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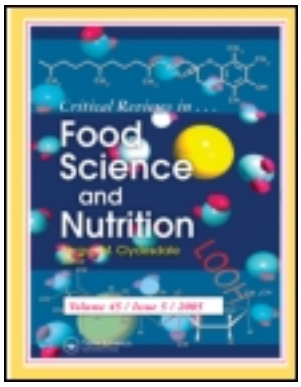

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Plant Food Supplements with Anti-Inflammatory Properties: A Systematic Review (I)

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Plant Food Supplements with Anti-Inflammatory Properties: A Systematic Review (I)

MARIO DELL'AGLI,[1] CHIARA DI LORENZO,[1] MIHAELA BADEA,[2] ENRICO SANGIOVANNI,[1] LORENA DIMA,[2] ENRICA BOSISIO,[1] and PATRIZIA RESTANI[1]

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Plant food supplements (PFS) receive great acceptance by European consumers. However, quality and efficacy of these products remain a question of concern. The aim of this systematic review is to summarize and critically evaluate the evidence for or against the efficacy of PFS for coping inflammatory conditions by considering epidemiological and human intervention studies. The review, which consists of two parts, considers Olea europea *L.,* Camellia sinensis *L.,* Vitis vinifera *L., and* Matricaria recutita *L., which are herbal material frequently used also as food. The search retrieved 1251 publications. By applying the inclusion/exclusion criteria, the final number of papers was 91.* Vitis vinifera *L. showed promising results, but other trials should be performed in order to assessing the efficacy. Surprisingly, it was impossible to draw conclusions for the anti-inflammatory effect of* Camellia sinensis *L. as green tea. No studies were found on the leaves of* Olea europea *L. whereas more human trials are needed to assess the anti-inflammatory effect of olive oil. Only one study for* Matricaria recutita *L. was selected. In conclusion, it is advisable to conduct further studies with more homogeneous population and larger number of subjects by avoiding the heterogeneity of the herbal preparations considered.*

Keywords *Olea europea* L., *Matricaria recutita* L., *Vitis vinifera* L., *Camellia sinensis* L., green tea, olive oil

INTRODUCTION

Inflammation is the first body's response to infection or injury, and is critical for both innate and adaptive immunity. It can be considered as part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Uncontrolled inflammation often results in chronic diseases such as arthritis, autoimmune disorders, degenerative joint diseases, rheumatisms, atherosclerosis, diabetes, and even cancer.

Inflammation can be classified as either *acute* or *chronic*. *Acute inflammation* is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system and the immune system, and various cells within the injured tissue. Prolonged inflammation, known as *chronic inflammation* and characterized by the development of specific humoral and cellular immune responses to the pathogens, leads to a progressive degeneration of tissue and fibrosis (Feghali and Wright, 1997).

Several mediators participate to the inflammatory process; some are released immediately (i.e., histamine, serotonin, etc.), some are synthesized and released within a short time (prostaglandins, leukotrienes, platelet-activating factor, etc.), some require the *de novo* synthesis (cytokines, adhesion molecules, etc.). Several cytokines such as tumor necrosis factor (TNF), interferon (IFN), interleukin 1β (IL-1β) or toll like receptor (TLR) ligands cooperate to induce the gene expression of specific promoters. The induction of most among these genes is dependent on the presence of binding sites for the nuclear factor kB (NF-kB).

NF-kB transcription factors regulate genes involved in many aspects of the inflammatory response (Bonizzi and Karin, 2004). In response to a variety of pro-inflammatory stimuli such as cytokines (i.e., TNF, IL-1β), or oxidative stress, NF-kB

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transcription factor induces pro-inflammatory genes encoding for the synthesis of cytokines, chemokines, adhesion molecules such as vascular cell adhesion molecules-1 (VCAM-1), intercellular adhesion molecules-1 (ICAM-1), and E selectin, cyclooxygenase-1 (COX-1) and 2, inducible nitric oxide synthase (iNOS) and metalloproteases (MMP), including MMP-9. However, excessive and prolonged expression of pro-inflammatory mediators could be harmful to the host; therefore, the search for compounds that are able to interfere with these mechanisms by preventing a prolonged inflammation could be useful for human health.

The plant kingdom has developed a multitude of secondary metabolites, many of which are recognized as useful tools for the maintenance of human health. Secondary metabolites, for which some anti-inflammatory properties are reported, belong to the chemical class of alkaloids (Souto et al., 2011), coumarins (Wu et al., 2009), flavonoids (Serafini et al., 2010), chalcones (Yadav et al., 2011), polyphenols (Gonzalez-Gallego et al., 2010), and triterpene derivatives (Braca et al., 2011).

Botanicals and in particular plant food supplements (PFS) receive great acceptance by European consumers. Potentially, they can deliver significant health benefits at relatively low costs. However, quality and efficacy of these products remain a question of concern, and bottlenecks in risk and benefit assessments need to be solved.

PlantLIBRA (PLANT food supplements: Levels of Intake, Benefit and Risk Assessment) is an European Community funded project aiming to foster the safe use of food supplements containing botanicals or their preparations, by evaluating the quality and health benefits of PFS, and by increasing science-based decision-making by regulators and food chain operators.

PlantLIBRA is structured to develop, validate, and disseminate data and methodologies for risk, and benefit assessment and implement sustainable international cooperation. Part of the project is dedicated to the methodology of benefit assessment for PFS, application and validation. The first step was to review the evidence for PFS benefit from epidemiological, clinical, and intervention studies. A number of pathological conditions, where PFS are commonly used, were identified and inflammation was one of those.

The aim of this systematic review is to summarize and critically evaluate the evidence for or against the efficacy of PFS or substances (compounds or foods) relevant to PFS for coping inflammatory conditions. Ten plants considered are: *Olea europea* L., *Camellia sinensis* L., *Vitis vinifera* L., *Boswellia serrata* Roxb., *Matricaria recutita* L., *Symphytum officinalis* L., *Calendula officinalis* L., *Curcuma longa* L., *Urtica dioica* L., and *Harpagophytum procumbens* L. The choice of these botanicals in the reviewing process is based on PlantLIBRA partners' suggestions and on the list of plants present in Annex 1 of the project.

Epidemiological, clinical/human intervention studies using PFS were then systematically examined and reviewed. The review will be divided in two parts: (1) a first one considering the literature regarding *Olea europea* L., *Camellia sinensis* L., *Vitis vinifera* L., and *Matricaria recutita* L., which are herbal material frequently used also as food; (2) a second part considering the literature of the other botanical species more commonly used as food supplements/medicinals. This publication relates to the first part.

METHODS

Source and Search Strategy

Electronic literature searches were conducted using the following databases: Cochrane library, Scifinder Scholar, Embase, and Pubmed from 1970 to 2010. They were searched for title and abstract using the following search terms: Latin name of the plant **or** common name matched with inflamm **or** phlogosis **or** anti-inflammatory. Search limits were human trial, and the English language. Keywords relevant to inflammation (i.e., cyclooxigenase, cytokines, adhesion molecules, etc.) were also used as search terms. Bibliographies of the articles thus located were scanned for further relevant publications.

For collecting epidemiological studies, the same terms were used for searching title, abstract, and index terms for the 10 plant food supplements (PFS) (1) and for health area inflammation (2). Terms used for searching epidemiological studies (3) were: "epidemiology"/exp **or** epidemiolog **or** "case control" **or** cohort. We selected epidemiological studies for applicable PFS and inflammation in two different ways and then merged the results: (1) **and** (2) filtered by study type or (1) **and** (2) **and** (3).

Inclusion and Exclusion Criteria

Controlled human studies performed on healthy/unhealthy populations were included. Randomization, even if preferable, was not considered essential. Inclusion criteria were the use of PFS as food, or pill/powder/extract, etc. Publications reporting incomplete qualitative and quantitative analysis of PFS were flagged but not excluded. Studies reporting co-treatments with other PFS or other bioactive compounds were included. Studies where general foodstuffs were fortified with PFS or studies reporting on single compounds were not considered.

Other criteria of exclusion were: the use of botanicals for cosmetic, homeopathy, aromatherapy, topical use, aerosol/inhalation, hygiene products (toothpaste, mouth rinse, etc.). Publications regarding reviews, commentary, and patents were not considered. Letters to the editor were considered only if they reported new data not previously published. The scientific quality of the publications was one of the criteria for inclusion/exclusion. The methodological quality of the studies was assessed by two authors (MDA and CDL) based on quality of results presentation, presence or not of adequate statistical analysis, well-characterized experimental design.

Two independent reviewers evaluated the papers; disagreement was resolved by discussion between reviewers. A study was included if both reviewers agreed that it met all the inclusion criteria.

Similar inclusion/exclusion criteria were used for epidemiological studies. From the bulk of papers selected by the search strategy described above, those not fulfilling the inclusion criteria were excluded by reading the abstract. For remaining studies, a customized version of the extraction database was used.

Data Extraction

A database (written in MS Access) was designed and implemented to aid the data extraction process. Publications were checked for duplicates, read in full by two authors, and subjected to the in/out process following the inclusion/exclusion criteria described above. 10% of the publications found were checked by a second reviewer and compared, whereas 5% of the publications not excluded by the in/out procedure were checked by a second reviewer and compared. Papers were stored in a reference manager (Endnote X1.0.3). A pdf file of each publication was retrieved.

RESULTS AND DISCUSSION

Human/Intervention Studies

The search by title and abstract retrieved 1251 publications. By removing the duplicates and applying the inclusion/ exclusion criteria above described, the final number of papers was 91. These publications were uploaded in the database and the in/out process led to 42 publications accepted and used for this systematic review.

Among the papers rejected in the in/out sheet process, 35% were excluded because the clinical trial was not controlled, 31% because the health area was not related to inflammation, 10% because the study was not dealing with the 4 plants chosen for the systematic review, 5% because the study was performed in vitro or ex vivo, 7% because the plant material was not used as supplement or food; 12% because the scientific quality was insufficient.

Tables 1–4 report the human trials related to *Vitis vinifera* L., *Camellia sinensis* L., and *Olea europea* L. For each PFS, the publications are listed in two columns: benefit/no benefit, depending whether the study reported beneficial/non-beneficial results. The change of biomarkers or hard end-points, that in this review is defined as "symptom or the change of a physiological state" (i.e., reduction of ulcer index in gastritis), was used as a criterion by which a publication is listed under the "benefit" or "no benefit" column.

Vitis vinifera L.

Thirteen publications were found: four studies described the effect obtained with the use of grapes (Zern et al., 2005; Gupta et al., 2008; Puglisi et al., 2008; Rankin et al., 2008), three the effect with grape juice (Albers et al., 2004; Castilla et al., 2006), three with seeds (Kalfin et al., 2002; Kar et al., 2006; Sano et al., 2007), two with grape skin (Young et al., 2000; Myers et al., 2010), and one with grape leaves (Abidov et al., 2006). The results are reported in Table 1. Studies reporting the biological activity of red wine were voluntarily excluded since it is not used as food supplement and the presence of alcohol was considered confounding.

Almost 20 inflammatory biomarkers including adhesion molecules, cytokines, C reactive protein (CRP), prostaglandins, nitric oxide (NO), tromboxane derivatives, and markers of oxidative stress such as malonyl dialdehyde (MDA) have been investigated. The subjects recruited in studies reporting benefits were 608 versus 84 with no benefits. In studies reporting hard end-points the number of subjects recruited in studies reporting benefits was 492 versus 0 subjects with no benefits.

The search has evidenced that in most studies the number of subjects is limited, and the type of treatment is heterogeneous, since they were performed with PFS of different composition, i.e.: entire fruit, fruit juice, seeds or fruit skin. In addition, epidemiological studies are not available (see below). Therefore, even if the available data are promising, it will be desirable to perform other trials in order to assessing the efficacy.

Camellia sinensis L.

The leaves of *Camellia sinensis* L. can be used to prepare green or black tea. The effect of *Camellia sinensis* L. on biomarkers of inflammation has been extensively investigated: 19 studies reported the effect of green tea (Freese et al., 1999; Klaunig et al., 1999; Goudev et al., 2000; Nagaya et al., 2004; Chiu et al., 2005; Erba et al., 2005; Fukino et al., 2005; Hirano-Ohmori et al., 2005; Nagao et al., 2005; Ryu et al., 2006; Rowe et al., 2007; Panza et al., 2008; Janjua et al., 2009; Nantz et al., 2009; Bakker et al., 2010; Eichenberger et al., 2010; Fenercioglu et al., 2010; Oyama et al., 2010; Basu et al., 2011) (Table 2), 6 studies for black tea (Hodgson et al., 2000; Hodgson et al., 2001; O'Really et al., 2001; Widlansky et al., 2005; Mukamal et al., 2007; Steptoe et al., 2007) (Table 3), and 4 studies considered both preparations (van het Hof et al., 1997; Hodgson et al., 2000; de Maat et al., 2000; Hodgson et al., 2002). As regards green tea and biomarkers, studies reporting benefit recruited 552 subjects versus 389 where no effect was observed. Similarly the studies reporting the positive effect of green tea on hard end-points recruited 539 subjects versus 419 with no benefits. The studies dealing with black tea, the number of subjects recruited in trials that do not reporting benefits was higher either in those investigating the change of biomarkers (334 vs. 129) and hard end-points (268 vs. 0).

In spite of 29 studies found, the available data are still much contradictory. As green tea is concerned, only MDA levels and oxidative stress was positively affected. Other biomarkers of inflammation remained unaffected or diminished in a limited number of subjects. It is also to be noted the heterogeneity of inflammatory conditions where green tea was tested. The consequence is the impossibility to draw conclusions as

Table 1 Clinical studies considering the effect of *Vitis vinifera* L. on ***biomarkers*** and/or hard endpoints

	No benefit		Benefit		
	N° studies	N° participants	N° studies	N° participants	Comments Efficacy
Biomarkers					
CRP	3 (Albers et al., 2004; Castilla et al., 2008; Rankin et al., 2008)	69	3 (Zern et al., 2005; Castilla et al., 2006; Kar et al., 2006)	117	OSN*
Complement C3 protein	1 (Castilla et al., 2008)	32			OSN
MDA	1 (Young et al., 2000)	15	2 (Kalfin et al., 2002; Sano et al., 2007)	263	YES
IL-6	1 (Rankin et al., 2008)	17	1 (Zern et al., 2005)	44	OSN
IL-8	1 (Albers et al., 2004)	20			OSN
CD-40 L			1 (Albers et al., 2004)	20	OSN
Monocyte chemotactic protein-1 (MCP-1)			2 (Castilla et al., 2006; Castilla et al., 2008)	73	OSN
TNF-α			2 (Zern et al., 2005; Puglisi et al., 2008)	78	OSN
E-selectin			1 (Kalfin et al., 2002)	202	YES
P-selectin	1 (Albers et al., 2004)	20			OSN
Phagocytosis of granulocytes			1 (Myers et al., 2010)	21	OSN
COX2 expression			1 (Myers et al., 2010)	21	OSN
8-epi-prostaglandin-F2-alfa			2 (Abidov et al., 2006; Rankin et al., 2008)	61	OSN
PG-F2 (Prostaglandin F2)			1 (Gupta et al., 2008)	60	OSN
VCAM-1	2 (Castilla et al., 2008; Rankin et al., 2008)	49	2 (Kalfin et al., 2002; Castilla et al., 2006)	243	YES
ICAM-1			4 (Kalfin et al., 2002; Castilla et al., 2006; Castilla et al., 2008; Puglisi et al., 2008)	309	YES
Tromboxane (B2) TXB2	1 (Albers et al., 2004)	20			OSN
11-deydro-TXB2			1 (Abidov et al., 2006)	44	OSN
Nitric oxide (NO)	1 (Albers et al., 2004)	20			OSN
TOTAL	**4[a]**	**84[b]**	**12[c]**	**608[d]**	
Hard end-points					
Reduction of platelet-dependent inflammatory indices			1 (Albers et al., 2004)	20	OSN
Reduction of oxidative stress in healthy subjects			5 (Young et al., 2000; Abidov et al., 2006; Castilla et al., 2006; Sano et al., 2007; Rankin et al., 2008)	178	YES
Reduction of oxidative stress in systemic sclerosis			1 (Kalfin et al., 2002)	202	YES
Reduction of inflammation in systemic sclerosis			1 (Kalfin et al., 2002)	202	YES
Reduction of oxidative stress in hemodialysis patients			1 (Castilla et al., 2006)	41	OSN
Reduction of inflammation in hemodialysis patients			2 (Castilla et al., 2006; Castilla et al., 2008)	73	OSN
Antipiretic effect			1 (Gupta et al., 2008)	60	OSN
TOTAL	**0[a]**	**0[b]**	**9[c]**	**492[d]**	

*OSN: other studies needed; a) number of studies where the effect was not observed; b) the total number of subjects recruited in the studies which reported no benefit; c) number of studies where the effect was observed; d) the total number of subjects recruited in the studies which reported benefit.

for the anti-inflammatory effect of green tea. As black tea is concerned, all data are against a possible anti-inflammatory activity.

Matricaria recutita L.

In the retrieved papers, chamomile was mainly used in formulations for aerosol/inhalation, toothpaste, and mouth rinse, then according to the in/out process only one paper could be selected (Becker et al., 2006). This study recruited 255 children with acute diarrhoea. A reduction of the duration of diarrhea and stool frequency, considered as hard end-points, was recorded. No human studies reported the effect of chamomile on inflammatory biomarkers. In spite of the long-term traditional use of chamomile for gastrointestinal inflammatory disorders, studies with chamomile as PFS addressing this state are inexistent, with the exception of the one selected for this review. Considering the absence of epidemiological studies (see below), then this topic urges further well-designed studies focusing on gastrointestinal inflammation.

Table 2 Clinical studies considering the effect of *Camellia sinensis* L. (green tea) on biomarkers and/or hard endpoints

	No benefit		Benefit		
	N° studies	N° participants	N° studies	N° participants	Comments Efficacy?
Biomarkers					
CRP	5 (de Maat et al., 2000; Fukino et al., 2005; Ryu et al., 2006; Bakker et al., 2010; Basu et al., 2011)	256	2 (Oyama et al. 2010; Eichenberger et al., 2010)	39	NO
Alpha-amiloid			1 (Nantz et al., 2009)	111	OSN*
MDA	2 (van het Hof et al., 1997; Erba, 2005)	49	5 (Freese et al., 1999; Klaunig et al., 1999; Nagao et al., 2005; Nantz et al., 2009; Fenercioglu et al., 2010)	307	YES
Adiponectin	2 (Bakker et al., 2010; Basu et al., 2011)	71			OSN
IL-6	4 (de Maat et al., 2000; Ryu et al., 2006; Eichenberger et al., 2010; Basu et al., 2011)	163			OSN
IL-1β	2 (de Maat et al., 2000; Basu et al., 2011)	99			OSN
CD-40 L			1 (Oyama et al. 2010)	30	OSN
MCP-1			1 (Oyama et al. 2010)	30	OSN
MIF (macrophage migration inhibitory factor			1 (Oyama 2010)	30	OSN
TNF-α	1 (de Maat et al., 2000)	64			OSN
IFN-γ			1 (Rowe et al., 2007)	124	OSN
Leptin	1 (Basu et al., 2011)	35			OSN
Fibrinogen	1 (de Maat et al., 2000)	64			OSN
F-2 isoprostanes	1 (Hodgson et al. 2002)	13			OSN
8-isoprostaglandin-F2-α	1 (Nagaya et al., 2004)	20	1 (Freese et al., 1999)	20	OSN
8-epi-prostaglandin-F2-α			1 (Hirano-Ohmori et al., 2005)	22	OSN
6-keto-PGF2α	1 (Hirano-Ohmori et al., 2005)	22			OSN
VCAM-1	1 (Basu et al., 2011)	35	1 (Goudev et al., 2000)	60	OSN
ICAM-1	1 (Basu et al., 2011)	35	1 (Goudev et al., 2000)	60	OSN
Metalloproteinases (MMPs)	1 (Hirano-Ohmori et al., 2005)	22			OSN
Tromboxane (B2) TXB2	1 (Hirano-Ohmori et al., 2005)	22			OSN
F2a, 2,3-dinor thromboxane B2	1 (Freese et al., 1999)	20			OSN
Nitric oxide (NO)	1 (Freese et al., 1999)	20			OSN
TOTAL	**12[a]**	**389[b]**	**10[c]**	**552[d]**	
Hard end-points					
Inflammation changes in diabetes or borderline diabetes	2 (Fukino et al., 2005; Ryu et al., 2006)	121	1 (Fenercioglu et al., 2010)	114	OSN
Reduction of oxidative stress in healthy subjects	3 (van het Hof et al., 1997; Hirano-Ohmori et al., 2005; Bakker et al., 2010)	83	9 (Freese et al., 1999; Klaunig et al., 1999; Hodgson et al., 2000); Nagaya et al., 2004; Erba, 2005; Nagao et al., 2005; Panza et al., 2008; Nantz et al., 2009; Oyama et al. 2010)	301	YES
Inflammatory status in metabolic syndrome	1 (Basu et al., 2011)	35			OSN
Reduction of flu symptoms			1 (Rowe et al., 2007)	124	OSN
Irritation in photoaging	2 (Chiu et al., 2005; Janjua et al., 2009)	96			OSN
TOTAL	**8[a]**	**419[b]**	**11[c]**	**539[d]**	

*OSN: other studies needed; a) number of studies where the effect was not observed; b) the total number of subjects recruited in the studies which reported no benefit; c) number of studies where the effect was observed; d) the total number of subjects recruited in the studies which reported benefit.

Olea europea L.

No studies were found concerning the use of the leaves of *Olea europea*. All the studies ($n = 6$) performed with *Olea europea* and selected by the in/out process were directed to evaluate the effect of olive oil consumption on human health. Five studies for a total of 985 subjects investigated a variety of inflammation biomarkers (Pacheco et al., 2008; Konstantinidou et al., 2010). The results showed that the levels of VCAM-1, ICAM-1, IL-6, and E-selectin, isoprostane and IFN-γ, were modified by the

Table 3 Clinical studies considering the effect of *Camellia sinensis* L. (black tea) on biomarkers and/or hard endpoints

	No benefit		Benefit		
	N° studies	N° participants	N° studies	N° participants	Comments Efficacy
Biomarkers					
CRP	3 (de Maat et al., 2000; Widlansky et al., 2005; Mukamal et al., 2007)	158	1 (Steptoe et al., 2007)	75	NO/OSN*
MDA	2 (van het Hof et al., 1997; O'Reilly et al., 2001)	57			YES
IL-6	2 (de Maat et al., 2000; Mukamal et al., 2007)	92			OSN
IL-1β	1 (de Maat et al., 2000)	64			OSN
TNF-α	2 (de Maat et al., 2000; Mukamal et al., 2007)	92			OSN
E-selectin	1 (Hodgson et al., 2001)	22			OSN
P-selectin	1 (Steptoe et al., 2007)	75	1 (Hodgson et al., 2001)	22	OSN
Fibrinogen	3 (de Maat et al., 2000; Hodgson et al., 2001; Mukamal et al., 2007)	114			OSN
8-isoprostane	1 (Widlansky et al., 2005)	66			OSN
F-2 isoprostanes	1 (Hodgson et al., 2002)	22			OSN
8-epi-prostaglandin-F2-α			1 (O'Reilly et al., 2001)	32	OSN
VCAM-1	2 (Hodgson et al., 2001; Mukamal et al., 2007)	50			OSN
ICAM-1	2 (Hodgson et al., 2001; Mukamal et al., 2007)	50			OSN
t-PA	2 (Hodgson et al., 2001; Mukamal et al., 2007)	50			OSN
PAI-1	1 (Hodgson et al., 2001)	22			OSN
vWF	1 (Mukamal et al., 2007)	28			OSN
Leukocyte-platelet aggregates			1 (Steptoe et al., 2007)	75	OSN
TOTAL	**8**[a]	**334**[b]	**3**[c]	**129**[d]	
Hard end-points					
Inflammation changes in diabetes or borderline diabetes	1 (Mukamal et al., 2007)	28			OSN
Reduction of oxidative stress in healthy subjects	5 (van het Hof et al., 1997; Hodgson et al., 2000; Hodgson et al., 2001; O'Reilly et al., 2001; Steptoe et al., 2007)	174			OSN
Reduction of oxidative stress in chronic artery disease	1 (Widlansky et al., 2005)	66			OSN
Reduction of inflammation in chronic artery disease	1 (Widlansky et al., 2005)	66			OSN
TOTAL	**7**[a]	**268**[b]	**0**[c]	**0**[d]	

*OSN: other studies needed; a) number of studies where the effect was not observed; b) the total number of subjects recruited in the studies which reported no benefit; c) number of studies where the effect was observed; d) the total number of subjects recruited in the studies which reported benefit.

treatment (Table 4). Other biomarkers did not change. A single study (Bitler et al., 2007) reported a reduction of pain evaluated by DAS-28 (Disease Activity Score-28) scoring system, and an improvement of the quality of life determined by HAQ-DI (Health Assessment Questionnaire Disability Index) in 105 subjects with arthritis. However, the number of recruited subjects is insufficient for supporting efficacy. As a general comment, more studies are needed before an anti-inflammatory effect may be claimed for olive oil.

Epidemiology Studies

The bibliographic search retrieved 24 papers for *Vitis vinifera* L., 144 papers for *Camellia sinensis* L., 23 papers for *Matricaria recutita* L., and 48 papers for *Olea europea* L. By application of the exclusion criteria, 13 studies related to *Camellia sinensis* L. (Table 5) and 5 related to *Olea europea* L. (Table 6) were accepted through the in/out process and used for this review. No study could be accepted for *Vitis vinifera* and *Matricaria recutita.*

The main outcome variables investigated by epidemiological studies in relation to PFS exposure were biological markers of inflammation and risk of atrophic gastritis, rheumatoid arthritis, and various other conditions differing from one study to another. Three cross-sectional studies on *Camellia sinensis* L., (as green or black tea) (De Bacquer et al., 2006; Chun et al., 2008; Maki et al., 2010), investigated the relation to CRP, with only one of these (De Bacquer et al., 2006) on 1031 healthy men from Belgium found a significant correlation of black tea

Table 4 Clinical studies considering the effect of *Olea europea* L. (olive oil) on biomarkers and/or hard endpoints

	No benefit		Benefit		
	N° studies	N° participants	N° studies	N° participants	Comments Efficacy
Biomarkers					
MMPs (1,2,3,9,13)	1 (Bitler et al., 2007)	105			OSN*
ILs (1β,8)	1 (Bitler et al., 2007)	105			OSN
C reactive protein	1 (Bitler et al., 2007)	105	1 (Konstantinidou et al., 2010)	90	OSN
VCAM-1			3 (Fuentes et al., 2008; Pacheco et al., 2008; Mena et al., 2009)	174	YES
ICAM-1			3 (Pacheco et al., 2008; Corella et al., 2009; Mena et al., 2009)	875	YES
IL-6	1 (Bitler et al., 2007)	105	2 (Corella et al., 2009; Mena et al., 2009)	833	YES
E-selectin			1 (Mena et al., 2009)	112	OSN
Nitrate/nitrite	1 (Fuentes et al., 2008)	20			OSN
NO	1 (Fuentes et al., 2008)	20			OSN
Isoprostanes			1 (Konstantinidou et al., 2010)	90	OSN
IL-10 gene	1 (Konstantinidou et al., 2010)	90			OSN
MCP-1	1 (Konstantinidou et al., 2010)	90			OSN
IFN-gamma			1 (Konstantinidou et al., 2010)	90	OSN
TOTAL	**3**[a]	**215**[b]	**5**[c]	**985**[d]	
Hard end-points					
Pain			1 (Bitler et al., 2007)	105	OSN
HAQ-DI			1 (Bitler et al., 2007)	105	OSN
TOTAL	**0**[a]	**0**[b]	**1**[c]	**105**[d]	

*OSN: other studies needed; a) number of studies where the effect was not observed; b) the total number of subjects recruited in the studies which reported no benefit; c) number of studies where the effect was observed; d) the total number of subjects recruited in the studies which reported benefit.

consumption with CRP, and also with serum amyloid A and haptoglobin. Fibrinogen levels were not different between habitual tea consumers and nonconsumers in this study. The other two studies, one on 10325 men and women aged 49–76 years in Japan (Maki et al., 2010), and the other in USA, on 8335 subjects $\geq$19 years (Chun et al., 2008), found no correlation of tea consumption with serum CRP. A prospective cohort study in USA found that intake of 2 or more cups of tea per day tended to be associated with higher adiponectin concentrations among diabetic women, but the association remained not significant after adjusting for lifestyle and medical history covariates ($p = 0.07$) (Williams et al., 2008).

Considering the modification of inflammation biomarkers, the general trend allows sustaining that the consumption of

Table 5 Epidemiological studies considering the effect of *Camellia sinensis* L. on biomarkers and/or hard endpoints

	No benefit		Benefit		
	N° studies	N° participants	N° studies	N° participants	Comments Efficacy
Biomarkers					
CRP	3 (Song et al., 2005; Chun et al., 2008; Maki et al., 2010)	19004	1 (De Bacquer et al., 2006)	1031	NO
IL-6	1 (Song et al., 2005)	344			OSN
Serum amyloid A and haptoglobin			1 (De Bacquer et al., 2006)	1031	OSN
Adiponectin	1 (Williams et al., 2008)	2040			OSN
Fibrinogen	1 (De Bacquer et al., 2006)	1031			OSN
TOTAL	**5**[a]	**22075**[b]	**1**[c]	**1031**[d]	
Hard end-points					
Atrophic gastritis	1 (Kuwahara et al., 2000)	566	2 (Shibata et al., 2000; Setiawan et al., 2001)	1368	OSN
COPD	1 (Tabak et al., 2001)	13651			OSN
Asthma	2 (Shaheen et al., 2001; Garcia et al., 2005)	1471			OSN
Periodontal disease			1 (Kushiyama et al., 2009)	940	OSN
TOTAL	**4**[a]	**15688**[b]	**3**[c]	**2308**[d]	

*OSN: other studies needed; a) number of studies where the effect was not observed; b) the total number of subjects recruited in the studies which reported no benefit; c) number of studies where the effect was observed; d) the total number of subjects recruited in the studies which reported benefit.

Table 6 Epidemiological studies considering the effect of *Olea europea* L. (olive oil) on biomarkers and/or hard endpoints

	No benefit		Benefit		
	N° studies	N° participants	N° studies	N° participants	Comments Efficacy
Biomarkers					
VCAM-1			2 (Serrano-Martinez et al., 2005; Salas-Salvado et al., 2008)	796	OSN*
ICAM-1	1 (Salas-Salvado et al., 2008)	772			OSN
IL-6	1 (Salas-Salvado et al., 2008)	772			OSN
CRP	1 (Salas-Salvado et al., 2008)	772	1(Esmaillzadeh and Azadbakht, 2008)	486	OSN
TNFα			2 (Serrano-Martinez et al., 2005; Esmaillzadeh and Azadbakht, 2008)	510	OSN
sICAM-1			1 (Esmaillzadeh and Azadbakht, 2008)	486	OSN
TOTAL	**1**[a]	**772**[b]	**3**[c]	**1282**[d]	
Hard end-points					
Rheumatoid arthritis	0	0	2 (Linos et al., 1991; Linos et al., 1999)	638	OSN
TOTAL	**0**[a]	**0**[b]	**2**[c]	**638**[d]	

*OSN: other studies needed; a) number of studies where the effect was not observed; b) the total number of subjects recruited in the studies which reported no benefit; c) number of studies where the effect was observed; d) the total number of subjects recruited in the studies which reported benefit.

Camellia sinensis L. does not affect these parameters significantly (22,075 subjects recruited in studies reporting no benefits vs. 1031 with benefits).

Similar discomforting results are observed in studies where the effect of green tea consumption was investigated in patients with various inflammatory diseases: 15,688 subjects were recruited in studies reporting no benefits versus 2308 reporting benefits. In a cross-sectional study in Japan (Shibata et al., 2000), and a case-control study in China (Setiawan et al., 2001), the protective effect against atrophic gastritis could only be observed when daily consumption was very high and/or in the case of long time consumption. In the study on 166 gastritis cases and 433 healthy controls in China, green tea drinkers had a 51% lower risk of chronic gastritis than nondrinkers after adjusting for potential confounders and a dose-response relationship with years of green tea drinking. In the study conducted in Japan on 636 subjects aged 30 years or older (mean age: 50.2), high green tea consumption (>10 cups/day) was negatively associated with the risk of atrophic gastritis, even after adjustment for *H. pylori* infection and lifestyle factors associated with green tea consumption (OR = 0.63; 95% CI, 0.43–0.93) (Shibata et al., 2000). In a third cross-sectional study conducted in Japan, performed on 566 men, 50–55 years, the association between green-tea consumption and a small decrease in the risk of chronic atrophic gastritis was statistically nonsignificant (Kuwahara et al., 2000).

Epidemiological studies found for *Olea europea* L. investigated the effects of olive oil or nonpartially hydrogenated vegetable oils (HVO), including olive oil (non-HVOs) in the diet (Esmaillzadeh and Azadbakht, 2008).

Two case-control studies performed in Greece suggest a protective effect of olive oil consumption for rheumatoid arthritis (Linos et al., 1991; Linos et al., 1999). Two studies performed in Spain (Serrano-Martinez et al., 2005; Salas-Salvado et al., 2008) found a beneficial correlation between olive oil consumption and vascular cell adhesion molecule 1 VCAM-1 in patients with high cardio-vascular risk or unstable angina. A cross-sectional study performed in Iranian females a higher consumption of non-HVOs was associated with lower circulating concentrations of serum amyloid A, TNF, CRP, and sICAM-1; however, olive oil consumption was not investigated separately from other non-HVOs in this study.

In view of the data available from epidemiology and interventional/human studies, the consumption of olive oil has sufficient credit to suggest the necessity of other studies for a claim of efficacy. Conversely for green tea, both intervention/human trials and epidemiology do not support the reduction on factors involved in the development of inflammatory states.

CONCLUSIVE REMARKS AND FUTURE WORK

The aim of this systematic review was to evaluate efficacy of PFS against inflammation and to direct researchers, health authorities, decision-makers/opinion leaders, about future research for the purpose of making claims on product labels or in promotional material. This review is the first part of a reviewing process of studies (clinical, interventional, and epidemiological) performed with PFS derived from plants known for their use in inflammatory conditions.

The conditions against which the PFS discussed in the present review were employed, are osteoarthritis, chronic pancreatitis, ulcerative colitis, type-2 diabetes, and inflammation associated to cardiovascular and kidney diseases. Among the reviewed studies, 43% were performed on healthy subjects.

The outcome of the evaluation process indicates for the need of well-designed randomized controlled trials for *Matricaria recutita* L., *Vitis vinifera* L., and olive oil. For these PFS, though the studies are insufficient, all outcomes support for a positive effect. Conversely, while the potential benefits of green tea have been reported in a wide range of health areas, and in particular metabolic syndrome (Williamson et al., 2011), the consumption

of green tea does not seem to affect significantly inflammation conditions.

Major drawbacks hampering the assessment of the beneficial health effect are insufficient characterization of PFS, and heterogeneity in dosing and time of exposure between studies. More uniformity of the target organ would be advisable, since it is difficult to compare an effect on the brain with that on the gastrointestinal tract. Where it is possible to identify likely active components within PFS, these levels should be reported to allow for future stratified meta-analysis. Interventions should be carried out over a timescale sufficient to observe a change in the endpoint measured. Studies must be controlled for the full length of the intervention, and the placebo effect must be included. The use of solely positive controls where a high placebo effect might be reasonably expected could be considered misleading. The metabolism of suspected active ingredients must be considered during study design, randomization, and analysis. The use of an adequate statistical analysis must be considered as a priority to evaluate the good quality of the work.

In conclusion, in the future, it is advisable to conduct studies with more homogeneous population and larger number of subjects by avoiding the heterogeneity of the herbal preparations considered.

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