

Review Article

Synergistic anti-cancer potential of fruit juice blends with plant-based compounds: a systematic review of randomized controlled trials

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ABSTRACT:

Background: The search for novel therapeutic agents for prevention of cancer as well as to intercept the progression of cancer and to improve health and quality of life among cancer survivors entails an important part of present-day research. Synergy of various compounds was found to be an important power to fight the cancer risk. **Objective:** The objective is to evaluate the effectiveness of juice blends in shifting human microenvironment from cancer promoting towards cancer preventing status by creating health promoting body states. **Method:** Systematic search following PRISMA guidelines in scientific databases was conducted to include human randomized controlled trials intervening with juice blends. **Results:** We included 10 trials from which the data is extracted and tabulated. The evidence from the study findings was evaluated to provide conclusive results. **Conclusion:** The juice blends were found to have synergic effect in providing protective effects against cancer-causing as well as cancer-promoting human environments.

Keywords: Anti-oxidants, Biomarkers, Cholesterol, Fruit blends, Gut microbiota, Inflammation.

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INTRODUCTION

About 9.7 million deaths from cancer worldwide and 20 million new cases, precisely in low- and medium-income countries, the number of cancer cases is expected to rise to 35 million by 2050, with 9.7 million fatalities (9.96 million in 2020) and 20 million new cases (19.6 million in 2020) expected in 2022. It's estimated that 1 in 9 males and 1 in 12 women will pass away from cancer.^[1] Such huge burden calls for developing various modalities of early detection and prevention. As per the saying "Food is medicine", diet can be harnessed as a wonderful aid for preventing disease and maintain a healthy body and mind. Recent research explores various dietary elements and their beneficial effects in modifying the risk of cancer and thereby preventing its incidence. Increasing the intake of fruits and vegetables stands amongst one of the 6 cancer prevention recommendations by World Cancer Research Fund.^[2] WHO also recommends to include 5 servings of vegetables and fruits per day for an

average adult. But these standards are hardly met by people across different countries due to various reasons. Due to their perishable nature, many plant-based foods are seasonal and therefore inappropriate for ingestion for reasons such as processing requirements. Plant-based diets benefit from the bioavailability of vital nutrients, which helps to prevent food degradation. By blending one or more pure vegetable or fruit juices combined for the value-added product, we can enhance the product's color, flavor, and nutritional value, and elevate polyphenol content compared to pure fruits and vegetables, as well as to reduce production costs.^[3] Although evidence from in vitro and animal studies strongly suggest cancer preventing benefits, the effectiveness is still in question due to scarcity of human interventions. Also, persists the question of differences in bioavailability and absorption.^[4] To add on this gap of evidence, the present systematic review explores the evidence from few trials conducted to

evaluate the cancer preventing efficacy of plant-based blends both directly and indirectly.

MATERIALS AND METHODS

Search strategy: We conducted a thorough search of the databases in PubMed, Elsevier Science Direct, and Wiley Online Library, Google scholar using the MeSH terms "juice or vegetable fruit blends" and "cancer prevention". We followed PRISMA guidelines to conclude the search.

Study selection: Eligibility criteria:

Criteria for inclusion were

- Original research articles published in the past 20 years.
- Articles for which full text is available.
- Articles testing the relationship between plant-based juice blends and cancer.

Criteria for exclusion were

- Studies available in languages other than English
- Review articles,
- Articles those are available only as abstracts.

Quality assessment: All Authors evaluated the quality of the study for appropriate search methods, bias, and standardization in a methodical and

independent manner. The Office of Health Assessment and Translation (OHAT) bias assessment for animal and human studies was employed to evaluate bias.^[5]

Data extraction: Data on authors, year, location, samples, study design, exposures, intervention, results, and outcome were extracted and then combined into a narrative synthesis, which was then tabulated and grouped.

RESULTS

Search results

A thorough investigation of online databases produced 24,093 research publications about plant-based juice blends and cancer. Following the elimination of duplicate entries, 10,106 unique articles have been identified. After assessing these papers in accordance with pre-established eligibility standards, 139 articles were ultimately chosen for quality evaluation. 10 of those publications passed the strict requirements and were added to the current systematic review [Fig 1]. Data relevant to included studies was extracted and tabulated [Table 1]. Bias assessment of included all studies included were found to be mostly at low risk of bias [Table 2].

Figure 1: PRISMA flow chart

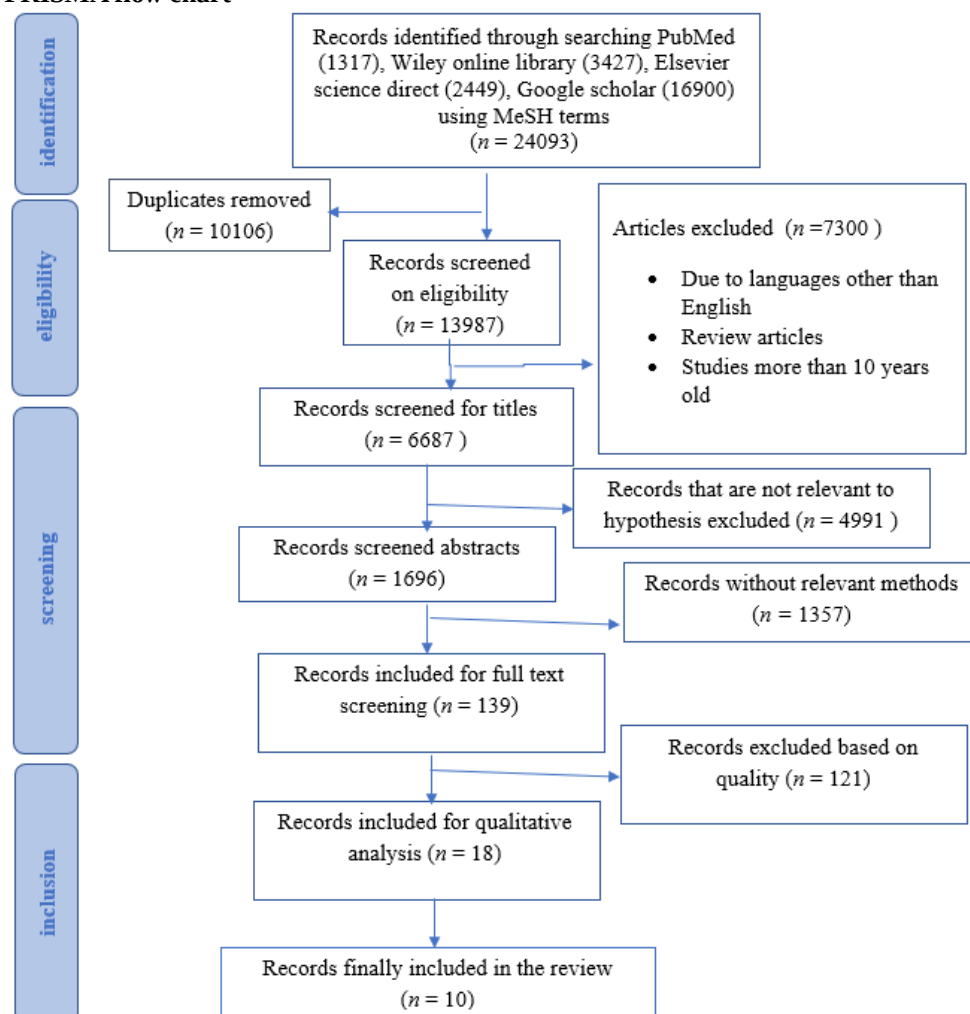


Fig:1: PRISMA flow chart indicating steps followed to include studies in the systematic review.

Table 1: Study characteristics.

S N O	AUTHOR, YEAR, AREA	DESIG N	SAMPLE	TECHNIQUE	RESULT	OUTCOME
1	Mridul Datta, et al ^[6] 2016 Multisite study USA	RCT	134 HNC patients above 18 years old who doesn't have recurrence in 6 months to 3 years time and got cured. Randomized into 2 groups intervention (72), control (62).	Juice plus, blend of dried powders from apples, oranges, pineapples, papaya, cranberries, and peaches(orchard blend);carrots, parsley, beets,broccoli, kale, cabbage, spinach, and tomatoes (garden blend); and citrus bioflavonoids, calcium ascorbate and carbonate, <i>Lactobacillus acidophilus</i> , d- α tocopherol, mixed tocopherols, <i>Dunaliella salina</i> , β -carotene, and folic acid was encapsulated separately in hard gelatin capsules to provide 850 mg of fruit powder and 750 mg of vegetable powder per capsule. Intervention group: 2 capsules per day Control group: placebo for 12 weeks. Biopsy specimens and serum micronutrient levels tested.	After 12 weeks, patients on JP had significantly higher serum α -carotene ($p = .009$), β -carotene ($p < .0001$), and lutein ($p = .003$) but did not differ significantly in p27 ($p = .23$) or Ki-67 ($p = .95$).	Juice plus supplementation improved overall micronutrient content within 12 weeks of supplementation. But it did not have significant effect on modification of Head and neck cancer biomarkers.
2	Evan J. Williams, et al ^[7] 2017 Australia	RCT	56 adult non-smokers, no irregular periods aged 40 years or more with a BMI ≥ 28 kg/m ² or more randomized into 2 groups intervention (28), placebo (28). All subjects took <2 servings F&V per day	Control group: placebo Intervention group: Supplement contained acerola, cherry, apple, bilberry, blackberry, black currant, blueberry, beetroot, broccoli, cabbage, carrot, concord grape, cranberry, elderberry, kale, orange, peach, papaya, parsley, pineapple, raspberry, red currant, spinach and tomato (Juice Plus+® Orchard, Garden and Berry Blends) given as 6 capsules per day for 8 weeks. Antioxidants, blood biomarkers, PCR tested before and after. Statistical analysis: paired t test and ANCOVA.	Comparison of the two groups showed the change in triglycerides was different between the F&V concentrate and placebo groups ($p < 0.02$) TNF α decreased ($p = 0.071$). Total lean mass increased ($p = 0.057$). Plasma α -carotene and total carotenoids were both increased within the F&V. Lycopene was significantly decreased within the placebo group Gene expression of BCL2, TNF-AIP3, ZFAND5 which are known inhibitors of NF- κ B signalling as was also significantly upregulated. The genes HK2, IRS2, PDE3B, PHKB,	Supplementation led to decrease in cholesterol, systemic inflammation, improved antioxidant potential and systolic blood pressure. It also improved metabolic health. Changes were significant in subjects with high baseline CRP.

					PRKAG2, PTPN1 and RHEB suggests that the intervention with the F&V concentrate increases insulin sensitivity.	
3	Faisal Khan, et al ^[8] 2014 Scotland	RCT	66 healthy adults who consume < 2 portions of fruit & vegetables per day. Randomized into 3 groups 22 each	Group 1: placebo-flavoured water Group 2: low blackcurrant juice drink (6.4% juice; final diluted concentration 1.1mg vitamin C/100ml, 27.3mg/100 ml total polyphenols, 4mg/100ml anthocyanins) Group 3: high blackcurrant juice drink (20% juice; 10.2mg vitamin C/100 ml, 81.5mg/100 ml total polyphenols, 14.3mg/100 ml anthocyanins) provided in ready to drink cartons with 250 ml of juice 4 times a day for 6 weeks. Blood markers were tested. Statistical analysis: ANOVA	Plasma vitamin C concentration increased significantly group 2 ($p < 0.001$) and to a greater extent in group 3 ($p < 0.001$). F2-isoprostanes (oxidative stress markers) were significantly lower in group 2 ($p < 0.003$) and group 3 ($p < 0.002$). Group 3 showed significant increase in FMD (flow mediated dilation) of blood vessels (CVD risk)	Blackcurrant juice supplementation resulted in significant improvement in plasma vitamin C levels and reduction in oxidative stress. No effect on cholesterol and BP were shown but it showed significant improvement in dilation of blood vessels.
4	Ingvald Paur, et al ^[9] 2017 Norway	RCT	79 patients with non-metastatic prostate cancer randomized to 3 groups	Control group: habitual diet. Tomato group: tomato products with a content of 30mg lycopene per day Tomato plus group: tomato products with a content of 30 mg lycopene per day plus green tea (a cup made from 1 sachet) and black tea (a cup made from 1 sachet), pomegranate and grape juice (330 mL of each), 200mg soy isoflavones, 200 mg 1-selenomethionin and 3.13 g n-3 fatty acids per day. PSA, carotenoids, fatty acids, selenium and steroid hormones were measured. Kruskal Wallis, Mann-Whitney, Fisher's, Freeman-Halton tests, Spearman's correlation tests were done.	Median PSA decreased by 0.23 mg/mL in the tomato group as compared to a 0.45 mg/L increase in the control group among low and intermediate risk patients. high risk patients no significant differences in PSA. lycopene was more than doubled in both intervention groups, ($p < 0.001$). Selenium nearly doubled in the tomato-plus group ($p < 0.001$). PUFAs increased in the subjects in the tomato-plus group, as compared to the controls ($p < 0.001$). PSA decreased in patients with the highest increase in lycopene alone ($p < 0.009$).	Patients with non-metastatic prostate cancer have decreased PSA after 3 wk therapy with tomato products alone or in conjunction with n-3 fatty acids and selenium and the impact might be influenced by the disease's severity, levels of omega-3 fatty acids, selenium, and lycopene.
5	Torsten Bohn, et al ^[10]	single-arm phase II	18 (9 men, 9 women) 28 ± 5 yr old	a soy germ-fortified tomato juice daily (300 mL supplying 66 mg isoflavones and 22 mg	The postprandial tests found that the amount of lycopene	The blood was markedly improved and

	2013 Ohio	human trial	healthy subjects	lycopene) given for all participants for 8 wk. Isoflavones, tocopherols, carotenoids, cholesterol, urine creatinine, C-Reactive Protein, Hemoglobin were assessed.	absorbed was $3.1\% \pm 2.3\%$; amount of isoflavones recovered in 24-hour urine samples was $49.3\% \pm 12.1\%$. After 8 weeks, the plasma concentration of lycopene increased from 0.60 ± 0.22 to 1.24 ± 0.30 $\mu\text{mol/L}$. Juice consumption enhanced the ratio of total-C/HDL-C (4.25 ± 1.59 to 3.63 ± 1.16 , $p < 0.001$), HDL-C (47.3 ± 15.8 to 51.7 ± 14.8 mg/dL , $p < 0.001$), and LDL+VLDL-C resistance to Cu^{2+} - mediated oxidation ($p = 0.039$) after 8 weeks.	maintained at reasonably high levels in biological fluids comparable to those identified in epidemiologic studies linked to a lower risk of cancer. Lipid and antioxidant status got improved in 8 weeks.
6	Amy C. Butalla et al ^[11] 2013 USA South Arizona	RCT	69 stage I, II, IIIa invasive breast cancer and to have completed primary cancer treatment at least 6m prior.	Balero orange carrot group and beta sweet carrot groups: juiced raw carrots using the study- provided juicer and consumed 8 fluid ounces of carrot juice (approximately 5) mixed with 2 teaspoons of olive oil daily for 3 weeks. Plasma carotenoids, oxidative stress and inflammatory biomarkers were analyzed.	For the BetaSweet and Balero carrot juices, total plasma carotenoids rose by 1.65 and 1.38 $\mu\text{mol/L}$, respectively. 8-iso-PGF α was inversely correlated with an increase in total plasma carotenoids for the entire sample (OR: 0.13; 95% CI: 0.20 to 0.75).	The mean plasma carotenoid level attained was in line with levels that have been demonstrated to be protective against a new incident or recurrence of breast cancer.
7	Tamara Bakuradze et al ^[12] 2019	RCT	Healthy male volunteers (n = 62, BMI = 19–25, age = 20–50) randomized into 2 groups 31 each.	Intervention group: anthocyanin- rich fruit juice was produced from red grape juice, lingonberry juice from concentrate, apple, blueberry and strawberry puree, aronia juice from concentrate and acerola puree (100% fruit content). Placebo: water, fructose, glucose,sucrose, citric acids, vitamin C and naturalflavours.	Both groups showed a significant decrease in background and total DNA strand breaks both after eight weeks and within 24 hours. Consuming fruit juice high in anthocyanins led to a notable decrease in body fat and an increase in fat-free mass.SOD activity was markedly increased followinganthocyani n-rich juice of fruit.	C vitamin containing juice and anthocyanin rich juice protect DNA and regulate lipid metabolism. Anthocyanin juice also increased antioxidant potential.
8	Zhe-Xuan L et al ^[13] 2020	RCT	522 H. pylori-positiv e	Each day, participants in the juice group, Low-polyphenol (23mg/bottle) group (group J-B)	H. pylori-negative rates in the cranberry juice groups with	Cranberry juice can partially suppress H.

	China		adults assigned into a high-dose, low-dose, or placebo groups.	drank one bottle (240 mL) of cranberry juice, Group J-C, the medium-polyphenol (44mg/bottle) group, finished one 240 mL bottle. High-polyphenol (44mg/bottle), group (J-D) drank two 240 mL juice bottles every day, every evening. In powder group, 280mg of cranberry powder in one or more capsules, containing 36mg polyphenols for 8 weeks.	placebo, low, medium, and high proanthocyanidin were 7.35%, 7.58%, 4.48%, and 20.00% ($p < 0.005$) at wk8, respectively and the change was statistically significant over time.	pylori when taken regularly and at the right dosage and frequency. This is notably true in China, where GC rates are high and endemic infection is common.
9	Rachna Kapoor et al ^[14] 2015 USA	RCT	48–64yr old post-menopausal women	Intervention: 4 sealed bottles of commercial fresh refrigerated 100% pomegranate juice Control: 3 sealed bottles of commercial 100% apple juice. 8 ounces per day for 3 wks.	When compared to women in the control group, women in the intervention group did not, on the whole, see a substantial decline in serum sex hormones or sex hormone binding globulin (SHBG). Within the subgroup studies limited to 38 women, the intervention group had a significant decline in testosterone and estrone levels ($P < 0.05$).	Except decrease in estrone levels in normal weight women, the study found no association between pomegranate juice intake and changes in hormones.
10	Saeed Pirouzpanah et al ^[15] 2019 Iran	RCT	85 pre-menopausal women afflicted with Benign breast disease 19-52 yr old.	Berberis vulgaris (BV) juice group (n = 44, BV juice: 480 ml/day) or placebo group (n = 41, BV placebo juice: 480 ml/day) for 8 weeks intervention a glass (serving size, 240 ml) in each meal at both lunch and dinner. Insulin growth factor (IGF), IGF-binding proteins (IGFBPs), Peroxisome proliferator-activated receptor- γ (PPAR- γ), Vascular endothelial growth factor (VEGF), Hypoxia-inducible factor (HIF) were measured post intervention.	IGF-1 concentration dropped by 16% and the IGF-1/IGFBP1 ratio dropped by 37% as a result of drinking BV juice. A 111 ng/ml increase in the mean differences of IGFBP-3 between the BV group and the placebo was the absolute treatment effect. Although it wasn't statistically significant, both groups' plasma levels of PPAR- γ rose. Also, fold changes in the expressions of VEGF, HIF, and PPAR- γ revealed down-regulation ($P < 0.05$).	Reductions in the expression noteworthy genetic alterations that may be able to stop the development of breast cancer by transcription of potential tumorigenesis-related genes and IGF-1-related bioavailability indicators.

Table 1: table presenting the data extracted from the included studies. HNC=Head and Neck Cancer. BMI=Basal Metabolic Rate. F&V=Fruit Vegetable. PCR=Polymerized Chain Reaction. ANOVA=Analysis of Variance. PSA=Prostate Specific Antigen. PUFA=Poly Unsaturated Fatty

Acids. HDL=High Density Lipoprotein, LDL=Low-Density Lipoprotein, VLDL=Very Low-Density Lipoprotein. SOD=Superoxide Dismutase.

Study results

A total of 10 studies included in the systematic review among which, 3 studies [6, 9,11] were randomized controlled trials conducted on cancer survivors and found that juice blends with fruits, vegetables, berries were effective in improving quality of life and stalling the progression of disease. Few studies focused on microenvironmental changes associated with

consumption of such juice blends. according to results, the blends were found to be effective in reducing systemic inflammation [7], improved anti-oxidant potential and reduced oxidative stress [5, 7, 8]. Juice blends also improved carotenoid levels [11], C vitamin levels, protect DNA against damage, regulated lipid metabolism [12], reduced the expression of genes associated with breast cancer progression [15] and reduced PSA levels in prostate cancer patients.[9] Interestingly, juice blends also found to be modifying H.pylori related gastric cancer risk by reducing inoculum.[13]

Table 2: bias assessment for included studies:

Author Name	Mridul Datta et al ^[6]	Evan J.Williams, et al ^[7]	Faisel Khan et al ^[8]	Ingvild Paur et al ^[9]	Torsten Bohn et al ^[10]	Amy C. Butalla, et al ^[11]	Tamara Bakuradze ^[12]	Zhe-Xuan L et al ^[13]	Rachna Kapoor et al ^[14]	Saeed Pirouzpanah ^[15]
Randomization	++	++	++	++	-	++	++	++	++	++
Allocation Concealment	++	+	-	++	-	-	-	++	+	++
Comparison Group	++	++	++	++	-	++	+	++	++	++
Confounding and Modifying Variables	+	+	+	-	+	-	++	++	-	+
Identical Study Groups	+	++	++	++	-	++	++	++	++	++
Blinding of Participants and Personnel	++	++	++	+	-	-	-	++	++	++
Incomplete Outcome Data	++	+	+	+	+	+	+	+	+	++
Exposure Characterization	++	++	++	++	++	++	++	++	++	++
Outcome Assessment	++	++	++	++	++	++	++	++	++	++
Reporting Of Measured Outcome	++	++	++	++	+	+	+	++	++	++
Other Potential Threats	+	+	+	-	-	-	-	+	++	+

Table 2: OHAT bias assessment results for included studies.  Definitely Low risk
 Probably Low risk  Probably high risk  Definitely high risk

DISCUSSION

The present systematic review included 10 randomized controlled trials that checked effectiveness of different juice blends of plant-based origin in modifying the microenvironment of human beings in such a way to prevent cancerous progression and incidence as well. The study by Mridul Datta et al indicated that juice and vegetable blend supplement successfully improved the micronutrient levels in the serum of head and neck patients. Although the biomarker levels were not modified in case of H&N cancer patients, this effect can be harnessed as a protective measure among general population who might be at risk of developing cancer. Similar supplementation resulted in decrease in cholesterol, systemic inflammation, improved anti-oxidant potential in a study by Evan J.Williams, et al. The study by Faisel Khan, et al indicated that blackcurrant juice supplementation resulted in significant reduction in oxidative stress and improvement in vitamin C levels in plasma. The intervention with tomato-based blends resulted in decreased PSA levels among non-metastatic prostate cancer patients and enhanced the

blood antioxidant status and isoflavone and carotenoid levels significantly according to Ingvild Paur, et al and Torsten Bohn, et al. According to Tamara Bakuradze et al, anthocyanin rich juice intake could protect DNA and regulate lipid metabolism. Helicobacter pylori infection, a prevalent risk factor for stomach cancer was found to be reduced to 20% by daily and regular intake of cranberry juice according to recent trial by Zhe-Xuan L et al. Abnormal levels in hormones in post-menopausal women is an established risk factor for breast cancer. Rachna Kapoor et al, when investigated the effect of pomegranate juice in modifying hormone levels found that there was no overall association between both except decrease in estrone levels. Also, post-menopausal women with benign breast disease are at risk of developing breast cancer. Supplementation with Berberis vulgaris juice for 8 weeks resulted in breast cancer predicting genetic expression and indicators related to tumorigenesis according to Saeed Pirouzpanah et al.

A systematic review and meta-analysis by Tonin FS et al reported that natural juices are possible candidates

for the management of oxidative stress.^[16] Another systematic review by Cirimi S et al highlighted the importance of Citrus juices and their extracts in a in the prevention of cancer and also their possible use as co-adjuvants in modern oncological therapies to improve quality of life.^[17] Cancer is a multifactorial disease. Modification of microenvironment of human body by modifying conditions like systemic inflammation, oxidative stress, immune related deficiencies, gut microbiota balance can be the best method to prevent cancer even before initiation.^[18] ^[19]The protective effects of these foods have been associated with the presence of bioactive food compounds. These are produced through secondary metabolism in plants and present distinct chemical and biological features. Examples include sulforaphane (broccoli), lycopene (tomatoes), catechins (green tea), allyl compounds (garlic), terpenoids (citrus fruits) and genistein (soy). These compounds have been shown to modulate several cellular and molecular targets deregulated in carcinogenesis.^[20] Limonoids and citrus fruits, Pomegranates have therapeutic qualities that protect against many malignancies and balance women's hormones. Citrus limonoids chemical compounds Limonin, Nomilin, Deacetylnomilinic acid, Isolimonelic acid, Nominilic acid have anticancer effect. Numerous bioactive substances found in berry fruits have actions that are cardioprotective, neuroprotective, anti-inflammatory, and antioxidant. Avocado seed extract is regarded as a high-quality antioxidant source. Despite research on fruit extracts' hepatoprotective properties cherry, peach, olive, plum, pear, apple, chestnut, and pistachio leaves are excellent sources of bioactive phenol chemicals due to their antioxidant properties.^[21]

The findings from current study cannot be generalized owing to small size of included studies. But since all included studies were randomized controlled trials that were conducted in human population, the findings can add up to the evidence regarding harnessing the potential of bioactive compounds available in fruits, vegetables and other plant products in a natural synergic way in order to protect against developing an internal environment that facilitates tumorigenic changes. Although effectiveness of bioactive components from plant products individually is well studied and established, the research on various combinations of plant products that would provide with synergic effect on health of humankind to prevent chronic diseases including cancers is not yet progressed.

CONCLUSION AND RECOMMENDATIONS

In conclusion fruit juice blends could help protecting against progression of tumorigenic changes in human body by reducing systemic inflammation, oxidative stress, improving antioxidant and carotenoid levels, regulate lipid peroxidation and fight DNA damage and encourage repair. Future research on studying various

such synergic combinations or blends and testing them in large scale human trials would be a boon to future generations to sow seeds for lessening the alarming burden of non-communicable diseases.

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