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RESEARCH

# Jaboticaba (*Myrciaria cauliflora*) Fruit Extract Suppressed Aberrant Crypt Formation in 1,2-Dimetylhydrazine-Induced Rats

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## Abstract

Early intervention can significantly improve the colorectal cancer survival rate. Foods rich in phenolic compounds, such as jaboticaba (*Myrciaria cauliflora*), may prevent tumorigenesis. We investigated the effectivity of jaboticaba whole fruit ethanolic extract (FEX) in suppressing aberrant crypt foci (ACF), the earliest lesion of colorectal cancer (CRC), in 1,2-dimethylhydrazine (DMH)-induced rats and the underlying mechanisms related to the gut microbiota composition and short chain fatty acid (SCFA). This study was approved by the Institutional Animal Care and Use Committee (IACUC) of Providence University (Trial Registration Number 20180419A01, registration date: 22 December 2018). The FEX contains gallic acid and an especially high ellagic acid concentration of $54.41 \pm 1.80$ and $209.79 \pm 2.49$ mg/100 g FEX. The highest total ACF number ($150.00 \pm 43.86$) was recorded in the DMH control (D) group. After 56 days of oral FEX treatment, the total ACF number in the low FEX dosage (DL) group was significantly lower compared to the D group ($p < 0.05$). The large-sized ACF (> 5 foci), which has a higher probability of progressing to later stage, was significantly decreased in the high FEX dosage (DH) group. The 16s rDNA metagenomic sequencing of the cecal material revealed that the CRC biomarker *Lachnoclostridium* was significantly suppressed in the DH group ($p < 0.05$), whereas some SCFA-producing taxa and the cecal butyrate concentration were significantly elevated in the DL and DH groups ($p < 0.05$). This study demonstrated the potential of jaboticaba whole fruit in CRC prevention, especially in the initial stage, by shifting gut microbiota composition and improving cecal butyrate level.

**Keywords** Colorectal cancer · Gut microbiota · 16s rDNA · SCFA · Sprague-Dawley rats · Whole fruit

**Abbreviations**

| | |
|---|---|
| ACF | Aberrant crypt foci |
| ANOSIM | Analysis of similarities |
| AOM | Azoxymethane |
| CRC | Colorectal cancer |
| DMH | 1,2-dimethylhydrazine |
| FEX | Jaboticaba whole fruit extract |
| LEFse | Linear discriminant analysis effect size |
| NMDS | Nonmetric multidimensional scaling |
| PCOA | Principal coordinates analysis |
| SCFA | Short chain fatty acid |
| SD | Sprague-Dawley |

## Introduction

Colorectal cancer (CRC) is the third most diagnosed and second most lethal cancer in the world [1]. Over 150,000 new cases and 52,000 deaths are expected in 2022 in the U.S. only [2]. Detection and treatment in the early stages may notably improve the five-year survival rates (91 and 72% for local and regional stages, respectively, compared to only 15% for the distant stage) [3]. The earliest identifiable precursors of CRC are abnormal crypt foci (ACF), which occur because of genetic alterations in a normal colonic mucosa. A minor fraction of ACF may retain malignant

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**Table 1** Aberrant crypt foci in the distal colon of the animals

| Treatments | ACF number | | | Total ACF |
|---|---|---|---|---|
| | Small (2–3 foci) | Medium (4–5 foci) | Large (> 5 foci) | |
| N | 0.00 ± 0.00* | 0.00 ± 0.00* | 0.00 ± 0.00* | 0.00 ± 0.00* |
| D | 88.50 ± 22.49 | 43.00 ± 19.37 | 9.00 ± 6.98 | 150.00 ± 43.86 |
| DL | 29.50 ± 9.88 | 10.75 ± 3.95* | 1.50 ± 1.29 | 49.25 ± 26.16* |
| DM | 85.00 ± 36.72 | 22.50 ± 4.20 | 1.75 ± 1.71 | 134.50 ± 61.46 |
| DH | 44.33 ± 18.77 | 9.67 ± 7.37* | 1.00 ± 1.00* | 65.33 ± 22.50 |

*Significantly different with D group ($p<0.05$). The one−way ANOVA followed by Tukey's HSD *Post−hoc* test was used whenever required assumptions were met, otherwise Kruskal Wallis Test as non−parametric equivalent was used. ACF: aberrant crypt foci, AC: aberrant crypt

characteristics and progress into polyps and then CRC. The number and size of ACF have been used as predictive biomarkers for CRC risks in early screening [4, 5]. In animal models, the formation of human-like ACF can be easily demonstrated using the carcinogens azoxymethane (AOM) or 1,2-dimethylhydrazine (DMH) [6].

Apart from the non-modifiable risk factors such as race, hereditary mutations, sex, age, and inflammatory disease, more than 55% of CRC cases are attributed to the behavioral component [3, 7]. An antioxidant-rich diet may reduce the risk and act as a long-term chemopreventive agent [8]. Jaboticaba (*Myciaria cauliflora*) fruit, an indigenous plant of the southern and southeast subtropical regions of Brazil, has gained scientific interest worldwide since it is rich in phenolic compounds and exhibits great antioxidant potential. The fruits are spherical, 2.2–2.9 cm in diameter, with a thick dark purple peel, white sweet pulp, and one to four small seeds [9]. The peel and seed fractions of Jaboticaba fruit contain up to 2,252 ± 69 and 986 ± 47 mg/100 g dwb phenolic compounds, respectively [10]. A variety of phenolic compounds with potential anti-tumorigenic properties, namely ellagic acid, gallic acid, quercetin, rutin, and anthocyanins, were detected in the peel and seeds of jaboticaba [10–13]. The anti-cancer potential of jaboticaba has also been supported by a study using jaboticaba seed extract in an ACF model [14]. However, despite the anti-tumorigenic potential in the peel and seed, the jaboticaba fruit is usually consumed by eating the pulp only. Thus, the chemoprevention potential of a whole fruit is intriguing to observe to get a full benefit from the fruits.

A balanced gut microbiota can prevent the progression of ACF tumorigenesis by modulating the immune system, especially the inflammatory response, preventing gut microbiota dysbiosis, and strengthening the barrier functions of epithelial cells [15, 16]. The gut microbiota assists in the bio-conversion of large unabsorbed dietary phenolic compounds in the colon into simpler phenolics, which shapes the gut microbiota composition by promoting the growth of SCFA (short chain fatty acid)-producing bacteria and selectively suppressing pathogenic bacteria [15, 17].

The present study observed the effect of whole jaboticaba fruit extract on ACF in DMH-induced Sprague-Dawley (SD) rats and attempted to explain this in terms of the gut microbiota and SCFA changes.

## Materials and Methods

The 'Materials and Method' section is reported in the Supplementary Material.

## Results and Discussion

### Dietary FEX Intake Decreased Aberrant Crypt Foci Number

Prevention and early detection are the most effective strategies in the CRC management program. Thus, ACF, the earliest lesion of CRC, has been very useful as a biomarker to predict CRC risk. A large-sized ACF has higher probability to develop into CRC [4], and the number of ACF is associated with risk of advancing adenoma [18]. In this study, the ACF formation in humans was imitated in rats by using the carcinogen DMH (total 160 mg/kg BW), and FEX was given orally for a consecutive 56 days in low, medium, and high dosage (DL: 0.1 g/kg BW of FEX, DM: 0.5 g/kg BW of FEX, and DH: 1.0 g/kg BW of FEX, respectively).

All treatments did not seem to cause the animals any additional stress. Compared to the negative control (N) group, the weight gain, food intake, and organ weight of the treated groups did not differ significantly (Supplementary Information Table S1). The hematological and biochemical blood parameters of all groups did not differ with the N group as well (Supplementary Information Table S2 and Table S3). The histopathology examination showed no significant lesion in the major organs of all rats.

The ACF was successfully induced in all DMH-induced groups (100% incidence), while there was no ACF formation observed in the N group (Table 1). The ACF was distinguished from normal colonic crypt by its larger crypt size, thicker pericryptal area, and slightly raised appearance (Fig. 1). The highest total ACF number (150.00 ± 43.86) was recorded in the DMH control (D) group. The number

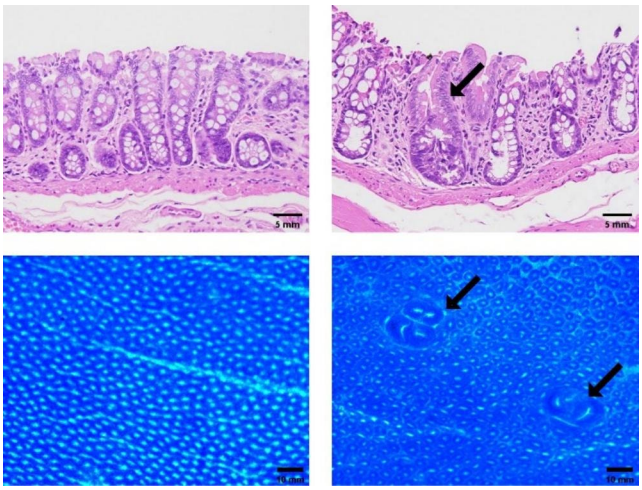

**Fig. 1** Distal colon aberrant crypt foci (black arrows). Above: longitudinal section, hematoxylin and eosin (H&E) stain. Below: methylene blue stain. Left: normal crypt. Right: aberrant crypt foci

of medium sized ACF (consisting of 4 to 5 foci) was significantly lower in the DL and DH group (10.75 ± 3.95 and 9.67 ± 7.37, respectively) compared to the D group (43.00 ± 19.37). The large (> 5 foci) ACF, which has a higher probability of progressing to later stage, was significantly decreased in only the DH group (1.00 ± 1.00, compared to 9.00 ± 6.98 in the D group), and the total ACF number was significantly lower in the DL group (49.25 ± 26.16) compared to the D group.

## Dietary FEX Intake Shifted Cecal Gut Microbiota

16s rDNA gene sequencing was used to characterize microbial profiles in the cecum, the primary site of colonic fermentation. As many as 80,490 to 99,581 high quality sequences with lengths of 153–298 bp were obtained from each sample. The rarefaction curves indicated that the sequencing depth was sufficient to cover the species richness. The treatments did not cause significant difference in the alpha diversity indexes of each group as well as beta diversity indexes among groups. However, while the weighted Unifrac distance in the principal coordinates analysis (PCOA), nonmetric multidimensional scaling (NMDS), and analysis of similarities (ANOSIM) did not significantly differ among groups, the unweighted analysis showed significantly different results (Supplementary Information Figure S1, Table S4). In unweighted PCOA, the N group and the DL group were clustered closely together, while the D, DM, and DH groups were scattered apart. The weighted and unweighted analysis answer different question; the weighted analysis takes abundance into consideration (quantitative), while the unweighted analysis only considers presence or absence (qualitative). While it seems that the DMH induction did not cause major changes on the major taxa composition, the significant unweighted analysis revealed some shifts in the rare taxa. LEFse (linear discriminant analysis effect size) analysis was useful to point out the biomarkers of each group, and could also point out some rare taxa in each group (Fig. 2). Some taxa that probably related to the CRC development were detected, such as Bifidobacteriales in the N group, and *Lachnospiraceae*_NK4A136 which scored highest in the DL group.

Based on the LEFse result, we did a manual statistical analysis especially on the SCFA- and CRC-associated microbiota to explain the ACF result. While the Bifidobacteriales was present in the small level only in the N and DL group, on the phylum level *Bacteroidetes* was significantly enriched in Jaboticaba-treated groups in a dose-dependent manner (Fig. 3). As a population, *Bacteroidetes* has multiple roles for its host, such as T-cell activation in the host immune system and limiting pathogen colonization [19]. In addition, the abundance of *Tannerelaceae* was significantly increased in the DH group compared to the D group, while *Lachnospiraceae* NK4A136 were significantly enriched in the DL group. Furthermore, the abundance of *Ruminococcus* 1, a beneficial genus especially related to butyrate production, was also significantly elevated in the DL group. *Lachnoclostridium* genus was just recently proposed as a biomarker for early detection of pre-cancerous adenoma stage of colorectal cancer [20]. This genus was increased in the D group, gradually restored by the FEX treatments, and significantly reduced in the DH group (Fig. 2).

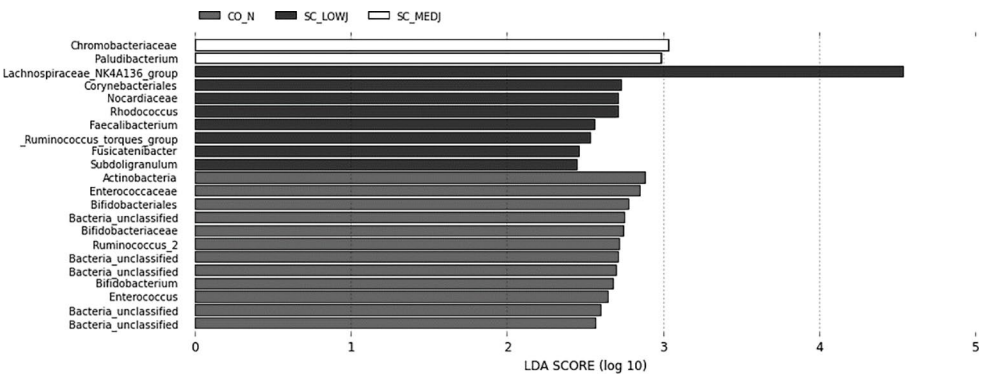


**Fig. 2** Linear discriminant analysis effect size (LEFse) analysis (*CO_N*: negative control group; *SC_LOWJ*: DL group, *SC_MEDJ*: DM group)

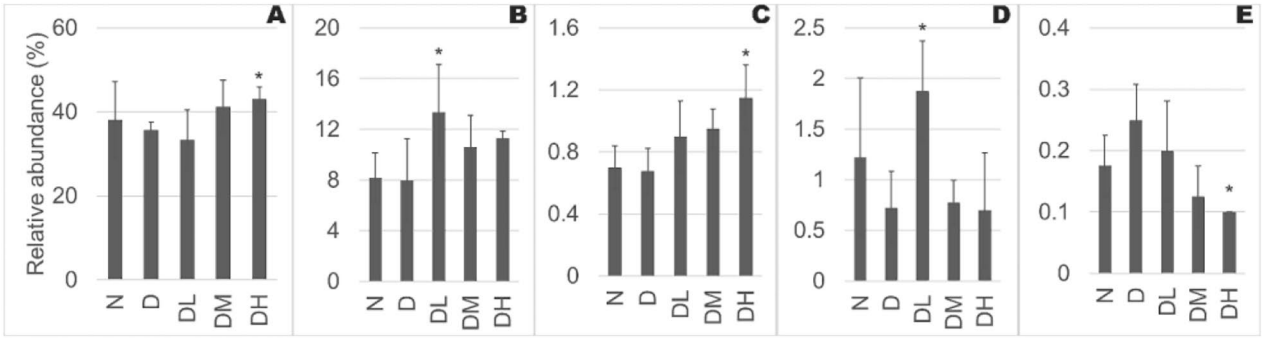


**Fig. 3** Relative abundance of (A) Bacteroidetes, (B) *Lachnospiraceae NK4A136*, (C) *Tannerelaceae*, (D) *Ruminococcus* 1 and (E) *Lachnoclostridium*. *Significantly different with D group ($p < 0.05$). The one-way ANOVA followed by Tukey's HSD *Post-hoc* test was used whenever required assumptions were met, otherwise Kruskal Wallis Test was used

**Table 2** Short chain fatty acid (SCFA) concentration of rat cecal material

| Treatments | Acetic acid (μmol/g) | Propionic acid (μmol/g) | Butyric acid (μmol/g) |
|---|---|---|---|
| N | 1.70 ± 0.08 | 0.74 ± 0.05 | 1.81 ± 0.03 |
| D | 1.80 ± 0.17 | 0.73 ± 0.06 | 1.71 ± 0.05* |
| DL | 1.73 ± 0.09 | 0.69 ± 0.01 | 1.82 ± 0.04 |
| DM | 1.76 ± 0.06 | 0.72 ± 0.05 | 1.82 ± 0.07 |
| DH | 1.72 ± 0.07 | 0.72 ± 0.03 | 1.79 ± 0.03 |

*Significantly different with N group ($p<0.05$). The one-way ANOVA followed by Tukey's HSD *Post-hoc* test was used whenever required assumptions were met, otherwise Kruskal Wallis Test as non-parametric equivalent was used

## Dietary FEX Intake Increased Cecal SCFA Level

The changes in gut microbiota composition were in line with SCFA concentrations in the cecum (Table 2). Although the concentrations of acetic acid and propionic acid among groups were similar, butyric acid concentrations were significantly lower in the D group compared to the others. In the FEX treated groups, the butyric acid was restored to its normal value.

SCFA, especially butyrate, has been extensively studied for its role in CRC prevention and inhibition. In humans, the level of butyrate in the human colon is inversely correlated with the incidence of CRC [21]. Butyrate could protect against CRC by alleviating inflammations and promoting cancer cell apoptosis, in addition to inhibit cell formation, cell proliferation, and cell invasion [22]. In our result, the increased level of butyrate in FEX-treated groups was in line with the decreasing ACF number. While oral butyrate does not protect against CRC due to the rapid absorption in the small intestine, colonic-fermented butyrate, such as that released from phenolic fermentation, was especially effective in suppressing ACF number [23]. The increased level of SCFA-producing taxa in our study, such as Bacteroidetes, *Tannerellaceae, Lachnospiraceae*, and *Ruminococcus* spp., could explain the increase in butyrate level. On the other hand, genus *Lachnoclostridium*, the biomarker for the early stages of CRC [20], was suggested to negatively impact the circulating SCFA acetate level [24].

The ability of FEX treatment to reduce the overall ACF profiles, increase butyrate level, and shift the gut microbiota composition, was probably linked with the gallic acid and rather high ellagic acid content in FEX (54.41 ± 1.80 and 209.79 ± 2.49 mg/100 g FEX, respectively). In comparison, ellagic acid-rich fruits, raspberries and blackberries, contain approximately 150 mg ellagic acid/100 g dw [25]. Gallic acid and ellagic acid act through the antioxidant route in CRC chemoprevention, maintaining the oxidative status while improving the performance of antioxidative enzyme activity [26, 27]. In addition, both are simple phenolic acids, which directly interact with gut microbiota. Ellagic acid is readily transformed by the gut microbiota into more potent anti-inflammatory and antioxidative urolithins [28]. Meanwhile, gallic acid is known to stimulate the growth of phylum *Bacteroidetes* [29] which is generally able to produce anti-inflammatory butyrate [19, 30]. The major phenolic compounds in jaboticaba, such as anthocyanins, ellagitannins and flavonoids, which have been reported in other studies were not analyzed in the present study due to the limitation of our HPLC system. Other studies on the phenolic compounds of jaboticaba can be found elsewhere [10, 12].

Ellagitannins (especially ellagic acid) have already been associated with jaboticaba seed effectivity in decreasing ACF number [14]. Similarly, jaboticaba seed extract incorporated into yogurt showed probiotic effect in cancer-bearing Wistar rats [31]. However, to the extent of our limited knowledge, ours was the first study investigating the whole fruit effectivity in CRC management. Jaboticaba in the DL and DH groups seemed to promote an overall better gut microbiota environment by acting as a 'duplibiotics' [29] by

promoting the growth of various beneficial bacteria, such as *Bacteroidetes, Tannerelaceae, Lachnospiraceae NK4A136*, *Ruminococcus 1* in one hand, while also inhibiting the CRC biomarker *Lachnoclostridium* in the other hand.

## Conclusion

Our study demonstrated that jaboticaba ethanolic whole fruit extract was rich in ellagic acid and can suppress ACF formation by improving the butyrate level and bi-directionally modulating the gut microbiota: suppressing the CRC marker *Lachnoclostridium* and promoting growths of the SCFA-producing *Tannerelaceae, Lachnospiraceae NK4A136*, *Ruminococcus 1*. This highlights the potential of jaboticaba fruit in suppressing CRC tumorigenesis especially at the initiation stage.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s11130-023-01051-z.

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**Authors' Contributions** K.A. and W.L. conducted animal study, data collections, and almost all the assays. K.A. did the data analysis. B.S. and Y.C. designed the study and supervised the research. J.L. supervised animal study. K.A. and Y.C. prepared the manuscript which then reviewed by all authors.

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**Data Availability** The data that support the findings of this study are available upon reasonable request.

## Declarations

**Ethical Approval** This study was approved by Institutional Animal Care and Use Committee (IACUC) of Providence University (Trial Registration Number 20180419A01, registration date 22 December 2018).

**Consent to Participate** Not applicable.

**Consent for Publication** Not applicable.

**Competing Interests** The authors declare that there is no conflict of interests.

## References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F (2021) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71(3):209–249. https://doi.org/10.3322/caac.21660
2. Siegel RL, Miller KD, Fuchs HE, Jemal A (2022) Cancer statistics, 2022. CA Cancer J Clin 72(1):7–33. https://doi.org/10.3322/caac.21708
3. Society AC (2022) Cancer facts & Fig. 2022. American Cancer Society. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2022.html. Accessed 13 October 2022
4. Bird RP (1995) Role of aberrant crypt foci in understanding the pathogenesis of colon cancer. Cancer Lett 93(1):55–71. https://doi.org/10.1016/0304-3835(95)03788-X
5. Takayama T, Katsuki S, Takahashi Y, Ohi M, Nojiri S, Sakamaki S, Kato J, Kogawa K, Miyake H, Niitsu Y (1998) Aberrant crypt foci of the colon as precursors of adenoma and cancer. N Engl J Med 339(18):1277–1284. https://doi.org/10.1056/NEJM199810293391803
6. Perše M, Cerar A (2010) Morphological and molecular alterations in 1,2-dimethylhydrazine and azoxymethane induced colon carcinogenesis in rats. J Biomed Biotechnol 2011. https://doi.org/10.1155/2011/473964
7. Rawla P, Sunkara T, Barsouk A (2019) Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Gastroenterol Rev 14(2):89–103. https://doi.org/10.5114/pg.2018.81072
8. Stone WL, Krishnan K, Campbell SE, Palau VE (2014) The role of antioxidants and pro-oxidants in colon cancer. World J Gastrointest Oncol 6(3):55. https://doi.org/10.4251/wjgo.v6.i3.55
9. Salomão LC, de Siqueira DL, Aquino CF, de Lins LC (2018) Jabuticaba—*Myrciaria* spp. Exotic fruits. Elsevier, pp 237–244
10. Inada KOP, Oliveira AA, Revorêdo TB, Martins ABN, Lacerda ECQ, Freire AS, Braz BF, Santelli RE, Torres AG, Perrone D (2015) Screening of the chemical composition and occurring antioxidants in jabuticaba (*Myrciaria jaboticaba*) and jussara (*Euterpe edulis*) fruits and their fractions. J Funct Foods 17:422–433. https://doi.org/10.1016/j.jff.2015.06.002
11. Reynertson KA, Wallace AM, Adachi S, Gil RR, Yang H, Basile MJ, D'Armiento J, Weinstein IB, Kennelly EJ (2006) Bioactive depsides and anthocyanins from jaboticaba (*Myrciaria cauliflora*). J Nat Prod 69(8):1228–1230. https://doi.org/10.1021/np0600999
12. Plaza M, Batista ÂG, Cazarin CBB, Sandahl M, Turner C, Östman E, Júnior MRM (2016) Characterization of antioxidant polyphenols from *Myrciaria jaboticaba* peel and their effects on glucose metabolism and antioxidant status: a pilot clinical study. Food Chem 211:185–197. https://doi.org/10.1016/j.foodchem.2016.04.142
13. Alam MN, Almoyad M, Huq F (2018) Polyphenols in colorectal cancer: current state of knowledge including clinical trials and molecular mechanism of action. Biomed Res Int 2018. https://doi.org/10.1155/2018/4154185
14. do Carmo MAV, Fidelis M, de Oliveira PF, Feitoza LQ, Marques MJ, Ferreira EB, Oh WY, Shahidi F, Hellström J, Almeida LA (2021) Ellagitannins from jabuticaba (*Myrciaria jaboticaba*) seeds attenuated inflammation, oxidative stress, aberrant crypt foci, and modulated gut microbiota in rats with 1,2-dimethyl hydrazine-induced colon carcinogenesis. Food Chem Toxicol 154:112287. https://doi.org/10.1016/j.fct.2021.112287
15. Kasprzak-Drozd K, Oniszczuk T, Stasiak M, Oniszczuk A (2021) Beneficial effects of phenolic compounds on gut microbiota and metabolic syndrome. Int J Mol Sci 22(7):3715. https://doi.org/10.3390/ijms22073715
16. De Santis S, Liso M, Vacca M, Verna G, Cavalcanti E, Coletta S, Calabrese FM, Eri R, Lippolis A, Armentano R (2021) Dysbiosis triggers ACF development in genetically predisposed subjects. Cancers 13(2):283. https://doi.org/10.3390/cancers13020283

17. Selma MV, Espin JC, Tomas-Barberan FA (2009) Interaction between phenolics and gut microbiota: role in human health. J Agric Food Chem 57(15):6485–6501. https://doi.org/10.1021/jf902107d
18. Anderson JC, Swede H, Rustagi T, Protiva P, Pleau D, Brenner BM, Rajan TV, Heinen CD, Levine JB, Rosenberg DW (2012) Aberrant crypt foci as predictors of colorectal neoplasia on repeat colonoscopy. Cancer Causes Control 23(2):355–361. https://doi.org/10.1007/s10552-011-9884-7
19. Thomas F, Hehemann J-H, Rebuffet E, Czjzek M, Michel G (2011) Environmental and gut Bacteroidetes: the food connection. Front Microbiol 2:93. https://doi.org/10.3389/fmicb.2011.00093
20. Liang JQ, Li T, Nakatsu G, Chen YX, Yau TO, Chu E, Wong S, Szeto CH, Ng SC, Chan FK (2020) A novel faecal *Lachnoclostridium* marker for the non-invasive diagnosis of colorectal adenoma and cancer. Gut 69(7):1248–1257. https://doi.org/10.1136/gutjnl-2019-318532
21. Goncalves P, Martel F (2016) Regulation of colonic epithelial butyrate transport: focus on colorectal cancer. Porto Biomed J 1(3):83–91. https://doi.org/10.1016/j.pbj.2016.04.004
22. Mirzaei R, Afaghi A, Babakhani S, Sohrabi MR, Hosseini-Fard SR, Babolhavaeji K, Akbari SKA, Yousefimashouf R, Karampoor S (2021) Role of microbiota-derived short-chain fatty acids in cancer development and prevention. Biomed Pharmacother 139:111619. https://doi.org/10.1016/j.biopha.2021.111619
23. Perrin P, Pierre F, Patry Y, Champ M, Berreur M, Pradal G, Bornet F, Meflah K, Menanteau J (2001) Only fibres promoting a stable butyrate producing colonic ecosystem decrease the rate of aberrant crypt foci in rats. Gut 48(1):53–61. https://doi.org/10.1136/gut.48.1.53
24. Nogal A, Louca P, Zhang X, Wells PM, Steves CJ, Spector TD, Falchi M, Valdes AM, Menni C (2021) Circulating levels of the short-chain fatty acid acetate mediate the effect of the gut microbiome on visceral fat. Front Microbiol:1943. https://doi.org/10.3389/fmicb.2021.711359
25. Daniel EM, Krupnick AS, Heur Y-H, Blinzler JA, Nims RW, Stoner GD (1989) Extraction, stability, and quantitation of ellagic acid in various fruits and nuts. J Food Compos Anal 2(4):338–349. https://doi.org/10.1016/0889-1575(89)90005-7
26. Kumar KN, Raja SB, Vidhya N, Devaraj SN (2012) Ellagic acid modulates antioxidant status, ornithine decarboxylase expression, and aberrant crypt foci progression in 1,2-dimethylhydrazine-instigated colon preneoplastic lesions in rats. J Agric Food Chem 60(14):3665–3672. https://doi.org/10.1021/jf204128z
27. Giftson JS, Jayanthi S, Nalini N (2010) Chemopreventive efficacy of gallic acid, an antioxidant and anticarcinogenic polyphenol, against 1,2-dimethylhydrazine induced rat colon carcinogenesis. Investig New Drugs 28(3):251–259. https://doi.org/10.1007/s10637-009-9241-9
28. Núñez-Gómez V, Periago MJ, Navarro-González I, Campos-Cava MP, Baenas N, González-Barrio R (2021) Influence of raspberry and its dietary fractions on the *in vitro* activity of the Colonic Microbiota from normal and overweight subjects. Plant Foods Hum Nutr 76(4):494–500. https://doi.org/10.1007/s11130-021-00923-6
29. Rodríguez-Daza MC, Pulido-Mateos EC, Lupien-Meilleur J, Guyonnet D, Desjardins Y, Roy D (2021) Polyphenol-mediated gut microbiota modulation: toward prebiotics and further. Front Nutr 8:689456. https://doi.org/10.3389/fnut.2021.689456
30. Kim YS, Milner JA (2007) Dietary modulation of colon cancer risk. J Nutr 137(11):2576S–2579. https://doi.org/10.1093/jn/137.11.2576S. S
31. Fidelis M, Santos JS, Escher GB, Rocha RS, Cruz AG, Cruz TM, Marques MB, Nunes JB, do, Carmo MAV, de Almeida LA (2021) Polyphenols of jabuticaba [*Myrciaria jaboticaba* (Vell.) O. Berg] seeds incorporated in a yogurt model exert antioxidant activity and modulate gut microbiota of 1,2-dimethylhydrazine-induced colon cancer in rats. Food Chem 334:127565. https://doi.org/10.1016/j.foodchem.2020.127565

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