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Potential anti-inflammatory effects of legumes: a review

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Abstract

Legumes are a staple of diets all around the world. In some least developed countries, they are the primary source of protein; however, their beneficial properties go beyond their nutritional value. Recent research has shown that legumes have bioactive compounds like peptides, polyphenols and saponins, which exhibit antioxidant, antihypertensive, anti-inflammatory and other biological activities. Thus, these compounds could be an alternative treatment for inflammatory diseases, in particular, chronic inflammation such as arthritis, obesity and cancer. Nowadays, there is a growing interest in alternative therapies derived from natural products; accordingly, the present review has compiled the bioactive compounds found in legumes that have demonstrated an anti-inflammatory effect in non-clinical studies.

Key words: **Inflammatory process: Phenolic compounds: Peptides: Carbohydrates: Bean: Soyabean**

The legume family (*Fabaceae*) comprises more than 13 000 species, different in colour, size, shape and texture. They are mainly grown for human consumption, representing a staple food worldwide. Moreover, legumes play a prime role in human nutrition as they constitute rich sources of protein (15–45 %), high in lysine but limited in sulphur-containing amino acids, complex carbohydrates (24–68 %), starch (0·2–57·8 %), dietary fibre (1·2–25·6 %), PUFA (linolenic and linoleic), phytosterols, vitamins (niacin, pantothenic acid and folate), minerals (such as K, P, Cu, Fe, Ca and Mg), but also antinutritional factors including phytates, lectins, polyphenols, enzyme inhibitors and others[1–4].

Edible legumes include bean (*Phaseolus vulgaris*), lima bean (*Vigna lunatus*), adzuki bean (*Vigna angularis*), mung bean (*Vigna radiata*), black gram (*Vigna mungo*), scarlet runner bean (*Phaseolus coccineus*), rice bean (*Vigna umbellata*), moth bean (*Vigna acontifolia*), tepary bean (*Phaseolus acutifolius*), broad bean (*Vicia faba*), garden pea (*Pisum sativum* var. sativum), chickpea (*Cicer arietinum*), dry cowpea (*Vigna unguiculata*), pigeon pea (*Cajanus cajan*), lentil (*Lens culinaris*), bambara groundnut (*Vigna subterranea*), vetch (*Vicia sativa*), lupins (*Lupinus spp.*), lablab (*Lablab purpureus*), sword bean (*Canavalia ensiformis, gladiata*), winged bean (*Psophocarpus teragonolobus*), velvet bean (*Mucuna pruriens* var. utilis), soyabean (*Glycine max*) and peanut (*Arachis hypogaea*)[5,6].

In addition to their dietary contribution, legumes have bioactive compounds that exhibit diverse biological activities, for example, antioxidant, antihypertensive, immunomodulatory, hypolipidemic, antimicrobial, anticancer, hypoglycaemic and anti-inflammatory. The anti-inflammatory factors are related to obesity, cancer, rheumatoid arthritis, type 2 diabetes, inflammatory bowel disease, among others[7]. Hence, bioactive compounds may be an alternative in the treatment. This review aims to summarise research on bioactive compounds present in legumes that exhibit anti-inflammatory effects.

Methods

A search was conducted in Science Direct, Google Scholar and PubMed databases, using the following key words, bioactive compounds in legumes, anti-inflammatory activity of legumes, biological activities of soyabean, bean, chickpea, pea, lupine, lentil and broad bean. Literature included was published in the last 15 years

Abbreviations: ERK, extracellular signal-regulated kinase; IFN, γ, interferon-γ; IκBα, inhibitor kappa B α; iNOS, nitric oxide synthase; JNK, c-Jun N-terminal kinase; LOX, lipoxygenase; MAPK, mitogen-activated protein kinase; NO, nitric oxide; LPS, lipopolysaccharide; TLR, Toll-like receptors.

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Results

Inflammation

Inflammation is one of the first biological responses of the immune system; it occurs when body tissues are injured by physical trauma, intense heat, irradiation, irritating chemicals, or pathogenic infections and/or immune reactions. The word *inflammation* derives from the Latin word *inflamo*, which means *I set fire*. Inflammation encompasses symptoms such as redness, fever, swelling, pain and altered physiological functions to alleviate the infection and repair the damaged tissue. Depending on time and pathological characteristics, inflammation can be acute or chronic. Acute inflammation occurs immediately upon injury, lasting some seconds, minutes, hours or days; in contrast, chronic inflammation persists over time, if untreated, it could lead to tissue damage and chronic diseases, namely obesity, type 2 diabetes, inflammatory bowel disease, rheumatoid arthritis, chronic hepatitis, pulmonary fibrosis, tumour development, atherosclerosis and CVD[8–11].

The inflammatory process leads to the recruitment and activation of protective molecules, initiating a macrophage response, which serves as the first line of defence against harmful agents. Inflammatory stimuli such as lipopolysaccharides (LPS) activate macrophages to produce a variety of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-8, interferon-γ (IFN-γ) and other inflammatory mediators such as PGE_2 and nitric oxide (NO), synthesised by the enzymes cyclo-oxygenase (COX-2) and inducible nitric oxide synthase (iNOS), respectively[3,12,13]. Two primary signalling pathways maintain the defence system against harmful stimuli: the NF-κB and the mitogen-activated protein kinase (MAPK) pathway. The NF-κB pathway participates in cytokine production (IL-1β, IL-6, IL-8 and TNF-α), iNOS expression and COX-2 regulation. NF-κB proteins normally exist in the cytoplasm of inactive cells; nevertheless, they respond to stimulation, translocating into the nucleus and inducing the transcription of various pro-inflammatory genes. MAPK pathway triggers extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and phosphorylation of p38 MAPK, which promote inflammation[3,13–15].

Common treatment of inflammation consists of steroidal anti-inflammatory drugs (EIA) and non-steroidal anti-inflammatory drugs; however, their prolonged use is associated with adverse side effects, evincing the necessity of new treatments for inflammatory diseases[14]. Bioactive compounds, such as phenols, polysaccharides, proteins and peptides, have been identified in legumes (Tables 1 and 2), displaying anti-inflammatory effects *in vivo* and *in vitro*. The anti-inflammatory effect is generally regulated through NO, IL, TNF-α, IFN-γ and other mediators; however, their mechanisms of action have been only partially characterised[16] and reported in a few studies (Fig. 1).

Bioactive compounds with anti-inflammatory activity

Phenolic compounds. Phenolic compounds represent one of the most common plants secondary metabolites. In legumes, they are typically concentrated in the seed coat; when highly pigmented, they have a higher phenolic content than non-pigmented or less pigmented ones. Phenolic compounds have an aromatic structure with one or more hydroxyl groups. Classified as flavonoids (flavones, flavonols, flavanones, isoflavones, anthocyanins, chalcones, dihydrochalcones and catechins), phenolic acids (hydroxybenzoic, hydroxyphenyl acetic, hydroxyphenyl pentanoic and cinnamic hydroxyl acids), tannins, stilbenes and lignans[6–8,17]. Over the last years, phenolic compounds have attracted significant attention due to the wide variety of biological activities they exhibit, in particular, antioxidant, antitumour and anti-inflammatory effects[3].

Isoflavones. Isoflavones are natural phenolic compounds in legumes such as lupin, chickpea and soyabean[18], which exert diverse biological activities, for instance, inflammatory effects.

Peptides and proteins. Currently, there is a growing demand for plant-derived proteins as a component of functional foods and as an alternative to the environmentally expensive production of animal protein[19]. In this regard, grain legumes are important sources of high-quality dietary protein; in many regions, proteins are obtained only from legumes[5]. Furthermore, proteins can also play a bioactive role by themselves and can be precursors of biologically active peptides with various physiological effects[5,20]. Bioactive peptides are short sequences of amino acids (2–20 amino acids) that remain inactive within their parental protein, but when released – by enzymatic hydrolysis, fermentation or germination, during food processing or gastrointestinal digestion – they can become immunomodulatory, antihypertensive, antithrombotic, opioid, anti-inflammatory and antioxidant agents[4,13,21].

Saponins. Saponins are a group of compounds characterised by their structure containing a carbohydrate fraction and an aglycone. When S derived from legumes (particularly lentil or soyabean), they present hypocholesterolemic, anticancer, anti-inflammatory and antioxidant activity[7,22]. Several *in vitro* and *in vivo* studies have shown the anti-inflammatory potential of legume bioactive compounds as described hereunder.

Bean

In vitro *studies.* Oomah *et al.*[23] obtained extracts (rich in phenolic compounds) from bean hulls (*P. vulgaris* L.); the acetone–water extract inhibited COX-1 and COX-2 enzyme expression with IC_{50} of 1·2 μg/ml and 38 μg/ml, respectively, whereas the aqueous extract suppressed lipoxygenase (15-LOX) enzyme expression with IC_{50} of 15·6 μg/ml. Likewise, Yu *et al.*[24] obtained an ethanolic extract (0–200 μg/ml) from adzuki bean (*P. angularis* Wight), which suppressed the release of NO, PGE_2, TNF-α, the expression of iNOS and COX-2 and the activation of NF-κB in RAW 264.7 macrophages stimulated with LPS. In a similar study, Fang *et al.*[25] obtained an ethanolic extract from *Phaseolus calcaratus Roxburgh* containing catechin-7-O-b-d-glucopyranoside as a bioactive compound(100 μg/ml), which inhibited the synthesis of NO, TNF-α, and IL-6, and COX-2 and iNOS enzymes expression in LPS-stimulated RAW 264.7 macrophages, potentially through the phosphorylation of ERK 1/2, p38 MAPK and inhibitor kappa B α (IκBα) and their subsequent degradation. Similarly, García-Lafuente *et al.*[3] reported

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Table 1. Bioactive compounds with *in vitro* anti-inflammatory activity found in legumes

Legume	Bioactive compound	Dose	Targeted inflammatory molecules	Ref
Medicago sativa				
M. sativa L.	Polysaccharides of pectic and hemicellulosic origin	50 μg/ml	Inhibition of IL-1β, IL-6 and COX-2 in RAW 264.7 macrophages stimulated with LPS.	(75,76)
Arachis hypogaea				
Seed	80 % ethanolic extract with phenolic compounds	IC_{50} of 0·01 mg/ml.	Inhibition of the lipoxygenase enzyme.	(63)
Sprouts	Ethanolic extract (trans-resveratrol)	0·01–1·0 mg/ml	Suppressed the expression of COX-2, NFG, NF-κB in HaCaT cells treated with compound 48/80.	(62)
Leaves	Hydroalcoholic extract (condensed tannins, flavonoids and phenolic compounds)	10 μg/ml	Decreased NO and IL-1β induced by exposure to H_2O_2 in human PBMC.	(64)
Skin	Aqueous extract (proanthocyanidins)	50 μM	Inhibition of TNF-α and IL-6 in THP-1 cells activated by LPS.	(61)
Sprout root	Extract (cichoric acid)	200 μg/ml	Inhibition of NO, TNF-α, IL-6, IL-1β, PGE_2, iNOS and COX-2 in RAW 264.7 macrophages stimulated by LPS.	(65)
Vigna				
V. sinensis K.	LA ((Z, Z)-9,12-octadecadienoic acid)	10 and 50 μM	Inhibition of NO, IL-1β, IL-6, TNF-α and iNOS in RAW 264.7 macrophages stimulated with LPS.	(70)
V. unguiculata	Acetone–water extract	2, 5, 10 and 20 mg GAE/l	Decreased expression of IL-8, TNF-α, VCAM-1 and inhibition of NF-κB mRNA expression in CCD18Co cells stimulated with LPS.	(72)
V.angularis	Ethanolic extract	100 μg/ml	Reduced histamine release, inhibited TNF-α and IL-6 gene expression and secretion of TNF-α and IL-6 in HMC-1 cells stimulated by PMACI.	(30)
V. angularis	Ethanolic extract	IC_{50} of 13–24 μM	Inhibited NO in LPS-stimulated RAW 264.7 macrophages.	(31)
V. radiate L.)	Acetone–water extract	100 mg/ml	Inhibited IL-1β, IL-6 and COX-2 mRNA expression in RAW 264.7 macrophages stimulated with LPS.	(71)
Pisum sativum				
Yellow pea (*P. sativum* L.)	Hydrolysate (≤3 kDa)	25 μg/ml	Inhibition of NO, TNF-α and IL-6 in LPS/IFN-γ-activated RAW 264.7 NO (-) macrophages.	(74)
Phaseolus				
Roxburgh	Ethanolic extract (catechin-7-O-β-D-glucopyranoside)	100 μg/ml	Inhibited NO, TNF-α, IL-6, COX-2 and iNOS in RAW 264.7 macrophages stimulated with LPS.	(25)
Pinto	Hydrolysate (peptides ≤3 kDa and phenolic compounds	0·01 μg/ml	Inhibited IL-6 synthesis in CCD-18Co cell line stimulated with IL-1β.	(4)
Hulls	Acetone–water and aqueous extracts (rich in phenolic compounds)	IC_{50} of 1·2 and 38 μg/ml	Inhibition of COX-1, COX-2 and 15-LOX.	(23)
Carioca Madreperola and Pontal	Peptide fractions (<10 kDa)	0. 1–5 mg/ml	Inhibited NO, TNF-α, IL-1β, PGE_2 and COX-2 in THP-1 cells stimulated with LPS.	(12)
Milk and yogurt analogues	Peptide fractions (≤10 kDa) and phenolic (hydroxybenzoic and hydroxycinnamic acid derivatives)	0·5 mg/ml	Inhibited IL-8 in Caco-2 and HT-29 cell lines stimulated with TNF-α.	(26,29)
P. angularis	Ethanolic extract	200 μg/ml	Suppressed NO, PGE^2, TNF-α, iNOS, COX-2 and NF-κB in RAW 264.7 macrophages stimulated with LPS.	(24)
Pinto Durango and Negro 8025	Hydrolysate (Alcalase)	IC_{50}, Pinto Durango of 34·9, 13·9, 5·0. and 3·7 μM. IC_{50}, for Negro 8025, of 43·6, 61·3 14·2 and 4·2 μM	Inhibited COX-2, iNOS, PGE_2, NO, NF-κB and the nuclear translocation of the NF-κB p65 subunit in RAW 264.7 macrophages stimulated with LPS.	(27)
White kidney beans round purple beans	Methanolic extracts (catechin derivatives, proanthocyanidins and catechin glucoside)	0·625 mg/ml	Reduced NO and iNOS in LPS-stimulated RAW 264.7 cells.	(3)
Sprouts	Hydrolysate (pepsin-pancreatin)	0·04 μg/μl	Inhibited NO in LPS-induced RAW 264.7 macrophages.	(28)
Cicer arietinum				
Germinated	Peptide fraction (24 peptides) and a phenolic fraction (formononetin and biochanin A)	0·5–5 mg/ml	Inhibited NO in RAW 264.7 macrophages stimulated with LPS.	(58)
C. cajan				
Pigeon pea	50 % Ethanolic extract (cyanidin-3-monoglucoside)	2 mg/ml	Attenuated H_2O_2-induced damage to RAW 264.7 macrophages and the production of NO, PGE_2, TNF-α, IL-1β and IL-6 in LPS-stimulated RAW 264.7 macrophages.	(66)

Table 1. (*Continued*)

Legume	Bioactive compound	Dose	Targeted inflammatory molecules	Ref
Leaves	Methanolic extract (pinostrobin and Cajanus lactone)	$IC_{50} < 22$ μM and < 40 μM, respectively.	Inhibited TNF-α and IL-1β in RAW 264.7 and J774A.1 cells stimulated with LPS	(67)
Leaves	Cajaninstilbene acid	20 μM	Inhibited NO, TNF-α and IL-6 and the phosphorylation of p-IκBα, p-p65 ERK (1/2), p-JNK (1/2) and p-p38 proteins in RAW 264.7 macrophages stimulated with LPS.	(14)
Leaves	Ethanolic extract (orientin, pinostrobin and vitexin)	100 μg/ml	Reduced IL-6, TNF-α and iNOS in LPS-stimulated RAW 264.7 macrophages.	(68)
L. esculenta				
Petite blonde de Dahra	80 % Aqueous ethanol extract	30 μg/ml	Inhibition of 15-LOX, COX-1 and COX-2.	(73)
Lupinus				
Seeds	Peptide (GPETAFLR) 889·6 Da	100 and 500 μg/ml	Inhibited TNF-α, IL-1β and CCL and induced the expression of IL-10 in THP-1 cell line stimulated by PMA.	(21)
Leaf	Recombinant β-conglutin proteins (rβ1, rβ3 y rβ6)	20 μg	Inhibition of NO and mRNA expression of iNOS, IL-1β, CCL5, TNF-α, IFN-γ, IL-IL-2, IL-6, IL-8 and IL-12 in PANC-1 pancreatic cells stimulated with LPS.	(19)
G. max L				
Seed	Lunasin peptide	0·1–300 μM	Inhibition of NO, PGE_2, iNOS and COX-2 in RAW 264.7 macrophages stimulated with LPS.	(45)
Seed	Isotrifoliol	12·5 and 25 μM	Inhibition of iNOS, COX-2, IL-1β, IL6, TNF-α, CCL2, CCL3, CCL4, and phosphorylation and degradation of the inhibitor of NF-κB. Suppressed the phosphorylation of (ERK 1/2) and protein p38 (MAPK) and the TLR receptor signalling pathway in LPS-stimulated RAW 264.7 cells.	(50)
Seed	Soyasaponin I	1, 2, 5 and 10 μM	Inhibited NO, PGE_2, TNF-α, IL-1β, COX-2, iNOS and the nuclear translocation of NF-κB in LPS-stimulated C57BL/6 mouse peritoneal macrophages.	(48)
Seed	Isoflavone (glyceollins)	3 mg/ml	Inhibited NO, IL-6, iNOS and COX-2 in RAW 264.7 cells activated by LPS.	(9)
Seed	Soyasaponinn Ab	1, 2, 5 and 10 μM	Inhibited NO, PGE_2, TNF-α, IL-1β and suppressed nuclear translocation of NF-κB in LPS-stimulated C57BL/6 mouse peritoneal macrophages. Inhibited the expression of TNF-α, IL-1β, IL-6, iNOS, COX-2, TLR4, the phosphorylation of IRAK1, IKK-β and p65, the binding of LPS to TLR4 and increased the expression of IL-10 in peritoneal macrophages from ICR mice with TNBS-induced colitis.	(49)
Seed	Tripeptide (VPY) 377·5 Da	2 and 4 mM	Inhibited IL-8 in Caco-2 cells stimulated with TNF-α and decreased the synthesis of TNF-α in LPS-stimulated THP-1 macrophages.	(42)
Seed	Phytoestrogens (genistein, daidzein and coumestrol)	Genistein and coumestrol (1 μM), daidzein (0·1 μM)	Decresed NO induced by LPS in HAPI cell line and reduced the iNOS mRNA levels.	(34)
Seed	Peptide (FLV)	0·01 to 0·1 μM	Inhibited TNF-α, MCP-1, and IL-6 in co-culture adipocytes and adipocytes/macrophages RAW 264·7 stimulated with TNF-α.	(20)
Seed	8-hidroxidaidzein	50 μM	Inhibited NO, decreased iNOS, COX-2 and TNF-α gene expression in RAW 264·7 macrophages stimulated with LPS, poly I: C and PGN.	(18)
Seed	Isoflavone glycosides	0–1 mg/ml	Inhibited NO, PGE_2, iNOS, COX-2, phosphorylation of IKK, and degradation of IκB in RAW 264.7 cells stimulated with LPS.	(15)
Seed	Trans-lunasin peptide	4 mg/ml	Inhibited NO, IL-1 and IL-6 in LPS-stimulated RAW 264.7 cells	(46)
Seed	Lunasin peptide	200 μM	Inhibition of TNF-α and IL-6 in RAW 264.7 cells stimulated with LPS.	(44)
Seed	Soyasaponins (A^1, A^2, I)	25–200 μg/ml	Inhibition of NO, TNF-α, iNOS and NF-κB in RAW 264.7 cells activated by LPS.	(22)
Seed	Daidzein	25–75 μM	Suppressed NO and IL-6 production derived from the reduction of mRNA expression and the phosphorylation of p38 in the MAPK pathway in the LPS-activated cell line (BV-2).	(35)
Seed	Genistein	25, 50 and 100 μM	Inhibited TNF-α, IL-1β and mRNA expression of TLR4 protein and IκB-α in C6 cells stimulated with Ab25–35.	(36)

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Table 1. (*Continued*)

Legume	Bioactive compound	Dose	Targeted inflammatory molecules	Ref
Seed	Soyasaponin Ab	2·5, 5 and 10 μM	Inhibited NO, TNF-α, IL-6, IL-1β, iNOS and COX-2 in LPS-stimulated MH-S.	(56)
Fermented	8-hydroxydaidzein-7–α-glucoside	IC_{50} of 173·2 μM	Inhibition of NO in RAW 264.7 macrophages stimulated with LPS.	(38)
Geminated	Peptide fraction (5–10 kDa) rich in glutamine	10 mg/ml	Inhibited NO and PGD_2 in RAW 264.7 macrophages stimulated with LPS.	(41)
Seed, milk analogue	Hydrolysate (pepsin-pancreatin)	400 μg	Inhibited NO, PGE_2, IL-1β, TNF-α, iNOS and COX-2 in RAW 264.7 macrophages stimulated with LPS.	(40)
Brazilian germinated	Hydrolysate (Alcalase)	5 μg	Inhibited NO, TNF-α, PGE_2, iNOS and COX-2 in RAW 264.7 cells stimulated with LPS.	(39)
Black soyabean seed coat	Anthocyanins	10, 50 and 100 μg/ml	Inhibited COX-2 expression in the TNF-α stimulated HaCaT cell line.	(32)
Black soyabean	Anthocyanins	12·5, 25 and 50 μg/ml	Inhibition of IL-8, NF-κB translocation, Ik$\beta\alpha$ degradation, iNOS and COX-2 mRNA expression in AGS cells infected by H. pylori.	(33)
Black soyabean	Tripeptide (RGD)	100 μg/ml	Inhibition of NO, TNF-α, IL1β and IL-6 in RAW 264.7 cells induced by LPS.	(43)
Wild soyabean	Soyasaponin (saponin I-αa and I-γa)	100 and 200 μg/ml	Inhibition of NO, TNF-α, and IL-1β, iNOS and COX-2 in RAW 264.7 cells stimulated with LPS.	(47)

COX-2, cyclo-oxygenase; LPS, lipopolysaccharides; NFG, nerve growth factor; NO, nitric oxide; PBMC, peripheral blood mononuclear cells; iNOS, inducible nitric oxide synthase; HMC, human mast cells; PMACI, phorbol 12-myristate 13-acetate and calcium ionophore A23187; IFN-γ, interferon-γ; LOX, lipoxygenase; IκBα, inhibitor kappa B α; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; TNBS, trinitrobenzene sulfonic acid; MAPK, mitogen-activated protein kinase; TLR, Toll-like receptors; IRAK, IL-1 receptor-associated kinases; IKK, IκB kinase; MCP-1, monocyte chemoattractant protein-1; PGN, peptidoglycan; VCAM, vascular cell adhesion molecule.

two extracts, one of *P. Vulgaris* var. white kidney bean (phenolic acids as the main components) and *P. Vulgaris* var. round purple bean (catechin derivatives, proanthocyanidins and glycosylated catechin) that at a concentration of 0·625 mg/ml. These extracts reduced the production of NO and mRNA expression of iNOS, IL-1β, IL-6 and TNF-α in macrophage RAW 264.7 cells stimulated with LPS, suggesting that they inhibited genetic expression by inactivating the NF-κB pathway. In addition, Chen *et al.*[26] tested a phenolic fraction. Using hydroxybenzoic and hydroxycinnamic acids derivatives from bean (*P. Vulgaris* var. navy bean and light red kidney bean), milk and yogurt analogues, later subjected to gastrointestinal digestion *in vitro* and using a concentration of 0·5 mg/ml. The authors observed inhibition of IL-8 synthesis in colon carcinoma (Caco-2) and human colorectal adenocarcinoma (HT-29) cell lines stimulated with TNF-α.

Correspondingly, alcalase-treated hydrolysates from common bean (*P. vulgaris* L. var. Pinto Durango and Negro 8025) inhibited the production of COX-2, PGE_2, iNOS and NO with IC_{50} (Pinto Durango) of 34·9 μM, 13·9 μM, 5·0 μM and 3·7 μM, respectively, and with IC_{50} (Negro 8025) of 43·6 μM, 61·3 μM, 14·2 μM and 4·2 μM, respectively. Hydrolysates also suppressed NF-κB transactivation in the nuclear translocation subunit NF-κB p65 in LPS-stimulated RAW 264.7 macrophage cell line[27]. Comparatively, pepsin-pancreatin hydrolysates from germinated black bean protein (*P. vulgaris* L.) at 0·04 μg/μl restricted NO synthesis in LPS-stimulated RAW 264.7 macrophages[28]. Moreover, a bean alcalase hydrolysate (*P. vulgaris* L. var. Pinto; peptides ≤ 3 kDa and phenolic compounds) at 0·01 μg/ml inhibited IL-6 synthesis in the IL-1β-stimulated colon myofibroblast cell line CCD-18Co[4]. In other studies, Galdino-Alves *et al.*[12] isolated peptide fractions (<10 kDa) from cooked beans (*P. vulgaris* var. carioca Madreperola and Pontal) and subjected them to pepsin-pancreatin (0. 1–5 mg/ml) simulated gastrointestinal digestion, decreasing TNF-α, IL-1β and PGE_2 synthesis and COX-2 expression in human THP-1 macrophage cells stimulated with LPS. And Chen *et al.*[26,29] obtained peptide fractions (≤ 10 kDa) – with a concentration of 0·5 mg/ml – from common bean (*P. vulgaris* var. navy bean and light red kidney bean) milk and yogurt subjected to *in vitro* gastrointestinal digestion, which restrained IL-8 synthesis in TNF-α-stimulated Caco-2 and HT-29 cell lines. On the other hand, Kim *et al.*[30] reported that an ethanolic extract (100 μg/ml) derived from adzuki bean (*V. angularis*) reduced the release of histamine in human mast cells (HMC-1) stimulated with phorbol 12-myristate 13-acetate and calcium ionophore A23187 (PMACI). The decrease in histamine occurs when reducing the levels of intracellular Ca, whose mobilisation throughout the mast cell membrane mediates histamine release. Additionally, the extract suppressed the gene expression and secretion of TNF-α and IL-6 in HMC-1 cells stimulated by PMACI, as it may block the activation of NF-κB and MAPK pathways. Lastly, Jiang *et al.*[31] isolated nine compounds (including four new furanylmethyl glycosides, angularides A-D; one ent-kaurane diterpene glycoside, angularin A; and four new triterpenoid saponins, angulasaponins A-D) from an ethanolic extract of azuki bean (*V. angularis*). The compounds inhibited NO production with IC_{50} of 13–24 μM in RAW 264.7 macrophage cells stimulated with LPS.

In vivo *studies.* Kim *et al.*[30] used an ethanolic extract from azuki bean (*V. angularis*) in a ICR mice model of compound 48/80-induced systemic anaphylaxis. As a result, it reduced mortality in mice when pre-treated with the extract at 50 mg/kg and 250 mg/kg.

Table 2. Bioactive compounds with *in vivo* anti-inflammatory activity found in legumes

Legume	Bioactive compound	Dose	Targeted inflammatory molecules	Ref
Arachis hypogaea				
Sprouts	Ethanolic extract (trans-resveratrol)	5 % three times a week/2 weeks	Suppressed OX in SKH1 mice treated with compound 48/80.	(62)
Vigna				
V.angularis	Ethanolic extract	50 and 250 mg/kg for 2 h	Reduced mortality in ICR mice pre-treated with compound 48/80.	(30)
V.mungo	Hydroalcoholic extract (polyphenolic and flavonoids)	400 mg/kg/28 d	Attenuation of inflammation in a model of papain-induced osteoarthritis in Wistar rats.	(77)
Pisum sativum				
Pea (*P. sativum* cv. Bilbo)	Albumin fraction	1·5 g/kg/d/9 d	Inhibited IL-6, IL-12, COX-2, TLR-4, TLR-6 and TLR-9 mRNA expression in C57BL/6J mice with DSS-induced colitis.	(78)
Cicer arietinum				
Seeds	Methanolic extracts	200 and 400 mg/kg for 1 h	Decreased the volume of paw oedema in rats with carrageenan-induced inflammation.	(59)
Seeds	Extract (biochanin A-7-O-β-D-glucoside, biochanin A and formononetin)	10 mg/kg/6 weeks	Inhibition of mRNA expression of TNF-α, NF-κB and COX-2 in Sprague-Dawley albino rats with $AlCl_3$-induced neuroinflammation.	(60)
C. cajan				
Pigeon pea	Hexane extract (campesterol, β-sitosterol and stigmasterol)	200 and 400 mg/kg for 12 h	Inhibited carrageenan-induced inflammation and decreased TNF-α, IL-6 and IgG serum levels in adult albino rats.	(69)
Leaves	Methanolic extract (pinostrobin and cajanus lactone)	20 mg/kg for 12 h	Inhibited TNF-α and IL-1β in plasma of Sprague-Dawley rats administered LPS.	(67)
G. max L				
Seed	Soyasaponin I	10 and 20 mg/kg once a day/5 d	Reduced inflammatory markers in TNBS-treated colitic mice.	(48)
Seed	Isoflavone (glyceollins)	60 or 300 μg/ml/30 min	Suppressed the phosphorylation of NF-κB p65 and TPA-induced skin inflammation in ICR mouse skin.	(9)
Seed	Soyasaponinn Ab	10 and 20 mg/kg once a day/5 d	Reduced the inflammatory markers and inhibited the expression of TNF-α, IL-1β, IL-6, iNOS, COX-2, TLR4, the phosphorylation of IRAK1, IKK-β and p65, the binding of LPS to TLR4 and increased the expression of IL-10 in ICR mice with TNBS-induced colitis.	(49)
Seed	Tripeptide (VPY) 377·5 Da	10 and 100 mg/kg body weight/14 d	Improved weight loss, reduced the symptoms of DSS-induced colitis and the gene expression of TNF-α, IL-6, IL-1β, IFN-γ and IL-17 in the colon of Balb/c mice.	(42)
Seed	Isoflavone glycosides	0·25 %, 0·5 % and 1 % w/v/2 weeks	Mitigated body weight loss and shortening of colon length in C57BL/6N mice with DSS-induced colitis.	(15)
Seed	Soya protein	7 g/kg/30 d	Inhibited TNF-α, IL-6, leptin and adiponectin in the serum of Sprague-Dawley rats with collagen-induced arthritis.	(54)
Seed	Dipeptide and tripeptide	250 mg/kg BW/18 d	Decreased TNF-α, IL-1β, IFN-γ and IL-17 expression in a model of intestinal inflammation induced by DSS in Yorkshire pigs.	(55)
Seed	Soyasaponin Ab	12. 5, 25 and 50 mg/kg/12 h	Reduced histopathological changes in LPS-stimulated Balb/c mice.	(56)
Fermented	Soluble fibre (uronic acid, fucose, xylose, mannose and galactose)	For 12 weeks	Reduced TNF-α, IL-6 levels and C-reactive protein in the plasma of C57BL/6 J mice.	(57)
Germinated and fermented	Extract with daidzein, glycitein and genistein; Bowman–Birk protease inhibitors	2 mg/kg/d/15 d	Decreased TNBS-induced damage and IL-1β levels and increased IL-10 levels in Wistar rats with TNBS-induced colitis.	(52)
Black soyabean	Ethanolic extract	100 and 200 mg/kg/1 h	Reduction in ear and paw oedema in ICR mice.	(51)

COX-2, cyclo-oxygenase; TLR, Toll-like receptors; DSS, dextran sulfate sodium; LPS, lipopolysaccharides; TNBS, trinitrobenzene sulfonic acid; iNOS, inducible nitric oxide synthase; IRAK1, IL-1 receptor-associated kinases; IKK-β, IκB kinase; VPY, Val-Pro-Tyr; IFN, γ, interferon-γ; TPA, 12-O-tetradecanoylphorbol-13-acetate.

*Soyabean (*Glycine max *L.)*

In vitro *studies.* Kim *et al.*[32] evaluated the effects of anthocyanins from black soyabean seed coat at concentrations of 10 μg/ml, 50 μg/ml and 100 μg/ml, which inhibited COX-2 enzyme expression in the TNF-α-stimulated HaCaT cell line. Besides, Kim *et al.*[33] assessed the effect of anthocyanins (cyanidin-3-glucoside, delphinidin-3-glucoside and petunidin-3-glucoside) from black soyabean on *Helicobacter pylori*-infected human gastric epithelium (AGS) cells. At concentrations of 12·5 μg/ml, 25 μg/ml and 50 μg/ml, anthocyanins decreased IL-8 secretion, iNOS, and COX-2 mRNA expression, ERK, JNK, and p38 MAPK phosphorylation, NF-κB translocation and degradation of Iκβα.

Moreover, studies have reported the inhibitory activity of isoflavones isolated from soyabean against inflammatory mediators. Genistein (1 μM), coumestrol (1 μM) and daidzein (0·1 μM) decreased NO production, reduced iNOS mRNA levels, down-regulated the transcription factor interferon regulatory factor 1 (IRF-1) and phosphorylated STAT1, which modulate iNOS expression in LPS-activated HAPI rat microglial cells[34]. Likewise, daidzein (25–75 μM) suppressed NO production, IL-6 mRNA expression and p38 phosphorylation in the MAPK pathway in the LPS-activated murine microglial cell line (BV-2)[35].

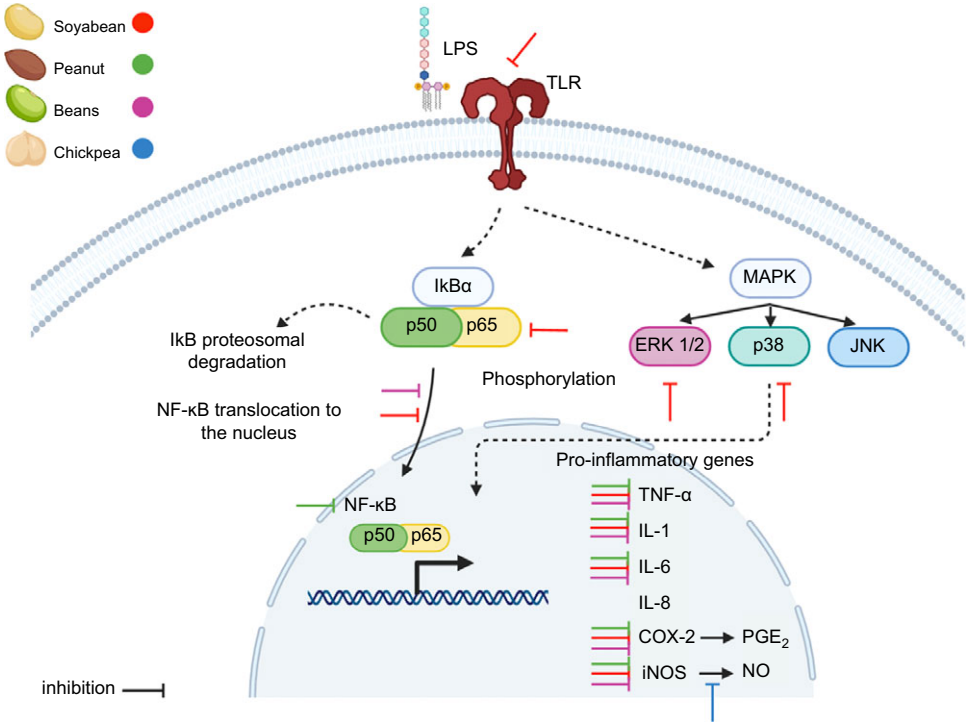

Fig. 1. Possible *in vitro* anti-inflammatory mechanisms proposed for some legumes related to LPS-activated TLR receptor. LPS, lipopolysaccharide; TLR, Toll-like receptor; COX, cyclo-oxygenase; PGE_2, prostanglandin E2; NO, nitric oxide; iNOS, inducible nitric oxide synthase; MAPK, mitogen-activated protein kinases; ERK, extracellular signal-regulated kinase; JNK, c-Jun NH2-terminal kinase. Created in BioRender.com.

Analogously, genistein (25 μM, 50 μM and 100 μM) prevented the release of TNF-α and IL-1β and inhibited the expression of Toll-like receptors 4 (TLR4) protein and Iκβ-α mRNA in rat glioma cells (C6) stimulated by β-amyloid peptides 25–35 (Ab25–35)[36]. Furthermore, a soyabean-derived compound consisting of genistein and Bowman–Birk trypsin inhibitor (100 mg/kg) reduced serum levels of TNF-α and IFN-γ and decreased TNF-α and IFN-γ mRNA expression in splenocytes of Balb/c mice with LPS-induced inflammation[37]. Another examination indicated that 8-hydroxidaidzein (50 μM) hindered NO synthesis, decreased iNOS, COX-2, and TNF-α gene expression, and constrained NF-κB and activator protein I (AP-1) transcriptional activities in RAW 264.7 macrophages stimulated with LPS, polyinosinic-polycytidylic acid (poly [I:C], a TLR3 inducer) and peptidoglycan (PGN, a TLR2 inducer)[18]. Similarly, 8-hydroxydazidzein-7-α-glucoside (IC_{50} of 173·2 μM) prevented the synthesis of NO in LPS-stimulated RAW 264.7 macrophages[38]. Also, isoflavone glycosides (3 mg/ml) limited the production of NO and PGE_2, suppressing iNOS, COX-2 and inflammatory mediators involved in the NF-κB signalling pathway, through inhibition of IKKB phosphorylation and IκB degradation in RAW 264.7 macrophages stimulated with LPS[15].

Comparably, an alcalase-treated hydrolysate from germinated soyabean protein (at 5 μg of protein) restricted the synthesis of NO, TNF-α, and PGE_2 and the expression of iNOS and COX-2 in LPS-stimulated RAW 264.7 macrophages[39]. In another study, Dia *et al.*[40] obtained pepsin-pancreatin hydrolysates from soya milk analogues with a concentration of 400 μg, which suppresses the production of NO, PGE_2, IL-1β, and TNF-α and the expression of iNOS and COX-2 enzymes in RAW 264.7 macrophages stimulated with LPS. González-Montoya *et al.*[41] isolated peptide fractions from soyabean sprouts hydrolysed with pepsin-pancreatin enzymes and observed that in 5 kDa to 10 kDa peptide fraction (rich in glutamine) at a concentration of 10 mg/ml, they induced the highest inhibition of NO and PGD_2 in RAW 264.7 macrophage cells stimulated with LPS, attributable to the ability of peptides to restrict the expression of iNOS and COX-2 enzymes. Besides, a Val-Pro-Tyr (VPY) tripeptide with a molecular mass of 377·5 Da isolated from soyabean at a concentration of 2 mM and 4mM hampered IL-8 secretion in Caco-2 cells stimulated with TNF-α, and at a concentration of 1 μM and 10 μM, and decreased the synthesis of TNF-α in human THP-1 macrophages stimulated with LPS[42]. Similarly, a Phe-Leu-Val (FLV) peptide derived from soyabean β-conglycinin, at concentrations of 0·01 μM to 0·1μM blocked the release of TNF-α, monocyte chemoattractant protein-1 (MCP-1) and IL-6, from both TNF-α-stimulated adipocytes and co-cultured adipocytes/macrophages. An effect was mediated by the inactivation of the signalling molecules JNK and IκB kinase (IKK) and the down-regulation of IκBα in the adipocytes[20]. In addition, Arg-Gly-Asp tripeptide (RGD) was purified from germinated black soyabean and treated with high hydrostatic pressure (150 MPa) at 100 μg/ml. It repressed the expression of NO, TNF-α, IL-1β and IL-6 in LPS-induced RAW 264.7 macrophages[43]. The lunasin peptide (43 amino acids) isolated from soyabean at a concentration of 200 μM hindered the synthesis of TNF-α and IL-6 in LPS-stimulated RAW 264.7 macrophages[44], and at concentrations of 0·1–300 μM, restricted the production of NO, PGE_2, and the expression of iNOS and COX-2 in the same cell line. These results suggest that lunasin could prevent inflammation by obstructing the COX-2/PGE_2 and iNOS/NO pathways[45]. Finally, the trans-

lunasin peptide, at a concentration of 4 mg/ml, inhibits the synthesis of NO, IL-1 and IL-6 in RAW 264.7 macrophages stimulated with LPS[46].

Soyasaponins in soyabean are important bioactive secondary metabolites that shown anti-inflammatory activity[47]. Lee *et al.*[48,49] isolated soyasaponin I and soyasaponin Ab, which exhibited an inhibitory effect (1, 2, 5 and 10 μM) on the production of NO, PGE_2, TNF-α, IL-1β and the phosphorylation of IκBα, and the nuclear translocation of NF-κB in LPS-stimulated peritoneal macrophages from C57BL/6 mice. Particularly, soyasaponin I attenuated the activation of the NF-κB transcription factor, and soyasaponin Ab decreased the expression of TLR4, the phosphorylation of IL-1 receptor-associated kinases (IRAK1), IKK-β, and p65 and increased IL-10 expression and blocked the binding of LPS to TLR4 in peritoneal macrophages. Similarly, soyasaponin structures (soyasaponin A^1, A^2, I) at a dose of 25–200 μg/ml restricted the production of NO and TNF-α, the enzymatic activity of iNOS and the activity of NF-κB in RAW 264.7 macrophages activated by LPS[22]. In another study, Yang *et al.*[47] tested a crude extract of soyasaponins (saponin I-αa and I-γa), which at a concentration of 100 μg/ml and 200 μg/ml decreased NO production and regulated iNOS and COX-2 enzymes expression in RAW 264.7 macrophages stimulated with LPS. Soyasaponins I-α also constrained TNF-α and IL-1β expression; however, soyasaponin I-γa only inhibited TNF-α expression. The authors proposed that the anti-inflammatory effect of soyasaponins I was mainly mediated through the phosphorylation of p38 and JNK proteins.

On the other hand, Li *et al.*[50] obtained coumestans (coumestrol, isotrifoliol and phaseol) from soyabean leaf. At concentrations of 12·5 μM and 25 μM, reduced NO and PGE_2 production in RAW 264.7 macrophages was activated by LPS. Isotrifoliol (at 12.5 μM) or 25 μM) showed the greatest reduction of mRNA expression of iNOS, COX-2, IL-1β, IL6, TNFα, CCL2, CCL3 and CCL4. Besides, isotrifoliol diminished phosphorylation and degradation of the NF-κB inhibitor, suppressed ERK1/2 and p38 MAPK phosphorylation, and restrained the TLR signalling pathway.

In vivo *studies.* *In vivo,* pharmacological evaluation studies have shown the soyabean capacity to attenuate inflammation. Yim *et al.*[51] reported that an ethanolic extract (200 mg/kg) from black soyabean reduced arachidonic acid-induced ear oedema and carrageenan-induced paw oedema in ICR mice models. Moreover, daidzein, glycitein, genistein and Bowman–Birk protease inhibitors administered for 15 d (2 mg/kg/d) decreased microscopic damage, enhanced intestinal permeability, visceral hypersensitivity, and intestinal proteolytic activity, and increased IL-1β and IL-10 levels in Wistar rats with colitis induced by 2, 4, 6 trinitrobenzene sulfonic acid (TNBS)[52].Comparably, apigenin administration to C57BL/6 mice with ulcerative colitis induced by dextran sulfate sodium attenuates clinical signs of the disease and down-regulated the expression of microsomal prostaglandins (mPGES), COX-2, iNOS and serum matrix metalloproteinase-3 (MMP-3). Authors demonstrated that apigenin action is linked with the inhibition of canonical and non-canonical inflammasome pathways[53]. In the same model, isoflavone glycosides (0·25 %, 0·5 % and 1 % [w/v]) mitigated body and colon weight loss[15]. In another study, soya protein (7 g/kg) limited TNF-α, IL-6, leptin and adiponectin production in the serum of Sprague-Dawley rats with collagen-induced arthritis[54].Consistent results were reported for 377·5-Da VPY tripeptide isolated from soyabean. When administered at concentrations of 10 mg/kg and 100 mg/kg body weight for 14 d to Balb/c mice, it reduced dextran sulfate sodium-induced colitis symptoms and decreased weight loss and gene expression of TNF-α, IL-6, IL-1β, IFN-γ and IL-17 in the colon[42]. Similarly, soya-derived di- and tripeptides (150–500 Da) decreased the expression of TNF-α, IL-1β, IFN-γ and IL-17 in a model of dextran sulfate sodium-induced intestinal inflammation in Yorkshire pigs[55]. Soyasaponin I and soyasaponin Ab (10 and 20 mg/kg) orally administered to ICR mice with TNBS-induced colitis improved body weight reduction and prevented colon shortening, myeloperoxidase catalytic activity, TNF-α, IL-1β, IL-6, iNOS and COX-2 expression[48,49]. Furthermore, soyasaponin Ab (12·5 mg/kg, 25 mg/kg and 50 mg/kg) diminished lung histopathological changes (interstitial oedema, hyperaemia, thickening of the alveolar wall and diffuse interstitial infiltration by inflammatory cells) in Balb/c mice stimulated with LPS to induce acute lung injury. It can also decreased the production of NO, TNF-α, IL-6, and IL-1β and the expression of iNOS and COX-2 in murine alveolar macrophages (MH-S) stimulated with LPS[56]. Lastly, Kim *et al.*[57] reported that soluble fibre – consisting of uronic acid, fucose, xylose, mannose and galactose – obtained from fermented soyabeans reduced TNF-α, IL-6 and C-reactive protein levels in the plasma of C57BL/6J mice.

Chickpea (C. arietinum L.)

In vitro *studies.* Chickpea isoflavones such as formononetin and biochanin A (0·5–5 mg/ml) show inhibitory activity on NO synthesis in RAW 264.7 macrophages stimulated with LPS[58]. Besides, a peptide fraction (24 peptides) with molecular weight between 1·1 kDa and 2·3 kDa isolated from a germinated and digested chickpea protein concentrate (0·5–5 mg/ml) lowered NO synthesis in RAW 264.7 macrophages stimulated with LPS[58].

In vivo *studies.* Masroor *et al.*[59] evaluated methanolic extracts of chickpea (var. Desi and Kabuli) at doses of 200 mg/kg and 400 mg/kg, which decreased paw oedema volume in rats with carrageenan-induced inflammation. Moreover, isoflavones were isolated from chickpea (*C. arietinum* L.) – that is, biochanin A-7-O-β-D-glucoside, biochanin A and formononetin – administered at a dose of 10 mg/kg to Sprague-Dawley albino rats with aluminium chloride ($AlCl_3$)-induced neuroinflammation, inhibiting TNF-α, NF-κB and COX-2 mRNA expression[60].

Peanut (A. hypogaea L.)

In vitro *studies.* Tatsuno *et al.*[61] obtained an aqueous extract (proanthocyanidins) from peanut skin at a concentration of 50 μM, and it attenuated TNF-α and IL-6 synthesis in human monocytic cells (THP-1) activated by LPS. Likewise, Choi *et al.*[62] reported that an ethanolic extract (trans-resveratrol) from peanut sprouts suppressed COX-2 and nerve growth factor expression.

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It also obstructed transcription factor NF-κB activity in a human epidermal keratinocyte cell line (HaCaT) treated with a polymer compound 48/80. Additionally, Limmongkon *et al.*[63] observed that a peanut seed-derived ethanolic extract inhibited the LOX enzyme, with an IC_{50} of 0·01 mg/ml. Cossetin *et al.*[64] obtained a peanut leaf extract using 70 % ethanol, which contained condensed tannins, flavonoids and phenolic compounds (10–100 μg/ml), and detected that the extract decreased NO production and IL-1*β* levels (10 μg/ml) induced by previous exposure to H_2O_2 in human peripheral blood mononuclear cells. In a recent study, Lee *et al.*[65] analysed an extract (cichoric acid) from peanut sprout root, which at a dose of 200 μg/ml reduced NO, TNF-*α*, IL-6, IL-1*β*, and PGE_2, and restrained iNOS and COX-2 expression in LPS-stimulated RAW 264.7 macrophage cells. The anti-inflammatory effect of the extract was explained through inhibition of MAPK (ERK, JNK and p38) phosphorylation and activation of NF-κB.

In vivo *studies.* A peanut sprout ethanolic extract rich in trans-resveratrol at 5 % concentration suppressed the oxazolone (OX)-induced effects of oedema, scaling and thickening in a model of OX-induced contact dermatitis in SKH1 mice[62].

Pigeon pea (C. cajan L.)

In vitro *studies.* Lai *et al.*[66] obtained an ethanol (cyanidin-3-monoglycoside) extract from pigeon pea. At a concentration of 2 mg/ml attenuated H_2O_2-induced DNA damage in RAW 264.7 macrophage cells and reduced NO, PGE_2, TNF-*α*, IL-1*β* and IL-6 levels in RAW 264.7 LPS-stimulated macrophages. In a similar examination, a pinostrobin and cajanus lactone isolate extracted with methanol hampered the synthesis of TNF-*α* (IC_{50} < 22 μM) and IL-1*β* (IC_{50} < 40 μM) in LPS-stimulated RAW 264.7 and J774A.1 cells[67]. Correspondingly, an ethanolic extract (100 μg/ml) from pigeon pea leaves containing orientin, pinostrobin, and vitexin reduced IL-6 and TNF-*α* secretion, and iNOS expression in RAW 264.7 macrophages cell line activated by LPS[68]. In another study, Huang *et al.*[14] isolated cajan instilbene acid from pigeon pea leaves, which at a concentration of 20 μM obstructed the release of NO, TNF-*α* and IL-6 in RAW 264.7 murine macrophages stimulated with LPS. Also, this compound blocked the phosphorylation of IκB*α*, p65, ERK (1/2), JNK (1/2), and p38 proteins, involved in NF-κB and MAPK pathways. These results suggest that the anti-inflammatory activity is due, at least in part, to the suppression of NF-κB and the activation of the MAPK pathway in LPS-stimulated macrophages.

In vivo *studies.* Patel *et al.*[67] obtained a methanolic extract from pigeon pea leaves, which at a dose of 20 mg/kg reduced TNF-*α* and IL-1*β* levels in the plasma of Sprague-Dawley rats treated with LPS. The authors ascribed the effect of pinostrobin and cajanus lactone content on the extract. Finally, Hassan *et al.*[69] tested a pigeon pea hexane extract, composed of unsaponifiable matter, that is, campesterol, β-sitosterol and stigmasterol at concentrations of 200 mg/kg and 400 mg/kg. It reduced carrageenan-induced inflammation and decreased TNF-*α*, IL-6 and IgG serum levels in adult albino rats.

Other legumes

In vitro *studies.* Although other legumes species contain bioactive compounds, literature remains scarce. Nevertheless, this section outlines the existing research. Lee *et al.*[70] obtained *n*-butanol fractions (oleanolic acid, LnA ((Z, Z, Z) −9,12,15-octadecatrienoic acid) and LA ((Z, Z) −9,12 -octadecadienoic acid)) from a methanolic extract of cowpea (*V. sinensis* K.). LA compound at concentrations of 10 μM and 50 μM inhibited the production of NO, IL-1*β*, IL-6, and TNF-*α* and the expression of iNOS, IL-1*β*, IL-6, and TNF-*α* mRNA in LPS-stimulated RAW 264.7 macrophage cells.

In another study, Zhang *et al.*[71] obtained an acetone–water extract (100 mg/ml) from mung bean (*V. radiate* L.), which suppressed IL-1*β*, IL-6 and COX-2 mRNA expression in LPS-stimulated RAW 264.7 macrophages. Analogously, an acetone–water extract from cowpea (*V. unguiculata*) at concentrations of 2 mg GAE/l, 5 mg GAE/l, 10 mg GAE/l and 20 mg GAE/l decreased IL-8, TNF-*α*, vascular cell adhesion molecule (VCAM)-1 and NF-*κ*B mRNA expression in non-malignant colon myofibroblast cells (CCD18Co) stimulated with LPS[72]. Moreover, Boudjou *et al.*[73] evaluated an 80 % ethanolic extract of lentil hulls (*Lens esculenta* var. Petite blonde de Dahra), which at a concentration of 30 μg/ml inhibited 15-LOX, COX-1 and COX-2 enzymes with an IC_{50} of 54·6 μg/ml, 65·8 μg/ml and 119 μg/ml, respectively. The activity is attributed to the phenolic acids in the extract, such as syringic acid, trans-p-coumaric acid, ferulic acid, trans-cinnamic acid and epicatechin.

On the other hand, recombinant *β*-conglutin proteins (20 μg) (r*β*1, r*β*3 and r*β*6) purified from narrow-leafed lupin (*L. angustifolius*) inhibited NO production and iNOS, IL-1*β*, CCL5, TNF-*α*, IFN-*γ*, IL-2, IL-6, IL-8 and IL-12 mRNA expression in pancreatic cells (PANC-1) stimulated with LPS[19]. Likewise, peptide Gly-Pro-Glu-Thr-Ala-Phe-Leu-Arg (GPETAFLR) – with a molecular mass of 889·6 Da, obtained by hydrolysis (alcalase) of lupine protein (*L. angustifolius* L.) and subsequently synthesised (100 and 500 μg/ml) – suppressed the expression of TNF-*α*, IL-1*β*, and CCL2 and induced the expression of IL-10 in human monocytic THP-1 cell line stimulated with phorbol 12-myristate 13-acetate (PMA)[21].

In another study, a hydrolysate (thermolysin, ≤3 kDa) of yellow pea protein (*Pisum sativum* L.) at a concentration of 25 μg/ml hindered the synthesis of NO, TNF-*α* and IL-6 in RAW 264.7 macrophage cells activated with LPS/IFN-*γ*[74]. Lastly, Chen *et al.*[75,76] purified two polysaccharides. One pectic (rhamnose, galactose, galacturonic acid and arabinose) and one hemicellulosic (xylose, glucuronic acid and arabinose) from an alkaline extract of alfalfa (*Medicago sativa* L.), which at a concentration of 50 μg/ml obstructed mRNA expression of IL-1*β*, IL-6 and COX-2 genes in RAW 264.7 mouse macrophage cells stimulated with LPS.

In vivo *studies.* Patel *et al.*[77] evaluated a hydroalcoholic extract containing polyphenols and flavonoids from black gram (*V. mungo*) in a model of papain-induced osteoarthritis in Wistar rats. The extract at a dose of 400 mg/kg attenuated the inflammatory process by reducing the diameter of the knee joint and improving grip strength and locomotion activity, with slight muscle degeneration and cartilage erosion. On the other hand,

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Utrilla *et al.*[78] assessed a pea (*Pisum sativum* cv. Bilbo) albumin fraction, administered at a dose of 1·5 g/kg/d to C57BL/6J mice with dextran sulfate sodium-induced colitis, which repressed the expression of IL-6, IL-12, COX-2 mRNA and TLR (TLR-4, TLR-6 and TLR-9).

Discussion

The anti-inflammatory activity of soyabean is highly documented in both *in vivo* and *in vitro* studies. Purified bioactive compounds from soyabean, for example, isoflavones, saponins and peptides, indicate promising results against inflammation. In addition, bean extracts and protein hydrolysates have shown anti-inflammatory activity (most examinations are *in vitro).* Few studies have analysed the exact compound from the extract that may induce the anti-inflammatory activity. Regarding protein hydrolysates, most research solely reports peptide fractions of certain molecular weights but not the peptide sequence that may exert biological activity. Therefore, it is necessary to purify the bean bioactive compounds that show anti-inflammatory activity and evaluate them via *in vivo* models. Research on chickpea, peanut, pea, lentil, and other legumes have identified extracts (phenolic compounds), carbohydrates, and hydrolysates with anti-inflammatory activity. Nevertheless, there are few *in vivo* and *in vitro* studies concerning bioactive compounds derived from these legumes. Therefore, it represents an area of opportunity for further research, especially on how bioactive compounds induce anti-inflammatory activity and testing such effects *in vivo*.

Conclusions

Legumes are a source of protein, carbohydrates, vitamins and minerals; however, their health benefits go beyond their nutritional value. To date, studies focus on bioactive compounds from legumes as alternative therapies to the pharmacological treatment of various chronic inflammatory diseases. Most research on the anti-inflammatory activity of bioactive compounds isolated from legumes is limited to soyabean and bean. In contrast, legumes such as lupin, alfalfa, lentil, pea and chickpea have been less studied, and a limited number of them have dealt with the possible mechanism of their anti-inflammatory action. Their activity could be explained because of inactivation of the signalling pathways of NF-KB and MAPK, through inhibition of the nuclear translocation of NF-κB and suppression of IκBα, ERK, JNK, and p38 phosphorylation, reducing the synthesis of inflammatory markers. These compounds may restrain the expression of enzymes, such as COX-2 and iNOS, decreasing the synthesis of NO and PGE_2. Due to the scarce information about how these bioactive compounds produce anti-inflammatory effects, a change in the research approach in this area is essential, especially, regarding the use and application of less studied legumes that represent a good alternative as a source of compounds with anti-inflammatory activity.

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