UDC 615.322.61.57.014

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To cite this article: Parchami Ghazaee S., Harnyk T., Gorova E., Marchenko-Tolsta K., Novykova L., Fedorytenko R. (2024). Uchast farmakohenetyky u farmakolohichnii dii likarskykh roslyn [Involvement of pharmacogenetics in pharmacological actions of medicinal plants (a narrative review)]. *Fitoterapiia. Chasopys – Phytotherapy. Journal*, 1, 52–61, doi: https://doi.org/10.32782/2522-9680-2024-1-52

INVOLVEMENT OF PHARMACOGENETICS IN PHARMACOLOGICAL ACTIONS OF MEDICINAL PLANTS (A NARRATIVE REVIEW)

Actuality. *Pharmacogenetics (PGx) and pharmacogenomics (PGx) involve variations of human genome sequencing amongst individuals, which may influence drug response. The application of PGx and personalized medicine may assist health care providers in administering optimal medication and doses to avoid adverse effects of treatment for specific patients. However, the impact of genetic variability on the pharmacokinetics of natural products and their influence on gene expression regulation is not fully understood.*

The purpose of the work. *This narrative review aims to demonstrate the effects of genetic heterogeneity on the pharmacokinetics of natural products and their role in the modulation of specific genes involved in the treatment of mental disorders and cancer, as well as herb-drug interactions.*

Material and methods. *A narrative review was conducted using PubMed, Google Scholar, and Scopus databases. 22 articles aligned with the inclusion criteria for this review.*

Research results. *Flavonoids, stilbenes, coumarins, quinones, and terpenes have been reported to impede UDP-glucuronosyltransferase (UGT) enzymes. Inhibition of UGT1A1- mediated bilirubin glucuronidation by herbs rich in certain polyphenolic acids, may lead to a high bilirubin-related adverse drug reactions. Silybins, the main component of milk thistle, may cause herb-drug interactions by inhibiting UGT1A1*1 and UGT1A1*6 genotypes. Tulbaghia violacea leaves extractions upregulate p53 and p21 gene expression, leading to a suppression of tumor development in HeLa cells. Resveratrol concomitant with other agents downregulates expression of the multi-drug resistance (MDR1) gene and the apoptosis-suppressing gene (Bcl-2). The MDR modulation*

*function of Traditional Chinese Medicine components (flavonoids, alkaloids, terpenoids, coumarins, quinonoids) and extracts (Bufo gargarizans, Salvia miltiorrhiza, and Schisandra chinensis) is achieved by decreasing the P-glycoprotein expression. In silico analyses have demonstrated the potential of some active ingredients of herbal antidepressants for inhibition of CYP2D6 WT and CYP2D6*53. In vivo administration of Carthamus tinctorius extract revealed a significantly different gene expression pattern associated with major depressive disorder, anxiety, and neurobehavior.*

Conclusion. *The application of PGx may support personalized administration of natural products, as well as provide opportunities to choose the most beneficial concomitant herb-conventional therapy to prevent drug toxicity or synergism.*

Key words: *pharmacogenetics, pharmacogenomics, medicinal plants, pharmacokinetics, herb-drug interactions, psychopharmacology, cancer.*

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Бібліографічний опис статті: Парчамі Газае С., Гарник Т., Горова Е., Марченко-Толста К., Новикова Л., Федоритенко Р. (2024). Участь фармакогенетики у фармакологічній дії лікарських рослин. *Фітотерапія. Часопис,* 1, 52–61, doi: https://doi.org/10.32782/2522-9680-2024-1-52

УЧАСТЬ ФАРМАКОГЕНЕТИКИ У ФАРМАКОЛОГІЧНІЙ ДІЇ ЛІКАРСЬКИХ РОСЛИН (НАРАТИВНИЙ ОГЛЯД)

Актуальність. *Фармакогенетика (PGx) і фармакогеноміка (PGx) включають варіації секвенування геному людини серед індивідів, що може вплинути на реакцію на ліки. Застосування PGx та персоналізованої медицини може допомогти медичним працівникам у призначенні оптимальних лікарських засобів і доз, щоб уникнути несприятливих наслідків лікування для конкретних пацієнтів. Однак вплив генетичної мінливості на фармакогенетику природніх засобів та їх вплив на регуляцію експресії генів не до кінця вивчений.*

Мета роботи. *Цей наративний огляд має на меті продемонструвати вплив генетичної гетерогенності на фармакокінетику природніх засобів та їхню роль у модуляції специфічних генів, які беруть участь у лікуванні психічних розладів і раку, а також взаємодії рослинних лікарських засобів.*

Матеріали та методи. *Наративний огляд було проведено з використанням баз даних PubMed, Google Scholar і Scopus. 22 статті відповідають критеріям включення до цього огляду.*

Результати дослідження. *Повідомлялося, що флавоноїди, стильбени, кумарини, хінони та терпени перешкоджають ферментам UDP-глюкуронозилтрансферази (UGT). Інгібування опосередкованої UGT1A1 і глюкуронізації білірубіну травами, багатими певними поліфенольними кислотами, може призвести до побічних реакцій, пов'язаних із високим рівнем білірубіну. Силібіни, основні компоненти розторопші, можуть спричиняти взаємодію рослини та ліків шляхом інгібування генотипів UGT1A1*1 та UGT1A1*6. Ектракції листя Tulbaghia violacea посилюють експресію генів p53 і p21, що призводить до пригнічення розвитку пухлини в клітинах Hela. Ресвератрол разом з іншими агентами знижує експресію гена стійкості до множинних лікарських засобів (MDR1) і гена, що пригничує апоптоз (Bc1-2). Функція модуляції MDR компонентів традиційної і китайської медицини (флаваноїди, алкалоїди, терпеноїди, кумарини, хіноноїди) та екстрактів (Bufo gargarizans, Salvia miltiorrhiza, Schisandra Chinensis) досягається шляхом зниження експресії P-глікопротеїну. Аналіз in silico продемонстрував потенціал деяких активних інгрідієнтів рослинних антидепресантів для інгібування CYP2D6WT і CYP2D6*53. Введення екстракту Carthamus tinctorius in vivo виявило суттєву відмінну модель експресії генів, пов'язану з великим депресивним розладом, тривогою та нейроповедінкою.*

Висновок. *Застосування PGx може підтримувати персоналізоване введення природних засобів, а також надавати можливість обрати найбільш вигідну супутню фітотерапію травами для запобігання токсичності або синергізму ліків.*

Ключові слова: *фармакогенетика, фармакогеноміка, лікарські рослини, фармакокінетика, взаємодія рослинних лікарських засобів, психофармакологія, рак.*

Actuality. OMICS sciences include genomics, proteomics, metabolomics, transcriptomics, lipidomics, cytomics, metallomics, ionomics, interactomics, and phenomics. They have been applied as a single sphere or a combination of technologies, in medical practice to recognize target molecules for diagnosis of diseases, as well as pharmaceutical research to determine the safety and efficacy of drugs. The term genomics referred to the technics (DNA-base sequencing and microarrays) of sequencing genome of one specific organism. (Yan et al., 2015, pp. 3-21; Plaza, García-Galbis, & Martínez-Espinosa, 2017, pp. 009-013; TP et al., 2009, pp. 191-194). Pharmacogenetics (PGx) and pharmacogenomics (PGx) involve variations of human genome sequencing (genetic polymorphism) amongst individuals, which may influence drug transport and metabolism, affecting drug response (Jin et al., 2018, p. 43; Chambliss & Chan, 2016, p. 25). Genomic technology contributes to PGx biomarker discovery, which has been considered by the FDA (Food and Drug Administration). They are known as predictive of efficacy of treatment and drug toxicity, due to encoding drug metabolizing enzymes, transporters and drug targets. (Arbitrio et al., 2021, pp. 113-119; Lauschke, Milani, & Ingelman-Sundberg, 2017, p. 4). For instance, genetic polymorphism of cytochrome P450 (CYP) enzyme may either lead to diminish therapeutic effects of medications, accelerating their metabolism, or frustrate metabolism, hence, enhancing the accumulation of higher-than-normal drug concentrations and the risk of toxicity (Coyle, 2017, p. 6198530). PGx-based pharmacotherapy aims to personalize drug treatment exactly according to the patient's genetic features, which is also known as Precision medicine (Cecchin & Stocco, 2020, p. 679). The application of PGx and personalized medicine can assist health care providers in administering optimal medication and doses to avoid adverse effects of the treatment for specific patients (McColl et al., 2019, pp. 477-481). Integrating the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines into clinical practice will provide more effective health treatment, as well as cost-effectiveness or cost-saving (Morris et al., 2022, pp. 1318-1328). PGx testing is currently applied in various therapeutic areas including cardiovascular, oncology, neurology, psychiatry, rheumatology, endocrinology, gastroenterology, hematology and infectious diseases (US Food and Drug Administration, 2024).

The application of herb-based drugs (phytotherapics) as complementary therapy has strongly attracted interest of populations and researchers in treating diseases. The presence of phytochemicals in plants can lead to therapeutic effects, including immunomodulatory, anti-inflammatory, antioxidant, and antimicrobial, depending on their content and concentration. (Allegra et al., 2023, pp. 75-89; Komariah, 2023, pp. 611-627). Pharmacokinetics (PKs) studies have revealed that phytochemicals in a manner similar to the synthetic agents, experience absorption, distribution, metabolism, and excretion (ADME) processes, which are to a great extent affected by an individual's digestive characteristics, membrane transporters, metabolizing enzymes, gut microbiota, and genetic variations. PGx allows to identify the role of specific polymorphisms (interindividual differences) in phytochemicals ADME and hence, their safety and effectiveness. Moreover, PGx may involve the PKs or pharmacodynamics pathways, affecting herb-drug interactions (HDIs) (Lampe & Chang, 2007, pp. 347-353; Rathaur & SR,

2019, pp. 1085-1102; Liu et al., 2015, p. 321091). However, the impact of genetic variability on the PKs of natural products and the regulation of gene expression by medicinal plants are poorly understood.

The purpose of the work. This narrative review aims to observe implementation of PGx in phytotherapy in order to demonstrate effect of genetic variability on the PKs of the natural products and the role of natural products and/or active ingredients alone or as adjuvant therapy in modulating of specific genes involved in treatment of mental disorders and cancer, as well as herb-drug interactions.

Material and methods. A narrative review was conducted using PubMed, Google Scholar, and Scopus databases from December 2023 to March 2024. Manual searches were performed independently by reviewers. In order to capture relevant data search terms such as 'Pharmacogenetics' or 'Pharmacogenomics' and 'Phytotherapy' and 'Natural Products' and 'Pharmacokinetic' and 'Herb-drug interaction were used. Inclusion criteria were limited to original, high-quality papers in English focusing on the PGx assessment of phytochemicals and herbal drugs (whole extracts, isolated phytoconstituents) in managing mental disorders, cancer, and herb-drug interactions based on *in vivo*, *in vitro*, *in silico*, volunteer investigations, and narrative reviews. Exclusion criteria were identified, considering items, such as inappropriate topics, study protocols, and letters to editors. Initially, 1015 papers were identified, with 845 unique ones subsequently screened. About 434 articles were recorded for eligibility. After excluding 412 studies, 22 articles aligned with the inclusion criteria for this review. Additional searches were carried out to support the finding of reviewed articles. Cited references of papers were also considered.

Research results

1. PGx application in drug-herb interactions

Recently, using herbal medicine independently or simultaneously with conventional drugs in the treatment of various diseases, including hypertension, cancer, and mental disorders, has attracted the interest of the world population (Azizah et al., 2021, pp. 259-270; Langeh et al., 2022, pp. 11009-11024; Kieling et al., 2024, p. e235051). Identifying PKs characteristics of natural compounds may provide evidence related to the interactions of herbs with conventional medicines. However, the use of combination therapy in treating multifactorial diseases is still controversial; some individuals may experience a synergistic effect, while others may experience antagonistic effects (Jia, 2022, p. 1107777).

PGx assists in determining potential HDIs, indicating genetic polymorphism of drug metabolizing enzymes or transporters, including CYP450 enzymes, P glycoprotein (P-gp), and UDP-glucuronosyltransferases (UGTs), which involve in the PKs of herbs and conventional medicines. Metabolic enzymes as well as transporter gene polymorphisms and HDIs have been reviewed by Liu et al. (Liu, 2015, p. 321091). However, recognizing the PKs behavior of complex products or herbal formulations that contain a mixture of active compounds is more critical (Pelkonen et al., 2012, p. 104510). For instance, medicinal plants, which are composed of various biological active compounds including flavonoids, stilbenes, coumarins, quinones, and terpenes have been reported to impede UGTs, enzymes contribute in phase II metabolism of drugs, and non-drug xenobiotics (Liu et al, 2019, p. 104510). Inhibition of UGT1A1- mediated bilirubin glucuronidation by herbs rich in certain polyphenolic acids (like *Salvia miltiorrhiza*) may lead to a high bilirubin-related adverse drug reaction (ADR) (Guo et al., 2017, pp. 2952-2966). Moreover, natural products may cause herb-drug interactions not only through interfering metabolism, but also influencing other PKs pathways such as the intestinal barrier (Berretta et al., 2022, p.5203). Genetic and transcriptomic analyses have revealed the regulatory role of gene variants (MUC19, MUC22, TFF1, PTGER4, MUC21, MUC22, GNA12, and HNF4A) in the integrity of components of the intestinal epithelial barrier, and their potential role in the pathogenesis of inflammatory bowel diseases. Additionally, these data support intestinal epithelial barrier as a therapeutic target for drugs, as well as its contribution to intestinal permeability, drug absorption, and bioavailability. However, further research is required to explore the involvement of these genes in the efficacy of drugs. Indeed, phytochemicals like citrus flavonoids (CFs) affect the intestinal barrier and gut microbiota, modulating epithelial biotransformation (Wang et al., 2020, pp. 225-251; Vancamelbeke et al., 2017, pp. 1718-1729). Traditional Chinese Medicine (TCM), which contains multiple plant-base remedies and herbal formulas capable in maintaining integrity of the intestinal barrier, as well as influencing mucus secretion by intestinal mucosal epithelial cells, affecting the PKs of drugs, potentially leading to herb-drug interactions (Che et al., 2022, p. 863779).

2. PGx of herbal medicine in cancer treatment

Activation of the tumor suppressor gene (p53) signaling pathway regulate cell cycle, DNA repair, senescence, and apoptosis, hence preventing tumor development (Marei et al., 2021, p. 703). PGx of the p53 provides information related to molecular signaling pathways involved in cancer progression and/or protection, its association with drug response, chemosensitivity, and chemoresistance

(Hientz et al., 2017, pp. 8921-8946; Aubrey et al., 2018, pp. 104–113). The anticancer properties of medicinal plants have been evaluated at molecular biology level. Motadi et al. (2020, p. 12924) examined the anticancer effects of different *Tulbaghia violacea* (TV) leaves extractions *in vitro*. They observed a significant upregulation of p53 and p21 gene expression, which leads to suppressed tumor growth in HeLa cells treated with hexane and methanol TV extracts (at 10 g per 100 mL). In this context, another study has been conducted by Budisan et al. (2019, p. 1199) to evaluate the anticancer characteristics of caffeic acid phenethyl ester (CAPE) and Kaempferol in colon cancer *in vitro*. Apoptosis of RKO and HCT-116 colon cancer cell lines was considered after treatment with CAPE (36.87 μM and 3.326 μM, respectively) and Kaempherol (17.42 μM and 9.427 μM, respectively) for 48 h compared to control cells. Analysis of the coding transcriptomic profile illustrated that CAPE and Kaempherol interfere with biological adhesion capability and cell invasion, as well as cell killing and induction of apoptosis. Kaempherol upregulates the expression of CASP2 genes in RKO cancer cell line, which are relevant to the suppression of tumor and cell death. Additionally, Kaempherol inhibited the NTRK3 gene, which modulates multiple intercellular biological processes.

Uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), being one of the isoforms of UGT1As, is responsible for the glucuronidation of SN-38 (7-ethyl-10-hydroxycamptothecin), the active metabolite of the anticancer drug irinotecan (Takano & Sugiyama, 2017, p. 61-68). Genetic information on UGT1A1 polymorphisms (UGT1A1*28, UGT1A1*93, and UGT1A1*6) and its implications in clinical practice assist oncologists in decision-making for an optimal irinotecan regimen in cancer therapy to reduce the risk of drug toxicity (Karas & Innocenti, 2022, pp. 270-277). Li et al. (2022, p. 110248) have investigated the effects of the extract of the plant *Silybum marianum* (milk thistle) on the PKs of irinotecan. They suggested that silybins, the main composition of milk thistle, may render herb-drug interactions by inhibiting the UGT1A1*1 and UGT1A1*6 genotypes.

Resistance of cancer cells to chemotherapeutic agents, which is known as multi-drug resistance (MDR), occurs through a number of transporter proteins encoded by a variety of genes. The distribution of these proteins, such as adenosine triphosphate binding cassette (ABC) pumps, in different organs depends on various factors including, their genetic characteristics. Thus, pharmacology investigators aim to introduce drugs having the potential to inhibit ABC subfamilies, including P-glycoprotein (P-GP/ABCB1), multidrug resistance-associated proteins (MRPs/ABCCs), and breast cancer resistance protein (BCRP/ABCG2), to prevent MDR (Catalano et al., 2022, p. 616).

Resveratrol (RSV) (3, 5, 4′-trihydroxystilbene) is a non-flavonoid polyphenol that contains a stilbene structure. Grapes, apples, blueberries, plums, and peanut are known as sources of RSV. The pharmacological properties of RSV, such as neuroprotective, hepatoprotective, anticancer, anti-inflammatory, antiviral, and antimicrobial, have been investigated through *in vitro* and *in vivo* experiments (Kaushik et al., 2018, pp. 2473-2490). Quan et al. (2008, pp. 622-629) examined the effect of RSV on MDR caused by anticancer agents (paclitaxel, Adriamycin, and vincristine). The results of gene detection revealed that exposure of KBv200 cells to RSV concomitantly with other agents downregulated expression of the MDR1 gene, the apoptosis-suppressing gene (Bcl-2), and induced apoptosis of cells, reducing the MDR of chemotherapeutic drugs. Hosein Poor Feyzi et al. (2015, pp. 113-115) analyzed the expression of the MDR1 gene in the lymphoblasts of five acute lymphoblastic leukemia patients after treatment with RSV (50 μmol/L for 48 hours). The expression of the MDR1 gene in four leukemic lymphoblasts was not altered. However, this index was very high for one patient in comparison with other patients, which may be related to genetic variability and the dose of the substrate. The MDR modulation function of Traditional Chinese Medicine components (flavonoids, alkaloids, terpenoids, coumarins, and quinonoids) and extracts (*Bufo gargarizans*, *Salvia miltiorrhiza*, and *Schisandra chinensis*) is achieved by decreasing the expression of P-glycoprotein (Cao et al., 2020, pp. 972-979).

3. OMICS application in the area of psychopharmacology of herbal medicine

According to World Health Organization (WHO) report, in 2019, 1 in every 8 people in the world experienced a mental disorder. The average prevalence was found to be 11.63%., and this number for anxiety and depressive disorders has increased in 2020 (Kieling et al., 2024, p. e235051; World Health Organization, 2022).

Concomitant administration of plant-based medicines including *Piper methysticum* (Kava), *Passiflora spp.* (passionflower), *Galphimia glauca* (galphimia), *St John's wort (SJW)*, *Crocus sativus* (saffron), *Curcuma longa* (turmeric), *Withania somnifera* (ashwagandha), and *Ginkgo biloba* (ginkgo) with synthetic drugs for affective disorders (anxiety, major depressive disorder (MDD), depression, and schizophrenia) has been proved (Sarris, 2018, pp. 1147-1162).

CYP2D6 is a highly polymorphic enzyme; hence, its inhibition (depending on the enzyme activity in

individuals) may result in a high plasma concentration of drugs with an increased risk of adverse reactions (Alali et al., 2022, p. 6). *In vitro* inhibition of CYP2D6, a CYP family member that plays an important role in metabolizing drugs, has been evidenced by *St. John's wort* (Don & Smieško, 2020, p. 683; Hellum & Nilsen, 2007, pp. 350–358). However, the standard phenotyping technique (assessing 8-hour debrisoquine urinary recovery ratios (DURR) for CYP2D6 activity) has revealed that administration of 300 mg of *St. John's wort* extract three times daily for 14 days in healthy volunteers didn't alter mean baseline DURR significantly, which testified no marked effects on CYP2D6 activity (Gurley et al., 2008, pp. 755-763). Moreover, results of the *in silico* study conducted by Don and Smieško (2020, p. 683) have revealed that some active ingredients of herbal antidepressants ((−)-cytisine, 5-isopropyl-2-methylphenol, s-auraptenol, D-(−)-synephrine, honokiol, magnolol, piperine, protopine, scopoletin, and cannabidiol) demonstrated potential for CYP2D6 WT and/or variant CYP2D6*53 inhibition. Numerous studies have proven that plant extracts applying for anxiety, depression and sleep disorder, capable to regulate gene expression in various parts of the brain. (Sahoo & S, 2019, pp. 1148-1162). *Carthamus tinctorius* (safflower) contains phytoconstituents, including polyphenols, flavonoids, glycosides, sterols, quinochalcones, polysaccharides, organic acids, polyacetylene, safflomin, cartorimine, and alkaloids. The pharmacological properties of the plant, such as antibacterial, anticancer, antidiabetic, hepatoprotective, cardiopretective, antianxiety, and antidepressant, have been reviewed by Fristiohady et al. (2023, parga. 2). According to an *in vivo* examination conducted by Alegiry et al. (2022, p. 5594), oral administration of safflower dried petals hot water extract (SFPWH), which contains the highest amount of the oleamide ingredient (50 mg/kg and 150 mg/kg for 15 consecutive days) in mice, represented antidepressant properties, which have been proven

Table 1

PGx of medicinal plants and/or phytoconstituents involved in herb-drug interactions, cancer treatment and psychopharmacology

Therapeutic area	Genotype/Gene	Medicinal plant/ phytoconstituent	PGx	Type of study	Reference
Herb-drug interactions	UGT1A1	*Salvia miltiorrhiza*/ polyphenolic acids	Inhibition	*In vitro*	Guo et al., 2017
	UGT1A1*1, UGT1A1*6	*Silybum marianum* (Milk thistle) / silybin	Inhibition	*In vivo*	Li et al., 2022
Cancer treatment	p53 and p21	*Tulbaghia violacea*	Upregulation	*In vitro*	Motadi et al., 2020
	NTRK3	Kaempherol	Inhibition	*In vitro*	Budisan et al., 2019
	CASP2	Kaempherol	Upregulation	*In vitro*	Budisan et al., 2019
	MDR1	Resveratrol	Downregulation	*In vitro*	Quan et al., 2008
			no changes in lymphoblasts	Volunteers	Hosein Poor Feyzi et al., 2015
sychopharmacology	CYP2D6	*St. John's wort*	Inhibition	*In vivo*	Don & Smieško, 2020; Hellum & Nilsen, 2007
			no effects	Volunteers	Gurley et al., 2008
	CYP2D6 WT and/or CYP2D6*53	(−)-cytisine, 5-isopropyl-2-methylphenol, s-auraptenol, D-(−)-synephrine, honokiol, magnolol, piperine, protopine, scopoletin, and cannabidiol	Inhibition	*In silico*	Don and Smieško, 2020
	CYP1A2, 2B1, 2E1, 2C11	safflower total flavonoids	Inhibition	*In vivo*	Li et al., 2021
	CYP2C19 and 2D4		Induction		Li et al., 2021

Note: Abbreviations are available in the main text

through neurobehavioral examinations. Results of the tail suspension test (TST) and forced swimming test (FST), as well as the Y Maze Test (YMT), demonstrated a significant reduction in immobility time and an improvement in performance (the percentage of spontaneous alternation) in the YMT compared to the control group. Hippocampus transcriptomic analysis (RNA-Seq) revealed a markedly different gene expression pattern (which was related to MDD, anxiety, and neurobehavior) compared to the control group. Moreover, a cocktail assay involving seven CYP isoenzymes in rats (*in vivo*) revealed that safflower total flavonoids represented dual paradoxical effects (inhibitory effect on CYP1A2, 2B1, 2E1, 2C11, and inducible effect on CYP2C19 and 2D4 isoenzymes), which should be considered as potential herb-drug interaction (Li et al., 2021, p. e5171).

PGx of medicinal plants and/or phytoconstituents involved in herb-drug interactions, cancer treatment and psychopharmacology is summarized (table 1).

Study limitations

It is obvious that PGx knowledge has been employed in various fields of medicine. However, we considered the use of PGx of medicinal herb in the area of oncology and psychology, which could be a limitation of our review. Moreover, according to recent studies, personalized treatment investigations are now focused on using combined OMICs technologies. Hence, it is recommended to conduct further reviews that incorporate combined OMICs technologies.

Conclusion and future perspectives

Knowledge of genetic polymorphisms might offer insights into better understanding the pathophysiology of diseases, optimal cancer therapy, and psychopharmacology. Phytochemicals have the potential to modulate gene expression patterns, affect PKs processes, and contribute to herb-drug interactions on the basis of individual polymorphisms. Conducting *in vitro*, *in vivo*, volunteers, and patients OMICS investigations provides lines of evidence to support PGx information in herbal medicine labeling. Application of PGx may support personalized administration of natural products as well as provide opportunities to choose the most beneficial concomitant herb-conventional therapy to prevent drug toxicity or synergism. Moreover, conducting multiple OMICS investigations beyond PGx analyses offers research opportunities for a comprehensive and deeper understanding of molecular events that underlie personalized drug responses.

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Стаття надійшла до редакції 11.10.2023
Стаття прийнята до друку 01.12.2023

Conflict of interests: none.
Contributions of authors:
Parchami Ghazaee S. – suggesting topic of the article, collecting sources of article, writing the article;
Harnyk T.P. – reviewing the article, collecting sources of article;
Gorova E.V. – literary editing, data collection, critical revive;
Marchenko-Tolsta K.S. – conclusions, proofreading of the text and analysis of literary sources;
Novykova L.H. – correction and literary editing;
Fedorytenko R. – collecting sources of article, conclusions.