Citrus Structure/Function Claims White Paper

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Summary

The purpose of this paper is to review the scientific evidence for potential fit with structure/function claims specific to citrus fruits (oranges, grapefruit, tangerines or mandarin oranges, lemons and limes). The paper also reviews evidence that may be of use in charting a path toward health claims specific to citrus fruit. This work should not be considered a substitute for legal advice.

Regulatory and Marketplace Background

Nutrition labeling for fresh fruits and vegetables is limited because of little or no packaging, and, in fact, the U.S. Nutrition Labeling and Education Act specifically exempts raw fruits and vegetables from mandatory labeling requirements.[1] Thus claims are likely to be utilized in integrated marketing efforts, such as Point-of-sale (POS) materials and web content. Food labeling is under the jurisdiction of the U.S. Food and Drug Administration (FDA), whereas advertising is the domain of the U.S. Federal Trade Commission (FTC). In place of package labeling, retailers must provide nutrition labeling information for the top 20 most frequently consumed raw fruits and vegetables (20 each). Conservatively, integrated marketing efforts should be considered an extension of food labels, in which case FDA labeling regulations would apply to web content and other marketing materials. New labeling regulations will go into effect July 26, 2018. However, manufacturers with less than $10 million in annual food sales will have an additional year to comply.[2]

From a food labeling perspective, fruits and vegetables are considered conventional foods versus foods for special dietary needs. There are three basic categories of labeling claims defined by statute and or FDA regulations: health claims, nutrient content claims, and structure function claims:[3]

- Health claims describe a relationship between a food substance (a food or food component) and reduced risk of a disease or health-related condition.
- Nutrient content claims describe the level of a nutrient in the product, using such terms as “high,” “excellent,” “good,” etc.
- A structure/function claim is a claim about an effect of a nutrient or other dietary component on the normal structure or function of the human body. Structure/function claims may:
    - Describe the role of a nutrient intended to affect the normal structure or function of the human body, for example, "calcium builds strong bones."
    - Characterize the means by which a nutrient acts to maintain such structure or function, for example, "fiber maintains bowel regularity."
    - Describe general well-being from consumption of a nutrient or dietary ingredient.

New health claims require approval from the FDA. Structure/function claims for conventional foods do not require prior authorization, nor does the FDA require a label disclaimer that the FDA has not evaluated the claim.

While the FDA has not issued guidance on substantiation of structure/function claims for labeling of conventional foods, but it has for dietary supplements and also recently drafted guidance for infant formulas, which has not yet been finalized.[4] Both of these sources may inform thinking about substantiation for structure/function claims for conventional foods. The FDA "intends to apply the 'competent and reliable evidence' standard for the substantiation of infant formula claims in a manner that is consistent with FTC's and FDA's approach for the substantiation of dietary supplement claims." The FDA recommends the use of systematic evidence-based review process for evaluating the strength of evidence for a structure/function claim.[2] The FDA considers randomized, controlled, double-blind intervention studies to be the most direct evidence for a cause-and-effect relationship, and therefore, recommends that the substantiation for structure/function claims in infant formula labeling rely primarily on the results of intervention studies.

It's important to note that structure/function claims address specific nutrients or dietary components, not foods. However, structure/function claims could go hand in hand with nutrient content claims for specific foods. For example, "Vitamin C helps grow and repair tissue, bones and teeth; oranges are an excellent source of vitamin C."

Non-nutritive components are not considered nutrients in the traditional sense but may provide positive health benefits. A number of bioactive components in citrus fruits have been identified as having potential health benefits.[5,6] Foods containing these food components are called functional foods. Fruits and vegetables have been identified as functional foods.[7] However, under the FDA, there is no legal definition of functional foods, whereas Japan has been a leader in regulation of functional foods. Related, a number of systematic reviews about potential health benefits of citrus have been published (see Table 1). While such work may not have application for structure/function claims, it can be evaluated for possible application with health claims.

Nutrient Content

Specific to citrus fruits, nutrient content claims can be made for vitamin C, folate, and fiber. In the case of pink/red grapefruit and tangerines, a vitamin A claim can be made. Additionally, tangerines are a good source of copper. Finally, citrus fruits contain calcium, thiamin, niacin, vitamin B6, potassium, phosphorus, magnesium, riboflavin and pantothenic acid,[8] though not in amounts that merit nutrition labeling claims. Table 1 and Table 2 summarize the key nutrients found in citrus expressed in terms useful for labeling regulation purposes. Nutrient content claims can be made for vitamins and minerals as follows: Excellent/high ≥20% of Daily Value (DV); Good 10-19% DV. No nutrient content claims exist for nutrients present in amounts less than 10%.

Retail POS for top-20 fruits is limited to data provided by the FDA. Oranges, grapefruits, lemons and limes are in the top 20; however, tangerines are not and therefore voluntary labels can be

developed. Also note that the FDA top-20 labeling does not differentiate between red and white grapefruit. Appendix A includes nutrition labels, under the new labeling guidelines, which have been developed by the Produce for Better Health Foundation using Genesis, a food labeling software program developed by ESHA.

Nutrient Intakes

The Dietary Guidelines for American, 2015,[9] concludes the following nutrients are underconsumed by many individuals in America: potassium, dietary fiber, choline, magnesium, and vitamins A, D, E and C. Iron has been identified as a nutrient underconsumed by adolescent girls and women ages 19-50. "Of the underconsumed nutrients, calcium, potassium, dietary fiber, and vitamin D are considered nutrients of public health concern because low intakes are associated with health concerns. For young children, women capable of becoming pregnant, and women who are pregnant, low intake of iron also is of public health concern." The Dietary Guidelines for Americans states absorption of iron from non-heme sources is enhanced by consuming these foods along with vitamin-C rich foods. "When consumed in the amounts recommended in the USDA Food Patterns, fruit contributes substantial amounts of two nutrients of public health concern: fiber and potassium. (Whole fruit and fruit juice provide about 16 percent of dietary fiber and 17 percent of potassium in the Food Patterns)." Table 2 presents intakes of select nutrients of interest to citrus in actual amounts and percent of population below recommended intakes.[10]

Functions and Health Benefits of Key Nutrients in Citrus

This section summarizes functions as well as health benefits of key nutrients that are found in significant amounts in citrus and are underconsumed by Americans, based on authoritative sources. Additionally, iron is addressed. Authoritative sources considered include the Dietary Guidelines for Americans or Advisory Committee report, Dietary Reference Intakes (DRI) and National Institutes of Health Office of Dietary Supplements (ODS).

Vitamin C

The following functions and health aspects of vitamin C are summarized by the ODS[11]: Vitamin C is required for biosyntheses of collagen, L-carnitine and certain neurotransmitters, and is also involved in protein metabolism. Collagen is an essential component of connective tissue, which plays a vital role in wound healing. Vitamin C has also been shown to regenerate other antioxidants in the body, including vitamin E. Vitamin C plays an important role in immune function and improved absorption of non-heme iron.

Ongoing research is examining whether vitamin C might help prevent or delay development of certain cancers, cardiovascular disease, age-related macular degeneration (AMD) and cataracts. At this time, the evidence is inconsistent on whether dietary vitamin C intake affects cancer risk. The authors of a 2008 meta-analysis of prospective cohort studies, including 14 studies reporting on vitamin C for a median follow-up of 10 years, concluded that dietary, but not supplemental, intake of vitamin C is inversely associated with coronary heart disease risk.

Results from two case-control studies indicate that vitamin C intakes greater than 300 mg/day reduce the risk of cataract formation by 70%–75%, but higher doses may increase risk of cataract extraction. Overall, the currently available evidence does not indicate that vitamin C, taken alone or with other antioxidants, affects the risk of developing AMD.

Vitamin A

The following functions and health aspects of vitamin A are summarized by the ODS[12]: Vitamin A is involved in immune function, vision, reproduction and cellular communication. Vitamin A is critical for vision as an essential component of rhodopsin, a protein that absorbs light in the retinal receptors, and because it supports the normal differentiation and functioning of the conjunctival membranes and cornea. Vitamin A also supports cell growth and differentiation, playing a critical role in the normal formation and maintenance of the heart, lungs, kidneys, and other organs.

Because of the role vitamin A plays in regulating cell growth and differentiation, several studies have examined the association between vitamin A and various types of cancer. However, the relationship between serum vitamin A levels or vitamin A supplementation and cancer risk is unclear.

Folate

The following functions and health aspects of folate are summarized by the ODS[13]: Folate functions as a coenzyme or co-substrate in single-carbon transfers in the synthesis of nucleic acids (DNA and RNA) and metabolism of amino acids. One of the most important folate-dependent reactions is the conversion of homocysteine to methionine in the synthesis of S-adenosyl-methionine, an important methyl donor. Another folate-dependent reaction, the methylation of deoxyuridylate to thymidylate in the formation of DNA, is required for proper cell division. An impairment of this reaction initiates a process that can lead to megaloblastic anemia, one of the hallmarks of folate deficiency. Due to its role in the synthesis of DNA and other critical cell components, folate is especially important during phases of rapid cell growth. Clear clinical trial evidence shows that when women take folic acid periconceptionally, a substantial proportion of neural tube defects (NTD) is prevented. Scientists estimate that periconceptional folic acid use could reduce NTDs by 50-60%. Since 1998, when the mandatory folic acid fortification program took effect in the United States, NTD rates have declined by 25-30%. Because approximately 50% of pregnancies in the United States are unplanned, adequate folate status is especially important during the periconceptual period before a woman might be aware that she is pregnant. The Food and Nutrition Board (FNB) advises women capable of becoming pregnant to "consume 400 mcg of folate daily from supplements, fortified foods, or both in addition to consuming food folate from a varied diet."

Additional research is needed to fully understand the role of dietary folate and supplemental folic acid in colorectal, prostate, and other cancers. Evidence to date indicates that adequate folate intake might reduce the risk of some forms of cancer. The authors of a 2012 meta-analysis of 19 randomized controlled trials that included 47,921 participants concluded that B-vitamin supplementation has no effect on the risk of cardiovascular disease, myocardial infarction, coronary heart disease, or cardiovascular death, although it does reduce the risk of

stroke by 12%. It is not possible to evaluate the impact of folic acid alone from these trials, but little evidence shows that supplemental folic acid with or without vitamin B12 and vitamin B6 can help reduce the risk or severity of cardiovascular disease. B-vitamin supplementation does, however, appear to have a protective effect on stroke. Most research has not shown that folic acid supplementation affects cognitive function or the development of dementia or Alzheimer's disease. Although additional research is still needed, evidence to date indicates that supplementation with folic acid alone or in combination with vitamin B12 or vitamin B6 does not appear to improve cognitive function in individuals with or without existing cognitive impairment. Additional research is needed to fully understand the association between folate status and depression and whether folic acid supplementation might be a helpful adjuvant treatment.

Potassium

Potassium, the major intracellular cation in the body, is required for normal cellular function.[14] Severe potassium deficiency results in hypokalemia, which then causes cardiac arrhythmias, muscle weakness, and glucose intolerance. Potassium plays critical roles in muscle function, cardiac function and regulation of blood pressure.[10] Potassium adequacy is also critical for health, as deficiency adversely affects numerous organ systems including the musculoskeletal, renal, and cardiovascular systems.[10] Moderate potassium deficiency, which typically occurs without hypokalemia, is characterized by increased blood pressure, increased salt sensitivity, an increased risk of kidney stones and increased bone turnover.[14] The 2005 DRI report on potassium concluded inadequate intake of dietary potassium may also increase the risk of cardiovascular disease, particularly stroke.[14] Since the 2005 report, additional research has shown that increased potassium intake reduces blood pressure in people with hypertension. A meta-analysis of 22 randomized controlled trials concluded high quality evidence shows that increased potassium intake reduces blood pressure in people with hypertension and has no adverse effect on blood lipid concentrations, catecholamine concentrations, or renal function in adults.[15] The same meta-analysis also showed that higher potassium intake was associated with a 24% lower risk of stroke (moderate quality evidence). Even though underconsumption is evident across the population, there is a particular concern for middle-aged and older adults, who are at increased risk for cardiovascular diseases. [10]

Dietary Fiber

The most important and well-recognized role for dietary fiber is health of the colon and maintenance of regular bowel movements, but a growing body of evidence also suggests that fiber may play a role in preventing coronary heart disease, colorectal and other cancers, type 2 diabetes, and obesity.[10] The Adequate Intake for fiber is based on an intake level associated with the greatest reduction in the risk of coronary heart disease.[10] The beneficial role of dietary fiber for regulation of weight, blood glucose and insulin sensitivity has previously been recognized.[16] A more recent prospective cohort study with 89,432 European participants examined the effect of total dietary fiber, cereal fiber, and fruit and vegetable fiber on weight and waist circumference.[17] Total fiber was inversely associated with subsequent weight and waist circumference change. Fruit and vegetable fiber was not associated with weight change

but had a similar association with waist circumference change when compared with intake of total dietary fiber and cereal fiber.

Bioactive Compounds

This section explores the potential for structure/function or health claims for bioactive compounds, compounds not classified as nutrients that may promote health. These bioactive compounds are not a fit for structure/function claims under the regulatory frameworks described above. However, the following analysis summarizes the state of the evidence for health and citrus, which may help identify research gaps related to the development of health claims specific to citrus.

Bioactive components include plant-based phytochemicals. To date, about 10,000 phytochemicals have been identified.[18] There several major categories of phytochemicals; those of interest to citrus include carotenoids and phenolics. Carotenoids include carotenes (including beta-carotene and lycopene) and xanthophylls, including lutein.[19] Phenolics encompass several sub-categories, including flavonoids, which are further subdivided. Flavonoids have been identified as the main non-nutritive components across citrus fruits, which can provide benefits for humans.[8] The flavonoid groups with most application to citrus are flavanones (hesperitin and naringenin).[20] Citrus fruit and citrus juice have been identified as primary contributors of total flavonoids or specific flavanones, along with tea and wine.[21] Citrus and its juices are the only fruit juices and the only commonly consumed foods that provide significant amounts of hesperidin (a hesperitin) and naringin (a neringenin) in the diet.[18] Other flavones are present in citrus, the most common of which are tangeretin and nobiletin, which are primarily found in orange, tangerine, and sour orange peel.[18] Other metabolites present in citrus include alkaloids, limonoids, coumarins and essential oils.[8]

The phytochemicals present in citrus include anti-oxidative, anti-inflammatory, anti-cancer, as well as cardiovascular protective effects, neuroprotective effects, etc.[8] It is thought that the additive and synergistic effects of phytochemicals in fruits and vegetables are responsible for these kinds of benefits, which suggests that bioactive compounds are best acquired through whole food consumption rather than dietary supplements.[17]

The strength of evidence for citrus and health varies. Meta-analyses, systematic reviews and other less rigorous reviews have been conducted specific to citrus fruits and body weight, risk factors for cardiovascular disease and various types of cancer. The evidence for fruit and vegetable consumption, fruit juice, citrus juice and antioxidants, and health has also been evaluated through reviews and meta-analysis (see Table 1). Because these studies either address bioactive components (not nutrients) and/or disease risk reduction, they cannot be used as the basis for structure/function claims. This research is foundational for further work that would need to be conducted to substantiate any health claims specific to citrus. Some of the study results could be considered for marketing or education materials, not related to labeling.

Model Structure/Function Claims for Citrus

Insert fruit and nutrient claim per Tables 3-5. These tables identify nutrient claims for both the current and new labeling regulations.

Vitamin C

_____ are a/an _____ source of vitamin C, an antioxidant that helps protect cells against free radical damage.

_____ are a/an _____ source of vitamin C, which helps maintain healthy skin, bones and teeth.

_____ are a/an _____ source of vitamin C, which helps maintain the immune system.

_____ are a/an _____ source of vitamin C, which helps the body absorb iron from plant sources.

Vitamin A

_____ are a/an _____ source of vitamin A, which is needed for eye and skin health.

_____ are a/an _____ source of vitamin A, which is needed for normal function of heart, lungs, kidneys, and other organs.

_____ are a/an _____ source of vitamin A, which helps maintain the immune system.

Folate

_____ are a/an _____ source of folate, a vitamin that contributes to normal cell growth and division.

_____ are a/an _____ source of folate, a vitamin that contributes to normal neural tube cell growth and division.

_____ are a/an _____ source of folate, a vitamin that helps maintain normal blood homocysteine levels.

Fiber

_____ are a/an _____ source of fiber, which helps maintain colon health and regularity.

_____ are a/an _____ source of fiber, helps maintain healthy blood sugar levels.

_____ are a/an _____ source of fiber, helps maintain heart health.

PBH Information for New Nutrition Labels

PBH previously compiled the following nutrient content claim and health claim guidance for the new nutrition labels, organized by fruit: orange, grapefruit, tangerines, lemon, lime.

Orange

Nutrient Content Claims

- fat free
- saturated fat free
- cholesterol free
- sodium free
- good source of fiber
- high in vitamin C

Health Claims

Dietary Fat & Cancer:

- Development of cancer depends on many factors. A diet low in total fat may reduce the risk of some cancers. Oranges are fat free.

Sodium & Hypertension:

- Diets low in sodium may reduce the risk of high blood pressure, a disease associated with many factors. Oranges are sodium free.
- Diets low in sodium may reduce the risk of high blood pressure. Oranges are sodium free.
- Oranges, as part of a low sodium diet, may reduce the risk of high blood pressure.

Dietary Saturated Fat & Cholesterol & Risk of Coronary Heart Disease

- While many factors affect heart disease, diets low in saturated fat and cholesterol may reduce the risk of this disease. Oranges contains no saturated fat or cholesterol.

Fiber-Containing Grain Products, Fruits, and Vegetables and Cancer

- Low fat diets rich in fiber-containing grain products, fruits, and vegetables may reduce the risk of some of cancers, a disease associated with many factors. Oranges are a good source of fiber.

Fruits & Vegetables & Cancer

- Low fat diets rich in fruits and vegetables (foods that are low in fat and may contain dietary fiber, Vitamin A, or Vitamin C) may reduce the risk of some types of cancer, a disease associated with many factors. Oranges are a good source of fiber and an excellent source of vitamin C.

Grapefruit

Nutrient Content Claims

- fat free
- saturated fat free
- cholesterol free
- sodium free
- a good source of vitamin A
- high in vitamin C

Health Claims

Dietary Fat & Cancer:

- Development of cancer depends on many factors. A diet low in total fat may reduce the risk of some cancers. Grapefruit is fat free.

Sodium & Hypertension:

- Diets low in sodium may reduce the risk of high blood pressure, a disease associated with many factors. Grapefruit is sodium free.
- Diets low in sodium may reduce the risk of high blood pressure. Grapefruit is sodium free.
- Grapefruit, as part of a low sodium diet, may reduce the risk of high blood pressure.

Dietary Saturated Fat & Cholesterol & Risk of Coronary Heart Disease

- While many factors affect heart disease, diets low in saturated fat and cholesterol may reduce the risk of this disease. Grapefruit contains no saturated fat or cholesterol.

Fruits & Vegetables & Cancer

- Low fat diets rich in fruits and vegetables (foods that are low in fat and may contain dietary fiber, Vitamin A, or Vitamin C) may reduce the risk of some types of cancer, a disease associated with many factors. Grapefruit is a good source of vitamin A and high in vitamin C.

Tangerines

Nutrient Content Claims

fat free

saturated fat free

cholesterol free

sodium free

high in vitamin C

Health Claims

Dietary Fat & Cancer:

- Development of cancer depends on many factors. A diet low in total fat may reduce the risk of some cancers. Tangerines are fat free.

Sodium & Hypertension:

- Diets low in sodium may reduce the risk of high blood pressure, a disease associated with many factors. Tangerines are sodium free.

- Diets low in sodium may reduce the risk of high blood pressure. Tangerines are sodium free.

- Tangerines, as part of a low sodium diet, may reduce the risk of high blood pressure.

Dietary Saturated Fat & Cholesterol & Risk of Coronary Heart Disease

- While many factors affect heart disease, diets low in saturated fat and cholesterol may reduce the risk of this disease. Tangerines contain no saturated fat or cholesterol.

Fruits & Vegetables & Cancer

- Low fat diets rich in fruits and vegetables (foods that are low in fat and may contain dietary fiber, Vitamin A, or Vitamin C) may reduce the risk of some types of cancer, a disease associated with many factors. Tangerines are an excellent source of vitamin C.

Lemon

Nutrient Content Claims

- fat free
- saturated fat free
- cholesterol free
- sodium free
- low in calories
- high in vitamin C

Health Claims

Dietary Fat & Cancer:

- Development of cancer depends on many factors. A diet low in total fat may reduce the risk of some cancers. Lemons are fat free.

Sodium & Hypertension:

- Diets low in sodium may reduce the risk of high blood pressure, a disease associated with many factors. Lemons are sodium free.
- Diets low in sodium may reduce the risk of high blood pressure. Lemons are sodium free.
- Lemons, as part of a low sodium diet, may reduce the risk of high blood pressure.

Dietary Saturated Fat & Cholesterol & Risk of Coronary Heart Disease

- While many factors affect heart disease, diets low in saturated fat and cholesterol may reduce the risk of this disease. Lemons contain no saturated fat or cholesterol.

Fruits & Vegetables & Cancer

- Low fat diets rich in fruits and vegetables (foods that are low in fat and may contain dietary fiber, Vitamin A, or Vitamin C) may reduce the risk of some types of cancer, a disease associated with many factors. Lemons are high in vitamin C.

Lime

Nutrient Content Claims

- fat free
- saturated fat free
- cholesterol free
- sodium free
- sugar free
- low in calories
- high in vitamin C

Health Claims

Dietary Fat & Cancer:

- Development of cancer depends on many factors. A diet low in total fat may reduce the risk of some cancers. Limes are fat free.

Sodium & Hypertension:

- Diets low in sodium may reduce the risk of high blood pressure, a disease associated with many factors. Limes are sodium free.
- Diets low in sodium may reduce the risk of high blood pressure. Limes are sodium free.
- Limes, as part of a low sodium diet, may reduce the risk of high blood pressure.

Dietary Saturated Fat & Cholesterol & Risk of Coronary Heart Disease

- While many factors affect heart disease, diets low in saturated fat and cholesterol may reduce the risk of this disease. Limes contain no saturated fat or cholesterol.

Fruits & Vegetables & Cancer

- Low fat diets rich in fruits and vegetables (foods that are low in fat and may contain dietary fiber, Vitamin A, or Vitamin C) may reduce the risk of some types of cancer, a disease associated with many factors. Limes are high in vitamin C.

Table 1 – Evidence for Fruit and Vegetable Consumption, Fruit Juice, Citrus Juice and Antioxidants, and Health (See accompanying journal articles)

Study	Food/ Constituent	Health Area	Description	Design	Conclusion
Hwang SL, et al., J Agr Food Chem, 2012.	Citrus flavonoids	Neuroprotective	Analyzes multiple neuroprotection mechanisms, and antioxidant and signaling properties of citrus flavonoids.	Review	Citrus flavonoids have antioxidant and anti-inflammatory bioactivities. In vitro and in vivo studies showed that they exert neuroprotection at high or low doses. Some citrus flavonoids can even promote cognition. Citrus fruits, which are rich in abundant sources of hesperetin and other flavonoids, are promising for the development of general food-based neuroprotection and brain foods.
Song JK, J Breast Ca, 2013.	Citrus fruit	Breast cancer	Investigated the association between dietary intake of citrus fruits and breast cancer risk. Included relevant articles on diet and breast cancer up to January 2012.	Systematic review	Pooled results from observational studies showed an inverse association between citrus fruit intake and the risk of breast cancer. There is a need for well-designed prospective observational and intervention studies to clarify the role of citrus fruit intake and breast cancer.
Bae JM, Kim EH, Epid Health, 2016.	Citrus fruit	Gastric cancer	Meta-analysis to evaluate whether there is an association between intake of citrus fruit and gastric cancer risk. Examined cohort studies	Meta-analysis	A total of five cohort studies were selected. The result was 13% reduction of gastric cancer according to the intake of citrus fruit. 100 g of citrus fruit intake per day inhibits CGC by 40%.

Sudong L, et al., Intl J FS Nutr, 2014.	Citrus fruit	Bladder cancer	Meta-analysis of currently available studies investigating the association between citrus fruit and bladder cancer. Eight case–control studies and six cohort studies were included in the meta-analysis.	Meta-analysis	There was a significant inverse association between citrus fruit intake and bladder cancer risk in all pooled studies and case–control studies, but not in the cohort studies. Results suggest that citrus fruit intake is related to decreased bladder cancer risk. Subsequent well-designed, large prospective studies are needed to obtain better understanding of this relationship.
Bae JM, et al., Pancrease, 2009.	Citrus fruit	Pancreatic cancer	Studies addressing diet and pancreatic cancer up to December 2007. Nine articles including 4 case-control studies and 5 cohort studies proved eligible.	Systematic review	Pooled results from observational studies showed an inverse association between intake of citrus fruits and the risk of pancreatic cancer, although results vary substantially across studies, and the apparent effect is restricted to the weaker study design. The results of this review provide only very low quality evidence supporting association between citrus intake and pancreatic cancer.

Lv X, et al., Chem Central J, 2015	Citrus fruit	Cancer, cardiovascular, neuroprotective	Summarizes global distribution and taxonomy, numerous secondary metabolites and bioactivities of citrus fruits to provide a reference for further study. Flavonoids as characteristic bioactive metabolites in Citrus fruits are mainly introduced.	Review	The multiple secondary metabolites in Citrus, including flavonoids, alkaloids, coumarins, limonoids, carotenoids, phenolic acids and volatile compounds, provide a rational basis for various biological activities. Among them, flavonoids (especially flavanones, flavanonols and methoxylated flavones) exhibit more bioactivities compared to other secondary metabolites. However, all these active metabolites work synergistically to exhibit anti-oxidative, anti-inflammatory, anti-cancer, anti-microbial and antiallergy effects, as well as presenting cardiovascular protection, neuroprotective effect, hepatoprotective effect, etc. Consequently, these multiple active metabolites with various bioactivities indicate that Citrus species are beneficial fruits when eaten daily, both for their nutrients contents and as chemotherapeutic or complementary medicine to promote health. Further investigations are required in order to make optimal use of these fruits.
Vingeliene S, et al., Ca Causes Contr, 2016.	Citrus fruit	Gastric & esophogeal cancers	Analyzes prospective studies on citrus fruit intake and risk of esophageal and gastric cancers through March 1, 2016.	Systematic review	With each 100 g/day increase of citrus fruit intake, a marginally significant decreased risk of esophageal cancer was observed. For gastric cancer, the nonsignificant inverse association was observed for gastric cardia cancer, but not for gastric non-cardia cancer. Citrus fruits may decrease the risk of esophageal and gastric cardia cancers, but further studies are needed.

Onakpoya I, et al., Crit Rev Food Sci Nutr, 2015.	Citrus fruit - grapefruit	Body weight, cardiovascular	Evaluate evidence for or against the effectiveness of grapefruit on body weight, blood pressure and lipid profile.	Systematic review	Paucity in the number of randomized clinical trials, short durations of interventions, and lack of an established minimum effective dose limit the conclusions that can be drawn about the effects of grapefruit on body weight and metabolic parameters. Further clinical trials evaluating the effects of grapefruit are warranted.
Rampersaud G, Valim F, Rev FS Nutr, 2017.	Citrus juice	Diet quality, anthropometric measures	Examines the contributions of orange juice and grapefruit juice to nutrient intake, diet quality, and fruit intake, and supports citrus juices as nutrient-dense beverages; also explores the research examining associations between orange juice and grapefruit intake and anthropometric measures.	Review	Moderate consumption of citrus juices may provide meaningful nutritional and dietary benefits and do not appear to negatively impact body weight, body composition, or other anthropometric measures in children and adults.
Hyson D, Adv Nutr, 2015.	100% fruit juice	Cancer, cardiovascular disease, cognition, hypertension, inflammation, oxidation, platelet function, urinary tract infection, and vascular reactivity	Summarizes data published between 1995 and 2012 related to 100% fruit juice. The effects of apple, cranberry, grape, grapefruit, orange, and pomegranate PFJ intake on outcomes linked various conditions and diseases were examined.	Review and critical analysis	Collective data are provocative although challenges and unanswered questions remain.

Vieira L, et al., Ann Onc, 2016.	Fruits & vegetables, subsets including citrus	Lung cancer	Analyzes prospective studies through 2014.	Systematic review & meta-analysis	Significant inverse dose–response associations were observed for each 100 g/day increase: for fruits and vegetables. There was evidence of non-linear dose–response relationship with 8% risk reduction in the range of citrus fruits intake up to around 70 g/day and no dose–response relationship is observed for increasing intakes above this value.
Zhang YJ, et al., Molecules, 2015.	Antioxidant phytochemicals	Cancer, cardiovascular disease, diabetes, obesity and neurogdegenerative diseases	Summarize recent progress on the health benefits of antioxidant phytochemicals, and discusses their potential mechanisms in the prevention and treatment of chronic diseases.	Review	Antioxidant phytochemicals possess many biological activities and health benefits, such as antioxidant and free radical scavenging abilities, anti-inflammatory action, anticancer, anti-aging, and protective action for cardiovascular diseases, diabetes mellitus, obesity and neurodegenerative diseases. It is recommended to consume fruits, vegetables, and grains as well as some medicinal plants more frequently because they contain many antioxidant phytochemicals. Their bioactivities and the mechanism of action should studied further.

Li NA, et al., Nutrients, 2014.	Polyphenols	Oxidative stress-related diseases, such as cardiovascular diseases, cancer, ageing, diabetes mellitus and neurodegenerative diseases	Summarizes current knowledge of natural polyphenols, including resource, bioactivities, bioavailability and potential toxicity.	Review	Emerging findings suggest the interaction with signal transduction pathways and cell receptors had an effect on polyphenols' biological activity. Achievable concentrations of polyphenols in the circulation after ingestion as well as the possibility of conjugation and metabolism of polyphenols are not illuminated very clearly. Exposure to high concentration of polyphenols, and over a long period, could induce DNA damage and obtain notably negative effects. Large scale randomized clinical trials should be conducted before the therapeutic use of polyphenols against human diseases can be fully established.

Table 2 – Mean Intakes of Select Nutrients – All Individuals 1 and Over

Nutrient	Mean Intake	% of Population Below EAR or AI*
Dietary fiber	15.6 g	95%
Vitamin A	616 µg RAE	40%
Folate	530 µg DFE	9%
Vitamin C	85 mg	37%
Potassium	2567 mg	97%
Magnesium	272 mg	49%
Iron (all individuals)	15 mg	5%
Iron (females 14-50)	13 mg	15-16%

*EAR: Estimated Required Intake; AI: Adequate Intake

Source: US Department of Agriculture, US Department of Health and Human Services. Scientific Report of the 2015 Dietary Guidelines Advisory Committee. 2015.

Table 3 – CURRENT FOOD LABELING – Nutrition Content for Key Nutrients – Grams, Milligrams or Percent of Daily Value (DV)[22] with Color Highlights for Excellent and Good

Citrus	Serving Size*	Amount					% DV				
		Fat g	Sat Fat g	Trans Fat g	Cholesterol mg	Sodium mg	Vit C	Vit A	Folate	Potassium	Fiber
Orange	1 (154 g)	0.23	0.03	0.00	0.00	2.00	137.8%	7.6%	13%	7.3%	13.6%
Grapefruit, Pink/Red	1/2 (154 g)	0.22	0.03	0.00	0.00	0.00	80.0%	35.4%	5%	5.9%	10.0%
Grapefruit, White	1/2 (154 g)	0.16	0.02	0.00	0.00	0.00	85.5%	1.0%	3.9%	6.5%	6.8%
Tangerine	1 (109 g)	0.34	0.04	0.00	0.00	2.00	48.5%	14.8%	4.3%	5.2%	8.0%
Lemon	1 medium (58 g)	0.17	0.02	0	0	1	51.2	0.26%	1.5%	2.3%	6.40%
Lime	1 medium (67 g)	0.13	0.02	0	0	1	32.5%	0.7%	1.3%	1.90%	7.60%
Excellent	**Good**										

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Table 4 – CURRENT FOOD LABELING – Allowable Nutrient Content Claims

Citrus	Serving Size*	Fat	Sat Fat	Trans Fat	Cholesterol	Sodium	Vit C	Vit A	Folate	Potassium	Fiber
Orange	1 (154 g)	Free	Free	0g/serving	Free	Free	Excellent		Good		Good
Grapefruit, Pink/Red	½ (154 g)	Free	Free	0g/serving	Free	Free	Excellent	Excellent			Good
Grapefruit, White	½ (154 g)	Free	Free	0g/serving	Free	Free	Excellent				
Tangerine	1 (109 g)		Free	0g/serving	Free	Free	Excellent	Good			
Lemon	1 medium (58 g)	Free	Free	0g/serving	Free	Free	Excellent				
Lime	1 medium (67 g)	Free	Free	0g/serving	Free	Free	Excellent				

Nutrient Content Claim: Excellent >20% of DV; Good 10-20% DV

*Serving size based on Top 20 Fresh Fruits and Vegetables – internal guidance to Produce for Better Health Foundation.

Table 5 – NEW FOOD LABELING – Nutrition Content for Key Nutrients – Grams, Milligrams or Percent of Daily Value (DV)[23] with Color Highlights for Excellent and Good

Citrus	Serving Size*	Amount					% DV				
		Fat g	Sat Fat g	Trans Fat g	Cholesterol mg	Sodium mg	Vitamin C	Vitamin A	Folate	Potassium	Fiber
Orange	1 (154 g)	0.23	0.03	0.00	0.00	2.00	101%	2%	13%	6%	12%
Grapefruit, Pink/Red	1/2 (154 g)	0.22	0.03	0.00	0.00	0.00	53%	10%	5%	4%	10%
Grapefruit, White	1/2 (154 g)	0.16	0.02	0.00	0.00	0.00	57%	0%	4%	5%	6%
Tangerine	1 (109 g)	0.34	0.04	0.00	0.00	2.00	32%	4%	4%	4%	7%
Lemon	1 medium (58 g)	0.17	0.02	0	0	1	34%	0%	2%	2%	6%
Lime	1 medium (67 g)	0.13	0.02	0	0	1	22%	0%	1%	1%	7%
Excellent	**Good**										

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Table 6 – NEW FOOD LABELING – Allowable Nutrient Content Claims

Citrus	Serving Size*	Fat	Sat Fat	Trans Fat	Cholesterol	Sodium	Vitamin C	Vitamin A	Folate	Potassium	Fiber
Orange	1 (154 g)	Free	Free	0g/serving	Free	Free	Excellent		Good		Good
Grapefruit, Pink/Red	1/2 (154 g)	Free	Free	0g/serving	Free	Free	Excellent	Good			
Grapefruit, White	1/2 (154 g)	Free	Free	0g/serving	Free	Free	Excellent				
Tangerine	1 (109 g)		Free	0g/serving	Free	Free	Excellent				
Lemon	1 medium (58 g)	Free	Free	0g/serving	Free	Free	Excellent				
Lime	1 medium (67 g)	Free	Free	0g/serving	Free	Free	Excellent				

Nutrient Content Claim: Excellent >20% of DV; Good 10-20% DV

*Serving size based on Top 20 Fresh Fruits and Vegetables – internal guidance to Produce for Better Health Foundation.

Appendix A – Citrus Nutrition Labels for NEW FOOD LABELING (Source: Produce for Better Health Foundation)

Orange

Nutrition Facts

Serving size 1 Medium (154g)

Amount per serving
Calories 80

	% Daily Value*
Total Fat 0g	**0**%
Saturated Fat 0g	**0**%
Trans Fat 0g	
Cholesterol 0mg	**0**%
Sodium 0mg	**0**%
Total Carbohydrate 19g	**7**%
Dietary Fiber 3g	**11**%
Total Sugars 14g	
Includes 0g Added Sugars	**0**%
Protein 1g	
Vitamin D 0mcg	**0**%
Calcium 60mg	**4**%
Iron 0mg	**0**%
Potassium 250mg	**6**%
Vitamin A 5mcg	**0**%
Vitamin C 78mg	**90**%

*The % Daily Value tells you how much a nutrient in a serving of food contributes to a daily diet. 2000 calories a day is used for general nutrition advice.

Calories per gram:
Fat 9 • Carbohydrate 4 • Protein 4

Grapefruit

Nutrition Facts

Serving size 1/2 medium (154g)

Amount per serving
Calories 60

	% Daily Value*
Total Fat 0g	**0**%
Saturated Fat 0g	**0**%
Trans Fat 0g	
Cholesterol 0mg	**0**%
Sodium 0mg	**0**%
Total Carbohydrate 15g	**5**%
Dietary Fiber 2g	**7**%
Total Sugars 11g	
Includes 0g Added Sugars	**0**%
Protein 1g	
Vitamin D 0mcg	**0**%
Calcium 40mg	**4**%
Iron 0mg	**0**%
Potassium 160mg	**4**%
Vitamin A 88mcg	**10**%
Vitamin C 60mg	**70**%

*The % Daily Value tells you how much a nutrient in a serving of food contributes to a daily diet. 2000 calories a day is used for general nutrition advice.

Calories per gram:
Fat 9 • Carbohydrate 4 • Protein 4

Tangerines (Mandarin Oranges)

Nutrition Facts

Serving size 2 small (152g)

Amount per serving
Calories 80

	% Daily Value*
Total Fat 0g	**0**%
Saturated Fat 0g	**0**%
Trans Fat 0g	
Cholesterol 0mg	**0**%
Sodium 0mg	**0**%
Total Carbohydrate 20g	**7**%
Dietary Fiber 3g	**11**%
Total Sugars 16g	
Includes 0g Added Sugars	**0**%
Protein 1g	
Vitamin D 0mcg	0%
Calcium 56mg	4%
Iron 0mg	0%
Potassium 252mg	6%
Vitamin A 52mcg	6%
Vitamin C 41mg	45%
Copper 0.1mg	10%

*The % Daily Value tells you how much a nutrient in a serving of food contributes to a daily diet. 2,000 calories a day is used for general nutrition advice.

Calories per gram:
Fat 9 • Carbohydrate 4 • Protein 4

Lemon

Nutrition Facts

Serving size	1 medium (58g)
Amount per serving	
Calories	**15**
	% Daily Value*
Total Fat 0g	**0%**
Saturated Fat 0g	**0%**
Trans Fat 0g	
Cholesterol 0mg	**0%**
Sodium 0mg	**0%**
Total Carbohydrate 5g	**2%**
Dietary Fiber 2g	**7%**
Total Sugars 2g	
Includes 0g Added Sugars	**0%**
Protein 0g	
Vitamin D 0mcg	**0%**
Calcium 20mg	**2%**
Iron 0mg	**0%**
Potassium 75mg	**2%**
Vitamin C 24mg	**25%**

*The % Daily Value tells you how much a nutrient in a serving of food contributes to a daily diet. 2000 calories a day is used for general nutrition advice.

Calories per gram:
Fat 9 • Carbohydrate 4 • Protein 4

Lime

Nutrition Facts

Serving size	1 medium (67g)
Amount per serving	
Calories	**20**
	% Daily Value*
Total Fat 0g	**0%**
Saturated Fat 0g	**0%**
Trans Fat 0g	
Cholesterol 0mg	**0%**
Sodium 0mg	**0%**
Total Carbohydrate 7g	**3%**
Dietary Fiber 2g	**7%**
Total Sugars 0g	
Includes 0g Added Sugars	**0%**
Protein 0g	
Vitamin D 0mcg	**0%**
Calcium 0mg	**0%**
Iron 0mg	**0%**
Potassium 75mg	**2%**
Vitamin C 21mg	**25%**

*The % Daily Value tells you how much a nutrient in a serving of food contributes to a daily diet. 2000 calories a day is used for general nutrition advice.

Calories per gram:
Fat 9 • Carbohydrate 4 • Protein 4

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