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Anti-inflammatory effects of phytochemicals from fruits, vegetables, and food legumes: A review

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ABSTRACT
Inflammation is the first biological response of the immune system to infection, injury or irritation. Evidence suggests that the anti-inflammatory effect is mediated through the regulation of various inflammatory cytokines, such as nitric oxide, interleukins, tumor necrosis factor alpha-α, interferon gamma-γ as well as noncytokine mediator, prostaglandin E_2. Fruits, vegetables, and food legumes contain high levels of phytochemicals that show anti-inflammatory effect, but their mechanisms of actions have not been completely identified. The aim of this paper was to summarize the recent investigations and findings regarding in vitro and animal model studies on the anti-inflammatory effects of fruits, vegetables, and food legumes. Specific cytokines released for specific type of physiological event might shed some light on the specific use of each source of phytochemicals that can benefit to counter the inflammatory response. As natural modulators of proinflammatory gene expressions, phytochemical from fruits, vegetables, and food legumes could be incorporated into novel bioactive anti-inflammatory formulations of various nutraceuticals and pharmaceuticals. Finally, these phytochemicals are discussed as the natural promotion strategy for the improvement of human health status. The phenolics and triterpenoids in fruits and vegetables showed higher anti-inflammatory activity than other compounds. In food legumes, lectins and peptides had anti-inflammatory activity in most cases. However, there are lack of human study data on the anti-inflammatory activity of phytochemicals from fruits, vegetables, and food legumes.

KEYWORDS
Fruits and vegetables; food legumes; anti-inflammatory property; phytochemicals; animal model

Introduction

Inflammation is a biological process in response to infection, injury or irritation (Wang et al., 2013). Chronic inflammation seems to be associated with different types of diseases, such as arthritis, allergy, atherosclerosis, and even cancer (Devi et al., 2015). The process of inflammation is a complicated immune response that can be defined as the sequential release of pro-inflammatory cytokines (Lin and Tang, 2008). Therefore, inhibition of the overproduction of inflammatory mediators, especially pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor alpha (TNF-α), may prevent or suppress a variety of inflammatory diseases (Kim et al., 2003). Since ancient times, inflammatory conditions and their related disorders have been treated with plants or plant-derived formulations. Furthermore, numerous natural products rich in antioxidants display protective effects against inflammation. The anti-inflammatory activities of several plant extracts and isolated compounds have already been scientifically demonstrated (Mueller et al., 2010). The anti-inflammatory properties of naturally occurring phytochemicals are attributed to the decrease in certain cancers in both in vitro and in vivo studies (Kang et al., 2005).

Nitric oxide (NO) is one of the major inflammatory mediators. The phytochemicals that reduce NO production by inducible NOS (iNOS) without affecting endothelial NOS or neuronal NOS may be beneficial for the development of anti-inflammatory agents (Kim et al., 2004). Therefore, inhibition of iNOS activity or down-regulation of iNOS expression is desirable to reduce the extent of inflammatory response. In addition to iNOS, cyclooxygenase-2 (COX-2) is involved with various inflammatory processes and is highly expressed in cell types related to inflammatory processes including macrophages and mast cells, when stimulated with pro-inflammatory cytokines and bacterial lipopolysaccharide (LPS) (Needleman and Isakson, 1997). However, TNF-α and IL-1β are also prominent contributors to chronic inflammatory diseases (Mcinnes and Georg, 2011). Phytochemicals mediate inflammation via kinases such as protein kinase C and mitogen-activated protein kinase. Phytochemicals inhibit these aforementioned enzymes by altering the DNA-binding capacities of transcription factors such as nuclear factor kappa-B (NF-κB). Consequently, the expression rate of the target gene is controlled. NF-κB is a major effector pathway involved in inflammation (García-Lafuente et al., 2009). Another anti-inflammatory effect of

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phytochemicals during the allergic reaction is inhibition of the release of histamine (Rathee et al., 2009).

We recently reviewed the anti-inflammatory effects of fungal beta-glucans (Du et al., 2015). A wide array of phytochemicals, particularly those present in edible and medicinal plants, have been reported to possess substantial anti-inflammatory activities. However, the exact mechanisms of action of phytochemicals need to be ascertained for majority of the fruits, vegetables, and food legumes. Herein, this review commences with the recent insights gained on the in vitro and in vivo studies on anti-inflammatory activities of phytochemicals from fruits, vegetables, and food legumes (Table 1 and Figure 1). The general anti-inflammation response pathways of phytochemicals are listed in Figure 2. However, the phytochemicals from different fruits, vegetables, and food legumes may dramatically differ based upon their species, investigation methods, and the media of extraction, the anti-inflammation response pathways of different food may differ in certain circumstances. The detailed mechanisms in terms of anti-inflammatory effects of individual compound or food were presented in the following text. Figure 3 presented the typical chemical structures of common compounds from fruits, vegetable, and food legumes that exhibited anti-inflammation effects.

Anti-inflamatory properties of fruits and vegetables

Crude extracts

Cytokine secretion regulatory activities using ethanolic extracts of strawberry and mulberry fruit juice were assessed in murine primary splenocytes and peritoneal macrophages (Liu and Lin, 2013). Strawberry and mulberry extracts with pine bark extract (0.5 g L^{-1}) significantly decreased (IFN-γ + IL-2 + IL-12)/IL-10 (Th1/Th2) cytokine secretion ratios of splenocytes in the absence or presence of LPS and TNF-α/IL-10 (pro-/anti-inflammatory) cytokine secretion ratios in the presence of LPS in dose-dependent manners. Frontela-Saseta et al. (2013) in their experiment with co-culture system showed cell barrier dysfunction and over-production of IL-8, NO and reactive oxygen species (ROS). In the inflamed cells, incubation with nondigested samples reduced ($p < 0.05$) the production of IL-8 and NO compared with the digested samples. ROS production increased in the inflamed cells exposed to the digested commercial red fruit juice (86.8 $\pm$ 1.3%) compared with fresh juice (77.4 $\pm$ 0.8%).

According to Etoh et al. (2013), citrus peel extract decreased the release of TNF-α and NO from RAW264.7 cells stimulated by LPS in a dose-dependent manner. In addition, citrus peel extract suppressed the expression of iNOS and nuclear translocation of NF-*k*B in RAW 264.7 cells. Fazio et al. (2013) evaluated *Sambucus* and *Rubus* spp. seeds extracts for their inhibitory effects on the production of LPS-induced inflammatory mediators (NO, CCL-20) in RAW 264.7 cells. Blackberry extract decreased NO release in a concentration-dependent way with almost 60% inhibition at the highest dose (50 μg/mL). The results showed that the methanolic extracts from *Rubus* seeds have strong anti-inflammatory properties.

Li et al. (2012) investigated the anti-inflammatory effects of the fractions of Chinese pear fractionated with petroleum ether, ethyl acetate, and *n*-butanol, respectively. In the carrageenan-induced rat paw edema test, the ethyl acetate fraction showed the strongest inhibition of edema formation 0.5–5 h after induction of edema, followed by *n*-butanol fraction. Ethyl acetate fraction also displayed potent anti-inflammatory activity against xylene-induced ear edema (22.0% and 43.7%, respectively) and acetic acid-induced extravasation of Evan's blue dye (39.58% and 49.92%, respectively) at a dose of 200 and 400 mg/kg, respectively. In another study, Hsu et al. (2012) evaluated the inhibitory effect of wild bitter melons on *Propionibacterium acnes*-induced inflammation. The results showed that ethyl acetate extract of wild bitter melons in vitro potently suppressed pro-inflammatory cytokine and matrix metalloproteinase-9 levels in *P. acnes*-stimulated THP-1 human monocytic cells.

Phenolics

Epidemiological evidence shows that supplementations with fruits and vegetables rich in polyphenols are beneficial in both forestalling and reversing the deleterious effects of aging on neuronal communication and behavior. For example, phytochemicals, especially phenolics in fruits and vegetables, are the major bioactive components known to show various health benefits (Pereira and Maraschin, 2015; Chen et al., 2016; Xiao, 2016; Xiao et al., 2016). The observed health benefits are due to the antioxidant and anti-inflammatory properties of the polyphenolic compounds found in these fruits and vegetables (Rice-Evans and Miller, 1996). Lau et al. (2007) found the preventive effect of blueberry polyphenols against inflammation-induced activation of microglia. Their results indicate that treatments with phenolic extract of blueberry inhibited the production of NO as well as IL-1β and TNF-α in cell-conditioned media from LPS-activated BV2 microglia. Furthermore, mRNA and protein levels of iNOS and COX-2 in LPS-activated BV2 cells were significantly reduced by treatments with blueberry phenolic extract. In another study, the inhibitory effects of phenolic compounds in ginger on NO and prostaglandin E_2 (PGE_2) production in LPS-induced RAW 264.7 macrophages were measured (Chien et al., 2008). Zerumbone and 3-*O*-methyl kaempferol demonstrated potent inhibition on nitric oxide (NO) production, and also significantly suppressed iNOS expression in a dose-dependent manner. However, zerumbone had greater anti-inflammatory effects than 3-*O*-methyl kaempferol. Comalada et al. (2006) elucidated that quercetin and luteolin inhibited the production of TNF-α and NO, and suppressed iNOS expression in LPS-activated macrophages, an effect that has been associated with the inhibition of the NF-κB pathway. Furthermore, García-Mediavilla et al. (2007) suggested that kaempferol significantly decreased iNOS, COX-2, and reactive C-protein (CRP) in a concentration-dependent manner at all concentration levels. The study suggests that the modulation of iNOS, COX-2, and CRP by kaempferol may contribute to the anti-inflammatory effects of these two structurally similar flavonoids in Chang Liver cells, via mechanisms likely to involve blockade of NF-κB activation and the resultant up-regulation of the pro-inflammatory genes. In another study, the effect of naringenin was characterized using LPS-stimulated macrophages (Bodet et al., 2008). The results indicate that naringenin is a potent inhibitor of the pro-inflammatory cytokine

Table 1. Summary of the anti-inflammatory effects of phytochemicals from fruits, vegetables, and food legumes.

Classes of Phytochemicals	Components	Dietary Sources	Mechanism of Actions	Experimental Model	References
Crude extracts	Procyanindin extract	Grape seeds	Inhibit the overproduction of NO and PGE_2	RAW 264.7 macrophages model	(Terra et al., 2007)
	Fruit juice ethanol extracts	Strawberry and mulberry	Decrease splenocytes' (IFN-γ + IL-2 + IL-12)/IL-10 (Th1/Th2) cytokine secretion ratios	Murine primary splenocytes and peritoneal macrophages model	(Liu and Lin, 2013)
	Fruit juice with pine bark extract	Pine bark	Reduce ($p < 0.05$) the production of IL-8 and NO	Caco-2 cells and RAW 264.7 macrophages as model	(Frontela-Saseta et al., 2013)
	Citrus peel extract	Citrus	Decrease the release of TNF-α and NO	RAW264.7 cells model	(Etoh et al., 2013)
	Sambucus and *Rubus* species seeds extracts	*Sambucus* and *Rubus* species	Inhibitory effects on the production of NO and CCL-20	RAW 264.7 cells model	(García-Lafuente et al., 2009)
	Ethyl acetate extract	Chinese pear	Inhibition of edema formation 0.5–5 h after edema induction	Carrageenan-induced rat paw edema model	(Li et al., 2012)
	Ethyl acetate extract	Wild bitter melons	Suppress pro-inflammatory cytokine and matrix metalloproteinase-9 levels	THP-1 cells model	(Hsu et al., 2012)
	Aqueous extract	Mung bean	Potent inflammatory mediator (NO) inhibitors; reduce ear edema in mice	In vitro and in vivo modelS	(Ali et al., 2014)
	Acetone-water extracts	Mung bean	Significant anti-inflammatory effects	RAW 264.7 macrophages model	(Zhang et al., 2013)
	Extracts	Mung bean	Attenuate LPS-induced release of several chemokines	RAW 264.7 macrophages model	(Zhu et al., 2012b)
	Acetone extract	Black bean	Strong COX-1 and COX-2 inhibitory effects	In vitro model	(Oomah et al., 2010)
	Ethanol extract	Adzuki bean	Suppress the release of PGE_2 and NO; down-regulated LPS-induced mRNA expression of iNOS and COX-2.	RAW 264.7 macrophages model	(Yu et al., 2011)
	Crude methanolic extracts	Legumes	Inhibit PGE_2	In vitro model	(Zia-Ul-Haq et al., 2013)
	Phenolic rich extracts	White kidney beans and round purple beans	Reduction of NO production and cytokine mRNA expression	RAW 264.7 macrophages model	(García-Lafuente et al., 2014)
	Ethanol extract	Red bean	Inhibit NO production	In vitro and in vivo models	(Park et al., 2011)
Phenolics	Polyphenols	Blueberry	Inhibit the production of NO, IL-1β and TNF-α	LPS-activated BV2 microglia model	(Lau et al., 2007)
	Zerumbone and 3-*O*-methyl kaempferol	Ginger	Inhibit NO and PGE_2 production, iNOS expression	RAW 264.7 macrophages model	(Chien et al., 2008)
	Quercetin and luteolin	—	Inhibit TNF-α production as well as iNOS expression and NO production	RAW 264.7 macrophages model	(Comalada et al., 2006)
	Kaempferol	—	Decrease of iNOS, COX-2 and reactive CRP level	Liver cells model	(García-Mediavilla et al., 2007)
	Naringenin	—	A potent inhibitor of the pro-inflammatory cytokine	RAW 264.7 macrophages model	(Bodet et al., 2008)
	Punicalagin, punicalin, strictinin A and granatin B	Pomegranate	reduce production of NO and PGE_2	RAW 264.7 macrophages model	(Lee et al., 2008; Romier et al., 2008)
	Granatin B	Pomegranate	A strong inhibitory effect against inflammation stimulators	Carrageenan-induced paw edema model	(Lee et al., 2010)
	Narirutin	Citrus	Inhibit the release of NO, PGE_2, IL-1β and TNF-α	RAW 264.7 macrophages model	(Ha et al., 2012)
	Flavone velutin	Acai fruit	Show excellent anti-inflammatory capacity	RAW 264.7 macrophages model	(Kang et al., 2011)
	Anthocyanin	Black soybean	Have anti-inflammatory activity for penile plaque formation	Rat Peyronie disease models	(Sohn et al., 2014)
	Phenolic compounds	Navy and black bean	Reduce mRNA expression of colonic inflammatory cytokines (IL-6, IL-9, IFN-γ and IL-17A) and increase anti-inflammatory IL-10	A mouse model of acute colitis	(Zhang et al., 2014)
Triterpenoids	monomeric compounds	Pear	Indicate stronger anti-inflammatory activities	RAW 264.7 macrophages model	(Li et al., 2014)
	Pentacyclic triterpenoids	Apple	Implicate in the anti-inflammatory properties	T84 colon carcinoma cells model	(Mueller et al., 2013)
Saponins	Soybean saponins	Soybean	Inhibit the release of PGE_2, NO, TNF-α and MCP-1	RAW 264.7 macrophages model	(Kang et al., 2005)
	Soyasaponins	Soybean	Suppress the iNOS enzyme activity and down-regulated the iNOS mRNA expression	RAW 264.7 macrophages model	(Zha et al., 2011)
	Soyasaponins	Soybean	Reduce inflammatory markers, colon length, myeloperoxidase, lipid peroxide, proinflammatory cytokines and NF-κB activation in the colon	TNBS-induced colitic mice model	(Lee et al., 2010)
	Angularin A, angulasaponins A-C, and azukisaponins III and VI	Adzuki bean	Inhibit NO production	RAW 264.7 macrophages model	(Jiang et al., 2014)
Lectins	Lectins	Butterfly pea	Anti-inflammatory activity	The paw edema induced by carrageenan model	(Leite et al., 2012)

	Monocot lectin	*Canna limbata* seeds	Reduction of inflammation	Formalin model	(Araújo et al., 2013)
	Lectin	*Canavalia boliviana*	Inhibit the paw oedema induced by carrageenan	In vivo model	(Bezerra et al., 2014)
	Soybean agglutinin	Soybean	Inhibitory effect on neutrophil migration	In vitro model	(Benjamin et al., 1997)
Polysaccharides	Polysaccharide	Welsh onion	reactive nitrogen species reduction; the increase in the activities of antioxidant enzyme	Mice model	(Wang et al., 2013)
	Water-soluble polysaccharide	*Chaenomeles speciosa* fruit	Reduced the gene induction of TNF-α, IFN-γ and granulocyte colony-stimulating factor	RAW 264.7 macrophages model	(Zhu et al., 2012a)
Peptides	Bioactive peptides	Soybean	Inhibition on inflammatory markers such as NO, iNOS, PGE_2, COX-2 and TNF-α	RAW 264.7 macrophages model	(Vernaza et al., 2012)
	Lunasin	Soybean	Reduce the production of ROS; inhibit the release of pro-inflammatory cytokines (TNF-α) and IL-6	RAW 264.7 macrophages model	(Hernández-Ledesma et al., 2009)
Other compounds	Monogalactosyldiacylglycerol	*Citrus hystrix*	Exhibit higher anti-inflammatory activity	TPA-induced edema ears mice model	(Murakami et al., 1995)
	Monogalactosyldiacylglycerol	Vegetables	Downstream inflammatory mediators, COX-2, iNOS, NO and PGE_2	RAW 264.7 macrophages model	(Hou et al., 2007)
	Phenethyl isothiocyanate	Cruciferous vegetables	Sppression of TRIF-dependent pathways of TLR3 and TLR4	RAW 264.7 macrophages model	(Park et al., 2013)
	Indole-3-carbinol	Broccoli, cabbage, cauliflower, brussels sprouts.	Attenuate the production of pro-inflammatory mediators such as NO, IL-6, and IL-1β	RAW264.7 cells and THP-1 cells models	(Jiang et al., 2013)

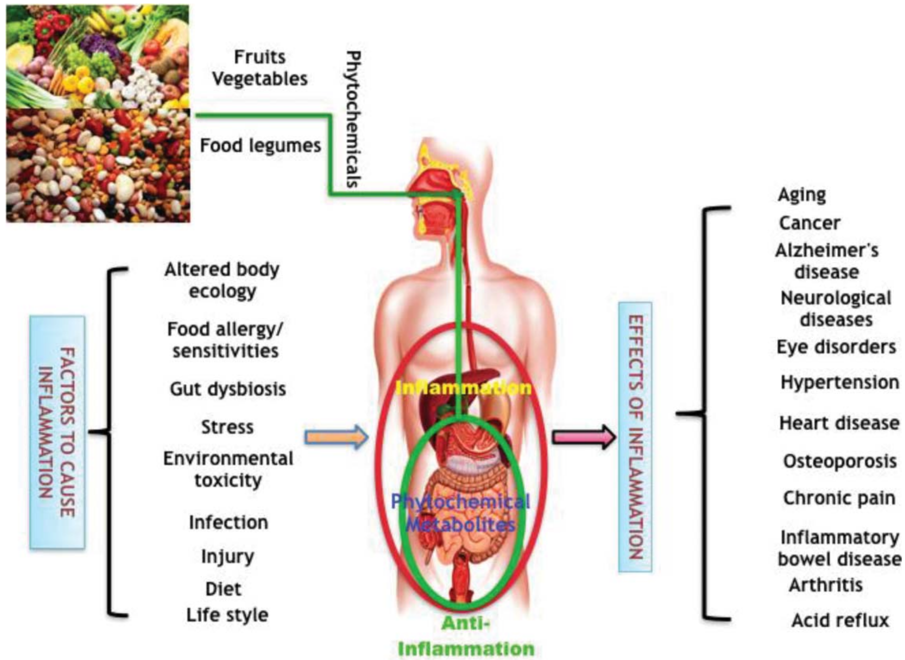

Figure 1. Causal relationship of inflammation and anti-inflammation.

response induced by LPS in both macrophages and in whole blood.

Pomegranate peels are characterized with substantial amounts of phenolic compounds, including flavonoids (anthocyanins, catechins, and other complex flavonoids) and hydrolyzable tannins (punicalin, pedunculagin, punicalagin, gallic acid, and ellagic acid) (Ismail et al., 2012). The anti-inflammatory components of pomegranate peel, that is, punicalagin, punicalin, strictinin A, and granatin B significantly reduced the production of NO and PGE_2 by inhibiting the expression of pro-inflammatory cytokines (Lee et al., 2008; Romier et al., 2008). In case of animal models, Ouachrif et al. (2012) investigated anti-inflammatory properties of the pomegranate peel following intraperitoneal (25, 50, and 100 mg/kg) and intracerebroventricular (10, 25, and 50 mg/3 mL/rat) administration in rats. The results indicated pain index reduction of 52–82%

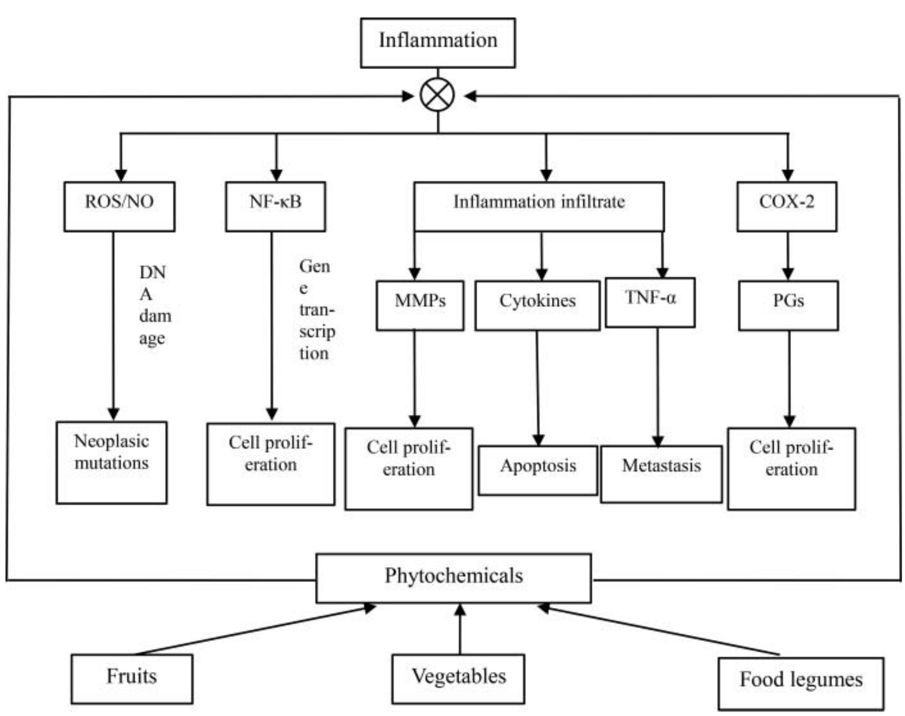

Figure 2. The pathway of anti-inflammatory effect of phytochemicals.

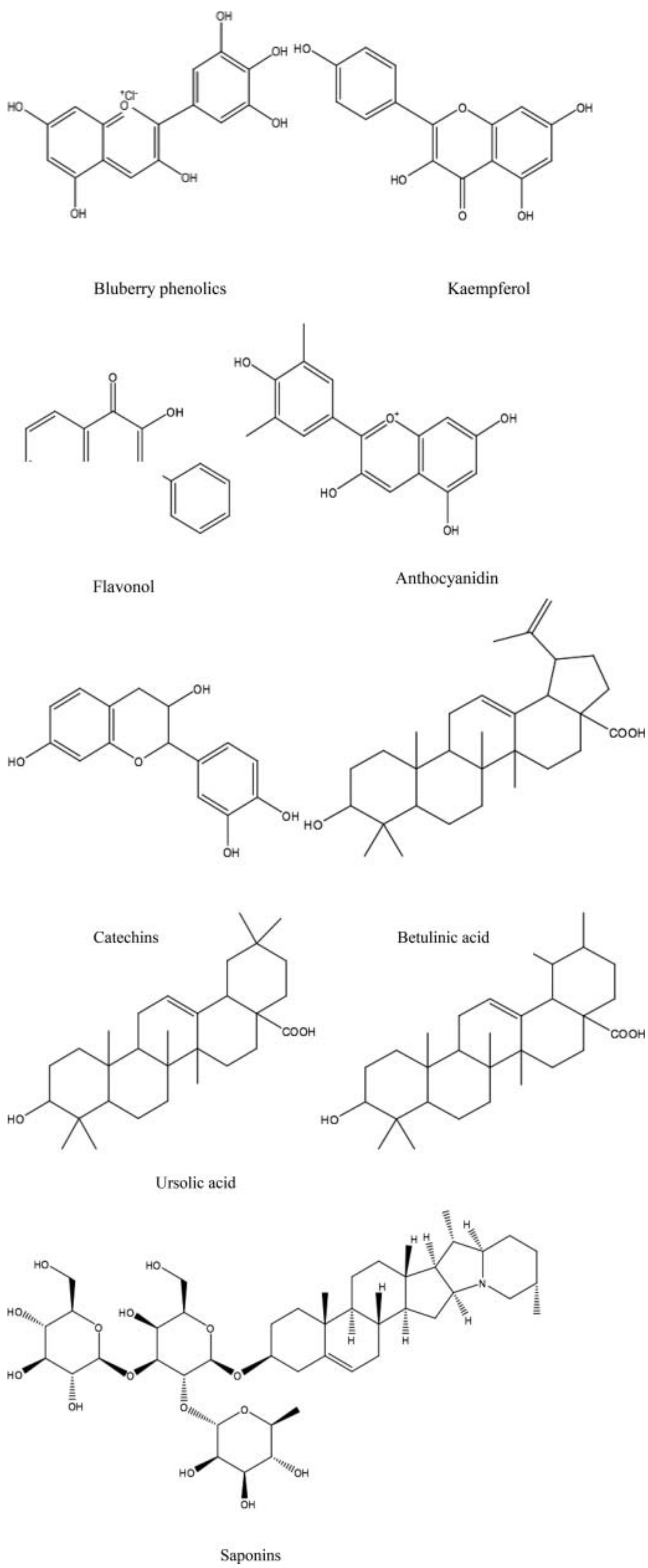

Figure 3. The typical chemical structures of anti-inflammatory phytochemicals in fruits, vegetables, and food legumes.

and a significant reduction in egg albumin-induced hind paw inflammation at the same levels of dosage as intra-peritoneal test. Moreover, Lee et al. (2010) evaluated a strong inhibitory effect against inflammatory stimulators during carrageenan-induced paw edema in mice following oral administration of granatin B (2.5 and 10 mg/kg). Significant inhibitory effects were observed after 6 h of pomegranate peel active component administration when compared to indomethacin. As a result of these properties, pomegranate peel extract and hydrolyzable tannins, in the form of standardized active components, are a very effective treatment strategy against inflammatory disorders. In one study, narirutin fraction from citrus peels inhibited the release of NO and PGE_2 through suppressing the expression of iNOS and COX-2, respectively in LPS-stimulated macrophages. The release of IL-1β and TNF-α was also reduced by narirutin fraction in a dose-dependent manner (Ha et al., 2012). Thus, narirutin fraction has the potential to be used as a functional dietary supplement and as an effective anti-inflammatory agent. The presence of polyphenolic components in acai (one of the Amazon's most popular fruits) is linked mainly to the antioxidant, anti-inflammatory, anti-proliferative, and cardioprotective activities (Yamaguchi et al., 2015). Kang et al. (2011) isolated five compounds from acai pulps. The flavones, velutin, from acai pulps showed excellent anti-inflammatory capacity in mouse macrophages, indicating a potential atheroprotective effect. Moreover, Terra et al. (2007) evaluated the anti-inflammatory effect of procyanindin extract from grape seeds in RAW 264.7 macrophages stimulated with LPS plus IFN-γ. The results showed that procyanindin extract from grape seeds caused a rapid enhanced production of PGE_2 and NO. The results demonstrated that procyanindin extract significantly inhibited the over production of NO in both dose and time dependent manners. Procyanindin extract caused a marked inhibition of PGE_2 synthesis when administered during activation.

Polysaccharides

Wang et al. (2013) investigated the anti-inflammatory effects of an aqueous extract (mainly polysaccharide) of Welsh onion green leaves with mice model. According to them, the anti-inflammatory and analgesic effects of Welsh onion green leaves may be related to the decrease in reactive nitrogen species and associated with the increase in antioxidant enzymes (catalase, superoxide dismutase (SOD), and glutathione peroxidase). Another study reported that water-soluble polysaccharide from fruits of *Chaenomeles speciosa* suppressed the gene induction of TNF-α, IFN-γ, and granulocyte colony-stimulating factor in LPS-induced RAW 264.7 cells (Zhu et al., 2012a).

Triterpenoids

Li et al. (2014) compared the contents of total triterpenes between peel and flesh of 10 different pear cultivars. The anti-inflammatory activities of monomeric compounds were also measured. All the chemical components found in the pear peel were approximately 6–20 times higher than those in the flesh of pear. Peel and flesh from Yaguang, Hongpi, Qingpi, and Guifei varieties contained relatively more total triterpenes and indicated stronger anti-inflammatory activities. In another study, Mueller et al. (2013) studied pentacyclic triterpenoids in apple peel for detecting in vitro anti-inflammatory effects using T84 colon carcinoma cells. Their results showed that triterpenoids present in apple peel could be implicated in the anti-inflammatory properties of apple constituents, suggesting that these substances might be helpful in the treatment of inflammatory bowel disease (IBD) when given as nutrient supplements.

Other compounds

Galactolipids are a class of compounds widely found in the plant kingdom, including edible plants, and are important components of their cell membranes. Several galactolipids have been shown to possess in vitro and/or in vivo anti-inflammatory activity (Christensen, 2009). In one study, monogalactosyldiacylglycerol, which is a predominant membrane lipid in seed plants and the most abundant polar lipid, exhibited potent anti-inflammatory activity in 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced edema formation on mouse ears (Murakami et al., 1995). Hou et al. (2007) found that monogalactosyldiacylglycerol had chemopreventive effects by suppressing cytoplasmic NF-κB and downstream inflammatory mediators, COX-2, iNOS, NO, and PGE_2. Moreover, phenethyl isothiocyanate (PEITC) found in cruciferous vegetables showed a positive effect on chronic inflammatory diseases, which are mediated through modulation of Toll/IL-1 receptor domain-containing adapter-inducing interferon-β (TRIF)-dependent signaling pathway of Toll-like receptors (TLR) (Park et al., 2013). The suppression of TRIF-dependent pathways of TLR3 and TLR4 by PEITC is accompanied by the down-regulation of the NF-κB activation and interferon regulatory factor 3, and the expression of their target genes, including IFN-β and IFN inducible protein-10. Similarly, Jiang et al. (2013) assessed in vitro and in vivo anti-inflammatory effects of indole-3-carbinol and its molecular mechanisms. Indole-3-carbinol attenuated the production of pro-inflammatory mediators such as NO, IL-6, and IL-1β in LPS-induced RAW 264.7 cells and THP-1 cells through the attenuation of TRIF-dependent signaling pathway.

Anti-inflammatory properties of food legumes

A large range of species of food legumes are cultivated and consumed throughout the world (Patto et al., 2014). In recent years, colored common beans, including pinto beans and black beans, have attracted a great deal of attention because of their functional pigments and health-promoting effects in relation to prevention of chronic diseases, including cancers, cardiovascular diseases, obesity, and diabetes (Xu and Chang, 2009). Phenolic compounds, such as phenolic acids, flavonols, flavones, isoflavones, anthocyanins, and condensed tannins, have been identified and characterized in food legumes (Xu and Chang, 2011; Djordjevic, 2011; Sreerama et al., 2012; Das and Parida, 2014).

Crude extracts

Ali et al. (2014) evaluated the anti-inflammatory and antinociceptive activities of untreated mung bean, germinated mung bean, and fermented mung bean on both in vitro and in vivo studies. The results indicated that both germinated and fermented mung bean aqueous extract exhibited potent anti-inflammatory and anti-nociceptive activities in a dose-dependent manner. In vitro results showed that both germinated and fermented mung bean were potent inhibitors of inflammatory mediator (NO) at both 2.5 and 5 mg/mL. Further in vivo studies showed that both germinated and fermented mung bean aqueous extract at 1000 mg/kg can significantly reduce ear edema in mice caused by arachidonic acid. Moreover, Oomah et al. (2010) reported that acetone extract of black bean hull exhibited strong COX-1 ($IC_{50} = 1.2$ μg/mL) and COX-2 ($IC_{50} = 38$ μg/mL) inhibitory effects, even outperforming than aspirin. Bean hull water extracts were stronger inhibitors of 15-lipoxygenase (15-LOX), than corresponding acetone extracts. In another study, Yu et al. (2011) suggested that adzuki bean (*Phaseolus angularis*) ethanol extract dose-dependently suppressed the release of PGE_2 and NO in macrophages and strongly down-regulated LPS-induced mRNA expression of iNOS and COX-2. The results showed that adzuki bean ethanol extract can be further developed as a promising anti-inflammatory remedy because it targets multiple inflammatory enzymes and transcription factors. Zhang et al. (2013) found that mung bean acetone-water extracts possessed significant anti-inflammatory effects in LPS-stimulated RAW264.7 mouse macrophage cells at 100 μg/mL concentration.

Furthermore, Zia-Ul-Haq et al. (2013) investigated crude methanolic extracts of black gram, green gram, soybean, and lentil for anti-inflammatory activity by COX-2 producing PGE_2 inhibitory assay. They observed 73.9%, 79.8%, 92.2%, and 74.5% inhibition for black gram, green gram, soybean, and lentil, respectively, at 20 μg/mL extract concentration. García-Lafuente et al. (2014) determined the anti-inflammatory activities of phenol rich extracts obtained from white kidney beans and round purple beans. Round purple bean extracts indicated a higher anti-inflammatory activity by decreasing the production of NO and expression of cytokine mRNA of LPS-stimulated macrophages. In another study, mung bean extracts dose-dependently attenuated LPS-induced release of several chemokines in macrophage cultures. Oral administration of mung bean extracts significantly increased animal survival rates from 29.4% to 70% (Zhu et al., 2012b).

Park et al. (2011) used in vitro and in vivo experimental models to investigate the anti-inflammatory potential of the butanol fraction of red bean ethanol extract. Treatment with butanol fraction of red bean ethanol extract inhibited NO production in LPS-stimulated macrophages through suppression of extracellular signal regulated kinase and inhibitory kappa B alpha (IκBα) activation. The result suggested the possible usefulness of red beans in the treatment of inflammatory diseases.

Saponins

Soyasaponins are found in soybeans and other legumes (Guang et al., 2014). Saponins have received much attention in relation to the health effects of food legumes. Kang et al. (2005) investigated the effects of soybean saponins on the production of pro-inflammatory mediators in LPS-stimulated peritoneal macrophages. Soybean saponins significantly inhibited the release of PGE_2, NO, TNF-α, and monocyte chemotactic protein-1 (MCP-1) in a dose-dependent manner. Soybean saponins also down-regulated the expression of COX-2 and iNOS at mRNA/protein levels. Moreover, soybean saponins suppressed NF-κB activation by blocking IκBα degradation. Successful in vitro assays indicated that soybean saponins exhibit anti-inflammatory properties by suppressing the transcription of inflammatory cytokine genes through the NF-κB signaling pathway. In addition, Zha et al. (2011) investigated the inhibitory effects of soyasaponins (25–200 μg/mL) on the induction of NO and iNOS in murine RAW 264.7 cells activated with LPS. The soyasaponins suppressed both the iNOS enzyme activity and down-regulated the iNOS mRNA expression in a dose-dependent manner. The findings showed that soyasaponin exhibited anti-inflammatory properties by suppressing NO production in LPS-stimulated RAW264.7 cells through attenuation of NF-κB-mediated iNOS expression. In a study based on animal model, Lee et al. (2010) investigated the inhibitory effects on inflammatory markers in 3,4,5-trinitrobenzenosulfonic acid (TNBS)-induced colitic mice. Oral administration of soyasaponin (10 and 20 mg/kg) to TNBS-treated colitic mice significantly reduced inflammatory markers, colon length, myeloperoxidase, lipid peroxide, proinflammatory cytokines, and NF-κB activation in the colon, as well as increased glutathione content, SOD, and catalase activity. Moreover, Jiang et al. (2014) reported that angularin A, angulasaponins A-C, and adzukisaponins III and VI from adzuki bean (*Vigna angularis*) presented inhibitory effects on NO production in LPS-activated RAW264.7 macrophages, with IC_{50} values ranging from 13 to 24 μM.

Peptides

Legumes are an important source of proteins from food. Biological activities of proteins and peptides from legume seeds have been observed (Duranti, 2006). Vernaza et al. (2006) investigated that soybean flours with bioactive peptides showed a significant ($p < 0.05$) inhibition on inflammatory markers such as NO (20.5–69.3%), iNOS (22.8–93.6%), PGE_2 (64.0–88.3%), COX-2 (36.2–76.7%), and TNF-α (93.9–99.5%) in LPS-induced RAW 264.7 macrophages. Moreover, Hernández-Ledesma et al. (2009) found peptide lunasin reduced the production of ROS in LPS-induced RAW 264.7 macrophages in a significant dose-dependent manner. Lunasin also inhibited the release of pro-inflammatory cytokines (TNF-α) and IL-6.

Phenolics

Dry beans are typically processed and the seed coats may be removed and discarded prior to consumption. Therefore, a better understanding of the anti-inflammatory activity of colored dry bean seed coats would be beneficial in determining their potential use as an ingredient in the functional food and nutraceutical industry (Pitura, 2011). Legume seed hulls are rich sources of polyphenolics and natural antioxidants (Moise et al., 2005; Luo, Cai, Wu, Xu, 2016). Boudjou et al. (2013) found that aqueous ethanolic (80%) extract of lentil hulls had high anti-inflammatory activities preferentially inhibiting 15-LOX (IC_{50} = 55 μg/mL), with moderate COX-1 (IC_{50} = 66 μg/mL) and COX-2 (IC_{50} = 119 μg/mL) inhibitory effects on the COX pathway. In addition, Pitura (2011) measured the cellular anti-inflammatory activity of seed coat crude extracts of colored common beans (*P. vulgaris* L.) in LPS-induced murine macrophage RAW 264.7 cells, the results showed anti-inflammatory activity of colored bean seed coat. For example, extracts of pinto bean (*P. vulgaris* cv. Windbreaker) and black bean (*P. vulgaris* cv. Eclipse) decreased TNF-α levels suggesting anti-inflammatory properties. In another study, Sohn et al. (2014) suggested that anthocyanins extracted from black soybean may have anti-inflammatory activity for penile plaque formation in rat Peyronie disease models. Zhang et al. (2014) assessed the in vivo effect of 20% navy and black bean (*P. vulgaris* L.) flours, with different phenolic compound levels and profiles, in a mouse model of acute colitis. The results showed that bean diets reduced mRNA expression of colonic inflammatory cytokines (IL-6, IL-9, IFN-γ, and IL-17A) and increased anti-inflammatory IL-10 ($p < 0.05$), while simultaneously reducing circulating cytokines (IL-1β, TNF-α, IFN-γ, and IL-17A, $p < 0.05$) and dextran sulfate sodium (DSS)-induced oxidative stress.

Lectins

Lectins are proteins that have the ability to bind specifically and reversibly to carbohydrates and glycoconjugates without altering the structure of the glycosyl ligand (Leite et al., 2012). In legumes, lectins make up about 10% of the total nitrogen of the seeds (Oliveira et al., 2008). Plant lectins can display either pro- or anti-inflammatory actions depending on the administration route used via lectin domain interaction (Assreuy et al., 1997; Assreuy et al., 1999; Alencar et al., 1999; Alencar et al., 2004). Leite et al. (2012) purified and characterized lectins in the seeds of butterfly pea (*Clitoria fairchildiana*) and verified their anti-inflammatory activity. It was observed that lectin had anti-inflammatory activity in the carrageenan induced paw edema inflammation model, in which a 64% diminution in edema was observed. Moreover, Araújo et al. (2013) evaluated anti-inflammatory activity of monocot lectin from the *Canna limbata* seeds. The lectin showed anti-inflammatory effect with the reduction of inflammation in the formalin test and neutrophil migration into the peritoneal cavity. Bezerra et al. (2014) characterized the anti-inflammatory properties of lectin from *Canavalia boliviana* using in vivo model. The paw edema induced by carrageenan was also inhibited in presence of lectin at 1 mg/kg concentration. In another study, when soybean agglutinin is present in the blood circulation, an inhibitory effect on neutrophil migration was observed suggesting an anti-inflammatory effect (Benjamin et al., 1997). The results showed that soybean agglutinin (5–200 μg/cavity) injected into rats with different cavities induced a typical inflammatory response characterized by dose-dependent exudation and neutrophil migration 4 h after injection.

Future perspective

The pharmacological relevance of active constituents is fully justified by the most recent findings indicating that fruits, vegetables, and food legumes are the medicinal and nutritional agents useful for treating a wide range of human disorders. Further investigations are needed to fully understand the modes of actions of phytochemicals and to fully exploit their preventive and therapeutic potential. Phytochemicals definitely deserve further studies with regard to biological activity, including studies into mechanism of action and structure-activity relationships. Other fruits, vegetables, and food legumes should be investigated in terms of a potential source of new chemical structures and biological activities. Future research works could focus on combining in vitro model, animal model, and human trials to thoroughly identify the anti-inflammatory properties of phytochemicals. In addition, it is difficult to make a judgment to say which food is the best for anti-inflammatory dietary therapy based on the literature data presented in this review work, because the investigations were done by different research groups with different experimental models and methodologies. Therefore, a future in-depth study is suggested to incorporate these commonly consumed fruits, vegetables and food legumes into one study, and compare their anti-inflammatory potential based on the same conditions, so that we can recommend the most potent food to consumers for gaining anti-inflammatory benefits. Processing methods for fruits, vegetables, and food legumes, such as boiling, pressure cooking, roasting, sprouting, and so on, should also be optimized to minimize the loss of therapeutic effects. The advances in biotechnological tools and the research community's capacity to develop imaginative strategies will help in framing a fruits, vegetables, and food legumes' development program for ensuring the nutritional security of the world. Moreover, food legumes differ in their composition regarding the content and type of bioactive compounds. Further studies should be aimed at random clinical trials to compare diverse types of food legumes to determine the most beneficial for a particular disease prevention and treatment. Although fruits, vegetables, and food legumes are natural foods and nontoxic substances, the purified compounds from fruits, vegetables and food legumes may still have certain potential side-effects, the over-dose usage may also cause side- effects. Therefore, the further study should also look on this point so that food scientist can give a rational suggestion to consumers in either choosing the original fruits, vegetables, and food legumes or choosing the purified compounds or processed nutraceuticals from these foods. In addition, there are lack of study on structure-activity relationship of isolated compounds from fruits, vegetable, and food legumes, this could be one of the future research areas.

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Conflict of interest

The authors have declared that there is no conflict of interest.

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