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Original Article

LITERATURE STUDY: INTERACTION BETWEEN NATURAL ANTIOXIDANT COMPOUNDS IN TROPICAL FRUITS

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ABSTRACT

Objective: This study aims to analyze selected articles on interactions in binary combinations of vitamin c, phenolic compounds, flavonoids, and carotenoids.

Methods: The method used in this research is a literature study approach through the *Google Scholar* database with the last 10 years (2013 – 2023) of research articles. The selected journals are internationally reputable with Scopus index Q1-Q4 and the results of experimental research.

Results: The analysis of the six selected articles showed synergistic interactions in the combination of vitamin c with phenolics, vitamin c with carotenoids, phenolics with flavonoids, phenolics with carotenoids, and flavonoids with carotenoids. However, antagonistic interactions can also occur in some of these combinations and the combination of vitamin c with flavonoids. This is influenced by several factors, such as the type of antioxidant compound derivative, variation in concentration ratio, differences in oxidation potential and antioxidant bond dissociation energy.

Conclusion: Overall, binary combinations of antioxidants result in different interactions. This is influenced by several factors. However, the lack of research articles on the combination of these antioxidant binary compounds means that it is not known exactly how the mechanism of interaction in these combinations can occur.

Keywords: Tropical fruits, Antioxidants, Natural antioxidant interaction

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INTRODUCTION

Fruit is known to contain vitamins, minerals, fiber, and *phytonutrients* as color providers as well as natural antioxidants [1]. These *phytonutrients* play an important role in regulating maintenance and growth, as well as reducing the risk of degenerative diseases [2]. Antioxidants play a role in counteracting the negative effects of oxidants by donating one electron to oxidant compounds that inhibit their activity [3]. One of the roles of antioxidants is the excellent anticancer effect against hepatocellular carcinoma and A549 lung adenocarcinoma [4, 5]. Other studies have also shown that some flavonoid compounds, such as naringenin and kaempferol can provide treatment effects against type 2 diabetes [6].

These antioxidant compounds can cause interactions when combined either binary (2 compounds) or ternary (3 compounds). There are 3 interactions resulting from the combination of antioxidant compounds, namely synergistic, additive, and antagonistic interactions [7]. Synergistic interaction is an interaction resulting from the combination of two or more antioxidant compounds that complement each other and even optimize their efficacy. An example of synergistic effect is shown in the combination of vitamin c and β-carotene in reducing leukoplakia malignancy rate by 17.4% [8]. In contrast to additive interactions, this interaction occurs in the combination of two or more antioxidant compounds of different types, but the antioxidant interactions that arise occur separately. This effect is shown in the combination of phenolic compounds (gallic and ferulic acids) based on the results of the free radical cation scavenging process through the ABTS (2, 2-Azinobis (3-ethylbenzatiazolin_6-sulfonic acid) test [9]. Meanwhile, antagonistic interactions, namely interactions in the combination of antioxidant compounds that can result in the weakening of one or both compounds or even provide toxicity effects in the body [7]. For example, in the combination of vitamin c and quercetin, which causes the weakening of quercetin by vitamin c due to differences in oxidation potential, while vitamin c is regenerated [10].

The selection and combination of tropical fruits as an appropriate source of natural antioxidants needs to be known in order to optimize their utilization in the body. Unfortunately, information related to the interaction between antioxidant compounds is still very minimal, so this underlies the literature study research so that it is expected to provide and add information about the interaction between natural antioxidant compounds.

MATERIALS AND METHODS

The method in this study uses a literature study approach or literature study on *Scopus*-indexed international journal articles (Q1-Q4) with a *search engine* using https://www/scimagojr.com/, through the Google Scholar database (www.scholar.google.com) with the keywords interaction between vitamin c and phenolic compounds, interaction between vitamin c and flavonoids compounds, interaction between vitamin c and carotenoid compounds, interaction between phenolic and flavonoid compounds, interaction between phenolic and carotenoid compounds, and interaction between flavonoid and carotenoid compounds. The journal articles used in this study were articles that met the inclusion criteria and, were published within the last 10 y (2013-2023) and were relevant to the research objectives.

RESULTS AND DISCUSSION

Tropical fruits as a source of natural antioxidants

Fruit is a plant that can be consumed in the pulp [11]. The content of natural antioxidants in tropical fruits such as vitamin c, phenolics, flavonoids, and carotenoids can have a health-enhancing effect on the body [12].

Based on the literature in table 1, it can be seen that tropical fruits contain many natural antioxidants. Phenolics are found in the form of gallic acid, vanillic acid, ferulic acid, rosmarinic acid, chlorogenic acid, curcumin, carnosic acid and caffeic acid [46]. While flavonoids are found in the flavonol class (quercetin, rutin, quercetrin and galangin), flavones (luteolin), epicatechin, epigalocatechin gallate, hesperetin, ferulic acid, and anthocyanidins (anthocyanins) [47]. In addition, carotenoids in tropical fruits are found in the form of lycopene, lutein, astaxanthin, β-carotene, and others [48].

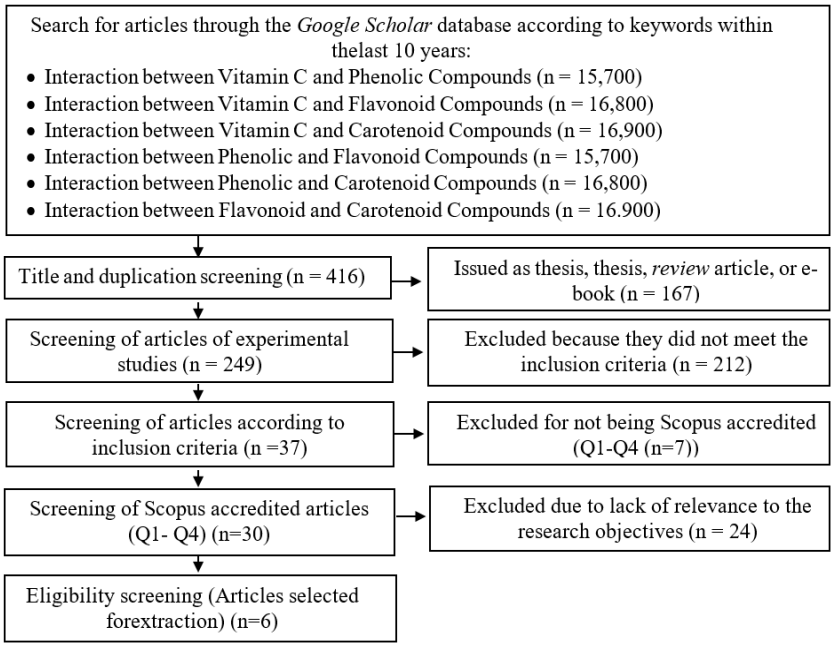

Fig. 1: Flow of article search

Table 1: Antioxidant content of selected tropical fruits

Fruit Type	Vitamin c	Phenolics	Flavonoids	Carotenoids	Reference
Avocado	1, 201	410, 202	21, 901	0, 861	[13]
Papaya	46, 891	60, 402	38, 121	0, 565	[14, 15]
Lemon	35, 2-56, 711	730, 46-825, 371	216, 61-219, 271	15, 66-20, 771	[16, 17]
Oranges	61, 381	123, 022	1, 411	111	[18, 19]
Ambon Banana	721	1, 89-29, 282	1, 45-133	0, 31-22, 885	[20, 21]
Tomato Fruit	22, 61-32, 211	1.992-2.1782	194-3473	8, 84-17, 496	[22]
Star fruit	351	161, 562	723	1, 131	[23, 24]
Pomegranate	54-105, 21	1.820-2.4502	170-3203	21-321	[25]
Pineapple	37, 791	902	803	0, 161	[26, 27]
Guava	67, 481	1.2642	232, 064	12, 496	[28]
Soursop	62, 421	160, 282	87, 173	0, 741	[15, 29]
Mango	231-4191	69, 932	3, 211	3, 44-14, 835	[30, 31]
Longan	43, 12-163[1]	58[2]	9[7]	0, 02[1]	[32, 33]
Durian	18, 87-25, 13[1]	690, 62-998, 29[2]	211, 36-220, 34[7]	0, 05-0, 08[1]	[34, 35]
Passsion Fruit	5, 1-9, 7[1]	27, 9-49, 1[2]	2, 9-5[7]	5-18, 1[5]	[36]
Jackfruit	56-87[1]	1.178[2]	68[3]	0, 04-0, 05[1]	[37, 38]
Mangosteen	2, 78[1]	225, 78[2]	0, 05[3]	-	[39, 40]
Watermelon	1.43-10, 17[1]	3, 9-7, 4[2]	3, 51-7, 76[3]	1.080[5]	[41, 42]
Rambutan	56, 37[1]	483, 72[2]	23, 37[3]	-	[43, 40]
Red Dragon	5.118-5.376[1]	53, 2[2]	3, 43[3]	0, 21[1]	[44, 45]

Units: 1 mg/100g, 2 mg GAE/100g, 3 mg QE/100g, 4 mg rutin/100g, 5 g BE/100g, 6 mg lycopene/100g, 7 mg CE/100g

Interaction between vitamin c and phenolic

Phenolic is one of the components that are part of the system of components in food ingredients, which allows for interaction with other components, such as vitamin c. A study observed the interaction of phenolic components in ginger extract combined with vitamin c. Ginger has a high phenolic content of 62.51 mg GAE/g dry weight with *antioxidant* activity (*Antioxidant Index %*) of 53.01-87.16%. *Response Surface Methodology* (RSM) analysis results showed a positive effect (P=0.0002) indicating an antagonistic interaction in the binary combination. The combined DPPH assay results also showed an increase in absorbance and a decrease in antioxidant activity [52]. This antagonistic interaction is thought to occur due to the presence of weak antioxidants that are regenerated by other stronger antioxidants, as well as the nature of vitamin c, which is easily oxidized and turns into a prooxidant agent, thus triggering an antagonistic interaction [55, 56]. Another study also showed an antagonistic interaction in the combination of vitamin c with phenolics, especially curcumin as evidenced by the CI (*Combination Index*) value in the binary combination of 1.9 (CI>1) [57]. The same thing also occurred in the combination of vitamin c with 5-caffeoylquinic acid with a ratio of 1:2 characterized by a decrease in antioxidant activity. However, different results were found in the 2:1 ratio, which actually showed a synergistic interaction characterized by an increase in antioxidant activity [58]. This suggests that the difference in antioxidant concentration ratio is one of the determining factors for the interaction that can occur in a combination. Unfortunately, it is not yet known exactly why there is a difference in the resulting interaction based on the difference in the ratio of the binary compound combination.

Table 2: Extraction data of selected journal articles

Author	Methods	Antioxidant combination	Results	Interaction	Reference
Zhang, J. Y., Lin, M. T., Zhou, M. J., Yi, T., Tang, Y. N., Tang, S. L., Yang, Z. J., Zhao, Z. Z., dan Chen, H. B.	MTT Assay	Phenolic (curcumin) and Flavonoids (quercetin)	The combination of 10.0 µM quercetin+5.0 µM curcumin and 10.0 µM quercetin+10.0 µM curcumin can inhibit the growth of MGC-803 gastric cancer cells, respectively by 76.99%±3.06% and 84.37%±4.99. In addition, the combination of 10.0 µM quercetin+5.0 µM curcumin also showed an apoptosis rate of 47.1%±2.4%.	Synergistic	[59]
Charlotte, S. Y., Dangels, O., Borel, P., dan Veyrat, C. C.	*ROS Level Assay* and UV-VIS *Spectroscopy*	Phenolics (chlorogenic acid) and Carotenoids	The combination of phenolics (chlorogenic acid) and carotenoids synergized in inhibiting peroxidation by MbFeIII with a decrease in absorbance. The combination of these binary compounds can reduce the level of linoleic acid peroxidation at pH 5.8 and 4, by 118.5% and 101.6%, respectively.	Synergistic	[67]
Levy, R., Okun, Z., dan Shpigelman.	HPLC	Vitamin c and Flavonoids (anthocyanins)	The combination of vitamin c with *Cyanidin-3-O-β-Glucoside* and *Cyanidin-3-Glucosyl-Rutinoside* significantly increased degradation ($p<0.05$) characterized by a significant decrease in anthocyanin residue<6% compared to control. The rate of degradation was in line with the increase in storage temperature. Storage of the binary compound combination at 37 °C increased the degradation rate significantly ($p<0.05$).	Antagonist	[52]
Singprecha, A., Yarovaya, L., dan Khunkitti, W.	DPPH dan *Response Surface Methodology* (RSA)	Vitamin c and Phenolic	Ginger extract has a high total phenolic content of 62.51 mg GAE/g dry weight, indicating strong antioxidant activity (53.01-87.87.16%). *Response Surface Methodology* (RSA) results showed an antagonistic interaction between total phenolics in ginger extract and ascorbic acid, characterized by an increase in absorbance and a decrease in antioxidant activity.	Antagonist	[47]
Oh, S., Kim, Y. J., Lee, E. K., Park, S. W., dan Yu, H. G.	DPPH dan DCFH-DA *Intracellular ROS Level Assay*	Vitamin c and Carotenoids (astaxanthin)	The combination of 20 µM astaxanthin and 90 µM ascorbic acid can reduce the level of *Reactive Oxygen Species* (ROS) up to 104%. The combination of the two showed a synergistic interaction with better antioxidant activity than each component. In addition, this combination also increased the viability value of ARPE-19 cells that had been treated with $H O_{22}$ by 129%.	Synergistic	[56]
Chen, X., Zheng, L., Zhang, B., Deng, Z., dan Li, H.	*Flow-cytometry* dan SIRT1 *Enzymatic Assay*	Flavonoids (quercetin) and Carotenoids (Lycopene)	The combination of lycopene: quercetin (1:5) (M2) synergized in reducing NoX4 expression by 3.5-fold compared to the control. In addition, this combination also has a strong synergistic effect in inhibiting the expression of phosphorylated p65, as well as maintaining the stability of SIRT1 up to 57 °C.	Synergistic	[71]

Interaction between vitamin c and flavonoids

A study was conducted to determine the stability of anthocyanins in the presence of vitamin c. It was found that the results of analysis using HPLC after 6 h showed a drastic decrease in the peak area of the vitamin c chromatogram in the anthocyanin solution at an absorbance of 270 nm compared to the control solution (only vitamin c). This indicates the degradation of anthocyanins combined with vitamin c. The results of stability testing of *Cyanidin-3-O-β-Glucoside* and *Cyanidin-3-Glucosyl-Rutinoside* with the combination of vitamin c experienced a significant increase in degradation ($p<0.05$), with a residual concentration of<6% after 146 h, while in the control sample (only vitamin c) the residual concentration was 77%. In addition, an increase in the storage temperature of both combinations is in line with the increase in the value of the degradation rate constant, thus accelerating the anthocyanin degradation process ($p<0.05$) [51].

Another study also revealed that the combination of vitamin c with anthocyanins can increase the brightness of pigments and reduce the chroma in pigments. In addition, it is known that the half-life of *Cyanidin-3-galactoside* is 546 h, *5-carboxypyranocyanidin-3-galacoside is* 978 h, while the combination of both with vitamin c has a half-life of 8 and 64 h, respectively. This decrease in half-life indicates that there is a significant decay of both anthocyanin compounds [59]. The longer the half-life obtained from a compound, the smaller the decay constant value [60], so the presence of vitamin c can certainly increase the decay of anthocyanin pigments. The binary combination can also decrease the chroma value as the vitamin c content increases after 48 h. Both anthocyanin pigments combined with vitamin c experienced significant changes in chroma value over 5 d ($p<0.001$). The impact of bleaching anthocyanin is believed to be a result of the electrophilic nature of vitamin c and attacks carbon-4 (C4) and the condensation of vitamin c, which results in the loss of conjugation in the C-ring so that the original color expression of the pigment decreases [59].

Table 3: FRAP test results and mixture effect (ME) value for the combination of vitamin c and flavonoids

Component/combination	FRAP value	ME value
0.1 mmol Vitamin c+0.1 mmol Quercetin	0.346	0.77
0.1 mmol Vitamin c+0.1 mmol Ferulic acid	0.264	1.13
0.1 mmol Vitamin c+0.1 mmol Hesperetin	0.054	0.39

Source: [10]

From the results of *Ferric Reducing Antioxidant Power* (FRAP) testing at 620 nm absorbance and *Mixture Effect* (ME) table 3, it is known that the combination of vitamin c with quercetin and hesperetin show an antagonistic interaction because the FRAP value increases and the ME value<1. This antagonistic interaction occurs because quercetin regenerates oxidized vitamin c and vitamin c regenerates hesperetin. Based on their oxidation potential, antagonistic interactions occur due to the regeneration of compounds with higher oxidation potential at the expense of compounds with lower action potential through the donation of H atoms [61]. On the other hand, the combination of ferulic acid and vitamin c showed an increase in FRAP value but had an ME value>1,

so the interaction of the binary compound combination cannot be confirmed and further studies are needed to clarify the resulting interaction. The difference in interaction in the combination of vitamin c and flavonoids is thought to occur due to differences in the type of derivative antioxidants combined and is one of the factors determining the interaction in a combination.

Interaction between vitamin c and carotenoids

Vitamin c and carotenoids have the same role as antioxidants. A study was conducted to determine the effect of vitamin c and astaxanthin intervention on *Adult Retinal Pigment Epithelial* (ARPE-19) cells that experience oxidative stress. It is known that giving a combination of 20M astaxanthin and 90M vitamin c produces an ARPE-19 cell viability value of 129% and reduces the level of ROS to reach 104% (much lower than the control, which is 200%) [53]. This shows synergistic interactions in increasing the probability of cells to be able to live after exposure to a material, namely H_2O_2, which is oxidative, and reducing the level of highly reactive ROS, in line with the increase in viability values in ARPE-19 cells. The decrease in the level of ROS occurs due to an increase in the phagocytic capacity of neutrophils so as to reduce the production of pro-inflammatory cytokines, as well as the protective effect against free radicals on cell membranes and neutralize them in the nonpolar area of phospholipid aggregates by astaxanthin [62].

Vitamin c also interacts synergistically with lycopene as an anti-inflammatory agent. The occurrence of inflammation is expressed by the production of pro-inflammatory cytokines such as *Tumor Necrosis Factor Alpha* (TNF-α) and Interleukin-8 (IL-8), which can be suppressed through compounds that are hydrophilic, lipophilic, and a combination of both, in this case, vitamin c and lycopene. This binary combination also significantly stimulated the expression of the anti-inflammatory cytokine gene Interleukin-10 (IL-10) and inhibited NFkB gene expression (P≤0.05). A study evaluating the potency of tomato sauce extract and its bioactive components on endothelial cell cultures or *Human Umbilical Vei Endothelial Cell* (HUVEC). HUVEC cells that had been treated with IL-8 and experienced inflammation were then intervened with tomato sauce extract combined with vitamin c and lycopene. This combination showed an effective decrease in monocyte chemotaxis by 69±4%, followed by a decrease in IL-8 concentration in HUVEC cells as a sign that there was a decrease in pro-inflammatory cytokine production [63].

The combination of vitamin c with carotenoids, especially astaxanthin and lycopene, with a certain ratio, shows a synergistic interaction. However, further studies are needed to determine the combination of vitamin c with other types of derived carotenoids and different ratios to determine the combination interactions that can occur.

Interaction between phenolic with flavonoids

A study combined curcumin and quercetin to determine the effect on MGC-803 gastric cancer cells. Both have IC50 values of 9.32±1.06 μM and 23.35±2.14 μM, respectively, so the combination of the two works synergistically as an anti-cancer by inhibiting the growth of MGC-803 gastric cancer cells by increasing apoptosis in cells [49].

Table 4: Test results of combination levels in inhibiting growth and apoptosis of MGC-803 gastric cancer cells

Component/combination	% Growth inhibition	Apoptosis rate
10.0 μM quercetin+5.0 μM curcumin	76.99%±3.06%	47.1%±2.4%
10.0 μM quercetin+10.0 μM curcumin	84.37%±4.99	-

Source: [59]

Apoptosis of MGC-803 cancer cells in table 4. Above significantly occurred in the combination of 10.0 μM quercetin and 5.0 μM curcumin. Apoptosis can be induced through intrinsic and extrinsic pathways. The intrinsic pathway is mediated by mitochondria, where when chemotherapy drugs enter the body, it will change the nature of the mitochondrial membrane and the release of cytochrome C as a biochemical sign of apoptosis [64]. This intrinsic apoptosis mechanism is also explained in this study. Intrinsic apoptosis testing of MGC-803 cells with a combination of 10.0 μM quercetin and 5.0 μM curcumin for 24 h showed a level of change/decrease in mitochondrial membrane properties to reach 48.14%±3.08%, thus increasing the occurrence of apoptosis of MGC-803 cancer cells ($p<0.05$) [49]. Curcumin can modulate various molecular targets, including transcription factors and cell growth, cytokines, enzymes, and genes that regulate cancer cell proliferation and apoptosis [65]. The level of apoptosis produced by quercetin is not more significant than curcumin. However, curcumin has a low level of bioavailability due to low water solubility so that its role as an anticancer agent cannot work optimally [66]. Quercetin has a role in increasing the bioavailability of curcumin by increasing its uptake into human carcinoma cells so that both work synergistically *in vitro* in inhibiting phosphorylation and inducing apoptosis of MGC-803 gastric cancer cells through the intrinsic pathway (mitochondrial pathway) [67].

Table 5: Synergy effect of phenolic and flavonoid binary combination based on FRAP testing

Combination	Concentration ratio (μM)	Interaction (%)
Gallic Acid+Quercetin	150+150	4.0
Gallic Acid+Rutin	150+150	1.6
Rosmarinic acid+Quercetin	150+150	12.6
Rosmarinic Acid+Rutin	150+150	-1.8
Caffeic Acid+Quercetin	600+150	37.9
Caffeic Acid+Rutin	600+150	3.6
Chlorogenic Acid+Quercetin	600+150	17.2
Chlorogenic Acid+Rutin	600+150	5.5

Source: [68], (+) Synergistic (-) Antagonistic

Based on some of the studies above, it is known that most of combinations with various concentration ratio variations show synergistic interactions. The differences in interactions that occur in both phenolic and flavonoid-derived compounds are known due to differences in the types and variations in the concentration ratios of antioxidant-derived compounds combined, resulting in differences in the resulting interactions. However, both synergistic, additive, and antagonistic interactions cannot be ascertained how the mechanism of these three interactions occurs because there are still very few studies that conduct such research.

Table 6: Synergistic interactions in binary combinations of quercitrin, epicatechin, and chlorogenic acid

Combination	Concentration ratio	Interaction
Quercitrin and Chlorogenic Acid	4:1	Synergistic
	2:1	Synergistic
	1:1	Synergistic
	1:2	Synergistic
	1:4	Synergistic
Epicatechin and Chlorogenic Acid	4:1	Synergistic
	2:1	Synergistic
	1:1	Synergistic
	1:2	Synergistic
	1:4	Additives

Source: [66]

Interaction between phenolics and carotenoids

An evaluation of the stability and antioxidant activity of a combination of phenolics and carotenoids was conducted in a study and showed that the combination can inhibit peroxidation initiated by MbFeIII, which is an iron component in food that acts as an inducer of lipid and protein oxidation. This inhibition of peroxidation is characterized by a decrease in absorbance compared to the control. Carotenoids (β-carotene and lycopene) play a role in stabilizing ferritin (MbFeIV=O) so that no conversion to the MbFeIII form occurs. The same is also done by chlorogenic acid, the hydrophilic nature of this compound plays a role in reducing peroxidation initiators. Known % synergy of acid combination chlorogenate with carotenoids in linoleic acid peroxidation at pH 5.8 and pH 4, 118.5% and 101.6%, respectively [50].

The same interaction also occurs in the combination of chlorogenic acid and β-carotene; these two compounds synergize in free radical scavenging (*t-BuO*). Not only that, chlorogenic acid also protects β-carotene from oxidation and also regenerates β-carotene from β-carotene radical cations formed due to the reaction of β-carotene with *t-BuO* radicals. Chlorogenic acid can regenerate β-carotene by 35.4% [70]. Regeneration of antioxidant compounds occurs when the bond dissociation energy possessed by an antioxidant is lower or equivalent to other antioxidants [71]. Chlorogenic acid has a bond dissociation energy of 80 kcal/mol, higher than the bond dissociation energy of β-carotene, which is 74 kcal/mol, so chlorogenic acid is able to regenerate β-carotene based on its bond dissociation energy.

The combination of phenolics and carotenoids not only synergize in inhibiting peroxidation, but also as anti-inflammatory agents. A study revealed that when inflammation in the body occurs, the NFkB transcription system will be activated to induce the secretion of cytokines, such as IL-6 as an inflammatory response. The combination of carnosic acid and lycopene showed an inhibitory effect on UVB-induced IL-6 release higher than the inhibition of each individual. These results suggest that the combination of these binary compounds can prevent the activation of NFB transcription induced by UV light and reduce the secretion of inflammatory cytokines such as IL-6. The prevention of oxidative stress by inhibiting peroxidation time, as described in the previous study certainly correlates with the suppression of inflammatory levels by this combination of phenols and carotenoids, so this combination of binary compounds works synergistically as a natural antioxidant agent [72].

Some of the studies above show that the combination of phenolics (chlorogenic acid and carnosic acid) with carotenoids (β-carotene and lycopene) produces synergistic interactions. However, this has not been able to represent the interaction of the combination of phenolics and carotenoids as a whole so further studies are needed regarding the combination of other phenolic and carotenoid derivative compounds to determine the interactions that can occur.

Interaction between Flavonoids and Carotenoids

The combination of flavonoids (quercetin and luteolin) with carotenoids (lycopene and lutein) was carried out to determine the effect of preventing oxidative stress on endothelial cell culture (HUVEC). There were 6 groups of combinations shown in this study, namely.

Table 7: Combination group between flavonoids and carotenoids

Group	Antioxidant combination	Concentration ratio
M1	Lycopene: Luteolin	1:5
M2	Lycopene: Quercetin	1:5
M3	Lutein: Luteolin	1:5
M4	Lutein: Luteolin	5:1
M5	Lutein: Quercetin	1:1
M6	Lutein: Quercetin	5:1

Source: [54]

A strong synergistic interaction was shown by the combination of M1-M5 in inhibiting ROS levels. M1-M3 also showed a synergistic effect in reducing NoX4 expression. An increase in NoX4 can be a sign of increased levels of *Reactive Oxygen Species* (ROS), which can trigger various diseases [73]. It is known that the combination of M2 can reduce NoX4 expression by 3.5 times and inhibit the expression of phosphorylated p65, which plays an important role in inducing inflammation. H_2O_2 treatment of HUVEC cells tries to activate p65 so that it triggers the activation of NF-kB transcription, which causes inflammation, but M2 works in the opposite way to prevent inflammation [54].

SIRT1 is a protein that plays a role in extending cell life and inhibiting metabolic disorders, as well as regulating oxidative stress [74]. In fact, there is a relationship between the combination of quercetin and lycopene on SIRT1 stability. This was proven by monitoring at 37 °C-47 °C; M2 showed higher SIRT1 expression and remained stable when the temperature was increased to 57 °C [54]. In theory, SIRT1 expression will decrease with increasing temperature [75], so it can be indicated that the combination of lycopene and quercetin (1:5) shows a synergistic effect on SIRT1 expression. The increase in SIRT1 expression in endothelial cell culture (HUVEC) is certainly significantly related to the decrease in NF-kB p65 expression induced by H2O2, as well as the suppression

of NoX4 production stimulated by NF-kB. This certainly has an impact on reducing the level of ROS through the SIRT1-NoX4 pathway, thus preventing oxidative stress.

These results show that combinations with a higher ratio of flavonoids to carotenoids actually provide a synergistic effect in terms of antioxidant activity. The reason why this happens is that flavonoids, both quercetin and luteolin, significantly increased lycopene uptake by 217% compared to individual lycopene alone, as well as lutein (M3 and M5). In contrast to M6, the much lower ratio of quercetin actually made lutein uptake decrease by 17% compared to lutein individually, so this result correlates with the synergistic effect on increasing antioxidant activity above and answers why M2 is the best combination in preventing oxidative stress.

In line with the above research, another study also revealed that the combination of *Carotenyflavonoids* has stronger antioxidant activity than its individual compounds. In addition, this combination was able to inhibit the peroxidation time for 3-3.2 h. This inhibition time is much longer than flavonoids and carotenoids individually, which is flavonoids inhibition time>2 h, while carotenoids<2 h [76]. The combination of other types of flavonoid and carotenoid derivatives also showed synergistic interactions. In a study conducted on the combination of EGCG and β-carotene, it was found that the combination with a higher concentration ratio of ECGC compared to β-carotene showed a *synergistic* interaction (*Synergistic Effect* value>1). Conversely, a lower ECGC concentration ratio triggers an antagonistic interaction [77]. This is because the role of ECGC can inhibit the oxidation of β-carotene, thereby enhancing the preservation of β-carotene. On the other hand, β-carotene also plays a role in increasing the antioxidant activity of ECGC so that the two synergize with each other. However, the combination with a higher β-carotene ratio showed an antagonistic interaction. The easily oxidized nature of β-carotene and turn into pro-oxidants actually favors in reducing the antioxidant effect of other compounds, thus reducing their antioxidant activity [78].

Similar to interactions in other compound combinations, differences in interactions occur in line with differences in the types and concentration ratios of flavonoid and carotenoid-derived compounds, so further studies are needed to determine interactions in each combination with different types and concentration ratios.

CONCLUSION

Based on the literature review above, it can be concluded that the natural antioxidants found in tropical fruits (vitamin c, phenolics, flavonoids, and carotenoids) can interact with each other causing synergistic, additive, and even antagonistic effects between antioxidant compounds. This interaction may strengthen the antioxidant activity between compounds or weaken the antioxidant activity of other compounds. This interaction is influenced by several factors, such as the type of antioxidant compound derivative, variation in concentration ratio, differences in oxidation potential and antioxidant bond dissociation energy. This either directly or indirectly affects the interaction of the combination between antioxidant compounds. The lack of studies on binary combinations of *antioxidant* compounds means that the mechanisms of *synergistic*, *additive* and *antagonistic* interactions are not clearly known, so this topic is very interesting to be studied further and in depth.

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Nil

AUTHORS CONTRIBUTIONS

Ardita T. Rahmasari devised and conceived of the presented ideas, planned the analysis method, searched, determined, and analyzed the selected articles, and wrote the final manuscript. Pramudya Kurnia devised and conceived of the presented ideas, verified the analysis method, and supervised the findings of this work.

CONFLICT OF INTERESTS

Declared none

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