Food & Function

Cite this: *Food Funct.*, 2011, **2**, 753

www.rsc.org/foodfunction

REVIEW

Review of the efficacy of green tea, isoflavones and aloe vera supplements based on randomised controlled trials†

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Received 6th June 2011, Accepted 8th August 2011
DOI: 10.1039/c1fo10101c

We assess the evidence for health benefits of three commonly consumed plant food supplements (PFS), green tea, isoflavone and aloe vera, based on published systematic reviews of randomised controlled trials (RCTs). Whilst the potential benefits of green tea have been reported in a wide range of health areas, it is only in the area of the metabolic syndrome that the number of RCTs is approaching sufficient to judge such efficacy. Isoflavone supplements are widely used, and RCTs indicate that they affect bone resorption at lower doses in postmenopausal women undergoing estrogen-related bone loss, but this is only translated to attenuation of bone loss at higher doses of isoflavones. A systematic review on RCTs concluded that the effects of isoflavones on hot flashes in postmenopausal women were highly variable and no conclusions could be drawn. Despite the popularity of aloe vera as a PFS, the evaluation of its efficacy as a coadjuvant therapy for certain metabolic or digestive pathologies remains scarce; it constitutes a typical example of a naturally occurring ingredient whose efficacy in topical applications presupposes its efficacy in systemic applications. Nevertheless, its possible toxic effects on oral consumption call for caution in its utility as a PFS. Since 2007, efficacy evaluation of PFS in Europe has been covered by European Union Nutrition and Health Claims legislation. The European Food Safety Authority has adopted an approach relying on RCTs, while medicinal effects are accepted based on traditional use. In general, there are insufficient RCTs for claims to be made, and conclusive results on PFS should be obtained in the future by conducting studies with more homogeneous populations, by using supplements with optimised and measured bioavailability, and by conducting larger RCTs.

1. Efficacy of plant food supplements and European regulatory aspects: the need for randomised controlled trials

There are a wide range of botanicals, preparations and derivatives used in products, and promoted for their beneficial effects on the body and health. Such products include foodstuffs, food supplements, cosmetics, medicinal products and even medical devices. The ways in which the efficacy of such effects is assessed and documented varies widely and differs depending on the legal requirements for these different product groups.[1] Under EU legislation, since 2002, food supplements have been considered as foodstuffs and need to be in conformity with all the requirements of food legislation.[2] This includes requirements for safety, composition, labelling and manufacture,[3] and also includes specific rules on nutrition and health claims. Botanical medicinal products fall under medicinal product legislation, and in this case there are also detailed rules relating to the safety, quality and efficacy of such products.[4] In this paper, we will focus in particular on the efficacy evaluation of plant food supplements (PFS) and the application of the European Nutrition and Health Claims Regulation (NHCR) to this category of products. We chose isoflavones, green tea and aloe vera as examples of three commonly consumed supplements, with different claimed active components and efficacies, and where multiple RCTs have been reported in the literature.

Since 2007, the efficacy evaluation of foodstuffs, including PFS, has been covered by the provisions of the NHCR.[5] This evaluation is entrusted to the European Food Safety Authority (EFSA), the European Union's food safety advisory body. The NHCR does not specify the criteria for such assessments, and thus a methodology was developed by the EFSA.[6] It is largely based on work that has been developed in the framework of two EU funded projects: FUFOSE and PASSCLAIM, and puts results of human

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† This paper forms part of the themed issue on Plant Food Supplements: regulatory, scientific and technical issues concerning safety, quality and efficacy.

randomised controlled trials (RCTs) in the centre of establishing cause–effect relationships between the intake of a food component and an effect on health.[7,8] Observations, experimental and animal studies are only considered as supporting evidence. This standard is very rigorous. The EFSA has already published opinions on about 2000 claim submissions and in the vast majority of cases it has indicated that the claimed effect had not been demonstrated by the evidence provided. Only in selected cases, *e.g.* claims relating to cholesterol lowering, bone mineralisation and dental caries, and in the case of essential nutrients (vitamins, minerals, essential fatty acids), the role of which in the body is well established, have claimed effects been accepted. No single botanical or botanical ingredient has received a positive opinion to date (August 2011).

Under medicinal law, traditional herbal medicinal products benefit from a simplified registration procedure if it can be demonstrated by bibliographical or expert evidence that the medicinal product in question, or a corresponding product, has been in medicinal use for at least 30 years, of which at least 15 years must have been in the EU.[4] Such simplified registration would not need to present data on efficacy if there are sufficient data on the traditional use of the medicinal product, in particular supporting a product that is proven not to be harmful in the specified conditions of use and if the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience. The reason was that the regulator realised that the lack of sufficient scientific literature would prevent products with a long tradition of use from obtaining a medical licence under the applicable rules. No such considerations have been considered for the use of botanicals in foods and food supplements, as the NHCR covers the efficacy demonstration of all food components. This creates a situation in which no proof of efficacy is needed when a certain plant is used for its medicinal properties, but when used for health promotion, the effects would need to be supported by RCTs. This led the EU to announce that it would not proceed with the efficacy assessment of botanicals until this discrepancy is resolved.[9]

2. Methodologies for evaluating efficacy

The criteria applied by the EFSA for the evaluation of the health effects of food components are largely based on those proposed by PASSCLAIM (see Fig. 1). This approach necessitates well-defined characterisation of the food component, and validated and measurable biomarkers. It can therefore only be applied to well-defined extracts or pure compounds isolated from plant material, such as isoflavones and other bioactives. Even in such cases, assessing a health effect on the basis of only RCTs has been questioned, and the need to address the strength, consistency and plausibility of the totality of the available evidence emphasised.[10–15] Its application to botanicals and botanical preparations is limited because often the compounds responsible for the effect are not identified, and the effects may be diffuse and not linked to specific markers.[16] To allow the continued use of botanicals, traditional use has been suggested as a valid and essential element of the totality of evidence to substantiate health effects. Criteria relating to the various sources of documentation for traditional use have been proposed.[17] The evaluation of the traditional basis of a claimed effect needs to be determined by the assessment of the totality of the evidence available on a case-by-case basis. The more independent sources of information that are available, the more substantiated the traditional health effects can be considered to be. These criteria include the following:

–Availability of an important body of documentation demonstrating a sufficiently long history of the observed effects, covering at least one generation (25 years).

–Documented use of the botanical or the botanical preparation in different regions, countries or continents, under the same or similar conditions of use.

–Documented information on the nature of the botanical preparation and the modalities of use (traditional forms, frequency and level of use, *etc.*).

–Support from observational evidence, which often constitutes a broad area of mainly unrecorded observations that are derived directly in humans.

–Availability of more recent compilations of traditional health effects in various monographs.

–Support of the available documentation described above in relation to the traditional use of the botanical or botanical preparation from various sources of scientific data (chemical, pharmacological, toxicological, clinical studies or other experimental data).

An overview of the evidence available for selected botanicals and botanical compounds, with an emphasis on systematic reviews of RCTs, is presented in the following sections.

The PASSCLAIM criteria for the scientific substantiation of claims[8]

1. The food or food component to which the claimed effect is attributed should be characterized.
2. Substantiation of a claim should be based on human data, primarily from intervention studies the design of which should include the following considerations:
2(a) Study groups that are representative of the target group.
2(b) Appropriate controls.
2(c) An adequate duration of exposure and follow-up to demonstrate the intended effect.
2(d) Characterisation of the study groups' background diet and other relevant aspects of lifestyle.
2(e) An amount of the food or food component consistent with its intended pattern of consumption.
2(f) The influence of the food matrix and dietary context on the functional effect of the component.
2(g) Monitoring of subjects' compliance concerning intake of food or food component under test.
2(h) The statistical power to test the hypothesis.
3. When the true endpoint of a claimed benefit cannot be measured directly, studies should use markers.
4. Markers should be:
- biologically valid in that they have a known relation to the final outcome and their variability within the target population is known;
- methodologically valid with respect to their analytical characteristics.
5. Within a study the target variable should change in a statistically significant way, and the change should be biologically meaningful for the target group consistent with the claim to be supported.
6. A claim should be scientifically substantiated by taking into account the totality of the available data and by weighing of the evidence.

Fig. 1 PASSCLAIM criteria for the scientific substantiation of claims (PASSCLAIM Consensus Document).[8] With kind permission from Springer Science+Business Media: P. J. Aggett *et al.*, *Eur. J. Nut.*, **44**, Suppl. 1, I5-I30, DOI:10.1007/s00394-005-1104-3.

3. Green tea

The dried product known as "tea" is essentially the processed leaf of *Camellia sinensis*. Early stage thermal inactivation of endogenous polyphenol oxidase ensures that green tea retains a high monomeric catechin content (flavan-3-ols), the principal component being epigallocatechin gallate (EGCG), comprising 9–13% of the total dry weight.[18]

In the 2007 National Health Interview Survey, 6.3 ± 0.7% of US adults using natural product supplements for health reasons reported using green tea pills within the previous 30 d, representing the 12th most reported non-vitamin, non-mineral supplement.[19] A vast body of evidence indicates that green tea has positive effects in diverse health areas, including (but not limited to) metabolic syndrome,[20] cognitive function and neuroprotection,[21] various cancers,[22] bone health[23] and arthritis.[24] Unfortunately, to date, there are relatively few health areas where sufficient RCTs have been conducted to properly judge the efficacy of oral green tea intervention as a complementary and alternative medicine (CAM, a range of therapies that include herbal medicine, naturopathy and homeopathy, among others, in which practitioners may advocate the use of food or herbal supplements). Consequently, several systematic reviews and meta-analyses of human intervention trials consider green, black and oolong teas together, consumed as both infusions and extracts.

3.1 Green tea and cardiovascular health

Atherosclerosis, whereby plaques gradually build up on the artery walls, results in a narrowing of the blood vessels and a subsequent increase in blood pressure. Ischemia may follow, and in advanced cases of cell oxygen starvation, angina or infarction can occur. Cholesterol, a major component of these plaques, is therefore an acknowledged risk factor for cardiovascular disease (CVD). In a wide-ranging meta-analysis of 133 RCTs concerning flavonoid-rich foods and CVD risk factors, green tea consumption (4 trials) significantly reduced LDL cholesterol (−0.23 mmol L^{-1}; 95% CI: −0.34, −0.12), thus suggesting a major preventative benefit.[25] Flow-mediated dilation (FMD) has become a popular non-invasive method to assess endothelial function. There was a significant effect of moderate tea consumption on FMD in a meta-analysis of 9 studies, with 213 adult participants in 15 arms.[26] A median dose of 500 ml increased FMD *vs.* placebo by 2.6% of arterial dilation (95% CI: 1.8–3.3%; *P*-value < 0.001). However of the 9 studies detailed, 7 reported solely on black tea, the majority of interventions were centred on acute effects and the authors chose to exclude interventions with tea extracts. Similarly, the beneficial effect of cocoa beverages on brachial FMD has been related to its flavan-3-ol content,[27] and was simultaneously associated with an enhanced availability of the vasodilatory factor nitric oxide *in vivo*. Subsequently, several tea catechin and epicatechin metabolites have been reported to inhibit NADPH oxidase activity in HUVEC cells,[28] decreasing the generation of endothelial superoxide, and potentially promoting nitric oxide longevity. However, any beneficial effects of (black) tea consumption on cardiovascular risk factors may not extend to a lowering of blood pressure. In conducting a meta-analysis of 5 RCTs involving 343 subjects, there was no significant effect of tea consumption on blood pressure, independent of age, hypertension status or intervention length.[29] All but one of these studies considered black rather than green tea. In a meta-analysis of 4 studies, acute black tea consumption increased both systolic (5.69 mmHg; 95% CI: 1.52, 9.86) and diastolic (2.56 mmHg; 95% CI: 1.03, 4.10) blood pressure, but it was further suggested that chronic black tea consumption had no overall effect.[25] The authors stated that whilst caffeine has previously been reported to increase blood pressure,[30] half of the studies investigated used caffeinated controls and still found a significant increase with black tea.

3.2 Green tea and glycemic control in type-two diabetes

In a systematic review of CAM and type-two diabetes, Nahas and Moger[31] reported finding only 1 RCT ($n = 49$) and 3 open label studies ($n = 141$) considering intervention with tea polyphenols. All of these studies reported no difference in glycosylated haemoglobin levels (HbA1c) as a consequence of intervention, although 1 open label study considering oolong tea did report a significant decrease in fasting blood glucose (30%, $P < 0.001$) from baseline. Whilst this data does not support the efficacy of tea components in glycemic control, the lack of RCTs means that potential benefits suggested by epidemiological,[32] animal and mechanistic studies[33,34] may still apply but more studies are required.

3.3 Green tea and weight loss/body shape

World levels of obesity remain on the increase,[35] hence the use of green tea as a dietary aid to weight loss/maintenance is of obvious interest. In a meta-analysis of 11 green tea intervention studies with 1226 participants, green tea catechins plus caffeine were effective in promoting weight loss and maintaining weight after a period of negative energy balance, with participants losing an estimated 1.31 kg more/gaining 1.31 kg less on average compared to the control (95% CI: −2.05 to −0.57; $P < 0.001$).[36] Individual decreases in apparent green tea efficacy through (i) increased habitual caffeine intake or (ii) Caucasian *vs.* Asian ethnicity were statistically insignificant, yet both remained significant moderators of green tea efficacy ($p = 0.04$). The importance of caffeine was also highlighted in a meta-analysis of 15 trials (1243 participants) considering body weight, waist circumference, waist to hip ratio and body mass index (BMI).[37] Green tea catechins taken alone had no significant effect on end points, but green tea catechins combined with caffeine significantly decreased body weight compared to a non-caffeinated control (−0.44 kg; 95% CI: −0.72, −0.15). However, caffeine was not the sole bioactive: body weight (−1.38 kg; 95% CI: −1.70, −1.06), waist circumference (−1.93 cm; 95% CI: −2.82, −1.04) and BMI (−0.55; 95% CI: −0.65, −0.40) were all decreased by green tea catechins plus caffeine intervention compared to a caffeine control. In addition to the potential inhibition of lipases[38] or the possible anorectic effects of consuming green tea,[39] weight control might be achieved by an increase in energy expenditure. A commercial green tea extract (AR25®) significantly increased 24 h energy expenditure in healthy men compared to a placebo (3.5%, $p < 0.01$).[40] An additive/synergistic relationship between oral catechins and caffeine has been suggested, namely through the inhibition of catechol-*O*-methyltransferase (COMT) by the former, and inhibition of phosphodiesterase by the latter, promoting the longevity of

noradrenalin and cyclic amino monophosphate (cAMP) respectively, and thus lipolysis.[41]

It is apparent from these meta-analyses and systematic reviews of human interventions that green tea shows benefits in more than one element of metabolic syndrome. However, heterogeneity in the active interventions considered raises issues; whilst all unprocessed tea leaves will contain high levels of catechin monomers, their partial oxidation during the manufacture of black or oolong teas produces theaflavin dimers and complex thearubigen polymers, resulting in significant differences in flavonoid profile between tea types. It is clear that more RCTs using well-characterised interventions are required to confirm efficacy in many of the areas in which *Camellia sinensis* shows promise.

4. Soy isoflavones

Isoflavones are dietary polyphenols derived predominantly from the consumption of soy and soy products. The main isoflavones are daidzein, genistein and glycitein, which are naturally found in soy as glycosides. A substantial number of supplements of soy are available from many different sources and provide a popular[19] way to consume isoflavones without needing to eat soy products such as tofu or soy milk. Typically supplements are of variable quality[42] and do not necessarily contain the amount of isoflavones stated on the label. However, many intervention studies have been performed on isoflavone supplements rather than food, since it is easier to placebo-control the study. Bioavailability is necessary for efficacy, and for isoflavones, bioavailability is high relative to other polyphenols.[43] Absorption occurs after deglycosylation by endogenous intestinal brush border enzymes[44] or by colonic microbiota,[45] the latter leading to further conversion of daidzein to equol in some individuals, with proposed additional benefits in "equol producers".[46] Isoflavones, including their conjugated metabolites, have been shown *in vitro* to act on multiple targets, especially estrogen receptors (ER)-β,[47] to affect cell signalling mechanisms[48] and to possess antioxidant properties.[49] Despite some safety concerns related to their estrogenic activity, they are generally regarded as safe, based on evidence from the scientific literature.[50] Because of their molecular interaction with the ER, they have been tested in many RCTs for effects on bone health and on menopausal symptoms in peri- and postmenopausal women.

4.1 Systematic reviews on the effect of soy isoflavones on bone

There have been several systematic reviews on studies of the relationship between soy consumption and bone health, mostly related to bone loss in postmenopausal women. Bone health can be measured either directly, using X-ray based techniques to measure bone mineral density where at least a year is required to measure an effect, or indirectly, using short term biochemical markers of bone turnover. Soy isoflavones decreased the bone resorption marker urinary deoxypyridinoline, but not markers of bone formation (serum bone alkaline phosphatase and serum osteocalcin) in 28 published studies involving a total of 2477 participants in RCTs, where an average of 56 mg aglycone equivalents of isoflavones were consumed per day for 10 to 52 weeks.[51] A meta-analysis of RCTs in menopausal women in 9 studies of 432 subjects showed the same effect.[52] Bone loss is characterised by an increase in bone turnover, leading to increased bone resorption, followed by a decrease in strength and eventually fracture. Deoxypyridinoline is a cross-link product of bone collagen and is excreted in urine during bone degradation. Although the effects of isoflavones on bone resorption are convincing in postmenopausal women, the effect on bone mineral density is less clear. In a systematic review, soy isoflavones did not affect diminishing bone mineral density in perimenopausal or postmenopausal women, based on 12 papers using 1433 subjects on placebo-controlled randomised trials.[53] However, in a different meta-analysis, soy isoflavones slightly affected spine bone mineral density, but the effect was more significant when consumed at >90 mg day^{-1}, when reviewing 10 studies on 608 subjects.[54] In conclusion, isoflavones affect bone resorption at lower doses (~50–60 mg day^{-1}) in postmenopausal women undergoing estrogen-related bone loss, but this is only translated into the attenuation of bone loss at higher doses (>90 mg day^{-1}) of isoflavones.

4.2 Systematic reviews on the effect of soy isoflavones on menopausal symptoms

Hot flushes (or flashes) are the most common symptom during the menopausal transition, can last for several years after the menopause and are related to decreasing estrogen levels. Since one of the actions of isoflavones is to interact with the estrogen receptor, especially ERβ, this action may mimic the effects of estrogen and hence affect estrogen related processes. Many human intervention studies have examined the effect of isoflavones from soy, but also from red clover, on menopausal symptoms. In a systematic review, 17 randomised, double-blind, placebo controlled trials on isoflavone extracts were identified on 1739 women, but no clear effect on hot flashes was observed.[55] Another systematic analysis on 17 studies showed a slight to modest reduction in hot flashes, but the effects were most apparent in women having a high number of flashes per day.[56] In a systematic review of 35 studies on circulating hormone levels in postmenopausal women, no significant effect of isoflavones was seen on estrone, follicle stimulating hormone, luteinizing hormone or sex hormone binding globulin, although there was a trend for increasing estradiol.[57] In 11 studies on premenopausal women, there were significant effects on follicle stimulating hormone and luteinizing hormone.[57] Another systematic review concluded that the effects of isoflavones on hot flashes in postmenopausal women, derived from 19 studies, was highly variable and no conclusions could be drawn.[58]

It is apparent that there is marked variability between studies on isoflavones and estrogen-related health. Some reasons for this could be due to differences in bioavailability between supplements, to inter-individual differences in metabolism and to the selection of heterogeneous target population groups. Obviously the effect of isoflavones on bone and menopausal symptoms is subtle, as for any dietary intervention. Food or supplements are essentially a chronic intervention over a lifespan and so must, in order to be safe, be less biologically active than specifically designed drugs. Hence, conclusive results on isoflavone supplements should be obtained in the future using studies with more homogeneous populations (*e.g.* selecting for equol production, equivalent absorption and metabolism, *etc.*) by using

supplements with optimised bioavailability and minimising factors that can affect isoflavone absorption.[59]

5. Aloe vera

There is a paucity of systematic reviews that have assessed the efficacy of aloe vera in clinical practice. The pioneer review from Vogler and Ernst[60] concluded that even though there were some promising results, the clinical effectiveness of oral or topical aloe vera was not sufficiently defined at that time. Hardly any additional studies and reviews have been conducted since then.

Aloe vera is the most well-known species of aloe, a desert plant resembling the cactus in the Liliaceae family. It is popularly used to treat burns and promote wound healing. The dried sap of *Aloe vera* is a traditional remedy for diabetes in the Arabian peninsula,[61] although aloe gel is preferred over the sap as the latter contains the laxative anthraquinone.[62] Aloe gel, obtained from the inner portion of the leaves, contains glucomannan, a water-soluble fiber which may in part account for its hypoglycemic effects.[63] Reports in animal models have been inconsistent.[62,64–66]

5.1 Aloe vera in type-2 diabetes and dyslipidemia

Two non-randomized clinical trials are available from the same investigator group that report improved fasting blood glucose with 6 weeks of juice made from aloe gel.[62,67] Case reports of five type-2 diabetic individuals reported decreases in fasting blood glucose, as well as HbA1c.[64] No adverse effects were reported in these trials. In a review article, Ulbricht *et al.*[68] concluded that the evidence regarding oral aloe vera efficacy in patients with diabetes mellitus was conflicting. Since this publication, additional studies investigating aloe vera for lowering fasting blood glucose and glycosylated haemoglobin ([HbA.sub.1c]) concentrations have been reported. Until very recently, no clinical review of aloe vera use in dyslipidemia had been performed. With the emergence of new data and a lack of consensus on the glycemic and lipid effects of aloe vera in humans, a thorough review was warranted analyzing the available literature on the efficacy of oral aloe vera in diabetes mellitus and dyslipidemia in humans.[69] Eight trials were found, including a total of 5285 patients, which assessed oral aloe vera use in humans. Seven of the studies evaluated diabetes endpoints and six evaluated the effects on lipids. Five of these studies evaluated endpoints for both conditions. Of the eight studies investigating aloe vera treatment for diabetes mellitus or lipid endpoints in humans, three were randomized, placebo-controlled trials available only as abstracts. The remaining reports included two placebo-controlled trials that used similar methods and produced similar results, and three uncontrolled clinical studies. The preponderance of evidence suggests a trend towards the benefit of oral aloe vera use in reducing fasting blood glucose concentration and [HbA.sub.1c]. Triglyceride levels also seem to be reduced, although evidence regarding changes in LDL, HDL and total cholesterol levels is conflicting. The weaknesses in study methods and inconsistency of data do not currently warrant the recommendation of oral aloe vera for the management of diabetes mellitus or dyslipidemia.[69]

The effects of oral aloe vera on electrocardiographic and blood pressure measurements were evaluated in a recent double-blind, placebo-controlled crossover study, assessing healthy volunteers older than 18 years receiving either 1200 mg of oral aloe vera powder or a matching placebo.[70] The primary endpoint was the maximum post-treatment Q-Tc interval over 8 h in both groups. A single dose of oral aloe vera had no effect on electrocardiographic or blood pressure measurements in young healthy volunteers.

5.2 Aloe vera anti-inflammatory and gastrointestinal actions

The herbal preparation of aloe vera has been claimed to possess anti-inflammatory effects and, despite the lack of evidence-based therapeutic efficacy, is widely used by patients with inflammatory bowel disease. A double-blind, randomized, placebo-controlled trial of the efficacy and safety of aloe vera gel for the treatment of mildly to moderately active ulcerative colitis showed that oral aloe vera taken for 4 weeks produced a clinical response more often than the placebo; it also diminished the histological disease activity and appeared to be free of contraindications. Further evaluation of the therapeutic potential of aloe vera gel in inflammatory bowel disease is needed.[71] In a recent clinical trial,[72] aloe vera did not alleviate symptoms and pain in patients with gastrointestinal reflux.

A Cochrane systematic review has been performed to evaluate the effectiveness of prophylactic agents employed for oral mucositis in patients with cancer receiving treatment, compared with other potentially active interventions, placebo or no treatment.[73] A total of 131 studies with 10 514 randomised participants were included. Nine interventions, in which there was more than one trial in the meta-analysis, were found to have some benefit with regard to preventing or reducing the severity of mucositis associated with cancer treatment, and aloe vera was involved in one of them. One study did not find any benefit for using aloe vera as an adjunct to head and neck radiotherapy side effects.[74]

A recent paper provides evidence that oral aloe vera could be used in the treatment of chronic non-cancer pain, particularly that caused by osteoarthritis.[75] Despite its application for centuries as a treatment for arthritis,[76] the evidence of the effectiveness of aloe vera remains anecdotal or is derived from studies with a limited sample size. The perceived benefits of prescribing aloe vera for osteoarthritis may be two-fold: it acts as an anti-inflammatory agent as well as a prophylactic against the gastrointestinal irritant effects of non-steroidal anti-inflammatory drugs. Long-term, randomized, controlled studies are required to address the lack of evidence base for the optimum prescription of pain medications for people with osteoarthritis.[77]

5.3 Aloe vera in other applications and adverse effects

Although there are some promising results with the use of aloe vera for diverse dermatological conditions, the clinical effectiveness of oral and topical aloe vera is not sufficiently and meticulously explored to date.[78] A certain degree of efficacy has been demonstrated for aloe vera gel in the treatment of oral lichen planus in a well designed randomized controlled trial.[78,79] A Cochrane systematic review process has been conducted to explore the effect of wound cleansing solutions and techniques on pressure ulcer healing with no conclusive results supporting the intervention.[80] A systematic review to determine the efficacy of topical aloe vera for the treatment of burn wounds, based only on controlled clinical trials, supported that aloe vera might be an

effective intervention in burn wound healing for first to second degree burns.[81]

Changes in urinary chemical composition were observed in children after consuming prepared oral doses of aloe gel, thus showing its potential for preventing kidney stone formation.[82]

The toxicological aspects of aloe vera have been carefully analyzed.[83] Aloe vera products contain multiple constituents with potential biological and toxicological properties, yet the active components elude definition. Ingestion of aloe vera is associated with diarrhea, electrolyte imbalance, kidney dysfunction and conventional drug interactions; episodes of contact dermatitis, erythema and phototoxicity have also been reported when applied topically. Yang *et al.*[84] have recently demonstrated the development of toxic hepatitis attributed to the ingestion of aloe vera over a period of months in three women.

The possible benefits of aloe vera use in certain pathologies described in the literature should be weighed against the potential toxic effects of this ingredient, whose activity depends on the purity and characteristics of the product utilised.

6. Summary, conclusions and future work

Efficacy evaluation of PFS, for the purpose of making claims on product labels or in promotional materials, has been since 2007 covered by EU Nutrition and Health Claims legislation. However, this legislation does not specify the criteria for such assessments. The European Food Safety Authority has adopted an approach relying on randomised controlled trials (RCTs), building on the work of the EU-funded FUFOSE and PASSCLAIM projects. Experience with the assessments so far have highlighted the limitations of this approach, and no health effect of botanicals has yet received a positive opinion. The lack of scientific data is recognised under medicinal law, and medicinal effects are accepted based on traditional use. This discrepancy has lead the European Commission to single out botanicals from the claims assessment process and start a reflection on how to integrate traditional use as an important factor in the totality of evidence. This creates the need to establish criteria for traditional use that can also be applied for assessing health effects. Three commonly used supplements are green tea, isoflavones and aloe vera, but each is very different in the number of RCTs performed. Most are available for isoflavones, least for aloe vera. Both green tea and isoflavone supplements have sufficient RCTs that some systematic reviews have determined whether they have an effect on health in humans. RCTs on isoflavones indicate that they affect bone resorption at lower doses in postmenopausal women undergoing estrogen-related bone loss, but this is only translated to the attenuation of bone loss at higher doses. A systematic review on RCTs concluded that the effects of isoflavones on hot flashes in postmenopausal women were highly variable and no conclusions could be drawn. Whilst the potential benefits of green tea have been reported in a wide range of health areas, it is only in the area of the metabolic syndrome that the number of RCTs in existence is approaching sufficient to judge efficacy. Although it is apparent that more than one element of metabolic syndrome may benefit from green tea consumption, it remains evident that yet more RCTs, with well-characterised interventions, are required in this and other promising health areas. Despite the popularity of aloe vera use as a PFS, the evaluation of its efficacy as a coadjuvant therapy for certain metabolic or digestive pathologies remains scarce; it constitutes a typical example of a naturally occurring ingredient whose efficacy in topical applications presupposes its efficacy in systemic applications. Possible toxic effects call for caution in its utility as a PFS.

The effects of PFS are subtle, as for any dietary intervention. Food or supplements are essentially a chronic intervention over a lifespan and so must, in order to be safe, be less biologically active than specifically designed medical products such as drugs. Hence, conclusive results can only be obtained in the future by using studies with more homogeneous populations, by using supplements with optimised bioavailability and running studies with a sufficient number of volunteers, using validated biomarkers for as long as is necessary to obtain conclusive results on a putative effect.

Acknowledgements

The writing of this review was funded by the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 245199. It has been carried out within the PlantLIBRA project (website: http://www.plantlibra.eu). "This report does not necessarily reflect the Commission's views or its future policy on this area."

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