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IN SILICO TARGETS AND PATHWAYS PREDICTION FOR A NOVEL MULTICOMPONENT POLYPHENOLIC LIGNIN-DERIVED COMPOSITION BP-CX

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Plant polyphenols are known to exert multiple actions such as antioxidant, anticancer, anti-inflammatory, etc. However, polyphenols molecular mechanisms of action are still poorly understood because of their binding with majority of membrane, cytoplasmic and nuclear proteins and therefore targeting multiple signaling pathways. In previous research we have shown that BP-Cx *in vivo* reduces toxicity and enhances radiation and chemotherapy efficacy. Identifying polyphenolic drug targets *in silico* would help to better understand their interactions with anticancer therapies.

Materials and methods. 17 benzene polycarboxylic acids were previously identified as main components of BP-Cx, including 10 well-known compounds (rosmarinic acid, rhamnetin, hesperetin, methylquercetin, etc.) and 7 other compounds. SwissTargetPrediction online tool (http://swisstargetprediction.ch/) was used to predict small molecules targets according to their 2D or 3D similarity with known ligands[1]. Network analysis was performed through mapping a list of targets to STRING database (http://string-db.org/) which integrates known protein-protein interactions[2] (evidence from curated databases and experiments, minimum interaction score 0.400). The pathways, molecular functions and protein domains of interest with highhest confidence scores ($p<1e-06$) were selected from the pathway enrichment results.

Results. 137 protein targets were identified and analyzed via SwissTargetPrediction and mapped to STRING database network. The resulting network had 361 edges (enrichment p-value=8.61e-05). GO (Gene Ontology) analysis has shown that the molecules under investigation may influence the following molecular functions: transmembrane signaling receptor activity(p=1.02e-20), signal transducer activity(p=1.45e-18), catalytic activity(p=8.74e-15), ion binding(p=4.01e-14), protein tyrosine kinase activity(p=2.24e-13) and others. According to KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analysis, 114 pathways were significantly enriched, including pathways related to cancer (PI3K-Akt signaling, p=5.49e-14, Ras signaling, p=3.69e-13, ErbB signaling, p=2.29e-10, proteoglycans in cancer, p=4.36e-10, HIF-1 signaling, p=1.83e-09 etc) and inflammation (cGMP-PKG signaling, p=4.21e-14, nitrogen metabolism, p=1.08e-08, chemokine signaling, p=2.59e-07, etc). PFAM protein domain analysis has revealed BP-Cx components binding with ligand-gated ion channels (p=3.89e-07), STAT protein domains(p=1.15e-06) 7 transmembrane receptor, rhodopsin family, (p= 2.24e-06), protein tyrosine kinase(p= 4.11e-06). Further literature mining confirmed polyphenols effect on identified processes and pathways.

Thus, small molecule binding prediction and network analysis may provide data and narrow the circle of targets for further *in vitro* and *in vivo* investigations.

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2. von Mering C. et al. *Nucleic Acids Res*, 2005, **33:** 433-437.

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