 2022; Zhou, 2024; Škubník, 2021).

Peripheral neuropathy is one of the most prevalent adverse effects of VCR, and its risk is strongly associated with genetic variations. Results from a genome-wide analysis of VCR-induced peripheral neuropathy (VIPN) in a large cohort of paediatric cancer patients, conducted by Mufti et al. in Canada, identified specific protective genes, including *FBN2*, *ZFAND3*, *SPDYA*, *METLL8*, *PDE4D*, *NFIB*, and others. In contrast, the *MCM3AP* (rs1815857) variant was found to increase the risk of VIPN. Notably, these genes are related to the development, structure, and regulation of the physiological functions of neurons. Hence, the authors concluded that VIPN could be associated with the involvement of genes related to pathophysiological mechanisms (Mufti, 2024, pp. 56).

The role of cytochrome P450 (CYP) enzymes in the metabolism of VCR has been examined *in vitro* (Dennison, 2008; Dennison, 2007). However, the involvement of CYP polymorphisms in the PKs of this phytomedicine and their impact on VIPN remain controversial. Interestingly, Li and colleagues (Li, 2024, pp. 80–85) have recently suggested that the PK of VCR was not mainly affected by hepatic CYP3A, particularly *CYP3A5*1* or *CYP3A5*3* genotypes in mice. Kayilioğlu et al. (Kayilioğlu, 2017, pp. 458–462) demonstrated that the neurotoxicity rate in Turkish children with malignancies treated with VCR was dose-independent and reported no significant difference between the *CYP3A5*1/*3* and *CYP3A5*3/*3* genotypes. Similarly, Yuan et al. (Yuan, 2025, pp. 454–464) observed no significant effects on VIPN for the *CYP3A5* (rs776746) and *CYP3A4* (rs2242480) variants. Nevertheless, Shalaby et al. (Shalaby, 2024, pp. 1391–1409) found a correlation between *CYP3A5* genotypes and various VCR toxicities in Paediatric rhabdomyosarcoma patients. Neuropathy was observed in 61.2% of patients with the *CYP3A5*3/*3* genotype, while the lowest incidence (1.3%) was associated with the *CYP3A5 *1/*6* genotype ($p < 0.05$). No significant correlation was found between *CYP3A5* mutation types and overall survival. This can be explained by the fact that individuals with the *CYP3A5*3/*3* genotype were associated with very low or no expression of *CYP3A5*, resulting in reduced clearance of VCR and an increased risk of VIPN. Zhang and Bai (2024, pp. 125–131) have presented a 19-year-old obese patient diagnosed with alveolar rhabdomyosarcoma, carrying the *CYP3A4* rs2740574 TT genotype, who developed VIPN.

They hypothesised that motor neuropathy, such as severe extremity weakness and even obesity, which may be correlated with VIPN (Sajdyk, 2020, pp. e637–e640), could be related to *CYP3A4* polymorphisms in adults.

The ATP-binding cassette subfamily B member 1 (*ABCB1*) gene, also known as the multidrug resistance protein 1 (*MDR1*) gene, encodes P-glycoprotein (P-gp), which functions as a drug efflux transporter (Tulsyan, 2016, pp. 47–58). PGx information about *ABCB1* gene polymorphisms and the safety, as well as the efficacy of VCR, has been provided by the Pharmacogenomics Knowledgebase (PharmGKB) clinical annotations. For instance, for the *ABCB1* gene rs1045642 variant, patients carrying the AA and AG alleles with acute lymphoblastic leukaemia (ALL), treated with VCR, may have a decreased likelihood of event-free survival compared to patients with the GG genotype. Patients with the rs4728709 variant and GG genotype, treated with VCR, may have an increased risk of grade 1-2 neurotoxicity compared to those with the AA genotype. However, Yuan et al. (2025, pp. 454–464) observed no significant effects on VIPN for various *ABCB1* variants, including rs1128503, rs2032582, rs1045642, rs4728709, rs4148737, and rs10276036 in Chinese paediatric ALL patients. The single nucleotide polymorphisms (SNPs) in genes such as *ABCB1, ABCC1, ABCC2, ABCC3, ABCC10, SLC5A7, CEP72, TUBB, ACTG, CAPG, MAP4*, and *MAPT*, along with their variants associated with VIPN in childhood ALL, have been comprehensively reviewed by Yang et al. (2021, pp. 771487).

Paclitaxel and related PGx. Paclitaxel (PTX, Taxol) belongs to the class of diterpene taxanes and is derived from the bark of the medicinal yew tree, *Taxus brevifolia* Nutt. It is widely used as a chemotherapeutic agent against various types of cancer. Numerous *in vitro* experiments have demonstrated its anticancer properties in human ovarian and breast cancer cells, particularly as a part of combination therapy. There are various types of PTX nanoformulations developed for the treatment of different cancers. For instance, PTX albumin-bound nanoparticles (nab-paclitaxel; Abraxane®) have been approved by the US Food and Drug Administration (FDA) for the management of breast and lung cancer (Sharifi-Rad, 2021, pp. 3687700). The effect of genetic polymorphisms on the treatment response to PTX has been extensively evaluated by numerous researchers. The role of SNPs in the *CYP* and *ABCB1* genes in the safety and efficacy of Taxol and nab-paclitaxel was examined by Demurtas et al. (2021, pp. 491–497) in a study of 125 cancer patients. No statistically significant associations were observed between the *CYP3A422* and *CYP2C8**3/*4 genotypes and overall drug-related adverse reactions, nor between the *ABCB1 3435TT* genotype and treatment efficacy. However, carriers of the *ABCB1 3435TT* genotype exhibited a higher treatment response. Interestingly, Maeda and colleagues (2024) found a significant association between the *ABCB1 C3435T (*rs1045642*)* TT genotype and early, extremely severe neutropenia in gastric cancer patients receiving PTX or nab-paclitaxel.

Deng et al. (2023, pp. 521-531) investigated genetic polymorphisms associated with hepatic, gastrointestinal, Haematological, skin, neurological, and ototoxic adverse effects in 101 ovarian cancer patients treated with carboplatin and PTX. They identified a notable association between the *LIG3* gene (encoding DNA ligase III) rs1052536 variant and an increased risk of neuropathy of any grade, as well as the rs7311358 variant in the organic anion-transporting polypeptide 1B3 (*SLCO1B3*) gene and the risk of severe toxicities. Furthermore, a pronounced correlation was reported between *GSTP1* rs1695 genotype (G allele carriers) and reduced efficacy. Additionally, improved overall survival was observed in *ABCB1* rs2032582 carriers.

The Eph receptors, the largest class of receptor tyrosine kinases, and their ligands (ephrins), contribute to neurogenesis, differentiation, and the regulation of cell migration during neuronal development (Cramer, 2016). An increased risk of chemotherapy (PTX)-induced peripheral neuropathy (CIPN) may be associated with genetic variations in genes encoding Eph receptors. Following the genotyping of 58 breast cancer patients who received 12 weekly infusions of PTX (80 mg/m²), Marcath et al. (2020, pp. 880–890) suggested that a synonymous homozygous variation in the rs7349683 locus of the *EPHA5* genotype was associated with a greater increase in CIPN8 scores with increasing cumulative exposure.

Gigantol and potential PGx insights. Gigantol is a bibenzyl phenolic compound derived from the medicinal plant *Dendrobium draconis*. Its antitumour properties have been studied in various cell lines of lung, liver, and breast cancers, demonstrating effects on multiple signaling pathways (Zhao, 2020, pp. 11337–11346).

The Wnt pathway, including both canonical and non-canonical forms, regulates cell proliferation, polarity, and migration. It establishes a network of mutual regulation and is essential for maintaining self-renewal in specific mammalian tissues. Disruption of Wnt/β-catenin signalling is frequently associated with the development of various serious conditions, including both cancerous and non-cancerous diseases. Genetic mutations in the Wnt/β-catenin pathway play a role in the development of various cancer types (Liu, 2022, pp. 3).

Several recent studies have linked alterations in the Wnt pathway in tumours to unfavourable clinical outcomes in non-small cell lung cancer (NSCLC). For instance, Coscio et al. (2014, pp.1284-1291) discovered a correlation between the rs2536182 variant near the *Wnt16* gene and the rs10898563 variant of the *FZD4* gene, which were associated with recurrence-free survival and overall survival in NSCLC patients who underwent surgery with chemotherapy and surgery-only, respectively. In a different context, Zhao et al. (2020, pp. 11337–11346) assessed the antitumorigenic effects of various concentrations (0, 40, 80, and 160 μM) of gigantol on human bladder cancer cell lines of G1 and G2 grades. A reduction in cell viability was observed in a dose- and time-dependent manner. Moreover, gigantol significantly diminished the number of invaded cancer cells, likely through the inhibition of RNA expression of Wnt target genes (*AXIN2* and *Survivin*) and two epithelial-mesenchymal transition (EMT) marker genes (*Slug* and *Vimentin*).

Worth noting, mutations in phosphoinositide 3-kinase (PI3K) family genes have been reported to be associated with various types of cancers. A mutation in the oncogenic protein AKT can disrupt various signalling pathways, contributing to the initiation and/or progression of cancer. Moreover, AKT-induced overactivation of mechanistic target of rapamycin complex 1 (mTORC1) may result in increased cancer cell survival and metastasis. Additionally, a connection between AKT expression and Wnt/β-catenin signalling has been established, highlighting their involvement in tumour development. Glaviano et al. (2023, pp. 138) have discussed various inhibitors targeting the PI3K, AKT, and mTOR signalling pathways, which have been proposed for cancer therapy in combination with other treatments such as surgery, hormonal therapy, and additional antitumour drugs. Furthermore, activation of Janus kinases (JAK1 and JAK2) and the signal transducer and activator of transcription (STAT3) has been reported to be associated with the initiation, viability, and invasion of cancer cells (Brooks, 2020, pp. 1971).

Considering the aforementioned mechanisms, Losuwannarak and colleagues (2019, pp. 2032) performed a proteomic analysis, focusing on the Gene Ontology (GO) biological processes of proteins, using human NSCLC H460 cell lines to identify the signalling regulatory pathways associated with the antitumorigenic effects of gigantol. Non-cytotoxic concentrations of gigantol (0 to 20 μM) significantly suppressed expression of protein kinases related to PI3K/AKT and JAK/STAT signalling pathways, which play crucial role in cancer stem cell (CSC) survival. Furthermore, non-toxic concentrations of gigantol have been reported to downregulate CD133 and ALDH1A1 proteins – widely recognised as stem cell markers in lung cancer – by suppressing AKT signalling in human NSCLC cell lines (Bhummaphan, 2015, pp. 836564). The potential effects of gigantol on the expression or inhibition of genes involved in signalling pathways, require further investigation.

Implications for future investigations. The relationship between genomic testing and drug response remains an area requiring further investigation (Pirmohamed, 2023, pp. 350–362). A comprehensive range of *in vitro* and *in vivo* studies, alongside clinical trials, is essential to facilitate the integration of medicinal plant-derived compounds with conventional chemotherapy based on genetic markers. Enhancing PGx-based guidelines for medicinal plants in cancer treatment will refine personalised therapy and minimise adverse drug reactions.

The implementation of PGx in low- and middle-income countries faces considerable challenges, including educational gaps, restricted access to genetic testing, high costs, and inadequate healthcare infrastructure. Governments have a responsibility to expand access to electronic courses to enhance the knowledge of both healthcare providers and the public, as well as to encourage insurance coverage to offset the costs of genomic testing (Ausi, 2024, pp. 4863–4874).

Conclusions. While certain gene polymorphisms have been associated with the safety of VCR, no specific polymorphism has been definitively identified as a predictor of its toxicities (Zhang & Bai, 2024, pp. 125–131). The impact of SNPs in the CYP and ABCB1 genes on the safety and efficacy of paclitaxel remains uncertain. Gigantol may serve as a potential antitumor agent by modulating signalling pathway genes, warranting further in vitro and in vivo investigations. This review may contribute to evaluating both the safety and efficacy of phytomedicines, as well as their potential for drug-drug interactions, particularly in the context of combined herbal and conventional therapies.

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