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A System Biology Approach with a Focus on Gene Enrichment and Hub Gene Interaction to Understand Methylparaben Toxicity on Human Physiology

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Abstract: Methylparaben is a specific form of paraben. These chemicals are commonly added to many products as preservatives to inhibit the growth of fungus and other harmful germs. In this study, we examined the detrimental effects of methylparaben on human physiology. Our investigation revealed that it had nephrotoxic effects on people. Additionally, it was found to target cytochrome CYP2C9 and may traverse the blood-brain barrier. The body does not retain Methylparaben. In actuality, the drug leaves the body really rapidly. Despite this, many consumers are still concerned about the safety of methylparaben. These concerns have escalated due to a suggested link to a higher risk of carcinoma. Hub genes are typically important for biological processes and gene regulation. The Cytoscape data indicate that the top ten hub genes, labeled ESR1, SRC, CA2, CA4, MAOA, CA1, DRD1, MAOB, DRD2, and CA12, are connected to a hub gene network. Using the ranked-by-degree method, the ESR1 score is 16; SRC is 12; CA2, CA4, and MAOA are 9 each; CA1, DRD1, and MAOB are 8 each, whereas DRD2 and CA12 are found 7. Future research using experimental animals is required.

Keywords: methylparaben; preservatives; cytochrome CYP2C9; carcinoma; hub genes.

1. Introduction

A common anti-fungal ingredient in many beauty products and feminine hygiene products is methylparaben [1]. It also serves as a food preservative. It is the methyl ester of p-hydroxybenzoic acid. As a synthetic preservative, methylparaben is used in processed foods, toothpaste, shampoos, topical/parenteral medications, cosmetics, and pharmaceutical products [2]. They work by preventing the growth of microbes, thereby prolonging the shelf life of products that contain them. Excessive intake of parabens causes the body to convert them into natural para-hydroxybenzoic acid and excrete them swiftly. Numerous studies have shown that a significant portion of parabens is eliminated in urine within a day [3]. Insufficient use of parabens can have negative health effects and lead to allergic reaction dermatitis, a serious form of skin inflammation that can cause blisters, rashes, and burning skin [4]. The primary receptor for parabens in the human body is P-hydroxybenzoic acid. Lately, it has been noted that these substances accumulate in blood and urine in varying amounts following repeated, prolonged exposure to parabens, due to their water-solubility, which allows them to be absorbed through the skin. It suppresses estrogen sulfotransferase activity in the human epidermis [5]. Numerous studies have shown that women with high urine paraben concentrations have shorter menstrual cycles; therefore, this study suggests that parabens could be a contributing factor to reproductive issues in the surrounding environment [6]. According to additional research, parabens are included in the compounds that alter endocrine systems, including the thyroid and adrenal glands. Conversely, studies have shown that women with high polyethylene paraben concentrations experience short menstrual cycles and low fertility [7]. More recently, studies on male rats have revealed that parabens adversely impact the male reproductive system and generally affect the quality of male semen [8].

In this study, we examined the negative effects of methylparaben on human physiology. Using a systems biology approach, we sought to determine the diverse methylparaben toxicity data and the molecular-level interactions of various genes in response to methylparaben exposure in humans.

2. Materials and Methods

2.1. Downloading the methylparaben structure from the database.

The chemical structure of methylparaben was downloaded in SDF format from the PubChem database and converted into PDBQT format using Open Babel 2.3.1 software for further study.

2.2. Target prediction.

To predict the various methylparaben targets, we used the SWISS target prediction server (http://swisstargetprediction.ch/). After uploading the structure and selecting the target organism, the target organism clicked on target prediction, and the resulting CSV file was downloaded [9].

2.3. Systemic toxicity study of methylparaben by using Pro Tox 3.0.

For the systemic toxicity study, a model computation was performed using the Pro Tox 3.0 open server [10]. It has provided complete oral toxicity prediction data, including the LD50 value and toxicity score. Here, toxicity model prediction results are also provided, including possible toxicity targets.

2.4. Network pharmacology study with STRING.

To understand the network pharmacology, we used all predicted targets in the STRING database (https://string-db.org/) [11]. After selecting the organism, click on search to get all protein target interaction networks. Further, the cluster analysis process divided the data into three clusters for further study.

2.5. Gene enrichment study.

To understand the gene enrichment process with respect to the GO Biological process, GO Cellular components, GO Molecular functions, and KEGG pathway, we used the ShinyGO 0.76 database (http://bioinformatics.sdstate.edu/go76/) [12]. Here, we used STRING results to continue said studies.

2.6. Finding hub genes by using Cytoscape.

Cytoscape 3.7.2 was used to display and analyze the protein-protein network of methylparaben-interacting genes. Using the average shortest path length for both options, the PPI network was analyzed as an undirected network. The network was visualized with node sizes set to lower or higher order with respective color annotations. To analyze the top 10 hub genes (ranked by degree) in human methylparaben toxicity, Cytoscape 3.7.2 was used [13].

3. Results and Discussion

3.1. Download the methylparaben structure from the database.

Thorough condensation of the carboxy group of 4-hydroxybenzoic acid with methanol yields methylparaben, a 4-hydroxybenzoate ester (Fig. 1). One type of conventional industrial allergen is methylparaben. Methylparaben has physiological effects on cell-mediated immunity and heightened histamine discharge [14].

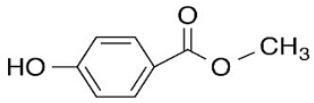

Figure 1. Chemical structure of methylparaben. (Structure taken from open source)

3.2. Target prediction.

The target prediction data from SWISS ADME showed 53.3% for lyase, 13.3% for various nuclear receptors, 6.7% for transferase, and a maximum of 13.3% for cytochrome P_{450} (Figure 2 and Supplementary Table S1).

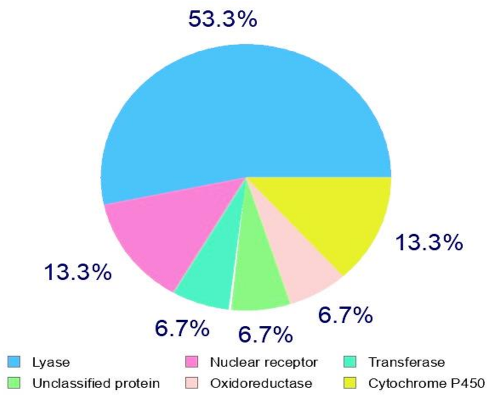

Figure 2. Pie chart of Swiss target prediction of Methylparaben in humans.

3.3. Systemic toxicity study of methylparaben by using Pro Tox 3.0.

ProTox 3.0 is a virtual laboratory designed to forecast the toxicities of small compounds [15]. An essential step in the development of new drugs is predicting compound toxicity. Methylparaben has a molecular weight of 152.15 and 3 H-bond acceptors and 1 H-bond donor.

LogP value is 1.18. ProTox predicted the LD50 value of methylparaben to be 2000 mg/kg as a type 4 toxicity class. According to the toxicity model report, methylparaben shows hepatotoxicity (probability score 0.57) and nephrotoxicity (probability score 0.72), with the blood-brain barrier as the toxicity endpoint (probability score 0.72). It was also found that methylparaben has a target on acetylcholinesterase (probability score 0.57) and Cytochrome CYP2C9 (probability score 0.58). According to the ProTox server, there were three targets where methylparaben can directly interact: the Androgen receptor, Amine oxidase A, and Prostaglandin G/H synthase 1 (Supplementary Table S2a and S2b).

3.4. Network pharmacology study with STRING.

The STRING database [16] includes knowledge from several sources, including public text mining, algorithmic prediction techniques, and experimental data. Protein interaction networks are a crucial component of our understanding of biological activities at the systemic level. These networks offer a user-friendly interface for tagging the structural, functional, and evolutionary characteristics of proteins and for filtering and evaluating functional genomics data [17]. Examining anticipated interaction networks can yield cross-species predictions for effective interaction mapping and open new avenues for future experimental study. STRING interaction analysis revealed that approximately 110 protein genes are involved in network construction (Figure 3; Supplementary Table S3a and S3b). The cluster analysis provided information as there were 19 protein genes (ALOX5AP, BRAF, CA12, CES2, CYP19A1, DYRK1B, ELANE, ESR1, ESR2, FUT7, GRM5, HDAC2, HDAC4, HDAC5, HDAC7, HDAC9, LTB4R, PDE6D, and SRC) in one node (red in color), 17 genes (ALPL, CA1, CA13, CA14, CA2, CA3, CA4, CA5A, CA5B, CA6, CA7, CA9, DDR1, EGLN1, HSD17, B8, MB, MIF, and PLAA) in second largest node (green in color) and 14 genes (ADAM9, CDKL2, CYP1A2, DAO, DCTPP1, DRD1, DRD2, DRD3, FADS1, IDO1, ITGAV, MAOA, MAOB, TYMS and VEGFC) in third node (blue in color).

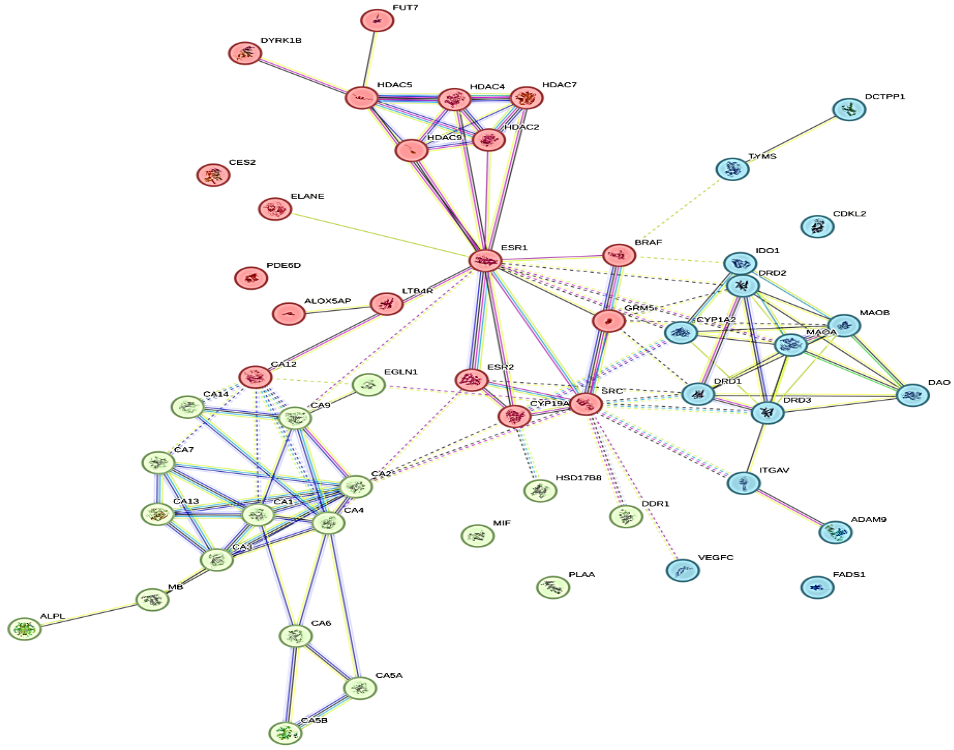

Figure 3. String cluster interaction. Number of nodes: 52, number of edges:109, Average node degree: 4.19, Average local clustering coefficient:0.58, expected number of edges: 28, and PPI enrichment p-value:< 1.0e-16.

3.5. Gene enrichment study.

ShinyGO is a user-friendly, graphical web tool that uses a vast ontology library built from Ensembl and STRING-db for 59 plants, 256 animals, 115 archaea, and 1678 bacterial species to enable investigators to generate useful knowledge from gene inventories. The Kyoto Encyclopedia of Genes and Genomes is a database repository covering illnesses, medications, biological pathways, chemical elements, and genomes [18]. In bioinformatics education and research, KEGG is used for simulations and modeling in systems biology, integrative research in the development of medicines, and data interpretation in genomics, metagenomics, metabolomics, and other omics projects [19]. It was found that a total of 82 enriched genes linked to methylparaben toxicity in humans had a substantial (p-value > 0.05). The top 10 KEGG pathways were found to be related to Nitrogen metabolism, Metabolic pathways, Alcoholism, Endocrine resistance, Gap junction, Neutrophil extracellular trap formation, Viral carcinogenesis, Tryptophan metabolism, Thyroid hormone signaling pathway, and Dopaminergic synapse (Figure 4 and Supplementary Table S4).

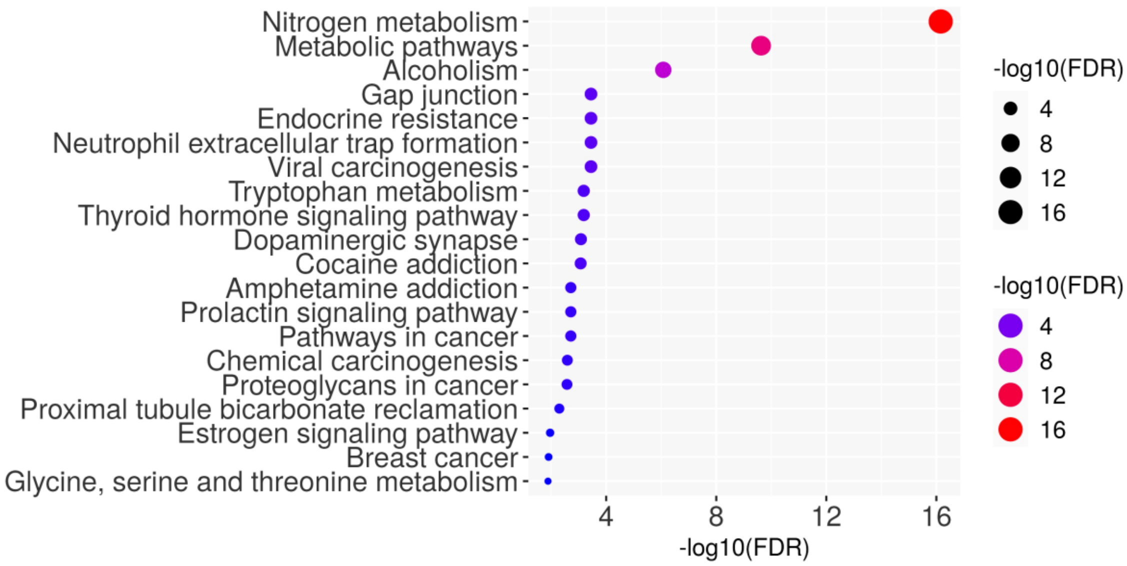

Figure 4. Dot plots of the top 20 enriched KEGG pathways related to Methylparaben toxicity in humans.

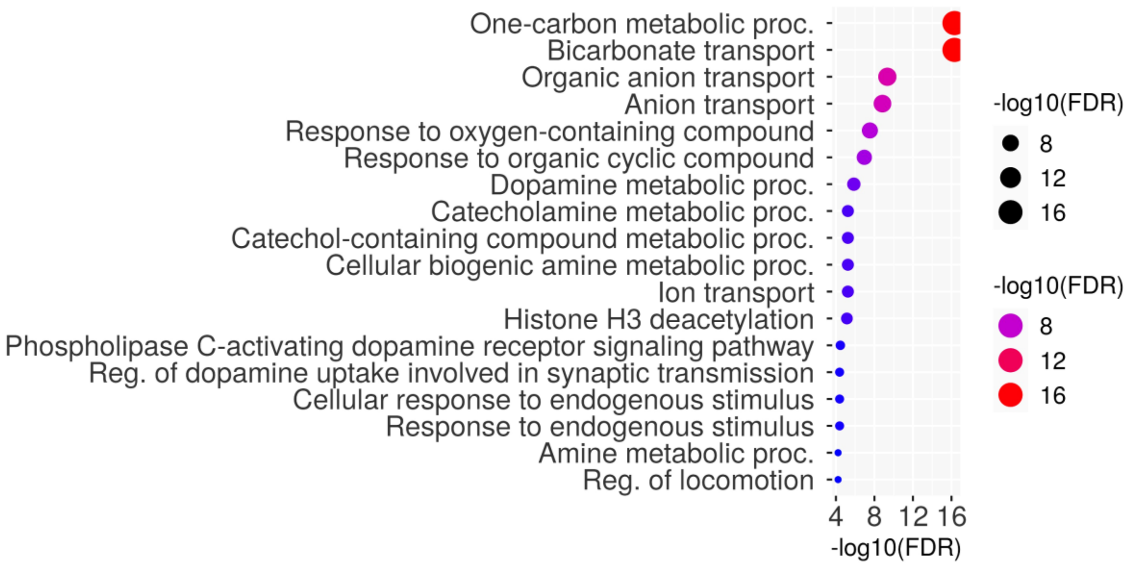

Figure 5. Dot plots of the top 20 enriched biological processes related to methylparaben toxicity in humans.

Biological Pathways, cellular components, and molecular functions, including KEGG, are important for advanced genomics research [20-22]. A total of 1000 biological pathway-enriched results were obtained from ShinyGO. The top 10 enriched biological pathways were as follows: One-carbon metabolic process, bicarbonate transport, organic anion transport, Anion transport, response to oxygen-containing compound, response to organic cyclic compound, dopamine metabolic process, cellular biogenic amine metabolic process, catecholamine metabolic process, and Ion transport (Figure 5 and Supplementary Table S5).

The Cellular Component Ontology describes subcellular formations, including complex macromolecular structures [23]. Gene product sites can, therefore, be annotated using GO-CCO keywords. According to the ShinyGO prediction, there were a total of 64 cellular component-enriched results. The top 5 were histone deacetylase complex, cell projection membrane, plasma membrane region, microvillus, microvillus membrane, postsynaptic density, transcription repressor complex, endocytic vesicle, asymmetric synapse, and integrin alpha-beta3 complex (Figure 6 and Supplementary Table S6).

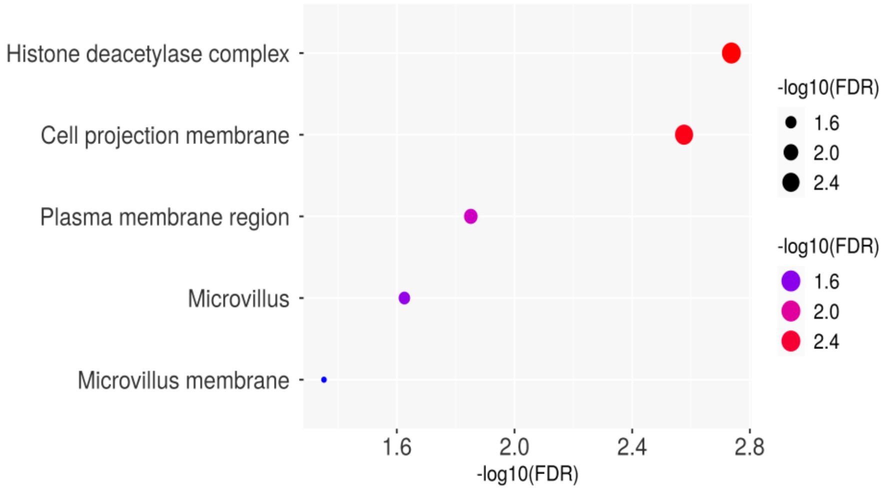

Figure 6. Dot plots of the top 5 enriched cellular components related to methylparaben toxicity in humans.

As per the ShinyGO prediction [24], there were a total of 182 molecular function-enriched results. The top 10 molecular function enriched results were carbonate dehydratase activity, hydro-lyase activity, carbon-oxygen lyase activity, lyase activity, transition metal ion binding, zinc ion binding, histone deacetylase activity (H3-K14 specific), NAD-dependent histone deacetylase activity (H3-K14 specific), NAD-dependent histone deacetylase activity, and NAD-dependent protein deacetylase activity (Figure 7 and Supplementary Table S7).

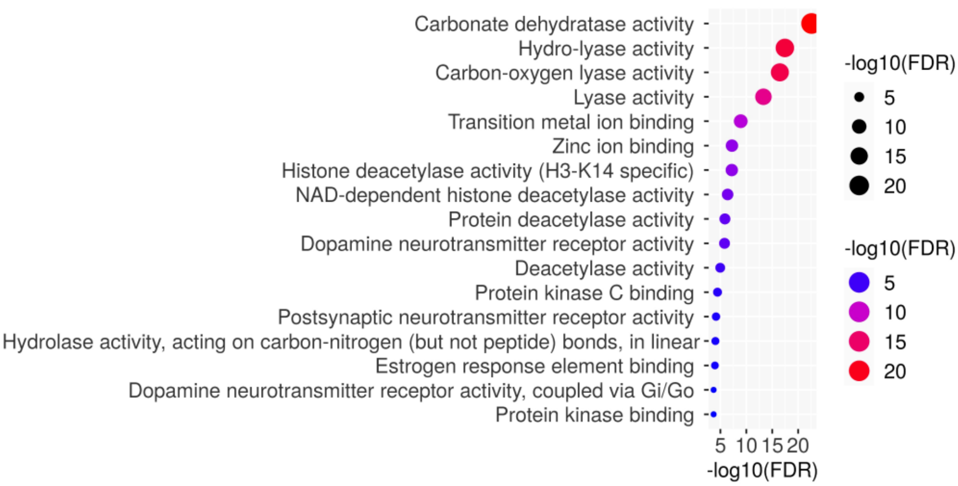

Figure 7. Dot plots of the top 20 enriched molecular functions related to methylparaben toxicity in humans.

3.6. Finding hub genes by using Cytoscape.

Gene regulatory networks provide insight into the mechanisms by which genes cooperate to perform biological tasks [25]. Gene network models from gene expression data offer new avenues for the discovery of biomarkers and drugs while also substantially advancing our comprehension of the underpinning biological mechanisms. A hub gene in a gene network interacts with many other genes [26]. Hub genes are typically important for biological processes and gene regulation [27,28]. From the CytoScape analysis by using CytoHubba, we found that the top 10 genes (as per rank, Supplementary Table S8), such as ESR1, SRC, CA2, CA4, MAOA, CA1, DRD1, MAOB, DRD2, and CA12, were involved in the methylparaben toxicity (Figure 8 and Supplementary Table S8). Among these, the ESR1 score was 16, SRC was 12, CA2, CA4, and MAOA were 9 each, CA1, DRD1, and MAOB were 8 each, whereas DRD2 and CA12 were found 7 each. The genes that were shared by this analysis are thought to be the primary regulators of human methylparaben toxicity.

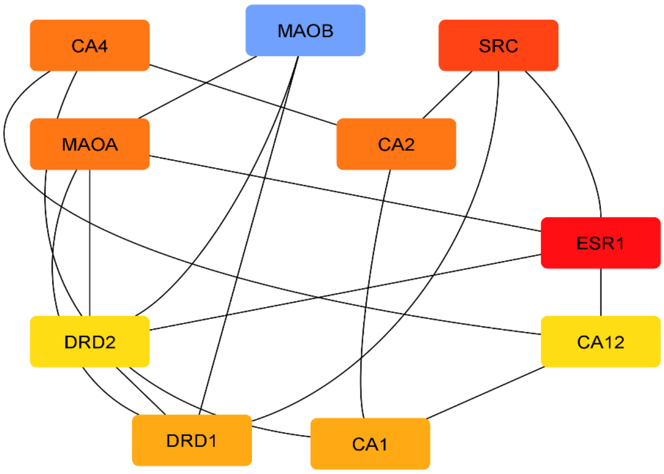

Figure 8. CytoHubba analysis (ranked by the degree method) of 10 major genes involved in methylparaben toxicity in humans.

The FDA is now investigating whether methylparaben could be considered safe when used in cosmetics and whether it can cause breast cancer or other health problems [29, 30]. Research suggests that products containing methylparaben are safe to use, but you can always buy products without them.

4. Conclusions

Chemical preservative methylparaben is now used in various cosmetics. In our research, we found that it has nephrotoxic effects on humans. Also found that it may cross the blood-brain barrier and has a target on cytochrome CYP2C9. The body doesn't retain methylparaben. Actually, the substance is eliminated from the body really quickly. Despite this, methylparaben safety continues to worry a lot of customers. Given a purported connection to an increased risk of carcinoma, these worries have grown. Hub genes are typically important for biological processes and gene regulation. Ten hub genes—designated as ESR1, SRC, CA2, CA4, MAOA, CA1, DRD1, MAOB, DRD2, and CA12—are linked to a hub gene network, according to the Cytoscape data. The FDA is still looking into whether methylparaben can cause breast cancer or other health issues and whether it should be regarded as safe when used in cosmetics. As of right now, research indicates that methylparaben-containing products are safe to use, but you always have the option to purchase items without them. Further study of animal models is needed in the future.

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Conflicts of Interest

The authors affirm that there is no conflict of interest in this study.

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