Journal of Immunotoxicology

ISSN: 1547-691X (Print) 1547-6901 (Online) Journal homepage: https://www.tandfonline.com/loi/iimt20

Anti-inflammatory and immunomodulatory properties of *Carica papaya*

Saurabh Pandey, Peter J. Cabot, P. Nicholas Shaw & Amitha K. Hewavitharana

To cite this article: Saurabh Pandey, Peter J. Cabot, P. Nicholas Shaw & Amitha K. Hewavitharana (2016) Anti-inflammatory and immunomodulatory properties of *Carica papaya*, Journal of Immunotoxicology, 13:4, 590-602, DOI: 10.3109/1547691X.2016.1149528

To link to this article: https://doi.org/10.3109/1547691X.2016.1149528

Published online: 14 Jul 2016.

JOURNAL OF IMMUNOTOXICOLOGY, 2016
VOL. 13, NO. 4, 590–602
http://dx.doi.org/10.3109/1547691X.2016.1149528

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Anti-inflammatory and immunomodulatory properties of *Carica papaya*

Saurabh Pandey, Peter J. Cabot, P. Nicholas Shaw and Amitha K. Hewavitharana

School of Pharmacy, The University of Queensland, Brisbane, Australia

ABSTRACT

Chronic inflammation is linked with the generation and progression of various diseases such as cancer, diabetes and atherosclerosis, and anti-inflammatory drugs therefore have the potential to assist in the treatment of these conditions. *Carica papaya* is a tropical plant that is traditionally used in the treatment of various ailments including inflammatory conditions. A literature search was conducted by using the keywords "papaya", "anti-inflammatory and inflammation" and "immunomodulation and immune" along with cross-referencing. Both *in vitro* and *in vivo* investigation studies were included. This is a review of all studies published since 2000 on the anti-inflammatory activity of papaya extracts and their effects on various immune-inflammatory mediators. Studies on the anti-inflammatory activities of recognized phytochemicals present in papaya are also included. Although *in vitro* and *in vivo* studies have shown that papaya extracts and papaya-associated phytochemicals possess anti-inflammatory and immunomodulatory properties, clinical studies are lacking.

ARTICLE HISTORY
Received 14 December 2015
Revised 27 January 2016
Accepted 29 January 2016
Published online 13 July 2016

KEYWORDS
Anti-inflammatory; bioactivity; *Carica papaya*; immunomodulatory; nutraceuticals

Introduction

Inflammatory conditions activate immune defense mechanisms and, under persistent stimuli, chronic inflammation may occur. Chronic inflammation thus triggers the generation and progression of pro-inflammatory cytokines, transcription factors and oncogenes (Dinarello & Pomerantz 2001; Khansari et al. 2009; Vidal-Vanaclocha 2009). Moreover, the immune-inflammatory components such as immunoglobulins, T-cells and antioxidant enzymes are also affected by chronic inflammation conditions (Di Sabatino et al. 2004; Agarwal et al. 2006; Pedicino et al. 2013). The variations in the levels of immune-inflammatory factors have significant implications in the pathophysiology of various diseases such as cancer, obesity, diabetes, fibrosis and atherosclerosis (Meyer et al. 2011; Scrivo et al. 2011; Ramos-Nino 2013). For these reasons, the role of inflammatory and immune markers in augmenting the therapeutic effect of drugs on chronic inflammation associated diseases (CID) has attracted the attention of researchers (Dinarello 2010; Esser et al. 2014). Anti-inflammatory agents such as non-steroidal anti-inflammatory drugs (NSAIDs) are successfully used in treating CID (Elizabeth et al. 2009; Ridker & Lüscher 2014); however, the long-term use of these drugs may result in damage to the gastric intestinal mucosa, heart and kidney (de Groot et al. 2007), thereby limiting their usage. A variety of plant extracts and their secondary metabolites exhibit a broad spectrum of anti-inflammatory and immunomodulatory activities with, to date, relatively few safety concerns (Aravindaram & Yang 2010; Recio et al. 2012).

The presence of a strong chemical defense system in tropical plants, comprising secondary metabolite compounds, has attracted the attention of researchers who study bioactive phytochemicals (Rasmann & Agrawal 2011). *Caricaceae* is a small family of angiosperms comprising six genera and 43 species (http://www.theplantlist.org). *Carica papaya* or papaw or papaya is the most popular and economically important species among the *Caricacae* family. Among the total tropical fruit production in the world (2012), papaya was ranked third (15.4%), following production of mango (52.9%) and pineapple (26.6%) (Edward & Fredy 2012). The digestive enzyme papain, isolated from papaya, is used as an ingredient in brewing, meat tenderizing, pharmaceuticals and cosmetic industries (Ezekiel Amri & Mamboya 2012).

Carica papaya (known in Ayurveda as Erand-karkati) is also well known for its medicinal properties (Khare 2004). Traditionally, different parts of the papaya plant are used in the treatment of various ailments such as asthma, ulcers, eczema, diabetes, helminth infections and fever (Nguyen et al. 2013). Research also demonstrated its beneficial traditional role in wound healing, and in the treatment of cardiovascular diseases, dengue fever,

CONTACT Dr. Amitha K. Hewavitharana a.hewavitharana@pharmacy.uq.edu.au School of Pharmacy, The University of Queensland, Brisbane, Australia

cancer, malaria, hypoglycemia, hyperlipidemia, fungal diseases and as a male contraceptive (Gupta et al. 1990; Nayak et al. 2007; Goyal et al. 2010; Otsuki et al. 2010; Iyer et al. 2011; Pedro et al. 2011; Kovendan et al. 2012; Yasmeen & Prabhu 2012; Nunes et al. 2013). Papaya extracts have also been reported to have significant anti-inflammatory activity (Owoyele et al. 2008; Lee et al. 2011).

This review focused on studies of the anti-inflammatory and immunomodulatory activities of *C. papaya* published since 2000. The literature search was based on several databases: PubMed, Scopus, Embase, Web of Science, Scifinder and Google Scholar. The keywords used were: "papaya", "anti-inflammatory and inflammation" and "immunomodulation and immune". In addition, cross-referencing was performed using relevant articles. In addition to examining the potential importance of bioactive phytochemicals in inflammation, the possible effects of papaya-associated phytochemicals on immune inflammatory markers are also discussed. This review will be useful for researchers and practitioners interested in the biological effects of papaya, and those scientists keen to identify novel target anti-inflammatory nutraceuticals.

In vitro studies

Several *in vitro* cell studies have focused on the role of bioactive compounds present in papaya in modulating immune-inflammatory markers. Most of these have been undertaken using papaya leaves extracted with polar solvents (primarily water and alcohol). Other studies have used papaya seeds extracted with both water and hexane.

An enhanced innate immune response is a potential biomarker in CID (Generaal et al. 2014). Endotoxin lipopolysaccharide (LPS) is used to stimulate innate immunity by regulating production of various inflammatory mediators (including tumor necrosis factor [TNF]-α, inter-leukin [IL]-1β, IL-6 and interferon [IFN]-γ) in monocytes/macrophages (Bertrand et al. 2014). TNFα secreted by monocytes/macrophages has an important role in the pathophysiology of inflammation by initiating other pro-inflammatory cytokines (such as IL-1β, IL-6 and IFNγ). Agents that blocked TNFα action during chronic inflammatory conditions accordingly demonstrated anti-inflammatory activity (Bradley 2008). An ethanolic papaya leaf extract (1 µg/ml) displayed significant ($p < 0.05$) inhibition of isopentenyl pyrophosphate (IPP) induced TNFα production in LPS (0.2 µg/ml)-induced dendritic cells. In addition, the same extract (at <12.5 µg/ml) also imparted an antioxidant effect by protecting DNA damage in *Escherichia coli* and lymphocytes (Bertrand et al. 2014). A methanol extract of papaya leaf (5 µg/ml) used to treat LPS (0.1 µg/ml)-stimulated human peripheral blood mononuclear cells (PBMC) inhibited the release of pro-inflammatory TNFα, IL-1α, IL-1β, IL-6 and IL-8 by 10.8%, 12.5%, 27.4%, 42.9%, and 8.4%, respectively (Salim et al. 2014). In another study, a methanol extract of papaya leaf inhibited nitric oxide (NO) production (IC_{50}: 60.18 µg/ml) in IFNγ (100 U/ml)- or LPS (5 µg/ml)-stimulated murine monocytic macrophages (RAW 264.7 cell line) (Lee et al. 2011).

Regulation of immune responses in a body demands balance between T helper (T_H)-1 and T_H2-cell cytokines (Sredni-Kenigsbuch 2002). An aqueous papaya leaf extract at concentrations of 0.0125–0.05 mg leaves/ml upregulated the production of T_H1-type cytokines (IL-12p40, IL-12p70, IFNγ and TNFα) and induced 23 immunomodulatory genes in immunosuppresed (anti-CD3 and anti CD-28 monoclonal antibody-treated) PBMC whereas reducing the amount of IL-2 and IL-4 (Otsuki et al. 2010). Papaya seed extracts (both water and hexane fractions), at concentrations of 200, 20 and 2 ng/ml, in the presence of phytohemagglutinin mitogen, imparted significant anti-inflammatory effects by inhibiting the classical complement-mediated lymphocyte hemolysis. In addition, it also promoted growth of lymphocytes (Mojica-Henshaw et al. 2003). The flavonoid-rich fraction of aqueous papaya seed extract at 10 µg/ml yielded significant ($p < 0.05$) anti-inflammatory effects by inhibiting expression of inflammatory IFNγ, TNFα, IL-6 and nuclear factor (NF)-κB in methyl isocyanate (MIC)-stimulated pancreatic (HPDE-6) epithelial cells. This extract also demonstrated cytoprotective, antioxidant and geno-protective activities in normal kidney (HEK-293), colon (FHC), lung (IMR-90) and pancreatic (HPDE-6) epithelial cell lines exposed to MIC (Pathak et al. 2014).

Collectively, the *in vitro* studies reported here indicated that papaya extracts (leaf and seed) possess an ability to modulate inflammatory markers in various cell types exposed to a variety of stressors. The role of tissue-resident macrophages in inflammation conditions is evident. With comparison to PBMC, differentiated THP-1 (acute monocytic leukemia) cells has been proposed to be a better *in vitro* model for anti-inflammatory studies of nutraceuticals (Chanput et al. 2014). However, there are no *in vitro* studies reported for anti-inflammatory effect of papaya extracts on THP-1 cells. To verify the effect of papaya extracts over inflammatory markers, comparative studies using different cells such as PBMC, THP-1, RAW-247 and lymphocytes are required. All *in vitro* studies (except one, described above) have used polar solvent extracts of

Table 1. *In vivo* studies of papaya extracts over immune-inflammatory markers.

Papaya				
Parts	Extract	Route of administration - dose	Results	References
Leaf	Ethanol	Oral - 25–200 mg/kg	Significant ($p < 0.05$) reduction in carrageenan-induced paw edema, granuloma (cotton pellet induced) and inflammation in arthritic rats.	(Owoyele et al. 2008)
Leaf	Aqueous	Oral - 100–200 mg/kg	Leaf extract found to contain alkaloids, tannins, cardiac glycosides and saponins. Extract displayed significant ($p < 0.05$) anti-inflammatory effect in rats (using acetic acid-induced writhing response and formalin test).	(Adeolu and Vivian 2013)
Leaf	Juice	Oral - 0.2 ml, 7 d	Platelet count was enhanced after 21 d (5.53×10^5/μl to 11.3×10^5/μl) in mice. Increment in RBC count also observed (6×10^6/μl to 9×10^5/μl)	(Dharmarathna et al. 2013)
Leaf	Ethanol (70%)	Oral - 1.1g, twice daily, 12 d	Significant ($p < 0.05$) increment in platelet count was observed in dengue fever patients (male and female)	(Fenny et al. 2012)
Leaf	Juice	Oral - 150 ml, daily, 5 d	Increment in thrombocytes (28×10^3/μl to 138×10^3/μl) and WBC (3000/μl to 7800/μl) in male dengue fever patient	(Osama et al. 2014)
Leaf	Juice	Oral - 25 ml, twice daily, 5 d	Increment in platelets (55×10^3/μl to 168×10^3/μl), RBC (5.0×10^6/μl to 5.3×10^3/μl), WBC (3.7×10^3/μl to 7.7×10^3/μl) and PMN (46.7% to 78.3%) in male dengue fever patient	(Ahmad et al. 2011)
Leaf	Juice	Oral - 0.72 ml/100 g	Both mature and immature leaves displayed platelet enhancing property with no signs of toxicity and stress in rats	(Achini et al. 2012)
Leaf	Juice	Oral - 50 g, daily, 3 d	Mean platelet count enhanced in dengue fever patients at 40 h of first dose. *ALOX12* (ΔCT mean = 16.02, FC = 15.00) and *PTAFR* genes (ΔCT mean = 14.87, FC =13.42) highly expressed	(Soobitha et al. 2013)
Fruit	–	Oral - 0.5 g/kg, daily, 3 weeks	Significant ($p < 0.05$) decrement in MPO and expression of iNOS in colitis-induced rat model	(Lima de Albuquerque et al. 2010)
Fruit	Aqueous	Oral - 0.25 g/kg, daily, 40 d	Significant ($p < 0.05$) decrement in MDA/SOD levels, increment in GSH/CAT levels in acrylamide (0.05%) toxicated rats (stomach, liver and kidney tissues)	(Mohamed Sadek 2012)
Fruit	–	Oral - 0.2 g and 1.6 g/kg for 5 weeks	No allergic potential displayed by transgenic and native papaya fruit on OVA-sensitized mouse model. Papaya green fruit (transgenic and non-transgenic) reduced IgM level (0.12–0.11 μg/ml vs. 0.15 μg/ml in control group)	(Chen et al. 2011)
Fruit	–	Oral - 100 g, thrice a day	Significant increments in $CD4^+CD25^+CD127^-$ T_{reg} cells (males) and level of IL-1β (male > female) were observed. Significant ($p < 0.05$) decrement in levels of IL-8, IL-6, IL-10, TNFα found in PBMC supernatants (*in vitro* study)	(Abdullah et al. 2011)
Fruit	Aqueous	Topical - 100 mg/kg, daily, 10 d	Significant ($p < 0.001$) increments in wound contraction capacity (77%) in diabetic rats and mass of granulation tissue were observed	(Nayak et al. 2007)
Seed	MeOH	Intraperitoneal - 50–200 mg/kg	Significant inhibition (57.1–64.2%) in inflammation observed in egg albumin-induced rat model	(Amazu et al. 2010)

MDA: malondialdehyde; SOD: superoxide dismutase; GSH: glutathione; CAT: catalase; OVA: ovalbumin.

papaya tissues and therefore, the anti-inflammatory activity of nonpolar extracts has not been thoroughly explored. *In vitro* studies are also lacking, which have studied the effects of other parts of papaya such as the fruit and peel.

In vivo studies

In vivo studies are essential to understand the in-use potential and activities of plant extracts. Table 1 summarizes the animal (stimulated inflammation and immune model) and human (healthy and dengue fever patients) studies that have demonstrated the potential for use of papaya extracts (consumed in the forms of leaf, fruit and peel) to modulate immune-inflammatory markers, antioxidant enzymes and platelets.

Various *in vivo* studies (mice and human) have demonstrated the anti-inflammatory (Owoyele et al. 2008; Adeolu & Vivian 2013) and platelet enhancing activities of papaya leaf (juice and aqueous ethanol extract) (Ahmad et al. 2011; Fenny et al. 2012; Dharmarathna et al. 2013; Osama et al. 2014). For example, Gammulle et al. reported significant anti-inflammatory activity of papaya leaf juice (at 0.72 ml/100 g body weight) against carrageenan-induced rat paw edema and impaired *in vivo* vascular permeability (82.0%); while inducing (10.1%) membrane-stabilizing activity of rat RBC. In addition, it also imparted an

immunomodulatory effect in the hydroxyurea-induced thryombocytopenic rat model. A significant increase in platelets, WBC and RBC (76.5%, 30.5% and 9.1%, respectively) was observed in this rat model in comparison with control hosts (Achini et al. 2012). Dengue fever patients, who consumed the leaf juice for three consecutive days had very significant ($p < 0.01$) increases in their mean platelet counts and platelet-producing gene expression (e.g. *ALOX 12*, *PTAFR*) (Soobitha et al. 2013).

Although no *in vitro* studies have yet examined the immunomodulatory activity of papaya fruit, several *in vivo* studies have investigated its immunomodulatory activities. Oral dose (500 mg/kg) of ripe papaya fruit in a rat model of colitis reduced the level of myeloperoxidase (MPO) and inducible nitric oxide synthase (iNOS) (Lima de Albuquerque et al. 2010). An aqueous extract of unripe papaya fruit administered to acrylamide-treated rats modulated the levels of malondialdehyde, superoxide dismutase, glutathione and catalase (Mohamed Sadek 2012). The same extract also significantly enhanced immunoglobulin IgG and IgM levels (from 0.120 → 0.132 and 0.892 → 0.108 mg/ml, respectively), in the same study.

Factors such as the degree of maturation, ripeness and plant cultivar type may affect extract bioactivity (due to variation in the composition and the levels of phytochemicals) (Pablito & Charles 2003; Ayoola & Adeyeye 2010; Tripathi et al. 2011). Topical application of the aqueous extracts of unripe fruit (5 mg/ml) exhibited faster wound healing (13 d) in mice than a similar aqueous extract of ripe fruit (17 d) (Anuar et al. 2008). This could be because chronic wounds are highly pro-oxidant microenvironments and unripe papaya has better antioxidant activity (unripe fruit > ripe fruit > seed) (Maisarah et al. 2012). Chen et al. examined and reported on the immunomodulatory properties of transgenic and native papaya fruits (both ripe and unripe) using an ovalbumin (OVA)-sensitized mouse model. An oral dose of 1.6 g/kg body weight [for five weeks] native green papaya fruit supplementation significantly decreased (0.04 µg/ml vs. 0.08 µg/ml in control group) the OVA-specific IgE titre. However, a significant increase in OVA-specific IgG_{2a} titre was observed with hosts provided native papaya fruit (green and ripe). The ripe transgenic papaya fruit significantly enhanced humoral immunity by increasing serum total IgM level (2062 vs. 1583 µg/ml in control group) (Mohamed Sadek 2012). Healthy male and female human subjects, following a pre-exposure period of 2 d (without papaya), were fed 100 g fresh papaya fruit for 2 d (in a day's three major meals consisting of bread/rice, chicken/fish, vegetables and liquid). A peripheral blood sample was collected at Day 3 that displayed significant suppression of $IFN\gamma^+CD4^+$ (1.48 vs. 3.52%; $p = 0.03$), and upregulation of $IL\text{-}4^+CD4^+$ (2.08 vs. 1.44%; $p = 0.04$) T-cells and $CD3^+CD4^+CD25^+CD127^-$ T-cells (9.01 vs. 5.30%; $p = 0.001$) (Abdullah et al. 2011). This study indicated papaya imparted an immunomodulatory effect in human subjects. However, it lacked information about control (no papaya after pre-exposure) and further studies are required with longer exposure times (>2 d).

Papaya seeds (methanol and aqueous extract) have also been examined and found to display anti-inflammatory activity in *in vivo* study (Amazu et al. 2010; Umana et al. 2014). However, their activity toward immune-inflammatory markers (such as those in *in vitro* studies) *in vivo* has not been reported to date. To investigate the bioactivity of phytochemicals, studies should include both polar and nonpolar extracts (Pandey et al. 2014). Unfortunately, none of the *in vivo* studies reported thus far investigated the anti-inflammatory or immunomodulatory effects of nonpolar extracts of any part of the papaya plant.

To date, seven papaya-based clinical studies are listed in the ClinicalTrials.gov (http://www.clinicaltrials.gov) database. Three of these investigated effects of papaya preparations on common cold symptoms, platelet counts and in treatment of impetigo. The other four studied effects of fermented papaya preparation in the treatment of inflammation (wound and systemic), diabetes and cardiac diseases. However, no clinical trials of the possible role of the anti-inflammatory activity of papaya in CID have been done. Although the potential anti-cancer activity of papaya is well established (Nguyen et al. 2013), and strong link between inflammation and cancer progression, the possible role of papaya anti-inflammatory effects individually or as an adjuvant in any anti-cancer activity should be explored.

Considering the nutritional and therapeutic effects of papaya, an increase in the intake of papaya supplements is expected. The possibilities of side effects (such as allergic reactions, changes in hematology parameters and gastric irritation) associated with consumption or topical application of high doses of papaya preparations are indicated (Oduola et al. 2007; Duru et al. 2012; Enaibe et al. 2014; http://www.drugs.com/npp/papaya.html). There are only a few scientific studies that have reported interactions between papaya components and synthetic conventional drugs (Fakeye et al. 2007; Rodrigues et al. 2014). For further confirmation of anti-inflammatory and immunomodulatory effects, as well as of any side effects and drug interactions with papaya extracts, double-blind placebo-controlled clinical trials still need to be carried out.

Anti-inflammatory activities of papaya-associated phytochemicals

Carica papaya, as noted above, is a tropical plant containing a wide range of bioactive secondary metabolites (e.g. alkaloids, phenolics, flavonoids, carotenoids, tannins, saponins, etc.) and proteolytic enzymes (papain and chymopapain) (Figure 1). A number of the phytochemicals found in papaya (though not restricted to papaya only) have been shown to reduce chronic inflammatory conditions and associated side-effects by modifying the levels of inflammatory markers (Duke 2015). Table 2 summarizes the role of papaya-associated bioactivities in the modulation of immune-inflammatory markers.

In addition to secondary metabolites, the proteolytic enzymes present in papaya (papain and chymopapain) have also shown immunomodulatory and anti-inflammatory activities (Rakhimov 2001; Rose et al. 2006; Mohr & Desser 2013). The role of transforming growth factor (TGF)-β in anti-inflammation is evident. Over-production and/or activation of TGFβ contribute to persistent inflammation (Chen & Wahl 1999). Papain – in combination with other proteolytic enzymes (trypsin and chymotrypsin) – significantly reduced TGF-β1 levels in patients with rheumatoid arthritis ($p < 0.005$), osteomyelofibrosis ($p < 0.05$) and herpes zoster (shingles) ($p < 0.05$) (Desser et al. 2001). It also reduced ($p < 0.001$) radiotherapy-associated inflammatory side effects (mucositis and skin reaction) in head and neck cancer patients (Gujral et al. 2001).

Papaya alkaloids (nicotine and choline) also displayed anti-inflammatory potential (Razani-Boroujerdi et al. 2004; Parrish et al. 2006; Yoshikawa et al. 2006; Takahashi et al. 2007; Aldhous et al. 2008; Nizri et al. 2009; Mehta et al. 2010; Mabley et al. 2011; Zhou et al. 2012). However, any anti-inflammatory activity of a major papaya alkaloid, carpaine, has not yet been reported. Other phytochemicals in papaya from the

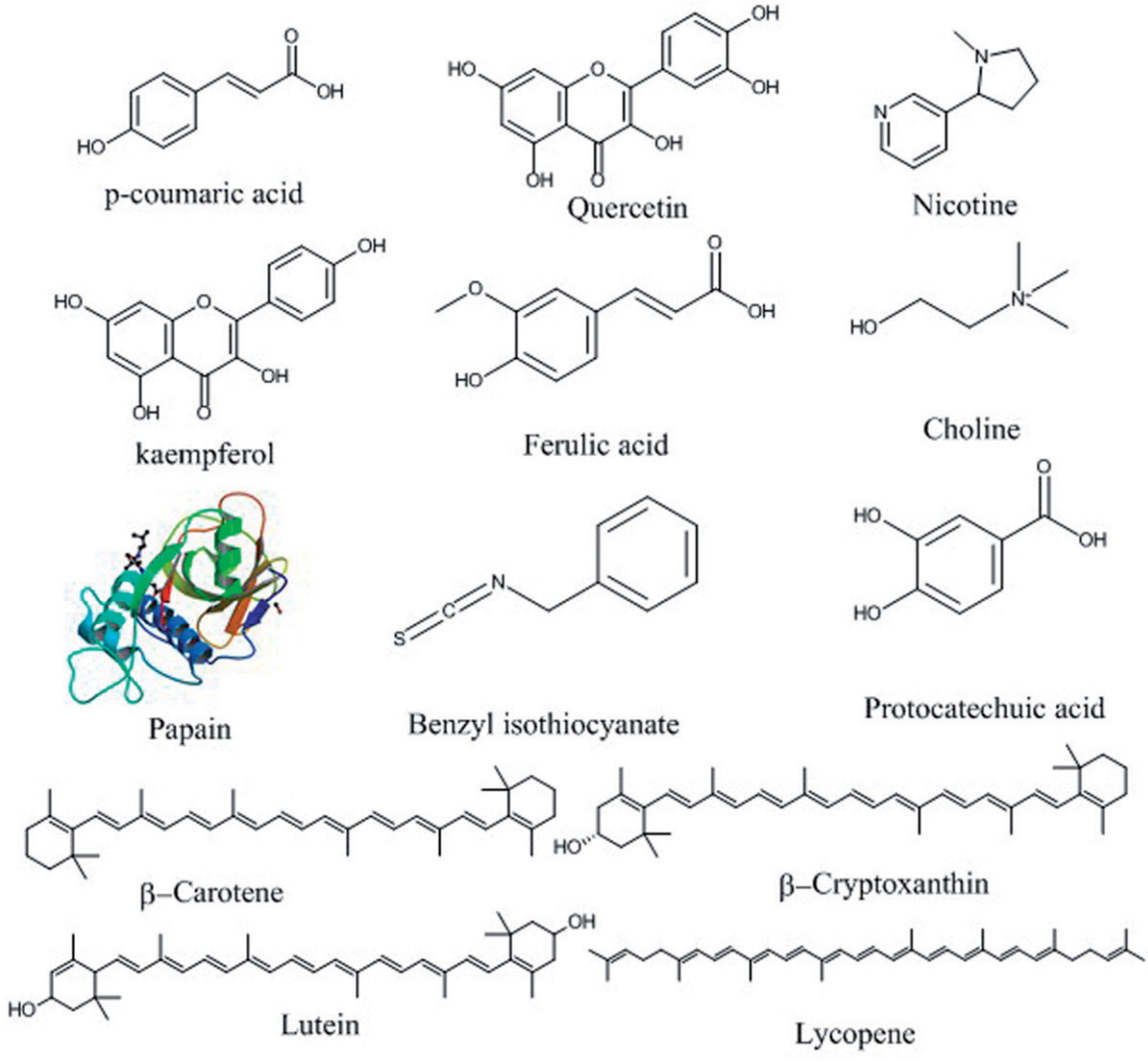

Figure 1. *Carica papaya*-derived substances.

Table 2. Proteolytic enzymes and phytochemicals of *C. papaya* and their responses over inflammatory immune markers.

Substances; amount (papaya part)	Dose	Experimental systems	Anti-inflammatory and immunomodulatory activity	References
Proteolytic enzyme		PBMC	Significant ($p < 0.05$) increments in IL-6 and IFNγ	(Rose et al. 2006)
Papain; 53 000 ppm (unripe fruit latex), 2.43 mg/g (ripe fruit latex) (Rubens et al. 2000; Duke 2015)	30 μg/ml			
	10 μg/ml	VEGF-activated human umbilical vein endothelial cells	Upregulation of ERK-1/2; downregulation of protein kinases AKT1, MEK1/2, p38-MAPK and SAPK/JNK.	(Mohr and Desser 2013)
Alkaloids		LPS stimulated PBMC	Significant ($p < 0.001$) decrements in the production of IL1β, IL10, TGFβ and TNFα	(Aldhous et al. 2008)
Nicotine; 102.8 ppm (leaf) (Duke 2015)	1, 10 and 100 μg/ml			
	0.1–100 μM	IL-18-enhanced PBMC	Inhibition of ICAM-1 expression, IFNγ production and proliferation of lymphocytes	(Takahashi et al. 2007)
	10 pM	LPS-activated monocytes	Significant decrements in TNFα, PGE_2, MIP-1α, MIP-1α production and mRNA expression of TNFα, MIP-1α, COX-2. Suppression of IκB phosphorylation, subsequent inhibition NF-κB transcriptional activity	(Yoshikawa et al. 2006)
	0.1–100 μM	TNFα-induced fibroblast-like synoviocytes	Reductions in mRNA expression (IL-6 and IL-8) and NF-κB translocation.	(Zhou et al. 2012)
	2 mg/kg	Encephalomyelitis-induced female C57BL/6 mice, oral, for 28 d	Decrements of encephalitogenic Ag stimulated T-cell proliferation, production of T_H1 (TNFα and IFNγ) and T_H17 cytokines (IL-17, IL-17F, IL-21 and IL-22).	(Nizri et al. 2009)
	0.2 or 0.4 mg/kg	Male BALB/c mice, intra-peritoneal	Significant ($p < 0.05$) reductions in BALF cell numbers, MPO activity, pro-inflammatory chemokine (MIP-1α, MIP-2, eotaxin) and cytokine (IL-1, IL-6 and TNFα) levels.	(Mabley et al. 2011)
	1–2 mg/kg BW	Rat and mice, subcutaneous	Decrement in leukocyte migration, levels of chemokinesis, chemotaxis and chemokine-induced Ca^{2+} responses in PBMC	(Razani-Boroujerdi et al. 2004)
Choline 0.2 mg/g (leaf) (Ogan 1971)		Asthma patients, oral, twice daily	Significant ($p < 0.01$) reductions in IL-4, IL-5, TNFα, cysteinyl leukotriene and leukotriene B_4 levels	(Mehta et al. 2010)
	1500 mg			
	5 and 50 mg/kg BW	Mice (endotoxin induced), intraperitoneal	Reduction of serum TNFα	(Parrish et al. 2006)
Phenolics	50 mg/kg BW	Mice (ionizing radiation-induced inflammation), oral, 5 d	Prevention of increase in levels of inflammatory markers (COX-2 protein, iNOS-2 gene expression, lipid peroxidation, NF-κB translocation, TNFα and IL-6). Enhancement of SOD and CAT enzyme activities and reduction in GSH activity.	(Das et al. 2014)
Ferulic acid (FA) 1.87–2.78 mg/g (dry peel) (Gayosso-García Sancho et al. 2011)				
	1.28 μg/gm BW	Mice (collagen-induced arthritis), IG, twice a day	Significant ($p < 0.01$) reduction of IL-1β and TNFα levels in serum and anti-inflammatory effects	(Zhu et al. 2014)
p-Coumaric acid (PC); 0.33 mg/g (dry leaf), 1.36–2.23 mg/g (peel) (Canini et al. 2007; Gayosso-García Sancho et al. 2011)	2.4 μM	LPS-induced Caco-2 and RAW 264.7 co-culture	Reduction of levels of NO, IL-6, PGE-2, IL-1β, iNOS, COX-2, IκBα phosphorylation, TNFα mRNA	(Kim et al. 2014)
	100 mg/kg BW	Mice (inflammation-induced), IP, 8 d	Significant ($p < 0.05$) reduction of synovial TNFα, delayed-hypersensitivity response and macrophage phagocytic function. Enhancement of serum IgG level and reduction of circulating immune complex.	(Pragasam et al. 2013)
Protocatechuic acid (PCA); 0.11 mg/g (dry leaf) (Canini et al. 2007)	2 mM	AGS	Significant ($p < 0.05$) decrement in migration of cells levels of MMP-2 and NF-κB protein.	(Lin et al. 2011)
	500 ppm	Rats (NMBA-induced esophageal cancer), SC	Decrements in expression of IL-1β, IL-2 and IL-10 (after 25 weeks).	(Peiffer et al. 2012)
	0.5–2%	Male Balb/cA mice, intraperitoneal, daily, 8 weeks	Significant ($p < 0.05$) decrements in levels of IL-1β, IL-6, TNFα, PGE_2, NF-κB and COX-2 protein (vs D-galactose-fed mice).	(Tsai & Yin 2012)
	25–100 mg/kg	Rats (edematous/arthritic model), oral, 8 d (for anti-inflammatory) and 14 d (for anti-arthritic)	Displayed anti-inflammatory and anti-arthritic activity. Significant reduction of NO and lipid peroxides	(Lende et al. 2011)

(continued)

Table 2. Continued

Substances; amount (papaya part)	Dose	Experimental systems	Anti-inflammatory and immunomodulatory activity	References
			activity. In addition, increment in levels of anti-oxidant enzymes (such as GSH, CAT and SOD).	
Quercetin; 0.04 mg/g (dry leaf), 0.83–2.57 μg/g (fruit) (Canini et al. 2007; Kongkachuichai et al. 2010)	1 μM	PBMC and human, 4 weeks	Decrement in levels of cytokines (77%). Enhancement in total anti-oxidant levels	(Boots et al. 2008)
	1–50 μM	Dendritic cells (DC isolated from C57BL/6 mice)	Inhibition of LPS-induced DC activation at 1 μM. Significant reductions in levels of various pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, IL-10, IL-12) and chemokines (MCP-1, MIP-1α, MIP-1β, RANTES). Suppression of endocytosis, DC migration and ability to induce Ag-specific T-cell activation	(Huang et al. 2010)
	50 μM and 1 mg/kg	Rats (colitis-induced) and macrophages, oral treatment to rats for 14 d	Significant inhibition of TNFα, IL-1β, iNOS expression and NF-κB activation	(Comalada et al. 2005)
	1–50 μM	PBMC	Reduction of TNFα and NF-κB gene expressions	(Madhavan et al. 2006)
Kaempherol; 0.03 mg/g (dry leaf), 0.004–0.006 μg/g (fruit) (Canini et al. 2007; Kongkachuichai et al. 2010)	40 mM	HL-60, U937, M12, and A1.1, PBMC, Primary BALB/c splenic cell	Decrements in activation of JAK3, STAT6 and mixed lymphocyte culture proliferation	(Cortes et al. 2007)
	1–10 μM	Aldosterone-induced primary HUVEC cells	Reductions in levels of ROS, OPN, CD44, phospho-p38MAPK expression and NF-κB	(Liu et al. 2014)
	10/20 mg/kg 1–20 μM	BALB/c mice (allergic asthma), oral for 3 d and BEAS-2B cells	Significant decrements in eotaxin-1 protein expression (LPS-induced), integrin β2, eosinophil adhesion (to TNFα-activated airway epithelium), MCP-1 transcription (TNFα-activated) and NF-κB. Reduced PMN and basophils count. Diminished IκB phosphorylation	(Gong et al. 2012)
	10–100 μM	BV2 (LPS-induced microglial cells)	Significant ($p < 0.05$) reductions in inflammatory markers (NO, PGE_2, TNFα, IL-1β, iNOS, cox-2, MMP-3) and blocked activation of TLR4. Inhibition of NF-κB activation and phosphorylation (p38 MAPK, JNK and AKT)	(Park et al. 2011)
	150 and 30 mg/kg BW	Cholesterol-fed rabbits	Significant reductions in TNFα, IL-1β, MDA levels. Enhanced serum SOD activity	(Kong et al. 2013)
Carotenoids				
Lycopene; 1.5–12 μg/g (unripe flesh), 11.5 μg/g (ripe red flesh) (Yamamoto 1964; Rivera-Pastrana et al. 2010)	1.5 mg/kg	Rats (myocardial infarct), gastric gavage, daily, 28 d	Significant ($p < 0.05$) inhibition of macrophage infiltration, TNFα expression, phosphorylation of IKKα/β and NF-κB activation	(Yongming & Wang 2014)
	0.5–2 μM	Cigarette smoke extract-induced THP-1 cells	Decrements in immune marker (IL-8 expression, ROS, NF-κB/p65 nuclear translocation) levels, phos-phorylation (IKKα and IkBα) and redox-sensitive kinases (ERK1/2, JNK and p38 MAPKs).	(Simone et al. 2011)
	0.5–2 μM	LPS-stimulated RAW 264.7, 3T3-L1	Significant inhibition of macrophage migration, TNF-α and mRNA (adiponectin, MMP-3, MMP-9) levels. Inhibition of JNK and NF-κB pathways.	(Marcotorchino et al. 2012)
	2 μM	C57BL/6j mice and 3T3-L1 pre-adipocytes	Decrements in levels of mRNA (IL-6, MCP-1, IL-1β, TNFα) and NF-κB (TNFα-activated).	(Gouranton et al. 2011)
β-Cryptoxanthin; 3.1–8.0 μg/g (unripe flesh), 16.9 μg/g (ripe red flesh) (Yamamoto 1964; Rivera-Pastrana et al. 2010;)	7.5 and 37.5 μg/kg BW	Ferrets (cigarette smoke-induced), oral 3 mo	Significant decrements in TNFα levels (bronchial and alveolar epithelial cells), NF-κB expression (AP-1), 8-OHdG and macrophages (lung tissue). Reduction in metaplasia (lung squamous) and inflammation (lung).	(Liu et al. 2011)

(continued)

Table 2. Continued

Substances; amount (papaya part)	Dose	Experimental systems	Anti-inflammatory and immunomodulatory activity	References
	5 and 10 mg/kg BW	Rabbit, oral, daily, 21 d	Enhancement in count of $CD4^+$ lymphocytes ($p < 0.01$) in rabbit blood. Significant ($p < 0.05$) enhancement in IL-4 and immunoglobulins (IgG, IgM, IgA).	(Ghodratizadeh et al. 2014)
	0.003%	C56BL/6J mice (cholesterol diet-induced), oral, 12 weeks	Downregulation of fibrosis, fat accumulation, increases in Kupffer and activated stellate cells. Suppression of T-cell markers and inflammatory gene expression.	(Kobori et al. 2014)
β-Carotene; 2.3–3.1 μg/g (unripe flesh), 7.0 μg/g (ripe red flesh) (Yamamoto 1964; Rivera-Pastrana et al. 2010)	60 mg/kg	C57BL/6 mice, IP, 5 doses for 5 d; and B16F-10 melanoma cells	Significant downregulation in TNFα, IL-6, VEGF. Significant enhancement in IL-2 and metalloprotease. Significant ($p < 0.001$) reduction in pro-inflammatory cytokine production (B16F-10 cells). Inhibition of NF-κB subunit (p65, p50, c-Rel) translocation	(Guruvayoorappan & Kuttan 2007)
	5 mg/kg	Mice, orally, 7 d	Significant enhancement in IL-2 and IFNγ levels	(Yamaguchi et al. 2010)
	2 - 20 μM	AGS (*Helicobacter pylori*-induced)	Decrements in levels of markers (ROS, iNOS, COX-2) and transcription kinase (MAPK, p38, JNK, NF-κB, AP-1) activation	(Jang et al. 2009)
Lutein; 7.1 μg/g (fruit) (Ben-Amotz & Fishler 1998)	0.1 g/100 g diet	Guinea pig, oral, 12 weeks	Significant ($p < 0.05$) reduction in inflammatory IFNγ, TNFα, IL-1β, IL-2, -4, -5, -6, -7, -10, -12 levels	(Kim et al. 2011)
	1–20 mg	Cat and dog, oral, daily,12 weeks	Significant enhancement in lymphocytes ($CD4^+$, $CD21^+$). Nonsignificant effect on pan-T, CD8, MHC-II marker levels. Enhanced plasma IgG ($p < 0.05$; cats)	(Kim et al. 2000a, 2000b)
Glucosinolates				
Benzylisothiocynate; 4.6 μmole/g seed, <0.003 μmole/g pulp, 141.7–342.7 ppm seed, 23.3–45.1 ppm pericarp, 21.2–43.1 ppm pulp, 2910 ppm (ripe fruit seed), 4 ppm ripe fruit pulp, 52.2 mg/kg leaf, 18 mg/kg unripe fruit, 3.6 mg/kg flower (Tang 1971; Sheu & Shyu 1996; Nakamura et al. 2007; Li et al. 2012)	150 and 300 nM 1–5 μM	Mice, topical and Raw 264.7 cells (LPS stimulated)	Reduction in ear edema. Decreased immune markers (NO production, iNOS protein/mRNA, PGE_2, COX-2 protein, NF-κB signaling) and IL-6, IL-1β, TNFα	(Lee et al. 2009)
	810 nmol	Mice (TPA-induced oxidative damage), topical and HL-60 cells	Significant ($p < 0.05$) inhibition of MPO activity and O^{2-} generation. Enhanced $TUNEL^+$ index in mouse skin.	(Miyoshi et al. 2004)

A1.1: murine lymphocyte; AGS: human gastric carcinoma cells; AKT: protein kinase B; BALF: bronchoalveolar lavage fluid; BEAS-2B: Human airway epithelial; CaCo-2: Colon cancer cell; CAT: catalase; Cox-2: cyclooxygenase-2; DC: dendritic cells; ERK: extracellular signal-regulated kinases; GSH: glutathione; HL-60: human promyelocytic leukemia cells; HUVEC: human umbilical vein endothelial cells; JNK: c-Jun N-terminal kinases; M12: human prostate cell line; MAPK: mitogen-activated protein kinase; MEK-1: mitogen-activated protein kinase kinase 1; MHC: major histocompatibility complex; MIP-2: macrophage inflammatory protein-2; MMP-2: matrix metalloproteinase; NK: natural killer cell; NMBA: *N*-nitrosomethylbenzylamine; NLRP-3: OPN: osteopontin; PGE-2: prostaglandin E2; RAW 264.7: murine macrophages; ROS: reactive oxygen species; SOD: superoxide dismutase; TGF-β: Transforming growth factor beta; THP-1: human acute monocyte leukemia cell; TLR-4: Toll-like receptor 4; TPA: 12-*O*-tetradecanoylphorbol-13-acetate; TUNEL: terminal deoxynucleotidyl transferase-dUTP nick end labeling; U937: human leukemic monocyte lymphoma cell line; VEGF: vascular endothelial growth factor; 8-OHdG: 8-Oxo-2′-deoxyguanosine.

phenolic, carotenoid and glucosinolate secondary metabolite compound classes have also been proven to modulate levels of cytokines, transcription factors and antioxidant enzymes (Table 2).

In general, papaya extracts and papaya-associated phytochemicals have demonstrated some potential anti-inflammatory and immunomodulatory activities. However, a safe, reliable and efficient extraction methodology is critical to study the bioactivity of plant extracts (Franz et al. 2013). Selective extraction using pH control and non-conventional extraction methods (such as supercritical fluid extraction, sonication, etc.) may potentially offer a better route for the isolation of papaya phytochemicals prior to bioactivity studies (Pandey et al. 2014).

Conclusions

Several studies have shown significant anti-inflammatory and immunomodulatory activities of different parts of the papaya plant by different mechanisms. Although extent of maturation, cultivar type, different parts of the plant and extraction method may affect the levels and types of bioactive phytochemicals (Pandey et al. 2015), there were no studies on the effects of these factors on the bioactivity of papaya. To date, *in vitro* studies have only focused on the extracts of leaves and seeds and not on the edible parts of the papaya plant. Only one *in vitro* study has examined the potential anti-inflammatory and immuno-modulatory activities of non-polar extracts of any parts of the papaya plant. Despite the encouraging information available, including a number of *in vitro* cell line and *in vivo* (animal and few human) studies, there are no clinical studies carried out to examine the role of papaya in the treatment of CID's (including cancer) either alone or as an adjuvant to anti-inflammatory drugs. Further, the safety and efficacy of papaya extracts as therapeutically active agents have not been subjected to additional scrutiny using high quality *in vivo* trials. In general, both the studied plant extracts and the phyto-chemicals in papaya that have been investigated show some promise as potential drug targets for inflammatory diseases.

Disclosure statement

The authors declare no conflicts of interest. The authors alone are responsible for the content of this manuscript.

Funding information

Saurabh Pandey is funded by an International Postgraduate Research Scholarship (IPRS) and Centennial Scholarship of the University of Queensland.

References

Abdullah M, Chai PS, Loh CY, Chong MY, Quay HW, Vidyadaran S, Seman Z, Kandiah M, Seow HF. 2011. *Carica papaya* increases regulatory T-cells and reduces IFNγ^+ CD4$^+$ T-cells in healthy human subjects. Mol Nutr Food Res. 55:803–806.

Achini G, Ratnasooriya WD, Jayakody JR, Charmain F, Chamini K, Preethi VU. 2012. Thrombocytosis and anti-inflammatory properties, and toxicological evaluation of *Carica papaya* mature leaf concentrate in a murine model. Online Int J Med Plants Res. 1:21–30.

Adeolu AA, Vivian EO. 2013. Anti-nociceptive and anti-inflammatory studies of the aqueous leaf extract of *Carica papaya* in laboratory animals. Asian J Exp Biol Sci. 4:89–96.

Agarwal A, Verma S, Burra U, Murthy NS, Mohanty NK, Saxena S. 2006. Flow cytometric analysis of T_H1 and T_H2 cytokines in PBMC as a parameter of immunological dysfunction in patients of superficial transitional cell carcinoma of bladder. Cancer Immunol Immunother. 55:734–743.

Ahmad N, Fazal H, Ayaz M, Abbasi BH, Mohammad I, Fazal L. 2011. Dengue fever treatment with *Carica papaya* leaves extracts. Asian Pacific J Trop Biomed. 1:330–333.

Aldhous MC, Prescott RJ, Roberts S, Samuel K, Waterfall M, Satsangi J. 2008. Does nicotine influence cytokine profile and subsequent cell cycling/apoptotic responses in inflammatory bowel disease? Inflamm Bowel Dis. 14:1469–1482.

Amazu LU, Azikiwe CC, Njoku CJ, Osuala FN, Nwosu PJ, Ajugwo AO, Enye JC. 2010. Anti-inflammatory activity of the methanolic extract of the seeds of *Carica papaya* in experimental animals. Asian Pacific J Trop Med. 3:884–886.

Anuar NS, Zahari SS, Taib IA, Rahman MT. 2008. Effect of green and ripe *Carica papaya* epicarp extracts on wound healing and during pregnancy. Food Chem Toxicol. 46:2384–2389.

Aravindaram K, Yang NS. 2010. Anti-inflammatory plant natural products for cancer therapy. Planta Med. 76:1103–1117.

Ayoola PB, Adeyeye A. 2010. Phytochemical and nutrient evaluation of *Carica papaya* (pawpaw) leaves. Int J Res Rev Appl Sci. 5:325–328.

Ben-Amotz A, Fishler R. 1998. Analysis of carotenoids with emphasis on 9-cis-β-carotene in vegetables and fruits commonly consumed in Israel. Food Chem. 62:515–520.

Bertrand S, Donatella F, Rita C, Carla M, Giancarlo F, Vittorio C. 2014. Anti-oxidant and anti-inflammatory activities of extracts from *Cassia alata*, *Eleusine indica*, *Eremomastax speciosa*, *Carica papaya*, and *Polyscias fulva* medicinal plants collected in Cameroon. PLoS One 9:e103999.

Boots AW, Wilms LC, Swennen EL, Kleinjans JC, Bast A, Haenen GR. 2008. *In vitro* and *ex vivo* anti-inflammatory activity of quercetin in healthy volunteers. Nutrition 24:703–710.

Bradley JR. 2008. TNF-mediated inflammatory disease. J Pathol. 214:149–160.

Canini A, Alesiani D, D'Arcangelo G, Tagliatesta P. 2007. Gas chromatography–mass spectrometry analysis of phenolic compounds from *Carica papaya* L. leaf. J Food Comp Anal. 20:584–590.

Chanput W, Mes JJ, Wichers HJ. 2014. THP-1 cell line: An *in vitro* cell model for immune modulation approach. Int Immunopharmacol. 23:37–45.

Chen W, Wahn SM. 1999. Manipulation of TGFβ to control autoimmune and chronic inflammatory diseases. Microbes Infect. 1:1367–1380.

Chen YN, Hwang WZ, Fang TJ, Cheng YH, Lin JY. 2011. The impact of transgenic papaya (TPY10-4) fruit supplementation on immune responses in ovalbumin-sensitized mice. J Sci Food Agric. 91:539–546.

ClinicalTrials.gov [Internet] . 2000. Bethesda (MD): National Library of Medicine (US) [cited 2015 May 27]. Available from: http://clinicaltrials.gov/show/Identifier: NCT016 18045, NCT02051634, NCT00778648, NCT02016027, NCT02189070, NCT01248143, NCT01943136.

Comalada M, Camuesco D, Sierra S, Ballester I, Xaus J, Gálvez J, Zarzuelo A. 2005. *In vivo* quercitrin anti-inflammatory effect involves release of quercetin, which inhibits inflammation through down-regulation of the NF-κB pathway. Eur J Immunol. 35:584–592.

Cortes JR, Perez GM, Rivas MD, Zamorano J. 2007. Kaempferol inhibits IL-4-induced STAT6 activation by specifically targeting JAK3. J Immunol. 179:3881–3887.

Das U, Manna K, Sinha M, Datta S, Das DK, Chakraborty A, Ghosh M, Saha KD, Dey S. 2014. Role of ferulic acid in the amelioration of ionizing radiation-induced inflammation: a murine model. PLoS One 9:e97599.

de Groot DJ, de Vries EG, Groen HJ, de Jong, S. 2007. Non-steroidal anti-inflammatory drugs to potentiate chemotherapy effects: from lab to clinic. Crit Rev Oncol Hematol. 61:52–69.

Desser L, Holomanova D, Zavadova E, Pavelka K, Mohr T, Herbacek I. 2001. Oral therapy with proteolytic enzymes decreases excessive TGFβ levels in human blood. Cancer Chemother Pharmacol. 47:S10–S15.

Dharmarathna SL, Wickramasinghe S, Waduge RN, Rajapakse RP, Kularatne SA. 2013. Does *Carica papaya* leaf-extract increase the platelet count? An experimental study in a murine model. Asian Pacific J Trop Biomed. 3:720–724.

Di Sabatino A, Carsetti R, Rosado MM, Ciccocioppo R, Cazzola P, Morera R, Tinozzi FP, Tinozzi S, Corazza GR. 2004. Immunoglobulin M memory B-cell decrease in inflammatory bowel disease. Eur Rev Med Pharmacol Sci. 8:199–203.

Dinarello CA. 2010. Anti-inflammatory agents: Present and future. Cell 140:935–950.

Dinarello CA, Pomerantz BJ. 2001. Pro-inflammatory cytokines in heart disease. Blood Purif. 19:314–321.

Drugs.com [Internet] [cited 2015 May 25]. Available from: http://www.drugs.com/npp/papaya.html.

Duke J. 2015. Dr. Duke's phytochemical and ethnobotanical databases [online]. [cited 2015 April 3] Available from: http://www.ars-grin.gov/duke.

Duru MK, Amadi BA, Amadi CT, Lele KC, Anudike JC, Chima-Ezika OR, Osuocha K. 2012. Toxic effects of *Carica papaya* bark on body weight, hematology, and some biochemical parameters. Biokemistri 24:67–71.

Edward AE, Fredy HB. 2012. An overview of global papaya production, trade, and consumption [Internet]. Gainesville, FL: Food and Resource Economics Department, Florida Cooperative Extension Service, Institute of Food and Agricultural Sciences, University of Florida [cited 2015 January 28]. Available from: http://edis.ifas.ufl.edu.

Elizabeth RR, Scharri JE, Ruiwen Z. 2009. Anti-inflammatory agents for cancer therapy. Mol Cell Pharmacol. 1:29–43.

Enaibe BU, Omotoso GO, Olajide OJ, Lewu SF, Adeyemi SO. 2014. Morphological evaluation of the superior colliculus of young Wistar rats following prenatal exposure to *Carica papaya* leaf extract. J Exp Clin Anat. 13:29–33.

Esser N, Paquot N, Scheen, AJ. 2014. Anti-inflammatory agents to treat or prevent Type 2 diabetes, metabolic syndrome, and cardiovascular disease. Expert Opin Invest Drugs 24:283–307.

Ezekiel A, Florence M. 2012. Papain, a plant enzyme of biological importance: A review. Am J Biochem Biotechnol. 8:99–104.

Fakeye T, Oladipupo T, Showande O, Ogunremi Y. 2007. Effects of co-administration of extract of *Carica papaya* Linn (family *Cariaceae*) on activity of two oral hypoglycemic agents. Trop J Pharm Res. 6:671–678.

Fenny Y, Endang H, Jusuf KJ. 2012. The effect of *Carica papaya* L. leaves extract capsules on platelets count and hematocrit level in dengue fever patient. Int J Med Aromatic Plants 2:573–578.

Franz B, Abraham W, Martin S. 2013. Natural product isolation - how to get from biological material to pure compounds. Nat Prod Rep. 30:525–545.

Gayosso-García Sancho LE, Yahia EM, González-Aguilar GA. 2011. Identification and quantification of phenols, carotenoids, and vitamin C from papaya (*Carica papaya* L., cv. Maradol) fruit determined by HPLC-DAD-MS/MS-ESI. Food Res Int. 44:1284–1291.

Generaal E, Vogelzangs N, Macfarlane GJ, Geenen R, Smit JH, Dekker J, Penninx BW. 2014. Basal inflammation and innate immune response in chronic multi-site musculoskeletal pain. Pain 155:1605–1612.

Ghodratizadeh S, Kanbak G, Beyramzadeh M, Dikmen ZG, Memarzadeh S, Habibian R. 2014. Effect of carotenoid β-cryptoxanthin on cellular and humoral immune response in rabbit. Vet Res Commun. 38:59–62.

Gong JH, Shin D, Han SY, Kim JL, Kang, YH. 2012. Kaempferol suppresses eosionphil infiltration and airway inflammation in airway epithelial cells and in mice with allergic asthma. J Nutr 142:47–56.

Gouranton E, Thabuis C, Riollet C, Malezet-Desmoulins C, El Yazidi C, Amiot MJ, Borel P, Landrier JF. 2011. Lycopene inhibits pro-inflammatory cytokine and chemokine expression in adipose tissue. J Nutr Biochem. 22:642–648.

Goyal S, Manivannan B, Ansari AS, Jain SC, Lohiya NK. 2010. Safety evaluation of long term oral treatment of methanol sub-fraction of the seeds of *Carica papaya* as a male contraceptive in albino rats. J Ethnopharmacol. 127:286–291.

Gujral MS, Patnaik PM, Kaul R, Parikh HK, Conradt C, Tamhankar CP, Daftary GV. 2001. Efficacy of hydrolytic enzymes in preventing radiation therapy-induced side-effects in patients with head and neck cancers. Cancer Chemother Pharmacol. 47:S23–S28.

Gupta A, Wambebe C, Parsons, DL. 1990. Central and cardiovascular effects of alcoholic extract of the leaves of *Carica papaya*. Pharmaceut Biol. 28:257–266.

Guruvayoorappan C, Kuttan G. 2007. β-Carotene inhibits tumor-specific angiogenesis by altering the cytokine profile and inhibits the nuclear translocation of transcription factors in B16F10 melanoma cells. Integr Cancer Ther. 6:258–270.

Huang RY, Yu YL, Cheng WC, Ouyang CN, Fu E, Chu CL. 2010. Immunosuppressive effect of quercetin on dendritic cell activation and function. J Immunol. 184:6815–6821.

Iyer D, Sharma BK, Patil UK. 2011. Effect of ether- and water-soluble fractions of *Carica papaya* ethanol extract in experimentally-induced hyperlipidemia in rats. Pharm Biol. 49:1306–1310.

Jang SH, Lim, JW, Kim H. 2009. β-Carotene inhibits *Helicobacter pylori*-induced expression of iNOS and COX-2 in human gastric epithelial AGS cells. J Physiol Pharmacol. 60(S7):131–137.

Khansari N, Shakiba Y, Mahmoudi M. 2009. Chronic inflammation and oxidative stress as a major cause of age-related diseases and cancer. Recent Pat Inflamm Allergy Drug Discov. 3:73–80.

Khare CP, editor. 2004. *Indian herbal remedies*. Heidelberg: Springer. p. 115–181.

Kim HW, Chew BP, Wong TS, Park JS, Weng BB, Byrne KM, Hayek MG, Reinhart GA. 2000a. Dietary lutein stimulates immune response in the canine. Vet Immunol Immunopathol 74:315–327.

Kim HW, Chew BP, Wong TS, Park JS, Weng BB, Byrne KM, Hayek MG, Reinhart GA. 2000b. Modulation of humoral and cell-mediated immune responses by dietary lutein in cats. Vet Immunol Immunopathol. 73:331–341.

Kim JE, Leite JO, Deogburn R, Smyth JA, Clark RM, Fernandez ML. 2011. A lutein-enriched diet prevents cholesterol accumulation and decreases oxidized LDL and inflammatory cytokines in the aorta of guinea pigs. J Nutr. 141:1458–1463.

Kim K, Kim Y, Lim, J, Min SJ, Ko H, Kim S, Kim Y. 2014. Intestinal anti-inflammatory activity of *Sasa quelpaertensis* leaf extract by suppressing lipopolysaccharide-stimulated inflammatory mediators in intestinal epithelial Caco-2 cells co-cultured with RAW 264.7 macrophage cells. Nutr Res Pract. 9:3–10.

Kobori M, Ni Y, Takahashi Y, Watanabe N, Sugiura M, Ogawa K, Nagashimada M, Kaneko S, Naito S, Ota T. 2014. β-Cryptoxanthin alleviates diet-induced non-alcoholic steatohepatitis by suppressing inflammatory gene expression in mice. PLoS One 9:e98294.

Kong L, Luo C, Li X, Zhou Y, He H. 2013. The anti-inflammatory effect of kaempferol on early atherosclerosis in high cholesterol fed rabbits. Lipids Health Dis. 12:115–121.

Kongkachuichai R, Charoensiri R, Sungpuag P. 2010. Carotenoid flavonoid profiles and dietary fiber contents of fruits commonly consumed in Thailand. Int J Food Sci Nutr. 61:536–548.

Kovendan K, Murugan K, Panneerselvam C, Aarthi N, Kumar P, Subramaniam J, Amerasan D, Kalimuthu K, Vincent S. 2012. Anti-malarial activity of *Carica papaya* (Family: *Carica-ceae*) leaf extract against *Plasmodium falciparum*. Asian Pacific J Trop Dis. 2(S1):S306–S311.

Lee K, Padzil A, Ahmad S, Abdullah N, Zuhainis S, Maziah M, Sulaiman M, Israf D, Shaari K, Lajis N. 2011. Evaluation of anti-inflammatory, anti-oxidant and anti-nociceptive activities of six Malaysian medicinal plants. J Med Plants Res. 5:5555–5563.

Lee YM, Seon MR, Cho HJ, Kim JS, Park JH. 2009. Benzyl isothiocyanate exhibits anti-inflammatory effects in murine macrophages and in mouse skin. J Mol Med. 87:1251–1261.

Lende AB, Kshirsagar AD, Deshpande AD, Muley MM, Patil R, Bafna P, Naik SR. 2011. Anti-inflammatory and analgesic activity of protocatechuic acid in rats and mice. Inflammopharmacology 19:255–263.

Li Z, Wang Y, Shen W, Zhou P. 2012. Content determination of benzyl glucosinolate and anti–cancer activity of its hydrolysis product in *Carica papaya* L. Asian-Pacific J Trop Med. 5:231–233.

Lima de Albuquerque C, Comalada M, Camuesco D, Rodríguez-Cabezas M, Luiz-Ferreira A, Nieto A, Monteiro de Souza Brito A, Zarzuelo A, Gálvez J. 2010. Effect of kale and papaya supplementation in colitis induced by trinitrobenzenesulfonic acid in the rat. e-SPEN Eur E J Clin Nutr Metab. 5:e111–e116.

Lin HH, Chen JH, Chou FP, Wang CJ. 2011. Protocatechuic acid inhibits cancer cell metastasis involving down-regulation of Ras/Akt/NF-κB pathway and MMP-2 production by targeting RhoB activation. Br J Pharmacol. 162:237–254.

Liu C, Bronson RT, Russell RM, Wang XD. 2011. β-Cryptoxanthin supplementation prevents cigarette smoke-induced lung inflammation, oxidative damage, and squamous metaplasia in ferrets. Cancer Prev Res (Phila) 4:1255–1266.

Liu ZK, Xiao HB, Fang J. 2014. Anti-inflammatory properties of kaempferol via its inhibition of aldosterone signaling and aldosterone-induced gene expression. Can J Physiol Pharmacol. 92:117–123.

Mabley J, Gordon S, Pacher P. 2011. Nicotine exerts an anti-inflammatory effect in a murine model of acute lung injury. Inflammation 34:231–237.

Madhavan PN, Supriya M, Jessica LR. 2006. The flavonoid quercetin inhibits pro-inflammatory cytokine (TNFα) gene expression in normal peripheral blood mononuclear cells via modula-tion of the NF-κB system. Clin Vaccine Immunol. 13:319–328.

Maisarah AM, Nurul Amira B, Asmah R, Fauziah O. 2012. Anti-oxidant analysis of different parts of *Carica papaya*. Int Food Res J. 20:1043–1048.

Marcotorchino J, Romier B, Gouranton E, Riollet C, Gleize B, Malezet-Desmoulins C, Landrier J. 2012. Lycopene attenuates LPS-induced TNFα secretion in macrophages and inflammatory markers in adipocytes exposed to macrophage-conditioned media. Mol Nutr Food Res. 56:725–732.

Mehta AK, Singh BP, Arora N, Gaur SN. 2010. Choline attenuates immune inflammation and suppresses oxidative stress in patients with asthma. Immunobiology 215:527–534.

Meyer M, Muller AK, Yang J, Sulcova J, Werner S. 2011. The role of chronic inflammation in cutaneous fibrosis: Fibroblast growth factor receptor deficiency in keratinocytes as example. J Invest Dermatol Symp Proc. 15:48–52.

Miyoshi N, Takabayashi S, Osawa T, Nakamura Y. 2004. Benzyl isothiocyanate inhibits excessive superoxide generation in inflammatory leukocytes: implication for prevention against inflammation-related carcinogenesis. Carcinogenesis 25:567–575.

Mohamed Sadek K. 2012. Anti-oxidant and immunostimulant effect of *Carica papaya* linn. Aqueous extract in acrylamide-intoxicated rats. Acta Inform Med. 20:180–185.

Mohr T, Desser L. 2013. Plant proteolytic enzyme papain abrogates angiogenic activation of human umbilical vein endothelial cells (HUVEC) *in vitro*. BMC Compl Alt Med. 13:231.

Mojica-Henshaw MP, Francisco AD, de Guzman F, Tigno XT. 2003. Possible immunomodula-tory actions of *Carica papaya* seed extract. Clin Hemorheol Microcirc. 29:219–229.

Nakamura Y, Yoshimoto M, Murata Y, Shimoishi Y, Asai Y, Park EY, Sato K, Nakamura Y. 2007. Papaya seed represents a rich source of biologically active isothiocyanate. J Agric Food Chem. 55:4407–4413.

Nayak SB, Pinto Pereira L, Maharaj D. 2007. Wound healing activity of *Carica papaya* L. in experimentally induced diabetic rats. Indian J Exp Biol. 45:739–743.

Nguyen TT, Shaw PN, Parat MO, Hewavitharana AK. 2013. Anti-cancer activity of *Carica papaya*: A review. Mol Nutr Food Res. 57:153–164.

Nizri E, Irony-tur-Sinai M, Lory O, Orr-Urtreger A, Lavi E, Brenner T. 2009. Activation of cholinergic anti-inflammatory system by nicotine attenuates neuroinflammation via suppres-sion of T_H1 and T_H17 responses. J Immunol. 183:6681–6688.

Nunes NN, Santana LA, Sampaio MU, Lemos FJ, Oliva ML. 2013. The component of *Carica papaya* seed toxic to *A. aegypti* and the identification of tegupain, the enzyme that generates it. Chemosphere 92:413–420.

Oduola T, Adeniyi FA, Ogunyemi EO, Bello IS. 2007. Evaluation of the effects of intake of extract of unripe pawpaw (*Carica papaya*) on liver function in sickle cell patients. World J Med Sci. 2:28–32.

Ogan AU. 1971. The basic constituents of the leaves of *Carica papaya*. Phytochemistry 10:2544–2547.

Osama S, Ayesha S, Mohammad FI. 2014. Effects of papaya leaves on thrombocyte counts in dengue: A case report. J Pakist Med Assoc. 64:364–366.

Otsuki N, Dang NH, Kumagai E, Kondo A, Iwata S, Morimoto C. 2010. Aqueous extract of *Carica papaya* leaves exhibits anti-tumor activity and immunomodulatory effects. J Ethnopharmacol. 127:760–767.

Owoyele BV, Adebukola OM, Funmilayo AA, Soladoye AO. 2008. Anti-inflammatory activities of ethanolic extract of *Carica papaya* leaves. Inflammopharmacology 16:168–173.

Pablito MM, Charles PM. 2003. *Determining the sex of papaya for improved production [Internet] [cited 2015 April 21]*. Taipei, Taiwan: The Food and Fertilizer Technology Center.

Pandey S, Shaw PN, Hewavitharana AK. 2014. Review of procedures used for the extraction of anti-cancer compounds from tropical plants. Anticancer Agents Med Chem. 15:314–325.

Park SE, Sapkota K, Kim S, Kim, H, Kim SJ. 2011. Kaempferol acts through mitogen-activated protein kinases and protein kinase B/AKT to elicit protection in a model of neuroinflammation in BV2 microglial cells. Br J Pharmacol. 164:1008–1025.

Parrish WR, Gallowitsch-Puerta M, Ochani M, Ochani K, Moskovic D, Lin X, Czura C, Miller EJ, Al-Abed Y, Tracey K, et al. 2006. Choline suppresses inflammatory responses. Shock 25:45–47.

Pathak N, Khan S, Bhargava A, Raghuram GV, Jain D, Panwar H, Samarth RM, Jain SK, Maudar KK, Mishra DK, et al. 2014. Cancer chemopreventive effects of the flavonoid-rich fraction isolated from papaya seeds. Nutr Cancer 66:857–871.

Pedicino D, Liuzzo G, Trotta F, Giglio AF, Giubilato S, Martini F, Zaccardi F, Scavone G, Previtero M, Massaro G, et al. 2013. Adaptive immunity, inflammation, and cardiovascular complications in Type 1 and Type 2 diabetes mellitus. J Diabetes Res. 2013:184258.

Pedro CQ, Tania GF, Ingrid RB, Santiago GT. 2011. Anti-fungal activity in ethanolic extracts of *Carica papaya* L. cv. maradol leaves and seeds. Indian J Microbiol. 51:54–60.

Peiffer D, Saddiqui JH, Kuo CT. 2012. Anti-inflammatory effects of black raspberries and antho-cyanin metabolite protocatechuic acid in N-nitrosomethylbenzylamine-induced esophageal cancer in rats. Eleventh Annual AACR International Conference on Frontiers in Cancer Prevention Research, 2012 Anaheim, CA. Philadelphia (PA): AACR.

Pragasam SJ, Venkatesan V, Rasool M. 2013. Immunomodulatory and anti-inflammatory effect of *p*-coumaric acid, a common dietary polyphenol on experimental inflammation in rats. Inflammation 36:169–176.

Rakhimov MR. 2001. Anti-inflammatory activity of domestic papain. Eksp Klin Farmakol. 64:48–49.

Ramos-Nino ME. 2013. The role of chronic inflammation in obesity-associated cancers. ISRN Oncol. 30:697521.

Rasmann S, Agrawal AA. 2011. Latitudinal patterns in plant defense: Evolution of cardenolides, their toxicity and induction following herbivory. Ecol Lett. 14:476–483.

Razani-Boroujerdi S, Singh SP, Knall C, Hahn FF, Peña-Philippides JC, Kalra R, Langley RJ, Sopori ML. 2004. Chronic nicotine inhibits inflammation and promotes influenza infection. Cell Immunol. 230:1–9.

Recio MC, Andujar I, Rios JL. 2012. Anti-inflammatory agents from plants: Progress and potential. Curr Med Chem. 19:2088–2103.

Ridker PM, Lüscher TF. 2014. Anti-inflammatory therapies for cardiovascular disease. Eur Heart J. 35:1782–1791.

Rivera-Pastrana DM, Yahia EM, Gonzalez-Aguilar GA. 2010. Phenolic and carotenoid profiles of papaya fruit (*Carica papaya* L.) and their contents under low temperature storage. J Sci Food Agric. 90:2358–2365.

Rodrigues M, Alves G, Francisco J, Fortuna A, Falcão A. 2014. Herb-drug pharmacokinetic interaction between carica papaya extract and amiodarone in rats. J Pharm Pharm Sci. 17:302–15.

Rose B, Herder C, Loffler H, Meierhoff G, Schloot NC, Walz M, Martin S. 2006. Dose-dependent induction of IL-6 by plant-derived proteases *in vitro*. Clin Exp Immunol. 143:85–92.

Rubens M, Carmelita AB, Henrique, CT, Jonas C. 2000. Purification of papain from fresh latex of *Carica papaya*. Braz Arch Biol Technol. 43:501–507.

Salim E, Kumolosasi E, Jantan I. 2014. Inhibitory effect of selected medicinal plants on the release of pro-inflammatory cytokines in LPS-stimulated human peripheral blood mononuclear cells. J Nat Med. 68:647–653.

Scrivo R, Vasile M, Bartosiewicz I, Valesini G. 2011. Inflammation as "common soil" of the multi-factorial diseases. Autoimmun Rev. 10:369–374.

Sheu F, Shyu YT. 1996. Determination of benzyl isothiocyanate in papaya fruit by solid phase extraction and gas chromatography. J Food Drug Anal. 4:327–334.

Simone RE, Russo M, Catalano A, Monego G, Froehlich K, Boehm V, Palozza P. 2011. Lycopene inhibits NF-κB-mediated IL-8 expression and changes redox and PPARγ signalling in cigarette smoke-stimulated macrophages. PLoS One 6:e19652.

Soobitha S, Choon TC, Cheong KC, Thayan R, Teck MB, Muniandy PK, Afzan A, Abdullah N, Ismail Z. 2013. *Carica papaya* leaves juice significantly accelerates rate of increase in platelet count among patients with dengue fever and dengue haemorrhagic fever. Evid Based Complement Alternat Med. 2013:1–7.

Sredni-Kenigsbuch D. 2002. T_H1/T_H2 cytokines in the central nervous system. Int J Neurosci. 112:665–703.

Takahashi HK, Iwagaki H, Hamano R, Kanke T, Liu K, Sadamori H, Yagi T, Yoshino T, Tanaka N, Nishibori M. 2007. The immunosuppressive effects of nicotine during human mixed-lymphocyte reaction. Eur J Pharmacol. 559:69–74.

Tang CS. 1971. Benzyl isothiocyanate of papaya fruit. Phytochemistry 10:117–121.

The Plant List. 2010. [Internet]. [cited 2016 January 23]. Avaialable from: http://www.theplantlist.org.

Tripathi S, Suzuki JY, Carr JB, McQuate GT, Ferreira SA, Manshardt RM, Pitz KY, Wall MM, Gonsalves D. 2011. Nutritional composition of rainbow papaya, the first commercialized transgenic fruit crop. J Food Comp Anal. 24:140–147.

Tsai SJ, Yin MC. 2012. Anti-glycative and anti-inflammatory effects of protocatechuic acid in brain of mice treated by D-galactose. Food Chem Toxicol. 50:3198–3205.

Umana UE, Timbuak JA, Danladi J, Samuel A, Joseph H, Anuka JA. 2014. Anti-inflammatory, anti-pyretic and anti-nociceptive activities of orally-administered aqueous extract of *Carica papaya* seeds in animal models. Ann Exp Biol. 2:21–27.

Vidal-Vanaclocha F. 2009. Inflammation in the molecular pathogenesis of cancer and atherosclerosis. Rheumatol Clin. 5(S1):40–43.

Yamaguchi M, Hasegawa I, Yahagi N, Ishigaki Y, Takano F, Ohta T. 2010. Carotenoids modulate cytokine production in Peyer's patch cells *ex vivo*. J Agric Food Chem. 58:8566–8572.

Yamamoto HY. 1964. Comparison of the carotenoids in yellow- and red-fleshed *Carica papaya*. Nature 201:1049–1050.

Yasmeen M, Prabhu B. 2012. Anti-hyperglycemic and hypolipidemic activities of aqueous extract of *Carica papaya* Linn. leaves in alloxan-induced diabetic rats. J Ayurveda Integr Med 3:70–74.

Yongming Z, Wang X. 2014. Cardioprotective effect of lycopene against inflammation via the modulation NF-κB pathway in myocardial infarction rat. Exp Clin Cardiol. 20:235–248.

Yoshikawa H, Kurokawa M, Ozaki N, Nara K, Atou K, Takada E, Kamochi H, Suzuki N. 2006. Nicotine inhibits the production of pro-inflammatory mediators in human monocytes by suppression of IκB phosphorylation and NF-κB transcriptional activity through nicotinic acetylcholine receptor α7. Clin Exp Immunol. 146:116–123.

Zhou Y, Zuo X, Li Y, Wang Y, Zhao H, Xiao X. 2012. Nicotine inhibits tumor necrosis factor-alpha induced IL-6 and IL-8 secretion in fibroblast-like synoviocytes from patients with rheumatoid arthritis. Rheumatol Int. 32:97–104.

Zhu H, Liang QH, Xiong XG, Chen J, Wu D, Wang Y. 2014. Anti-inflammatory effects of the bioactive compound ferulic acid contained in *Oldenlandia diffusa* on collagen-induced arthritis in rats. Evid Based Complement Alternat Med. 2014:573801.