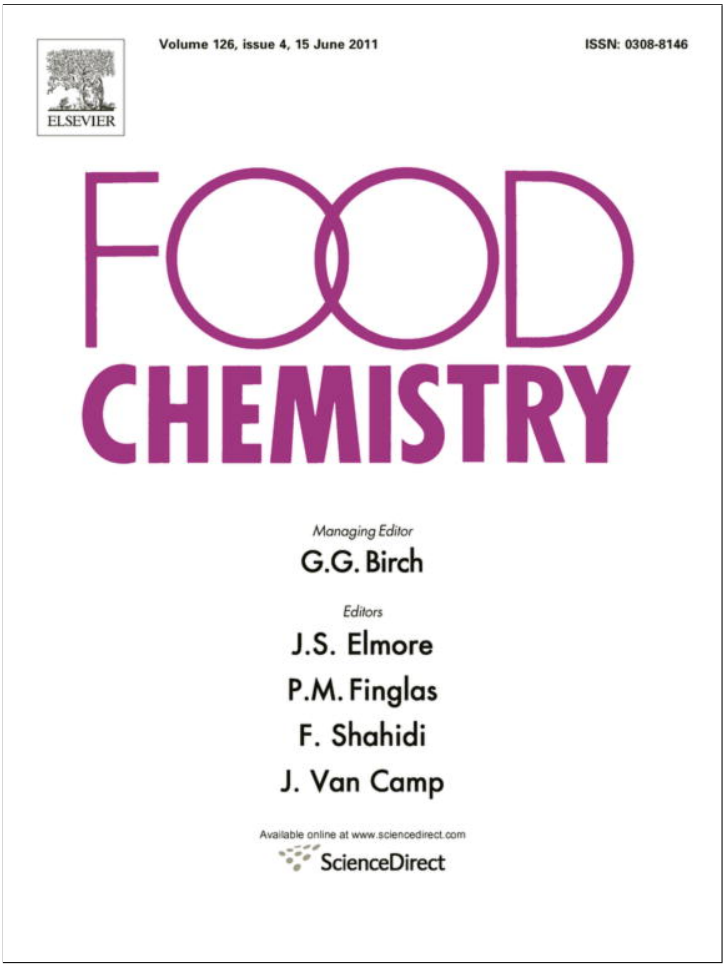

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Screening of selected Asian spices for anti obesity-related bioactivities

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ABSTRACT

The potential health effects of 30 spices, commonly used for daily consumption, were submitted to bioactivity screening with several anti-obesity related bioassays: adenosine A1 receptor binding, cannabinoid CB1 receptor binding, TNF-α and 3T3-L1 adipocytes differentiation induction. Sesame seed and red chilli exhibited high binding activity to the adenosine A1 receptor and nutmeg, mace, black pepper and turmeric to the cannabinoid CB1 receptor, while piment and turmeric showed high inhibition of TNF-α accumulation. Black onion seed proved to be the only spice with high 3T3-L1 adipocyte differentiation induction activity. Several well known major compounds found in these active spices were tested with the respective bioassays but did not show activity. Thus, it appears that other minor compounds or the synergistic effects of different constituents are responsible for the observed activity.

1. Introduction

Since ancient times, there has been an awareness of the fact that there is much more to herbs and spices than a merely culinary function as seasonings, used to improve sensory properties of food. In cooking, the term herb refers to the leaves of a plant, while spices refer to any other part of plants (Tapsell et al., 2006). The history of the evolution of the knowledge of herbs and spices between 5000 and 1000 BC in human civilisation (e.g. the use of thyme by the Sumerians, coriander, fennel, juniper, cumin, garlic, cardamom, cinnamon by the Egyptians, or juniper and saffron by the Assyrians), has been reviewed together with the attempts of modern scientists to find evidence of their various bioactivities, identification of responsible active compounds and their molecular targets (Tapsell et al., 2006). It is clear that spices are important elements of traditional medicine, being exclusively categorised as superior herbals in Chinese Traditional Medicine (Yu, Shirai, & Suzuki, 2007) and of great importance in Ayurvedic preparations.

In recent times, various bioactivities of herbs and spices, when consumed as food seasoning (especially those related to degenerative diseases), have been reported. The supplementation of rat diets with doses of 1% (w/w) of star anise or cloves decreased their levels of blood and liver lipids (Yu et al., 2007). A reverse correlation between consumption of spices and risk of cancer in India, China and the USA, has been reported (Aggarwal, Van Kuiken, Iyer, Harikumar, & Sung, 2009). Certain spices are included as among the main components of the Mediterranean diet, and studies have shown that Mediterranean people have a lower risk of several disorders, such as cardiovascular diseases, metabolic disorders and certain types of cancer (Ortega, 2006). The addition of 1.5% w/w of lemon balm and marjoram herbs was found to increase antioxidant capacity of a portion of salad by 150% and 200%, respectively (Ninfali, Mea, Giorgini, Rocchi, & Bacchiocca, 2007). Several studies on the bioactivity of spice- derived compounds have also been performed. Capsaicin, a phenolic compound from red pepper (Capsicum), for example, was found to have a sympathomimetic thermogenic activity (Watanabe, Kawada, Yamamoto, & Iwai, 1987) and other compounds, such as allylisothiocyanate, zingerone, and curcumin, were found to inhibit the production of TNF-α, nitric oxide and monocyte chemoattractant protein-1 (MCP-1), mediators resulting from obesity induced-inflammation (Woo et al., 2007). Other examples are the ginger-derived compounds, 6-shogaol and 6-gingerol, which showed significant inhibition of downregulation of adiponectin expression mediated by TNF-α in 3T3-L1 adipocytes (Isa et al., 2008).

In our preliminary research to find plant derived-compounds with reported anti-obesity activity, various spices commonly used in Asian cuisine were screened, using several bioassays related to obesity at receptor and cellular levels: adenosine A1 receptor, cannabinoid CB1 receptor, TNF-α suppression, and lipolytic activity on 3T3-L1 adipocyte. The blockage of the adenosine A1 receptor by antagonists or inverse agonists has been reported to have a correlation with lipolytic activity (Barakat, Davis, Lang, Mustafa, & McConnaughey, 2006; Johansson, Lindgren, Yang, Herling, &

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Fredholm, 2008), while blocking of the cannabinoid CB1 receptor reduces the appetite and stimulates lipid metabolism (Cota et al., 2003). Conversely, TNF-α expression induces appetite and body fat percentage by stimulating leptin release from adipocytes (Kirchgessner, Uysal, Wiesbrock, Marino, & Hotamisligil, 1997). The spices to be tested were either fresh or dried. Fresh spices were purchased in a supermarket, and dried ones from major suppliers whose products are widely available at local retail stores in the Netherlands. In total 30 samples thus obtained were evaluated.

2. Materials and methods

2.1. Spices

The following spices were obtained from TRS Co. Ltd UK in a dried form and identified by Mr. Anil Shah from TRS Co. Ltd: *Foeniculum vulgare*, *Coriandrum sativum*, *Cuminum cyminum*, *Anethum graveolens*, *Levisticum officinale*, *Bixa orellana*, *Brassica juncea*, *Aleurites moluccana*, *Trigonella foenum-graecum*, *Illicium verum, Cinnamomum verum*, *Syzygium aromaticum*, *Pimenta officinalis*, *Myristica fragrans*, *Papaver somniferum*, *Sesamum indicum*, *Piper nigrum*, *Punica granatum*, *Nigella sativa*, *Capsicum annuum*, *Amomum subulatum. Cymbopogon citratus*, *Alpinia galanga*, *Zingiber officinale, Kaempferia galanga*, *Allium cepa*, *Allium sativum* and *Pangium edule* were purchased fresh from a local supermarket in Leiden, The Netherlands.

2.2. Chemicals and reagents

Methanol, *n*-hexane, ethyl acetate, HCl, NaOH, and DMSO were purchased from Biosolve BV (Valkenswaard, The Netherlands). Tris buffer was provided by Gibco BRL (New York, NY, USA) and *n*-BuOH by JT Baker BV (Deventer, The Netherlands). HEPES powder, bovine serum albumine, MeOH-d_4 NMR solvents and CP55940 were obtained from Sigma Aldrich (St. Louis, MO, USA). Human Cannabinoid CB1 receptor membrane and [^{3}H]CP55940 were purchased from Perkin Elmer (Boston, MA, USA), EDTA and $MgCl_2.7H_2O$ from Merck (Darmstadt, Germany), [^{3}H]DPCPX (8-cyclopentyl-1,3-dipropylxanthine) from DuPont NEN, and CPA (N6 cyclopentyladenosine) from RBI Inc. Kieselguhr was obtained from Fluka Analytical. Fetal bovine serum (FBS), penicillin, streptomycin and RPMI1640 were purchased from GIBCO (Grand Island, NY) and U937 cell lines from ATCC (CRL-1593.2). Lipopolysaccharide (*Escherichia coli* O111:B4) and phorbol 12-myristate 13-acetate (PMA) were from Sigma–Aldrich (St. Louis, MO, USA). The Human TNF-α ELISA kit was purchased from BioSource International Inc.(Camarillo, CA, USA). DMEM, fetal bovine serum (FBS), penicillin and streptomycin solution, phosphate buffered saline, TrypLE Express and Hanks Balanced Salt Solution (HBBS) were supplied by GIBCO Netherlands BV (Breda, The Netherlands), 3-Isobutyl-1-methylxanthine (IBMX), dexamethasone, insulin from bovine pancreas, isoproterenol, glycerol, free glycerol assay reagent, 10% sterile BSA Solution and DMSO were from Sigma Aldrich (St. Louis, MO, USA) and3T3-L1 pre adipocyte cell line was obtained from the American Type Culture Collection (Rockville, Md., USA). Plastic ware for tissue culture was supplied by Greiner Bio-One GmbH (Frickenhausen, Germany). All solvents and reagents were of analytical grade.

2.3. Extraction method

Cymbopogon citratus, *Alpinia galanga*, *Zingiber officinale*, *Kaempferia galanga*, *Allium cepa*), *Allium sativum,* and *Pangium edule* were powdered and then freeze-dried, while other spices were powdered and then directly used in this experiment.

One gramme of each dried powdered spice was placed in a reaction tube to which 2 ml of 80% MeOH were added, vortexed, then sonicated for 15 min and filtered to obtain the extract. The marc was submitted to the same procedure twice and the filtrates were pooled and taken to dryness with a vacuum rotavapor. The dried extracts were redissolved in DMSO, at 1.5 mg/ml concentration, and prepared for the assays.

2.4. Adenosine A1 receptor assay

This assay followed the procedure described by Chang, Brussee, and IJzerman (2004), with a minor modification consisting of taking the final volume of the total mixture to 200 μl. The radioactive ligand used for the assay was 0.4 nM [^{3}H] DCPCX (8-cyclopentyl-1,3-dipropylxanthine) (K_d = 1.6 nM). Membranes were prepared from Chinese hamster ovary (CHO) cells, stably expressing human adenosine receptors by a method previously described by Dalpiaz, Townsend-Nicholson, Beukers, Schofield, and Ijzerman (1998), and CPA (N6-cyclopentyladenosine) was used to determine non-specific binding. The mixture consisting of 50 μl of [^{3}H] DPCPX, 50 μl of CPA/50 mM Tris–HCl buffer/test compounds at different concentrations, 50 μl of 50 mM Tris–HCl buffer pH 7.4, and 50 μl of membrane, was incubated at 25 °C for 60 min and then filtered over a GF/B Whatman filter under reduced pressure. The filters were rinsed three times with 2 ml of ice-cold 50 mM Tris/HCl buffer, pH 7.4, and 3.5 ml of scintillation liquid was added to each filter. The radioactivity of the washed filters was counted, using a Hewlett–Packard Tri-Carb 1500 liquid scintillation detector. The bioactivity was expressed as percentage inhibition of [^{3}H]DPCPX binding to the adenosine A1 receptor extract and was calculated using the software package Prism (Graphpad, Inc.).

2.5. CB1 receptor assay

The CB1 binding assay employed was a modified version of the method described previously by Ross et al. (1999). Incubation buffer was prepared from 20 mM Hepes buffer pH 7.4, containing 5 mM $MgCl_2$, 1 mM EDTA, and 0.3% BSA. The CB1 membrane was diluted 200 times with assay buffer. An assay cocktail, consisting of 25 μl of incubation buffer/extract/CP 55940, which was used to determine unspecific binding at final concentrations of 5 μM, 25 μl of 8.10^{-5} μM [^{3}H]CP55940 and 500 μl of diluted membrane, was incubated at 30 °C for 60 min and filtered over the GF/B filter. The filters were rinsed 3 times with 2 ml portions of ice-cold 20 mM Hepes buffer, pH 7.4, containing 0.01% BSA, followed by the addition of 3.5 ml of scintillation liquid to each filter. The radioactivity of the washed filters was counted with a Hewlett–Packard Tri-Carb 1500 liquid scintillation detector. The bioactivity was expressed as a percentage of inhibition of [^{3}H]CP55940 binding to the CB1 receptor and was calculated using the software package Prism (Graphpad, Inc.).

2.6. Induction of 3T3-L1 pre-adipocyte differentiation assay

This assay was performed according to manufacturer indications for use in the Adipolysis Assay kit (Article number OB100) from Chemicon (Millipore).

2.7. Inhibition of LPS-induced TNF-α accumulation assay

Human monocyte-like histiocytic lymphoma cells U937, obtained from the ATCC (CRL-1593.2), were grown according to Sundstrom and Nilsson (1976). The TNF-α production *in vitro* and cell viability determination, after treatment of various plant extracts, using a MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) reagent, was performed according to Cho

et al. (2000). A cell suspension with a concentration of 10^5 cells/ml was plated in a 96- well plate. After 48 h of culture, various concentrations of test extracts and LPS (2 μg/ml), as a positive control, were added to each well and cultured for a further 4 h. Finally, 20 μl of MTT solution (5 mg/ml in phosphate buffered saline) were added to each well and incubated for a further 2.5 h at 37 °C. After that, the medium was discarded and formazan blue, which was produced by reaction of MTT with mitochondrial dehydrogenase in living cells, was dissolved with 100 μl of DMSO. The optical density (OD) was measured at 540 nM with a microplate reader.

3. Results and discussion

The results obtained for the different spices are shown in Table 1. As can be observed, all spices exhibited some type of activity.

A high inhibitory capacity of adenosine A1 receptors binding (complete displacement of radioligand) was exhibited by sesame seeds and red chilli, while nutmeg, poppy seeds, pomegranate seeds, and onion displayed a medium activity.

Sesame seeds and oil are already known to be a rich source of lignans, among which sesamin is the most abundant. Sesamin was found to suppress hepatic fatty acid synthase expression in rats via suppression of the sterol regulatory element binding protein-1 mRNA expression (Ide et al., 2001). However, it is important to bear in mind that sesame seeds are also a rich source of oil (total oil content is 40% w/w), with linoleic acid and oleic acids as the two most abundant unsaturated fatty acids, representing 40% each of the total fatty acid content of the oil (Ryan, Galvin, O'Connor, Maguire & O'Brien, 2007). It has been reported that unsaturated fatty acids bind unselectively to adenosine A1 receptor (Ingkaninan et al., 1999).

Capsaicin, myristicin, and papaverine, major components of red chilli, nutmeg, and poppy seed, respectively, were tested, in order to determine whether the high and medium binding activities of these spices could be attributed to their presence, but no significant binding for any of the pure compounds was detected (results not shown).

The structures of these three compounds were then compared to the structures of compounds from plant sources which are known to be adenosine A1 receptor ligands: caffeine and 3′,3-dihydroxy-4′,5,6,7-tetramethoxyflavone (eupatoretin) (Fig. 1). The Ki values of these natural adenosine A1 receptor ligands are 29 μM and 5.4 μM, respectively (Jacobson, Van Galen, & Williams, 1992; Yuliana et al., 2009). The methoxy substituent groups which are present in eupatoretin do not appear to be crucial for the binding activity of this compound, since they are also present in myristicin, papaverin and capsaicin. Similarly, papaverine has a N-heterocyclic aromatic ring substitution which is also found in caffeine. What these 3 compounds lack, however, is a ketone substituent which is thus most probably an important requirement for the adenosine A1 binding activity exhibited by caffeine and eupatoretin.

Spices with high binding activity to the cannabinoid CB1 receptor were found to be nutmeg, mace, black pepper and turmeric, while annatto and sand ginger displayed a medium activity. Nutmeg has been used since ancient times to cure many kinds of disorders, such as digestion problems, fever, skin diseases, respiratory ailments, and it was also reported to have an effect on the

Table 1
Bioactivity of spices toward adenosine A1 receptor binding, CB1 receptor binding, inhibition of LPS-induced TNF-α accumulation, and induction of 3T3-L1 adipocyte differentiation.

Spices	The used part	Common name	Family	Activity*			
				Adenosine A1[a]	CB1[b]	TNF-α[c]	3T3-L1 adipocyte differentiation[d]
Foeniculum vulgare Mill.	Seed	Anis	Apiaceae	Low	na	na	na
Coriandrum sativum L.	Seed	Coriander	Apiaceae	na	na	na	na
Cuminum cyminum L.	Seed	Cumin	Apiaceae	Low	na	na	na
Anethum graveolens L.	Seed	Dill	Apiaceae	Low	na	na	na
Allium sativum L.	Bulb	Garlic	Alliaceae	na	na	na	na
Levisticum officinale L. Koch	Seed	Lovage	Apiaceae	na	na	na	na
Bixa orellana L.	Seed	Annato	Bixaceae	Low	Medium	na	na
Brassica juncea L. Czern.	Seed	Brown mustard	Brassicaceae	na	na	na	na
Aleurites moluccana L. Willd.	Seed	Candle nut	Euphorbiaceae	Low	Low	na	na
Trigonella foenum-graecum L.	Fruit	Fenugreek	Fabaceae	na	na	Medium	na
Illicium verum Hook.f.	Nut	Star anise	Illiciaceae	na	na	Medium	na
Cinnamomum verum J. Presl.	Bark	Cinnamon	Lauraceae	na	na	Medium	na
Syzygium aromaticum Merrill & Perry	Flower	Cloves	Myrtaceae	na	Low	Medium	na
Pimenta officinalis Lindl.	Fruit	Piment	Myrtaceae	Low	na	High	na
Myristica fragrans Gronov.	Seed	Nutmeg	Myristicaceae	Medium	High	Medium	na
Myristica fragrans Gronov.	Seed aril	Mace	Myristicaceae	Low	High	Medium	na
Papaver somniferum L.	Seed	Poppy seed	Papaveraceae	Medium	Low	na	na
Sesamum indicum L.	Seed	Sesame seed	Pedaliaceae	High	Low	na	na
Piper nigrum L.	Seed	Black pepper	Piperaceae	na	High	na	na
Punica granatum L.	Seed	Pomagranate	Punicaceae	Medium	na	na	na
Cymbopogon citratus DC. Stapf.	Stem	Lemon grass	Poaceae	na	na	Low	na
Nigella sativa L.	Seed	Black onion	Ranunculaceae	na	Low	na	High
Capsicum annuum L.	Fruit	Red chilli	Solanaceae	High	na	na	na
Amomum subulatum Roxb.	Seed pod	Black cardamom	Zingiberaceae	na	Low	Medium	na
Alpinia galanga L. Wild.	Rhizome	Great galangal	Zingiberaceae	na	na	na	na
Zingiber officinale Rosc.	Rhizome	Ginger	Zingiberaceae	na	na	Low	na
Kaempferia galanga L.	Rhizome	Sand ginger	Zingiberaceae	na	Medium	na	na
Curcuma longa Linn.	Rhizome	Turmeric	Zingiberaceae	Low	High	High	nd
Allium cepa L.	Bulb	Onion	Alliaceae	Medium	na	na	nd
Pangium edule Reinw.	Seed	Kluwek nut	Achariaceae	na	Medium	na	nd

* Determined base on the average of three independent replications, activity value is presented as High = 75–100%, Medium = 50–75%, Low = 30–50%, Not active (na) ⩽30%, nd = not determined.

[a] Percentage of activity represents the binding activity of extract to the receptor; concentration tested was 50 μg/ml in the assay.

[b] Percentage of activity represents the binding activity of extract to the receptor; concentration tested was 70 μg/ml in the assay.

[c] Percentage of activity represents the ability of the extract to inhibit TNF-α production in the medium; concentration tested was 15 μg/ml in the assay.

[d] Percentage of activity represents the amount of glycerol released to the medium, concentration tested was 40 μg/ml in the assay.

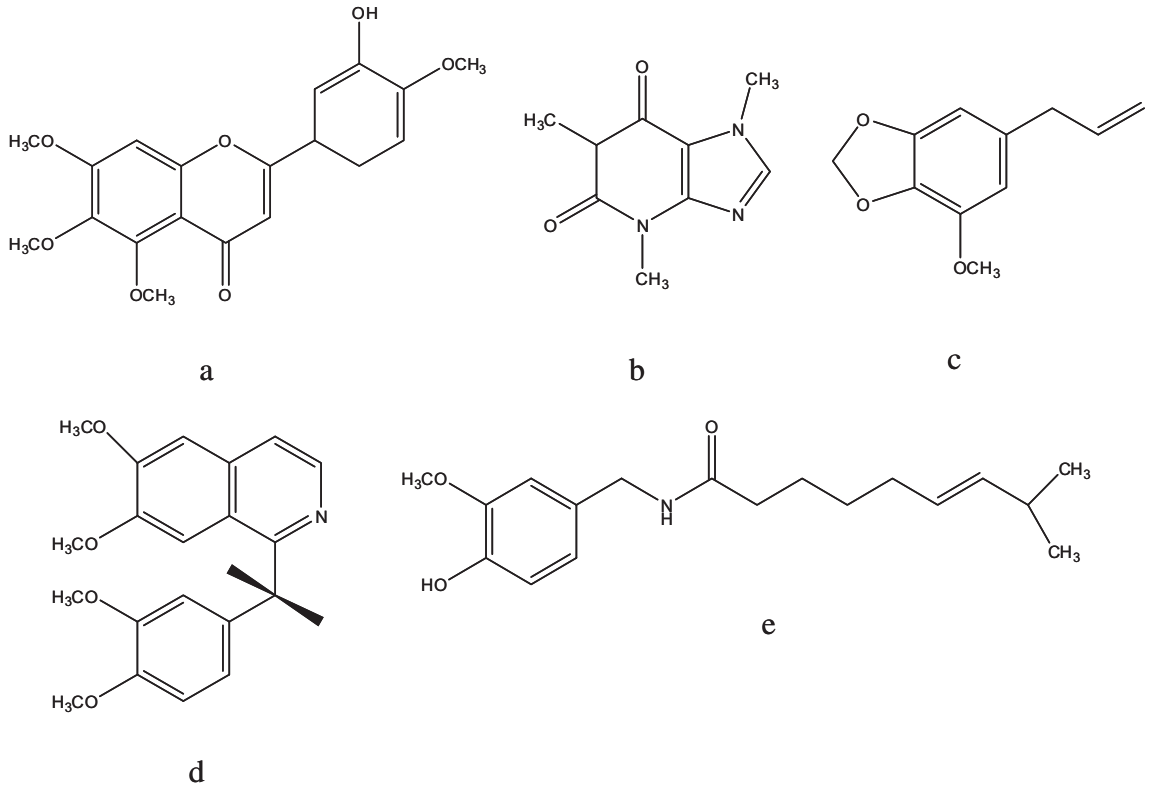

Fig. 1. Chemical structures of: (a) Eupatoretin, (b) Caffeine, (c) Myristicin, (d) Papaverin, (e) Capsaicin.

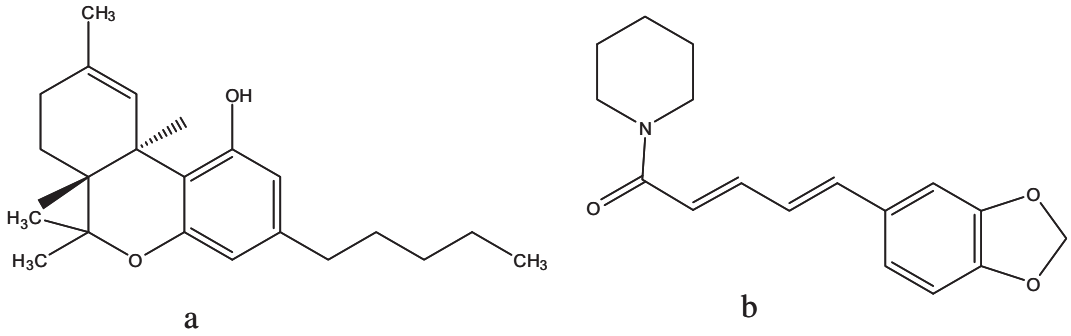

Fig. 2. Chemical structures of: (a) Delta-9-tetrahydrocannabinol (THC), (b) Piperine.

central nervous system (CNS). Myristicin is a major compound in nutmeg essential oil (accounting for 70% of the essential oil). The pharmacological effects, however, cannot only be attributed to myristicin (Conley, 2002). In this paper, the author reported a high binding activity to the CB1 receptor for both mace and nutmeg but, when myristicin was tested, no binding activities were detected (results not shown). It was suggested that the bioactivity, especially that related to the CNS, might result from a synergism between myristicin, saffrol and elemicin (Conley, 2002). Individually, these three compounds are psychoactive, but the effect is potentiated when they are present together (Conley, 2002). The activity shown in this screening can thus probably be explained by a synergism between myristicin and other compounds found in the nutmeg essential oil. Other spices which have high binding activity to CB1 are black pepper and turmeric. Black pepper alone is traditionally used to stimulate the appetite but piperine (1-piperoylpiperidine), the primary pungent alkaloid in black pepper, did not exhibit binding activity to CB1 (results not shown). This is not surprising, since the structures of myristicin (Fig. 1) and piperine (Fig. 2) are quite different from that of delta-9-tetrahydrocannabinol (THC), an agonist ligand of the CB1 receptor from *Cannabis sativa* (Fig. 2).

Additionally, the monoterpenes, α-pinene, camphene and borneol, which are commonly abundant in spices, showed no binding activity to either adenosine A1 nor CB1 receptors.

Inhibition of TNF-α accumulation was found at high levels for piment and turmeric while fenugreek, star anise, cinnamon, cloves, nutmeg, mace and black cardamom showed medium inhibition. Though nutmeg displayed a medium TNF-α inhibition activity, its major compound, myristicin, did not show any activity whatsoever (results not shown). Further work, to isolate active compounds from these two spices, is currently in progress in our laboratories.

Surprisingly, sesame seeds did not show significant inhibition of TNF-α accumulation, despite the high content of sesamin, its typical lignan with two fused tetrahydrofuran rings. Eudesmin, a furofuran-type lignan, isolated from *Magnolia fargessi*, exhibited

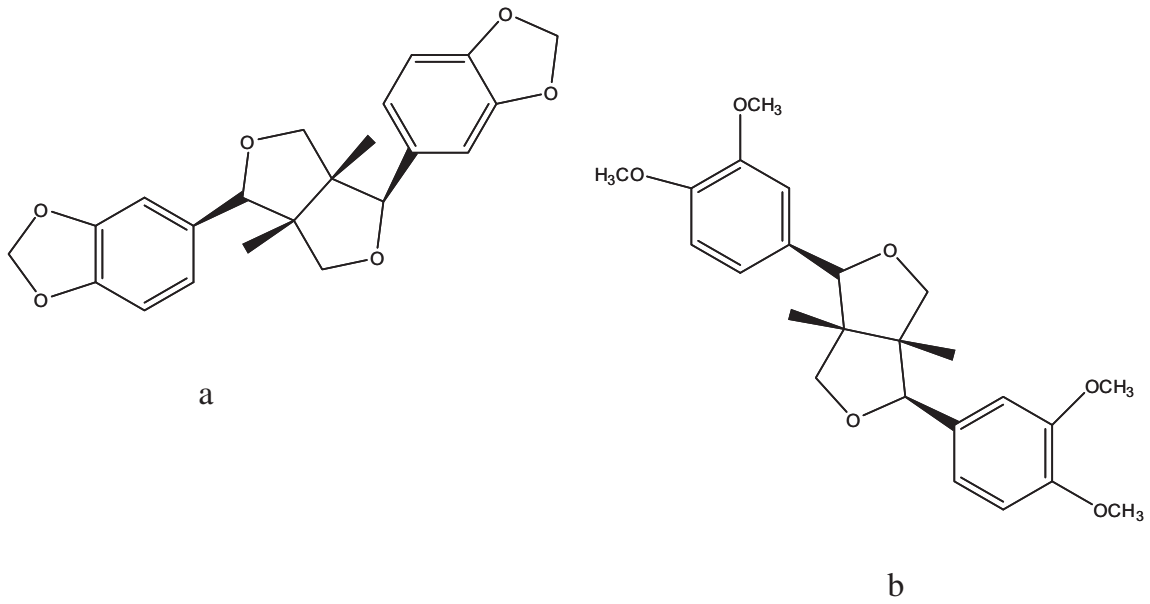

Fig. 3. Chemical structures of: (a) Sesamin, (b) Eudesmin.

inhibition of TNF-α with an IC_{50} of 51.3 μM (Cho, Yoo, Baik, & Park, 1999). Apparently, the substitution of the methoxy groups by two oxygenated furan groups in the sesamin structure could be responsible for the lower activity (Fig. 3).

Black onion seed is the only spice which showed a high activity on the induction of 3T3-L1 adipocyte differentiation. *In-vivo*, it has been reported to improve the lipid profile of albino rats by decreasing ITG, TC and LDL cholesterol and increasing HDL cholesterol as compared to controls (Buriro & Tayyab, 2007). In spite of reports of an anorexic effect of its petroleum ether extract on rats (Le et al., 2004), it has a low binding activity to the CB1 receptor, indicating that a different pathway may be involved. It would be interesting to perform further work to identify the active principles.

Spices, reported here to have activity more than 75%, were tested at a concentration of 40–70 μg/ml. Whether a significant effect can be observed at a reasonable amount for daily consumption needs further confirmation by *in vivo* studies. The daily consumption of spices worldwide varies, and its mostly reported as a mixture of common spices, such as red chilli, black/white pepper, mustard and turmeric. As reviewed by Lampe (2003), the average daily intake of common spices per person has been estimated at 0.5 g in Europe, 1.0 g in New Zealand and 4.0 g in the USA. More detail on the average daily intake per person of a few spices found active in our study in south India was reported by Pradeep, Geervani, and Eggum (1993): 3.08 g for red chilli, 0.33 g for black pepper and 0.87 g for turmeric. Although the *in vitro* active dose reported in this study seems reasonable compared with the aforementioned data, an *in vivo* evaluation, to verify the efficacy of these active spices, especially in humans, is needed. This preliminary study seems a good basis for further studies on the activity found.

4. Conclusion

Several of the spices tested with the bioassays in this study proved to be highly active. Sesame seeds and red chilli showed a very high binding activity to the adenosine A1 receptor while nutmeg, mace, black pepper and turmeric displayed high binding activity to the cannabinoid CB1 receptor. Piment and turmeric exhibited a strong inhibition of TNF-α accumulation, but black onion was the only spice with a high induction capacity of 3T3-L1 adipocyte differentiation. Several reference compounds, which are known to be bioactive major constituents of these spices, were tested with the respective bioassays, but none of them exhibited the activity which had been detected with the spices. This phenomenon, which is quite usual in many natural products, may be due to the fact that the responses to the tested activities are due to other, perhaps minor components or that the observed bioactivity is a product of synergism between several compounds. This is undoubtedly an interesting subject for further studies in which a different, more holistic approach (as that provided by the combination of GC–MS-based metabolomics and multivariate modelling) could be applied. This would allow the simultaneous detection of different types of metabolites in the sample and such information could then be used to detect active compounds and probable synergistic effects between them.

One of obesity stimulators is the overconsumption of adiposity-promoting food, such as high-carbohydrate and high-fat foods. Commercially, some companies have intensively advertised so called weight-controlling foods, such as food with low-fat but high-calcium, beverages rich in a green tea catechin extract, and deserts containing galactolipids. Although still quite preliminary, the results obtained in this screening suggest the potential of herbs and spices as active ingredients for the development of new weight management products.

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