Natural Antioxidants: Therapeutic Prospects for Cancer and Neurological Diseases

J.M. Matés*, J.A. Segura, F.J. Alonso and J. Márquez

Department of Biología Molecular y Bioquímica, Facultad de Ciencias, Campus de Teatinos, Universidad de Málaga, 29071 Málaga, Spain

Abstract: An all out war is continuously occurring between oxidants and antioxidants inside the cells. This mini-review will provide an updated revision of the function of some natural compounds having main roles in antioxidant function. We will point on some phytochemicals working at two outstanding targets, tumour cells and neurons.

Key Words: Celastrol, curcumin, flavonoid, polyphenol, proteasome, resveratrol, silymarin.

INTRODUCTION

Under normal conditions, antioxidant systems of the cell minimize the perturbations caused by reactive oxygen species (ROS). When ROS generation is increased to an extent that overcomes the cellular antioxidants, the result is oxidative stress, which can be defined as the imbalance between cellular oxidant species production and antioxidant capability [1]. Antioxidants are substances that delay or prevent the oxidation of cellular oxidizable substrates. The various antioxidants exert their effect by scavenging ROS, or by activating of a battery of detoxifying/defensive proteins [2]. The prevention of oxidation is an essential process in all organisms and cells, as decreased antioxidant protection may lead to cytotoxicity, mutagenicity and/or carcinogenicity [3].

Several strategies of antioxidative defence exist: while transition metals can be inactivated by chelating proteins, ROS can be reduced enzymatically, by the glutathione reductase (GR), glutathione peroxidase (GPX), catalase (CAT), and superoxide dismutase (SOD) or non-enzymatically by antioxidants [4]. Many biologically important compounds have been reported to have non enzymatic antioxidant functions as vitamin C (ascorbic acid), vitamin E (α-tocopherol), vitamin A (retinol), β-carotene, polyamines, melatonin (5-methoxy-N-acetyltryptamine), NADPH, urate, coenzyme Q-10 (ubiquinol), polyphenols, flavonoids, phytoestrogens, terpenes, lipoic acid, glutathione (GSH), cysteine, homocysteine, taurine, methionine, adenosine, s-adenosyl-L-methionine, nitroxides and selenium [5, 6]. Among the huge amount of antioxidant explored in recent years, there are some of them showing important effects on both cancer and neurological disorders [7]. In this mini-review we will focus on the antioxidant function of dietary antioxidants as the quinone triterpene celastrol, the polyphenols curcumin and resveratrol, and the flavonoid silymarin. Broadly, we will point out on these chemicals because of their therapeutical action on cancer and brain through a redox-based strategy.

*Address correspondence to this author at Department of Biología Molecular y Bioquímica, Facultad de Ciencias, *Campus de Teatinos*, Universidad de Málaga, 29071 Málaga, Spain; Tel: +34- 95-2133430; Fax: +34-95-2132041; E-mail: jmates@uma.es

1. NATURAL ANTIOXIDANTS AND CANCER

Cancer is an aggressive disease with multiple biochemical and genetic alterations. In this battle against cancer, natural antioxidants are considered as the most promising chemopreventive agents against various human tumours. However, a primary property of effective and acceptable chemopreventive agents should be free from toxic effects [8]. In spite of identification and use of effective cancer chemopreventive agents have become an important issue in public health-related research, it is necessary an evaluation of safety before recommending use of antioxidant supplements for chemoprevention. Tested chemopreventive and chemotherapeutic agents include sesquiterpenes (celastrol), phenols (catechins, resveratrol, curcumin), and isoflavonoids (silymarin) [9].

1.1. Celastrol

Celastrol [(2R,4aS,6aS,6aR,14aS,14bR)-10-hydroxy-2, 4a, 6a,6a,9,14a-hexamethyl-11-oxo-1,3,4,5,6,13,14,14b-octahydropicene-2-carboxylic acid] is a quinone methide triterpene (Fig. (**1**)) present in *Celastraceae* plants and is known to have multitude arrays of pharmacological activities. A common source of celastrol is found in vines or in the stem bark of other perennial creeping plants. *Celastraceae* has been used as a traditional medicine in China for hundreds of years. Celastrol can inhibit cancer cell proliferation and induce leukemic cell death *in vitro* [10]. In fact, celastrol and its methyl ester derivative, pristimerin, are significantly active against a panel of human cancer cell lines, including A549, MCF-7, HCT-8, KB, KB-VIN, U-87-MG, PC-3, 1A9,

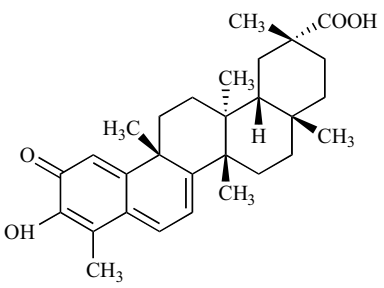

Fig. (1). Celastrol.

1389-5575/09 $55.00+.00

and PTX10 cell lines [11]. Regardless, it exhibits strong but non-specific *in vitro* cytotoxicity against P-388 murine lymphocytic leukemia cells [12].

The proteasome is a multi-enzymatic multi-catalytic complex, localized in the cytoplasm and nucleus of all eukaryotic cells, which regulates several cellular processes involved in cell-cycle regulation, apoptosis, and degradation of oxidized, unfolded and misfolded proteins. *In vitro*, *in vivo*, and clinical studies suggest the potential use of proteasome inhibitors as novel anticancer drugs. Celastrol potently and preferentially inhibits the chymotrypsin-like activity of purified 20S proteasome and human prostate cancer cellular 26S proteasome. Inhibition of the proteasome activity by celastrol in PC-3 (androgen receptor- or AR-negative) or LNCaP (AR-positive) cells results in the accumulation of ubiquitinated proteins and three natural proteasome substrates (IκB-α, Bax, and p27), accompanied by suppression of AR protein expression (in LNCaP cells) and induction of apoptosis. Treatment of PC-3 tumor-bearing nude mice with celastrol results in inhibition of the tumor growth. Multiple assays using the animal tumor tissue samples show *in vivo* inhibition of the proteasomal activity and induction of apoptosis after celastrol treatment [13].

Celastrol can disrupt a heat shock protein (Hsp)-cell division cycle (Cdc) interaction. This interaction in the superchaperone complex exhibits antitumor activity *in vitro* and *in vivo*, down-regulating many oncogenes simultaneously against cancer cells. Molecular docking and molecular dynamic simulations showed that celastrol blocks the critical interaction of Glu33 (Hsp90) and Arg167 (Cdc37). Immunoprecipitation confirmes that celastrol disrupted the Hsp90-Cdc37 interaction in the pancreatic cancer cell line Panc-1. In contrast to classic Hsp90 inhibitor (geldanamycin), celastrol does not interfere with ATP binding to Hsp90. However, celastrol induces Hsp90 client protein degradation (CDK4 and Akt), and increased Hsp70 expression. Celastrol induces apoptosis *in vitro* and significantly inhibits tumor growth in Panc-1 xenografts. Moreover, celastrol effectively suppresses tumor metastasis in transgenic mouse model with pancreatic islet cell carcinogenesis [14]. Celastrol (1 μM) sensitizes melanomas to apoptosis and inhibits their growth and metastatic potential by molecules that mimic the activities of activating transcription factor 2 (ATF2)-driven peptides. Celastrol increases c-Jun transcriptional activity. Derivatives of celastrol have been identified as potent inducers of cell death in mouse and human melanomas. Celastrol and its derivative (CA19) can also efficiently inhibit growth of human and mouse melanoma tumors and reduce the number of lung metastases in xenograft mouse models [15].

Celastrol can activate heat shock gene transcription synergistically with other insults and exhibits cytoprotection against subsequent exposures to other forms of lethal cell stress [16]. Celastrol is a potent activator of the mammalian heat shock transcription factor HSF1. Transcriptional profiling revealed that celastrol treatment induces a battery of oxidant defense genes in addition to heat shock genes [17]. Although AR-mediated signaling is central to prostate cancer, the ability to modulate AR signaling states is limited. Celastrol is an AR activation inhibitor that inhibits Hsp90 activity and Hsp90 clients, upon induction of apoptosis [18, 19].

Notably, celastrol potentiates the apoptosis induced by tumor necrosis factor α (TNF-α), a potent proinflammatory cytokine, and inhibits invasion, both regulated by nuclear factor kappaB (NF-κB) activation. TNF-α induces the expression of gene products involved in antiapoptosis (IAP1, IAP2, Bcl-2, Bcl-XL, c-FLIP, and survivin), proliferation (cyclin D1 and COX-2), invasion (MMP-9), and angiogenesis (VEGF), and celastrol treatment suppresses their expression. Because these gene products are regulated by NF-κB, celastrol can be considered as an inhibitor of NF-κB. Recent studies indicate that TNF-induced IKK (inhibitor of NF-κB kinase) activation requires activation of the ubiquitin-dependent kinase TAK1, and indeed, celastrol inhibits the TAK1-induced NF-κB activation [20]. In fact, celastrol inhibits a variety of stimuli-induced NF-κB-regulated gene expression and the DNA-binding of NF-κB in different cell lines. Importantly, celastrol inhibits IKK activity and the constitutively active IKK β activity without either affecting the NF-κB activation or directly suppressing the DNA-binding of activated NF-κB. Celastrol prevents not only lipopolysaccharide (LPS)-induced mRNA expression of inducible nitric oxide synthase (iNOS) and TNF-α, but also TNF-α-induced Bfl-1/A1 expression, a prosurvival Bcl-2 homologue. Consistent with these results, celastrol significantly suppresses the production of NO and TNF-α in LPS-stimulated RAW264.7 cells [21].

1.2. Curcumin

High cancer mortality rates aimed at identifying cancer chemopreventive agents, especially naturally occurring compounds derived from the diet, which have the advantage of being relatively non-toxic [22]. Polyphenols represent a wide class of phenolic phytochemicals which constitute an important component of the human diet, and that can be administered at pharmacological doses (milligrams) or consumed as a polyphenol-rich diet (grams). The biological properties of polyphenols are strongly affected by their chemical structure. Recent studies have shown that natural polyphenols can also modulate the functionality of the proteasome [23]. Following, we will describe antioxidant and anti-inflammatory properties, as well as the mode of action of curcumin, and its therapeutic usage against cancer. In Asian countries, curcumin was consumed in the diet in amounts in excess of 100 mg/day without any side effects. In Southeast Asia, up to 4 g per adult/day appears to lower the incidence rate of colorectal cancer. Further studies show that curcumin prevents cancer in many tissues of mice and rats and has been associated with regression of established solid malignancies in humans [22]. Curcumin (1, 7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5- dione) is a diferuloylmethane (Fig. (**2**)). It is a biologically active compound extracted from *Curcuma* species. This polyphenol is major component of turmeric, the powdered rhizome from this plant, frequently used in Southeast Asia to give yellow color and flavor to curries. It is also

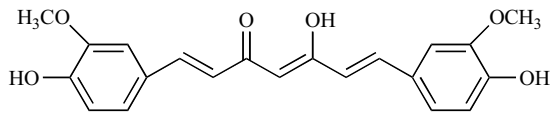

Fig. (2). Enol tautomeric form of curcumin.

used as a cosmetic and in some medical preparations. This spice and food-coloring agent has been considered as nutraceutical because of its strong anti-inflammatory, antitumour and antioxidant properties. The possible mechanisms of the antiproliferative and apoptotic effects of curcumin have been studied, among others, in rat aortic smooth muscle cell line (A7r5). Curcumin inhibits cell proliferation, arrestes the cell cycle progression and induces cell apoptosis in these vascular smooth muscle cells [24]. It produces similar effect on human leukemia HL-60, mouse leukemia WEHI-3 cells, and on the population of B cells from murine leukemia *in vivo* [25].

Curcumin may inhibit the transduction signals leading to DNA synthesis. Besides, curcumin protects against phorbol ester-mediated promotion of mouse skin cancers modulating the expression of proto-oncogenes, c-fos, c-jun and c-myc. The antiproliferative and the apoptotic effect may partly be mediated through inhibition of protein tyrosine kinase and protein kinase C (PKC) activities, and c-myc mRNA and Bcl-2 mRNA expression. As a result, curcumin may be useful as a template for the development of new drugs [24]. Mechanisms of curcumin-mediated anti-initiation have been investigated in mice employing benzo[a]pyrene (B[a]P) as a model carcinogen. Induction of levels of glutathione S-transferase, and NAD(P)H:quinone oxidoreductase-1 by dietary curcumin in mice paralleled the curcumin-mediated activation of nuclear erythroid-related factor 2 (Nrf2), leading to increased detoxification of B[a]P. In agreement with the observed curcumin-transcriptional regulatation of phase I and phase II enzymes, pretreatment with dietary curcumin resulted in significant reduction of B[a]P-induced DNA adduct, oxidative damage and inflammation [26]. Other studies reports the protective effect of curcumin on B[a]P induced DNA damage in human peripheral blood lymphocyte cells [27]. Curcumine is also useful in the prevention of skin cancer and other UV-mediated damage in humans [28]. Topical or dietary administration of curcumin reduces tumor incidence at other organ sites (Table **1**). Additionally, after feeding with a 2% curcumin diet the incidence of lymphomas/leukemias induced by dimethylbenz[a]anthracene is strongly reduced in mice [29]. The anti-inflammatory effect of curcumin is most likely mediated through its ability to inhibit cyclooxygenase 2 (COX-2), lipoxygenase, and iNOS, which are important enzymes that mediate inflammatory processes and cancer. Hence, the past few decades have witnessed intense research devoted to the antioxidant and anticancer properties of curcumin [30, 31].

Chronic irradiation causes cancer, and dysfunctions to almost all organ of the body. Curcumin has been evaluated for its radioprotective and radiosensitizing activities. Curcumin exerts a dual mode of action after irradiation depending on its dose. It has been reported to protect various study systems against the deleterious effects induced by ionizing radiation and to enhance the effect of radiation. Administration of curcumin in patients will be able to kill the tumor cells effectively by enhancing the effect of radiation and, at the same time, protect normal cells against the harmful effects of radiation. The available information on curcumin suggests that the radioprotective effect might be mainly due to its ability to reduce oxidative stress and inhibit transcription of genes related to oxidative stress, whereas the radiosensitive activity might be due the upregulation of genes responsible for cell death [32].

Prominent among the signaling events inhibited by curcumin are phosphorylations catalyzed by protein kinases, c-Jun/AP-1 activation and prostaglandin biosynthesis. Curcumin may promote the translocation of Bax from the cytosol to the mitochondrial membrane, leading to the release of cytochrome *c*. Indeed, curcumin causes apoptosis and DNA fragmentation of human renal Caki cells, which is preceded by the sequential dephosphorylation of Akt, down-regulation of the anti-apoptotic Bcl-2, Bcl-XL and IAP proteins, release of cytochrome *c* and activation of caspase 3 and caspase 7 [33]. Nonetheless, liver and kidney carcinogenesis in rats is not altered by curcumin treatment. The lack of chemoprevention of liver and kidney tumors in these rats by curcumin may be caused by enhanced toxicity and oxidative stress due to copper ions that catalyze Haber-Weiss and Fenton type reactions, thus producing hydroxyl radicals. Consequently, curcumin should be contra-indicated for patients suffering

Table 1. Natural Antioxidants, Source, Cancer, Targets, and Key References. Type of Cancers where Positive Effects have been Described are Enclosed. Main Molecular Targets are Also Included

Compound	Origin	Cancer	Main Targets	References[a]
Celastrol	*Tripterygium wilfordii, Celastrus orbiculatus, Koboona ochracea*	pancreas, skin	c-Jun, Hsp, NF-κB, NO, proteasome, TNF-α	[13-15, 20, 21]
Curcumin	*Curcuma longa* Linn	colon, duodenum, forestomach, leukemia, skin	Bcl-2, caspases, cytochrome c, PKC, proteasome	[21, 22, 24, 28, 29, 33]
Resveratrol	*Smilacis chinae*	brain, breast, colon, oesophagus, gastric, leukaemia, lung, pancreas, prostate, skin	Bax, Bcl-2, caspases, COX, CYP, GSH, iNOS, NF-κB, p53	[23, 39, 40, 43, 45]
Silymarin	*Silybum marianum* (L.) Gaertneri	bone, bladder, breast, kidney, liver, lung, ovary, skin, tongue	Bax, COX, HIF-1α, iNOS, NF-κB, PARP, p53, p21, SIRT1, VEGF	[50, 53, 56, 57]

[a]To refer to the numbered reference in the text.

from inherited and acquired metal storage diseases that include patients with hepatitis C virus infection [34].

In spite of curcumin´s anticarcinogenic effects, some studies suggest that this natural compound possesses both pro- and antioxidative effects. Really, curcumin can induce DNA damage to both the mitochondrial and nuclear genomes in human hepatoma G2 cells. The lack of DNA damage at low doses suggested that curcumin (5 μg/ml) does not induce DNA damage and may play an antioxidant role in carcinogenesis. But at higher doses (20-40 μg/ml), curcumin imposes oxidative stress. In fact, in human peripheral blood lymphocytes, curcumin itself resulted in ROS that damage DNA. Besides, the extensive mitochondrial DNA damage might be an initial event triggering curcumin-induced cell death [22]. The effects of administration of curcumin on lipid peroxidation, hepatic GSH, and hematopoietic cells have ben examined during N-nitrosodiethylamine and phenobarbital promoted hepatocarcinogenesis in rats. Treatment with curcumin prevents the drop in hepatic GSH antioxidant defense, decreases lipid peroxidation, minimizes the histological alterations, but shows toxic effects on the hematopoietic cells [35]. Curcumin may exhibit carcinogenic potential through oxidative DNA damage by its metabolite O-demethyl curcumin, which is synthethized by the action of cytochrome P450 (CYP) in the presence of Cu(II) [36]. Lastly, curcumin modulates multiple cellular machineries, such as the ubiquitin proteasome system. In HeLa cells treated with curcumin was found a reduction of almost 30% in the activities of the 20S proteasome, accompanied by a marked accumulation of ubiquitin-protein conjugates. Like resveratrol, curcumin is able to attenuate the expression of the ubiquitin-proteasome proteolytic pathway [21].

1.3. Resveratrol

Stilbenes have been shown to protect lipoproteins from oxidative damage and to have cancer chemopreventive activity [37]. Trans-resveratrol (Fig. (**3**)), 3,5,4'-trihydroxystilbene or (E)-5-(*p*-hydroxystyryl)resorcinol, is a phytoalexin produced naturally by several plants when under attack by pathogens such as bacteria or fungi. Mostly, resveratrol is found in the skin and seeds of red grapes. There have been dozens of studies of anti-cancer activity of resveratrol in animal models. In a similar way, clinical trials to investigate the effects on colon cancer and melanoma are currently recruiting patients [38]. *In vitro*, resveratrol interacts with multiple molecular targets, and has positive effects on many tumour cells (Table **1**). Effective concentrations can be reached in the intestinal lumen after consumption of plant foods or food supplements. Nevertheless, the study of pharmacokinetics of resveratrol in humans concluded that even high doses of resveratrol (50 mg–1000 mg) might be insufficient to achieve resveratrol concentrations required for the systemic prevention of cancer. Resveratrol given orally also had no effect on leukemia and lung cancer; however, injected intraperitoneally, slowed the growth of metastatic Lewis lung carcinomas in mice. Resveratrol also reduces the number and size of the esophageal tumors in rats. In several studies, small doses of resveratrol, given prophylactically, reduces or prevents the development of intestinal and colon tumors in rats given different carcinogens. Injected in high doses into mice (40 mg/kg body weight), resveratrol slowed the growth of neuroblastomas [39].

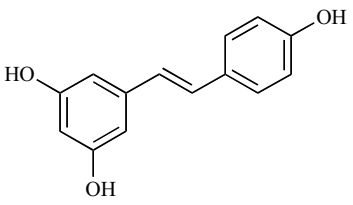

Fig. (3). Resveratrol.

Nrf2, a redox-sensitive transcription factor, is involved in transcriptional regulation of many antioxidant genes. Cigarette smoke is known to cause oxidative stress and deplete GSH levels. Resveratrol has antioxidant signaling properties by inducing GSH biosynthesis *via* the activation of Nrf2 [40]. In last years, it has been proposed to have beneficial effects in cancer pathologies that may involve oxidative stress. Resveratrol is able to prevent oxidative damage to cellular DNA in C6 glioma cells [41]. Resveratrol also induces cell loss by apoptosis [42]. Resveratrol has been also evaluated as inhibitor of the NF-κB pathway. NF-κB represents an important and very attractive therapeutic target for drugs to treat many diseases, as well as for being involved in the control of the expression of genes encoding inducible enzymes (COX-1, COX-2 and iNOS) related to oxidative stress [43]. Using a mouse mammary organ culture model, carcinogen-induced preneoplastic lesions were significantly inhibited by resveratrol [44].

Besides, resveratrol is a selective human CYP inhibitor [45], and may have utility in protecting against the environmental pollutant chromium. The protective effects of this free radical scavenger against Cr(III)-induced carcinogenesis may relate to their direct scavenging ability [46]. Resveratrol shows a strong effect on breast cancer resistance protein induction in MCF-7 wild-type cells. Apart from the modulation of detoxifying enzymes in the intestine, induction of breast cancer resistance protein by dietary constituents may contribute to the detoxification of food-derived procarcinogens such as B[a]P [47]. Resveratrol is also a selective estrogen receptor modulator. It has been evaluated for their potential in the next generation of prostate cancer therapies, exhibiting specific inhibition of kinase activities [48]. Mechanism of action of resveratrol is influenced by numerous intracellular pathways leading to cell growth arrest through the inhibition of extracellular signal-regulated kinases (ERK1/2)-mediated signal transduction pathways, the downregulation of β-catenin expression, the inhibition of cyclin-dependent kinases CDK1 and CDK4 activities, and the induction of apoptotic events (Table **1**). Conversely, moderate to high doses of resveratrol (1-100 mg/kg diet) can damage lymphocyte DNA and induce low levels of preneoplastic liver lesions in experimental animals [49].

1.4. Silymarin

Flavonoids are the most abundant polyphenols in our diets (Fig. (**4**)). They can be found in fruit, vegetables, flowers, seeds, sprouts and beverages, providing them with much of their flavour and colour. Flavonoids have been shown to act as scavengers of various oxidizing species, such as hy-

droxyl radical, peroxy radicals or superoxide anions, due to the presence of a catechol group in the B-ring in conjunction with several hydroxyl groups (Fig. (**5**)).

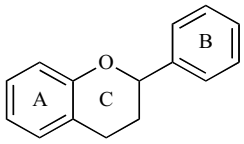

Fig. (4). Basic structure of flavonoids.

Recent years have seen an explosion of scientific papers that deal with drugs from the fruits of milk thistle, and its active substance silymarin containing approximately 65-80% silymarin flavolignans (silymarin complex) with small amounts of flavonoids and approximately 20-35% fatty acids and other polyphenolic compounds. The key constituent in milk thistle seed is silymarin, and the major component of this complex is silybin that is synonymous with silibinin [3,5,7-trihydroxy-2-(3-(3-hydroxy-4-methoxyphenyl)-2-(hydroxymethyl)-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)chroman-4-one], together with other flavonolignans (Fig. (**5**)), namely isosilybin, silychristin (**5**), silydianin (**6**), and flavonoid taxifolin [(2R,3R)-3,3',4',5,7-pentahydroxyflavanone, or (2R,3R)-dihydroquercetin]. Silybin A (**1**), silybin B (**2**), isosilybin A (**3**), and isosilybin B (**4**), shows most consistent antiproliferative effects in three different human prostate carcinoma LNCaP, DU145, and PC3 cell lines. In further expanding these preliminary observations, recently it was found that isosilybins exert growth inhibition and cell death together with a strong G1 arrest and apoptosis in human prostate carcinoma LNCaP and 22Rv1 cell. Several studies using *in vitro* and *in vivo* cancer models suggest a potential therapeutical effect of silymarin, suppressing the proliferation of tumor cells in additional cancers (Table **1**). Other studies have shown that silymarin and silybin down-regulate epidermal growth factor receptor (EGFR) signaling *via* the inhibition in the expression and secretion of growth factors, and by inhibiting growth factor binding and activation of EGFR and subsequent impairment of downstream mitogenic events cause anti-cancer efficacy in different tumor cell lines [50].

Pharmacokinetic studies have shown that silymarin is absorbed by the oral route and that it distributes into the alimentary tract (liver, stomach, intestine, pancreas). It is mainly excreted as metabolites in the bile, and is subject to enterohepatic circulation. Toxicity is very low. Moreover, silymarin is included in the pharmacopoeia of many countries under the trademark Legalon™ or Hepatron™, being devoid of embryotoxic potential. There are no known contraindications to milk thistle supplements. There is, however, a caution for HIV patients, because some medications taken by individuals diagnosed with HIV/AIDS such as protease inhibitors are processed by the liver enzyme CYP which is decreased by silymarin [51, 52]. Bioavailability of silybin has been increased when combined with phosphaditylcholine as Silipide, Siliphos or IdB 1016. Silybin synergizes human prostate carcinoma DU145 cells to doxorubicin, cisplatin, and carboplatin inducing growth inhibition and apoptotic death. Similar synergistic effects have been reported in breast and ovarian cancer cell lines [50]. Silymarin also

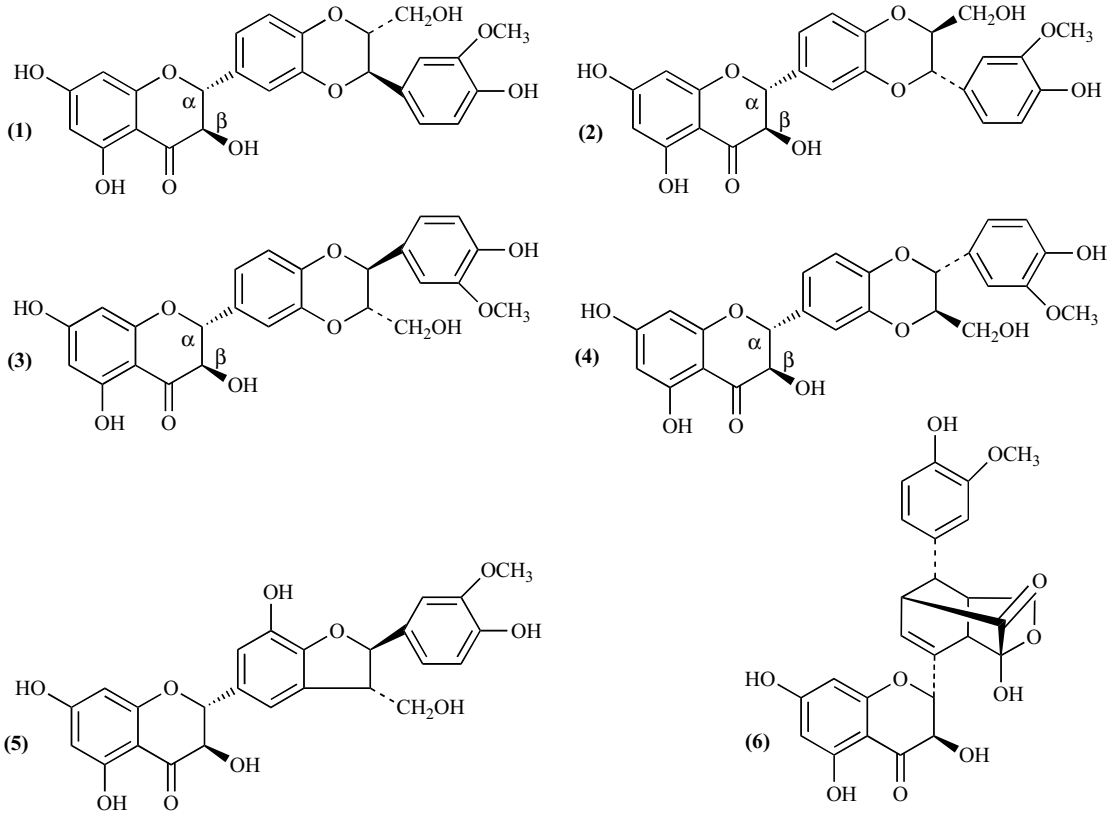

Fig. (5). Major components of silymarin. Silybin A (**1**), silybin B (**2**), isosilybin A (**3**), isosilybin B (**4**), silychristin (**5**), and silydianin (**6**).

modulates imbalance between cell survival and apoptosis through interference with the expressions of cell cycle regulators and proteins involved in apoptosis. Additionally, silymarin shows anti-metastatic activity. Silymarin induces growth arrest at the G1 and G2 checkpoints, and, in lower doses induces the growth arrest through ERK1/2 inhibition and in higher doses leads to apoptosis through mitogen activated protein kinase (MAPK)/c-Jun pathway. Anti-inflammatory effects of silymarin are related to inhibition of the transcription factor NF-κB, which regulates and coordinates the expression of various genes involved in cell survival, differentiation and growth [50].

Of particular significance, silymarin was found to modify specifically the functions related to various transporters and receptors located in the cell membranes; that it is, organic anion uptake transporter peptides, ABC transporters, bile salt export pump, as well as TNF-α-dependent phenomena. In the cytoplasm, some antioxidant properties and the inhibition of the lipoxygenase pathway seem quite selective and could concur to the antitoxic effects. Some effects, like the inhibition of iNOS and NF-κB, are indicative of DNA/RNA-mediated effects. Topical and systemic silymarin has skin protective properties against UV-induced damage in epidermis and causes an up-regulation of tumour-suppressor genes p53 and p21 [53]. In fact, topical treatment to mouse skin prevents photocarcinogenesis. Silymarin treatment also resulted in significant reduction of UVB-induced immunosuppressive cytokine interleukin-10 producing cells and its production. Topical treatment of silymarin also resulted in significant reduction of the number of inducible iNOS expressing cells concomitant with decrease in H_2O_2 and NO production [54]. Silybin is the most active agent preventing photocarcinogenesis. Analyses of skin tumors show a strong decrease in iNOS and COX-2 levels by silybin. Simultaneously, silybin decreased UVB-caused increase in cell proliferation and microvessel density in tumors. Hypoxia-inducible factor 1α (HIF-1α) and vascular endothelial growth factor (VEGF) protein levels are equally decreased by this molecule [55]. Antiproliferative and proapoptotic effects of silybin are associated with down-regulation of ERK1/2 and Akt phosphorylation as well as cyclin D1 expression. Antiangiogenic effect of silybin is coupled with a strong decrease in iNOS and NOS3, COX-1 and COX-2, and HIF-1α and VEGF. These findings suggest *in vivo* antitumor efficacy of silybin involving its antiproliferative, proapoptotic, and antiangiogenic activities. The inhibition of ERK1/2 and Akt signaling may account for antiproliferative and proapoptotic effects, whereas down-regulation of NOS, COX, HIF-1α, and VEGF expression could lead to antiangiogenic effect of silybin against colorectal carcinoma [56].

The treatment with silymarin during the promotion phase of induced rat tumorigenesis exerts chemopreventive ability against tongue squamous cell carcinoma through modification of phase II enzymes activity, decreasing cell proliferation and increasing apoptotic index [57]. Administration of silymarin increases the activities of antioxidant enzymes like SOD, CAT, GPX, and GR together with a decrease in the levels of malondialdehyde, in erythrocytes exposed to H_2O_2. Silymarin application extensively reduces GSH depletion and ROS production as well as lipid peroxidation in UVA irradiation-induced damage in human keratinocytes. Formation of UVA-induced DNA single strand breaks and caspase-3 activity are similarly decreased by silymarin [50]. Silymarin inhibits invasion and motility of SCC-4 tongue cancer as well as A459 lung cancer cells by down-regulating matrix metallopeptidase 2 (MMP-2), through reducing ERK1/2 and Akt phosphorylation, which in turn led to the reduced invasiveness of the cancer cells. Likewise, in human osteosarcoma MG-63 cells, silymarin inhibits cell invasiveness by reducing MMP-2 expression, as well as IL-6-induced ERK 1/2 and c-Jun phosphorylation [50]. It also induces apoptotic cell death in CH11-treated human malignant melanoma A375-S2 cells by increasing the expression of Fas-associated proteins with death domain (FADD), a downstream molecule of the death receptor pathway followed by cleavage of procaspase-8 that induces apoptosis. In UV-irradiated human malignant melanoma A375-S2 cells, silymarin activated silent information regulator 1 (SIRT1), a cell survival protein, down-regulated Bax and poly(ADP-ribose) polymerase (PARP) expression with decreased release of cytochrome *c* and induced G2-M arrest. Silymarin also promotes apoptosis of human hepatoma HuH7 cells by down-regulating survivin and up-regulating activated caspase-3 and caspase-9. Other studies have demonstrated that silymarin decreases the secreted VEGF levels in prostate DU145 and breast MCF and MDA-MB-468 cancer cells [50]. Silymarin equally inhibits the growth of tumors in several rodent models, including urethane-induced lung tumors in mice. Regarding mechanism, it decreases lung tumor expression of VEGF and iNOS and COX-2, two enzymes that promote lung tumor growth and progression by inducing VEGF expression [58].

2. NATURAL ANTIOXIDANTS AND NEUROLOGICAL DISEASES

Many lines of evidence suggest that oxidative stress resulting in ROS generation and inflammation play a pivotal role in the age-associated cognitive decline and neuronal loss in neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's (PD) and Huntington's diseases (HD). Because free-radical-mediated peroxidation of membrane lipids and oxidative damage of DNA and proteins are believed to be associated with a variety of neurodegenerative diseases, natural antioxidants are thought to play a vital role against these pathological conditions. In recent years, there has been increasing interest in investigating terpenes and polyphenols from botanical source for possible neuroprotective effects against these diseases. Polyphenols and flavonoids have been widely used in treating inflammatory diseases in man, and they are well tolerated; therefore, they are promising therapeutic candidates for the treatment of human neurodegenerative diseases.

2.1. Celastrol

Sesquiterpene celastrol has effectively been used in the treatment of autoimmune diseases, chronic inflammation, asthma and neurodegenerative diseases [10]. Neurodegenerative disorders such as AD, PD, and amyotrophic lateral sclerosis (ALS) are protein misfolding disorders that are characterized by the neuronal accumulation of protein aggregates. Manipulation of the cellular stress-response involving induction of Hsps in differentiated neurons offers a therapeutic

strategy to counter conformational changes in neuronal proteins that trigger pathogenic cascades resulting in neurodegenerative diseases. Hsps are protein repair agents that provide a line of defense against misfolded, aggregation-prone proteins. These proteins are not induced in differentiated neurons by conventional heat shock. Celastrol induces expression of a wider set of Hsps, including Hsp70, in differentiated human neurons grown in tissue culture [59]. Heat shock proteins are also protective against the harmful effects of mutant expanded polyglutamine repeat proteins that occur in diseases such as HD, prompting the search for pharmacologic compounds that increase Hsp expression in cells as potential treatments for this and related diseases. Celastrol significantly decreases killing of cells expressing mutant polyglutamine protein. This effect requires the presence of the transcription factor responsible for mediating inducible Hsp gene expression, HSF1. These results suggest the potential of celastrol as a therapeutic agent in the treatment of human polyglutamine expansion diseases [60]. Alterations in protein folding and the regulation of conformational states have become increasingly important to the functionality of key molecules in signaling, cell growth, and cell death. Molecular chaperones, because of their properties in protein quality control, afford conformational flexibility to proteins and serve to integrate stress-signaling events that influence aging and neurological diseases [16].

Stress tolerance in neurons is not solely dependent on their own Hsps but can be supplemented by Hsps from adjacent glial cells. Then, application of exogenous Hsps at neural injury sites is an effective strategy to maintain neuronal viability. Arimoclomol, a coinducer of Hsps, delayes progression of ALS in a mouse model in which motor neurons in the spinal cord and motor cortex degenerate. Following hyperthermia, constitutively expressed Hsp70 increases in synapse-rich areas of the brain where it associates with Hsp40 to form a complex that can refold denatured proteins [61]. There is substantial evidence that both inflammation and oxidative damage contribute to the pathogenesis of motor neuron degeneration in the SOD transgenic mouse model of ALS. Celastrol exerts potent anti-inflammatory and antioxidative effects in this model, acting potently to increase expression of Hsps including Hsp70. Celastrol treatment significantly improved weight loss, motor performance and delayed the onset of ALS. Survival of celastrol-treated mice increases. Cell counts of lumbar spinal cord neurons confirmed a protective effect. Celastrol treatment reduces TNF-α, iNOS, and CD40 in the lumbar spinal cord sections of celastrol-treated mice compared to untreated mice [62].

Mice treated with celastrol before and after injections of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a dopaminergic neurotoxin, produces a model of PD. A 48% loss of dopaminergic neurons induced by MPTP in the substantia nigra is significantly attenuated by celastrol treatment. Moreover, this treatment significantly reduces the depletion in dopamine concentration induced by MPTP. Similarly, celastrol significantly decreases the striatal lesion volume induced by 3-nitropropionic acid, a neurotoxin used to model HD in rats. Celastrol induces Hsp70 within dopaminergic neurons and decreases NF-κB immunostainings as well as astrogliosis [63].

The presence of nitrotyrosine in the cell bodies of neurons in AD suggests that peroxynitrite contributes to the pathogenesis of the disease. A drug with antioxidant and anti-inflammatory activity may prevent neuronal degeneration in AD. Celastrol (1 nM) was found to suppress the production by human monocytes and macrophages of the proinflammatory cytokines TNF-α and IL-1β. Celastrol also decreases the induced expression of class II major histocompatibility complex (MHC) molecules by microglia. Of interest, in macrophage lineage cells and endothelial cells, celastrol decreases induced but not constitutive NO production. Celastrol (1-5 nM) administered to rats significantly improve their performance in memory, learning and psychomotor activity tests [64]. Consequently, celastrol is a promising neuroprotective agent for the treatment of ALS, PD, HD and AD.

2.2. Curcumin

Oxidative stress has been regarded as an important underlying cause for neuronal damage and curcumin a valious tool fighting against it. Ischemic changes are preceded by a rapid increase in lipid peroxidation and followed by decrease in mitochondrial membrane potential, increased cytochrome *c* release, and subsequently caspase-3 activation and apoptosis. Administration of curcumin or by supplementation to the diet significantly attenuates ischemia-induced neuronal death as well as glial activation. Curcumin administration also decreases apoptotic indices. The biochemical changes resulting from curcumin correlated well with its ability to ameliorate the changes in locomotor activity induced by cerebral ischemia/reperfusion (I/R) injury [65]. Curcumin treatment attenuates forebrain ischemia-induced neuronal injury and oxidative stress in hippocampal tissue [66], and significantly attenuates MPTP-induced striatal dopamine depletion in mice, which is in accordance with the increase in the density of dopaminergic neurons when compared with MPTP-treated mice [67]. Together, these findings attribute the neuroprotective effect of curcumin against I/R-induced neuronal damage to both, its antioxidant capacity and its ability for modifying the signaling cascade leading to apoptosis.

Curcumin derivatives seem to be the most promising neuroprotective agents. Manganese complexes of curcumin and diacetylcurcumin exhibit potent SOD-like activity *in vitro*. NO is a free radical playing a multifaceted role in the brain and its excessive production is known to induce neurotoxicity. Curcumin and diacetylcurcumin protect against induced neuronal cell death by suppression of induced increase in NO levels probably by their NO scavenging and antioxidative activities [67, 68]. Consequently, these manganese complexes of curcumin may be useful neuroprotective agents in the treatment of acute brain pathologies associated with NO-induced neurotoxicity and oxidative stress-induced neuronal damage (Table **2**).

In the central nervous system, the heme oxygenase system has been reported to be active and to operate as a fundamental defensive mechanism for neurons exposed to an oxidant challenge. Curcumin potently induces heme oxygenase-1 expression and activity in rat astrocytes [69]. A significant expression of quinone reductase and glutathione S-transferase, two members of phase II detoxification en-

Table 2. Natural Antioxidants, Neurological Diseases, Targets, and Key References. Neurological Diseases where Positive Effects have been Described are Enclosed. Main Molecular Targets are Also Included

Compound	Neurological Diseases	Main Targets	References[a]
Celastrol	AD, ALS, HD, PD	CD40, Hsp, iNOS, NF-κB, TNF-α	[59, 62, 64]
Curcumin	AD, epilepsy, stroke, traumatic brain injury, vascular dementia	Abeta, Bcl-2, caspase-3, cytochrome c, GSH, iNOS, NO, PARP	[65, 67, 68, 71-74]
Resveratrol	AD, HD, stroke	Abeta, AMPK, caspase-7, NF-κB, PKC, SIRT1	[75-78, 80, 84, 85]
Silymarin	AD	NO, NF-κB, TNF-α	[89-91]

[a]To refer to the numbered reference in the text.

zymes, was found in astrocytes exposed to curcumin [70]. Exposure of oxidants to neurons results in cytochrome *c* release, and subsequent activation of caspase-3 and PARP cleavation, and cell apoptosis. Treatment with curcumin abrogates cytochrome *c* release, blocks activation of caspase 3, and alters the expression of Bcl-2 family. Further curcumin treatment also prevents cellular GSH and decreases intracellular ROS generation in cortical neurons [71].

Curcumin confers significant protection against neurotoxic and genotoxic agents. The neurotoxic amyloid beta peptide (Abeta) elicits a poisonous effect *in vitro* and *in vivo*. AD involves Abeta accumulation, oxidative damage, and inflammation, and risk is reduced with increased antioxidant and anti-inflammatory consumption. Curcumin has potent anti-inflammatory and antioxidant activities and can suppress cognitive deficits, and amyloid accumulation. The molecular structure of curcumin suggested potential Abeta binding. *In vivo* studies showed that curcumin injected peripherally into mice crossed the blood-brain barrier and bound plaques. Hence, curcumin directly binds small β-amyloid species to block aggregation and fibril formation *in vitro* and *in vivo*. Curcumin (0.125 μM) effectively disaggregates Abeta as well as prevents fibril and oligomer formation, supporting the rationale for curcumin use in clinical trials preventing or treating AD [72]. Whereas infusion of Abeta peptides induces oxidative damage, synaptophysin loss, microglial response, and widespread Abeta deposits, dietary curcumin suppresses oxidative damage and synaptophysin loss. Because of its low side-effect profile and long history of safe use, curcumin may find clinical application for AD prevention [73], exerting general anti-aging benefits [74]. These studies give additional support to the possible use of curcumin as a dietary preventive agent against oxidative stress-related neurological diseases.

2.3. Resveratrol

Resveratrol has been demonstrated to be effective against cerebral ischemic injury, having a therapeutic role in stroke [75-78], and been able to protect hippocampal cells against toxic effects induced by Abeta peptides [79]. Most of the neuroprotective actions of resveratrol are associated with its intrinsic radical scavenger properties. Thus far, however, other mechanisms for neuroprotection have been proposed, including activation of PKC, as well as suppression of caspase-7 activity and NF-κB DNA binding activity [80]. Resveratrol does not inhibit Abeta production, because it has no effect on the Abeta-producing enzymes β- and γ-secretases, but promotes instead intracellular degradation of Abeta *via* a mechanism that involves the proteasome. Indeed, the resveratrol-induced decrease of Abeta could be prevented by several selective proteasome inhibitors and by siRNA-directed silencing of the proteasome subunit β5 [81]. Resveratrol also inhibits N-methyl-D-aspartic acid (NMDA)-induced neuronal death, and increase Ca^{2+} levels in cultured cortical neurons [80].

Piceatannol (trans-3,4,3',5'-tetrahydroxystilbene), has a structure homologous to resveratrol (Fig. (**6**)). Piceatannol treatment attenuates the intracellular accumulation of ROS induced by treatment of PC12 cells with Abeta, thereby protecting PC12 cells from oxidative stress [82]. Resveratrol, piceatannol (**1**) and catechins (**2**) have a synergistic protective action. Such a protective effect probably is not due only to their antioxidant activity. The different chemical and biological activity shown by these compounds on several cell types, and the complexity of the Abeta toxicity may explain the synergistic protective effect, suggesting that the utilization of different compounds with synergistic activity may protect more effectively from complex mechanisms of toxicity [83]. Taken together, these results support the hypothesis that dietary intake of resveratrol and piceatannol may exert beneficial effect in aging.

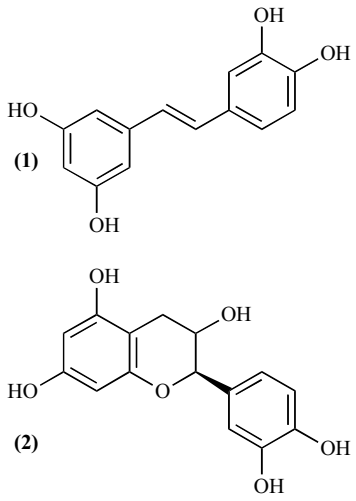

Fig. (6). Piceatannol **(1)** and catechin **(2)**.

On the other hand, it is well established that reducing food intake (caloric restriction) extends the life-span in a wide range of species. The protein implicated in this protective process is a protein deacetylase, the silent information regulator 2 (SIR2, SIRT1 in mammals). Moreover, it has been demonstrated that AD and HD neurons are rescued by the over-expression of SIRT1, induced by either caloric restriction or administration of resveratrol, a potential activator of this enzyme [84]. One key enzyme thought to be activated during caloric restrition is the AMP-activated kinase (AMPK), a sensor of cellular energy levels. AMPK is activated by increases in the cellular AMP:ATP ratio, whereupon it functions to help preserve cellular energy. In this regard, the regulation of dietary food intake by hypothalamic neurons is mediated by AMPK. The suppression of nonessential energy expenditure by activated AMPK along with the caloric restrintion mimetic, and neuroprotective properties of resveratrol, suggest that neuronal activation of AMPK could be another important component of resveratrol activity. For instance, resveratrol activates AMPK in Neuro2a cells and primary neurons *in vitro* as well as in the brain [85]. Correspondingly, treatment of mice with resveratrol significantly increased their aerobic capacity. These effects have been associated with an induction of genes for oxidative phosphorylation and mitochondrial biogenesis. Therefore, resveratrol impacts mitochondrial function and metabolic homeostasis [86].

Finally, resveratrol may protect the brain from neuronal damage due to chronic ethanol administration, which damages the developing nervous system by augmenting apoptosis. Ethanol may enhance ROS production in brain through a number of pathways including increased generation of hydroxyethyl radicals, alteration of the cytokine signaling pathways for induction of iNOS, and production of prostanoids through the COX pathway [87]. In other study, treatment of fetal neurons with resveratrol prevented ethanol-associated apoptosis through quenching of ROS and upstream expression of pro-survival genes [88]. Nowadays, the use of resveratrol and related compounds as therapeutic agents to ameliorate this and other neurodegenerative processes is beeing explored.

2.4. Silymarin

An inflammatory response in the central nervous system mediated by activation of microglia is a key event in the early stages of the development of neurodegenerative diseases. Flavonoid silymarin has anti-inflammatory, cytoprotective and neuroprotective effect against LPS-induced neurotoxicity in mesencephalic mixed neuron-glia cultures. In fact, silymarin significantly inhibits the LPS-induced activation of microglia and the production of inflammatory mediators, such as TNF-α and NO, and reduces the damage to dopaminergic neurons. It has been clearly demonstrated that silymarin significantly reduces the LPS-induced nitrite, iNOS mRNA and protein levels, effectively reducing LPS-induced superoxide generation and NF-κB activation. It suggests that the inhibitory effect of silymarin on microglia activation is mediated through the inhibition of NF-κB activation [89].

As stated before, excessive NO production in neuroglial cells surrounding neurons has been correlated with neurotoxicity and the pathogenesis of several neurodegenerative diseases. The suppression of NO production in these cells may be beneficial in retarding many of these disorders. Silymarin reduces NO production at less than 300 ppm. These results demonstrate a possible value for dietary silymarin to inhibit the excessive production of NO in C6 astrocyte cell culture [90].

Silymarin is also a well-known hepatoprotective agent. Tacrine, the first drug marketed for AD induces an elevation of serum liver transaminase, prohibiting an effective dosage in many patients. Silymarin reduces the rate of gastrointestinal and cholinergic side effects without any impact on cognitive status. As a consequence, silymarin could be co-administered with tacrine to improve tolerability in the initial phases of AD treatment [91]. Lastly, human MHC class I expression is usually suppressed in neuronal cells and neuroblastoma cells. Silymarin treatment enhances the transcriptional activity of a reporter construct containing MHC class I promoter. Such results suggest that silymarin acts on the enhancer activity in the MHC class I promoter. Accordingly, treatment of neuroblastoma cells with silymarin resulted in the expression of MHC class I molecules [92].

3. SUMMARY AND PERSPECTIVES

This mini-review examines the chemotherapeutic capacity, and the protective effects of some natural antioxidants found in fruits and vegetables. Research over the last three decades has provided convincing evidence to support that healthy diet may be protective against the risk of different types of cancers and neurological diseases. Of late, several medicinal herbs from plant origin have also received great attention due to their wide range of pharmacological effects [93]. Dietary agents, phytochemicals present in foods, medicinal plants and herbs have been tested for their antioxidant activity. Lack of toxicity associated with high intake of natural products suggest that specific concentrations of these compounds may produce cancer and brain chemopreventive effects without causing significant levels of toxicity [50].

The proteasome is responsible for degrading most intracellular proteins, including oxidized proteins and the proteins involved in cell-cycle regulation and apoptosis, processes crucial to oncogenesis and neuronal death. Then, the proteasome can be considered a potential target in cancer and brain therapy and its modulation by celastrol and polyphenols may contribute to its preventive effect. Furthermore, when combined with other therapies, natural antioxidants may enhance their therapeutic activity in a synergistic way. Studying natural occurring antioxidants, and the structure-activity relations, represent a promising starting point for designing and developing novel anticancer drugs [23], as well as chemicals against brain damage [81]. Celastrol and celastrol-containing medicinal plant show anti-inflammatory and anti-tumor activities in animal models, acting as an inhibitor of NF-κB. New findings suggest the potential use of natural proteasome inhibitors as celastrol not only as chemopreventive and chemotherapeutic agents, but also tumor sensitizers to conventional radiotherapy and chemotherapy [94]. Besides, celastrol is a promising candidate as an agent to counter neurodegenerative diseases, inducing expression of a set of Hsps in differentiated neurons grown in tissue culture [61].

Bioactive phenols like curcuminoids and resveratrol are naturally occurring phytochemicals which show a wide range of pharmacological properties including anti-oxidative, anti-inflammatory, anti-cancer and iron-chelating activities [41]. Spices and herbs often contain active phenolic substances endowed with potent antioxidative properties. Curcumin may attenuate oxidative damages by reducing intracellular production of ROS and protecting mitochondria from oxidative damage [71], exhibiting potent inhibitory activities against proliferation, inducing cell cycle arrest, and enhancing apoptosis in several tumor cell lines [95]. Resveratrol interferes with initiation, promotion and progression of carcinogenesis. Experiments in cell cultures of varied types imply different mechanisms in the pharmacological activity of resveratrol (Table **1** and **2**). Interestingly, recent clinical trials performed with resveratrol administered at pharmacological doses (hundreds of milligrams) or consumed as a polyphenol-rich diet (1 g·dose^{-1}) combined with chemotherapeutic treatments indicated that resveratrol was capable of enhancing the chemotherapeutic efficacy in various human cancers. It is unclear, at this stage, whether the molecular mechanisms mediated by resveratrol against tumour progression involve proteasome inhibition directly, even though it has been suggested that resveratrol may interfere with the NF-κB proteasome mediated degradation [23]. On the other hand, incubation with piceatannol led to a significant proportion of apoptotic cells and caused an arrest in the G2-M phase of the cell cycle in human HL-60 promyelocytic leukemia cells [96]. The antileukemic, and antitumorigenic activities in several cell lines and animal models have also been recently studied in T24 and HT1376 human bladder cancer cells by blocking cell cycle progression in the G0/G1 phase and inducing apoptosis [97]. Topical or dietary silimanin treatment causes a strong protection against photocarcinogenesis in terms of delay in tumor appearance, multiplicity, and volume [68]. Silymarin can also inhibit tumor angiogenesis in animal models and merits investigation as a chemopreventive agent for suppressing cancer progression [58].

Overall, a growing number of studies suggest that cited natural antioxidants have a positive impact on brain aging. The brain is particularly vulnerable to oxidative injury, because it contains high concentrations of readily oxidizable poly-unsaturated fatty acids, has a high rate of oxygen consumption per unit mass, and has only a relatively modest antioxidant defense system [98]. Very recent experiments show effectivity of curcumin in reducing amyloid plaque burden, insoluble Abeta, and carbonyls, in an AD model [99]. In addition, treatment of fetal neurons with two phenolics: curcumin and resveratrol, selectively prevents ethanol-associated apoptosis [88]. In aging and in diseases associated with the elderly, such as AD or PD, the loss of cells in vital structures or organs may be related to several factors, among which the production of ROS by mitochondria is a common denominator, one that leads to DNA damage, apoptosis and death. Although a diet rich in antioxidants seems to offer hope in delaying the onset of unhealthy disorders that accompany aging, no clinical treatment as such has yet been developed and anti-aging drugs are still unavailable [84]. Additional clinical research is needed to evaluate the chemopreventive as well as chemotherapeutic effects of celastrol, curcumin, resveratrol, silymarin, and their analogues against various neurological diseases and human cancers.

ACKNOWLEDGEMENTS

Thanks are due to the Ministerio de Ciencia y Tecnología of Spain, SAF2007-61953, and Junta de Andalucía, Proyectos de Investigación de Excelencia, Convocatoria 2006, CVI-01543, Spain.

ABBREVIATIONS

Abeta	=	Amyloid beta peptide
AD	=	Alzheimer's disease
ALS	=	Amyotrophic lateral sclerosis
AMPK	=	AMP-activated kinase
AR	=	Androgen receptor
ATF2	=	Activating transcription factor 2
B[a]P	=	Benzo[a]pyrene
CDK	=	Cyclin-dependent kinase
CAT	=	Catalase
Cdc	=	Cell division cycle
COX	=	Cyclooxygenase
CYP	=	Cytochrome P450
EGFR	=	Epidermal growth factor receptor
ERK1/2	=	Extracellular signal-regulated kinases
GPX	=	Glutathione peroxidase
GR	=	Glutathione reductase
GSH	=	Glutathione
HD	=	Huntington's disease
HIF	=	Hypoxia-inducible factor
HSF	=	Heat shock transcription factor
Hsp	=	Heat shock protein
IKK	=	Inhibitor of NF-κB kinase
iNOS	=	Inducible nitric oxide synthase
I/R	=	Ischemia/reperfusion
LPS	=	Lipopolysaccharide
MAPK	=	Mitogen activated protein kinase
MHC	=	Major histocompatibility complex
MMP	=	Matrix metallopeptidase
MPTP	=	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NF-κB	=	Nuclear factor kappaB
NMDA	=	N-Methyl-D-aspartic acid
NO	=	Nitric oxide
Nrf2	=	Nuclear erythroid-related factor 2

PD = Parkinson's disease

PKC = Protein kinase C

ROS = Reactive oxygen species

SIR = Silent information regulator

SOD = Superoxide dismutase

TNF = Tumour necrosis factor

VEGF = Vascular endothelial growth factor

REFERENCES

[1] Lora, J.; Alonso, F. J.; Segura, J. A.; Lobo, C.; Márquez, J.; Matés, J.M. Antisense glutaminase inhibition decreases glutathione antioxidant capacity and increases apoptosis in Ehrlich ascitic tumour cells. *Eur. J. Biochem.*, **2004**, *271*, 4298-306.

[2] Matés, J. M.; Pérez-Gómez, C.; Núñez de Castro, I. Antioxidant enzymes and human diseases. *Clin. Biochem*., **1999**, *32*, 595-603.

[3] Matés, J. M. Effects of antioxidant enzymes in the molecular control of reactive oxygen species toxicology. *Toxicology*, **2000**, *153*, 83-104.

[4] Gosslau, A.; Rensing, L. *Z.* Oxidative stress, age-dependent [correction of age-related] cell damage and antioxidative mechanisms. *Gerontol. Geriatr*., **2002**, *35*, 139-50.

[5] Matés, J. M.; Pérez-Gómez, C.; Núñez de Castro, I.; Asenjo, M.; Márquez, J. Glutamine and its relationship with intracellular redox status, oxidative stress and cell proliferation/death. *Int. J. Biochem. Cell Biol*., **2002**, *34*, 439-58.

[6] Matés, J. M.; Segura, J. A.; Alonso, F. J.; Márquez, J. Intracellular redox status and oxidative stress: implications for cell proliferation, apoptosis, and carcinogenesis. *Arch. Toxicol*., **2008**, *82*, 273-99.

[7] Matés, J. M.; Segura, J. A.; Alonso, F. J.; Márquez, J. Pathways from glutamine to apoptosis. *Front. Biosci*., **2006**, *11*, 3164-80.

[8] Kawanishi, S.; Oikawa, S.; Murata, M. Evaluation for safety of antioxidant chemopreventive agents. *Antioxid. Redox Signal*., **2005**, *7*, 1728-39.

[9] Gerhäuser, C.; Klimo, K.; Heiss, E.; Neumann, I.; Gamal-Eldeen, A.; Knauft, J.; Liu, G. Y.; Sitthimonchai, S.; Frank, N. Mechanism-based *in vitro* screening of potential cancer chemopreventive agents. *Mutat. Res*., **2003**, *523-524*, 163-72.

[10] Lee, N. H.; Ho, J. W. Celastrol and terpenes as anti-infective agents. *Anti-Infect. Agents Med. Chem.*, **2008**, *7*, 97-100.

[11] Chang, F. R.; Hayashi, K.; Chen, I. H.; Liaw, C. C.; Bastow, K. F.; Nakanishi, Y.; Nozaki, H.; Cragg, G. M.; Wu, Y. C.; Lee, K. H. J. Antitumor agents. 228. five new agarofurans, Reissantins A-E, and cytotoxic principles from Reissantia buchananii. *Nat. Prod*., **2003**, *66*, 1416-20.

[12] Ngassapa, O.; Soejarto, D. D.; Pezzuto, J. M.; Farnsworth, N. R. Quinone-methide triterpenes and salaspermic acid from Kokoona ochracea. *J. Nat. Prod*., **1994**, *57*, 1-8.

[13] Yang, H.; Chen, D.; Cui, Q. C.; Yuan, X.; Dou, Q. P. Celastrol, a triterpene extracted from the Chinese "Thunder of God Vine," is a potent proteasome inhibitor and suppresses human prostate cancer growth in nude mice. *Cancer Res*., **2006**, *66*, 4758-65.

[14] Zhang, T.; Hamza, A.; Cao, X.; Wang, B.; Yu, S.; Zhan, C. G.; Sun, D. A novel Hsp90 inhibitor to disrupt Hsp90/Cdc37 complex against pancreatic cancer cells. *Mol. Cancer Ther*., **2008**, *7*, 162-70.

[15] Abbas, S.; Bhoumik, A.; Dahl, R.; Vasile, S.; Krajewski, S.; Cosford, N. D.; Ronai, Z. A. Preclinical studies of celastrol and acetyl isogambogic acid in melanoma. *Clin. Cancer Res*., **2007**, *13*, 6769-78.

[16] Westerheide, S. D.; Bosman, J. D.; Mbadugha, B. N.; Kawahara, T. L.; Matsumoto, G.; Kim, S.; Gu, W.; Devlin, J. P.; Silverman, R. B.; Morimoto, R. I. Celastrols as inducers of the heat shock response and cytoprotection. *J. Biol. Chem*., **2004**, *279*, 56053-60.

[17] Trott, A.; West, J. D.; Klaic, L.; Westerheide, S. D.; Silverman, R. B.; Morimoto, R. I.; Morano, K. A. Activation of heat shock and antioxidant responses by the natural product celastrol: transcriptional signatures of a thiol-targeted molecule. *Mol. Biol. Cell*., **2008**, *19*, 1104-12.

[18] Hieronymus, H.; Lamb, J.; Ross, K. N.; Peng, X. P.; Clement, C.; Rodina, A.; Nieto, M.; Du, J.; Stegmaier, K.; Raj, S. M.; Maloney, K. N.; Clardy, J.; Hahn, W. C.; Chiosis, G.; Golub, T. R. Gene expression signature-based chemical genomic prediction identifies a novel class of HSP90 pathway modulators. *Cancer Cell*, **2006**, *10*, 321-30.

[19] Yang, H.; Murthy, S.; Sarkar, F. H.; Sheng, S.; Reddy, G. P.; Dou, Q. P. Calpain-mediated androgen receptor breakdown in apoptotic prostate cancer cells. *J. Cell. Physiol*., **2008**, *217*, 569-76.

[20] Sethi, G.; Ahn, K. S.; Pandey, M. K.; Aggarwal, B. B. Celastrol, a novel triterpene, potentiates TNF-induced apoptosis and suppresses invasion of tumor cells by inhibiting NF-kappaB-regulated gene products and TAK1-mediated NF-kappaB activation. *Blood*, **2007**, *109*, 2727-35.

[21] Lee, J. H.; Koo, T. H.; Yoon, H.; Jung, H. S.; Jin, H. Z.; Lee, K.; Hong, Y. S.; Lee, J. J. Inhibition of NF-kappaB activation through targeting I kappaB kinase by celastrol, a quinone methide triterpenoid. *Biochem. Pharmacol*., **2006**, *72*, 1311-21.

[22] Cao, J.; Jia, L.; Zhou, H. M.; Liu, Y.; Zhong, L. F. Mitochondrial and nuclear DNA damage induced by curcumin in human hepatoma G2 cells. *Toxicol. Sci*., **2006**, *91*, 476-83.

[23] Bonfili, L.; Cecarini, V.; Amici, M.; Cuccioloni, M.; Angeletti, M.; Keller, J. N.; Eleuteri, A. M. Natural polyphenols as proteasome modulators and their role as anti-cancer compounds. *FEBS J.,* **2008**, *275*, 5512-26.

[24] Chen, H. W.; Huang, H. C. Effect of curcumin on cell cycle progression and apoptosis in vascular smooth muscle cells. Effect of curcumin on cell cycle progression and apoptosis in vascular smooth muscle cells. *Br. J. Pharmacol*., **1998**, *124*, 1029-40.

[25] Su, C. C.; Yang, J. S.; Lin, S. Y.; Lu, H. F.; Lin, S. S.; Chang, Y. H.; Huang, W. W.; Li, Y. C.; Chang, S. J.; Chung, J. G. Curcumin inhibits WEHI-3 leukemia cells in BALB/c mice *in vivo*. *In Vivo*, **2008**, *22*, 63-8.

[26] Garg, R.; Gupta, S.; Maru, G. B. Dietary curcumin modulates transcriptional regulators of phase I and phase II enzymes in benzo[a]pyrene-treated mice: mechanism of its anti-initiating action. *Carcinogenesis*, **2008**, *29*, 1022-32.

[27] Polasa, K.; Naidu, A. N.; Ravindranath, I.; Krishnaswamy, K. Inhibition of B(a)P induced strand breaks in presence of curcumin. *Mutat. Res*., **2004**, *557*, 203-13.

[28] Afaq, F.; Adhami, V. M.; Ahmad, N.; Mukhtar, H. Botanical antioxidants for chemoprevention of photocarcinogenesis. *Front. Biosci*., **2002**, *7*, d784-92.

[29] Huang, M. T.; Lou, Y. R.; Xie. J. G.; Ma, W.; Lu, Y. P.; Yen, P.; Zhu, B. T.; Newmark, H.; Ho, C. T. Effect of dietary curcumin and dibenzoylmethane on formation of 7,12-dimethylbenz[a]anthracene-induced mammary tumors and lymphomas/leukemias in Sencar mice. *Carcinogenesis*, **1998**, *19*, 1697-700.

[30] Menon, V. P.; Sudheer, A. R. Antioxidant and anti-inflammatory properties of curcumin. *Adv. Exp. Med. Biol*., **2007**, *595*, 105-25.

[31] Eybl, V.; Kotyzová, D.; Lesetický, L.; Bludovská, M.; Koutenský, J. The influence of curcumin and manganese complex of curcumin on cadmium-induced oxidative damage and trace elements status in tissues of mice. *J. Appl. Toxicol*., **2006**, *26*, 207-12.

[32] Jagetia, G. C. Radioprotection and radiosensitization by curcumin. *Adv. Exp. Med. Biol*., **2007**, *595*, 301-20.

[33] Woo, J. H.; Kim, Y. H.; Choi, Y. J.; Kim, D. G.; Lee, K. S.; Bae, J. H.; Min, D. S.; Chang, J. S.; Jeong, Y. J.; Lee, Y. H.; Park, J. W.; Kwon, T. K. Molecular mechanisms of curcumin-induced cytotoxicity: induction of apoptosis through generation of reactive oxygen species, down-regulation of Bcl-XL and IAP, the release of cytochrome c and inhibition of Akt. *Carcinogenesis*, **2003**, *24*, 1199-1208.

[34] Frank, N.; Knauft, J.; Amelung, F.; Nair, J.; Wesch, H.; Bartsch, H. No prevention of liver and kidney tumors in Long-Evans Cinnamon rats by dietary curcumin, but inhibition at other sites and of metastases. *Mutat. Res*., **2003**, *523-524*, 127-35.

[35] Sreepriya, M.; Bali, G. Effects of administration of embelin and curcumin on lipid peroxidation, hepatic glutathione antioxidant defense and hematopoietic system during N-nitrosodiethylamine/phenobarbital-induced hepatocarcinogenesis in Wistar rats. *Mol. Cell. Biochem*., **2006**, *284*, 49-55.

[36] Sakano, K.; Kawanishi, S. Metal-mediated DNA damage induced by curcumin in the presence of human cytochrome P450 isozymes. *Arch. Biochem. Biophys*., **2002**, *405*, 223-30.

[37] Vitrac, X.; Bornet, A.; Vanderlinde, R.; Valls, J.; Richard, T.; Delaunay, J. C.; Mérillon, J. M.; Teissédre, P. L. Determination of

stilbenes (delta-viniferin, trans-astringin, trans-piceid, cis- and trans-resveratrol, epsilon-viniferin) in Brazilian wines. *J. Agric. Food. Chem*., **2005**, *53*, 5664-9.

[38] Baur, J. A.; Sinclair, D. A. Therapeutic potential of resveratrol: the *in vivo* evidence. *Nat. Rev. Drug Discov*., **2006**, *5*, 493-506.

[39] Athar, M.; Back, J. H.; Tang, X.; Kim, K.H.; Kopelovich, L.; Bickers, D.R.; Kim, A.L. Resveratrol: a review of preclinical studies for human cancer prevention. *Toxicol. Appl. Pharmacol*., **2007**, *224*, 274-83.

[40] Kode, A.; Rajendrasozhan, S.; Caito, S.; Yang, S. R.; Megson, I. L.; Rahman, I. Resveratrol induces glutathione synthesis by activation of Nrf2 and protects against cigarette smoke-mediated oxidative stress in human lung epithelial cells. *Am. J. Physiol. Lung Cell. Mol. Physiol*., **2008**, *294*, L478-88.

[41] Quincozes-Santos, A.; Andreazza, A. C.; Nardin, P.; Funchal, C.; Gonçalves, C. A.; Gottfried, C. Resveratrol attenuates oxidative-induced DNA damage in C6 Glioma cells. *Neurotoxicology*, **2007**, *28*, 886-91.

[42] Kaindl, U.; Eyberg, I.; Rohr-Udilova, N.; Heinzle, C.; Marian, B. The dietary antioxidants resveratrol and quercetin protect cells from exogenous pro-oxidative damage. *Food Chem. Toxicol*., **2008**, *46*, 1320-6.

[43] Nam, N. H. Naturally occurring NF-kappaB inhibitors. *Mini Rev. Med. Chem*., **2006**, *6*, 945-51.

[44] Rimando, A. M.; Cuendet, M.; Desmarchelier, C.; Mehta, R. G.; Pezzuto, J. M.; Duke, S. O. Cancer chemopreventive and antioxidant activities of pterostilbene, a naturally occurring analogue of resveratrol. *J. Agric. Food Chem*., **2002**, *50*, 3453-7.

[45] Schwarz, D.; Roots, I. *In vitro* assessment of inhibition by natural polyphenols of metabolic activation of procarcinogens by human CYP1A1. *Biochem. Biophys. Res. Commun*., **2003**, *303*, 902-7.

[46] Burkhardt, S.; Reiter, R. J.; Tan, D. X.; Hardeland, R.; Cabrera, J.; Karbownik, M. DNA oxidatively damaged by chromium(III) and H_2O_2 is protected by the antioxidants melatonin, N(1)-acetyl-N(2)-formyl-5-methoxykynuramine, resveratrol and uric acid. *Int. J. Biochem. Cell Biol*., **2001**, *33*, 775-83.

[47] Ebert, B.; Seidel, A.; Lampen, A. Phytochemicals induce breast cancer resistance protein in Caco-2 cells and enhance the transport of benzo[a]pyrene-3-sulfate. *Toxicol. Sci*., **2007**, *96*, 227-36.

[48] Ho, S. M. Estrogens and anti-estrogens: key mediators of prostate carcinogenesis and new therapeutic candidates. *J. Cell. Biochem*., **2004**, *91*, 491-503.

[49] Breinholt, V. M.; Mølck, A. M.; Svendsen, G. W.; Daneshvar, B.; Vinggaard, A. M.; Poulsen, M.; Dragsted, L. O. Effects of dietary antioxidants and 2-amino-3-methylimidazo[4,5-f]- quinoline (IQ) on preneoplastic lesions and on oxidative damage, hormonal status, and detoxification capacity in the rat. *Food Chem. Toxicol*., **2003**, *41*, 1315-23.

[50] Ramasamy, K.; Agarwal, R. Multitargeted therapy of cancer by silymarin. *Cancer Lett*., **2008**, *269*, 352-62.

[51] Wu, J. W.; Lin, L. C.; Hung, S. C.; Lin, C. H.; Chi, C. W.; Tsai, T. H. Hepatobiliary excretion of silibinin in normal and liver cirrhotic rats. *Drug Metab. Dispos*., **2008**, *36*, 589-96.

[52] Sun, N.; Zhang, X.; Lu, Y.; Wu, W. *In vitro* evaluation and pharmacokinetics in dogs of solid dispersion pellets containing Silybum marianum extract prepared by fluid-bed coating. *Planta Med*., **2008**, *74*, 126-32.

[53] Saller, R.; Melzer, J.; Reichling, J.; Brignoli, R.; Meier, R. An updated systematic review of the pharmacology of silymarin. *Forsch. Komplementmed*., **2007**, *14*, 70-80.

[54] Katiyar, S. K. Treatment of silymarin, a plant flavonoid, prevents ultraviolet light-induced immune suppression and oxidative stress in mouse skin. *Int. J. Oncol*., **2002**, *21*, 1213-22.

[55] Gu, M.; Singh, R. P.; Dhanalakshmi, S.; Agarwal, C.; Agarwal, R. Silibinin inhibits inflammatory and angiogenic attributes in photocarcinogenesis in SKH-1 hairless mice. *Cancer Res*., **2007**, *67*, 3483-91.

[56] Singh, R. P.; Gu, M.; Agarwal, R. Silibinin inhibits colorectal cancer growth by inhibiting tumor cell proliferation and angiogenesis. *Cancer Res*., **2008**, *68*, 2043-50.

[57] Yanaida, Y.; Kohno, H.; Yoshida, K.; Hirose, Y.; Yamada, Y.; Mori, H.; Tanaka, T. Dietary silymarin suppresses 4-nitroquinoline 1-oxide-induced tongue carcinogenesis in male F344 rats. *Carcinogenesis*, **2002**, *23*, 787-94.

[58] Singh, R. P.; Deep, G.; Chittezhath, M.; Kaur, M.; Dwyer-Nield, L. D.; Malkinson, A. M.; Agarwal, R. Effect of silibinin on the growth and progression of primary lung tumors in mice. *J. Natl. Cancer Inst*., **2006**, *98*, 846-55.

[59] Chow, A. M.; Brown, I. R. Induction of heat shock proteins in differentiated human and rodent neurons by celastrol. *Cell Stress Chaperones*, **2007**, *12*, 237-44.

[60] Zhang, Y. Q.; Sarge, K. D. Celastrol inhibits polyglutamine aggregation and toxicity though induction of the heat shock response. *J. Mol. Med*., **2007**, *85*, 1421-8.

[61] Brown, I. R. Heat shock proteins and protection of the nervous system. *Ann. N. Y. Acad. Sci*., **2007**, *1113*, 147-58.

[62] Kiaei, M.; Kipiani, K.; Petri, S.; Chen, J.; Calingasan, N. Y.; Beal, M. F. Celastrol blocks neuronal cell death and extends life in transgenic mouse model of amyotrophic lateral sclerosis. *Neurodegener. Dis*., **2005**, *2*, 246-54.

[63] Cleren, C.; Calingasan, N. Y.; Chen, J.; Beal, M. F. Celastrol protects against MPTP- and 3-nitropropionic acid-induced neurotoxicity. *J. Neurochem*., **2005**, *94*, 995-1004.

[64] Allison, A. C.; Cacabelos, R.; Lombardi, V. R.; Alvarez, X. A.; Vigo, C. Celastrol, a potent antioxidant and anti-inflammatory drug, as a possible treatment for Alzheimer's disease. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **2001**, *25*, 1341-57.

[65] Wang, Q.; Sun, A. Y.; Simonyi, A.; Jensen, M. D.; Shelat, P. B.; Rottinghaus, G. E.; MacDonald, R. S.; Miller, D. K.; Lubahn, D. E.; Weisman, G. A.; Sun, G. Y. Neuroprotective mechanisms of curcumin against cerebral ischemia-induced neuronal apoptosis and behavioral deficits. *J. Neurosci. Res*., **2005**, *82*, 138-48.

[66] Al-Omar, F. A.; Nagi, M. N.; Abdulgadir, M. M.; Al Joni, K. S.; Al-Majed, A. A. Immediate and delayed treatments with curcumin prevents forebrain ischemia-induced neuronal damage and oxidative insult in the rat hippocampus. *Neurochem. Res*., **2006**, *31*, 611-8.

[67] Vajragupta, O.; Boonchoong, P.; Watanabe, H.; Tohda, M.; Kummasud, N.; Sumanont, Y. Manganese complexes of curcumin and its derivatives: evaluation for the radical scavenging ability and neuroprotective activity. *Free Radic. Biol. Med*., **2003**, *35*, 1632-44.

[68] Sumanont, Y.; Murakami, Y.; Tohda, M.; Vajragupta, O.; Watanabe, H.; Matsumoto, K. Prevention of kainic acid-induced changes in nitric oxide level and neuronal cell damage in the rat hippocampus by manganese complexes of curcumin and diacetylcurcumin. *Life Sci*., **2006**, *78*, 1884-91.

[69] Scapagnini, G.; Butterfield, D. A.; Colombrita, C.; Sultana, R.; Pascale, A.; Calabrese, V. Ethyl ferulate, a lipophilic polyphenol, induces HO-1 and protects rat neurons against oxidative stress. *Antioxid. Redox Signal*., **2004**, *6*, 811-8.

[70] Scapagnini, G.; Colombrita, C.; Amadio, M.; D'Agata, V.; Arcelli, E.; Sapienza, M.; Quattrone, A.; Calabrese, V. Curcumin activates defensive genes and protects neurons against oxidative stress. *Antioxid. Redox Signal*., **2006**, *8*, 395-403.

[71] Zhu, Y. G.; Chen, X. C.; Chen, Z. Z.; Zeng, Y. Q.; Shi, G. B.; Su, Y. H.; Peng, X. Curcumin protects mitochondria from oxidative damage and attenuates apoptosis in cortical neurons. *Acta Pharmacol. Sin*., **2004**, *25*, 1606-12.

[72] Yang, F.; Lim, G. P.; Begum, A. N.; Ubeda, O. J.; Simmons, M. R.; Ambegaokar, S. S.; Chen, P. P.; Kayed, R.; Glabe, C. G.; Frautschy, S. A.; Cole, G. M. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid *in vivo*. *J. Biol. Chem*., **2005**, *280*, 5892-901.

[73] Frautschy, S. A.; Hu, W.; Kim, P.; Miller, S. A.; Chu, T.; Harris-White, M. E; Cole, G. M. Phenolic anti-inflammatory antioxidant reversal of Abeta-induced cognitive deficits and neuropathology. *Neurobiol. Aging*, **2001**, *22*, 993-1005.

[74] Cole, G. M.; Lim, G. P.; Yang, F.; Teter, B.; Begum, A.; Ma, Q.; Harris-White, M. E.; Frautschy, S. A. Prevention of Alzheimer's disease: Omega-3 fatty acid and phenolic anti-oxidant interventions. *Neurobiol. Aging*, **2005**, *26*, 133-6.

[75] Huang, S. S.; Tsai, M. C.; Chih, C. L.; Hung, L. M.; Tsai, S. K. Resveratrol reduction of infarct size in Long-Evans rats subjected to focal cerebral ischemia. *Life Sci*., **2001**, *69*, 1057–1065.

[76] Sinha, K.; Chaudhary, G.; Gupta, Y, K. Protective effect of resveratrol agaist oxidative stress in middle cerebral artery occlusion model of stroke in rats. *Life Sci*., **2002**, *71*, 655–665.

[77] Wang, Q.; Xu, J.; Rottinghaus, G. E.; Simonyi, A.; Lubahn, D.; Sun, G. Y.; Sun, A. Y. Resveratrol protects against global cerebral ischemic injury in gerbils. *Brain Res*., **2002**, *958*, 439–47.

[78] Inoue, H.; Jiang, X. F.; Katayama, T.; Osada, S.; Umesono, K.; Mamura, S. Brain protection by resveratrol and fenofibrate against stroke requires peroxisome proliferator-activated receptor α in mice. *Neurosci. Lett*., **2003**, *352*, 203–6.

[79] Bastianetto, S.; Quirion, R. Natural extracts as possible protective agents of brain aging. *Neurobiol. Aging*, **2002**, *23*, 891-97.

[80] Ban, J. Y.; Cho, S. O.; Choi, S. H.; Ju, H. S.; Kim, J. Y.; Bae, K.; Song, K. S.; Seong, Y. H. Neuroprotective effect of Smilacis chinae rhizome on NMDA-induced neurotoxicity *in vitro* and focal cerebral ischemia *in vivo*. *J. Pharmacol. Sci*., **2008**, *106*, 68-77.

[81] Marambaud, P.; Zhao, H.; Davies, P. Resveratrol promotes clearance of Alzheimer's disease amyloid-beta peptides. *J. Biol. Chem*., **2005**, *280*, 37377-82.

[82] Kim, H. J.; Lee, K. W.; Lee, H. J. Protective effects of piceatannol against beta-amyloid-induced neuronal cell death. *Ann. N. Y. Acad. Sci*., **2007**, *1095*, 473-82.

[83] Conte, A.; Pellegrini, S.; Tagliazucchi, D. Synergistic protection of PC12 cells from beta-amyloid toxicity by resveratrol and catechin. *Res. Bull*., **2003**, *62*, 29-38.

[84] Pallàs, M.; Verdaguer, E.; Tajes, M.; Gutierrez-Cuesta, J.; Camins, A. Modulation of sirtuins: new targets for antiageing. *Recent Pat. CNS Drug Discov*., **2008**, *3*, 61-9.

[85] Dasgupta, B.; Milbrandt, J. Resveratrol stimulates AMP kinase activity in neurons. *Proc. Natl. Acad. Sci. USA*, **2007**, *104*, 7217-22.

[86] Lagouge, M.; Argmann, C.; Gerhart-Hines, Z.; Meziane, H.; Lerin, C.; Daussin, F.; Messadeq, N.; Milne, J.; Lambert, P.; Elliott, P.; Geny, B.; Laakso, M.; Puigserver, P.; Auwerx, J. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. *Cell*, **2006**, *127*, 1109-22.

[87] Sun, A. Y.; Sun, G. Y. Ethanol and oxidative mechanisms in the brain. *J. Biomed. Sci*., **2001**, *8*, 37-43.

[88] Antonio, A. M.; Druse, M. J. Antioxidants prevent ethanol-associated apoptosis in fetal rhombencephalic neurons. *Brain Res*., **2008**, *1204*, 16-23.

[89] Wang, M. J.; Lin, W. W.; Chen, H. L.; Chang, Y. H.; Ou, H. C.; Kuo, J. S.; Hong, J. S.; Jeng, K. C. Silymarin protects dopaminergic neurons against lipopolysaccharide-induced neurotoxicity by inhibiting microglia activation. *Eur. J. Neurosci*., **2002**, *16*, 2103-12.

[90] Soliman, K. F.; Mazzio, E. A. *In vitro* attenuation of nitric oxide production in C6 astrocyte cell culture by various dietary compounds. *Proc. Soc. Exp. Biol. Med*., **1998**, *218*, 390-7.

[91] Allain, H.; Schück, S.; Lebreton, S.; Strenge-Hesse, A.; Braun, W.; Gandon, J. M.; Brissot, P. Aminotransferase levels and silymarin in de novo tacrine-treated patients with Alzheimer's disease. *Dement. Geriatr. Cogn. Disord*., **1999**, *10*, 181-5.

[92] Sakai, K.; Li, Y.; Shirakawa, T.; Kitagawa, Y.; Hirose, G. Induction of major histocompatibility complex class I molecules on human neuroblastoma line cells by a flavoid antioxidant. *Neurosci. Lett*., **2001**, *298*, 127-30.

[93] Furst, A. Can nutrition affect chemical toxicity? *Int. J. Toxicol*., **2002**, *21*, 419-24.

[94] Yang, H.; Landis-Piwowar, K. R.; Chen, D.; Milacic, V.; Dou, Q. P. Natural compounds with proteasome inhibitory activity for cancer prevention and treatment. *Curr. Protein. Pept. Sci*., **2008**, *9*, 227-39.

[95] Srichairatanakool, S.; Thephinlap, C.; Phisalaphong, C.; Porter, J. B.; Fucharoen, S. Curcumin contributes to *in vitro* removal of non-transferrin bound iron by deferiprone and desferrioxamine in thalassemic plasma. *Med. Chem*., **2007**, *3*, 469-74.

[96] Fritzer-Szekeres, M.; Savinc, I.; Horvath, Z.; Saiko, P.; Pemberger, M.; Graser, G.; Bernhaus, A.; Ozsvar-Kozma, M.; Grusch, M.; Jaeger, W.; Szekeres, T. Biochemical effects of piceatannol in human HL-60 promyelocytic leukemia cells-synergism with Ara-C. *Int. J. Oncol*., **2008**, *33*, 887-92.

[97] Kuo, P. L.; Hsu, Y. L. The grape and wine constituent piceatannol inhibits proliferation of human bladder cancer cells *via* blocking cell cycle progression and inducing Fas/membrane bound Fas ligand-mediated apoptotic pathway. *Mol. Nutr. Food Res*., **2008**, *52*, 408-18.

[98] Koenig, M. L.; Meyerhoff, J. L. *In vitro* neuroprotection against oxidative stress by pre-treatment with a combination of dihydrolipoic acid and phenyl-butyl nitrones. *Neurotox. Res*., **2003**, *5*, 265-72.

[99] Begum, A. N.; Jones, M. R.; Lim, G. P.; Morihara, T.; Kim, P.; Heath, D. D.; Rock, C. L.; Pruitt, M. A.; Yang, F.; Hudspeth, B.; Hu, S.; Faull, K. F.; Teter, B.; Cole, G. M.; Frautschy, S. A. Curcumin structure-function, bioavailability, and efficacy in models of neuroinflammation and Alzheimer's disease. *J. Pharmacol. Exp. Ther*., **2008**, *326*, 196-208.

Received: 11 April, 2009 **Revised: 12 June, 2009** **Accepted: 12 June, 2009**