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Synergistic anti-inflammatory effects and mechanisms of combined phytochemicals

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Abbreviations

AKT, serine/threonine-specific protein kinase

AMPK, 5'AMP-activated protein kinase

AP-1, activated activator protein 1 (AP

CCL2, chemokine (C-C motif) ligand 2

COX-2, cyclooxygenase-2

CRP, C-reactive protein

DHA, docosahexaenoic acid

EC50, median effective dose

EGCG, epigallocatechin-3-gallate

EPA, eicosapentaenoic acid

H_2O_2, hydrogen peroxide

HO-1, heme oxygenase-1

HUVEC, human umbilical vein endothelial cell

ICAM-1, intercellular adhesion molecule-1

IFN, interferon

IL-1, interleukin-1

iNOS, inducible nitric oxide

JNKs, c-Jun N-terminal kinases

LPS, lipopolysaccharides

MAPK, mitogen-activated protein kinases

MCP-1, monocyte chemoattractant protein-1 (MCP-1)

MMPs, matrix metalloproteinases

NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells

NO, nitric oxide

Nrf2, nuclear factor (erythroid-derived 2)-like 2

$O2^{\bullet-}$, superoxide,

$OH^{\bullet}$, hydroxyl

$ONOO^{\bullet-}$, peroxynitrite

PEG2, prostaglandin E2

PUFA, polyunsaturated fatty acid

SIRT1, sirtuin 1

ROS, reactive oxygen species

SOD, superoxide dismutase

TGF-β, transforming growth factor-β

TNF-α, tumor necrosis factor-α

VCAM-1, vascular cell adhesion molecule-1

Abstract

The anti-inflammatory effects of phytochemicals, bioactive components from plants having health benefits, have been heavily investigated in the last several decades. However, the gap between the high dosage demands (μM) of phytochemicals in vitro studies and the low bioavailability (nM) of most phytochemicals after consuming relevant foods/supplements in humans undermines the application of these phytochemicals in the prevention of chronic inflammation and its related chronic diseases in humans. One of the approaches to bridging this gap is to combine two or more phytochemicals/foods to synergistically prevent chronic inflammation. While increasing combinations of phytochemicals on anti-inflammation studies have been reported, there is no report dedicating why combining two or more phytochemicals synergistically attenuates chronic inflammation. In the present review, we summarized different types of combinations exerting synergistic anti-inflammatory effects such as the combination of phytochemicals from the same foods, and the combination of phytochemicals from different foods/plants. Particularly, we proposed five mechanisms including enhancing the bioavailability of phytochemicals, increasing antioxidant capacity, interacting with gut microbiome and targeting same and different signaling pathways, to understand how the combination of phytochemicals exerts synergistic anti-inflammatory effects in cells, animals, and humans. This review provides clues to boost more studies to combine several phytochemicals/foods to reduce chronic inflammation and prevent chronic diseases in humans.

Key Words: Anti-inflammatory, synergistic, combination, phytochemicals, mechanism

1. Introduction

While acute inflammation protects the body by contesting microbial invasion and healing injuries, chronic inflammation attacks critical molecules, cells, and organs to develop various chronic diseases such as cardiovascular disease, diabetes, cancer, and neurological diseases, therefore, accelerate aging [1]. Comparing to the signs of acute inflammation such as fever, swelling, redness, and pain, chronic low-grade inflammation is invisible and difficult to notice and is called silent inflammation. The chronic inflammation is characterized by high circulating levels of pro-inflammatory markers including interleukin-1 (IL-1), IL-6, IL-8, IL-13, C-reactive protein (CRP), interferon (IFN), transforming growth factor-β (TGF-β), tumor necrosis factor-α (TNF-α) and its soluble receptors and serum amyloid A [2]. These elevated pro-inflammatory molecules further recruit more immune cells such as neutrophils, eosinophils, monocytes, mast cells and platelets to produce more pro-inflammatory molecules as well as nitric oxide (NO), reactive oxygen species (ROS), resulting the damage of structure, function and integrity of lipids, proteins and nucleic acids, and then induce various chronic diseases [3]. The major risk factors of chronic inflammation are aging [1], unhealthy lifestyle involving tobacco use, alcohol use, stress, lack of regular physical activity and obesity [4, 5] as well as environmental pollution [6].

Strong evidence has been repeatedly presented to support that a healthy lifestyle reduces the risks of chronic inflammation and other chronic diseases [7, 8], particularly selecting healthy foods can significantly prevent chronic diseases from the epidemiological studies. For instance, taking a Mediterranean-like diet was closely associated with relatively lower levels of glucose,

lipids, CRP, blood pressure and 10-year cardiovascular risk in men [9]. The Dietary Approaches to Stop Hypertension (DASH) diet, which was originally developed to prevent cardiovascular diseases, significantly reduced circulating CRP and apolipoprotein as well as the rate of cardiovascular disease in humans [10]. Based on these observations, Barry Sears initiated the concept "anti-inflammatory diet" to fight obesity and obesity-induced metabolic syndrome characterized by chronic inflammation about 20 years ago [11]. All these healthy/anti-inflammatory diets comprise high consumption of fruits and vegetables (about half of the plate), and these fruits and vegetables contain high levels of phytochemicals, bioactive components from plants having protective effects. These phytochemicals may contribute to the beneficial effects of these healthy diets on the attenuation of chronic inflammation and thereby prevent various chronic diseases [9-11].

However, the understanding of the mechanism of these anti-inflammatory diets remains unclear because **1)** one food may contain several and even hundreds phytochemicals [12] and our diets usually have multiple foods; **2)** the complexity of the digestion, absorption, and metabolism of phytochemicals and foods; **3)** the disagreement between the high dosage demands of most phytochemicals in in vitro/vivo studies and the low bioavailability of most phytochemicals after consuming relevant foods/supplements in humans [13]. One of the approaches of solving these issues is to combine two or more phytochemicals to investigate if and how the combination synergistically exerts anti-inflammatory effect than the individual chemicals. In the present review, for the first time to our knowledge, we summarized the synergistic anti-inflammatory effects of different types of combinations of phytochemicals, particularly on reducing low-grade chronic inflammation, and proposed possible mechanisms of the synergistic anti-inflammatory effects of the combinations of phytochemicals using cardiovascular disease as a model.

2. Phytochemicals and the major issues of anti-inflammatory research using phytochemicals

2.1 Phytochemicals

Phytochemicals literally mean chemicals from a plant and there is no universal definition acceptable for everyone. However, this term in nutrition is used to describe plant-derived bioactive compounds having the potential health benefits [14, 15]. Most phytochemicals are secondary plant metabolites which are present in a large variety of foods including fruit, vegetables, cereals, nuts, and cocoa/chocolate as well as in beverages including juice, tea, coffee, and wine. More than 1 g of phytochemicals per day is commonly ingested with the diet [16]. According to the chemical structures, phytochemicals can be classified as seven main categories: phenolic compounds, terpenes, betalains, organosulfides, indoles/glucosinolates/sulfur compounds, protein inhibitors, and other organic acids. Table 1 lists some of the phytochemicals now attracting serious scientific attention, identifies food sources and outlines potential anti-inflammatory effects.

Table 1. Classification, food sources, and outlines potential anti-inflammatory effects of phytochemicals

Category			Chemical(s)	Food/Plant resources	Anti-inflammatory Effects
Phenolic compounds	Flavonoids	Flavonols	Fisetin	Strawberries, apples, persimmons, onions, and cucumbers	Inhibits the activity of several pro-inflammatory cytokines, including TNFα, IL- 6, and NF-κB [17]
			Kaempferol	Apples, grapes, tomatoes, green tea, potatoes, onions, broccoli	Reduces the release of TNF-α and IL-1β; Down-regulation the gene and protein expressions of pro-atherogenic molecules, such as E-sel, ICAM-1, VCAM-1 and MCP-1 [18]

		Galangin	Alpinia officinarum, Helichrysum aureonitens, and rhizome	Decrease IL-4, IL-5, and IL-13 levels, TNF-α induced p65 nuclear translocation and expression of MCP-1, CXCL10, and VCAM-1 [19]
		Myricetin	Grape, apple, berries, nuts, tea, and red wine	Prevent NF-κB activation in a monocyte; Inhibits the secretion of IL-6, IL-8 [20]
		Quercetin	Red onions, kale, apples, parsley, sage, tea	Reduce IL-6 and TNF-α levels via modulation of NF-kB [21]
	Flavanones	Hesperetin	lemons and sweet oranges	Reduce inflammatory targets including NF-κB, iNOS, and COX-2, and the markers of chronic inflammation [22]
		Naringenin	Grapefruit, herbs	Decrease the expression and production of TNF-α and MCP-1, suppress NF-κB activation [23]
	Flavones	Apigenin	Parsley, onions, tea, wheat sprouts	Inhibit TNFα-induced NF-κB transcriptional activation; inhibits TNFα-induced JNK activation [24]
		Luteolin	Beets, artichokes, leaves, rinds, barks, clover blossom, and ragweed pollen	Active anti-oxidative enzymes, suppress the NF-κB pathway and inhibits pro-inflammatory substances [25]
	Flavan-3-ols	Catechin	Tea, wine, cocoa,	Inhibit TNF-α -induced NF-κB activity and consequently strongly diminished the secretion of IL-8 [26]
		Epicatechin	Tea, wine, beans, cocoa	Inhibit diet-induced NF-κB activity [27]
		Epigallocatechin gallate	Tea, apple skin, plums, onions, hazelnuts, pecans, and carob powder	Decrease lipid peroxidation, oxidative stress and the production of NO radicals by inhibiting the expression of iNOS; Reduces the activity of NF-κB and AP-1 [28]
		Theaflavin	Black tea	Inhibit TNF-α-mediated activation of IκB kinase and subsequent activation of the IκB-α/NF-κB pathway [29]
		Proanthocyanins	Apples, berries, cocoa-based products, red grapes, red wine	Reduce serum levels of CRP, VCAM-1, and IL-1β [30]
	Anthocyanins	Malvidin	Blueberry, raspberry, black rice, and black soybean	Reduce serum levels of CRP, VCAM-1, and IL-1β [30]
	Isoflavones	Genistein	Lupin, soybeans, kudzu, and psoralea	Reduce peripheral and central NF-κB, NO system and pro-inflammatory cytokine over-activation [31]
		Daidzein	Soybeans	Inhibit the activation of the signal transducer and activator of transcription 1 (STAT-1) [32]
	Chalconoids	Phlorizin	Apple, pear, cherry	Inhibit the levels of NO, PGE2, IL-6, TNF-α, iNOS , and COX-2; suppress the p65 proteins, and decreased phosphorylation in MAPK pathways [33]
Phenolic acids		Ellagic acid	Walnuts, pecans, cranberries, raspberries, strawberries, grapes	Down-regulation of NF–κB, reduce biosynthesis of iNOS and ultimately inhibits the production of NO [34]
		Curcumin	Curcuma longa, Curcuma aromatic, Curcuma zedoaria	suppress the action of IL-6 through the downregulation of STAT3 activation; negatively regulates the action of IL-2;

					suppresses the activation of the transcription factor NF–κB [35]
	Hydroxycinnamic acids		Caffeic acid	Coffee, argan oil, thyme, sage, spearmint	Decrease levels of IL-6, IL-1β, TNF-α and MCP-1 [36]
	Stilbenoids		Resveratrol	Skin of grapes, blueberries, raspberries, mulberries	Inhibit iNOS and COX-2 via its inhibitory effects on NF-κB or the activator protein-1 (AP-1) [37]
Terpenes	Carotenoids	Carotenes	Carotene	Sweet potato, carrots, mustard greens, apricots, asparagus, broccoli	Downregulation of iNOS, COX-2, and NADPH oxidase protein and mRNA expression and synergistic inhibition of TNFα secretion [38]
			Lutein	Spinach, kale and yellow carrots	Reduce the level of nuclear NF-κB, IL-1β, and Cox-2 [39]
	Monoterpene	Limonene		Oils of citrus, cherries, spearmint	Inhibit the production of ROS; diminished MCP-1 production via NF-κB activation; inhibits cell chemotaxis in a p38 MAPK dependent manner [40]
	Saponins			Vegetables, beans and herbs, soapwort, soaproot, soapbark, and soapberry	Inhibit of COX-2 activity and TNFα production [41]
	Lipids		β-Sitosterol	Vegetable oil, nuts, avocados	Inhibit the phosphorylation of NF-kB [42]
	Triterpenoid		Lupeol	Mango, Acacia visco, abronia villosa	Reduce CD4 + T and CD8 + T cell counts and the level of IL-2, IFN-gamma and IL-4 [43]
Betalains	Betacyanins	Betanin		Beets, Opuntia cactus, Swiss chard	Reduce superoxide anion, TNF-α, and interleukin IL-1β levels , increase IL-10 levels [43]
	Betaxanthins	Indicaxanthin		Beets, Mirabilis jalapa flowers, prickly pears, red dragonfruit	Inhibit the release of PGE2, NO, IL-1b, and TNF-α, decrease IL-1b, TNF-α, iNOS, and COX2 mRNA [44]
Indoles, sulfur compounds	Indole-3-carbinol			Broccoli, cabbage, cauliflower, brussels sprouts, collard greens, and kale	Reduce the production of pro-inflammatory mediators such as NO, IL-6, and IL-1b in through attenuation of the TRIF-dependent signaling pathway; suppress pro-inflammatory cytokine production such as IL-6, TNF-α [45]
	Sulforaphane			Broccoli, Brussels sprouts, and cabbages	Inhibit LPS-stimulated mRNA expression, protein expression, and production of TNF-α, IL-1β, COX-2 and iNOS [46]
	Allicin			Garlic	Increase the phosphorylation of Akt and endothelial nitric oxide synthase (eNOS) [47]
Protein inhibitors	Protease inhibitors			Orange, spinach, rhubarb	Inhibit the downstream portion of the NF-kB pathway; reduce the production of IL-1, TNF-α, IL-6, and IL-10 [48]
Other organic acids	Lactic acid			Koumiss, laban, yogurt, kefir, cottage cheeses	Decrease TNF-α secretion; inhibits NF-kB activation [49]
	Anacardic acid			Cashews, mangoes	Inhibit NF-κB activation; suppress the activation of IκBα kinase; inhibits acetylation and nuclear translocation of p65 [50]

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2.2 Major issues and solutions of anti-inflammatory research using phytochemicals

Although many phytochemicals of each category exert anti-inflammatory effects, the complexity of the digestion, absorption, metabolism, and interactions of phytochemicals and foods undermines the understanding and application of these anti-inflammatory phytochemicals/foods to attenuate chronic inflammation and thereby prevent chronic diseases [51]. For instance, the quantity and composition of phytochemicals in plants are significantly influenced by species, age, part of the plant, cultivation method, harvesting season, preservation method and geographical distribution [52]. Particularly, the range of concentrations of phytochemicals typically used to study mechanisms in cell culture models (1–100 μM, or sometimes higher) is generally higher than the levels in the bloodstream (usually at nM to very low μM) following consumption of typical doses in foods and supplements [53, 54]. The low bioavailability of phytochemicals may be caused by [13]: **1)** special molecular structures such as attached to β-glucosides, high molecular weights, isomeric configuration, hydrophobic and low solubility in the lumen; **2)** most phytochemicals do not have the optimal physicochemical properties necessary for passive diffusion, trans-membrane transporters are needed for enhancing their permeability; **3)** complex metabolism and interactions between different nutrients and phytochemicals. For instance, after entered into an enterocyte, the phytochemical may be subjected to several phase II enzymes leading to conjugation with methyl (catechol-O-methyltransferases-COMT), sulfate (sulphotransferases-SULT) and glucuronyl groups (uridine-5'-diphosphate glucuronosyltransferases-UDPGT) and resulted as different chemicals from the original form [55].

However, many phytochemicals and whole foods appear to effectively prevent or ameliorate the symptoms of metabolic syndrome even at low dietary doses in animals [56, 57]

and humans [58, 59]. For example, theobromine, a phytochemical from cocoa, synergistically enhanced the anti-hypertensive effect of (−)-epicatechin, the major phytochemicals in cocoa, by increasing the circulating level of (−)-epicatechin in humans [59], indicating whole cocoa (extract) intake is better in reducing blood pressure than that of pure (−)-epicatechin alone. Another study found that co-administrating nutrient mixture (ascorbic acid, selenium, L-lysine, L-proline, L-arginine, N-acetyl cysteine, magnesium, calcium, copper, and manganese) or red onion can increase epigallocatechin-3-gallate (EGCG) level blood by stabilizing EGCG in the lumen in rats and humans [60]. Therefore, whole foods or a combination of several phytochemicals may enhance the health benefits of the phytochemical without increasing dosages. Furthermore, one food may contain multiple even hundreds phytochemicals (for instance, there are about 200 phytochemicals in pomegranate) [12] and one phytochemical may produce many metabolites in the body [51], and these phytochemicals may interact and produce more efficient beneficial effects than individual phytochemicals. Indeed, combinations of a couple of phytochemicals synergistically improve osteoporosis [61] and suppress obesity and oxidative stress [62]. In addition, a mixture of wild bilberry, cranberry, elderberry, raspberry, and strawberry exhibited higher antioxidant capacities when compared with the individual berries [63]. Breda et al proposed combinations of fruits and vegetables with high levels of phytochemicals to prevent chronic inflammation and chronic diseases [64]. In fact, the major characteristics of famous Mediterranean diet [9] and DASH diet [10] are combinations of high phytochemicals foods such as legumes, olive oil, wine, nuts as well as fruits and vegetables, and the typical Mediterranean diet contains 18 subclasses of phytochemicals and 290 different phytochemicals [65]. Therefore, combine two or more phytochemicals/foods is a reasonable way to bridge the gap between the high dosages of demands in cells/animals and the low levels in

humans by consuming the foods or supplements, and then reduce chronic inflammation and prevent chronic diseases in humans.

2.3 Measurements of the effects of a combination of two or more phytochemicals

Combing two or more phytochemicals is not always enhancing the specific effect. In fact, combination of two or more active chemicals can produce an additive (combined effect is equal to the sum potency of individual components of the mixture), synergistic (combined effect is greater than the sum potency of individual components of the mixture), or antagonistic (combined effect is less than the sum potency of individual components of the mixture) effect [66]. To evaluate and interpret scientifically, in 2006 Chou et al [67] developed the Combination Index (CI): CI < 1 indicates synergy; CI =1 means addition; CI > 1 means antagonism. CI is calculated from the below equations.

For binary combination of A and B at 50% activity: $CI_{50} = C_A/ IC_{50}(A) + C_B/IC_{50}(B)$, where CI_{50} is Combination Index for the binary mixture at 50% activity; C_A and C_B is the proportional dose of compound A and compound B (respectively) in the mixture that shows 50% activity; $IC_{50}(A)$ and $IC_{50}(B)$ is the single dose of each compound A and B that provides 50% activity.

For n-phytochemical combination at x% inhibition: $^{n}(CI)x = \sum_{j=1}^{n} \frac{(D)j}{(Dx)j}$, where $^{n}(CIx)$ is a combination index for n compound mixture at x% activity; $(D)_j$ is the proportional dose of each compound in n- phytochemical mixture that shows x% activity; $(D_X)_j$ is the single dose of each compound that provides x% activity.

Based on this CI equation, more and more software (CalcuSyn, Chalice, CompuSyn, Combenefit, Genedata Screener, SynergyFinder) have been developed and widely used to evaluate the interaction of a combination of chemicals [68].

In this review, CI has been used in numerous articles to screen relevant combinations. CI and synergy based on the equation have been used, and only the phytochemicals/foods combinations having synergistic anti-inflammatory effects were discussed.

3. Synergistic anti-inflammation effects of combined phytochemicals

3.1 Combination of phytochemicals from the same foods

To overcome the controversy that whole food or raw extracts exert beneficial effects but the individual major phytochemicals from the food lose the health benefits, combining several phytochemicals from the same food may exert synergistic anti-inflammatory effects. Indeed, while resveratrol and quercetin can be found from many different foods/plants, both of them are detected from fresh grape skin (50–100 μg/g and 40 μg/g of resveratrol and quercetin respectively) and red wine (7–13 μM and 7.4 μM of resveratrol and quercetin respectively) [69]. A recent study found that combination of resveratrol (120 mg/kg/day) and quercetin (240 mg/kg/day) attenuates high fat diet-induced circulating inflammatory markers such as TNF-α, IL-6, and monocyte chemoattractant protein-1 (MCP-1) in rats [70]. The same author also reported that combination of resveratrol (2g/kg/day) and quercetin (2g/kg/day) synergistically reversed high fat diet-changed genes of inflammation/immunity compared to the individual chemicals in mice [71]. Similarly, two studies show that combined treatments of flavonoid quercetin and ω-3 polyunsaturated fatty acids (PUFA, available from grape seed) had synergistic

anti-inflammatory and antioxidant effects in rats [72, 73]. In a randomized double-masked controlled human studies, a combination of theobromine and (−)-epicatechin, two phytochemical from cocoa, synergistically lowered blood pressure and mobilized circulating immune cells [75]. Supplementation with 255 mg/day of a chokeberry flavonoid extract (about 25% anthocyanins, 50% polymeric procyanidins and 9% phenolic acids) for 6 weeks significantly reduced hs-CRP by 23% in patients after myocardial infarction [74].

3.2 Combination of phytochemicals from different foods

Most combinations of phytochemicals having synergistic anti-inflammatory effects are combining phytochemicals from different foods/plants. For instance, green tea major phytochemical EGCG (40 nM) and soybean-derived genistein (2 μM) were combined at lower concentrations synergistically inhibits iNOS generation in a murine macrophage RAW264.7 [62]. Rinwa et al reported that co-administration of black pepper-derived piperine (20 mg/kg) with curcumin (100, 200 mg/kg) from spice turmeric synergistically lowered brain TNF-α and caspase 3 levels compared to their effects alone in olfactory bulbectomy-induced depression rat [75]. This synergistic anti-inflammatory effects of combined curcumin and piperine have been confirmed in humans [76]. Daily administration of policosanol (majorly from sugar cane) and/or 10-dehydrogingerdione at a dose level 10 mg/kg BW synergistically resulted in reducing sP-selectin and interferon-gamma (IFN-γ) in dyslipidemic rabbits [77]. Combination of arctigenin and curcumin or curcumin and EGCG synergistically increased bax/bcl-2 ratio and inhibited NF-KB levels compared to the individual chemicals, but the most efficient one is the combination of three chemicals together (arctigenin 1 μM, curcumin 5–10 μM, EGCG 40 μM respectively) [78]. Similarly, a combination of curcumin and resveratrol synergistically inhibited inflammation both in vitro and in vivo [79, 80]. Ka Lung Cheung et.al reported [81] that curcumin combined with

sulforaphane or phenethyl isothiocyanate synergistically inhibited LPS-induced inflammation in RAW 264.7 cells, which was evidenced by the decrease in inducible nitric oxide (iNOS), cyclooxygenase-2 (COX-2) protein expression and NO, TNF-α and IL-1 production in the medium. Synergistic interaction between Astragali Radix and Rehmanniae Radix in a Chinese herbal formula to promote diabetic wound healing [82].

Another study found that combination treatment with cocoa polyphenols and ω-3 fatty acids is a promising approach to inhibit inflammation and reduce cardiovascular risk factors associated with aging in humans [83]. Similarly, combinations of eicosapentaenoic acid (EPA) (0.125 μM) with carnosic acid (0.2 μM) and lutein (0.2 μM) caused a synergistic inhibition of prostaglandin E2 (PGE2) release, IL-6 secretion, superoxide and NO production in microglia exposed to lipopolysaccharides (LPS) [84]. 1% curcumin or 0.02% limonin combined with fish oil synergistically suppressed $CD4^+$ T-cell proliferation, IL-2 production and NF-KB activity in mice [85]. A combination of lycopene (7.5 μM), α-tocopherol (1.4 μM) or ascorbic acid (55 μM) significantly reduced gene expression and release of the pro-inflammatory cytokines TNF-α and IL-8 but increased anti-inflammatory cytokine IL-10 in human umbilical vein endothelial cell (HUVEC) cells, with similar results of tomato ketchup extracts [86]. A 3-week randomized, double-blind, placebo-controlled, 2 × 2 factorial clinical study shows that combination of n-3 PUFA (1.4 g/d) and plant sterols (2 g/d) per day, synergistically reduced inflammatory markers such as hs-CRP (39%), TNF-α (10%), IL-6 (10.7%) and leukotriene B4 (29.5%) but increased adiponectin by 29.5% [87]. Most importantly, the overall cardiovascular risk was reduced by 22.6% ($P = 0.006$) in the combination group in hyperlipidemic individuals [87]. Lay Saw et.al [88] reported that combinations of curcumin and docosahexaenoic acid (DHA) or EPA have synergistic effects in suppressing LPS-stimulated NO, iNOS, COX-2 in RAW 264.7 cells.

We randomly screened combinations (combined two of 20 phytochemicals at various concentrations) to select the combinations having synergistic anti-inflammatory effects using TNF-α-induced monocyte adhesion to endothelial cells. We found that combinations of resveratrol and luteolin (high contents from radicchio, peppers, and celeries) or luteolin and curcumin, at physiological achievable levels, synergistically inhibited TNF-α-induced monocyte adhesion to endothelial cells while the individual chemical did not have significant effects. Moreover, the synergistic anti-inflammatory effects of these two combinations were mediated through regulating intercellular adhesion molecule 1(ICAM-1), MCP-1 and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) expressions both in in vitro and in vivo. Particularly, the CI values of these two combinations are around 0.7 in the in vitro studies (data not shown).

4. Mechanisms of the synergistic anti-inflammation of combined phytochemicals

4.1. Enhance the bioavailability/uptake of each other

Suganuma et al. found that (−)-epicatechin enhanced the incorporation of EGCG into a human lung cancer cell line PC-9 [89]. Genistein increased cytosolic EGCG by 2- to 5-fold compared with treatment with EGCG only in human colon cancer cells [90]. The same authors also reported that genistein increased the levels of EGCG in the small intestine and plasma following oral dosing of EGCG and genistein in mice [91]. Another study reported that the circulating level of EGCG was significantly increased by co-administrating nutrient mixture

because ascorbic acid, selenium, and other nutrients stabilize EGCG in the lumen and help to build up its concentration in the intestine [60]. Similarly, combining DHA (10 μM) with curcumin (10 μM) significantly enhanced the curcumin uptake in human breast cancer SK-BR-3 cells possibly through alteration of membrane lipid composition [92]. This has been observed for DHA in which it enhances the effects of other anti-cancer compounds 5-fluorouracil in colon cancer cells [93], celecoxib in prostate cancer cells [94], and doxorubicin in breast cancer patients [95]. Shoba et al [96] showed that co-administration of piperine and curcumin to humans and rats enhanced the bioavailability of curcumin by 2000% and 154%, respectively. This may be a result of the inhibition of the glucuronidation of curcumin by piperine because curcumin is heavily metabolized in the form of glucuronide conjugates prior to reaching the plasma and piperine is a well-known inhibitor of hepatic and intestinal glucuronidation [97]. The absorption rate of rosmarinic acid in Caco-2 cells is significantly boosted in the presence of luteolin and apigenin because luteolin and apigenin inhibit the efflux of rosmarinic acid by inhibiting ABC transporters [98]. Similarly, the bioavailability of quercetin is increased in the presence of proanthocyanidins via forming hydrogen bonds between these chemicals, which possibly contribute to improving the solubility and stability of quercetin [99]. A recent study reported that theobromine, a phytochemical from cocoa, synergistically enhanced the anti-hypertensive effect of (−)-epicatechin by increasing the circulating level of (−)-epicatechin in humans [59].

4.2 Synergistically boost antioxidant capacity

The critical roles of oxidative stress on the development of chronic inflammation and chronic diseases have been well recognized [100]. Oxidative stress is a state of imbalance between oxidants and antioxidants in favor of the oxidants, also called the reactive oxygen species (ROS),

includes free radicals such as O_2•− (superoxide), ONOO•− (peroxynitrite) and OH• (hydroxyl), and non-radicals such as hydrogen peroxide (H_2O_2). Many individual phytochemicals are found to have the antioxidant capacity of directly scavenging ROS, metal chelating, tempering the mitochondrial respiratory chain, inhibiting certain enzymes as well as increasing endogenous antioxidants enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase both in vitro [101] and in vivo [102]. At the whole food level, Sinha et al [103] tested the total antioxidant capacity (using four assays: ferric reducing antioxidant power, 2,2-diphenyl-1-picrylhydrazyl, radical scavenging capacity, and oxygen radical absorbance capacity) of combinations between different foods. Within the same food category, 13% of the tested combinations showed synergistic effect, while across food categories 21% of the tested combinations demonstrated a synergistic effect. The strongest antioxidant capacity is the combination of raspberry and adzuki bean [103]. Fruit with fruit combination also synergistically increased antioxidants capacity [104]. For instance, the combination of orange, apple, grape, and blueberry displayed a synergistic effect in antioxidant activity because the median effective dose (EC50) of each fruit after combination was 5 times lower than the EC50 of each fruit alone [105]. Tomatoes contain a matrix of many bioactive components including vitamin C, vitamin E, other carotenoids (a-, beta-, gamma- carotene, lutein), and flavonoids, and mixtures of lycopene and vitamin E appear to have the greatest synergistic antioxidant activity [106].

The possible mechanisms of the synergistic enhancing antioxidant capacity are **1)** protection each other because the combined phytochemicals act in different ways of antioxidation that enable them to protect each other from oxidative agents. For instance, a chain breaking antioxidant scavenges free radicals to protect a singlet oxygen quencher from oxidation and that enables the latter to stay active longer to protect the former against singlet oxygen oxidation

[107]; **2)** one antioxidant reacts with free radicals or singlet oxygen first to protect the partner from oxidants ; **3)** one antioxidant is oxidized and becomes a free radical, and this free radical then receive electrons or hydrogen atoms from the other antioxidant to regenerate itself [108]; **4)** the chelates metal ions of one antioxidant to allow the oxidant to remain active [109]; **5)** the different orientation or position at the water/lipid interface or within the membrane of antioxidants facilitates synergistic interactions [110]; **6)** formation of a very strong antioxidant. For example, phytochemical-enhanced heme oxygenase-1 (HO-1) makes stronger antioxidant bilirubin and lead to a higher cellular antioxidant capacity [111]; **7)** two or more above six mechanisms may be contributing to the synergistic antioxidants of combined foods or phytochemicals [109, 110, 112].

4.3 Target gut microbial profiles and gut integrity

The gut microbiome, composed of bacteria, archaea, viruses, and eukaryotic microbes, play critical roles in maintaining healthy physiology and contributing to diseases [113]. Particularly, gut microbiome has critical influences on systemic immune and inflammatory components [114, 115]. The interactions between phytochemicals and gut microbiota have been reviewed [116, 117]. A combination of resveratrol (120 mg/kg/day) and quercetin (240 mg/kg/day) attenuates high fat diet-induced circulating inflammatory markers such as TNF-α, IL-6 and MCP-1 in rats through regulating gut microbiota, particularly the ratio of *Firmicutes/Bacteroidetes* ratio and other groups, which are associated with inflammation and immune system [118]. Interestingly, while resveratrol [119] and quercetin alone can regulate the *Firmicutes/Bacteroidetes* ratio, resveratrol can inhibit the growth of *Enterococcus faecalis*, and increase the growth of *Lactobacillus* and *Bifidobacterium* [119], but quercetin attenuates the growth of *Erysipelotrichaceae, Bacillus, Eubacterium cylindroides* in rats [120]. In addition, the

synergistic anti-inflammatory effect of a combination of resveratrol and quercetin may result from the protective effect of resveratrol on the mucosal barrier integrity [120] which can reduce the circulating endotoxin [121], one of the major stimulators of inflammation. Moreover, a combination of resveratrol and quercetin can up-regulate *Blautia stercoris, Clostridium clariflavum, and Clostridium methylpentosum* [120], which in turns the metabolism of quercetin and other phytochemicals and increased the bioavailabilities of these phytochemicals [117].

4.4 Target different cells, inflammatory markers, and signaling pathways

Inflammation plays a central role in the etiology and development of several vascular diseases including atherosclerosis [122, 123] and ischaemic heart disease [124]. The endothelium is activated by abnormal shear stress, high glucose and result in an increase in permeability to lipoproteins and upregulation of adhesion receptors, and facilitate deposition of lipoproteins in the sub-endothelial space. Activated endothelial cells also promote the recruitment of circulating monocytes by secreting cell-adhesion molecules such as ICAM-1, P-selectin, MCP-1and VCAM-1, these endothelial cells and immune cells further produce chemokines and chemokine receptors such as chemokine (C-C motif) ligand 2 (CCL2), CCL5, CX3C and CCR2, CCR5 to facilitate the transmigration, differentiation and proliferation of monocytes, macrophages, eosinophils and neutrophils as well as T and B lymphocytes. These activated immune cells secrete more pro-inflammatory cytokines such IL-1, IL-4, IL-6, IL-10 and TNF-α, which in turn escalate the inflammation process and generate more ROS as well as NO to damage macromolecules DNA, proteins and oxidize more lipids [125, 126].

Resveratrol attenuated monocyte-to-macrophage differentiation, and monocyte infiltration in cells and mice via restoring intracellular glutathione (GSH) levels [127]. Dietary resveratrol

significantly lowered levels of mac-3-positive macrophages (a measure of the infiltration of activated macrophages) and reduced ICAM-1, VCAM-1 and MCP-1 expression/levels both in the aorta and plasma as well as reduced the activity of the transcriptional regulator NF-kB in aortic tissues of diabetic mice [128]. However, quercetin can increase the macrophages cholesterol efflux [129] and macrophage migration [130] as well as modulate M1/M2 macrophage polarization [131]. These complementary effects of each chemical at least partly contribute to the synergistic anti-inflammatory effects of combined quercetin and resveratrol in animals [70, 71].

While both curcumin [132] and piperine [133] can regulate common signaling pathways including NF-kB, 5' AMP-activated protein kinase (AMPK), mitogen-activated protein kinases (MAPKs) and nuclear factor (erythroid-derived 2)-like 2(Nrf2)/HO-1, curcumin [134] can significantly increase the endothelial nitric oxide level, which is critical for the integrity of endothelial cells and the production of pro-inflammatory markers ICAM-1, VCAM-1 and MCP-1, but there is no report if piperine increases nitric oxide level in endothelial cells. Moreover, the piperine can significantly increase the curcumin bioavailability by inhibiting the hepatic and intestinal glucuronidation of curcumin [97]. Moreover, curcumin alone did not have an effect on the IL-10 level, but it significantly increased the piperine-increased IL-10 level in periodontal disease animal model after 15 days treatment [135]. Therefore, these common and different targets complementary contribute to the synergistic anti-inflammation of a combination of piperine and curcumin both in rats [75] and humans [76].

4.5. Target same cells, inflammatory markers, and signaling pathways

While each phytochemical has its specific interactions on cells, inflammatory markers, and signaling pathways as described above, two or more phytochemicals may also target the same immune and other cells, produce same inflammatory markers by the same pathways. The critical point of the shared targets by different phytochemicals is that a combination of two or more phytochemicals reaches the threshold the level of activating the shared pathway while the individual phytochemical cannot reach this level. This is particularly vital for the low circulating levels of phytochemicals by dietary intake.

Because of the key roles in inflammation, macrophages are the major target of anti-inflammation research, particularly in vitro studies. Indeed, resveratrol [136], quercetin, kaempferol [137], curcumin [138], genistein [137], luteolin [139], EGCG [28], epicatechin and various food extracts [140, 141] have been shown in inhibiting pro-inflammatory molecules such as TNF-α, IL-1β, IL-6, PGE2 and NO in macrophages. Moreover, resveratrol [142], luteolin [143], and EGCG [144] stimulate anti-inflammatory markers IL-10 and TGF-beta1 expression in macrophages. Quercetin [145] and kaempferol [146] as well as resveratrol [147] inhibits typical pro-inflammatory enzymes, iNOS and COX-2 and therefore decreases NO production via interference with the NF-κB pathway and iNOS/COX-2 induction in Raw264.7 cells. Moreover, luteolin, quercetin, and resveratrol [148, 149] are able to stimulate the expression of the anti-inflammatory cytokine IL-10 in macrophages.

Another example is the endothelial cells, the frontline of interaction between environmental factors through circulating blood and inner body, interact with various immune cells to initiate the vascular inflammation. Interestingly, genistein [150, 151], EGCG [152], curcumin [153], resveratrol [154], quercetin [155], luteolin [156] and epicatechin [157] can maintain the integrity of endothelium and reduce adhesion molecules ICAM-1, VCAM-1 and

MCP-1 via regulating endothelial nitric oxide level. These reduced adhesion molecules further reduce the adhesion and migrations of monocytes to endothelial cells [132, 158].

NF-kB pathway plays a critical role of chronic-inflammation because IL-1 and/or TNF-α-activated NF-kB increase production of cytokines, chemokines, and adhesion molecules as well as leukocyte recruitment, and attenuating NF-kB pathway is a key approach to fight chronic inflammation [159]. Indeed, tea extracts and EGCG [160], genistein [161] and resveratrol [162] inhibit inflammation by diminishing NF-kB cascade. Irigenin (3-30μM) inhibits iNOS and COX2 expression via interference with NF-κB translocation and binding in Raw264.7 cells [163]. Quercetin (~40 μM) has been reported to inhibit IP-10 and MIP-2 expression in intestinal epithelial cells via NF-κB modulation [164]. Curcumin inhibits IL-8, COX-2, and HO-1 expression through inhibiting NF-kB in the airway epithelium [165, 166]. Chrysin, ellagic acid, genistein or EGCG at 50 μM reduced IκB-α phosphorylation and diminished IL-8 secretion in intestinal Caco-2 cells [167].

The transcription factor nuclear factor (erythroid-derived 2)-like 2(Nrf2), a master regulator of redox homeostasis by regulating the expression and activity of enzymes NADPH, NAD(P)H quinone oxidoreductase 1, glutathione peroxidase, ferritin, heme oxygenase-1 (HO-1), also affects pro-inflammatory mediators including cytokines, COX-2 and iNOS. The most investigated phytochemicals including epicatechin [168], resveratrol [169, 170], quercetin [171, 172], curcumin [173, 174], EGCG [175], luteolin [176], genistein [177], piperine [178] and apigenin [179] exerts anti-oxidative and anti-inflammatory effects via regulating Nrf2/HO-1 pathway [180].

Mitogen-activated protein kinases (MAPKs) are a family of serine/threonine protein kinases that mediate fundamental biological processes and cellular responses to external stress signals. Increased activity of MAPK, in particular, p38 MAPK, and their involvement in the regulation of the synthesis of inflammation mediators at the level of transcription and translation make them potential targets for anti-inflammatory therapeutics. The anti-inflammatory activity of curcumin has been associated with a reduction in the activation of p38 MAPK but not c-Jun N-terminal kinases (JNKs) in vivo [181], and resveratrol attenuates inflammation by regulating p38 MAPK [182, 183], therefore, the mutual target p38MAPK mediates the reductions COX-2, IL-6 and IL-8 production by combination of curcumin and resveratrol in normal prostate epithelial [184]. Similarly, the anti-inflammatory actions of quercetin [185], EGCG [186] and curcumin [187] were also associated with activation of the AMPK pathway, suggesting that activation of AMPK may serve as a key mechanism of the phytochemicals anti-inflammatory effects.

AMPKα1/sirtuin 1 (SIRT1) signaling pathway exerts its anti-inflammatory effects both in endothelial cells [32], adipocytes [188] and macrophages [189], and AMPKα1 inhibits the activation of the NF-κB system [190]. Activation of AMPKα1 suppresses the synthesis of pro-inflammatory cytokines, such as IL-6 and IL-8 in adipocytes [191]. A combination of resveratrol (120 mg/kg/day) and quercetin (240 mg/kg/day) attenuates high fat diet-induced circulating inflammatory markers such as TNF-α, IL-6, and MCP-1 through regulating AMPKα1/SIRT1 signaling pathway in rats [70]. This synergistic effect of combined resveratrol

and quercetin at least results from the shared AMPKα1/SIRT1 signaling pathway because both resveratrol [192] and quercetin [193] can regulate this pathway alone.

The complicated interactions between endothelial cells and immune cells and the interactions between these major signaling pathways may contribute to the synergistic anti-inflammatory effects of combined phytochemicals. For instance, both resveratrol and quercetin dose-dependently inhibited thrombin-activated endothelial cells, neutrophil migration via regulating MAPK, pMAPK, and JNKs molecules [194], which may partly interpret how the combination of resveratrol and quercetin synergistically reverses high fat diet-induced chronic inflammation in animals [70, 71]. Similarly, a combination of curcumin and sulforaphane synergistically up-regulated HO-1invovling Nrf2, NF-kB and activated activator protein 1 (AP-1) signals and lead to a higher cellular antioxidant capacity by the formation of the very strong antioxidant bilirubin [111], and therefore reduced iNOS and COX-2 protein expression and their related inflammatory molecules [81]. Combination of sulforaphane and EGCG synergistically enhanced antioxidant capacity and AP-1, a transcription factor regulates gene expression of inflammation [195]. For instance, both Nrf2/HO-1 pathways and NF-KB pathways mediate the anti-inflammatory effect of the combination of curcumin and resveratrol [196].

5. Conclusions

The synergistic anti-inflammatory effects of combined phytochemicals may be the results of regulating multiple pathways, multiple cells, and inflammatory markers. For the case of combination of curcumin and piperine, in colon and liver, piperine inhibits the hepatic and intestinal glucuronidation of curcumin and increases the curcumin bioavailability, at the same

time, the gut microbiome metabolize these chemicals and chemicals, in turn, affect the profiles of the microbiome and finally promote the levels of chemicals in the blood and tissues. After interacting with endothelial cells and various immune cells, the chemicals may directly scavenge the elevated ROS, increase endogenous antioxidants/enzymes such as SOD and/or promotes the Nrf2/HO-1 system to fight oxidative stress. These reduced ROS and/or the chemicals directly further regulates AMPK/SIRT1 or MAPK cascades to attenuate NF-kB pathway. The attenuated NF-kB molecules then deregulate the transcription and translation of pro-inflammatory markers ICAM-1, VCAM-1, MCP-1, TNF-α, IL-1β, IL-6, PGE2 and NO as well as upregulate anti-inflammatory molecules such as IL-10 level and endothelial NO, which in turn suppress the proliferation, migration of immune cells and maintain the integrity of endothelial cells to further reduce the production of pro-inflammatory markers and eventually inhibit chronic inflammation (see hypothetical mechanisms using vascular inflammation model as **Figure 1**). This review provides clues to boost more studies to combine several phytochemicals/foods to reduce chronic inflammation and prevent chronic diseases in humans.

Disclosure statements

The authors have nothing to disclose.

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Figure legends

Fig. 1. Hypothetical mechanisms of the synergistic anti-inflammatory effect of combined phytochemicals using vascular inflammation as a model. Combination of phytochemicals A and B exerts synergistic anti-inflammatory effects through multiple mechanisms: B increases bioavailability/uptake of A in the blood and tissues by regulating A's metabolism in the gut and liver. At the same time, the interactions between the gut microbiome and phytochemicals result in the changes of the profiles of the microbiome and promotion of the levels of phytochemicals. After interacting with endothelial cells and various immune cells, phytochemicals may directly scavenge the elevated ROS, increase endogenous antioxidants/enzymes such as SOD and/or promotes the Nrf2/HO-1 system to fight oxidative stress. These reduced ROS and/or the chemicals directly further regulates AMPK/SIRT1, Nrf2/HO-1 and/or MAPK cascades to attenuate NF-kB pathway in the cytosol. The attenuated NF-kB molecules then transfer into nuclear to regulate the transcription and translation of pro-inflammatory markers ICAM-1, VCAM-1, MCP-1, TNF-α, IL-8, IFNβ as well as upregulate anti-inflammatory molecules such as IL-10 level, Nrf2/HO-1, and endothelial NO. These changed molecules, in turn, suppress the proliferation, migration of immune cells and maintain the integrity of endothelial cells to further reduce the production of pro-inflammatory markers and eventually inhibit chronic inflammation in vasculature.

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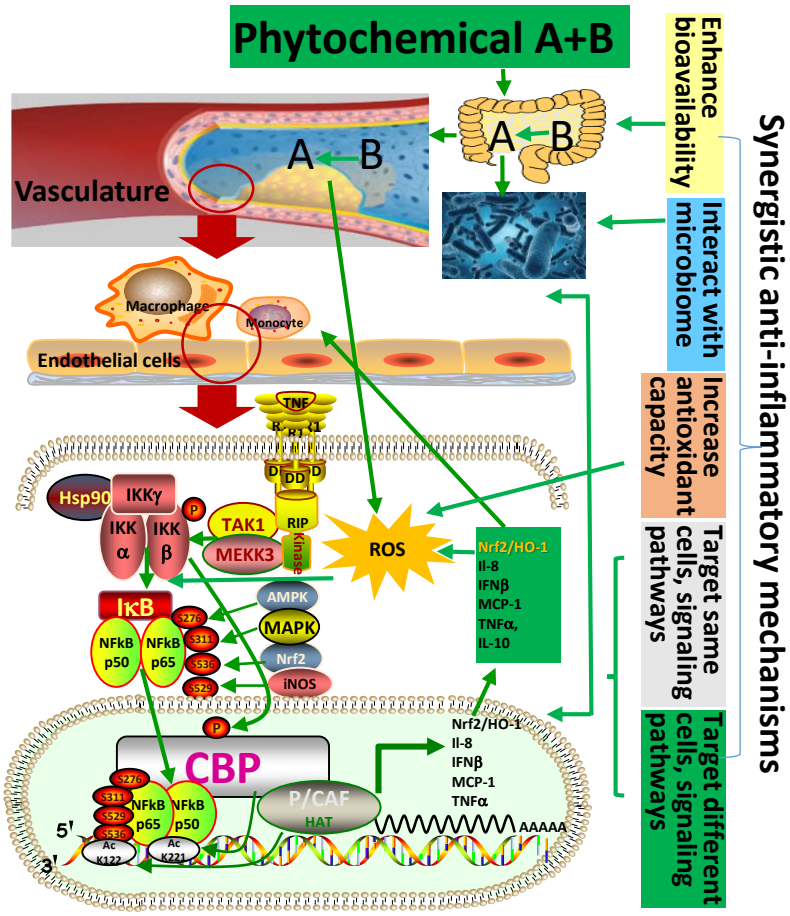
Phytochemical A+B
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Monocyte
Endothelial cells
TNF
TNFR1
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Hsp90
IKKγ
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IKK β
P
TAK1
MEKK3
RIP
Kinase
ROS
Nrf2/HO-1
Il-8
IFNβ
MCP-1
TNFα,
IL-10
AMPK
MAPK
Nrf2
iNOS
IκB
NFkB p50
NFkB p65
S276
S311
S536
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CBP
P/CAF
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Nrf2/HO-1
Il-8
IFNβ
MCP-1
TNFα
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5'
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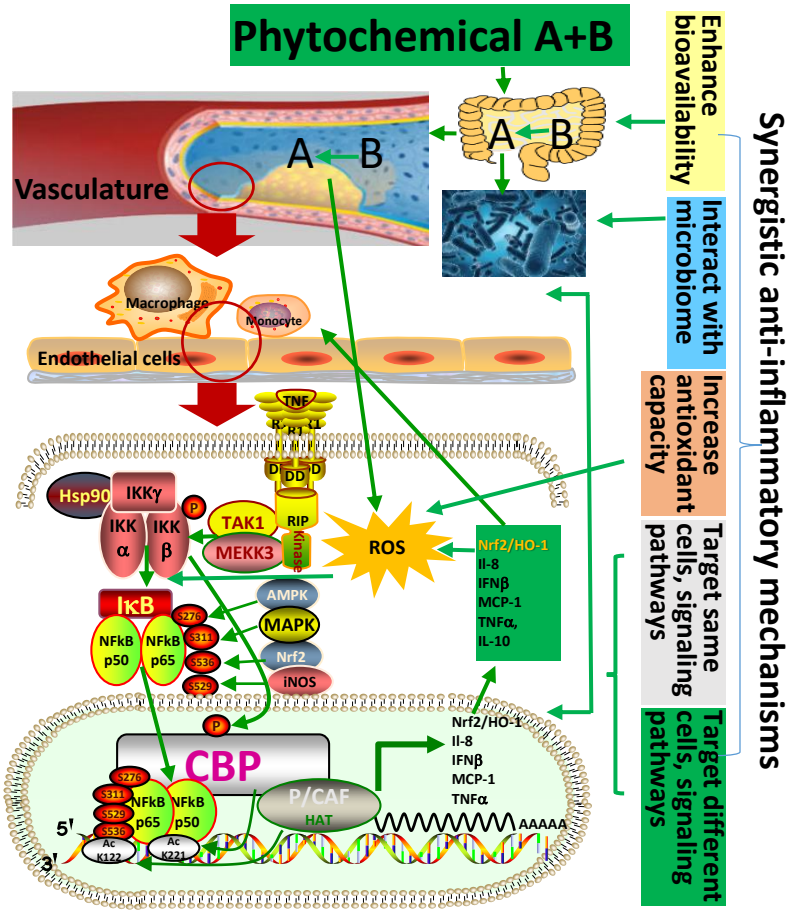
Ac K221
Enhance bioavailability
Interact with microbiome
Increase antioxidant capacity
Target same cells, signaling pathways
Target different cells, signaling pathways
Synergistic anti-inflammatory mechanisms

Figure 1


Phytochemical A+B
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