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Anti-cancer Drug Development by Rapid and Synchronized Dormancy-Breaking Kyoho Grape Seed Endosperm

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INTRODUCTION & AIM

We evaluated the direct cytotoxic effects and toxicity of a dried powder sample derived from Japanese Kyoho grapes. This sample utilized a digestive and absorption treatment process designed for oral administration, without extraction or concentration. The sample rapidly and synchronously broke seed dormancy and promoted phase transitions in its constituents. We assessed the effects on human pancreatic cancer, breast cancer, and liver cancer cells, as well as on fibroblasts as normal cells.

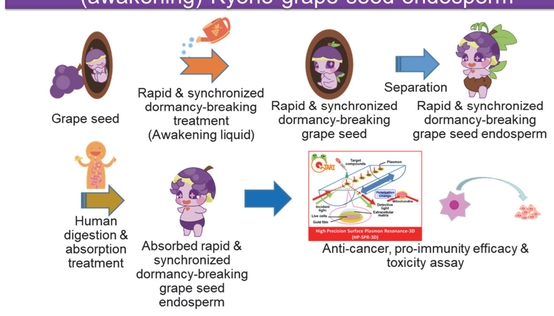
Furthermore, we investigated the immune-activating effects using human natural killer (NK) cells. Evaluation methods employed a novel, proprietary 1h phenotypic screening method—high-precision surface plasmon resonance (HP-SPR-3D)—used as an *in vivo*-like drug sensitivity test, along with cell assays.

METHOD

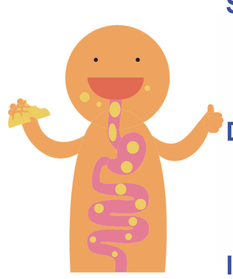
For anti-cancer assay, the following cancer cells were used; cell lines for human of pancreas MIA-PaCa2, breast MCF-7 and liver Hep G2, and that for canine breast SNP. Normal cell line for human was skin fibroblast HFB16D. Kyoho grape seeds produced in Tamushimaru, Kurume-shi, Fukuoka prefecture, Japan was used after rapid and synchronized dormancy-breaking. The endosperm was separated, ground and dried to be utilized. Assuming oral administration, the samples were digested in the stomach step and duodenum step using a human model system including enzymes and bile extract. Then the fraction of molecular weight of 10,000 or less was filtered as an intestinal absorption fraction for assay. Two-dimensionally cultured viable cells were self-adhered onto a high-precision surface plasmon resonance sensor chip, then collagen was overlaid to obtain *in vivo*-like cell status. The cell response change was measured for 1h after the sample addition. The Collagen gel droplet embedded culture drug sensitivity test was also used as a 3D cell culture method. For pro-immunity assay, human cell line KHYG-1 was used as NK cells. As target cells, human acute T lymphoblastic cell line CCRF-CEM was hired. Released lactate dehydrogenase was assayed and T lymphocytes cytotoxic activity by NK cells was measured by colorimetric method.

Sample

Rapid and synchronized dormancy-breaking (awakening) Kyoho grape seed endosperm



Digestion/Absorption



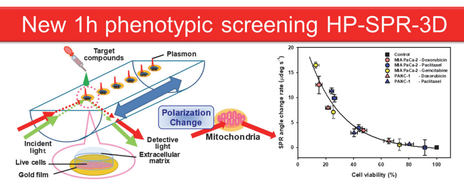
Stomach step
- Pepsin

Duodenum step
- Pancreatin + Bile acid extract

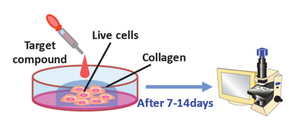
Intestinal step
- MW of 10,000 or less

Cell-based assay

New 1h phenotypic screening HP-SPR-3D

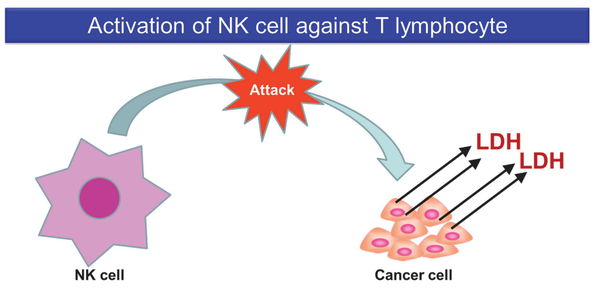


3D cell culture CD-DST



Pro-immunity assay

Activation of NK cell against T lymphocyte



Measurement of T lymphocytes cytotoxic activity by NK cells as released lactate dehydrogenase (LDH) using colorimetric method

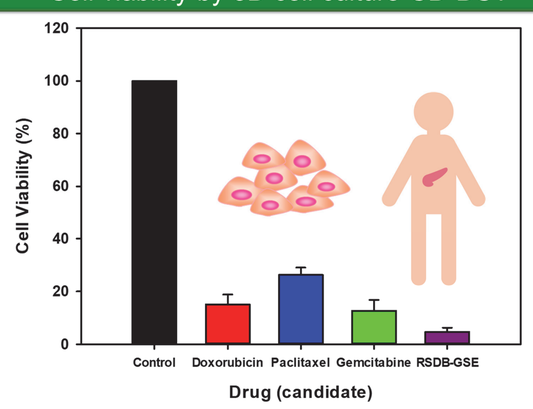
RESULTS & DISCUSSION

For all cancers, concentration-dependent efficacy was observed, with effects noted at 2.5 mg/ml or higher. Maximum apoptotic efficacy was different for cancers as 5.0 mg/ml for pancreas and liver, 7.5mg/ml for human breast, and 3.0mg/ml for canine breast. Higher concentrations exhibited toxicity consistent with mitochondria shutdown, distinct from typical necrosis. In pancreatic cancer, efficacy equivalent to or exceeding that of doxorubicin, paclitaxel, and gemcitabine was achieved despite oral administration. Immune activation was observed from at least 3.75 mg/ml up to 5.0 mg/ml. At these concentrations, normal cells showed almost no effect. These findings indicate that the anti-cancer effects of rapid and synchronized dormancy-breaking Kyoho grape seed endosperm (RSDB-GSE) result from both direct cancer cell killing and indirect immune-mediated effects, both occurring at the same physiologically active concentration.

Based on the above, it is anticipated that synergistic effects, such as those achieved by combining two types of anti-cancer drugs, can be obtained simultaneously without side effects.

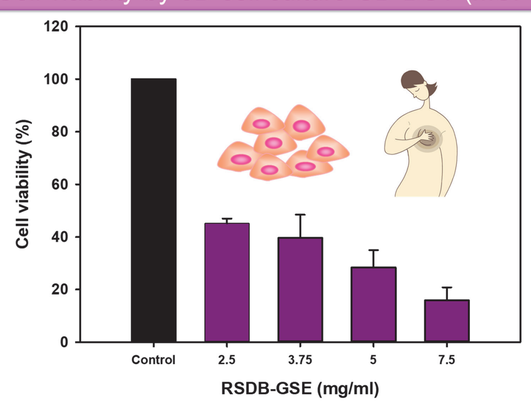
Anti-pancreatic cancer efficacy by direct cell-killing

Cell viability by 3D cell culture CD-DST



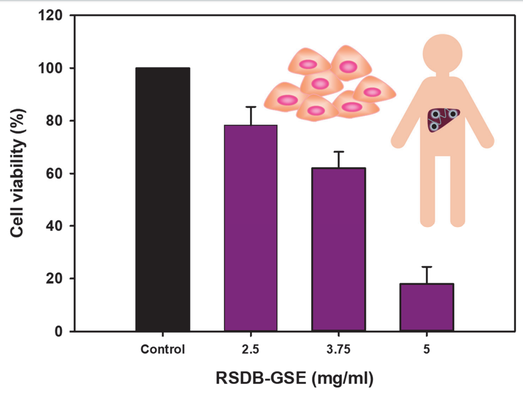
Anti-breast cancer efficacy by direct cell-killing

Cell viability by 3D cell culture CD-DST (MCF-7)



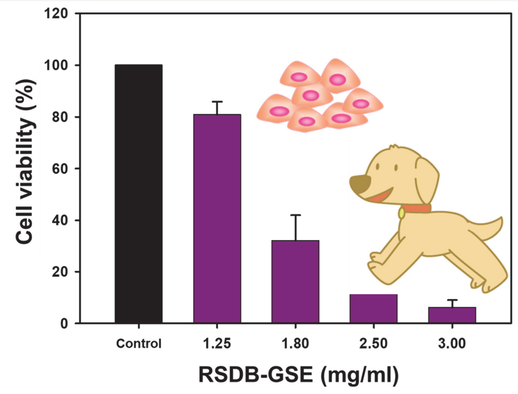
Anti-liver cancer efficacy by direct cell-killing

Cell viability by 3D cell culture CD-DST (Hep G2)



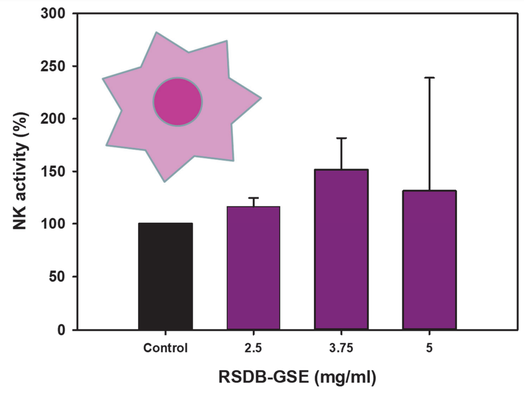
Anti-canine breast cancer efficacy by direct cell-killing

Cell viability by 3D cell culture CD-DST (SNP)



Pro-immunity efficacy

Activation of NK cell against T lymphocyte



CONCLUSIONS

Two types of anti-cancer efficacy

Direct efficacy by cancer cell-killing

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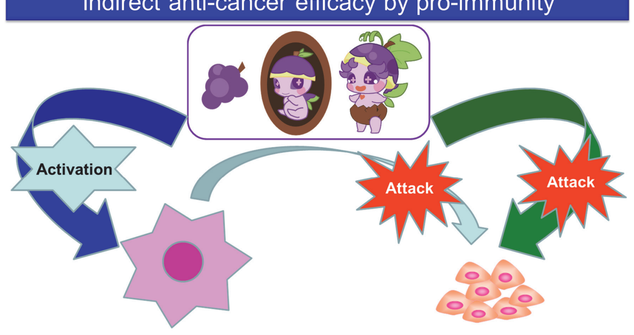
Indirect anti-cancer efficacy by pro-immunity



ACKNOWLEDGMENT

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