The therapeutic effect of milk-derived extracellular vesicles (MDEs) on diabetes

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Background: Type 2 diabetes (T2D) is a high prevalent chronic disease associated with pancreatic β cell dysfunction related to inflammation and metabolic stress. Exosomes are nanovesicles released to the extracellular space that transport microRNAs (miRNA), mRNA, and proteins between and into cells. Exosomes have been found in physiological fluids, such as serum, urine, and breast milk. MiRNAs control gene expression and a wide range of cellular functions. We and others found that milk contains high exosome concentrations, carrying beneficial miRNAs. Interestingly we have found previously that some of the miRNAs involved in T2D; miR-375, miR-26a and miR-146a are highly expressed in milk derived extracellular vesicles (MDEs). MiR-375 is a known pancreatic islet-specific miRNA, expressed at high levels during human pancreatic islet development in human islet β- as well as non-β-cells. Based on MDE characteristics and biological functions, we hypothesize that MDEs may halt TD2 progression via their miRNA content.

Methods. We analyzed the therapeutic and preventive effect of MDE on unique rat model of nutritionally induced diabetes, the CDs rats. The therapeutic effect: Hyperglycemic rats receive a daily MDE treatment by gavage for ten days. The preventive effect: MDE treatment was administered 3 times a week by gavage during the 3 weeks induction of diabetes. MDE. isolated from cow milk by sequential centrifuge cycles, filtration and ultracentrifuge, was administered by gavage

Results. The therapeutic effect of MDE: Improved glucose tolerance was demonstrated by oral glucose tolerance test (OGTT) in MDE treated rats (Fig 1). MDE treatment reduced the disease appearance index of the pancreas and the liver (Fig 2A and B) (from 1 to 0, $p<0.05$) and the liver (from 3.5 to 1, $p<0.05$) of untreated compared to MDEs treated CD rats.
The preventive effect of MDE: MDE treatment reduces pancreas fat surrounding the pancreas, and the appearance of the tissue (Fig 3). We also found that MDE administered as a preventive treatment, significantly ($p<0.01$) improved glucose tolerance at 90 and 120 minutes of glucose administration during the OGTT in MDE treated compared to untreated CDs rats (Fig 4). Furthermore, we found that pancreas damage was reduced in MDEs treated compared to untreated CDs rats (Fig 5) (disease appearance index 1 compared to 2.75, $p<0.05$) (Fig 6).

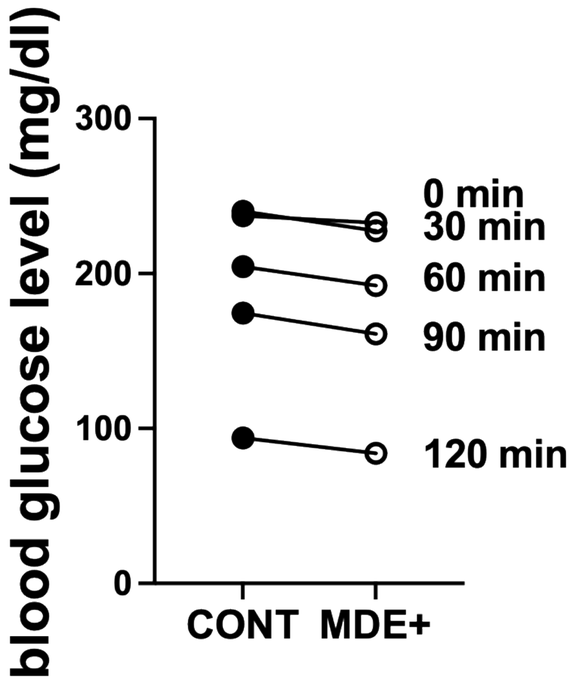

Figure 1. OGTT test in preventive MDE treated diabetic rat (**MDE+**) compared to untreated animals (**CONT**)

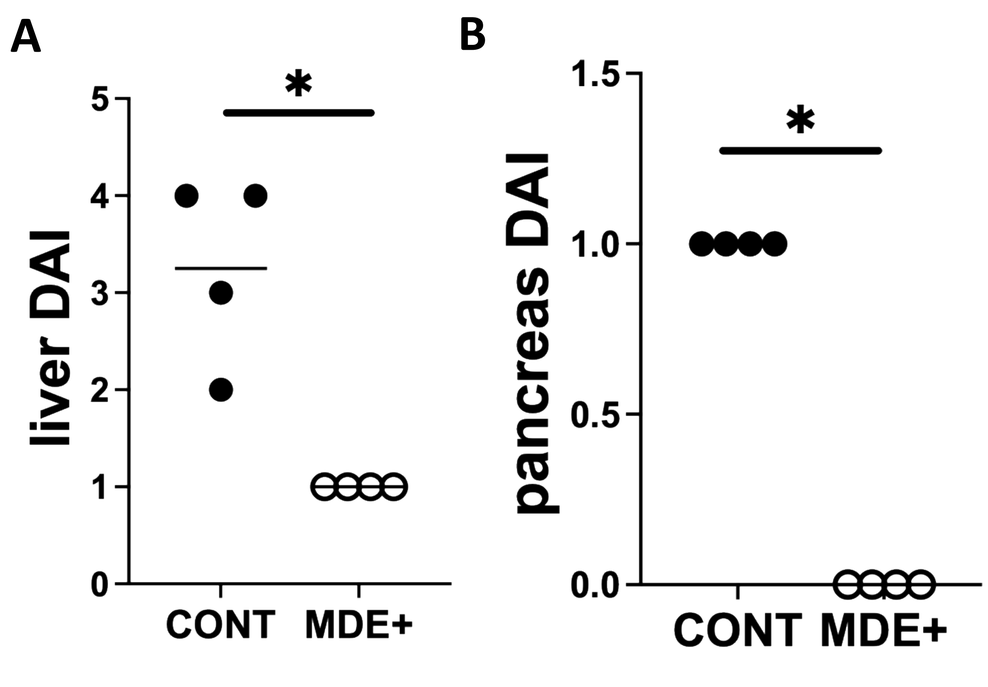

Figure 2. Disease appearance index (DAI) of pancreas (**A**) and liver (**B**) appearance index in preventive MDE treated diabetic rat (**MDE+**) compared to untreated animals (**CONT)**.

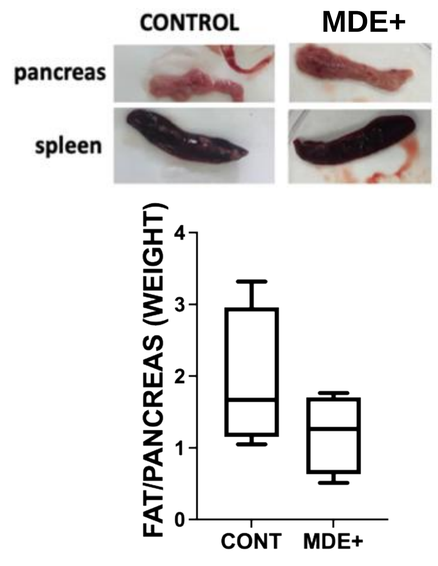

Figure 3. Weight of fat associated to the pancreas in preventive MDE treated diabetic rat (**MDE+**) compared to untreated animals (**CONT**). Fat associated to the pancreas was weighted and compared to the pancreas weight.

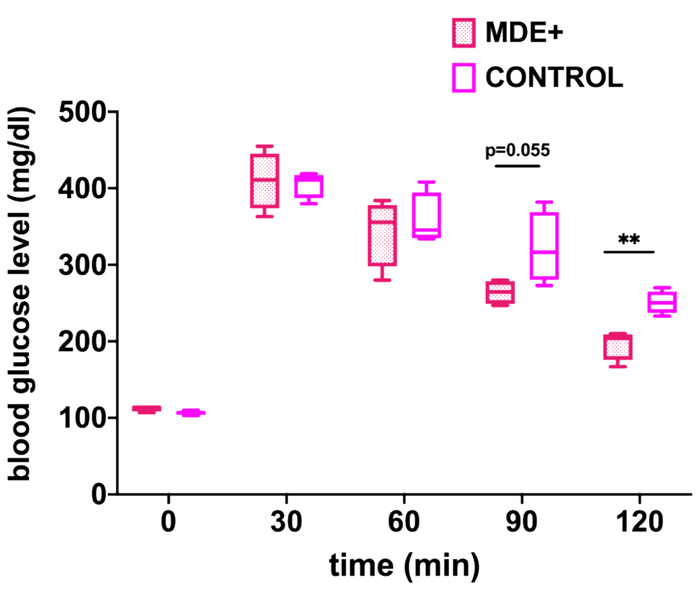

Figure 4. OGTT test in pancreas in MDE preventive treatment in diabetic rats (**MDE+)** compared to untreated rats (**CONTROL**)

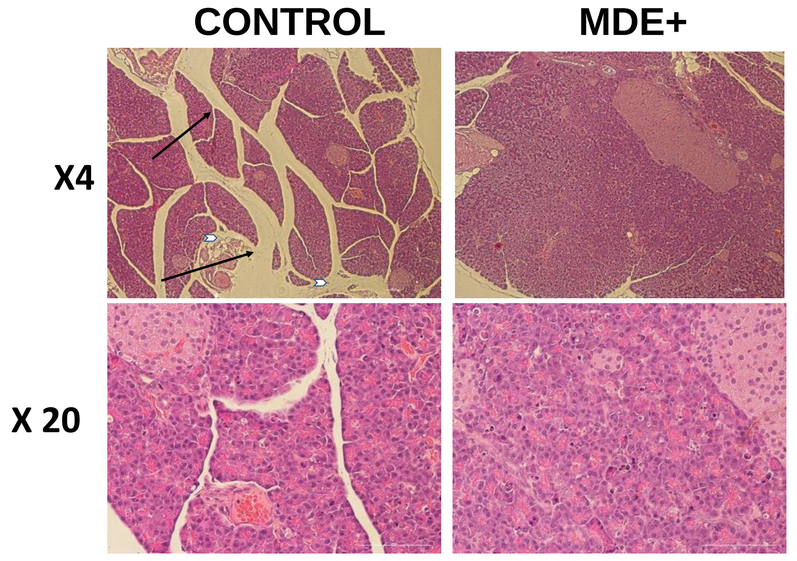

Figure 5. Representative microscopy images of hematoxylin and eosin (H&E)-stained pancreas sections from MDE-treated (**MDE+**) and untreated mice (**CONT**). MDE treated pancreas sections demonstrated dense and well preserve structure of the pancreas parenchyma. Untreated sections exhibited a relatively loose and sparse structure, intra-pancreatic duct proliferation (arrow) fat deposits and atrophic parenchyma.

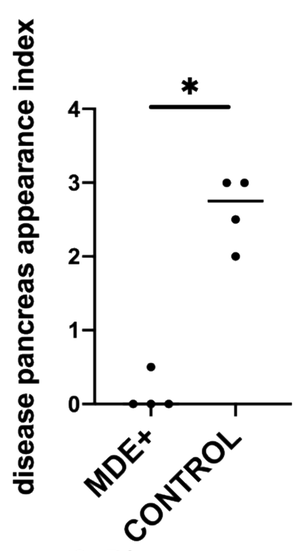

Figure 6. Disease pancreas appearance index in MDE preventive treatment in diabetic rats (**MDE+**) compared to untreated (**CONT**).

Conclusion: Proving the effect of MDE in diabetes will have implications for the possible addition of MDE as a digestible nutrient to T2D patients.

No conflict of interests