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Garlic decreases liver and kidney receptor for advanced glycation end products expression in experimental diabetes

Khaled K. Al-Qattan*, Mohamed H. Mansour, Martha Thomson, Muslim Ali

Department of Biological Sciences, Faculty of Science, Kuwait University, P.O. Box 5969, Safat 13060, Kuwait

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ABSTRACT

The up-regulation of the receptor for advanced glycation end products (RAGE) has been implicated as a major mediator in the development and progression of diabetic nephropathy and hepatic fibrogenesis. The present study was designed to investigate the potential of garlic (*Allium sativum* L.) to modulate the level of expression of RAGE in renal and hepatic tissues of diabetic rats. Three groups of rats were studied after 8 weeks following diabetes induction: normal, streptozotocin-induced diabetic (control diabetic), and garlic-treated diabetic rats. A polyclonal antibody of proven specificity to RAGE indicated in immunohistochemical assays that RAGE labeling was significantly increased in renal and hepatic tissues of control diabetic rats compared to the normal group. The increased RAGE labeling involved mesangial cells in glomeruli exhibiting signs of mesangial expansion, mesangial nodule formation and glomerulosclerosis. In the liver, a significant up-regulation of RAGE was observed in hepatocytes and bile ducts and vessels in portal tracts. In 2-dimensional Western blots, RAGE expression in both tissues was dominated by heterogeneous charge variants, represented by 46–50 kDa isoforms with more basic pIs compared to their counterparts in normal rats. Compared to control diabetic rats, RAGE labeling in the garlic-treated diabetic group was significantly reduced throughout renal and hepatic regions and was marked by the expression of 43–50 kDa acidic charge variants comparable to those observed in normal rats. The capacity of garlic to modulate diabetes-induced up-regulation of selective RAGE polymorphic variants may be implicated in attenuating the detrimental consequences of excessive RAGE signaling manifested by diabetes-associated disorders.

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1. Introduction

The receptor for advanced glycation end products (RAGE) is a pattern-recognition receptor that binds to diverse ligands including the products of nonenzymatic glycation and oxidation of proteins and lipids that form in response to cellular stress, the advanced glycation end products (AGE) [1]. Although RAGE is normally expressed in a wide range of tissues such as lungs, brain, kidneys, liver, heart, and the vasculature [2], its upregulation and excessive AGE/RAGE ligation leading to downstream pro-inflammatory signaling is the hallmark in various pathophysiological processes, including immune/inflammatory disorders, aging, Alzheimer's disease, diabetic arteriosclerosis and nephropathy, hepatic fibrogenesis, tumorigenesis, and metastasis [3–5]. RAGE consists of 404 amino acids with a molecular mass of 45–55 kDa, which can be variable depending on differential glycosylation states, and structurally belongs to the immunoglobulin superfamily. The fully-expressed membrane-bound protein consists of an N-terminal V-type immunoglobulin-like domain, two tandem C-type immunoglobulin-like domains, a single transmembrane domain, and a short C-terminal intracellular cytoplasmic tail [1]. The V domain is the binding site for AGEs that interact with RAGE at the micromolar level, although other domains also play a role in ligand binding [6]. Besides the full-length RAGE protein, extensive natural occurring RAGE alternative splice variants, including a soluble (sRAGE) and endogenous secretory RAGE (esRAGE) isoforms, were described in mammals at the mRNA and protein levels [7,8]. These naturally occurring isoforms are characterized by either N-terminal or C-terminal truncations [9] and have been implicated as possible regulators of the full-length RAGE, either by competitive ligand binding or by displacing the full-length protein in the membrane [10,11]. Accordingly, expression deregulations of these naturally occurring isoforms are currently considered to have significant effects on RAGE-mediated disorders [12].

* Corresponding author.
E-mail addresses: khaled.alqattan@ku.edu.kw, kkaq6000@gmail.com (K.K. Al-Qattan).

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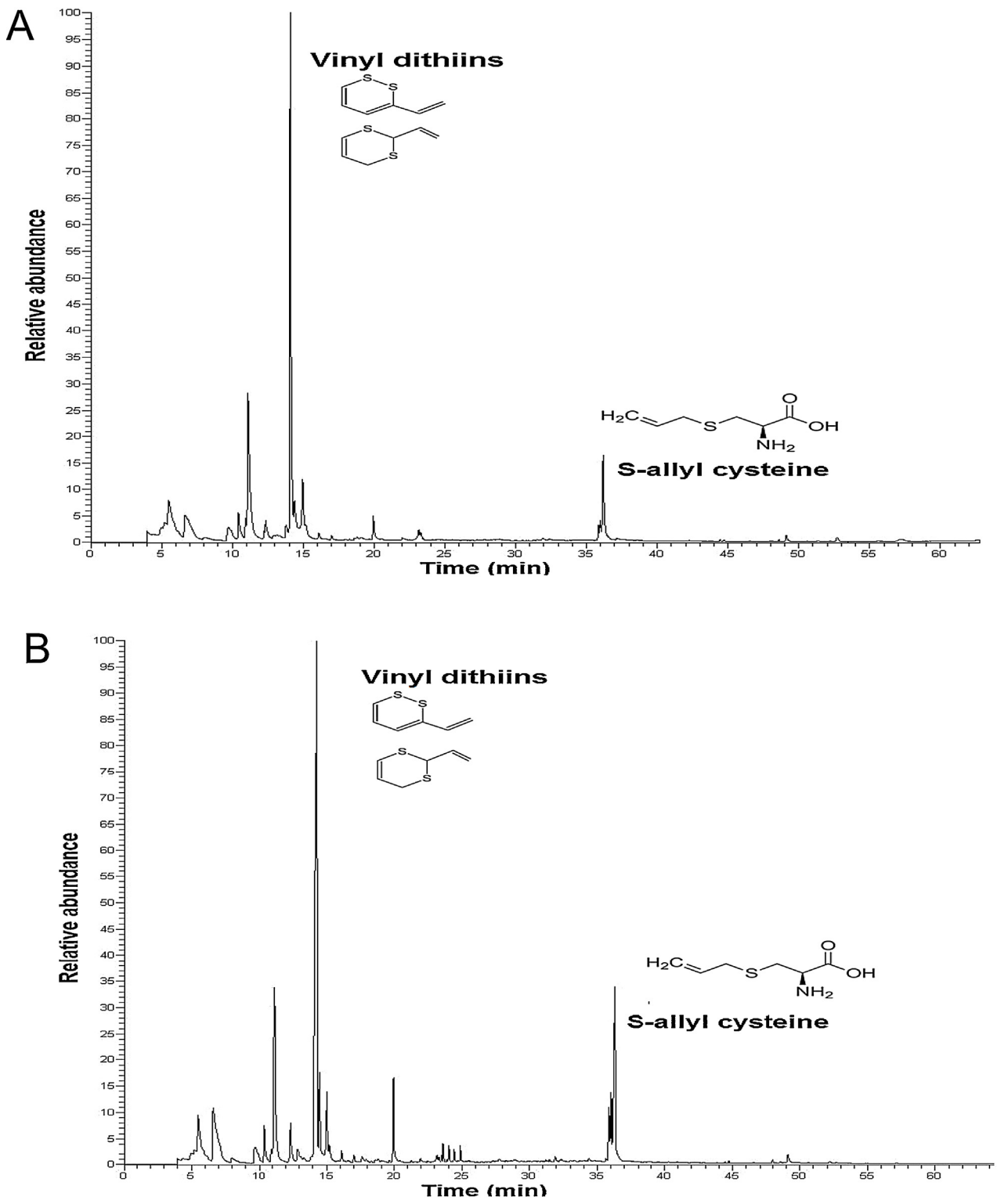

Fig. 1. GC–MS chromatograms of fresh garlic aqueous extract (A) and garlic aqueous extract stored frozen at −20 °C for 8 weeks (B). The IUPAC name of S-allyl cysteine is 2-amino-3-prop-2-enylsulfanyl propanoic acid. The IUPAC names of the 2 vinyldithiins show in the figure are: 1,2 vinyl dithiin: 2-ethenyl-4-H-1,2-dithiin and 1,3 vinyl dithiin: 2-ethenyl-4-H-1,3-dithiin.

In high AGE states, as in diabetes, tissue expression of RAGE is enhanced [13]. In diabetic liver, up-regulated RAGE signaling in hepatocytes, hepatic stellate cells and bile duct epithelia stimulates a spectrum of fibrogenic actions, including cell migration, cell proliferation, the production of intracellular reactive oxygen species, secretion of proinflammatory cytokines and collagen synthesis, which drive hepatic fibrogenesis [14–16]. The accumulation and hyperactivation of the AGE-RAGE axis in the kidneys has been particularly implicated in the progressive alteration in renal architecture, loss of renal function and the development of diabetic nephropathy and vasculopathy. In a receptor–independent mechanism, accumulation of AGEs on the glomerular extracellu-

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