

Brief Report

Not peer-reviewed version

Occurrence of Geranylgeranoic Acid in Selected Plant-Based Foods: A Quantitative Screening Using LC/MS/MS

[Yuki Tabata](#) *

Posted Date: 1 August 2025

doi: 10.20944/preprints202508.0072.v1

Keywords: eranylgeranoic acid; LC/MS/MS; dietary isoprenoids; cancer prevention; diterpenoid; hepatoma; nutritional biochemistry; plant lipids



Preprints.org is a free multidisciplinary platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This open access article is published under a Creative Commons CC BY 4.0 license, which permit the free download, distribution, and reuse, provided that the author and preprint are cited in any reuse.

Disclaimer/Publisher's Note: The statements, opinions, and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.

Brief Report

Occurrence of Geranylgeranoic Acid in Selected Plant-Based Foods: A Quantitative Screening Using LC/MS/MS

Yuki Tabata

Nutritional Biochemistry, Faculty of Wellness Studies, Department of Nutritional Health, Kwassui Women's University, Nagasaki, Japan

* Correspondence: tabata-yu@kwassui.ac.jp

Abstract

Geranylgeranoic acid (GGA), a bioactive acyclic isoprenoid, has been developed as a preventive agent against secondary primary hepatoma. While previous studies have identified GGA in certain medicinal herbs, such as turmeric, its presence in other commonly consumed plant-based foods remains largely unexplored. In this study, we screened 14 plant-based food items using a validated LC/MS/MS method to quantify their GGA content. Among the tested samples, turmeric powder exhibited the highest GGA concentration (20.2 ± 8.25 ng/g dry weight), consistent with previous findings. GGA was also detected in several nuts, including almonds (Italy: 7.59 ± 2.45 ng/g; USA: 6.48 ± 1.28 ng/g), cashew nuts (4.12 ± 1.12 ng/g), and pistachios (3.48 ± 0.95 ng/g). Importantly, azuki beans (7.21 ± 2.12 ng/g) and soybeans (1.21 ± 0.29 ng/g) were also found to contain GGA, suggesting that some legumes may serve as additional dietary sources of this compound. In contrast, GGA was not detected above the limit of quantification for the following seven items: chickpea, walnut, sesame seeds, and dried parsley. These negative results are also informative for defining the boundaries of GGA distribution in plant-based food. This study provides new data on the occurrence of GGA in plant-derived foods and contributes to a comprehensive understanding of its potential dietary sources.

Keywords: geranylgeranoic acid; LC/MS/MS; dietary isoprenoids; cancer prevention; diterpenoid; hepatoma; nutritional biochemistry; plant lipids

Introduction

Geranylgeranoic acid (GGA) was originally developed as an acyclic diterpenoid retinoid (Muto et al., 1996; Muto et al., 1999). It exhibits ligand activity for RAR and RXR and can induce differentiation in hepatoma cell lines (Araki et al., 1995). Subsequently, Shidoji et al. reported that, unlike naturally occurring retinoids, GGA induces non-apoptotic cell death in human hepatoma-derived cell lines at micromolar concentrations. Recently, it has been shown to induce cell death in human hepatoma cells via TLR4-mediated pyroptosis (Yabuta et al., 2020; Shidoji et al., 2024).

They also identified GGA as a naturally occurring compound present in medicinal herbs, such as turmeric (*Curcuma longa*), which is widely used in traditional Ayurvedic medicine (Shidoji et al., 2004). Furthermore, their studies demonstrated that oral intake of turmeric tablets significantly elevated plasma GGA concentrations in humans within 2–4 h, followed by a gradual decrease over the next 8 h, thereby confirming the gastrointestinal absorption of dietary GGA (Mitake et al., 2010). In addition to plant-derived sources, our group has shown that GGA is endogenously biosynthesized in mammals, including humans (Shidoji et al., 2019; Tabata et al., 2020; Tabata et al., 2022). Recently, we investigated the relationship between endogenous hepatic GGA levels and spontaneous hepatocarcinogenesis in male C3H/HeN mice, a strain known to develop liver tumors naturally at approximately two years of age. We observed a significant age-related decline in hepatic GGA

content, which was completely depleted in tumor-bearing livers. Notably, when GGA was orally administered at 11 months of age, just prior to the significant decline in hepatic GGA levels, the incidence of liver cancer at 23 months was markedly suppressed, suggesting the potential of dietary GGA supplementation as a chemo-preventive strategy against hepatocellular carcinoma (Tabata et al., 2021).

These findings highlight the potential of GGA as a bioactive nutrient for cancer chemoprevention. Specifically, increasing hepatic GGA levels through dietary intake may offer a promising approach to suppress liver tumorigenesis, forming the basis of a future paradigm of "diet-based liver cancer prevention."

To date, GGA has only been reported in a limited range of plant materials, notably turmeric. However, turmeric is not widely consumed in large amounts in most populations, especially outside South Asian cuisines, raising questions about its practicality as a dietary source of GGA for the public. Therefore, to evaluate the feasibility of dietary strategies for GGA supplementation, it is essential to expand our knowledge of the distribution of GGA in the commonly consumed foods.

In the present study, we conducted a targeted screening of 14 commercially available plant-based foods, including nuts, legumes, oilseeds, and herbs, to identify new dietary sources of GGA. Our findings aim to provide foundational data for the development of nutritional approaches to prevent liver cancer and promote metabolic health.

Materials and Methods

Chemicals

GGA was prepared by Kuraray Co. (Okayama, Japan) and Kowa Pharmaceutical (Tokyo, Japan). Acetonitrile (LC/MS grade) and ethanol were purchased from Sigma-Aldrich (St. Louis, MO). Methanol was from Wako Pure Chemical Industries (Osaka, Japan). Chloroform was obtained from Kanto Chemical Co. (Tokyo, Japan). All chemicals other than those stated above were of reagent grade.

Sample preparation

Fourteen types of commercially available plant foods (Table 1) were used in powder form.

Table 1. List of plant-based food items analyzed for geranylgeranoic acid (GGA) content, along with country of origin and classification.

No.	Common Name	Scientific Name	Category	Sample Form	Country of Origin
1	Turmeric Powder	<i>Curcuma longa</i>	Spice	Powder	India
2	Almond	<i>Prunus dulcis</i>	Nut	Powder	Italy
3	Almond	<i>Prunus dulcis</i>	Nut	Powder	United States
4	Cashew Nut	<i>Anacardium occidentale</i>	Nut	Powder	India
5	Pistachio	<i>Pistacia vera</i>	Nut	Powder	Italy
6	Azuki Bean	<i>Vigna angularis</i>	Legume	Powder	Japan
7	Soybean	<i>Glycine max</i>	Legume	Powder (kinako)	Japan
8	Hazelnut	<i>Corylus avellana</i>	Nut	Powder	Italy
9	Walnut	<i>Juglans regia</i>	Nut	Powder	United States
10	Chickpea	<i>Cicer arietinum</i>	Legume	Powder	India
11	White Sesame	<i>Sesamum indicum</i>	Oilseed	Roasted and ground (surigoma)	Paraguay
12	Black Sesame	<i>Sesamum indicum</i>	Oilseed	Roasted and ground (surigoma)	China
13	Dried Mango Powder	<i>Mangifera indica</i>	Dried fruit powder	Powder	— (not specified)
14	Dried Parsley	<i>Petroselinum crispum</i>	Dried herb	Dried and crushed	— (not specified)

Lipid extraction and quantitative measurement of GGA contents

Addition of 10 mL of methanol for approximately 1 g of each sample and left to stand overnight. Subsequently, a volume of 20 mL of chloroform was added, and the mixture was vortexed to extract total lipids. The extract was centrifuged at 3000 × g for 10 minutes and the supernatant was collected.

This procedure was repeated three times, and the extracts were pooled, evaporated to dryness under a nitrogen atmosphere, and redissolved in 1 mL ethanol. The resultant ethanolic solution was applied onto ethanol-equilibrated C18 solidphase cartridges (Bond Elute C18; Agilent, Tokyo, Japan), and the flow-through fractions were used as lipid extracts. The lipid extracts were finally filtered through a cartridge of Cosmonice Filter S, PTFE (Nacalai Tesque, Kyoto, Japan; 0.45 μ m, 13 mm) just prior to LC/MS/MS analysis. LC/MS/MS analysis was conducted using a Waters Acquity UPLC system coupled with a tandem quadrupole mass spectrometer (Waters, Milford, MA) operating in MRM mode, as previously described (Tabata et al., 2022). Separation was achieved on an Acquity UPLC-HSS T3 column (2.1 mm $\times$ 100 mm, 1.8 μ m) using a binary gradient system composed of acetonitrile (solvent A) and water (solvent B). The elution profile included an initial isocratic phase (74% A), followed by linear gradients to 100% A and back, with a total run time of 19 min and a flow rate of 0.3 mL/min. Nitrogen was employed as both cone and desolvation gas, and argon served as the collision gas. Instrument parameters, including source and desolvation temperatures, capillary voltage, and collision energy, were set according to our previously validated method for GGA quantification (Shidoji et al., 2019).

Results

GGA was detected in 7 of the 14 plant-based food items analyzed (Table 2). The highest concentration was observed in turmeric powder (20.2 $\pm$ 8.25 ng/g DW), followed by azuki bean (7.21 $\pm$ 2.12 ng/g), almond (Italy, 7.59 $\pm$ 2.45 ng/g), almond (USA, 6.48 $\pm$ 1.28 ng/g), cashew nut (4.12 $\pm$ 1.12 ng/g), pistachio (3.48 $\pm$ 0.95 ng/g), and soybean (1.21 $\pm$ 0.29 ng/g). These results confirm that GGA is present not only in turmeric and nuts as well as legumes such as azuki bean and soybean, which are widely consumed in many diets. No detectable GGA levels were found in hazelnut, walnut, chickpea, sesame (white and black), dried mango powder, or dried parsley.

Table 2. Concentration of geranylgeranoic acid (GGA) in 14 plant-based food items (ng per g dry weight, mean $\pm$ SD).

No.	Common Name	GGA Content (ng/g DW)	SD
1	Turmeric Powder	20.2	8.25
2	Almond (Italy)	7.59	2.45
3	Almond (USA)	6.48	1.28
4	Cashew Nut	4.12	1.12
5	Pistachio	3.48	0.95
6	Azuki Bean	7.21	2.12
7	Soybean	1.21	0.29
8	Hazelnut	ND	–
9	Walnut	ND	–
10	Chickpea	ND	–
11	White Sesame	ND	–
12	Black Sesame	ND	–
13	Dried Mango Powder	ND	–
14	Dried Parsley	ND	–

All samples were analyzed in triplicate (n = 3). “ND” indicates that GGA was not detected above the limit of quantification.

GGA: geranylgeranoic acid

Discussion

In this study, we quantified the levels of GGA in 14 plant-based food items commonly consumed by humans. Consistent with previous reports, turmeric (*Curcuma longa*) contains the highest levels of GGA among the tested samples (Shidoji et al., 2004). However, this study also identified GGA in various nuts, including almonds, cashew nuts, and pistachios. These findings suggest that tree nuts, in addition to being rich in lipids, may serve as practical dietary sources of GGA.

Epidemiological evidence supports the relevance of these results. Two large prospective US cohort studies, the Nurses' Health Study and the Health Professionals Follow-up Study, have reported a suggestive association between increased intake of tree nuts (averaging 1.25 servings per week) and a reduced risk of hepatocellular carcinoma (Jing et al., 2019). Although this protective effect has primarily been attributed to antioxidant constituents such as polyphenols and vitamin E, our data raise the possibility that GGA, a bioactive lipid uniquely found in certain nuts, may also play a contributory role. This hypothesis warrants further exploration in both mechanistic and population-based studies in the future.

Beyond tree nuts, we detected GGA in two types of legumes, azuki beans and soybeans, which are widely incorporated into East Asian diets (Rizzo et al., 2018). This is particularly notable because legumes have traditionally been considered protein-rich foods rather than lipid-rich foods. The identification of GGA in both nut and legume matrices indicates that its biosynthesis or accumulation in plants is not limited to lipid-dense tissues, suggesting a broader metabolic and ecological role.

In contrast, GGA was not detected in several tested items, including chickpeas, walnuts, hazelnuts, sesame seeds, dried mango powder, and parsley. Although negative findings are often underreported in nutritional science, they provide critical reference points for delineating the dietary landscapes of bioactive compounds. These data help define the practical boundaries of GGA availability in common foods, thereby enabling more accurate dietary intake assessments and the formulation of dietary strategies.

The biological significance of dietary GGA intake lies in its emerging role as a regulator of hepatocyte stability. Recent evidence has demonstrated that GGA can induce pyroptotic cell death via TLR4 signaling in hepatoma cells (Yabuta et al., 2020; Shidoji et al., 2024), and our previous study has shown that GGA levels in the liver decline with age and are depleted in hepatocarcinogenesis. Importantly, oral GGA supplementation in mice significantly suppressed spontaneous liver tumor development (Tabata et al., 2021), supporting its potential as a functional food component for liver cancer chemoprevention.

Together, these results provide novel insights into the food-based distribution of GGA and its potential contribution to human health. By identifying accessible and commonly consumed sources of GGA beyond turmeric, this study lays the groundwork for the development of diet-based preventive strategies targeting liver carcinogenesis and possibly other chronic conditions associated with lipid signaling or immune regulation. In addition to its anti-carcinogenic potential, GGA has been shown to exert reproductive benefits in mammals. A study in C3H/HeN mice reported that GGA supplementation during mating, pregnancy, and lactation significantly improved offspring survival and litter size. This evidence supports the notion that GGA's physiological role extends beyond tumor suppression and may influence developmental and reproductive health. It further highlights the potential value of dietary GGA intake across the lifespan (Tabata et al. 2020). Further research is needed to elucidate the bioavailability, metabolism, and functional outcomes of GGA derived from different dietary sources.

However, this study has several limitations. First, the sample size was relatively small ($n = 3$ per food item), which may not capture the full variability within or between batches of food products in the market. Second, the extraction method employed was optimized for lipophilic compounds and may not recover all forms of GGA, including potential conjugated or esterified derivatives of GGA. Additionally, the study only assessed powdered commercial food products and did not evaluate the impact of food preparation or cooking on GGA content. Future studies should include a broader range of food matrices, processing conditions, and cultural diets to better understand dietary availability of GGA. Moreover, controlled dietary intervention studies in humans are needed to determine whether the consumption of GGA-rich foods leads to measurable increases in circulating or tissue GGA levels. Finally, epidemiological studies linking GGA intake with liver health outcomes would be valuable for clarifying its relevance as a nutritional factor in cancer chemoprevention.

Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions: The author confirms being the sole contributor to this work and has approved it for publication.

Funding: This work was supported by JSPS KAKENHI Grant Number JP23K16802.

Data Availability Statement: The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

References

1. Muto, Y., Moriwaki, H., Ninomiya, M., Adachi, S., Saito, A., Takasaki, K. T., Tanaka, T., Tsurumi, K., Okuno, M., Tomita, E., Nakamura, T., and Kojima, T. (1996). Prevention of second primary tumors by an acyclic retinoid, polyprenoic acid, in patients with hepatocellular carcinoma. *N. Engl. J. Med.* 334, 1561–1567. <https://doi.org/10.1056/NEJM199606133342402>
2. Muto, Y., Moriwaki, H., and Saito, A. (1999). Prevention of second primary tumors by an acyclic retinoid in patients with hepatocellular carcinoma. *N. Engl. J. Med.* 340, 1046–1047. <https://doi.org/10.1056/NEJM199904013401315>
3. Araki H, Shidoji Y, Yamada Y, Moriwaki H, Muto Y. (1995). Retinoid agonist activities of synthetic geranylgeranoic acid derivatives. *Biochem Biophys Res Commun* 209:66–72. <https://doi.org/10.1006/bbrc.1995.1471>
4. Yabuta S, Shidoji Y. (2020). TLR4-mediated pyroptosis in human hepatoma-derived HuH-7 cells induced by a branched-chain polyunsaturated fatty acid, geranylgeranoic acid. *Biosci Rep* 40:BSR20194118. <https://doi.org/10.1042/BSR20194118>
5. Shidoji, Y. (2024). Induction of Hepatoma Cell Pyroptosis by Endogenous Lipid Geranylgeranoic Acid—A Comparison with Palmitic Acid and Retinoic Acid. *Cells* 13(10), 809. <https://doi.org/10.3390/cells13100809>
6. Shidoji Y, Ogawa H. (2004). Natural occurrence of cancer-preventive geranylgeranoic acid in medicinal herbs. *J Lipid Res* 45:1092–1103. <https://doi.org/10.1194/jlr.M400085-JLR200>
7. Mitake, M., Ogawa, H., Uebaba, K., and Shidoji, Y. (2010). Increase in plasma concentrations of geranylgeranoic acid after turmeric tablet intake by healthy volunteers. *J. Clin. Biochem. Nutr.* 46, 252–258. <https://doi.org/10.3164/jcbrn.09-109>
8. Shidoji Y, Tabata Y. (2019). Unequivocal evidence for endogenous geranylgeranoic acid biosynthesized from mevalonate in mammalian cells. *J Lipid Res* 60:579–593. <https://doi.org/10.1194/jlr.M090381>
9. Tabata, Y., and Shidoji, Y. (2020). Hepatic monoamine oxidase B is involved in endogenous geranylgeranoic acid synthesis in mammalian liver cells. *J. Lipid Res.* 61, 778–789. <https://doi.org/10.1194/jlr.RA119000610>
10. Tabata, Y., and Shidoji, Y. (2022). Hepatic CYP3A4 enzyme compensatively maintains endogenous geranylgeranoic acid levels in MAOB-knockout human hepatoma cells. *Metabolites* 12, 140. <https://doi.org/10.3390/metabo12020140>
11. Tabata, Y., Omori, M., and Shidoji, Y. (2021). Age-dependent decrease in hepatic geranylgeranoic acid content in C3H/HeN mice and its oral supplementation prevents spontaneous hepatoma. *Metabolites* 11, 634. <https://doi.org/10.3390/metabo11090634>
12. Sui, J., Yang, W., Ma, Y., Li, T. Y., Simon, T. G., Meyerhardt, J. A., Liang, G., Giovannucci, E. L., Chan, A. T., and Zhang, X. (2019). A prospective study of nut consumption and risk of primary hepatocellular carcinoma in U.S. women and men. *Cancer Prev. Res.* 12, 625–634. <https://doi.org/10.1158/1940-6207.CAPR-18-0442>
13. Rizzo, G., and Baroni, L. (2018). Soy, soy foods and their role in vegetarian diets. *Nutrients* 10, 43. <https://doi.org/10.3390/nu10010043>
14. Tabata Y, Uematsu S, Shidoji Y. (2020). Supplementation with geranylgeranoic acid during mating, pregnancy and lactation improves reproduction index in C3H/HeN mice. *Jpn Pharmacol Nutr* 23:1–9. <http://doi.org/10.4014/jpan.23.1>

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

