The characterization of natural products from E. Officinalis as aldose reductase inhibitors and potential lead therapeutics against diabetic eye disease

Daniel Vincent LaBarbera; Hadi Ali; Linfeng Li; Kun-Che Chang; G Bhanuprakash Reddy; Biehuoy Shieh; Jonathan Mark Petrash

Abstract

**Purpose:** The medicinal plant Emblica officinalis (Gooseberry) has been used for a thousand years as an Indian Ayurvedic preparation to treat diabetes and to promote overall eye health. In the eye, human aldose reductase (AKR1B1) metabolism of glucose to sorbitol is linked to cataract formation. Previously, we isolated and characterized β-glucogallin (BGG) from E. officinalis, as a potent and selective inhibitor (IC50 = 8 μM) of AKR1B1. Herein we have surveyed this plant for additional compounds that may offer therapeutic potential as AKR1B1 inhibitors.

**Methods:** A standardized extract of the Emblica officinalis (Gooseberry) fruit was obtained from India. The fruit powder (160 g) was further extracted three times in 95% ethanol to yield 46 grams of crude gooseberry extract after filtering off the insoluble material. 3.5 grams of this crude extract were dissolved in 90% methanol and loaded onto an LH-20 column, which yielded eight distinct fractions (A-H). These fractions were purified by reverse phase HPLC using bioassay-guided purification with a recombinant AKR1B1 enzyme inhibition assay.

**Results:** Fraction E showed the greatest inhibition of AKR1B, thus, HPLC was used to fractionate and collect 12 distinct peaks, resulting in fractions E1-E12. Peak E7 was the most predominant peak, yielding the most material. The fraction was tested in the AKR1B1 assay and was shown to have an IC50 of 47 μM and reduced enzyme activity by 88%. The structure of E7 was determined using 1H-NMR, 13C-NMR, and...
mass spec analysis. E7 was determined to be a mucic acid derivative with molecular weight 358.25. Based on our analytical data, other purified gooseberry fractions contain compounds that show significant activity against AKR1B1. Purification and structure elucidation of these active fractions is ongoing.

**Conclusions:** These results show the Indian Gooseberry plant is a rich source for compounds that display activity against AKR1B1 and potentially other molecular targets implicated in diabetic eye disease.

**Keywords:** 445 cataract • 498 diabetes • 503 drug toxicity/drug effects