Cytokinins from plant to human

Eman M. Othman , Muhammad Naseem, Thomas Dandekar

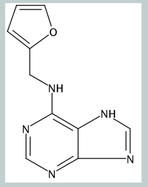
Department of Bioinformatics, Biocenter, University of Würzburg, Am Hubland, Wuerzburg, Germany

eman@toxi.uni-wuerzburg.de

Background

The plant hormones cytokinins; play a major role in cell division and cell differentiation and affect organogenesis in plant cell cultures and contribute in many other physiological and developmental processes in plants . 60 years ago, was the first discovery of kinetin, the first known member of cytokinines. In market, kinetin is formulated as cosmetic anti-againg topical preparations, without defined dose or mechanism of actions, and till now no systemic formulations with specific dose and mechanism were reported.

Why Kinetin ?

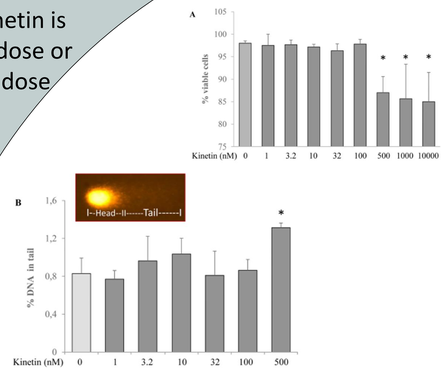


- Cheap and green as well as available
- Safety, naturally produced during oxidative stress in humans as well as ingested in body by eating leafy vegetables as well as plant-based foods and fruits.
- Low effective dose
- Multi-mechanisms, targets and protective functions
- Has link to human gut-microbiomes

insulin insulin +FPG

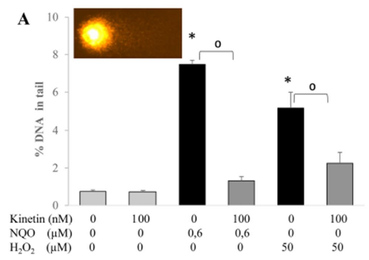
Results

Safety of kinetin in mammalian cells *in vitro*



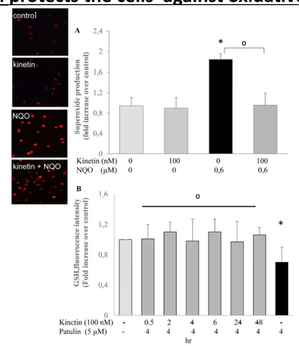
A) Cytotoxicity, B) DNA damage (% DNA in tail) measured by comet assay in HL-60 cells treated with different concentrations of Kinetin for 24 hr.

Kinetin protects the mammalian cells against genotoxicity



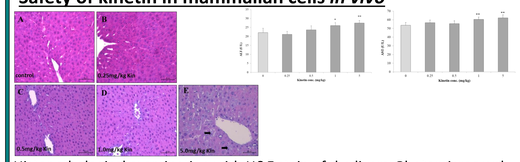
Antigenotoxic activity of Kinetin measured as DNA damage (% DNA in tail) by comet assay in HL-60 cells treated with A) kinetin for 24 hr, NQO, H_2O_2 for 30 min, and combination of kinetin and the reagents

Kinetin protects the cells against oxidative stress

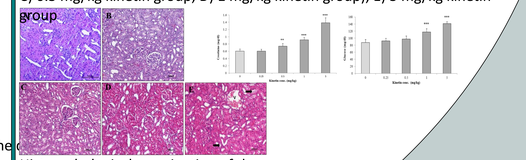


Microscopic detection of superoxide formation using the DHE dye in HL-60 cells treated for 24 hr with kinetin, NQO and the combination of both.
B) Cellular GSH level after 24 hr incubation with kinetin and for 4 hr with patulin. Analysis was done by flow cytometry using the dye monochlorobimane.

Safety of kinetin in mammalian cells *in vivo*



Histopathological examination with H&E stain of the livers. Photomicrograph of liver in adult male albino rats A) Control group, B) 0.25 mg/kg kinetin group C) 0.5 mg/kg kinetin group, D) 1 mg/kg kinetin group), E) 5 mg/kg kinetin group



Histopathological examination of the kidneys. Shown are photomicrograph with H&E stain of kidneys from adult male albino rats. A) Control group, B) 0.25mg/kg kinetin group, C) 0.5 mg/kg kinetin group
D) 1 mg/kg kinetin group,
E) 5 mg/kg kinetin group

Discussion

The biggest challenge today in pre-clinical drug discovery is the identification of a drug candidate that is ,effective with low cost production as well as non-toxic. We reported that in low concentrations (up to 100 nM), kinetin did not induce cytotoxicty, oxidative stress or genotoxicity , whereas high concentrations (from 500 nM) exhibited an opposite effect as it induces significant level of genotoxicity and cytotoxicity in the treated cells. We tested cells with diverse potencies and functional capabilities such as HL60 cells, and human peripheral lymphoytes. To emulate conditions where cell burst occurs and oxidative stress as well as genotoxicity induced, and to examine the protective effect of kinetin, we exposed the kinetin treated cells to H_2O_2 or NQO . A low dose of kinetin protected the cells against H_2O_2 /NQO-induced oxidative stress and genotoxicity, but by increasing the concentration of kinetin the protective effect was lost. To confirm the safety of kinetin for the systemic use in mammals, we assessed its acute toxicity after 14 days by analyzing different biochemical and histological markers in adult male albino rats. Kinetin at a dose up to 1 mg/kg had no adverse effects on the different biochemical mar

Conclusion

The plant hormones cytokinins are one of the promising natural products for their pharmacological and prophylactic activities in mammalian cells, showing available, novel and safe therapeutic candidate for many pathophysiological conditions.

Abstract

Nature is a rich source of biologically active novel compounds. 60 years ago was the first discovery of the plant hormone Kinetin; one of the cytokinins hormones. Different studies reported the effect of kinetin on different human diseases , such as its ability to prevent age-related changes in human skin by protecting the DNA in skin cells from damage (antioxidant effects) and decreasing skin water loss and its therapeutic potential in treatment of the human splicing disease familial dysautonomia in vitro. Our research with kinetin started from studying of its activity in the plants , followed by first screening for the systemic activity of kinetin in mammalian cells at the level of the in vitro study, where we showed for the first time that kinetin exerts anticytotoxic, antioxidant, antigenotoxic and antiapoptotic activities in different cell lines from different origins. The promising in vitro results transferred us to the in vivo stage of the investigations, where we examined the safety of the kinetin for the systemic administration in rats .

Othman EM, Naseem M, Awad E, Dandekar T, Stopper H. The Plant Hormone Cytokinin Confers Protection against Oxidative Stress in Mammalian Cells. PLoS One. 2016;11(12):e0168386.

Naseem, M.; Othman, E. M.; Fathy, M.; Iqbal, J.; Howari, F. M.; AlRemeithi, F. A.; Kodandaraman, G.; Stopper, H.; Bencurova, E.; Vlachakis, D.; Dandekar, T., Integrated structural and functional analysis of the protective effects of kinetin against oxidative stress in mammalian cellular systems. Sci Rep 2020, 10 (1), 13330.

Othman, E. M.; Fathy, M.; Bekhit, A. A.; Abdel-Razik, A. H.; Jamal, A.; Nazzal, Y.; Shams, S.; Dandekar, T.; Naseem, M., Modulatory and Toxicological Perspectives on the Effects of the Small Molecule Kinetin. Molecules 2021, 26 (3).