

# Is It Possible to Establish a Tumor-Suppressive Microenvironment With Glycine and Valine Supplement?

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## Abstract

A tumorigenic microenvironment can give rise to neoplasm. A shift from this condition to a tumor-suppressive microenvironment is of significant benefit to susceptible individuals. The carbonyl groups of glycine and valine have long bond lengths, consequently generating potent affinities to divalent cations such as calcium. We hypothesize that the formation of insoluble and rigid calcium oxalate augmented by glycine and valine counteracts strong acids such as HCl chemically, thus reducing cancer risks. The anticancer effects of the 2 amino acids can be explained from a chemical and biochemical perspective. A tumor-suppressive microenvironment could be established via the modification of the proteome without genome editing at the DNA level.

## Keywords

tumorigenic microenvironment, tumor-suppressive microenvironment, glycine, valine, calcium

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## Introduction

Amino acids are fundamental building blocks of proteins which execute vital functions in human body. Different patterns of amino acid content in human proteins appear when comparisons are made on risk factors of diseases. However, their biological and biochemical significances have not been well elucidated yet. A chemical and biochemical perspective can shed light on the inherent mechanism underlying these patterns in the causative factors of human disorders.

### *High Valine and Glycine Content in the Risk Factors for Heart Disease and Alzheimer's Disease Inversely Related to Cancer Risk*

Valine and glycine are overrepresented in numerous causative factors of heart disease, Alzheimer's disease or dementia.<sup>1-3</sup> The bond lengths of the carbonyl group in the 2 amino acids are longer than their counterparts in other amino acids,<sup>4-5</sup> enabling secondary chemical bonding to divalent cations such as calcium. The insoluble and rigid calcium oxalate was

proposed as the trigger of heart disease and Alzheimer's disease, since ethanol and acetic acid, similar in structure to oxalate, are beneficial to patients with these diseases and can extend lifespan.<sup>1,6</sup> Red wine's high level of polyphenol antioxidants is considered to be able to reduce the risk of high blood pressure, high cholesterol, and metabolic disorders.<sup>7</sup> The cardioprotective effects of red wine have been attributed to several polyphenolic antioxidants including resveratrol and proanthocyanidins by adapting the heart to oxidative stress.<sup>8</sup> Resveratrol and proanthocyanidins are effective in reducing

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myocardial ischemic reperfusion injury.<sup>9</sup> However, the amount of resveratrol in red wine is minimal, requiring about 1000 cups of red wine to reach a daily dose of resveratrol for extending longevity.

Oxalate is produced with aging via the pathways of energy metabolism. Calcium oxalate stones are the primary component of renal stones which can lead to kidney failure.<sup>10</sup> Could the presence of insoluble salts be a general mechanism involved in human disorders? Alzheimer's disease and cancer are mutually protective, since insoluble salts and strong acids such as HCl counteract each other chemically,<sup>11</sup> and HCl was postulated as a major inducer of tumorigenesis.<sup>12,13</sup> The coexistence of hydrogen bond donors and acceptors and basic amino acids can gather anions and cations, and build up strong acids such as HCl locally.<sup>12,13</sup> Interestingly, oncoproteins and tumor suppressors usually possess over 10% to over 20% basic amino acids, attract strong anion  $\text{Cl}^-$ , enhance the local formation of HCl, and promote tumor growth when additional amino acid polymorphism is present.

### *Enhancement of tRNA Aminoacylation Via Glycine and Valine Supplement*

Food regimens such as plant-based diet have demonstrated antitumor effects before, including vegetables, fruits and nuts. The composition of plant biomass is different from that of animal flesh. For instance, animal meat harbors higher amount of essential amino acids than plants.<sup>14</sup> This difference could shape the human proteome after food intake. Modest food supplement of valine and glycine to individuals at risk of cancer or with family history of malignancies could increase the protein levels rich in the 2 amino acids, consequently contributing to the formation of insoluble calcium salts and eliciting anticancer effects. It may convert oncogenic microenvironment to tumor-suppressive microenvironment by changing the proteome profile. If excess of glycine increases translation efficiency by 1.05 fold per residue, 10 glycine residues in a protein cumulatively increase translation efficacy by 1.05<sup>10</sup> fold, a rise of protein abundance for approximately 1.63 fold. Amino acid supplement can enhance tRNA aminoacylation by raising substrate concentrations, consequently augmenting protein translation. A protein with more glycine or valine residues will increase more in abundance, and thus glycine-rich or/and valine-rich proteins can be expressed at higher levels and collectively elicit anticancer effects.

### *The Secondary Chemical Bonding of Carbonyl Oxygen in Valine and Glycine to Various Divalent Cations*

The secondary chemical bonding of carbonyl oxygen in valine and glycine residues is not limited to calcium, and it is presumably effective to a number of divalent cations. This property is pertinent to the van der Waals radius of the atom. Yet, calcium is the most abundant divalent cation in the body, a constituent of bones and teeth. Previous reports have demonstrated that glycine and aliphatic amino acid mixtures including valine

elicited anticancer effects respectively,<sup>15,16</sup> corroborating the aforementioned hypothesis. An investigation indicated that the amino-terminal domain with repeats of PHGGGWGQ in prion protein PrP<sup>C</sup> exhibited a number of sites that bind the divalent  $\text{Cu}^{2+}$  via glycine chelating.<sup>17</sup> Zinc and calcium can form complexes with valinate and isovalinate as metal alpha-amino acid-ates.<sup>18</sup> Various types of insoluble and stiff salts can be found in renal stones, many of which may possess antineoplastic properties.

### *Concerns for the Anticancer Regimen in Human Subpopulations*

Since the bond length of carbonyl group in glycine is slightly longer than its counterpart in valine,<sup>4</sup> it is expected that the divalent cation-binding capacity is slightly more potent in glycine, contributing to the formation of higher levels of insoluble salts. Calcium supplement has previously been shown to reduce cancer risks.<sup>19</sup> Glycine and valine may synergize with calcium supplement to bring about more potent antitumor effects. However, people with risks of renal stones, cardiovascular disorders, Alzheimer's disease, dementia, constipation, allergy, or symptoms of COVID-19 and SARS infections, should be cautious for this novel anticancer therapy as the intake of glycine and valine may worsen these diseases, since insoluble salts might be already present in these conditions.<sup>1,20-25</sup> Despite that insoluble and rigid salts may give rise to huge benefits against neoplasm, there is a concern that excess of the insoluble calcium oxalate is presumed to mediate cell and human death.<sup>1,22,25</sup> Calcium oxalate crystals were detected within 5 hours after death in the thyroids in 85.2% of the disease sufferers aged 70 and above.<sup>26</sup>

### *Limitations of the Amino Acid Supplement and Future Directions*

The proposed glycine/valine antitumor regimen is hypothetical currently, despite of certain reports on the beneficial effects of these amino acids.<sup>27</sup> Basic research need to be performed on the transcriptome and proteome of amino acid supplement group versus controls. Clinical trials should be conducted to confirm the feasibility of the regimen, and adverse effects should be closely monitored. Only then can this anticancer regimen move from bench-top to bedside, and serve the needs of susceptible human subpopulations with familial history of cancer or environmental exposure.

### **Authors' Note**

Ethical approval is not applicable in this commentary, as no animal or human subject was involved.

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