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Original article

Introducing Estrogen Metabolism as the Main Target of *Wedelia chinensis* in Prostate Cancer Cells

Vahid Mansouri[1], Mahmood Khodadoost[2*], Reza Mahmoud Robati[3], Zahra Razzaghi[4], Mitra Rezaei[5]

[1]Proteomics Research Center, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[2]Traditional Medicine and Materia Medica Research Center and Department of Traditional Medicine, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[3]Skin Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[4]Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[5]Genomic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Abstract

Background and objectives: Investigations indicate that *Wedelia chinensis* extract increases efficacy of prostate cancer treatment. In the present study, the differentially expressed genes (DEGs) of prostate cancer cell line 22RV1 in the presence of *W. chinensis* extract derived from Gene Expression Omnibus (GEO) were evaluated by gene ontology and pathway analysis. **Methods:** Gene expression profiles of GSE100224 were analyzed by GEO2R. The significant DEGs were assessed via action map analysis. The related biological terms were identified for the significant DEGS. The highlighted dysregulated genes and pathways were discussed. **Results:** Seventy significant DEGs including 49 up-regulated genes and 21 down-regulated ones were assessed by inhibition, activation, expression, and binding actions. Cytochrome P450 and PTGS2 were highlighted as the crucial DEGs. Estrogen metabolism was pointed as the main targeted pathway. **Conclusion:** Findings indicated that "estrogen metabolism" and UGT1A1, MAOA, PTSG2, and cytochrome P450 in the 22RV1 cells were the main targeted pathway and genes by *W. chinensis*.

Keywords: estrogen; gene; pathway; prostate cancer; *Wedelia*

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Introduction

About 1 414 259 new cases of prostate cancer have been reported in 2020 worldwide. Total mortality was reported as 375 304 related deaths [1]. New therapeutics, better use of current therapies in early-stage disease, next-generation sequencing, and using advanced functional imaging has been the renovated treatments of prostate cancer over the last decade [2]. Androgen receptor is known as a crucial driver of pathophysiology, metabolism and migration, and for regulating the proliferation of prostate cancer. This receptor is also a confirmed target for prostate cancer treatment [3]. Beside chemical drugs many herbal anti-cancers have been introduced that can be used as therapeutic sources in cancer treatment [4]. *Wedelia chinensis* (Osbeck) Merr is known as a public component of anti-inflammatory herbal medicines in Taiwan

*Corresponding author: mkodadoost@sbmu.ac.ir

and southern China. Investigations have indicated that *Wedelia chinensis* extract consumption increases efficacy of prostate cancer treatment. As it is reported, apigenin, luteolin, and wedelolactone, the compounds from *Wedelia chinensis* suppress androgen receptors [5,6].

Since dysregulation of many genes occurs in cancer patients, gene expression study is a powerful method to detect molecular mechanism of cancers. Gene expression regulation of The highlighted genes that are involved in cancer is a main goal in cancer therapy [7,8]. It is a well-known process in treatment of prostate cancer [9]. Integration of bioinformatics and genomics, is a common trend to analyze gene expression process in cancer diagnosis and treatment [10]. Sun et al. published a document about gene expression analysis of prostate cancer. They used gene ontology and pathway analysis to find the critical pathways due to mutation in prostate cancer. As it is reported by the authors, data were extracted from "The Cancer Genome Atlas" and were analyzed via gene ontology , using, "Gene set enrichment analysis" and Kyoto Encyclopedia of Genes and Genomes (KEGG) database [11]. Fan et al. reported a document about analysis of GSE55 945 from GEO which is related to prostate cancer. Data were analyzed via protein-protein interaction network, KEGG pathway analysis, and gen ontology. They found that cell development, cell division, cell cycle and cell junction were the most affected processes by the studied DEGs. In their report, the key genes related to prostate cancer were identified as RPS21, FOXO1, BIRC5, POLR2H, RPL22L1 and NPM1 [12]. In the present study, gene expression profiles of prostate cancer cell line 22RV1 (GSE100224) from GEO were analyzed via gene ontology and pathway analysis to find molecular mechanism of *Wedelia chinensis* effect on the prostate cancer cells; the effect that leads to increase treatment efficacy.

Material and Methods

Ethical considerations

This project was approved by IR.SBMU.RETECH.REC.1401.427 code, ethical committee of Shahid Beheshti University of Medical Sciences.

Data collection

Data was derived from GSE100224 from GEO (data is publish at 2017 and updated at 2021) (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=gse100224). Gene expression profiles of the human prostate cancer cell line 22RV1 in the presence of 10 µg/mL of *Wedelia chinensis* extract versus control were down-loaded and analyzed by GEO2R. Top 250 DEGs based on expression change were selected as queried DEGs. Considering "fold change" > 2 the significant DEGs were identified. The gene expression profiles were assessed via volcano plot to evaluate fold change based on p-value.

The significant DEGs were included in CluePedia; the application of Cytoscape software to explore the regulatory relationships between the genes. Four actions including binding, expression, activation, and inhibition were investigated. The regulatory network was formed via directed edges.

To assess the related biological terms, the significant DEGs were included in ClueGO. The biological terms were extracted from WikiPathways, GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP, GO_CellularComponent-EBI-UniProt-GOA-ACAP-ARAP, KEGG, REACTOME_Pathways, REACTOME_Reactions, and GO_MolecularFunction-EBI-UniProt-GOA-ACAP-ARAP update 08.05.2020.

Statistical analysis

P-value < 0.01 was considered to determine the significant DEGs. To analyze the biological terms, Term p-value, term-p-value corrected with Bonferroni step down, group p-value, group p-value corrected with Bonferroni step down less than 0.01 were considered .

Results and Discussion

Among the 250 top DEGs 70 significant DEGs based on "fold change" > 2 and p-value < 0.01 were selected for more analysis. Volcano plot was provided for the gene expression profiles. The significant up and down-regulated genes are shown in the volcano plot (Figure 1).

The 70 significant DEGs were included in CluePedia to find binding, expression, activation, and inhibition relations between the recognized significant DEGs. Among 70 significant DEGs, 58 individuals (including 36 isolated, 6 paired, a triple, and a main connected component) were recognized by CluePedia. The recognized

significant DEGs and the related relationships are shown in Figure 2.

The 70 significant DEGs were analyzed by ClueGO to find the related biological terms. As shown in Table 1, sixty-four biological terms appeared as the dysregulated individuals. The biological terms were clustered in four groups including: "apoptosis-related network due to altered Notch3 in ovarian cancer", "oxidative stress", "tryptophan metabolism", and "estrogen metabolism" as groups 1-4, respectively. Distribution of the biological terms in the introduced groups was presented in Figure 3. More evidences were required to detect the critical DEGs. So relationship between DEGs and the introduced biological terms was interpreted.

GEO database is a useful source of data to analyze different diseases. Prostate cancer is a disease that is evaluated by researchers by using GEO database as the source of data in several investigations [13,14]. Box plot presentation of the dysregulated genes of the treated prostate cancer cells indicated that considerable numbers of DEGs were dysregulated significantly. Assessment revealed that the significant DEGs included 49 up-regulated DEGs versus 21 down-regulated ones. Range of log (fold change) for up and down-regulated DEGs was as 1.0 - 5.8 and (-1.0) – (-2.1). CYP1A1 and PMEPA1 were the most up-regulated and down-regulated genes, respectively.

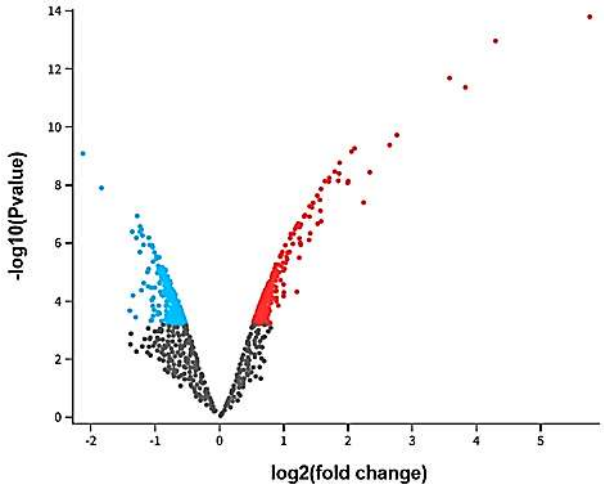

Figure 1. Volcano plot for the gene expression profiles of GSE100244; The up and down regulated spots were determined based on "fold change 1.5.

Since network analysis is a useful tool to screen data, the significant DEGs are assessed via this method [15]. As it is shown in Figure 2, CYP1A1, CYP1A2, and CYP1B1 (the members of cytochrome P450 enzyme) are presented in the main connected component. These enzymes were the top up-regulated ones in the gene expression profiles. Prostaglandin-endoperoxide synthase 2 (PTGS2) is the other important gene that appeared in the action map (Figure 2). Its expression was regulated by ELF3, HMOX1, and TQO1 and it activated CYP1B1. Based on report of Ellinger et al., noncancerous PTGS2 DNA fragments which were presented in the sera of the prostate cancer patients can be considered as diagnostic and prognostic biomarkers [16]. Chen et al. published a paper about role of cytochrome P450 members in prostate cancer development and treatment [17] .

As it is depicted in Table 1 and Figure 3, 64 biological terms were related to the significant DEGs. The terms were categorized in four groups. The main group of the biological term was "estrogen metabolism". Forty-nine biological terms were attributed to the "estrogen metabolism" pathway. Prominent role of estrogen and estrogen metabolites in prostate cancer was confirmed by researchers [18]. As it is depicted in Table 1, this category is related mostly to cytochrome P450 members. Among the 49 biological terms of group 4, 47 individuals (96% of terms) depend to cytochrome P450 members. PTSG2 is the other gene that is highlighted in the Table 1. As it is shown in Table 1, eight biological terms are related to PTSG2.

Monoamine oxidase A (MAOA) is the another gene that is related to the considerable terms of groups 4, 3, and 2.As it is highlighted in the report of Lin et al., MAOA is over-expressed in prostate cancer [19]. Down-regulation of MAOA by *Wedelia chinensis* is consisted with cancer therapeutic properties of *W. chinensis*. Investigation of Xu et al. indicated that inhibition of MAOA impairs prostate cancer development [20].

The other highlighted gene in Table 1 is "UDP glucuronosyltransferase family 1 member A1" (UGT1A1). Role of UGT1A was investigated in several diseases such as , hepatobiliary disease, diabetes, Gilbert's syndrome, cardiovascular disease, leukemia, Crigler–Najjar syndrome, neurological disease, tumorigenesis, metabolic difficulties, Crohn's disease (CD), gallstone, myelosuppression, and obesity [21].

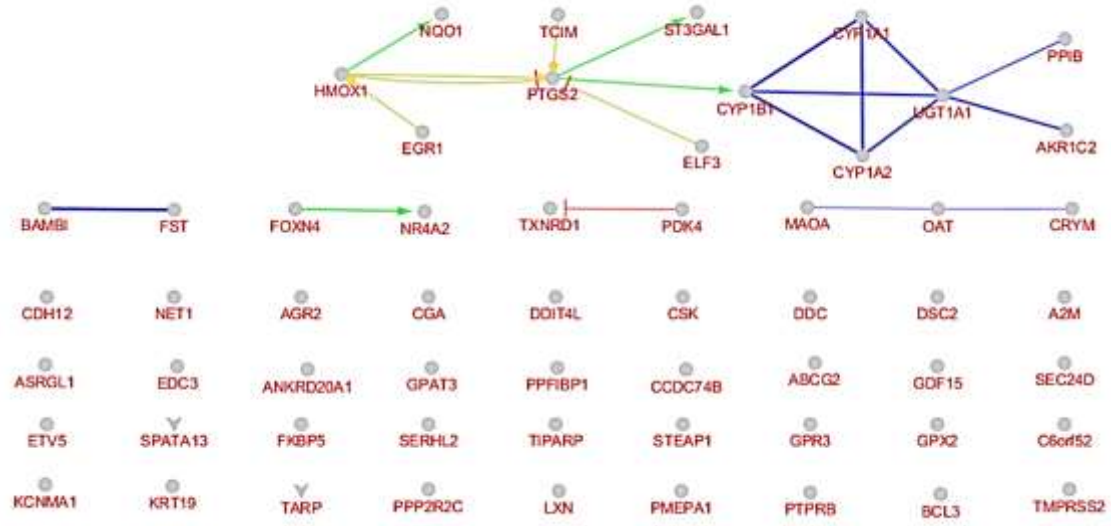

Figure 2. Regulatory relationship between the 58 recognized significant DEGs; blue, green, red, and yellow refer to binding, activation, inhibition, and expression, respectively.

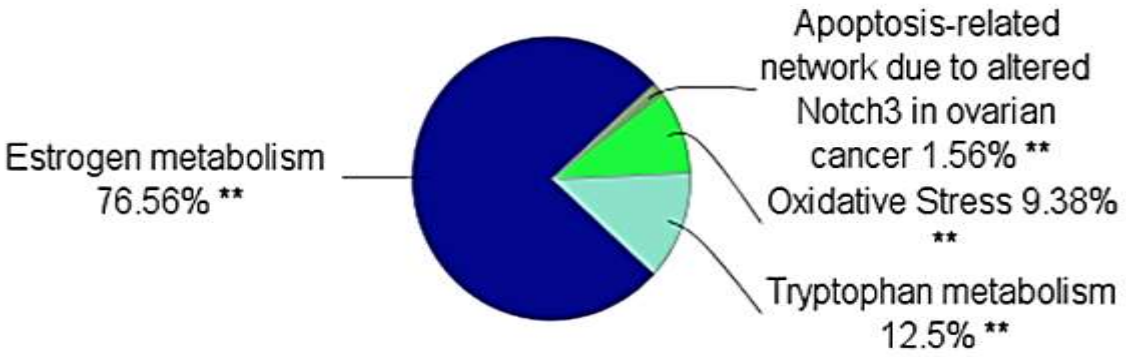

Figure 3. Percentage of gene ontology terms per group

Table 1. The 64 related biological terms of the significant DEGs

R	GO Term	% AG	Associated Genes Found
1	Apoptosis-related network due to altered Notch3 in ovarian cancer	5.56	[BCL3, NET1, NQO1]
2	Dopamine metabolism	21.43	[DDC, MAOA, NQO1]
	NRF2 pathway	4.11	[EGR1, GPX2, HMOX1, NQO1, TXNRD1, UGT1A1]
	Photodynamic therapy-induced NFE2L2 (NRF2) survival signaling	12.50	[ABCG2, HMOX1, NQO1]
	Oxidative Stress	14.71	[CYP1A1, HMOX1, MAOA, NQO1, TXNRD1]
	Excretion	4.05	[ABCG2, HMOX1, KCNMA1]
	Caveola	4.30	[HMOX1, KCNMA1, NR4A2, PTGS2]
3	Tryptophan metabolism	11.90	[CYP1A1, CYP1A2, CYP1B1, DDC, MAOA]
	Dopamine metabolism	21.43	[DDC, MAOA, NQO1]
	Amino Acid metabolism	4.40	[DDC, MAOA, OAT, PDK4]
	Oxidative Stress	14.71	[CYP1A1, HMOX1, MAOA, NQO1, TXNRD1]
	Phenol-containing compound metabolic process	4.03	[CGA, CRYM, DDC, MAOA, NR4A2]
	Catecholamine metabolic process	5.17	[DDC, MAOA, NR4A2]
	Catechol-containing compound metabolic process	5.17	[DDC, MAOA, NR4A2]
	Dopamine metabolic process	7.32	[DDC, MAOA, NR4A2]
4	Steroid hormone biosynthesis	8.20	[AKR1C2, CYP1A1, CYP1A2, CYP1B1, UGT1A1]
	Tryptophan metabolism	11.90	[CYP1A1, CYP1A2, CYP1B1, DDC, MAOA]
	Retinol metabolism	4.48	[CYP1A1, CYP1A2, UGT1A1]
	Metabolism of xenobiotics by cytochrome P450	5.19	[CYP1A1, CYP1A2, CYP1B1, UGT1A1]
	Drug metabolism	4.17	[CYP1A2, MAOA, UGT1A1]
	Ovarian steroidogenesis	7.84	[CGA, CYP1A1, CYP1B1, PTGS2]
	Chemical carcinogenesis	7.23	[AKR1C2, CYP1A1, CYP1A2, CYP1B1, PTGS2, UGT1A1]
	Cytochrome P450 - arranged by substrate type	4.55	[CYP1A1, CYP1A2, CYP1B1]
	Synthesis of epoxy (EET) and dihydroxyeicosatrienoic acids (DHET)	37.50	[CYP1A1, CYP1A2, CYP1B1]
	Arachidonic acid metabolism	8.47	[CYP1A1, CYP1A2, CYP1B1, GPX2, PTGS2]
	Synthesis of (16-20)-hydroxyeicosatetraenoic acids (HETE)	33.33	[CYP1A1, CYP1A2, CYP1B1]
	Arachidonic acid is hydroxylated to 16/17/18-HETE by CYP (1)	100.00	[CYP1A1, CYP1A2, CYP1B1]
	Arachidonic acid is hydroxylated to 19-HETE by CYP (2)	37.50	[CYP1A1, CYP1A2, CYP1B1]
	Arachidonic acid is epoxidated to 5,6-EET by CYP (4)	75.00	[CYP1A1, CYP1A2, CYP1B1]
	Arachidonic acid is epoxidated to 8,9/11,12/14,15-EET by CYP (5)	42.86	[CYP1A1, CYP1A2, CYP1B1]
	Arachidonic acid is hydroxylated to 20-HETE by CYP (3)	50.00	[CYP1A1, CYP1A2, CYP1B1]
	Metabolic disorders of biological oxidation enzymes	8.33	[CYP1B1, MAOA, UGT1A1]
	Biosynthesis of DHA-derived SPMs	17.65	[CYP1A1, CYP1A2, PTGS2]
	Biosynthesis of specialized proresolving mediators (SPMs)	15.79	[CYP1A1, CYP1A2, PTGS2]
	Dopamine metabolism	21.43	[DDC, MAOA, NQO1]
	Aryl Hydrocarbon Receptor Netpath	10.42	[CYP1A1, CYP1A2, CYP1B1, NQO1, PTGS2]
	Aryl Hydrocarbon Receptor Pathway	10.42	[CYP1A1, CYP1A2, CYP1B1, NQO1, UGT1A1]
	Estrogen Receptor Pathway	30.77	[CYP1A1, CYP1A2, CYP1B1, PDK4]
	Melatonin metabolism and effects	9.52	[CYP1A1, CYP1A2, CYP1B1, MAOA]
	Oxidation by Cytochrome P450	4.76	[CYP1A1, CYP1A2, CYP1B1]
	Tryptophan metabolism	9.52	[CYP1A1, CYP1A2, CYP1B1, DDC]
	Tamoxifen metabolism	14.29	[CYP1A1, CYP1A2, CYP1B1]
	Benzo(a)pyrene metabolism	33.33	[AKR1C2, CYP1A1, CYP1B1]
	Estrogen metabolism	26.32	[CYP1A1, CYP1A2, CYP1B1, NQO1, UGT1A1]
	Toxin metabolic process	12.90	[CYP1A1, CYP1A2, CYP1B1, DDC]

Table 1. Continued

R	GO Term	% AG	Associated Genes Found
	Hydro-lyase activity	4.23	[CYP1A1, CYP1A2, CYP1B1]
	Tetrapyrrole metabolic process	5.63	[CYP1A1, CYP1A2, HMOX1, UGT1A1]
	Cellular hormone metabolic process	4.76	[AKR1C2, CYP1A1, CYP1A2, CYP1B1, EGR1, TIPARP, UGT1A1]
	Porphyrin-containing compound metabolic process	8.70	[CYP1A1, CYP1A2, HMOX1, UGT1A1]
	Primary alcohol metabolic process	4.08	[AKR1C2, CYP1A1, CYP1A2, CYP1B1]
	Catecholamine metabolic process	5.17	[DDC, MAOA, NR4A2]
	Estrogen metabolic process	11.63	[CYP1A1, CYP1A2, CYP1B1, TIPARP, UGT1A1]
	Steroid hydroxylase activity	7.50	[CYP1A1, CYP1A2, CYP1B1]
	Catechol-containing compound metabolic process	5.17	[DDC, MAOA, NR4A2]
	Oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, reduced flavin or flavoprotein as one donor, and incorporation of one atom of oxygen	8.11	[CYP1A1, CYP1A2, CYP1B1]
	Hydroperoxy icosatetraenoate dehydratase activity	50.00	[CYP1A1, CYP1A2, CYP1B1]
	Dopamine metabolic process	7.32	[DDC, MAOA, NR4A2]
	Estrogen 16-alpha-hydroxylase activity	33.33	[CYP1A1, CYP1A2, CYP1B1]
	Aromatase activity	10.71	[CYP1A1, CYP1A2, CYP1B1]
	Retinol metabolic process	5.77	[CYP1A1, CYP1A2, CYP1B1]
	Arachidonic acid metabolic process	6.35	[CYP1A1, CYP1A2, CYP1B1, PTGS2]
	Long-chain fatty acid biosynthetic process	8.33	[CYP1A1, CYP1A2, PTGS2]
	Epoxygenase P450 pathway	15.00	[CYP1A1, CYP1A2, CYP1B1]
	Omega-hydroxylase P450 pathway	33.33	[CYP1A1, CYP1A2, CYP1B1]

AG: associated genes; R: group number.

Investigations indicated that UGT1A1 enzyme play role in metabolic pathway of estrogen detoxification in prostate [22]. The findings open new windows to explore medical properties of *Wedelia chinensis*.

Conclusion

In conclusion, "estrogen metabolism" is the main biochemical pathway which is affected by *W. chinensis* in the prostate cancer cell line 22RV1. Cytochrome P450 members as the main targeted gene was highlighted. Prominent roles of UGT1A1, MAOA, PTSG2 in response to presence of *W. chinensis* were identified. It can be suggested that investigation about effect of the various compounds of *Wedelia chinensis* on cancer cells is a useful approach in cancer therapy.

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Author contributions

Vahid Mansouri, Mahmood Khodadoost, Reza Mahmoud Robati, Zahra Razzaghi and Mitra Reaei were involved in project design, data collection and analysis; all authors approved the final draft of the manuscript.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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Abbreviations

DEGs: differentially expressed genes; GEO: gene expression omnibus; KEGG: Kyoto encyclopedia of genes and genomes; AG: associated gene; CD: Crohn’s disease