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ORIGINAL PAPER

In Vitro Intestinal Bioaccessibility and Colonic Biotransformation of Polyphenols from Mini Bell Peppers (*Capsicum annuum* L.)

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Abstract

To the best of our knowledge, "sweet mini bell" peppers have not been extensively investigated. In this study, we evaluated the bioaccessible phenolic compounds released during intestinal digestion and identified and quantified the microbial metabolites derived from phenolic compounds bioconversion during the *in vitro* colonic fermentation. A total of 66 phenolic compounds were determined. The results obtained in this study indicate that hydroxycinnamic acids (22 to 32 mg/100 g dw) and flavonoids (99 to 102 mg/100 g dw) headed by quercetin, luteolin and kaempferol glycosidic derivatives were the main bioaccessible phenolic compounds during *in vitro* intestinal digestion of mini bell peppers. The yellow variety contained the highest concentration of bioaccessible flavonoids (80 mg/100 g dw). For the first time in mini bell peppers, dihydroferulic acid was detected, in the three varieties studied. 3-(4-hydroxyphenyl)propionic acid was the major metabolite found after 12–24 h fermentation of all samples (44 to 102 μM/L). Further cell culture or *in vivo* studies are needed to elucidate the biological activities of the phenolic compounds identified in mini bell peppers.

Keywords Gut microbiota · Mini bell pepper · Phenolic compounds

Introduction

Bell pepper (*Capsicum annuum* L.) is a plant of the genus *Capsicum* that includes approximately 25 species and has its origin in the tropical and subtropical regions of America [1]. Bell peppers are an important crop cultivated around the world. To the best of our knowledge, among the multiple bell peppers varieties, those known as "sweet mini bell" pepper, which occur in different colors (*e.g.*, yellow, orange and red) have not been investigated according to their functional features. In particular, the metabolic transformation of the phenolic compounds (PC) of these peppers during human digestion is a key to the advancement of research about health-beneficial effects attributed dietary PC [2].

PC must be released from the food matrix during the intestinal digestion (bioaccessibility) becoming potentially absorbable into the blood stream [2]. Also, PC associated with the indigestible fraction (IF) may reach the colon, where they can be bioconverted by the microbiota to metabolites with increased absorbability. Overall, gut microbiota-related metabolic processes can modulate the effects of the PC on health, since they modify the PC absorption, bioavailability and biological activity [2].

As previously mentioned, there is no report on the release of colored sweet mini bell peppers PC during intestinal digestion, their bioconversion. Keeping this in view, this work aimed at 1) to evaluate the bioaccessible phenolic compounds released during intestinal digestion and 2) to identify and quantify the microbial metabolites derived from phenolic compounds bioconversion during the *in vitro* colonic fermentation of the indigestible fractions isolated from sweet mini bell peppers (orange, red and yellow).

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Materials and Methods

The material and methods section is presented as Supplementary Material.

Results and Discussion

Potential Bioavailable Phenolic Compounds Released During *In Vitro* Intestinal Digestion of Sweet Mini Bell Peppers

Retention time (R_T), molecular formula, and accurate mass of the quasimolecular ion [M-H]- after negative ionization of the proposed phenolic compounds (PC) and microbial metabolites identified in orange, red, and yellow mini bell peppers are shown in Supplementary Material 1. Sixty-six compounds were identified after *in vitro* intestinal digestion and those associated with the indigestible fraction. The *in vitro* colonic fermentation proceeded along with the microbial metabolites derived from PC bioconversion. Besides comparing R_T of accurate mass measurements with analytical standards, tentative identification was generated considering the literature data. Concerning flavonoids, glycosidic derivatives of flavonoids headed this group with eight glycosidic derivatives of quercetin (ID: 24, 25, 32, 39, 40, 43, 48 and 49), six glycosidic derivatives of luteolin (ID: 23, 28, 29, 34, 37, 51), two glycosidic derivatives of quercetin or luteolin (ID: 57 and 58) and eight glycosidic derivatives of kaempferol (ID: 33, 38, 41, 42, 50, 54, 56 and 60) (see Supplementary Material 1). Thus, in this work, the profile of bioaccessible phenolic compounds after *in vitro* intestinal digestion, the phenolic compounds available for the gut microbiota and their microbial-metabolites produced during *in vitro* colonic fermentation of orange, red and yellow mini bell pepper, are reported for the first time.

Twenty-six of the proposed PC have been reported previously in bell pepper ((see Supplementary Material 1) (ID: 5, 8, 10, 13, 15, 20, 21, 23, 24, 25, 26, 29, 31, 34, 35, 36, 37, 40, 43, 44, 45, 47, 49, 52, 57 and 58) [3, 4]. Sixteen of the other proposed PC (see Supplementary Material 1) (ID: 1, 3, 4, 6, 7, 9, 12, 14, 16, 18, 19, 22, 27, 28, 38 and 42), were detected in other Solanaceae species, mainly in tomato and various pepper [5–7]. The six microbial metabolites detected in our study (see Supplementary Material 1) (ID: 61–66), have also been identified during colonic fermentation of different pepper varieties [5, 7, 8]. On the other hand, the biological activity of PC is partly determined by its stability and release during the intestinal digestion [9]. It is worth mentioning that there is no relation between the content of PC in a food and their bioaccessibility during human intestinal digestion [10]. Thereby, identifying and quantifying the PC that might be available for absorption in the intestine or later bioconversion in the colon is the first step to evaluating the real/final health effects that PC intake may exert [9].

Thirty-nine phenolic compounds were identified as bioaccessible in orange, red and yellow mini bell pepper (Table 1). PC in colored mini bell peppers mainly belong to two chemical groups: hydroxycinnamic acids and derivatives and flavonoids. Most studies concerning non-pungent pepper varieties have described the PC and carotenoids profile of bell pepper but those of mini bell peppers have not been investigated.

Concerning hydroxycinnamic acids and derivatives group, 12 compounds were identified. They comprise about 22 to 32% of the total PC identified. Caffeoylquinic acids derivatives and ferulic acids derivatives dominated this group, while free phenolic acids (caffeic, ferulic and *p*-coumaric acid) were detected in lower amounts (Table 1). In all the studied samples, the amounts of the bioaccessible amount of proposed dihydroferulic acid (see Supplementary Material 1), was the highest of the hydroxycinnamic acids and derivatives. Dihydroferulic acid has been mainly found in cereals, where it in plant internodes but not directly in grains [11]. Although dihydroferulic acid is associated/bound with the insoluble dietary fiber portion of the plant cell wall, this compound could be released due the action of enzymes and pH changes as it was simulated during the *in vitro* gastrointestinal digestion. Nevertheless, there are no reports on the absorption of dihydroferulic acid in humans; thus, it is hypothesized that it is further metabolized by the gut microbiota [12]. In accordance to this, dihydroferulic acid was identified during the *in vitro* colonic fermentation (see Supplementary Material 3).

Flavonoids, mainly represented by quercetin, luteolin and kaempferol glycosidic derivatives, were identified in all colored mini bell peppers, accounting for 75, 68 and 78% of the total phenolic compounds quantified in orange, red and yellow mini bell pepper, respectively (Table 1). This agrees with data reported [13] who found that phenolic compounds in red bell peppers comprise flavonoids (70%) and hydroxycinnamic acids (30%) where flavonoids profile mainly consisted of luteolin and quercetin derivatives. Yellow mini bell pepper showed the highest content of total bioaccessible flavonoids. Recently, it was found that in whole yellow sweet pepper showed the highest content of total flavonoids compared to red and orange sweet pepper [14] which agrees with the results shown in Table 1. In the cited study, quercetin and luteolin aglycone were the most abundant flavonoids and the PC extracted from yellow sweet pepper exhibited the high acetylcholinesterase enzyme inhibitory activity, ranging from 57.52 to 91.69% inhibition (IC_{50}: 5.17 to 13.38 g/L).

Table 1 Phenolic compounds (PC) considered as bioaccessible released during *in vitro* intestinal digestion of orange, red and yellow sweet mini bell pepper

ID	Proposed compound as:	Orange	Red	Yellow
Hydroxycinnamic acids and derivatives				
1	1-Caffeoylquinic acid	2.14 ± 0.04^{a}	2.10 ± 0.04^{a}	2.32 ± 0.05^{b}
2	Caffeoyl dihexoside	0.92 ± 0.06^{b}	1.54 ± 0.22^{a}	1.46 ± 0.06^{a}
3	5-Caffeoylquinic acid	< LOQ	2.58 ± 0.03^{b}	2.31 ± 0.02^{a}
5	3-Caffeoylquinic acid (Chlorogenic acid)	2.98 ± 0.06^{a}	3.10 ± 0.03^{a}	2.89 ± 0.05^{a}
6	4-Caffeoylquinic acid	1.98 ± 0.09^{a}	< LOQ	2.09 ± 0.06^{a}
7	Caffeic acid	< LOD	< LOD	< LOQ
8	1-Caffeoyl-*β*-D-glucopyranoside or Caffeic acid 4-O-*β*-D-glucopyranoside (Isomer I)	< LOQ	nd	< LOQ
9	*p*-coumaric acid	< LOQ	< LOQ	< LOQ
10	Ferulic acid	0.57 ± 0.20^{a}	nd	0.62 ± 0.06^{a}
11	Dihydroferulic acid	18.52 ± 3.27^{a}	21.27 ± 1.53^{a}	10.80 ± 3.13^{b}
12	Feruloylquinic acid isomer I	nd	3.44 ± 0.13	nd
13	1-Caffeoyl-*β*-D-glucopyranoside or Caffeic acid 4-O-*β*-D-glucopyranoside (Isomer II)	< LOQ	< LOD	< LOQ
Total (mg/100 g dw)		25.48 ± 0.35^{ab} (25%)*	32.04 ± 3.08^{b} (32%)*	22.51 ± 2.97^{a} (22%)*
Phenylacetic acids and derivatives				
20	Homovanillic acid hexose I	< LOQ	< LOQ	< LOQ
Flavonoids				
23	Luteolin 6-C-*β*-D-glucopyranoside-8-C-*α*-L-arabinopyranoside or Luteolin 7-*O*-[2-(*β*-D-apiofuranosyl)-*β*-D-glucopyranoside	1.47 ± 0.05^{a}	< LOQ	1.49 ± 0.11^{a}
24	Quercetin dihexoside I	< LOD	< LOQ	< LOD
25	Quercetin dihexoside II	0.55 ± 0.13	< LOQ	< LOD
27	Apigenin acetyl hexoside	< LOQ	1.01 ± 0.10^{a}	1.09 ± 0.01^{a}
29	Dihydroxyflavone-*O*-hexoside	< LOQ	< LOQ	< LOQ
33	Kaempferol-*O*-(6″-*O*-acetyl-glycoside)	3.04 ± 0.59^{b}	4.22 ± 0.37^{c}	1.76 ± 0.31^{a}
34	Theaflavanoside	< LOQ	< LOQ	< LOQ
35	Kaempferol-3-*O*-rhamnoside or Apigenin 8-C-glucoside	< LOQ	nd	< LOQ
36	Diosmetin-7-*O*-*β*-glucoside	< LOQ	< LOQ	1.33 ± 0.10
37	Luteolin 7-*O*-(2-apiofuranosyl-4-glucopyranosyl-6-malonyl) glucopyranoside	< LOQ	< LOQ	< LOQ
38	Kaempferol diglycoside	nd	nd	< LOQ
39	Quercetin-3-vicianoside	0.56 ± 0.06^{a}	0.58 ± 0.05^{a}	0.33 ± 0.02^{b}
40	Rutin pentoside	0.89 ± 0.01^{a}	1.01 ± 0.06^{a}	0.59 ± 0.05^{b}
42	Kaempferol rutinoside pentoside	2.02 ± 0.03^{a}	1.96 ± 0.10^{a}	< LOQ
45	Quercetin	< LOD	< LOD	< LOQ
46	Quercetin-3-galactoside or Myricetin-3-*O*-rhamnoside	0.42 ± 0.01^{a}	0.32 ± 0.08^{a}	0.36 ± 0.01^{a}
48	Quercetin acetyl glycoside	0.43 ± 0.01^{b}	< LOD	0.39 ± 0.01^{a}
49	Quercetin dihexoside III	< LOD	< LOD	< LOQ
50	Dihydrokaempferol hexoside I or Eriodictyol hexoside	2.45 ± 0.39^{a}	2.04 ± 0.13^{a}	2.48 ± 0.26^{a}
51	Trihydroxy-methoxyflavone II	0.97 ± 0.09^{a}	< LOQ	1.15 ± 0.02^{a}
52	Quercetin-3-*O*-glucoside or Myricetin-3-*O*-rhamnoside	0.90 ± 0.03^{a}	0.71 ± 0.05^{b}	0.88 ± 0.02^{a}
54	Dihydrokaempferol hexoside I or Eriodictyol hexoside	23.84 ± 2.10^{a}	22.15 ± 0.95^{a}	24.90 ± 1.32^{a}
56	Kaempferol-di-acetyl-rhamnoside	4.37 ± 0.56^{b}	3.09 ± 0.17^{a}	4.24 ± 0.59^{ab}
57	Quercetin-3-rhamnopyranoside or Luteolin-8-glucoside	5.79 ± 0.38^{a}	3.65 ± 1.15^{b}	5.79 ± 0.74^{a}
58	Quercetin-3-rhamnopyranoside or Luteolin-8-glucoside	11.83 ± 0.99^{ab}	10.51 ± 0.73^{a}	12.98 ± 0.45^{b}
60	Dihydrokaempferol hexoside II	17.97 ± 2.73^{a}	16.19 ± 0.16^{a}	20.40 ± 2.13^{a}
Total (mg/100 g dw)		77.06 ± 5.44^{ab} (75%)*	67.49 ± 2.94^{a} (68%)*	80.07 ± 2.87^{b} (78%)*
Total bioaccessible PC (mg/100 g dw)		102.55 ± 5.38^{a}	99.54 ± 3.92^{a}	102.58 ± 3.24^{a}

Values represent mean ± SD ($n = 3$). Different lowercase letters in the same row indicate significant difference ($p < 0.05$). *Percentage of phenolic compounds groups quantified per sample according to their total bioaccessible PC

< LOD limit of detection, *< LOQ* below the limit of quantification

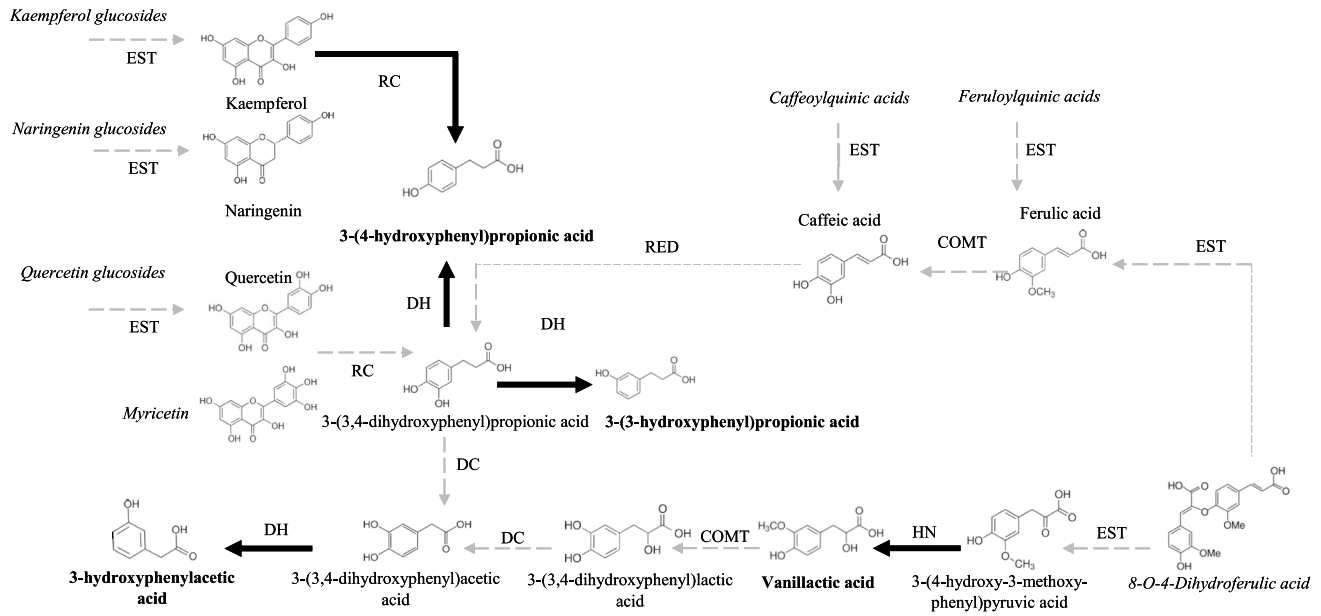

Fig. 1 Proposed metabolic bioconversion pathways of the main phenolic compounds in orange, red and yellow mini bell peppers available for the gut microbiota proposed based on data [6, 12, 15]. RC: ring cleavage. DC: decarboxylases. DH: dehydrogenases. EST: esterases. RED: reductases. COMT: Catechol-*O*-methyltransferases. HN: hydrogenases. Italic font indicated phenolic compounds found as initial substrate. Non-detected intermediates metabolites are indicated in grey arrows. Bold arrows indicate metabolites identified

This is an interesting property since the enzyme is involved in the Alzheimer´s disease [14]. As reported [4] for colored bell peppers, two possibilities were speculated for two isomeric forms corresponding to an accurate mass ([M-H]-) of 447 (see Supplementary Material 1) (ID: 57 and 58). These proposed identities of these compounds were quercetin-3-rhamnopyranoside or luteolin-8-glucoside. The three isomeric forms corresponding to an accurate mass ([M-H]-) of 449 (Supplementary Material 1) (ID: 50, 54 and 60) were the most abundant proposed flavonoids in the colored mini bell peppers.

No significant differences ($p > 0.05$) were showed in the total contents of bioaccessible phenolic compounds for orange, red and yellow mini bell pepper, which was 114.60, 109.19 and 110.66 mg/100 g dw, respectively (Table 1). Nevertheless, in terms of the number of identified compounds, yellow mini bell pepper was the richest variety, containing 36 of the potentially bioavailable compounds recorded.

Microbial Metabolites Derived from Phenolic Compounds Bioconversion by Gut Microbiota: *In Vitro* Colonic Fermentation of IF Isolated from Sweet Mini Bell Peppers

There was a remarkable decrease in total phenolic compounds available for the gut microbiota (associated to the IF) compared with those bioaccessible. In this context, the total phenolic compounds in orange, red and yellow mini bell pepper diminished 80, 95 and 70%, respectively (see Supplementary Material 2) considering the total bioaccessible phenolic compounds presented in Table 1. This indicated the possible passive diffusion absorption through the cellulose membrane during the dialysis step that followed the simulated intestinal digestion (see Supplementary Material 2).

On the other hand, only differences in the total amount of microbial metabolites were observed between all colored mini bell peppers, but no differences were shown in the profile of hydroxyphenylacetic and hydroxyphenylpropionic acids microbial metabolites (see Supplementary Material 3). Despite the low initial concentration of phenolic compounds available for the gut microbiota in all colored mini bell peppers (see Supplementary Material 2), the fermentation produced a wide range of metabolites including one hydroxylated form of phenylacetic acid, three hydroxyphenylpropionic acids and vanillin. This observation is in line with data reported [15] during the fermentation of low initial amounts of quercetin.

Gut microbiota plays a key role in the metabolism of phenolic compounds consumed, converting undigested phenolic compounds into smaller molecules through deglycosylation, C-ring cleavage, hydroxylation, decarboxylation, demethylation, dehydroxylation, hydrogenation, ester hydrolysis and methylation [16]. It is hypothesized that the release of

phenolic compounds is a complex process where during colonic fermentation, the gut microbiota (esterases action) also releases phenolic compounds that may be interacting with other components of food matrix, mainly dietary fiber [8, 12].

As shown in Fig. 1, the proposed metabolic pathway for the flavonoid's glycosides involves ester hydrolysis and C-ring cleavage of the aglycone released. However, aglycones were not identified in this work, an observation that is in line with the fact that no free hydroxycinnamic acids were detected in the fermented materials (see Supplementary Material 3). This may be explained by rapid degradation of flavonoids aglycones and free hydroxycinnamic acids, which is in agreement with previously reported results [5, 7]. In this context, several microbial metabolites are proposed as "intermediates" during the proposed metabolic pathway (Fig. 1). They may be present in low quantities at the different time points (6, 12, 24 and 48 h) evaluated in this study. Regarding final microbial metabolic products, 3-(4-hydroxyphenyl)propionic acid was identified as the main microbial metabolite produced from the colored mini bell peppers (see Supplementary Material 3). Besides, 3-(3-hydroxyphenyl) propionic acid was also identified after 12 and 24 h fermentation of all samples. According to the proposed metabolic pathway, 3-(3-hydroxyphenyl)propionic acid could be produced since the bioconversion of hydroxycinnamates or myricetin (Fig. 1).

Of note, it has been reported that two of the main microbial metabolites produced (see Supplementary Material 3), 3-(3-hydroxyphenyl)propionic acid significantly inhibited osteoclastogenesis and bone osteoclastic resorptive activity [17] and 3-(4-hydroxyphenyl)propionic acid inhibited the conversion of macrophage into foam cells through the regulation of cellular lipid metabolism and suppressing cellular oxidative stress and inflammation [18].

Conclusion

Present results indicate that hydroxycinnamates and flavonoids headed by quercetin, luteolin and kaempferol glycosidic derivatives were the main bioaccessible phenolic compounds during *in vitro* intestinal digestion of orange, red and yellow mini bell peppers. Yellow mini bell pepper contained the highest concentration of bioaccessible flavonoids. In some of the cases the identities of the compounds were proposed, but further studies investigating, for instance, fragmentation-pattern determination are required. Complementary studies on the absorption into the blood stream of the main phenolic compounds in colored mini bell peppers are needed.

The amounts of proposed dihydroferulic acid released during the *in vitro* colonic fermentation of all colored mini bell peppers were remarkable. To our knowledge, this is the first time that the presence of this hydroxycinnamate is suggested in bell peppers varieties. 3-(4-hydroxyphenyl) propionic acid was the major metabolite found after 12 and 24 h fermentation of all samples, a compound with promising cardiovascular disease-protective potential. Further cell culture or *in vivo* studies will be useful to elucidate the biological activities exerted by the phenolic compounds present in mini bell peppers.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11130-022-00948-5.

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Data Availability Authors can confirm that all relevant data included in the article and//or its supplementary information.

Declarations

Human or Animal Studies This article does not contain any studies with human or animal subjects.

Conflict of Interest The authors declare no conflict of interest.

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