

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2021 October 28; 27(40): 6737-7004



## FRONTIER

- 6737 Hepatocellular carcinoma risk after viral response in hepatitis C virus-advanced fibrosis: Who to screen and for how long?

Ahumada A, Rayón L, Usón C, Bañares R, Alonso Lopez S

## OPINION REVIEW

- 6750 Higher doses of ascorbic acid may have the potential to promote nutrient delivery *via* intestinal paracellular absorption

Sequeira IR

## EVIDENCE REVIEW

- 6757 Venous and arterial thromboembolism in patients with inflammatory bowel diseases

Stadnicki A, Stadnicka I

## REVIEW

- 6775 Understanding the immune response and the current landscape of immunotherapy in pancreatic cancer

Ostios-Garcia L, Villamayor J, Garcia-Lorenzo E, Vinal D, Feliu J

- 6794 Artificial intelligence in gastroenterology: A state-of-the-art review

Kröner PT, Engels MM, Glicksberg BS, Johnson KW, Mzaik O, van Hooft JE, Wallace MB, El-Serag HB, Krittanawong C

## MINIREVIEWS

- 6825 Emerging artificial intelligence applications in liver magnetic resonance imaging

Hill CE, Biasioli L, Robson MD, Grau V, Pavlides M

- 6844 Role of human nucleoside transporters in pancreatic cancer and chemoresistance

Carter CJ, Mekawaty AH, Morris DL

- 6861 Management of hepatitis B and C in special population

Kulkarni AV, Duvvuru NR

- 6874 Endoscopic ultrasound-guided vascular interventions: Current insights and emerging techniques

Mann R, Goyal H, Perisetti A, Chandan S, Inamdar S, Tharian B

## ORIGINAL ARTICLE

## Basic Study

- 6888 Metabolomics of *Fuzi-Gancao* in CCl<sub>4</sub> induced acute liver injury and its regulatory effect on bile acid profile in rats

Wang MF, Zhao SS, Thapa DM, Song YL, Xiang Z

- 6908 Transforming growth factor beta-1 upregulates glucose transporter 1 and glycolysis through canonical and noncanonical pathways in hepatic stellate cells

Zhou MY, Cheng ML, Huang T, Hu RH, Zou GL, Li H, Zhang BF, Zhu JJ, Liu YM, Liu Y, Zhao XK

## Retrospective Cohort Study

- 6927 Serum hepatitis B core-related antigen as a surrogate marker of hepatitis B e antigen seroconversion in chronic hepatitis B

Chi XM, Wang XM, Wang ZF, Wu RH, Gao XZ, Xu HQ, Ding YH, Niu JQ

- 6939 Long-term follow-up of liver alveolar echinococcosis using echinococcosis multilocularis ultrasound classification

Schuhbauer J, Schweizer M, Philipp J, Schmidberger J, Schlingeloff P, Kratzer W

## Observational Study

- 6951 Hepatic and gastrointestinal disturbances in Egyptian patients infected with coronavirus disease 2019: A multicentre cohort study

Shousha HI, Afify S, Maher R, Asem N, Fouad E, Mostafa EF, Medhat MA, Abdalazeem A, Elmorsy H, Aziz MM, Mohammed RS, Ibrahim M, Elgarem H, Omran D, Hassany M, Elsayed B, Abdelaziz AY, El Kassas M

- 6967 Factors affecting anxiety, depression, and self-care ability in patients who have undergone liver transplantation

Akbulut S, Ozer A, Saritas H, Yilmaz S

## META-ANALYSIS

- 6985 Prophylactic transcatheter arterial embolization reduces rebleeding in non-variceal upper gastrointestinal bleeding: A meta-analysis

Boros E, Sipos Z, Hegyi P, Teutsch B, Frim L, Váncsa S, Kiss S, Dembrovsky F, Oštarijaš E, Shawyer A, Erőss B

## LETTER TO THE EDITOR

- 7000 Gastrointestinal and hepatic involvement during COVID-19 pandemic: A focus on pediatric population and possible future implications

Sica R, Pennoni S, Penta L, Riccioni S, Di Cara G, Verrotti A

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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Jia-Hui Li; Production Department Director: Yu-Jie Ma; Editorial Office Director: Ze-Mao Gong.

**NAME OF JOURNAL**

*World Journal of Gastroenterology*

**ISSN**

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

**LAUNCH DATE**

October 1, 1995

**FREQUENCY**

Weekly

**EDITORS-IN-CHIEF**

Andrzej S Tarnawski, Subrata Ghosh

**EDITORIAL BOARD MEMBERS**

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

**PUBLICATION DATE**

October 28, 2021

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<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

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## Higher doses of ascorbic acid may have the potential to promote nutrient delivery *via* intestinal paracellular absorption

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**Author contributions:** Sequeira IR conceptualized, drafted and wrote the manuscript.

**Conflict-of-interest statement:** The author declares no conflict of interest.

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**Manuscript source:** Unsolicited manuscript

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** New Zealand

**Peer-review report's scientific quality classification**

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### Abstract

The significance of plasma ascorbic acid (AA) is underscored by its enzymatic and antioxidant properties as well as involvement in many aspects of health including the synthesis of biomolecules during acute illness, trauma and chronic health conditions. Dietary intake supports maintenance of optimal levels with supplementation at higher doses more likely pursued. Transient increased intestinal paracellular permeability following high dose AA may be utilised to enhance delivery of other micronutrients across the intestinal lumen. The potential mechanism following dietary intake however needs further study but may provide an avenue to increase small intestinal nutrient co transport and absorption, including in acute and chronic illness.

**Key Words:** Aspirin; Ascorbic acid; Paracellular permeability; Antioxidant; Lactulose mannitol test

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**Core Tip:** The significance of plasma ascorbic acid (AA) is underscored by its enzymatic and antioxidant properties as well as involvement in many aspects of health including the synthesis of biomolecules during acute illness, trauma and chronic health conditions. Dietary intake supports maintenance of optimal levels with supplementation at higher doses more likely pursued. Transient increased intestinal paracellular permeability following high dose AA may be utilised to enhance delivery of other micronutrients across the intestinal lumen. The potential mechanism following dietary intake however needs further study but may provide an avenue to increase small intestinal nutrient co transport and absorption, including in acute and chronic illness.



Grade A (Excellent): 0  
 Grade B (Very good): B  
 Grade C (Good): 0  
 Grade D (Fair): 0  
 Grade E (Poor): 0

**Received:** July 1, 2021

**Peer-review started:** July 1, 2021

**First decision:** July 13, 2021

**Revised:** July 16, 2021

**Accepted:** September 19, 2021

**Article in press:** September 19, 2021

**Published online:** October 28, 2021

**P-Reviewer:** Subramanian VS

**S-Editor:** Wang JJ

**L-Editor:** A

**P-Editor:** Li JH



**Citation:** Sequeira IR. Higher doses of ascorbic acid may have the potential to promote nutrient delivery *via* intestinal paracellular absorption. *World J Gastroenterol* 2021; 27(40): 6750-6756

**URL:** <https://www.wjgnet.com/1007-9327/full/v27/i40/6750.htm>

**DOI:** <https://dx.doi.org/10.3748/wjg.v27.i40.6750>

## INTRODUCTION

Ascorbic acid (AA) or Vitamin C is an essential micronutrient in the human diet, due to the non-functional gene encoding L-glucono lactone oxidase that is involved in the catalysis of the last biosynthetic step in the pathway. The physiology and pathophysiology of AA has been extensively studied and the estimated plasma half-life reported to be between 7-14 d on the basis of depletion-repletion studies, conducted in healthy male subjects. Ergo, providing an approximation of the plasma half-life in those individuals that may have acute illness, trauma or chronic health conditions. The importance of maintaining optimal AA levels is underscored by both its antioxidant and non-antioxidant, *i.e.*, enzymatic roles and involvement in many aspects of health which include being an essential factor in the synthesis of collagen, carnitine and norepinephrine. Reduced dietary consumption, due to lower intake of fresh fruit and vegetables, or increased utilization *via* intracellular uptake are important aspects in the maintenance of plasma AA levels. Increased cellular distribution of AA has been shown to be associated with high leukocyte turnover and oxidative stress, whereby the redox potential of AA mitigates the production of reactive oxygen species (ROS). Dehydroascorbic acid (DHA), formed by the loss of electron by the ascorbic radical, has the same biological activity as the reduced form. The subsequent hydrolysis of DHA, if not reduced back to AA, to 2,3-diketogulonic acid is an irreversible step that results in the loss of antioxidant properties and its degradation.

Exogenous AA uptake is provided by, but not limited to, dietary intake. Due to AAs proposed antioxidant as well as enzymatic health benefits it is a widely sought-after dietary supplement that is available for consumption alone or as a multivitamin. Notably, AA has been co-formulated not only with other vitamins but also with anti-inflammatory pharmacological agents[1-3], in particular with aspirin. Monotherapy with aspirin has been shown to decrease the concentration of AA not only within the intestinal enterocytes[4] but also in gastric juice[5] potentiating negative impacts by reducing the ability of intestinal mucosal cells to manage oxidative stress[4]. Therefore, the co-formulation of AA with aspirin is considered to mitigate and ameliorate ROS induced gastrointestinal damage that has been implicated with the etiology of aspirin monotherapy[6].

Of interest is, a body of work conducted by our group that demonstrated that a single dose of aspirin has the potential to cause transient increases in small intestinal permeability over a 6 h period in healthy individuals. More importantly that rather than mitigating the aspirin induced increase in intestinal permeability[7], assessed by the lactulose mannitol test[8], the administration of 500 mg AA augmented absorption of lactulose either when given alone or in combination with the single 500 mg dose of aspirin (Table 1).

Therefore, it appears that while simultaneous dosage of AA with aspirin may potentially have longer term beneficial effects, related to the antioxidant properties of AA, in the short term however it may not mitigate the aspirin-induced increase in intestinal permeability. It is notable that, in the investigation, participants received an aspirin drink thirty minutes prior to the AA drink[7] in contrast to other studies where AA and aspirin were administered together as a single solution or in the form of a tablet[1-3,5,9]. Hence, it may be considered that the extent of ionization of each of these weak organic acids could have differed in the intestinal lumen consequentially affecting their ability to access transporters in the gut wall. The proportion of unionized AA increases to 99% and 15% in the stomach (pH 1) and small intestine (pH 5) respectively, and under these conditions passive diffusion is thought to play a significant role in AA uptake[10]. Indeed, it has been previously shown that co-administration of aspirin with AA decreased the rate at which AA was absorbed *in vivo*[11] and could have resulted from interference with sodium dependent secondary active transport *via* sodium-dependent vitamin C transporters (SVCT1 and SVCT2) [12]. These transporters are differentially expressed along the length of the gastrointestinal tract, with the pattern of expression mediated in part by transcriptional and epigenetic mechanisms[13].

**Table 1 Variation in the cumulative excretion of lactulose in bulked urine samples collected over two time periods (first three hours and the second three hours) during a six hours collection period in 28 healthy female participants**

Treatment	Lactulose excretion (% recovery of ingested dose)	
	First 3 h	Second 3 h
Aspirin	0.37 ± 0.05 <sup>a,b</sup>	0.46 ± 0.05 <sup>d</sup>
Ascorbic acid	0.47 ± 0.05 <sup>a,c</sup>	0.53 ± 0.04
Combined dosage	0.68 ± 0.09 <sup>b,c</sup>	0.77 ± 0.14 <sup>d</sup>

<sup>a</sup>Statistically significant ( $P < 0.05$ ) differences between treatments during the first 3 h, results expressed as mean ± SEM.

<sup>b</sup>Statistically significant ( $P < 0.05$ ) differences between treatments during the first 3 h, results expressed as mean ± SEM.

<sup>c</sup>Statistically significant ( $P < 0.05$ ) differences between treatments during the first 3 h, results expressed as mean ± SEM.

<sup>d</sup>Statistically significant ( $P < 0.05$ ) differences between treatments during the second 3 h during the lactulose mannitol test, results expressed as mean ± SEM.

Pertinent however is that increased small intestinal mucosal permeability, even if transient, following dosage with AA raises questions as to whether similar changes may occur following dietary ingestion of foods that are rich in AA. It is noteworthy that the dose of 500 mg AA administered in our study[7] is higher than the recommended daily allowance (RDA 60-120 mg)[14], guidelines for which are variable. An increase in the RDA to 200 mg has been proposed[15] to maximize the attributed health benefits, with evidence suggesting that regular supplement users consume more than 1 g AA per day[16]. Whether the increase in intestinal permeability detected in our study was dose dependent is not known and a comparison with other publications is not possible as the effect of AA on intestinal permeability has not been previously studied. We hypothesize that the dose of AA induced increase in intestinal permeability could be due to its action on apical transporters. Glucose has been shown to modulate vitamin C transport at the small intestinal brush border membrane with similar rates of uptake of DHA and AA reported in the absence of glucose[17]. The reduced form, AA, is absorbed *via* SVCT1 and SVCT2[18]. Given that the stoichiometry of the SVCTs are similar to those of the sodium dependent glucose transporter (SGLT1)[19,20] it is possible that absorption of AA may bring about intracellular changes that modulate, *i.e.*, relax, tight junctions in a manner similar to that of glucose transport *via* SGLT1[21]. Additionally, the oxidised form DHA has been shown to compete with glucose for transport *via* glucose transporters[22] in particular GLUT2 and GLUT8[23], which have been suggested along with SGLT1 to cause cytoskeletal contraction[24]. The modulation of the tight junctions in this manner has been shown to increase mucosal permeability[25], allowing greater quantities of larger molecules to be absorbed *via* the paracellular pathway[26].

Relating and extending the results of our study to AA levels from dietary intake maybe difficult and may necessitate human intervention studies using whole foods or extracts at comparable doses. However, an extrapolation of the effect of foods/extract would require careful study design as the amount of available AA in different foods may vary widely[27]. Particularly in fruits and vegetables where the quantity of AA is determined by a variety of factors which include cultivars, environmental conditions including regional and seasonal conditions as well as maturation[28]. Additionally, depending on the levels of hydration it is very likely that there may be inherent variability in the proportion of reduced and oxidized AA within fruits and vegetables, much like AA in solutions which have a greater susceptibility to oxidation. At pH < 4 [29] the concentration of AA deteriorates, with greater losses shown to occur in frozen products that are processed/canned [mean: 26 % (0% - 78 %)] than from frozen fresh products [mean: 18 % (0% - 50 %)] [30]. Furthermore, supplementation of products with synthetic AA has been shown to facilitate oxidation within products[31].

The degradation of AA not only occurs during processing and storage of the food/extract but also once it is consumed and introduced into the gastrointestinal lumen. Being an antioxidant, AA gets oxidized in the gastrointestinal tract to maintain the reduced state of other nutrients, *e.g.*, iron or form metal-oxygen-ascorbate complexes[32]. However, the acidic conditions of the gastrointestinal tract protect AA against chemical and enzymatic oxidation[32] with 93% of AA from bioactive broccoli inflorescence[33] and 71% from pomegranate juice[34] shown to be stable following *in vitro* gastric digestion. Conversely, in the small intestinal environment greater amounts

of AA was oxidized, with 39% of AA recovered[35] in this segment of the gut following *in vitro* small intestinal digestion of blended fruit juice. While this information is pertinent to our understanding, the bioavailability of luminal AA also requires consideration of the interaction with other contained dietary constituents *e.g.*, fiber and other bioflavonoids. Micronutrients within fruit juice have been shown to inhibit the absorption of AA[36] at doses between 50-500 mg. One mechanism for the inhibition is thought to occur *via* competition with transporters which has been particularly attributed to flavanoids such as quercetin and myricetin that are shown to decrease ascorbate as well as DHA absorption in *in vitro* models[37,38]. Vinson *et al*[39] further demonstrated in guinea pigs that dosage with a citrus fruit extract, containing 18% bioflavonoids, 15% proteins and 30% carbohydrates, resulted in a significantly slower rise in plasma ascorbate concentrations in comparison to a simple ascorbate solution. In alignment with these findings, a similar effect was also reported in human participants following the intake of citrus fruit extract[40].

Contrary to these findings it has also been shown that flavonoids, following consumption of half a golden kiwi fruit a day (50 g) over six weeks, did not alter the bioavailability of contained AA when compared to 50 g of synthetic AA[41]. This inferred effect appeared consistent as the administration of AA with blackcurrant juice [42] or orange juice[43] containing flavonoids did not impede absorption. Therefore, it seems likely that these differences in the manner in which AA is absorbed when co-administered could have arisen due to the differential gastric transit times[44]. Gastric emptying of liquid meals or beverages is dependent on the pressure gradient across the gastroduodenal junction and in part by the composition of the duodenal content, and hence it is conceivable that the nutrient content and composition of these different solutions or fruit slowed down gastric emptying[44]. Alternatively, these incongruent results may in part have been due to the different forms and dosages at which AA was administered, *i.e.*, as solutions or gels. Ergo resulting in potentially variable gastrointestinal residence and emptying times to influence absorption and the subsequent appearance of AA in sampled biological fluids *i.e.*, plasma, urine *etc.*

Given these inconsistencies in evidence regarding the bioavailability when co-administered with other substances, it remains unclear as to whether the effects of AA on intestinal permeability can be extended to situations when it is delivered in foods. This in particular considering the dose and quantity of the foods/extract that would have to be consumed to show comparable effects. All the same, the ability of a pharmaceutical dose of 500 mg AA to augment absorption of larger inert sugars such as lactulose does raise the possibility that AA could be a putative agent that could be co-administered with poorly absorbed drugs, nutrients or food substances of similar or larger molecular weight to enhance their absorption[45,46].

Increased paracellular permeability, *via* the modulation of tight junctions, has been reported after consumption of a meal especially in the presence of glucose[47] and alanine[48]. Using Caco 2 models, food components such as plant extracts[49-51] and isolated food components[52-54] have been shown to increase paracellular permeability with a the resultant flux in macromolecules, such as mannitol[51,55,56]. These authors, including Kosińska *et al*[57], postulated that food components could be safe alternatives to reversibly 'open' tight junctions in order to enhance the absorption of molecules of interest. Conversely, glutamine, polyunsaturated fatty acids and polyphenols have been shown to 'tighten' tight junctions through increased expression of tight junction associated proteins[58].

## CONCLUSION

Whilst the molecular mechanism by which AA increases paracellular permeability remains to be elucidated, a dose of 500 mg, which is higher than the current RDA, has been shown to increase small intestinal permeability in healthy individuals. Whether this effect is dose dependent requires further exploration however together with its antioxidant properties, the alteration of intestinal permeability by AA can be potentially explored as a safe and novel application for the delivery of molecules *via* the paracellular pathway. Indeed it is also conceivable the co-administration of AA, as a supplement or through consumption of a rich food source, with aspirin may potentiate its serum levels and analgesic effects.



## ACKNOWLEDGEMENTS

The studies were conducted at the Human Nutrition Unit at Massey University, Palmerston North under the supervision of Prof Roger G Lentle, Prof Marlana C Kruger and Dr Roger D Hurst.

## REFERENCES

- 1 **Konturek PC**, Kania J, Hahn EG, Konturek JW. Ascorbic acid attenuates aspirin-induced gastric damage: role of inducible nitric oxide synthase. *J Physiol Pharmacol* 2006; **57** Suppl 5: 125-136 [PMID: [17218764](#)]
- 2 **Dammann HG**, Saleki M, Torz M, Schulz HU, Krupp S, Schürer M, Timm J, Gessner U. Effects of buffered and plain acetylsalicylic acid formulations with and without ascorbic acid on gastric mucosa in healthy subjects. *Aliment Pharmacol Ther* 2004; **19**: 367-374 [PMID: [14984384](#) DOI: [10.1111/j.1365-2036.2004.01742.x](#)]
- 3 **McAlindon ME**, Muller AF, Filipowicz B, Hawkey CJ. Effect of allopurinol, sulphasalazine, and vitamin C on aspirin induced gastroduodenal injury in human volunteers. *Gut* 1996; **38**: 518-524 [PMID: [8707080](#) DOI: [10.1136/gut.38.4.518](#)]
- 4 **Buffinton GD**, Doe WF. Altered ascorbic acid status in the mucosa from inflammatory bowel disease patients. *Free Radic Res* 1995; **22**: 131-143 [PMID: [7704184](#) DOI: [10.3109/10715769509147535](#)]
- 5 **Pohle T**, Brzozowski T, Becker JC, Van der Voort IR, Markmann A, Konturek SJ, Moniczewski A, Domschke W, Konturek JW. Role of reactive oxygen metabolites in aspirin-induced gastric damage in humans: gastroprotection by vitamin C. *Aliment Pharmacol Ther* 2001; **15**: 677-687 [PMID: [11328262](#) DOI: [10.1046/j.1365-2036.2001.00975.x](#)]
- 6 **Patel V**, Fisher M, Voelker M, Gessner U. Gastrointestinal effects of the addition of ascorbic acid to aspirin. *Pain Pract* 2012; **12**: 476-484 [PMID: [22151399](#) DOI: [10.1111/j.1533-2500.2011.00517.x](#)]
- 7 **Sequeira IR**, Kruger MC, Hurst RD, Lentle RG. Ascorbic Acid may Exacerbate Aspirin-Induced Increase in Intestinal Permeability. *Basic Clin Pharmacol Toxicol* 2015; **117**: 195-203 [PMID: [25641731](#) DOI: [10.1111/bcpt.12388](#)]
- 8 **Sequeira IR**, Lentle RG, Kruger MC, Hurst RD. Standardising the lactulose mannitol test of gut permeability to minimise error and promote comparability. *PLoS One* 2014; **9**: e99256 [PMID: [24901524](#) DOI: [10.1371/journal.pone.0099256](#)]
- 9 **Hanan S**, Ahmed S, Zolfakar. Effect of aspirin versus aspirin and vitamin C on gastric mucosa [fundus] of adult male albino rats: histological and morphometric study. *Egypt J of Histol* 2010; **33**: 313-326
- 10 **Lykkesfeldt J**, Tveden-Nyborg P. The Pharmacokinetics of Vitamin C. *Nutrients* 2019; **11** [PMID: [31601028](#) DOI: [10.3390/nu11102412](#)]
- 11 **Ioannides C**, Stone AN, Breacker PJ, Basu TK. Impairment of absorption of ascorbic acid following ingestion of aspirin in guinea pigs. *Biochem Pharmacol* 1982; **31**: 4035-4038 [PMID: [6818974](#) DOI: [10.1016/0006-2952\(82\)90652-9](#)]
- 12 **Tsukaguchi H**, Tokui T, Mackenzie B, Berger UV, Chen XZ, Wang Y, Brubaker RF, Hediger MA. A family of mammalian Na<sup>+</sup>-dependent L-ascorbic acid transporters. *Nature* 1999; **399**: 70-75 [PMID: [10331392](#) DOI: [10.1038/19986](#)]
- 13 **Subramanian VS**, Srinivasan P, Wildman AJ, Marchant JS, Said HM. Molecular mechanism(s) involved in differential expression of vitamin C transporters along the intestinal tract. *Am J Physiol Gastrointest Liver Physiol* 2017; **312**: G340-G347 [PMID: [27932501](#) DOI: [10.1152/ajpgi.00369.2016](#)]
- 14 **Carr AC**, Lykkesfeldt J. Discrepancies in global vitamin C recommendations: a review of RDA criteria and underlying health perspectives. *Crit Rev Food Sci Nutr* 2021; **61**: 742-755 [PMID: [32223303](#) DOI: [10.1080/10408398.2020.1744513](#)]
- 15 **Frei B**, Birlouez-Aragon I, Lykkesfeldt J. Authors' perspective: What is the optimum intake of vitamin C in humans? *Crit Rev Food Sci Nutr* 2012; **52**: 815-829 [PMID: [22698272](#) DOI: [10.1080/10408398.2011.649149](#)]
- 16 **Johnston CS**. Biomarkers for establishing a tolerable upper intake level for vitamin C. *Nutr Rev* 1999; **57**: 71-77 [PMID: [10101920](#) DOI: [10.1111/j.1753-4887.1999.tb06926.x](#)]
- 17 **Malo C**, Wilson JX. Glucose modulates vitamin C transport in adult human small intestinal brush border membrane vesicles. *J Nutr* 2000; **130**: 63-69 [PMID: [10613768](#) DOI: [10.1093/jn/130.1.63](#)]
- 18 **Wilson JX**. Regulation of vitamin C transport. *Annu Rev Nutr* 2005; **25**: 105-125 [PMID: [16011461](#) DOI: [10.1146/annurev.nutr.25.050304.092647](#)]
- 19 **Lindblad M**, Tveden-Nyborg P, Lykkesfeldt J. Regulation of vitamin C homeostasis during deficiency. *Nutrients* 2013; **5**: 2860-2879 [PMID: [23892714](#) DOI: [10.3390/nu5082860](#)]
- 20 **Goldenberg H**, Schweinzer E. Transport of vitamin C in animal and human cells. *J Bioenerg Biomembr* 1994; **26**: 359-367 [PMID: [7844110](#) DOI: [10.1007/BF00762776](#)]
- 21 **Turner JR**. Show me the pathway! *Adv Drug Deliv Rev* 2000; **41**: 265-281 [PMID: [10854686](#) DOI: [10.1016/s0169-409x\(00\)00046-6](#)]
- 22 **Vera JC**, Rivas CI, Fischbarg J, Golde DW. Mammalian facilitative hexose transporters mediate the transport of dehydroascorbic acid. *Nature* 1993; **364**: 79-82 [PMID: [8316303](#) DOI: [10.1038/364079a0](#)]

- 10.1038/364079a0]
- 23 **Corpe CP**, Eck P, Wang J, Al-Hasani H, Levine M. Intestinal dehydroascorbic acid (DHA) transport mediated by the facilitative sugar transporters, GLUT2 and GLUT8. *J Biol Chem* 2013; **288**: 9092-9101 [PMID: [23396969](#) DOI: [10.1074/jbc.M112.436790](#)]
  - 24 **Schmitt CC**, Aranas T, Viel T, Chateau D, Le Gall M, Waligora-Dupriet AJ, Melchior C, Rouxel O, Kapel N, Gourcerol G, Tavitian B, Lehuen A, Brot-Laroche E, Leturque A, Serradas P, Grosfeld A. Intestinal invalidation of the glucose transporter GLUT2 delays tissue distribution of glucose and reveals an unexpected role in gut homeostasis. *Mol Metab* 2017; **6**: 61-72 [PMID: [28123938](#) DOI: [10.1016/j.molmet.2016.10.008](#)]
  - 25 **Pappenheimer JR**. Intestinal absorption of hexoses and amino acids: from apical cytosol to villus capillaries. *J Membr Biol* 2001; **184**: 233-239 [PMID: [11891547](#) DOI: [10.1007/s00232-001-0094-1](#)]
  - 26 **Groschwitz KR**, Hogan SP. Intestinal barrier function: molecular regulation and disease pathogenesis. *J Allergy Clin Immunol* 2009; **124**: 3-20; quiz 21 [PMID: [19560575](#) DOI: [10.1016/j.jaci.2009.05.038](#)]
  - 27 **Gregory JF**, III. Ascorbic acid bioavailability in foods and supplements. *Nutr Rev* 1993; **51**: 301-303 [DOI: [10.1111/j.1753-4887.1993.tb03059.x](#)]
  - 28 **Erdman JW**, Klein BP. Harvesting, processing, and cooking influences on vitamin C in foods. In: Seib PA, Tolbert BM, eds. *Ascorbic Acid: Chemistry, Metabolism, and Uses*. 1982: 499-532
  - 29 **Jeney-Nagy E**, Fodor P. The stability of vitamin C in different beverages. *Brit Food J* 2008; **110**: 296-309 [DOI: [10.1108/00070700810858709](#)]
  - 30 **Belitz H-D**, Grosch W, Schieberle P. *Vitamins*. Food Chemistry. Germany: Springer, 2009: 403-420
  - 31 **May J**, Asard H. Ascorbate recycling. In: Asard H, May J, Smirnoff N. *Vitamin C: its functions and biochemistry in animals and plants*. Taylor & Francis, 2003; 153-175
  - 32 **Ball GFM**. Intestinal absorption and bioavailability of vitamins. In: *Vitamins in foods: analysis, bioavailability, and stability*. Boca Raton: CRC Press, 2005; 23-3
  - 33 **Vallejo F**, Gil-Izquierdo A, Pérez-Vicente A, García-Viguera C. In vitro gastrointestinal digestion study of broccoli inflorescence phenolic compounds, glucosinolates, and vitamin C. *J Agric Food Chem* 2004; **52**: 135-138 [PMID: [14709026](#) DOI: [10.1021/jf0305128](#)]
  - 34 **Pérez-Vicente A**, Gil-Izquierdo A, García-Viguera C. In vitro gastrointestinal digestion study of pomegranate juice phenolic compounds, anthocyanins, and vitamin C. *J Agric Food Chem* 2002; **50**: 2308-2312 [PMID: [11929289](#) DOI: [10.1021/jf0113833](#)]
  - 35 **Rodríguez-Roque MJ**, Rojas-Graü MA, Elez-Martínez P, Martín-Belloso O. Changes in vitamin C, phenolic, and carotenoid profiles throughout in vitro gastrointestinal digestion of a blended fruit juice. *J Agric Food Chem* 2013; **61**: 1859-1867 [PMID: [23374081](#) DOI: [10.1021/jf3044204](#)]
  - 36 **Uchida E**, Kondo Y, Amano S, Aizawa S, Hanamura T, Aoki H, Nagamine K, Koizumi T, Maruyama N, Ishigami A. Absorption and excretion of ascorbic acid alone and in acerola (Malpighia emarginata) juice: comparison in healthy Japanese subjects. *Biol Pharm Bull* 2011; **34**: 1744-1747 [PMID: [22040889](#) DOI: [10.1248/bpb.34.1744](#)]
  - 37 **Song J**, Kwon O, Chen S, Daruwala R, Eck P, Park JB, Levine M. Flavonoid inhibition of sodium-dependent vitamin C transporter 1 (SVCT1) and glucose transporter isoform 2 (GLUT2), intestinal transporters for vitamin C and Glucose. *J Biol Chem* 2002; **277**: 15252-15260 [PMID: [11834736](#) DOI: [10.1074/jbc.M110496200](#)]
  - 38 **Park JB**, Levine M. Intracellular accumulation of ascorbic acid is inhibited by flavonoids via blocking of dehydroascorbic acid and ascorbic acid uptakes in HL-60, U937 and Jurkat cells. *J Nutr* 2000; **130**: 1297-1302 [PMID: [10801933](#) DOI: [10.1093/jn/130.5.1297](#)]
  - 39 **Vinson J BP**. Comparative bioavailability of synthetic and natural vitamin C in guinea pigs. *Nutr Rep Int* 1983; **27**: 875-879
  - 40 **Vinson JA**, Bose P. Comparative bioavailability to humans of ascorbic acid alone or in a citrus extract. *Am J Clin Nutr* 1988; **48**: 601-604 [PMID: [3414575](#) DOI: [10.1093/ajcn/48.3.601](#)]
  - 41 **Carr AC**, Bozonet SM, Pullar JM, Simcock JW, Vissers MC. A randomized steady-state bioavailability study of synthetic versus natural (kiwifruit-derived) vitamin C. *Nutrients* 2013; **5**: 3684-3695 [PMID: [24067392](#) DOI: [10.3390/nu5093684](#)]
  - 42 **E J**, RE H. The influence of bioflavonoids on the absorption of vitamin C. *IRCS Med Sci* 1984; **12**: 320
  - 43 **Pelletier O**, Keith MO. Bioavailability of synthetic and natural ascorbic acid. *J Am Diet Assoc* 1974; **64**: 271-275 [PMID: [4813067](#)]
  - 44 **Collins PJ**, Horowitz M, Cook DJ, Harding PE, Shearman DJ. Gastric emptying in normal subjects--a reproducible technique using a single scintillation camera and computer system. *Gut* 1983; **24**: 1117-1125 [PMID: [6642275](#) DOI: [10.1136/gut.24.12.1117](#)]
  - 45 **Deli MA**. Potential use of tight junction modulators to reversibly open membranous barriers and improve drug delivery. *Biochim Biophys Acta* 2009; **1788**: 892-910 [PMID: [18983815](#) DOI: [10.1016/j.bbame.2008.09.016](#)]
  - 46 **Salama NN**, Eddington ND, Fasano A. Tight junction modulation and its relationship to drug delivery. *Adv Drug Deliv Rev* 2006; **58** (1): 15-28 [PMID: [16517003](#) DOI: [10.1016/j.addr.2006.01.003](#)]
  - 47 **Pappenheimer JR**, Reiss KZ. Contribution of solvent drag through intercellular junctions to absorption of nutrients by the small intestine of the rat. *J Membr Biol* 1987; **100**: 123-136 [PMID: [3430569](#) DOI: [10.1007/BF02209145](#)]
  - 48 **Sadowski DC**, Meddings JB. Luminal nutrients alter tight-junction permeability in the rat jejunum: an

- in vivo perfusion model. *Can J Physiol Pharmacol* 1993; **71**: 835-839 [PMID: [7511482](#) DOI: [10.1139/y93-125](#)]
- 49 **Hashimoto K**, Matsunaga N, Shimizu M. Effect of vegetable extracts on the transepithelial permeability of the human intestinal Caco-2 cell monolayer. *Biosci, Biotech, and Bioch* 1994; **58**: 1345-1346 [DOI: [10.1271/bbb.58.1345](#)]
  - 50 **Konishi Y**. Modulations of food-derived substances on intestinal permeability in Caco-2 cell monolayers. *Biosci Biotechnol Biochem* 2003; **67**: 2297-2299 [PMID: [14586128](#) DOI: [10.1271/bbb.67.2297](#)]
  - 51 **Epriliati I**, D'Arcy B, Gidley M. Nutriomic analysis of fresh and processed fruit products. 2. During in vitro simultaneous molecular passages using Caco-2 cell monolayers. *J Agric Food Chem* 2009; **57**: 3377-3388 [PMID: [19290640](#) DOI: [10.1021/jf802226n](#)]
  - 52 **Ohno Y**, Naganuma T, Ogawa T, Muramoto K. Effect of lectins on the transport of food factors in caco-2 cell monolayers. *J Agric Food Chem* 2006; **54**: 548-553 [PMID: [16417319](#) DOI: [10.1021/jf052040y](#)]
  - 53 **Isoda H**, Han J, Tominaga M, Maekawa T. Effects of capsaicin on human intestinal cell line Caco-2. *Cytotechnology* 2001; **36**: 155-161 [PMID: [19003326](#) DOI: [10.1023/A:1014053306343](#)]
  - 54 **Rapin JR**, Wiernsperger N. Possible links between intestinal permeability and food processing: A potential therapeutic niche for glutamine. *Clinics (Sao Paulo)* 2010; **65**: 635-643 [PMID: [20613941](#) DOI: [10.1590/S1807-59322010000600012](#)]
  - 55 **Laitinen LA**, Tammela PS, Galkin A, Vuorela HJ, Marvola ML, Vuorela PM. Effects of extracts of commonly consumed food supplements and food fractions on the permeability of drugs across Caco-2 cell monolayers. *Pharm Res* 2004; **21**: 1904-1916 [PMID: [15553239](#) DOI: [10.1023/b:pham.0000045246.94064.ab](#)]
  - 56 **Vaidyanathan JB**, Walle T. Cellular uptake and efflux of the tea flavonoid (-) epicatechin-3-gallate in the human intestinal cell line Caco-2. *J Pharmacol Exp Ther* 2003; **307**: 745-752 [PMID: [12970388](#) DOI: [10.1124/jpet.103.054296](#)]
  - 57 **Kosińska A**, Andlauer W. Modulation of tight junction integrity by food components. *Food Res Int* 2013; **54**: 951-960 [DOI: [10.1016/j.foodres.2012.12.038](#)]
  - 58 **Amasheh M**, Andres S, Amasheh S, Fromm M, Schulzke JD. Barrier effects of nutritional factors. *Ann N Y Acad Sci* 2009; **1165**: 267-273 [PMID: [19538315](#) DOI: [10.1111/j.1749-6632.2009.04063.x](#)]



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