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REVIEW ARTICLE

Concise Reviews and Hypotheses in Food Science

An overview of the nutritional quality and health benefits linked to the world diversity of citrus fruits/juices

Claudie Dhuique-Mayer[1,2] | **Adrient Servent**[1,2]

[1]QualiSud, Univ. Montpellier, CIRAD, Institut Agro, Université d'Avignon, Université de La Réunion, Montpellier, France

[2]CIRAD, UMR QualiSud, Montpellier, France

Correspondence
Claudie Dhuique-Mayer, QualiSud, Univ. Montpellier, CIRAD, Institut Agro, Université d'Avignon, Université de La Réunion, Montpellier, France.
Email: claudie.dhuique-mayer@cirad.fr

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WCO World Citrus Organization

Abstract

Citrus juices represent a nutrient-dense beverage due to the remarkable balance in their bioactive compounds (vitamins, minerals, dietary fibers, and phytochemicals such as flavonoids and carotenoids). This review aims to examine the nutritional quality and the health benefits of citrus juice consumption linked to the world diversity of citrus fruits. This work provides heterogenous data found on the main citrus bioactive compounds, especially carotenoids and flavonoids, which are difficult to correlate to particular geographic areas. Through an example of study, this work addresses the question of how and to what extent the content of citrus bioactive compounds is linked to the health benefits observed in humans. We explore through the more recent human clinical trials, the health effects of consuming citrus fruit or taking dietary supplements of bioactive compounds to prevent the exponential increase of world chronic diseases (type 2 diabetes, cardiovascular diseases, and obesity) and discuss the effects of dose. Finally, even if the data highlight the importance of geographical origin in accumulation of carotenoids or flavonoids from different *Citrus* species, the difference of content in front of the complex human metabolism of their absorption has lesser consequences for health than the fact of consuming citrus or not. The citrus health effect results in a synergistic action of numerous phytochemicals whose targeted health benefits vary depending more on the diversity of *Citrus* species than their geographic origin. Therefore, the use of the diversity of *Citrus* species could be an interesting approach to providing functional food.

KEYWORDS

bioactive compounds, citrus health benefits in humans, diversity of citrus species, geographical origin, metabolic syndrome

1 | INTRODUCTION

Citrus fruits and their juices, consumed worldwide, are naturally balanced in the main bioactive compounds such as vitamins (C and B_9), minerals (K), dietary fibers (pectin), and phytochemicals such as flavonoids and carotenoids (precursors of vitamin A) (Rampersaud & Valim, 2017). It was epidemiologically observed that the synergies between these citrus bioactive compounds probably contribute to their numerous health benefits for the prevention of different chronic diseases (Saini et al., 2022). The genus *Citrus* features 150 genera and 1600 species and are currently cultivated in more than 140 countries in subtropical, tropical, and Mediterranean climates between 40° N and 40° S latitude (Zhong & Nicolosi, 2020). Citrus originated in south-east Asia and the high diversity of world *Citrus* reflects their long history of crop domestication (Luro et al., 2017). With 158 million tons (Mt) citrus world production shared between Asia (51%), South America (18%), Europe (15%), and Africa (13%), the main species are represented by orange (76.1Mt), Mandarin/tangerine (39.5 Mt), lemon (9.7 Mt), and grapefruit (2Mt) (Worldcitrusorganisation.org, 2024). Brazil is particularly known for its oranges, China excels in a variety of citrus fruits including mandarins and the Mediterranean Basin is renowned for its production of various citrus fruits, including clementines, mandarins, oranges, and lemons. While Brazil and the United States also export large quantities of citrus, Spain often leads in terms of overall export volume and quality, especially for fresh fruits. Europe is the first consumers of citrus followed by Russia and United States (12–14.5 kg/capita). Oranges are consumed in Europe and Canada (4.3–6.5 kg/capita); mandarin/tangerine are consumed by Russia, Japan, and France (4.1–6.1 kg/capita); lemon is mainly consumed by Europe and United States (2.4–3 kg/capita); finally, grapefruits are mostly consumed by Ukraine, United States, and Europe (0.65–0.84 kg/capita) (Worldcitrusorganisation.org, 2024). In view of these data, it would seem that it is rather the northern countries that consume citrus fruits than others. Thus, the most exported species for consumption or transformation are orange (*Citrus sinensis L.*), tangerine (*Citrus reticulata Blanco or Citrus clementina* Hort. Ex Tan.), lemon (*Citrus limon L.*), and grapefruit (*Citrus paradisi* Macf.) (Karn et al., 2021). These species are of major commercial importance in the industry and are among the main species used for fruit juice processing (Kimball, 2012). The phytonutrient content in citrus fruits is highly influenced by their genetics and environmental factors (Dhuique-Mayer et al., 2009; Fanciullino et al., 2006). In addition, the contents of nutrients and bioactive compounds strongly evolve during ripening and maturation, and thus in function of the fruit maturity index. Finally, they can also be impacted by processing conditions during juice transformation.

However, to date, the link between geographical origin of citrus and their nutritional quality and/or their health benefits remains unexplored due to multiple factors such as the lack of identification of these critical characterizations (genetic origins, environmental factors, or even growth stage). Moreover, the pluralism of the supply chains of fruits and the diversity of analytical methodologies to characterize the bioactive compounds has resulted in highly heterogeneous data. The recent bibliographic reviews on the composition of citrus fruits and their health effects describe neither their cultivars nor their geographical origin or methodology analysis and so precision is lacking on plant material (Lu et al., 2023; Saini et al., 2022). Likewise, databases such as USDA or CIQUAL rarely give information on variety/cultivar identification, geographical origin, or maturity stage for a given *Citrus* species. The complexity of the logistics needed to obtain citrus varieties from well-identified genotypes and derived from the same germplasm collection could explain the poor identification available in the bibliography. The effects of genotype and environment on citrus juice carotenoid content has been previously assessed (Dhuique-Mayer et al., 2009). In this article, the genetic identification of two citrus species (orange and mandarin) and four varieties cultivated under three climates (Mediterranean, subtropical, and tropical) as well as their maturity index was considered to compare carotenoid content in fruits from different geographical origins. Results highlighted that interaction between *Citrus* accessions and environmental factors may occur with respect to carotenoid biosynthesis in juice vesicles.

Relevant information is needed on bioactive compound levels in citrus varieties from different continents and countries to better understand if the concentrations of these compounds influence various potential health benefits from the consumption of these fruits and their nutrient-dense beverages as their juices.

After an overview of the level of the main citrus bioactive compounds from classical databases, this bibliographic review, complete with original data, aims to address the question of how and to what extent the variations in bioactive compound content of citrus can be linked to a difference in health effects observed in humans. The objective is to explore, through the more recent human clinical trials, health effects of *Citrus* to prevent an exponential increase of certain chronic diseases, that is, type 2 diabetes, cardio-vascular diseases, and obesity generated by the metabolic syndrome (MetS), which represents a set of risk factors. Accurate information on what determines the variability of the nutritional quality of citrus fruits and juices is a major issue for growers and needs to be taken into account.

2 | OVERVIEW OF AVAILABLE DATA ON CITRUS BIOACTIVE COMPOUNDS WITH DIETARY INTEREST

First of all, it is important to distinguish citrus micronutrients, a general term involving vitamins and minerals, as well as dietary fibers which are needed by the human body to function, from the other citrus

TABLE 1 (A) The main bioactive compounds of four widely consumed citrus species in the world and (B) their recommended dietary allowances of vitamins.

(A)	Citrus species	Sample type	Fibers (g/100 g)	β-carotene (µg/100 g)	β-cryptoxanthin (µg/100 g)	Folate B9 (µg/100 g)	Vitamin C (mg/100 g)
	Citrus sinensis	Pulp	2.0–4.5	<5–87	116	17–34	45–59
		Juice	0.0–0.3	8–79	27 - 191	10–77	29–50
	Citrus Clementina	Pulp	1.7–1.8	147–155	407	16–28	27–49
		Juice	0.1	30	–	19	18
	Citrus Paradisi	Pulp	1.1–1.6	156–686	6	9–13	31–38
		Juice	0.1–0.3	4–188	1–5	10–19	24–38
	Citrus lemon	Pulp	<0.5–2.8	<5–3	20	11–28.4	45–53
		Juice	0.3–0.7	0–1	4–40	9–20	39–42
(B)	**RDA (%) for 100 g pulp**		**Orange**	**Mandarin/clementine**		**Grapefruit**	**Lemon**
	Vitamin C		43	45		29	41
	Vitamin B9		13	14		6.5	14
	Vitamin A (RAE eq)[a]		1–4	7-9		11-13	0.2-0.3
	Fibers[b]		8–18	7-8		4-6	2-11

[a]RAE: β-carotene/12 – RDA: 900 µg eq vit A people between 19–53 years old.
[b]25 g per day recommended by WHO.
Source: CIQUAL (2024); USDA (2024).

phytochemicals (secondary metabolites of plants). Micronutrients are the object of dietary deficiencies and are subject to recommended daily allowance (RDA). However, these dietary indications do not exist for phytochemicals such as polyphenols. Thus, the content of the four main bioactive compounds in citrus having an RDA (fibers, pro-vitamin A carotenoids, vitamins B9, and vitamin C) for currently consumed species are reported in Table 1a. For these data extracted from USDA/CIQUAL tables, the origin or variety was generally not mentioned, but for a few values either one origin or the variety was given. Data on provitamin A carotenoids (β-cryptoxanthin and β-carotene) were heterogeneous and sometimes unexpected. For example, values reported on β-carotene content in orange are similar in the pulp (87 µg/100 g) and in the juice (79 µg/100 g). However, it is known that the total carotenoid content in citrus pulp is generally higher than in juice (Rodrigo et al., 2015). Likewise, the β-cryptoxanthin content found in these tables for oranges was higher in the juices than in the pulp with 191 versus 116 µg/100 g, respectively. For grapefruits, a very wide range in β-carotene content from 4 to 188 µg/100 g was reported and this can be explained by the fact that the variety is not specified. Indeed, pink or white grapefruits (depending on the variety) implied presence or absence of carotenoids (β-carotene and lycopene) (Xu et al., 2006). Table 1b shows the RDAs for the main micronutrients and fibers. In any case, evidence from this average data is that the mandarin and pink grapefruit groups provide the most vitamin A equivalent, and to a lesser extent vitamins B9 and C, and fibers whatever the variety and geographical origin.

Complementary data on carotenoid and flavonoid contents of citrus juices from different origins/species/varieties were extracted from conventional scientific databases such as the Web of Science and are reported in Tables 2 and 3. Note that in these tables, lemon juice was not included because we focused on frequent citrus juice consumption as beverage. Lemon juice is generally not consumed as a standalone beverage as frequently as orange or grapefruit juice. Although lemon juice is popular for its flavoring and culinary uses, it tends to be more commonly used in small quantities, such as an ingredient or as a flavor enhancer in drinks rather than as a primary beverage. Orange/mandarin and grapefruit juices have a sweeter and more palatable taste, making them more appealing for direct consumption.

Some authors have described significant variability in phytochemical content of Citrus species according to their geographical origins (Centonze et al., 2019; Dhuique-Mayer et al., 2009; Mouly et al., 1999). Authors unanimously agree that these variations are linked to several factors, the main ones being genetic factors and growing/postharvest conditions. A large number of publications have assessed the nutritional quality of *Citrus* species, particularly the carotenoid and flavonoid content of their pulp. However, data aggregation is complex, as results are highly variable, and reliable genetic or maturity indications are often missing. In order to illustrate the variability of the available data, some studies report the provitamin

TABLE 2 Carotenoid/flavonoid contents of three *Citrus sinensis* varieties from Mediterranean area.

Citrus Sinensis—Mediterranean area							
Type of supply	**Genetic**	**Maturity (index)**	**Origin**	**β-Carotene + β-cryptoxanthin (mg/L)**	**RDA vitamin A for two glasses (%)**	**Hesperidin or naringin (mg/L)/ anthocyanin**	**References**
Valencia							
Collection	++	+ (7)	France (Corsica)	1.9–3.0	5.2–7.0	257	(Dhuique-Mayer et al., 2009; Dhuique-Mayer et al., 2005)
Firm juices	–	+ (12)	Spain	1.6	4.4	–	(Melendez-Martinez et al., 2007)
Production	–	–	Spain	1.4	14.5	–	(Giuffrida et al., 2019)
Local market	–	–	Spain	3.7	10.0	–	(Sanchez-Moreno et al., 2003)
Ag. cooperative	+	+	Greece	–		162	(Vavoura et al., 2022)
Exp. Field	–	+	Spain	2.1	4.7	–	(Stinco et al., 2016)
Collection	+	–	Spain	–		577	(Cano et al., 2008)
Washington Navel							
Exp. Field	+	+	Italy	2.58	6.3	195.7	(Multari et al., 2020)
Exp. Field	+	+	Spain	1.57–3.12[a]	4.1–11.3[a]	–	(Stinco et al., 2016)
Sanguinelli							
Collection	++	+ (7)	France (Corsica)	4.2	10.6	537	(Dhuique-Mayer et al., 2005)
Collection	++	+ (8.5)	France (Corsica)	4.3	10.7	–	(Fanciullino et al., 2006)
Collection	+	+ (9.5)	Spain	–		465/46	(Legua et al., 2022)
Collection	+	–	Spain	–		481	(Cano et al., 2008)
Exp. Field	–	+ color	Spain	–		234/145	(del Río et al., 2022)
Exp. Field	–	+ (nd)	Spain	1.9	4.4	–	(Stinco et al., 2016)
Exp. orchard	–	+ (nd)	Turkey	–		113/43	(Kelebek et al., 2008)
Gardens	–	+ (10)	Italy	–		493	(Canterino et al., 2011)

Note: Genetic: ++: mean at least two informations on genetic origin; +: one information ; –: no information; maturity index: +: mentioned but not calculated ; not mentioned; + (): mentioned and calculated.

Abbreviations: Exp, experimental; Ag, agricultural.

[a]Range between navel Late and Cara-cara cv. When data were expressed in μg/g DW, converted units in μg/g FW are calculated using the classical water percentage of grapefruit 90% (CIQUAL-USDA).

A carotenoids (β-carotene and β-cryptoxanthin) and the main citrus flavonoid (hesperidin or naringin) contents of three orange varieties grown in the Mediterranean region (Spain, France, Italy, and Turkey) are listed in Table 2. The vitamin A RDA was calculated based on a consumption of two glasses of juice per day. It is clear that even within the Mediterranean area, one of the main production zones for Citrus species, phytonutrient levels in the Valencia, Washington navel, and Sanguinelli varieties varied widely. Overall, in regard to provitamin A content and taking into account the RDA for vitamin A, the values vary from 4.1–4.4 to 10%–14% within the same cultivar. The diversity of methodologies for carotenoid analysis can lead to significant discrepancies in data. The extraction process, particularly saponification, is critical and can vary greatly in both duration and the concentration of potassium hydroxide (KOH) used. These variations affect the stability of xanthophyll carotenoids, which can be sensitive to both time and concentration. Using an internal standard is a useful strategy to minimize losses during extraction, but not all studies implement this, leading to inconsistencies in reported results. Additionally, the choice of solvents, temperatures, and even the specific equipment used can further complicate comparisons across different studies. Thus, considering only secondary metabolite concentrations, fruits from these different Mediterranean countries would present a significant difference in bioactivity when consumed. Variations reported in flavonoids were even greater, with levels

TABLE 3 Carotenoid/flavonoid contents of three Citrus species (orange, clementine and grapefruit) from tropical and temperate areas worldwide.

Citrus juice worldwide					
Genetic	**Growth stage Maturity index**	**Origin**	**β-carotene + β-cryptoxanthin (mg/L)**	**Hesperidin or naringin (mg/L)**	**References**
Valencia Orange					
–	–	Belize	0.45	–	(Mouly et al., 1999)
–	–	USA (Florida)	1.56	–	
–	–	Cuba	0.88	–	
–	3.5	Brazil	1.83	–	(Gama & Sylos, 2005)
–	–	USA	0.47	–	(Lee & Coates, 2003)
–	–	South Africa	0.34	–	(Etzbach et al., 2020)
–	–	Brazil	3.38	–	(Gama & de Sylos, 2007)
–	–	South Africa	–	82	(Hunlun et al., 2017)
–	« Ripe »	Japan	3.3	–	(Yano et al., 2005)
–	–	USA (Florida)	–	189	(Massenti et al., 2016; Nogata et al., 2006)
Tanaka System	« Mature »	Japan	–	962	(Nogata et al., 2006)
–	1.0	Brazil	–	54	(Coelho et al., 2021)
–	–	USA (Florida)	1.6	75	(Bai et al., 2013)
Germplasm*	–	Korea	–	595	(Yang et al., 2019)
Washington Navel					
Fundecitrus Co “Bahia”	“Mature”	Brazil	0.43	150.8	(Brasili et al., 2017)
Fundecitrus Co “Cara-cara”	“Mature”	Brazil	3.67	131.7	(Brasili et al., 2017)
Tangerine/Clementine/Mandarin					
–	–	South Africa	–	63–81	(Hunlun et al., 2017)
Identified in Tanaka System	« Mature »	Japan	–	412–594	(Nogata et al., 2006)
Germplasm*	–	Korea	–	428–1485	(Yang et al., 2019)
–	« Ripe »	Japan	13.3	–	(Yano et al., 2005)
–	–	Thailand	7.32	146	(Stuetz et al., 2010)
–	–	Brazil	8.3	–	(Petry & Mercadante, 2017)
–	–	Taiwan	12.55	–	(Lin & Chen, 1995)
Pink grapefruit					
–	« Ripe »	Japan	4.5	–	(Yano et al., 2005)
Rio red	–	USA (Texas)	6.00	600–1300	(Chaudhary et al., 2016)
Repository number#	7.0	China	8.11	–	(Zheng et al., 2016)
–	–	USA (Florida)	7–9.60	–	(Rouseff et al., 1992)
Germplasm*	–	Korea	–	743	(Yang et al., 2019)
–	4.4	Argentina	–	18–76	(Sgroppo et al., 2015)
–	–	USA (California)	23.4	–	(Khachik et al., 1989)
–	1.0	USA (Texas)	3.90	–	(Chebrolu et al., 2012)
–	–	South Africa	4.3	–	(Xu et al., 2006)
–	–	USA (Florida)	–	140	(De Castro et al., 2006)
–	–	China	–	192	(Zhang et al., 2011)
–	–	USA (Florida)	–	3090	(Ameer et al., 1996)

*Plant germplasm accession number in National Agrobiodiversity Center in Korea.

#Nationa lCitrus Germplasm Repository in the Citrus Research Institute at the Chinese Academy of Agricultural Sciences, Chongqing, China.

ranging from 157 to 577 and 43 to 537 mg/L for Valencia and Sanguinelli cultivars, respectively. No link could be established between available information on fruit ripeness or genetic identification and these variations. In most cases, this information was not always mentioned (Table 2).

This wide range of results was all the more significant when this exercise was carried out across all *Citrus*-growing areas, including examples from the United States (mainly Florida and Texas), Central America (Belize), Latin America (Brazil and Argentina), South Africa, and Asia (Japan, China, South Korea, Thailand, and Taiwan) (Table 3). At this scale, the main provitamin A carotenoid contents ranged from 0.34 to 3.67, from 8.3 to 13.3, and from 4.5 to 23.4 mg/L for orange, clementine/mandarin, and grapefruit, respectively. Flavonoid concentration varied by a factor of 11, 24, and up to 70 between the lowest and highest values reported for orange, clementine/mandarin, and grapefruit, respectively. Once again, no link could be shown between the values described, often without any specific description of ripeness, species, genetics, or postharvest history.

Based on the aggregation of existing data, it is therefore currently impossible to draw clear conclusions on the differences in the average phytonutrient contents according to geographical origin. However, potential bioactivity from consumption, based on provitamin A carotenoid content, may be significant. There is therefore a strong interest in assessing the heterogeneity of phytonutrient contents through a rigorous study carried out on well-identified fruits from several origins. It is also unclear if these variations can induce, beyond the simple consideration of provitamin A carotenoid or flavonoid concentration in the pulp, significant health benefits due to the combination of other citrus bioactive compounds, for instance on MetS disorders, including those of intestinal microbiota.

3 | EXAMPLE OF STUDY ON EFFECT OF GENOTYPE AND GEOGRAPHICAL ORIGIN ON FLAVONOID AND CAROTENOID CONTENT

Flavonoids and carotenoids are the major classes of citrus secondary metabolites that are biologically active. Among the flavonoids, flavanone glycosides such as hesperidin in oranges and mandarins, or naringin in grapefruits, represent 95% of the total flavonoids (Lv et al., 2015). Citrus fruits and juices are also an important source of dietary pro-vitamin A carotenoids such as β-cryptoxanthin as well as β-carotene from the orange/mandarin group or non-provitamin A such as lycopene from pink grapefruit. Their abundance in these two classes of compounds makes citrus fruits relevant from a dietary and health perspective.

To better assess the influence of the genotype and environmental factors (defined by the geographical origin) on the main carotenoid and flavonoid content of three *Citrus* species (orange, clementine, and grapefruit), a short study was carried out in our laboratory. All the material and methods of this part of the study are described in the Supporting Information associated with this bibliographic review. In this study, the carotenoid and hesperidin/naringin content of genetically identified citrus fruits from different geographical areas were compared. The aim was to establish if significant differences between *Citrus* species grown under a tropical climate (Florida) or a Mediterranean climate (citrus fruits from countries such as France [Corsica], Spain, and Morocco) existed intra or inter areas.

In order to obtain citrus fruits from the same germplasm, the fruit material from all geographical regions has the same genetical identification number "SRA" from the INRA Agronomic Research Station of San Giuliano in Corsica (France). One variety of each of the three species of citrus fruits (orange, clementine, grapefruit) was selected: Sanguinelli orange (*Citrus sinensis (L.) Osbeck*) (SRA 243), Fina Sodea, a clementine hybrid (*Citrus clementina Hort. Ex Tan.*) (SRA 85), and Star Ruby grapefruit (*Citrus paradisi Macf.*) (SRA 293), respectively.

Based on the content of phytochemicals quantified in the selected fruit juices, principal component analysis (PCA) was carried out to discriminate the variations considering the citrus species (Figure 1). The PCA based on the content of nine carotenoids and two flavanone glycosides clearly discriminated the three *Citrus* species (orange, clementine, and grapefruit), whatever the geographical origin. The pink grapefruits were characterized by their high levels of β-carotene, lycopene, and naringin, while a higher content of β-cryptoxanthin was associated with clementine and xanthophylls (violaxanthin, neoxanthin, lutein, and zeaxanthin) as well as hesperidin to orange.

Thus, specific health benefits might be attributed to the consumption of each citrus species, independent of their origins. These results suggest that genetic variation is the main factor that drives the accumulation of bioactive compounds in interspecific manners.

To understand the contribution of geographical origin to the variation, individual PCAs for each species were created based on the same dataset. Figure 2 shows the intraspecific variation of bioactive compounds of citrus coming from different geographic zones for each species. The Sanguinelli orange juices were divided into three distinct groups showing inter- and intra-geographic area variations (Figure 2a). The oranges from France (Corsica) and Spain accumulated more carotenoids and hesperidin than those of Morocco and the United States (Florida) suggesting a clustered subtropical and tropical climate.

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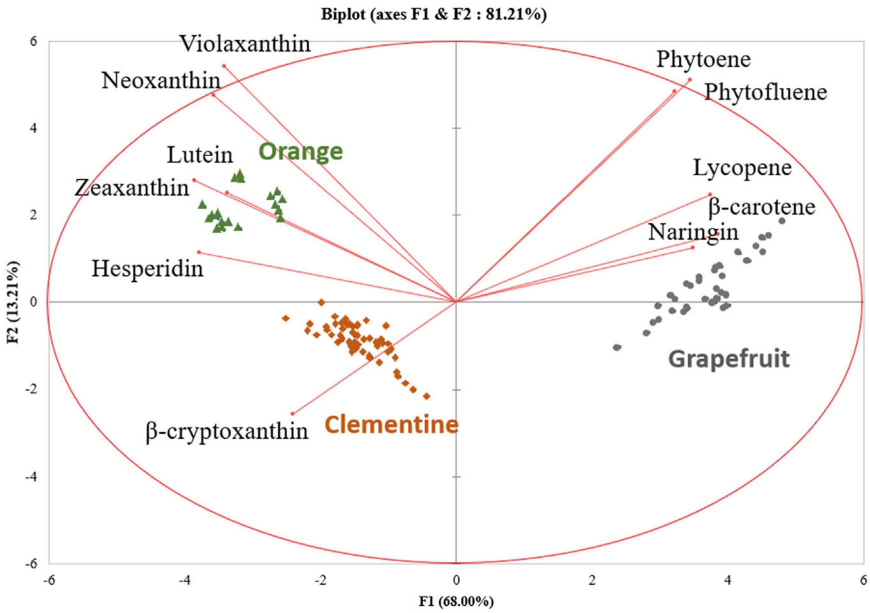

FIGURE 1 Differentiation of citrus species by principal component analysis (PCA) analysis based on their contents of carotenoids and flavanone glycosides.

For example, the main provitamin A carotenoid of orange (*β*-cryptoxanthin) displayed 4.09 ± 0.22[a] and 2.49 ± 0.12[b] mg/L, respectively, for Corsican and Spanish oranges comparatively with 1.31 ± 0.06[c] and 1.01 ± 0.08[c] mg/L for oranges from Morocco and Florida, respectively ($p < 0.0001$). As previously reported by Dhuique-Mayer et al. (2009), temperate climates amplified the carotenogenesis, especially by increasing the provitamin A carotenoid content. Mouly et al. (1999) also observed that the oranges grown in Mediterranean regions had a higher provitamin A carotenoid content, compared to those grown in tropical and subtropical regions. Alternations of elevated daytime and cool night temperatures in Corsica and Spain favor carotenoid synthesis compared to the low temperature difference between Morocco and Florida. The variability of hesperidin seemed to be explained less by the geographical origin since the concentrations ranged from 828 ± 66[a] to 691 ± 47[a] mg/L for Corsica, Spain, and Florida, which are similar. Moroccan oranges presented a lower content with 485 ± 34[b] mg/L ($p < 0.002$).

The geographical origins were also less discriminant for clementine juices by PCA (Figure 2). However, clementine juices from Spain and Corsica formed a differentiated group associated with a higher content of carotenoids (for *β*-cryptoxanthin: 11.4 mg/L[a]), while clementine juices from Florida and Morocco (as well as orange juices) were lower in carotenoid (*β*-cryptoxanthin 6.80 mg/L[b]) and hesperidin (691 mg/L[a] *vs* 292 mg/L[b]).

The similar trends observed for orange and clementine were not surprising knowing that clementine is the hybrid of orange and mandarin. Finally, the third PCA for pink grapefruits revealed three different groups according to their geographical origin: Florida, Corsica, or Spain/Morocco. The tropical climate of Florida seemed to increase lycopene content, boosting the red color of its flesh (average lycopene content: 19.2 mg/L[a] vs. 11.7[b], 9.3[b], and 7.8[c] mg/L, respectively, for Florida, Corsica, Spain, and Morocco). The higher the content of lycopene in the pink grapefruit juices from Florida, the lower the naringin content (332 mg/L vs. 1050 mg/L on average for Mediterranean origin). The opposite was true for the red grapefruit juices of Mediterranean origin such as Spain and Morocco, Corsica having an extremely specific climate in the Mediterranean area for the growing of citrus. The level of *β*-carotene concentration was similar for Corsica, Florida, and Morocco (4.6 mg/L on average) grapefruit juices, the highest being for Spanish fruit juices (7.06 mg/L) (Supporting Information).

To conclude this part of the study, a three-dimensional (3D) diagram based on three nutritional qualities was created, as shown in Figure 3. As each axis is linked to a specific bioactivity, the lycopene content was associated with a higher antioxidant biological activity, the flavonoid concentration with better anti-inflammatory activity, and vitamin A was represented by the retinol activity equivalent (RAE). As shown in the (3D) representation, it was easier to differentiate the grapefruit and clementine juices according to their geographical origin than the orange group which was more centered. Globally, if clementine from Spain and Corsica represented the best source of provitamin A, Florida grapefruits were richer in lycopene than the fruit from the Mediterranean region and could be associated with greater antioxidant activity in the organism. On the other hand, the lower content of lycopene in Spanish pink grapefruit juice was compensated by a higher

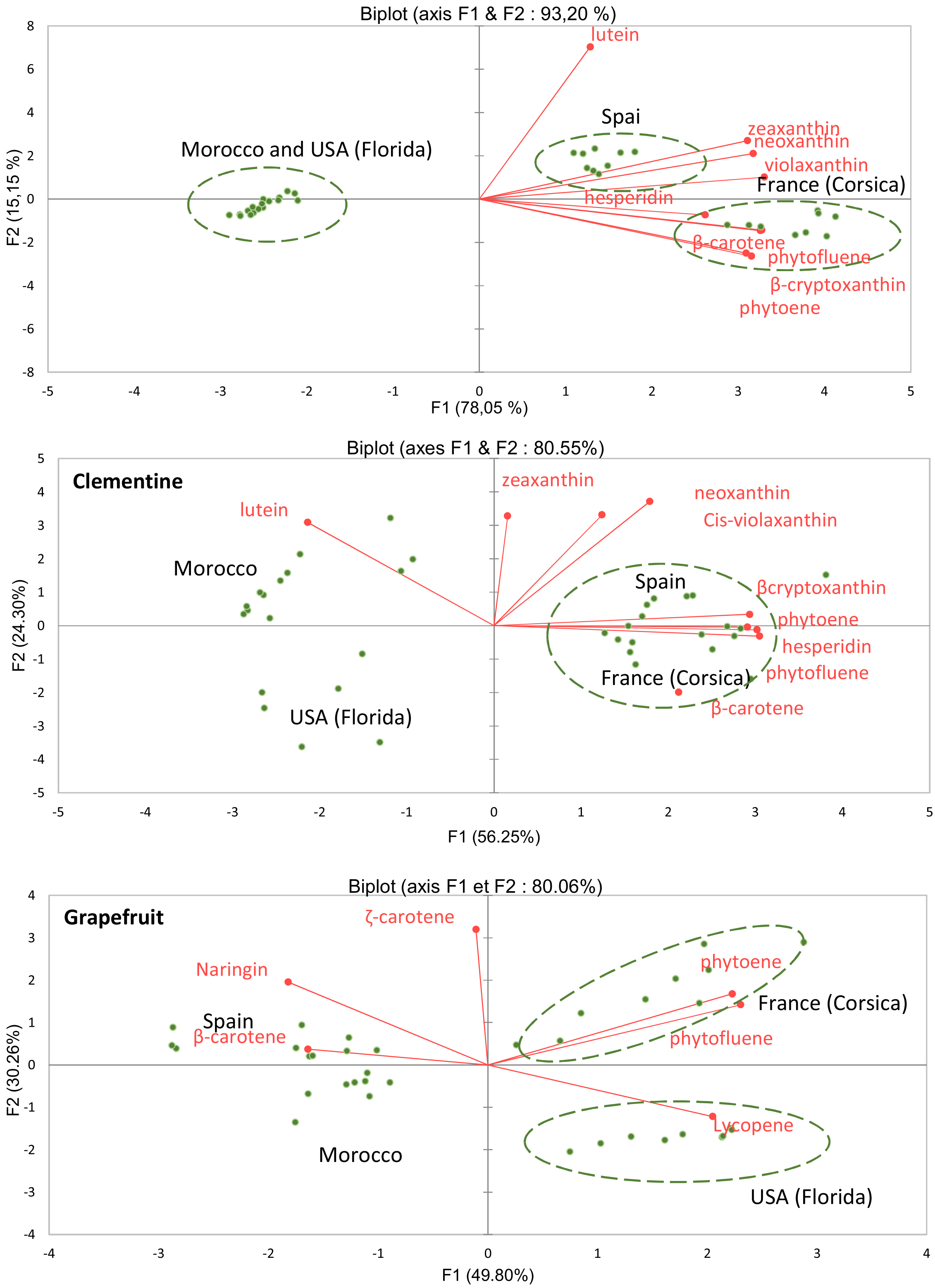

FIGURE 2 Principal component analysis (PCA) analysis of carotenoid and flavanone glycoside content of orange, clementine, and grapefruit from four geographical origins (Spain, Morocco, France—Corsica and USA—Florida).

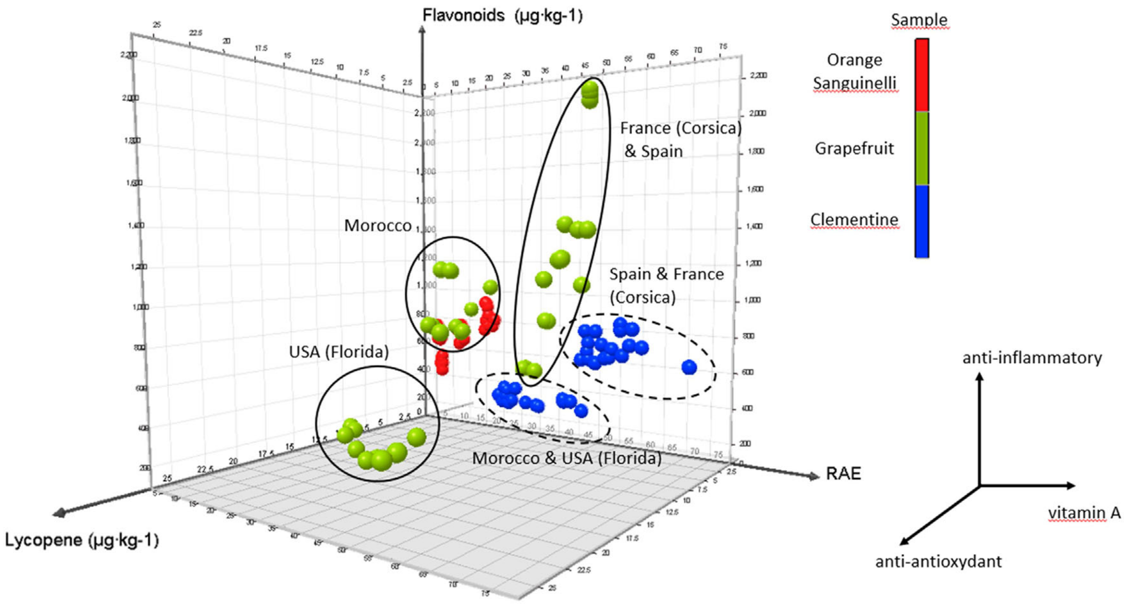

FIGURE 3 3D diagram based on the content of flavonoids, lycopene, and the retinol activity equivalent of orange, pink grapefruit, and clementine. Circle in dotted line: clementine group; circle in solid line: grapefruit group.

flavonoid content representing a higher anti-inflammatory effect. Finally, in relation to the micronutrients, orange juices have a central position on the graph, intermediate between the three nutritional axes. Each *Citrus* species associated with a geographical origin may have a different nutritional specificity.

However, even if these results might suggest that geographical origin is of interest to consider the potential health benefits of *Citru*, the main point is to know if the levels of bioactive compounds strongly determine health effects. To better understand this link, an extended review of the bibliography on health effects of *Citrus* consumption was realized.

4 | HEALTH EFFECTS OF CITRUS CONSUMPTION INVOLVED IN THE PREVENTION OF METABOLIC SYNDROME

The aim of this section is to review the health effects of the mainly consumed citrus juices especially those attributed to citrus flavonoids and carotenoids in the prevention of MetS. MetS is currently defined as a cluster of cardiometabolic abnormalities related to abdominal obesity, hypertension, hyperglycemia, and dyslipidemia, all risk factors for developing type 2 diabetes, cardiovascular diseases, or obesity (Rochlani et al., 2017). According to FAO (2023), by 2025, half of the world's population will be overweight, and there is growing interest in modifying lifestyle and dietary factors. The role of citrus flavonoids, carotenoids, as well as dietary fibers as intermediary biomarkers of a healthy diet is of particular interest in preventing metabolism disorders associated with MetS (Beydoun et al., 2018; Lu et al., 2023; Yari et al., 2020). Among bioactive flavonoids, flavanone glycosides are the dominating compounds but polymethoxylated flavones (PMFs), including nobiletin and tangeretin, could contribute with health-promoting functions such as anti-inflammatory, anti-diabetic, or anti-atherosclerotic to the global health effects (Toledo et al., 2024). However, PMFs are distributed mainly in the peels and their amount is much less in the pulp or juice. Thus, hesperidin and naringin, the most predominant flavanone glycosides from the orange/mandarin and grapefruit group, respectively, exhibit a plethora of biological properties widely studied in vitro and in animal models (antioxidant, anti-inflammatory, anti-hyperglycemic, anti-hypercholesterolemic, and anti-adipogenic effects, etc.) (Karim et al., 2022; Zhao et al., 2020). Likewise, eriocitrin from lemon is a flavanone well distributed, especially in peels and juice, and exhibits a range of beneficial biological activities, including antidiabetic and anti-inflammatory activities. Eriocitrin's potential effects in managing conditions like diabetes mellitus and other chronic diseases linked to oxidative stress make it a significant compound of interest in nutrition and health research (Yao et al., 2022). Moreover, following dietary intervention in mice, eriocitrin improved the beta diversity of the gut microbiota and increased the production of short-chain fatty acid demonstrating that some intestinal bacteria may be involved in the metabolism of eriocitrin

(Meng et al., 2022). Evidence from these data obtained from in vitro or animal studies supports the fact that hesperidin and naringin or eriocitrin play a role in the management of MetS and the main associated dysfunctions such as oxidative stress and inflammation. However, data from human clinical studies were less conclusive (Pla-Paga et al., 2019). Moreover, the low bioavailability of these flavanone glycosides, added to the inter-individual variation, can affect the physiological responses of flavonoids in humans (Visvanathan & Williamson, 2023). Hesperidin and naringin are rutinosides, which are not directly absorbed in the small intestine but hydrolyzed and metabolized by colonic microflora making them strongly dependent on gut microbiota. Unlike citrus flavonoids, citrus carotenoid bioavailability is unlimited and among all the carotenoids available in Citrus, six of them were found in human blood (α and β-carotene, lycopene, β-cryptoxanthin, lutein, and zeaxanthin) as well as the two precursors phytoene and phytofluene (Melendez-Martinez et al., 2013; Olmedilla-Alonso et al., 2021). Briefly, carotenoids are absorbed by intestinal cells and incorporated into chylomicron to enter the bloodstream via the lymph (Karn et al., 2021). Some of them are provitamin A, such as α, β-carotene, and β-cryptoxanthin, which undergo bioconversion into retinol after intestinal absorption (Nishino et al., 2022). Among the citrus carotenoids, the bioavailability of β-cryptoxanthin is higher than the others (Burri et al., 2016). Due to the frequency intake of satsuma mandarin in Japan, the bioavailability and health effects of β-cryptoxanthin have been extensively studied in this country (Nakamura & Sugiura, 2019; M. Nakamura et al., 2017; Sugiura, 2015, 2002, 2015; Takagi et al., 2020). β-cryptoxanthin is a dietary carotenoid that strongly contributes to the beneficial health effects of Citrus fruits against MetS (Karn et al., 2021). Lycopene, a non-provitamin A carotenoid found in high content in pink grapefruits, has attracted attention as a potent antioxidant. Lycopene plays a role in oxidative stress implied in cardiovascular diseases, autoimmune disorders, or diabetes (Neyestani et al., 2008). Other minor citrus bioactive compounds constituting essential oil rich in terpenes (e.g., D-limonene), limonoids (limonin), and localized mainly in the peel can work synergistically with the major enhancing health effects of citrus juices to fight against MetS (Saini et al., 2022).

4.1 | Clinical studies conducted with citrus juice consumption

Some chosen examples of clinical studies with consumption of orange, mandarin, grapefruit, and lemon were reported in Table 4. On average, one or two glasses (250–500 mL) of orange juice consumed daily over a period of 2–3 months improves glucose levels, lipid profile, and microbiota in obese patients, patients presenting MetS symptoms, or healthy participants (Fidelix et al., 2020; Lima et al., 2019; Ponce et al., 2019; Ribeiro et al., 2017; Simpson et al., 2016).

Media often claim that consumption of pure orange juice adversely affects body weight, insulin sensitivity, and blood lipid profile. However, several recent studies have not observed these detrimental consequences but rather improvement of these parameters. Thus, orange juice consumption, associated with a balanced diet, mitigated risk factors of MetS (Ponce et al., 2019; Ribeiro et al., 2017; Simpson et al., 2016). Besides the improvement of blood biochemical parameters, such as lipid profile, glycemia, and insulin sensitivity after orange juice consumption. Fidelix et al. (2020) reported that consumption of orange juice positively modulated microbiota and increased short-chain fatty acids (SCFA). These beneficial metabolites are involved in the epithelial intestinal barrier functions and promote healthy microbiota (Wang et al., 2021). Citrus pectin, but also hesperidin and naringin, have prebiotic properties which can modulate microbiota while improving glucose and lipid homeostasis (Fidelix et al., 2020). Citrus dietary fibers as pectin also have prebiotic properties and the SCFAs produced by pectin degradation can modulate glucose homeostasis and regulate lipid metabolism by controlling the glycemic level, reducing lipogenesis and cholesterol synthesis (Peredo-Lovillo et al., 2020). Hesperidin can act as prebiotics, promoting the growth of beneficial bacteria in the gut and contributing to the crosstalk between gut microbiota and intestinal immune tissues (Estruel-Amades et al., 2019). These last findings underlined the importance of gut microbiota in the metabolization of the citrus bioactive compounds knowing that the in vivo biotransformation leads to improved bioactivities in the body participating to health-promoting effects (Karn et al., 2021).

A more limited number of intervention studies have reported the effect of consumption of mandarin juice on cardiovascular risk in humans. High serum of β-cryptoxanthin was associated with improving MetS disorders or maintaining vitamin A status in three out of four studies (Masako Iwamoto et al., 2012; Nakamura et al., 2017; Turner et al., 2013). Nakamura et al. (2017) specified that 4 mg of β-cryptoxanthin, obtained from mandarin juice, administrated for 12 weeks, was sufficient for reducing cardiovascular risk, but that an additional supplementation of β-cryptoxanthin did not enhance this effect. Likewise, Iwamoto et al. (2012) proved that 4 mg of β-cryptoxanthin from mandarin juice consumed daily for 3 weeks was sufficient to have a beneficial effect on the serum adipocytokine status and alleviated progression

TABLE 4 Characteristics of interventional human studies with citrus juice consumption on biomarkers of MetS.

Citrus species	Diet/intake	Clinical studies	Results	References
Orange juices	500 mL/day 12 weeks	78 obese participants	+Obesity/biomarkers (Insulin; lipid)	(Ribeiro et al., 2017)
FCOJ Hes:135.4 mg	250 mL/day 12 weeks	36 obese participants	+MetS-TG	(Simpson et al., 2016)
OJ Hes: 72.9 mg	300 mL/day 2 months	10 healthy women	+Cholesterol, insulinemia Gut microbiota Increased SCFA	(A. C. D. Lima et al., 2019)
OJ Pera Brazil Hes: 121.6 mg	300 mL/day 2 months	10 healthy women	+Lipid sugar metabolism Gut microbiota	(Fidelix et al., 2020)
–	500 mL/day 12 weeks	84 men/women MetS (40-60y)	Metabolic syndrome mitigated by OJ	(Ponce et al., 2019)
FOJ Hes : 345 mg	500 mL/day 12weeks	129 participants	+BP, PP	(Valls et al., 2021)
Mandarin juices Bcx: 4 mg	Mandarin juice 125 mL/day 12 weeks	118 healthy men and women	+Cardiovascular risk Reduction oxidative stress biomarkers	(M. Nakamura et al., 2017)
Bcx: 5.3 mg	Tangerine juice 127 g/day 6day/week and 3 weeks	136 lactating women with low vit A status	+ Vit A status	(Tami Turner & Burri, 2013)
–	Clementina juice 550 mL/day 4 weeks	40 obese children	+Oxidant biomarkers MDA, GSH	(Codoner-Franch et al., 2010)
Bcx: 4 mg	Mandarin juice 200 Ml/day 3 weeks	17 obese women	+MetS Adipocytokine status	(M. Iwamoto et al., 2012)
Grapefruit juices Nar: 213 mg	Grapefruit juice 340 mL/day 6 months	48 healthy post-menopausal women	+Reducing pulse wave velocity, thus arterial stiffness	(Habauzit et al., 2015)
	1 serving/day Juice or fruit	12,789 men and women	+Reduce BW, BMI, TG, HDL-C, CRP	(Murphy et al., 2014)
Rio Star Texas	1.5 grapefruit/day 6 weeks	69 overweight men and women	+Improvement in SBP and WC	(Dow et al., 2012)
Nar: 39.6 mg	127 g grapefruit /day 12 weeks	85 obese adults	+Increase HDL-C GF and GFJ	(Silver et al., 2011)
Lemon juices	140 g lemon juice/day 11 days	84 women 20–50 years overweight	+Lemon detox diet Inflammation Reduce hs-CRP	(Kim et al., 2015)
	1 juice/day 5 months	101 women	+SBP	(Kato et al., 2014)
	125 mL/day Dilutedx2	18 healthy participants	+Glycemic response GI	(Freitas et al., 2021)

Abbreviations: Bcx, β-cryptoxanthin; BM, body mass index; BW, body weight; FCOJ, FOJ, OJ, fresh (concentrate) orange juice; GI, glycemic index; GFJ, grapefruit juice; GSH, gluthatione; Hes, hesperidin; hs-CRP, high sensitive C reactive protein; MetS, metabolic syndrome; MDA, malonaldehyde; Nar, naringin; SBP, systolic blood pressure; SCFA, short chain fatty acid; TG, triglyceride; WC, waist circumference.

of MetS in obese women. Finally, T. Turner et al. (2013) showed that the daily consumption of tangerine juice with around 5 mg of β-cryptoxanthin for 18 days helped to maintain vitamin A status in breastfeeding Bangladeshi women. Another study provided new insight into changes in oxidative stress biomarkers following consumption of two glasses of clementine juice per day for 4 weeks in obese children (Codoner-Franch et al., 2010). These health effects observed in this last study were attributed to the balance of bioactive antioxidant compounds in citrus juice.

The effects of grapefruit juice consumption on body weight and cardiovascular risk were more moderate than those for orange or mandarin may be due to the fact that there are less randomized clinical trials available. However, the common point of these studies is that they agree that the risk of being obese was not associated with grapefruit consumption. A cross-sectional study in women showed that grapefruit consumption reduced waist circumference, body mass index (BMI), triglycerides, and C reactive protein (CRP), and increased high density lipoprotein (HDL) cholesterol (Murphy et al., 2014). The authors attributed these effects to the bioactive compounds (carotenoids, vitamin C, and potassium). The other studies observed an improvement in arterial stiffness as well as a reduction in waist circumference, systolic blood pressure, or increased serum HDL cholesterol levels (Dow et al., 2012; Habauzit et al., 2015; Murphy et al., 2014; Silver et al., 2011).

Clinical studies on health effects of lemon juice consumption are scarcer since this acidic drink was generally less accepted than other fruit juices. However, two studies reported a reduction of blood pressure and inflammation biomarkers in women often associated with a low-calorie diet and exercise (Kato et al., 2014; Kim et al., 2015). The effects were attributed to a higher mineral intake from lemon juice and its citric acid content. Citric acid of citrus promotes the absorption of calcium and magnesium and in doing so participates in maintaining normal blood pressure. The last randomized crossover study showed that lemon juice consumption reduces the glycemic response after bread consumption in healthy volunteers (Freitas et al., 2021). The underlying mechanism proposed was the key role of this low-pH drink as a strategy to reduce postprandial glycemic response of starchy food.

4.2 | Clinical studies with supplementation of citrus flavonoids or carotenoids

The health effects of isolated compound consumption in supplementation human studies to prevent MetS disorders are reported in Table 5. Conversely to intervention studies with consumption of real food, several supplementation interventions with hesperidin failed to confirm any health benefits, especially in lipid profile or cardiovascular parameters such as blood pressure. This observation was previously reported in a systematic review and meta-analysis (Mohammadi et al., 2019). In addition, the insulin level or fasting blood glucose (FBG) is a subject of controversy among studies. A systematic review and meta-analysis on cardiovascular effects revealed that a hesperidin supplementation of around 1000 mg/day during more than 8 weeks was needed to decrease FBG and insulin levels (Khorasanian et al., 2023). Another meta-analysis study on the anti-inflammatory and antioxidant effect of hesperidin concluded that the contribution, more dominant in anti-inflammatory than antioxidant properties, was independent of dosage (Buzdagli et al., 2023).

Interestingly, the intervention studies with orange juice gave better outcomes on glucose and lipid metabolism than the intervention supplementation studies with hesperidin, whereas hesperidin content from orange juice was lower (73–345 mg/d vs. 292–1000 mg/day). Likewise, this was the same trend for intervention studies with grapefruit juices versus supplementation in naringin (40–219 vs. 200–500 mg/day). The health benefits of orange juice can be attributed to its diverse array of bioactive compounds. While hesperidin is indeed the dominant flavonoid, the synergistic effects of other components—such as PMFs, limonoids, carotenoids, vitamin C, vitamin B9 (folate), minerals, and dietary fiber—enhance its overall health benefits observed in clinical studies following dietary intake of orange juice. The combination of these citrus bioactive compounds provides antioxidant effects, supports immune function, improves cardiovascular health, and may even play roles in reducing inflammation and supporting metabolic health (Borghi & Pavanelli, 2023). Clinical studies that focus on the whole food, like orange juice, often reveal a broader range of benefits than studies targeting individual compounds, highlighting the importance of dietary diversity. Together these bioactive compounds from orange whole fruit or juices can have significant effects, particularly when consumed regularly contributing to various health benefits.

The effect of carotenoid supplementation in available human trials were above all reported on lycopene because of the numerous studies on tomato. The dose used in the cited studies of Table 5 went from 7 to 30 mg of lycopene and was sometimes associated with lipids to obtain more bioavailable formulations. Two studies with different daily doses and durations (7 mg for 8 weeks and 10 mg for 12 weeks) did not improve blood pressure, lipid profile, insulin sensitivity, or inflammatory biomarkers except for endothelial function in one of the studies (Gajendragadkar et al., 2014; Thies et al., 2012). These results supported a more recent meta-analysis on lycopene and cardiovascular risk factors (Cheng et al., 2017). This last review highlighted the greater effect of lycopene from dietary intake (tomato-based products) versus supplementation in lipid inflammatory or oxidative biomarkers. Conversely, Neyestani et al. (2008) and Wiese et al. (2019) showed that administration of lycopene resulted in a reduction of inflammation, oxidative damage, and lipid-lowering effects. Note that in the publication of Wiese et al. (2019), lycopene was provided using a formulation with lipids (medium saturated or polyunsaturated fatty acids). Other carotenoids (lutein and β-carotene) as well as bioactive compounds (polyphenols and vitamins C and E) coexist in tomato and tomato products. According to Shah et al. (2021), the consumption of tomato, thanks to their array of bioactive compounds,

TABLE 5 Characteristics of interventional human studies with supplementation of citrus bioactive compounds on biomarkers of metabolic syndrome (MetS).

Citrus bioactive compounds	Dose supplementation	Clinical studies	Results	References
Hesperidin	1000 mg/day 12 weeks	49 SMet participants	(+) FBG, TG, SBP, TnFα (−) Crp, iNs, G, C-HDL, C-LDL	(Yari et al., 2020)
	292 mg/day 4 weeks	24 overweight participants	(+) DBP (-) CVD factors	(Morand et al., 2011)
	500 mg/day 6 weeks	60 diabetics patients	(+) BP IL6-CRP	(Homayouni et al., 2018)
	500 mg/day 8 weeks	45 diabetic patients—T2D	(+) FBG, HbA1c, TC (-) CRP, IL6	(Eghtesadi et al., 2016)
	500 mg/day 3 weeks	24 metabolic syndrome patients	(+) hsCRP, SAA, S-E selectin (-) SBP, DBP	(Rizza et al., 2011)
Naringin	450 mg/day 12 weeks	28 obese patients	(+) BMI, TC, LDL Adinopectin	(Barajas-Vega et al., 2020)
	500 mg/day 4 weeks	204 healthy participants	(-) TC, LDL	(Demonty et al., 2010)
	200 mg/day 4 weeks	44 obese patients	(+) TC HDL, LDL BMI, SBP	(Naeini et al., 2021)
Lycopene	7 mg/day 8 weeks	36 patients (CVD) and 36 healthy participants	(+) endothelial function only in CVD patients	(Gajendragadkar et al., 2014)
	10 mg/day 8 weeks	35 T2M patients	(+) TAC/MDA IgM Ox-LDL	(Neyestani et al., 2008)
	7 or 30 mg formulations 4 weeks	30 moderately obese patients	(+) IOD, LDL LDL-Px Prebiotic effect Gut microbiome	(Wiese et al., 2019)
	10 mg/day 12 weeks	225 overweight volunteers	(-) CVD markers Inflammatory Lipid profile insulin sensitivity	(Thies et al., 2012)

Note: Inflammatory biomarkers: TnFα; CRP, IL6; hsCRP, SAA, SE-Selectin.
Abbreviations: BMI, body mass index; BP, blood pressure; C-HDL, cholesterol-high density lipoprotein; C-LDL, cholesterol-low density lipoprotein; CVD, cardiovascular disease; iNs, insulin sensitivity; DBP, diastolic blood pressure; IOD, inflammatory oxidative damage; FBG, fast blood glucose; HbA1c, hemoglobin glycated; IgM, immunoglobulin M; LDL-Px, low density lipoprotein -peroxidase; MDA, malonaldehyde; SBP, systolic blood pressure; TAC, total antioxidant; TC, total cholesterol; TG, triglyceride; Ox-LDL, oxidase LDL.

is able to prevent cardiovascular diseases, atherosclerosis, and hypertension (Shah et al., 2021). The results of the study of Tsitsimpikou et al. (2014) provide some evidence for the beneficial effect of tomato juice on reducing cardiovascular risk factors, ameliorating endothelial dysfunction in patients with MetS, and improving glycemic control by decreasing insulin resistance in patients with MetS (Tsitsimpikou et al., 2014). All these results underline that supplementation of an isolated compound was not able to fully replace the health benefit of citrus consumption

5 | CONCLUDING REMARKS AND PERSPECTIVES

Together the analysis of data from clinical trials on citrus juice and on supplementation of flavanone glycoside or carotenoid help to answer the question of whether or not the content of bioactive compounds from citrus juices was a determinant for health effects. Indeed, even the data highlight the importance of geographical origin in accumulation of carotenoids or flavonoids, the difference in contents has fewer consequences than the fact of consuming or not citrus fruits. Even if the Mediterranean conditions amplify pro-vitamin A carotenoid levels in orange, the same juice from tropical/subtropical climates exhibited other bioactive compounds participating in health effects. For example, data extracted from our study indicate that if two glasses of Sanguinelli orange juice from Florida provide only 3% of RDA in vitamin A, the hesperidin content (345 mg) compensates for the potential health benefit. What is more, the juices from Florida used in clinical studies displayed a range of 73–345 mg of hesperidin/day, sufficient to improve MetS biomarkers. The lower level of lycopene in the Moroccan grapefruits compared to that of grapefruits from Florida (10 mg vs. 4 mg for two glasses of juice) was rebalanced by its naringin content (473 mg). Moreover, in addition to the level of bioactive compounds in citrus juice, the effect of citrus consumption on human metabolism is complex, which involves the high inter-individual variation in bioactive compound bioavailability as well as changes in gut microbiota specific to each individual. Indeed, it is important to underline the key role of gut microbiota in the in vivo biotransformation of the citrus bioactive compounds to contribute to overall gut health and metabolic function specific to each individual. These compounds, including flavonoids, dietary fibers, and carotenoids, can act as prebiotics, promoting the growth of beneficial bacteria in the gut preventing conditions like obesity, diabetes, and MetS disorders.

Evidence is building suggesting that whole citrus fruits or juices used in clinical trials offer health benefits beyond what can be obtained from individual compounds found in supplementation trials. The amount of citrus juice needed to provide health benefits is often within reasonable limits for most people. Research suggests that moderate consumption of citrus juice can contribute to overall health without leading to excessive calorie or sugar intake. Moreover, some compounds such as carotenoids from juice were more bioavailable than those of fruit.

Initially well-known for being rich in vitamin C, the citrus health effect actually results in a synergistic action of numerous phytochemicals whose targeted health benefits vary depending more on the diversity of species than the geographic origin. Therefore, the use of the diversity of *Citrus* species to provide functional food could be an interesting approach. Although a moderate amount of citrus juice as part of a healthy diet and lifestyle can be recommended, the development of functional citrus-based food could be an alternative to the disadvantage of citrus juice consumption. Indeed, juices have disadvantages such as sugar content, acidity, and lack of fiber compared to whole fruits. Processing can provide citrus-based food enriched in bioactive compounds in order to compensate for the differences found in the diversity of citrus species (di Corcia et al., 2022; Hammad et al., 2021). The development of citrus-based functional foods could be a promising way to prevent MetS and associated T2D (Dhuique-Mayer et al., 2020). Overall, investing in citrus research and development can play a significant role in enhancing food security and improving public health, especially in South countries where malnutrition is a public health problem. On the other hand, by increasing research development on lesser known citrus varieties, which often have unique nutritional profiles, can attract consumer interest and diversify diets. This could help address nutritional gaps in regions with limited access to traditional fruits.

Although in vivo transformation mechanisms are gradually becoming better understood, further randomized clinical trials in humans are needed to better explore the diversity of citrus species grown all over the world.

AUTHOR CONTRIBUTIONS

Claudie Dhuique-Mayer: Conceptualization; methodology; investigation; funding acquisition; writing—original draft; validation; project administration; supervision; data curation; visualization; writing—review and editing; resources; formal analysis. **Adrient Servent**: Investigation; writing—original draft; writing—review & editing; conceptualization; visualization; data curation; validation.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Claudie Dhuique-Mayer https://orcid.org/0000-0001-7153-2897
Adrient Servent https://orcid.org/0000-0002-9670-6707

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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