Polydatin Administration Improves Serum biochemical Parameters and Oxidative Stress Markers During Chronic Alcoholism: A Pilot Study

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Abstract. Aim: Polydatin, a hydroxystilbene derived from the rhizome of Polygonum cuspidatum, elicits hepatoprotective and neuroprotective effects through its antioxidant properties. The present study aimed to determine the effects of oral administration of polydatin in alcoholic patients in order to improve liver biochemical parameters, serum oxidative stress and mental state. We enrolled 20 chronic alcoholic patients hospitalized for rehabilitative therapy. The patients were divided into two groups receiving the following treatment regimes for two weeks: administration of an anti-oxidant nutritional supplement containing glutathione and vitamin C (group 1), or glutathione, vitamin C and polydatin (group 2). Results: The results of the present study show that elevated plasma aspartate aminotransferase and alanine aminotransferase levels in patients after two weeks of alcohol withdrawal were significantly reduced by polydatin (group 2), when compared to group 1. Polydatin also significantly reduced lipid peroxidation levels. Finally, our preliminary data resulting from the analysis of the Mini-Mental Status suggest that polydatin improves cognitive performance. Conclusion: Daily dietary administration of polydatin should be considered for prevention and treatment of liver disease and cognitive impairment in alcoholic patients.

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Alcohol abuse is deemed to be one of the most frequent causes of serious health effects in humans, such as coronary heart disease, alcohol liver disease and several other manifestations, including neurological disorders, for which therapeutic approaches are sought (1, 2). It is now well-accepted that the progression of liver injury consequent to chronic alcohol abuse is a multi-factorial event that involves a number of genetic and lifestyle factors. Among these factors there is a growing interest in the role of free radical-mediated oxidative stress. Experimental studies have shown that ethanol promotes the formation of a variety of free radical intermediates (oxygen-derived radicals, 1-hydroxyethyl radicals, NO, lipid-derived radicals) by several cell types, including hepatocytes, Kupffer cells, endothelial cells and infiltrating inflammatory leucocytes (3). Interestingly, after six weeks of ethanol administration to rats, replacement of fish oil with poorly oxidizable palm oil or with medium-chain triacylglycerols lowered lipid peroxidation and ameliorated already established liver damage (4). Moreover, chronic ethanol induces up-regulation of NADPH oxidase that forms reactive oxygen species that, in turn, cause neurodegeneration (5). Among the different treatments administered to improve patients’ health, the nutritional approach, associated with the use of natural substances derived from plants, represents an opportunity for physicians who care for rehabilitation. In accordance to these findings, several other studies have demonstrated that supplementation with different anti-oxidants and free radical scavengers reduce hepatic injury in alcohol-fed rodents (6-10). Polydatin, a resveratrol-glucoside with potent antioxidant properties widely used in traditional Chinese medicine for thousands of years, also had influence on lipid metabolism. In hyperlipidemic rabbits, polydatin markedly lowered the serum levels of total cholesterol, triglyceride and low-density lipoprotein cholesterol (11, 12). Direct radical-
scavenging ability of polydatin vs. lipid peroxidation was investigated in micelles and monolamellar liposomes by Fabris et al. (13). Other studies also showed that it exhibited neuroprotective effects from brain injury induced by ischemia–reperfusion in the middle cerebral artery occlusion model, likely via inhibition of the expression of various cell adhesion molecules (14, 15).

The present study aimed to determine the effects of polydatin supplementation on chronic alcoholic patients during the first two rehabilitative weeks, recording liver biochemical parameters, serum oxidative stress and mental state.

**Patients and Methods**

**Patient characteristics and treatment modalities.** Twenty consecutive alcoholic patients were enrolled in this study. All the patients were informed of the research and gave permission for the use of their serum samples. The patients were hospitalized for two weeks by the Pain Therapy, Anesthesia and Emergency Toxicology Service, Second University of Naples, Italy. Patients were treated with a rehabilitative therapy that consisted of interruption of alcohol intake, and administration of an antioxidant nutritional supplement containing glutathione and vitamin C (group 1), or glutathione, vitamin C and polydatin (group 2). Ten healthy blood donors were the control group. All patients and subjects enrolled in the study were matched for age, gender and socio-demographic characteristics. Glutathione was administered at doses of 600 mg intravenously twice a day, vitamin C orally administered at doses of 40 mg twice a day. Venous blood samples from patients were collected before starting therapy (T0) and after 14 days from the beginning of the treatment (T14). Blood was carried on ice to the laboratory, and serum was separated by centrifugation and stored at –80˚C until analyzed. Laboratory parameters aspartate aminotransferase activity (AST), alanine aminotransferase activity (ALT), total cholesterol, triglycerides, and γ-glutamyltransferase (G-GT) were determined using standard clinical chemical methods. Venous blood samples obtained from these patients were used for the estimation of thiobarbituric reactive substances (TBARS) and nitric oxide. Both assays used in this work were described in De Maria et al. (16).

**Mini-mental status examination (MMSE).** The MMSE (17) was administered in ~10 min and included simple questions, such as the time and place of the test, as well as simple tasks, such as repeating lists of words, performing arithmetic calculations, using and comprehending language, and engaging in basic motor skills.

**Statistical analysis.** All data are expressed as the mean±S.D. The significance of the difference between the control and experimental groups was analyzed by unpaired Student’s t-test, and a value of p<0.05 was considered statistically significant.

**Results**

**Treatment with polydatin significantly ameliorates liver injury in alcoholic patients.** Liver enzyme activity and protein levels of alcoholic patients enrolled in this study are indicated in Table I. The patients on the first day of hospitalization (T0) had about 2-fold and 7-fold elevated levels of both AST and G-GT, respectively, compared to reference values (AST=8-48 U/l and G-GT=9-48 U/l). ALT activity was near the upper reference value (55 U/l). After two weeks of treatment (T14), in group 1, the average AST value was 47.2±11.97 (p=0.0515), whereas in group 2, AST and ALT significantly decreased to 34.9±7.7 (p=0.0131) and 19.7±7.1 (p=0.0342), respectively, compared to values at T0. In groups 1 and 2, G-GT values decreased 3.8- and 3.1-fold, respectively, but were still higher when compared to the reference values.

**Polydatin significantly reduces serum lipid peroxidation in alcoholic patients.** Aldehyde levels, final products of lipid peroxidation, were measured as TBARS and are reported in Figure 1. At hospitalization, in alcoholic patients, the serum TBARS values (0.0059±0.006 μM) were about 4-fold higher compared to values obtained from 10 healthy participants (0.0015±0.0002 μM). After two weeks of alcohol abstinence in group 1 and group 2, the serum levels of lipoperoxide significantly decreased 1.5-fold (p=0.0141) and 3-fold (p=0.0001), respectively, compared to values at T0. On the other hand, serum NO concentrations did not change in either group (data not shown).

**Effect of polydatin supplementation on cognitive function.** The assessment of global cognitive function in alcoholic patients can be readily carried-out by the use of the MMSE (17). This instrument has been validated and extensively used to estimate the severity of cognitive impairments, as well as to follow the course of cognitive changes. The alcoholic patients enrolled in the study were matched for age, gender and socio-demographic characteristics. The MMSE was administered to all 20 alcoholic patients before and after treatment and to group 1 and group 2 after 14 days of therapeutic treatment and the results are reported in Figure 2. Cognitive abilities (by MMSE) did not differ between groups at baseline. Alcoholic patients at T0 had significantly lower overall scores on the MMSE compared to the control group (ten healthy blood donors) other 10 non-alcoholic subjects. Group 2 at T14 demonstrated a significant increase of cognitive functions compared to those of the whole patient cohort at T0. On the other hand, the recovery of the cognitive functions in group 1 was not significant.

**Discussion**

Hepatic metabolism of ethanol results in the generation of large quantities of cytosolic and mitochondrial NADH, leading to disruptions in normal metabolic processes in the liver. Factors contributing to the progression of liver damage and failure are increased production of reactive oxygen species within the mitochondria as a consequence of the
increased levels of mitochondrial NADH. These, in turn, cause mitochondrial stress leading to the triggering of the mitochondrial apoptotic pathway and hepatocyte death (18). Alcoholism remedies include promising novel therapeutic strategies involving phytochemicals and the use of natural extracts from plant foods aiming to reduce the risk of oxidative stress (19). In this light, polydatin is the natural precursor of resveratrol, presents a glucose molecule linked to resveratrol that modifies its pharmacodynamic and pharmacokinetic properties. In fact, polydatin uses specific membrane transporters for glucose to pass the brush-border membrane, mainly through sodium-dependent glucose transporter-1 (20, 21). Some studies reported that polydatin has cerebral-protective effects in the acute focal ischemia reperfusion model, such as the middle cerebral artery occlusion model (14).

The present study suggests the use of a therapeutic strategy for alcoholic injury based on the administration of oral polydatin. Our study evidenced the therapeutic efficacy of polydatin in vivo not only by reducing serum TBARS, markers of lipid peroxidation, but also by ameliorating the characteristic changes observed in alcoholic patients in liver cytolytic enzymes ALT and AST, reliable markers of liver damage (22). Elevated serum levels of AST and ALT have been attributed to damage of the structural integrity of the liver. One notable exception to the predominance of serum AST activity in chronic liver disease is alcoholic liver disease where AST activity is generally higher than that of ALT. AST and ALT are released into the circulation when cell membrane permeability increases after damage to hepatocytes (23). Nevertheless, treatment with polydatin for 14 consecutive days reversed these changes, suggesting that polydatin protected the liver against alcohol-induced hepatotoxicity. In a model of vascular dementia, the therapeutic potential of polydatin on learning and memory impairments was due, at least in part, to its direct antioxidant activity (24). At least other two beneficial mechanisms of the action of polydatin on brain function, over its direct antioxidants effects, have also been suggested to be due to its activity on NR2B nr2b and CDK5 cdk5 (25-27). Our data showed a significantly increase of the MMSE score in group 2, treated with polydatin, and a trend in this direction in group 1, encouraging the use of glutathione–polydatin combination to improve cognitive functions in alcoholic patients.

In conclusion, on the basis of these data and considerations, we suggest that daily intake of 80 mg of polydatin is active against serum lipid peroxidation and cognitive function impairment in patients with alcohol dependence.

Conflicts of Interest

The Authors have no conflicts of interest to disclose with regard to this study.
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