Conclusion Administration of metformin in combination with caffeine or itraconazole or nitroglycerin might be an effective and safe approach in novel nontoxic adjuvant anticancer treatment.
Keywords: metformin; caffeine; itraconazole; nitroglycerin; hamsters; fibrosarcoma
Conflict of interest: None declared.
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Experimental evaluation of the effects of anticancer modulation therapy on MAPK/PI3K/AKT/mTOR/NF-kB signaling with non-toxic drugs

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Introduction/Objective The large diversity in molecular mechanisms of cancer regulation allows some marketed pleiotropic non-oncological non-toxic pharmaceuticals to be used in oncology, which may reduce the duration and cost of research on novel anticancer treatment. At present, there are no published results *in vivo* on the anticancer effects of certain combinations of non-oncological pleiotropic drugs (disulfiram, diclofenac, nitroglycerin, metformin, deoxycholic acid, mebendazole) that influence MAPK/PI3K/AKT/mTOR/NF-kB signaling.
Methods The anticancer effects of the aforementioned repurposed drug combinations at 20-50% LD_{50} (equivalent to the usual human dose) were assessed by fibrosarcoma growth kinetics (measured daily *in vivo* with calipers) and tumor apoptosis markers (COX4, cytochrome C) in hamsters, randomly allocated to control and experimental groups (6 animals per group). The animals were sacrificed 15-18 days after BHK-21/C13 tumor inoculation. Tumors were excised, measured and blood collected. Biophysical, pathohistological, toxicological, hematological, biochemical and statistical analyses were performed.
Results Disulfiram with metformin, disulfiram with deoxycholic acid and deoxycholic acid with metformin were combinations that showed significant antitumor effects on fibrosarcoma growth kinetics and tumor apoptosis markers in hamsters ($P < 0.05$). All examined drugs in efficacious combinations could inhibit MAPK/PI3K/AKT/mTOR/NF-kB signaling. Addition of the NF-kB stimulator, mebendazole, to effective two-drug combinations rescued cancer growth, indicating that these pathways may be responsible for the antitumor action.
Conclusion The combinations of non-oncological drugs: disulfiram with metformin, disulfiram with deoxycholic acid and deoxycholic acid with metformin have the potential to be used as effective non-toxic adjuvant anticancer therapy in oncology.
Keywords: disulfiram; deoxycholic acid; metformin; hamsters; BHK-21/C13; fibrosarcoma; signal pathway
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