Türk Biyokimya Dergisi [Turkish Journal of Biochemistry - Turk J Biochem] 2006; 31 (2); 57–68.

Review Article [Derleme Makalesi]

Yayın tarihi 21 Haziran, 2006 © TurkJBiochem.com

[Published online 21 June, 2006]

Dietary Compounds As Anti-cancer Agents: A Preliminary Evaluation of Ion Channels And Membrane Excitability As Possible Target Mechanisms

[Anti-Kanser Ajan Olarak Diyet-Kaynaklı Bileşikler: İyon Kanalları ve Membran Uyarılabilirliğinin Olası Hedef Mekanizma Yönünden Ön Değerlendirilmesi]

Mustafa B. A. Djamgoz[1]
Banu Isbilen[2]

[1] Neuroscience Solutions to Cancer Research Group, Division of Cell and Molecular Biology, Imperial College London, South Kensigton Campus, London SW7 2AZ, U.K.

[2] Canakkale State Hospital, Biochemistry Laboratory, Canakkale 17100, TURKEY.

Yazışma Adresi
[Correspondence Address]

Neuroscience Solutions to Cancer Research Group, Division of Cell and Molecular Biology
Imperial College London, South Kensington Campus, London SW7 2AZ, U.K.
Tel: +44 207 594 5370
Fax: +44 207 584 2056
E-mail: m.djamgoz@imperial.ac.uk

ABSTRACT

Although a variety of natural, dietary compounds have been suggested to have anti-cancer properties, their modes of action are not well understood. In this article, we adopt membrane excitability and associated ion channel expression / activity as possible target mechanisms. Our previous work has shown that in a number of major human metastatic carcinomas (breast, prostate, small-cell lung cancers) functional voltage-gated Na+ channels are upregulated concomitantly with down-regulation of voltage-gated K+ channels. Such characteristics would render the cells' membranes potentially 'excitable', in line with such cells' 'hyperactive' behaviour. We call this the "cellular excitability" ("CELEX") hypothesis of cancer progression. Here, we evaluate a number of natural anti-cancer compounds from the point of view of their possible effects mainly upon VGSC, and to a lesser extent K+ channel expression / activity, in accordance with the hypothesis. The compounds evaluated include phytochemicals (resveratrol, curcumin, capsaicin, genistein and ginseng), those of marine origin (omega-3 polyunsaturated fatty acids) and minerals (zinc). The review does not intend be exhaustive and the emphasis is upon demonstrating sufficient detail in the examples given to establish 'proof of principle'. It is concluded (1) that many dietary compounds, for which there is evidence for anti-cancer effects, work broadly in accordance with the CELEX hypothesis and (2) that this is a viable, futuristic field of study, but the modes of action of dietary compounds and natural products need to be evaluated much more systematically.

Key Words: Cancer; metastasis; ion channels; membrane excitability; resveratrol; curcumin; capsaicin; genistein; ginseng; omega-3 polyunsaturated fatty acids; zinc.

ÖZET

Birçok doğal diyet-kaynaklı bileşik anti-kanser özellikleri nedeniyle bilinmelerine rağmen, etki mekanizmaları halen anlaşılamamıştır. Bu derlemede, olası bir mekanizma olarak membran uyarılması ve bununla bağlantılı iyon kanalı ekspresyonu / aktivitesi üzerine yoğunlaştık. Daha önceki çalışmalarımızda, bir grup major metastatik karsinomada (meme, prostat, küçük-hücreli akciğer kanseri gibi) fonksiyonel voltaj-kapılı Na+ kanallarının up-regülasyonu ve beraberinde voltaj-kapılı K+ kanallarının down-regülasyonunu bildirmiştik. Bu özellikler hücre membranını hiperaktif doğalarına uygun olarak potansiyel uyarılabilir hale getirmektedir. Bu makalede, bir grup doğal anti-kanser maddenin özellikle voltaj-kapılı Na+ kanallarının, kısmen de voltaj-kapılı K+ kanalları aktivitesi / ekspresyonu üzerinden etkilerini inceledik. Fitokemikaller (resveratrol, curcumin, capsaicin, genistein ve ginseng), deniz kaynaklı bileşikler (omega-3 poliansatüre yağ asidleri), ve mineraller (çinko) bu derlemede incelendi. Çalışmamız, tüm alanı ayrıntılı incelemek üzere tasarlanmadı. Bunun yerine, vurgulanan asıl nokta, prensibin ispatına dair örneklerin detaylı olarak açıklanmasıydı. Özetle, (1) anti-kanser etkilerine dair kanıt bulunan birçok diyet bileşeni, CELEX hipotezi kapsamında geniş olarak incelendi ve (2) bu inceleme oldukça yenilikçi ve uygulanabilir olmasına rağmen, diyet-kaynaklı bileşiklerin ve doğal ürünlerin etki mekanizmalarının çok daha sistematik olarak incelenmesi gerektiği sonucuna varıldı.

Anahtar Kelimeler: Kanser; metastaz; iyon kanalları; membran uyarılabilirliği; resveratrol; curcumin; capsaicin; genistein; ginseng; omega-3 poliansatüre yağ asidleri; çinko.

Abbreviations: VGSC, voltage-gated Na+ channel; VGPC, voltage-gated K+ channel; CELEX, cellular excitability; DRG, dorsal root ganglia; TTX, tetrodotoxin; CFTR, cystic fibrosis transmembrane conductance regulator; TRP, transient receptor potential; TG, trigeminal ganglion; PTK, protein tyrosine kinase; ω-3 PUFA, omega-3 polyunsaturated fatty acid; ALA, α-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Kısaltmalar: VGSC, voltaj-kapılı Na+ kanalı; VGPC, voltaj-kapılı K+ kanalı; CELEX, hücresel uyarılma; DRG, dorsal kök gangliyon; TTX, tetrodotoksin; CTFR, kistik fibroz iletkenlik regülatörü; TRP, geçici reseptör potensiyali; TG, trigeminal gangliyon; PTK, protein tirozin kinaz; ω-3 PUFA, omega-3 poliansatüre yağ asidi; ALA, α-linolenik acid; EPA, eikozapentaenoik asid; DHA, dokozahekzaenoik asid.

Kayıt tarihi 02 Mayıs 2006; kabul tarihi 11 Mayıs 2006
[Received 02 May 2006; accepted 11 May 2006]

1. INTRODUCTION

Dietary factors are well known to play an important role in cancer [e.g. 1,2] and some 55 % of all cancers have been related to nutritional habits [3]. Consequently, it is becoming increasingly popular to use diet or natural dietary supplements against cancers, since at appropriate doses, dietary compounds are naturally non-toxic [4]. For example, Mediterranean diets are generally thought to be favourable against cancer [e.g. 5] and the low incidence of many (but not all) cancers in China and Japan are thought to be related to local diet [e.g. 6]. One potential problem with consumption of 'anti-cancer' dietary compounds, as natural supplements, is their unknown compatibility with clinical medicines. However, recent evidence suggests, at least for some cases, that potential chemopreventative foods, in fact, may enhance the efficacy of conventional therapy [7,8].

There are several types of natural products, especially fish oils, phytochemicals, including carotenoids and phenolics, dietary fibres, some micronutrients present in foods of both plant and animal origin, that are successful cancer drugs [9,10]. However, in many cases, the modes of action of the dietary compounds in question, and in some cases, even the active ingredient(s) are not known.

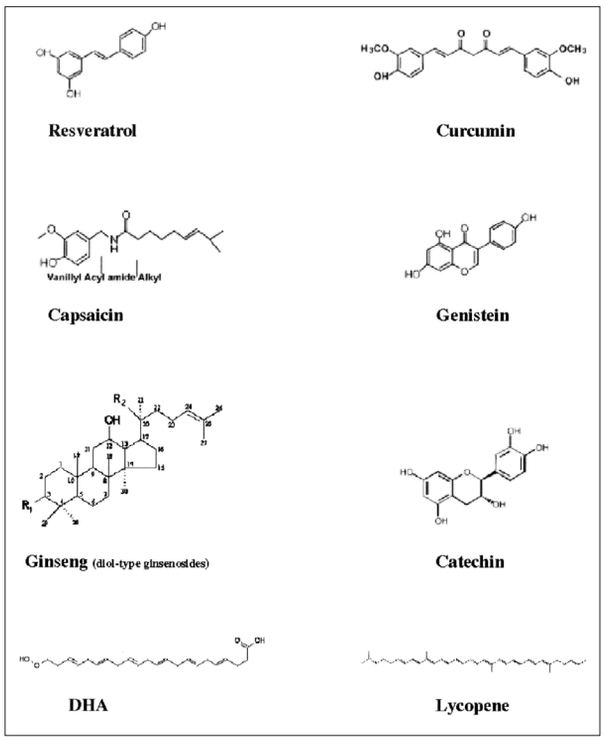

Figure 1. Chemical structures of some of the dietary compounds covered in this review.

Ion channels, the main mechanistic focus of the review, are membrane-bound proteins, which permeate a single or a combination of ion species flowing down their electrochemical gradients. The resulting changes in the intracellular concentration(s), in turn, can lead to a variety of cellular effects, including enzyme activity, change in pH or Ca2+, cytoskeletal modifications etc. There are three main types of ion channel, distinguished by the stimulus (and the corresponding molecular mechanism) responsible for their activation: voltage-gated, ligand-gated and mechanosensitive. Various cancer cells and tissues express ion channels, e.g. prostate [11-13], breast [14,15], lung [16-18], colon [19], melanoma [20] and lymphoma [21]. Expression of ion channels in cancer cells/tissues is probably because of their powerful functional characteristics [e.g. 22]. It would follow, therefore, that there is a possible basis for ion channels being a major target for the anti-cancer effects of some natural compounds. In this review, we make an attempt to outline the relevant evidence. The chemical structures of the dietary compounds covered are shown in Figure 1. The approach adopted is not exhaustive and instead of dealing with a specific cancer, we draw examples from various cancers randomly, in attempt to establish 'proof of principle'. A complementary hypothesis dealing with "cause and development of neoplasms" is in the press at the time of writing [23].

Although voltage-gated Na+ channels (VGSCs) and voltage-gated K+ channels (VGPCs) are commonly associated with 'excitation' and impulse conduction, there is increasing evidence that they are also expressed in 'non-excitable', including epithelial cells [24,25]. Recent evidence shows that significant in vitro (and in some cases, in vivo) upregulation of functional VGSCs occurs in cancers of prostate [11-13], breast [14,15], and small-cell lung carcinoma [17,18].

Where VGPC activity has also been studied, an inverse relationship with metastatic potential has been found, i.e. strong metastatic potential was associated with VGPC down-regulation [11-13]. Some examples are illustrated in Figure 2. Importantly, therefore, the data taken together would imply that metastatic cell membranes are potentially excitable and, indeed, action potentials have been recorded from some aggressive carcinoma cells [e.g. 17]. This notion would appear to parallel the hyperactive cellular behaviours associated with metastasis. Indeed, ion channel activity has been found to control / enhance a variety of cellular behaviours that would be involved in the metastatic cascade: morphological change [26], galvanotaxis [27], motility [28], secretory membrane activity [29,30], adhesion [31] and invasion [11,12]. Bennett et al. (2004) have demonstrated that VGSC expression increased with the invasiveness of human prostate carcinoma cells [13]. It was stated, in fact, that VGSC expression "is necessary and sufficient" for the upregulation of invasiveness.

Upregulation of VGSC expression and its positive correlation with metastasis have also been demonstrated in human breast and prostate cancer in vivo [15,32]. There is also some evidence for downregulation of VGPC expression at least in some prostate cancers in vivo [33].

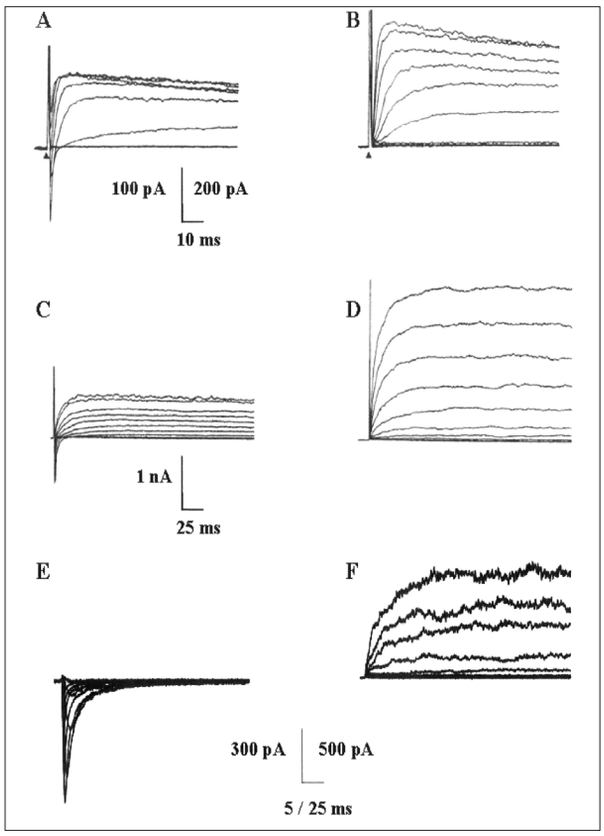

Figure 2. Voltage-gated membrane current recordings from various cancer cell lines. A, Mat-LyLu. B, AT-2. These are isogenic rat prostate cancer cell lines of strong and weak metastatic potential, respectively. C, PC-3. D, LnCaP. These are human prostate cancer cell lines of strong and weak metastatic potential, respectively. E, MDA-MB-231. F, MCF-7. These are human breast cancer cell lines of strong and weak metastatic potential, respectively. In all three pairs the following 2 key features are apparent: The strongly metastatic cell lines are associated with (i) expression of a voltage-gated inward (Na+) membrane current (sharp downward signal); and (ii) down-regulation of the sustained outward currents. The combination of (i) and (ii) renders these cells 'excitable', and this is the basis of the CELEX hypothesis. Note the differences in some of the respective scales, which underestimate the visual impact of the differences mentioned. Modified from 11,12,15.

Thus, VGSCs could act as an independent prognostic marker and/or a promising target for cancer therapy. Indeed, VGSC blockers (e.g. anti-convulsant drugs) have been suggested to have clinical potential as cytostatic agents against prostate carcinoma [34].

1.1 The 'cellular excitability' (CELEX) hypothesis of cancer progression

From the available data, taken together, we have adopted the following two-part working hypothesis for the role of membrane ion channels in cancer:

1. In primary tumorigenesis, where cancer cells would be undergoing uncontrolled cell division, facilitated by K+ channel activity, compounds blocking K+ channels would have anti-proliferative / anti- cancer effects.
2. In secondary tumorigenesis (metastasis), facilitated by functional VGSCs upregulation, VGSC blockers would have anti-metastatic effects. However, since increase in metastatic potential is accompanied by concomitant VGPC downregulation, which would normally be antagonistic to VGSC functioning, VGPC blockers could have a pro-cancer effect.

For convenience, this will be referred to here as the "CELEX" hypothesis of cancer progression. Metastasis is the main cause of death in most cancer patients. An ideal anti-metastasis compound, therefore, would suppress VGSC whilst promoting VGPC activity.

2. PHYTOCHEMICALS

Phytochemicals are described as bioactive extra-nutritional constituents in fruits, vegetables, grains, and other plant foods [35]. There are thousands of individual phytochemicals which occur in diet. Epidemiologic studies have suggested that a reduced risk of cancer is associated with high consumption of vegetables and fruits [36], although this area is controversial [37]. According to the CELEX hypothesis, the apparent inconsistency could be due the noted potentially complex role of K+, high in such diet.

1.1 Resveratrol

Resveratrol (3,4',5-trihydroxystilbene; 228.2 Da) is a plant polyphenol present in significant levels in red grapes (hence, red wine), berries and peanuts [38]. In addition, it is the active constituent of the roots of Polygonum cuspidatum, which is used as a drug in Asian medicine [39]. This is a strong antioxidant which has been shown to exert substantial cytotoxic effects upon a variety of tumour cell lines, including those of prostate, colorectal and leukaemia [39-41].

There is also evidence that resveratrol affects ion channels. Wu et al. (2005) showed that resveratrol inhibited VGSC currents in male rat dorsal root ganglion (DRG) neurones with an IC50 of about 11 μM [42]. Kim et al. (2005) found a similar effect on rat DRG neurones and, additionally, showed that tetrodotoxin (TTX)-sensitive VGSCs were about 5-fold more sensitive than TTX-resistant VGSCs [43]. In both cases, the Hill coefficient was ~1 implying a 1:1 interaction between the VGSC and resveratol [43]. As regards K+ channels, effects were mixed: inhibition [42,44] and potentiation [45,46].

It would appear; therefore, that resveratrol could have anti-cancer effects in accordance, at least partially, with the CELEX hypothesis. We should note that a number of other targets have also been associated with resveratrol, including caspase-3, p38 MAP kinase [47] and cAMP [48], which could have knock-on effects upon VGSC and/or VGPC activity.

1.2 Curcumin

Curcumin (diferuloylmethane; 368.4 Da) is a naturally occurring yellow pigment isolated from ground rhizomes of the plant Curcuma longa L. (Zingiberaceae). It is also the primary active ingredient of the spice, turmeric which is used for colouring and flavoring food. Curcumin is also used as a drug in Asian medicine and is well known for its anti-inflammatory, potent antioxidant, hypocholesterolemic and hypoglycemic effects [49]. Independently of these, however, curcumin has been shown to be effective against metastatic melanoma [50], prostate cancer [51] and certain lymphomas [52]. Aggarwal et al. (2005) showed that dietary curcumin would inhibit lung metastases of human breast cancer cells injected into nude mice [53]. The underlying cellular effects were suggested to involve inhibition of angiogenesis and induction of apoptosis.

Although a major mode of action of curcumin is thought to be inhibition of the NF-κB pathway, there is also some evidence for ion channel involvement. Keller et al. (2005) showed that curcumin partially rescued the loss of function in the L325R mutation of Nav1.5 [54]. This effect was mimicked by mexiletine, a well established antiarrhythmic VGSC blocker. Although, the mode of action of curcumin may, therefore, be comparable to that of VGSC suppression, this needs to be tested more directly. There is indirect evidence that curcumin may also affect K+ channels. This comes from work on the cystic fibrosis transmembrane conductance regulator (CFTR), the Cl- channel gating and phosphorylation of which are modulated by curcumin. Interestingly, CFTR may also regulate other ion channels including K+ channels, so cascade effects are possible [55]. Other potentially interesting modes of action include modulation of inositol 1,4,5-triphosphate receptor, responsible for releasing Ca2+ from intracellular stores [56] and a range of other signalling mechanisms, e.g. cyclooxygenase-2, nitric oxide synthase and cytokines [57]. Furthermore, curcumin may affect epidermal growth factor signalling [58] which is known to regulate ion channel, including VGSC expression [e.g. 59].

It seems possible, therefore, that curcumin may have ion channel effects that need further investigation as regards both precise modes of action and relevance to the cancer process, including the CELEX hypothesis.

1.3 Capsaicin

Capsaicin (8-methyl-N-vanillyl-6-nonenamide; 305.4 Da), a type of vanilloid, is the major pungent ingredient in a variety of red peppers of the genus Capsicum capsaicin. Capsaicin has been reported to induce apoptosis in many human cancer cell types, including breast cancer cells [60], colon cancer [61] and gastric adenocarcinoma [62]. More recent evidence suggests that red peppers (hence, capsaicin) can also be good against prostate cancer by inhibiting androgen-independent growth [63].

Capsaicin is a specific ligand (activator) for the vanilloid receptor TRPV1, a member of the TRP ("transient receptor potential") family of ion channels; it's basic action is to activate a non-selective cation channel [64]. However, capsaicin may have significant effects upon a variety of ion channels. As regards VGSCs, the available data are consistent in showing that capsaicin inhibits VGSC activity. This has been shown for VGSCs in a range of cells, as follows: rat DRG colon sensory neurones [65], rat trigeminal ganglion (TG) neurones [66] and rat atrial myocytes [67]. Furthermore, capsaicin potentiated the in vivo local anaesthetic activity of VGSC blockers [68]. An indirect effect upon membrane elasticity has been suggested [69]. It is not known if capsaicin may affect VGSC activity directly. However, Bielefeldt (2000) showed that capsaicin would block VGSCs in rat visceral sensory neurones that did not respond to capsaicin itself [70]. As regards K+ channels, most evidence suggest a blocking effect, as for the delayed rectifier of rabbit Schwann cells [71], slow-inactivating K+ currents of rat pituitary melanotrophs [72], outward rectifying K+ currents of rat taste receptor cells [73], transient K+ (IA) current of rat TG neurones [74], and VGPCs of rat visceral sensory neurones [70]. Interestingly, in rabbit coronary arteries, delayed-rectifier VGPCs were activated by 1 – 30 μM capsaicin [75].

In conclusion, the range of effects of capsaicin on ion channels is broadly in agreement with at least the VGSC part of the CELEX hypothesis.

1.4 Genistein

Genistein (270.2 Da) is one of the predominant isoflavones that found in soy products [76]. It has powerful biologic activity including as an antioxidant, as well as an inhibitor of angiogenesis and proliferation [76,77]. Importantly, genistein inhibits protein tyrosine kinases (PTKs) and DNA topoisomerases I and II [76]. Moreover, it can act as an agonist for the beta isoform of the estrogen receptor [78].

Some work has been done on effects of genistein (and its inactive analogues, daidzein and genisitin) on expression and activity of ion channels. Hilborn et al. (1998) and Bouron et al.(1999) showed originally that functional expression of VGSCs (e.g. in PC12 cells by nerve growth factor stimulation) would involve PTK activity [79,80]. Consistent with this effect, genistein decreased excitability of rat TG nociceptive neurones [81]. However, in the study of Liu et al. (2004) daidzein was also effective and it was suggested that the primarily role of genistein was 'general' and independent of PTK [81]. A similar conclusion was reached earlier by Kusaka and Sperelakis (1996) showing that bath application of genistein and daidzein inhibited VGSC currents in human uterine smooth muscle cells; the genistein-induced block was maximally ~98 % (IC50 ~9 μM) [82]. Genistein also suppressed VGSC activity in neurones cultured from neonatal rat brain [83]. In neonatal rat ventricular cells (myocytes), modulation of VGSC activity (involving

enhancement of peak current amplitude) by lysophosphatidylcholine (normally derived intracellularly from membrane phospholipids) was completely blocked by genistein [84]. Wang et al. (2003) showed similarly that genistein (but not genistin) inhibited VGSC currents in rabbit myocytes [85]. Thus, it would appear that the major effect of genistein on a variety of VGSCs is consistently one of inhibition. Considerable work has also been done on effects of genistein on K+ channels. The results are consistent in showing inhibition of various K+ channels by genistein, as for delayed rectifiers in guinea pig myocytes [86], mouse Schwann cells [87], rat TG neurones [81] or guinea pig colon smooth muscle cells, Kv1.3 of human T lymphocytes [88], and cloned human Kv1.4 expressed in CHO cells [89]. As regards, mode(s) of action of genistein, src kinase was proposed to have a major role [79]. On the other hand, the effectiveness of daidzein [7,82,83,86] as well as the fast action of genistein, having an effect within ~2 mins [83] in some experiments (on both VGSCs and VGPCs) would suggest also a direct effect, independent of PTK. In fact, Paillart et al. (1997) showed that the effects of genistein and veratridine on VGSCs were competitive, implying binding upon the same site within the channel complex [83].

In conclusion, the available evidence would strongly support the main, VGSC part of the CELEX hypothesis. However, the net effect on cancer progression may be complex due to the strong inhibitory effects on K+ channels, and the multitude of knock-on effects that may result from any PTK inhibition.

2.5 Ginseng

Ginseng, the root of Panax species, has been used as a traditional medicine in Asia for thousands of years; it is now a popular worldwide natural medicine [90]. The active ingredients of ginseng are ginsenosides, also called “ginseng saponins” [91]. Ginseng is well known as a potent antioxidant and also has inhibitory effects on proliferation, apoptosis and angiogenesis [92]. Indeed, administration of ginseng suppressed colon cancer in rats [93].

The effect of ginseng on VGSC activity is consistently one of inhibition. Thus, ginseng and/or its bioactive ingredients (e.g. ginsenosides, Rg3, Rf, Rb1), where tested, have been shown to suppress various VGSCs in a dose dependent manner. Lee et al. (2005) showed inhibition of rat brain Nav1.2 VGSCs expressed in Xenopus oocytes; both resting and open states were suppressed [94]. A similar effect of ginseng aqueous extract (or Rb1) was reported for Nav1.2 VGSC transfected into tsA201 cells [95]. In a structural approach, Kang et al. (2005) found that ginseng inhibited mouse Nav1.5 (also expressed in Xenopus oocytes); this effect was voltage dependent [96]. Jeong et al. (2004) showed that VGSC inhibition by the ginsenoside Rg3 was sterospecific and involved mainly the inactive state of the channel [97]. Interestingly, most studies suggested that ginseng would enhance K+ activity. Such effects have been reported for guinea pig recombinant HERG channels (a type of VGPC) expressed in Xenopus oocytes [98], guinea pig cardiomyocyte delayed rectifier [99] and tetraethyl ammonium-sensitive K+ channels of rat aorta [100]. Only one study reported VGPC inhibition by Rg3 [97]. The effects of ginseng and ginsenosides have been suggested to involve a variety of modes of action, including non-covalent allosteric modification of neurotoxin binding site-2 [101], interaction with the S4 segment of domain DII [94], or via nitric oxide / direct S-nitrosylation [99].

In conclusion, it would appear, therefore, that the effects of ginseng on various VGSCs and VGPCs are strongly in agreement with the CELEX hypothesis.

3. MARINE COMPOUNDS

Marine natural products, including dietary compounds, have been a source of new leads for the prevention / treatment of many deadly diseases, in particular cancer [102]. Nowadays, a number of marine compounds and their synthetic derivates are undergoing clinical trials as anticancer drugs [103]. Here, we focus on marine long-chain **ω-3** polyunsaturated fatty acids (PUFAs) for which there is considerable evidence as regards possible ion channel effects.

3.1 Omega-3 polyunsaturated fatty acids

There are three biologically significant members of the **ω-3** PUFA family: Alpha-linolenic acid (ALA; 18:3n-3), which has the main function of being a precursor of the other two, eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3), the latter two being the most active. ALA can be synthesised in plants (e.g. dark green leafy vegetables, soybeans, canola oil, flaxseeds, some nuts, especially walnuts, and fenugreek), but not in humans. Therefore, **ω-3** PUFAs are “essential” to humans and must be obtained from diet. However, the conversion of ALA to the more active, longer-chain metabolites is inefficient [104] and the major source of DHA and EPA intake in humans is marine food, especially oily fish and fish oils [105]. Indeed, epidemiologic data from populations with high consumption of fish and fish oil have shown that there is a positive correlation between reduced incidence of various cancers and marine food intake. There is also substantial experimental evidence for a protective role of **ω-3** PUFAs against carcinogenesis in in vitro and animal models of cancer, including breast, prostate, colon, melanoma [106-109]. We should note, however, that a recent analysis of a range of earlier data produced a rather surprising ‘null’ effect [110]. Nevertheless, **ω-3** PUFAs have been used in clinical trials, since no serious side effects or complications were apparent [111]. Furthermore, **ω-3** PUFAs would increase the cytotoxicity of several antineoplastic agents [112].

Strong inhibitory effects of **ω-3** PUFAs on VGSC activity has been established in several studies, although not

always on cancer or cancer cell lines [113,114]. Xiao et al. (1995) showed that there is a potent inhibitory effect of **ω-3** PUFAs on VGSC expression in isolated neonatal rat cardiac myocytes [115]. Inhibition of VGSC activity was dose, time and voltage-dependent, but not use dependent. Although DHA, EPA and ALA also blocked VGSCs in adult rat cardiac myocytes, generally around 3-fold higher concentrations were needed [116]. More recently, similar inhibitory effects of PUFAs on VGSC were reported on human bronchial smooth muscle cells [113]. The inhibition was dose-dependent, with a half-maximal inhibitory concentration (IC50) for EPA of some 2 μM. Beside the direct / acute effect of EPA on the VGSC activity, EPA also had a chronic effect on VGSC gene expression.

More recently, we have investigated the effects of DHA on the VGSC expressed in the strongly metastatic human breast cancer line, MDA-MB-231 [117]. We have also tested the influence of DHA on the in vitro metastatic cell behaviour (migration) of this cell line. Micromolar levels both short-term (acute) and long-term (48 – 72 h) application of DHA significantly blocked the VGSC current. In addition, long-term (48 h) application of the fatty acid down-regulated both mRNA and total and plasma membrane protein levels of the VGSC. Moreover, DHA exhibited a potentially anti-metastatic effect, reducing in vitro migration by ~25 %. Importantly, this effect appeared to be mediated via the VGSC inhibition, since co-application of DHA and TTX, a highly specific blocker of VGSCs had the same quantitative effect as DHA or TTX by itself [117].

As regards K+ channels, in cardiac cells, 30 μM DHA, but not ALA, produced a direct open channel block of the cardiac delayed-rectifier K+ channel (Kv1.5), possibly by direct binding to an extracellular domain [118]. DHA blocked the human transient outward K+ (Ito) current encoded by the Kv4.3 gene [119]. Xiao et al. (2002) also reported that **ω-3** PUFAs (DHA and EPA) inhibited two outward K+ currents: Ito and the delayed rectifier K+ current (IK) in adult ferret cardiomyocytes cultures [120]. Interestingly, it was noted that the **ω-3** PUFA-induced inhibition of cardiac Ito and IK was much less potent than the effect on VGSC [120]. However, Leifert et al. (2000) reported that dietary **ω-3** PUFAs supplementation did not significantly affect whole-cell cardiac outward K+ currents in rat cardiomyocytes [121]. Jude et al. (2003) studied Ito in rat ventricular myocytes by whole-cell patch clamp recording and found that 10 μM DHA blocked Ito but activated a delayed outward current [122]. Human HERG channels, expressed in CHO cells, were blocked by 10 μM DHA in a time, voltage and use dependent manner [123]. On the other hand, 20 μM DHA significantly increased the activity of the cardiac delayed rectifier channel expressed in Xenopus oocytes [124].

The mechanism by which ω-3 PUFAs may regulate ion channels especially, VGSCs are unclear. There is increasing evidence indicating that free fatty acids may act directly on channels themselves and not via metabolites [118,125,126]. Xiao et al. (2001) proposed that the binding site of EPA upon Nav1.4 was located on the cytoplasmic segment linking transmembrane domains DIII and DIV in the α-subunit [126]. Alternatively, it has also been proposed that ω-3 PUFAs may affect ion channels indirectly by altering the fluidity of the phospholipid bilayer [127].

On the whole, therefore, it would appear that ω-3 PUFAs inhibit VGSCs but may potentiate the activity of some delayed rectifier VGPCs. This is precisely the reversal of the VGSC - VGPC pattern seen in metastatic carcinoma cells (Fig. 2). Thus, the effects of ω-3 PUFAs on VGSC and VGPC activity can be synergistic, consistent with suppression of membrane excitability and the CELEX hypothesis.

4. MINERALS

Several minerals, including trace elements, are thought to have anti-cancer properties [128]. These are likely to have a diversity of biological actions. Particularly interesting examples are zinc and selenium [129].

4.1 Zinc

This is an important part of diet. Several foods are rich in zinc, including pumpkin seeds, flax seeds, fish, wholegrains and legumes, and these may have anti-cancer effects [130]. Zn2+ is a metal (65.4 Da) and occurs in solution as inorganic cation Zn2+. There are specific membrane transporters for Zn2+ and both intracellular and extracellular Zn2+ are biologically highly active. Lower levels of Zn2+ have been found in prostate cancer patients compared with the normal and it has been suggested that zinc supplementation could be good against prostate cancer [131].

Zn2+ has been found to have a variety of effects on ion channels at dietary concentrations (~100 μM). In the original work on the squid giant axon model, Zn2+ inhibited VGSC functioning by slowing channel opening kinetics [132]. In a comparative study of cations, sub-mM Zn2+ was found to be very effective in inhibiting VGSC current in canine Purkinje fibres by inducing a depolarizing shift in voltage dependence of activation as well as a delaying of time to peak [133,134]. Ravindran et al. (1991) studied effects of Zn2+ on rat skeletal and canine cardiac (Nav1.5) VGSCs and found voltage-dependent blocking effects with differential sensitivity (~100-fold higher, KB ~60 μM) for the latter [135]. In mammalian heart VGSCs, the effect was direct upon the VGSC protein since sub-conductance effects could be observed upon VGSCs inserted into planar bilayers [136]. The site of action of Zn2+, indeed, was determined to be near or within the saxitoxin binding site [137]. As regards, K+ channels, both inhibitory and enhancement effects have been reported. Thus, micromolar Zn2+

inhibited cloned mammalian Kv1.1, Kv1.3, Kv1.4 and Kv1.5 channels by shifting the voltage dependency of activation and inactivation in the depolarizing direction [138,139], as well as a reduction in peak conductance [140]. Differential effects were seen on human two-pore K+ channels. TREK-1 and TASK-3 were inhibited by micromolar Zn2+ whilst TASK-1 and TASK-2 (all expressed in Xenopus oocytes) were not affected [141,142]. On the other hand, TREK-2 channels were activated by Zn2+ with an EC50 of ~90 μM [143]. Interestingly, KATP channels were also activated by both intracellular and intracellular Zn2+ in transfectant COS-7 cells [144], an insulinoma cell line [145] and rat hippocampal neurones [146]. At a different level, it has also been shown that Zn2+ is necessary for the assembly of VGPC tetramers, i.e. Zn2+ could also promote VGPC activity indirectly [147,148].

In spite of the broad range of possible actions and proteins associated with Zn2+, the effect on VGSCs is consistently one of inhibition. On the other hand, K+ channels are either inhibited or activated by Zn2+. Taken together, therefore, the potential beneficiary effects of Zn2+ on cancer is in accordance with the CELEX hypothesis. Indeed, Zn2+ has been suggested to be an endogenous and exogenous modulator of cellular excitability [149].

6. CONCLUSIONS AND FUTURE PERSPECTIVES

In this review, we made an initial attempt to evaluate the modes of action of a number of dietary compounds for which evidence exits for anti-cancer role. As targets of action, we specifically focused on ion channels and membrane excitability in the light of our recent work in this area. The CELEX hypothesis proposed here for the first time assumed that compounds that would block VGSC activity would be good anti-metastatic agents since VGSC activity has been shown previously to enhance metastatic cell behaviours and correlate with in vivo metastatic potential [references given in the Introduction]. The evidence for almost all of the dietary compounds reviewed – phytochemicals (resveratrol, curcumin, capsaicin, genistein and ginseng), marine foods (ω-3 PUFAs) and minerals (Zn2+) would appear to support the CELEX hypothesis, at least for the main VGSC component. The role of K+ channels would be more complex since K+ channel blockage could suppress proliferation (i.e., primary tumorigenesis), whilst in advanced (metastatic) disease when proliferation could of secondary importance, it would be K+ channel (especially VGPC) enhancement, concurrent with VGSC suppression, that would be beneficial. Such mixed role of K+ channels may cause some of the discrepancy in the reported effects of vegetables and fruit in cancer [37]. Such diet would be high in K+ and elevated plasma K+ (reduced trans-membrane electrochemical gradient) could have an effect in the same direction as K+ channel suppression. One might expect, therefore, that dietary compounds blocking K+ channel activity would be good against early-stage cancer (primary tumorigenesis) but not late-stage (metastatic) cancer. However, this viewpoint is likely to be simplistic since it is increasingly been recognized that the relationship between proliferative and metastatic disease stages may not be one of a direct progression and that tumours may be 'pre-programmed' as metastatic [150]. According to our current understanding, therefore, the VGSC part of the CELEX hypothesis may be viewed as being relatively the more significant. In any case, as noted already in the Introduction, it is metastasis that is the main cause of death in most cancer cases.

There are several dietary compounds, with varying evidence for anti-cancer effects, that remain to be tested in the context of the CELEX hypothesis. These include lycopene, a potent antioxidant carotenoid, mostly found in tomatoes, which has been shown to inhibit tumour cell growth [151]. In combination with vitamin E and selenium, lycopene suppressed metastatic tendency in human prostate cancer [152]. Catechins are the active ingredients of green tea for which there is substantial anti-cancer / metastasis effects with a range of modes of action [153]. A particularly important such effect appears to involve angiogenesis [154]. It would be of interest to determine if such effects of catechins might involve ion channels, including VGSCs, known to be expressed in human endothelial cells [155]. Another potentially interesting dietary supplement is "kava kava" which a strong "calming agent", associated with low incidence of cancer [23]. Finally, vitamins A, C, D and E have been associated with anti-cancer effects and some are currently undergoing clinical trials [156], but it is not known if any would affect ion channels. Importantly, the association of vitamin D with Ca2+ homeostasis is well known, so ion channel effects would seem feasible.

Extending diet to natural products generally, additional candidates emerge. Aspirin, digitalis and taxol are known to have anti-cancer effects and their modes of action may involve ion channels, including VGSCs. Our own work already would suggest that the highly specific VGSC blocker TTX (produced naturally by puffer fish) is a potential anti-metastasis drug. Although TTX is can be lethal, clinical trials are underway for its use as a novel analgesic (www.wextech.ca). There is preliminary [157] and anectodotal evidence (www.escozul.com) that scorpion toxin may be effective against certain gliomas. Scorpion toxin is another potent VGSC blocker [158].

In this review, we focused on VGSC and K+ channels as novel targets for cancer therapy, in particular, the VGSC + VGPC combination as a minimal functional unit to elicit membrane excitability. We should stress, however, that ion channels work broadly as an 'orchestra' and, indeed, there is some evidence for other types of ion channels, especially voltage-gated Ca2+ channels, to be involved in the cancer process [e.g. 159]. Interestingly, an inverse correlation has been found between use of Ca2+ channel blocker drugs and incidence of prostate cancer

[160]. Finally, returning to natural products, conotoxins (from marine snails), which are potent Ca2+ channel blockers, have also been suggested to have clinical potential as drugs [161].

In conclusion, several dietary compounds could have anti-cancer, especially anti-metastatic effects via action upon ion channels and reduction of membrane excitability. We propose that this is a viable field of study warranting further, more detailed studies on modes of action, concentration and possible time-dependent effects [e.g. 162].

Acknowledgements

Our collaboration was initiated by a grant from the Scientific & Technological Research Council of Turkey (TUBITAK). Additional support was provided by the Pro Cancer Research Fund (PCRF). We thank Dr Scott Fraser for help in preparing the manuscript.

References

[1] Williams GM, Williams CL, Weisburger JH. (1999) Diet and cancer prevention: the fiber first diet. Toxicol. Sci. 52 (2 Suppl), 72-86.

[2] Wayne SJ, Baumgartner K, Baumgartner RN, Bernstein L, Bowen DJ, Ballard-Barbash R. (2006) Diet quality is directly associated with quality of life in breast cancer survivors. Breast Cancer Res. Treat. 96 (3), 227-32.

[3] Weisburger JH. (1999) Antimutagens, anticarcinogens, and effective worldwide cancer prevention. J. Environ. Pathol. Toxicol. Oncol. 18 (2), 85-93.

[4] Frenkel M, Ben-Arye E, Baldwin CD, Sierpina V. (2005) Approach to communicating with patients about the use of nutritional supplements in cancer care. South Med. J. 98 (3), 289-94.

[5] Serra-Majem L, Roman B, Estruch R. (2006) Scientific evidence of interventions using the Mediterranean diet: a systematic review. Nutr. Rev. 64 (2), S27-47.

[6] Sarkar FH, Li Y. (2003) Soy isoflavones and cancer prevention. Cancer Invest. 21 (5), 744-57.

[7] Constantinou AI, White BE, Tonetti D, Yang Y, Liang W, Li W, van Breemen RB. (2005) The soy isoflavone daidzein improves the capacity of tamoxifen to prevent mammary tumours. Eur. J. Cancer. 41 (4), 647-54.

[8] Sarkar FH, Li Y. (2006) Using chemopreventive agents to enhance the efficacy of cancer therapy. Cancer Res. 66 (7), 3347-50.

[9] Harlan WR. Jr. (2001) New opportunities and proven approaches in complementary and alternative medicine research at the National Institutes of Health. J. Altern. Complement. Med. 7 (Suppl 1), S53-9.

[10] Ray A. (2005) Cancer preventive role of selected dietary factors. Indian J. Cancer. 42 (1), 15-24.

[11] Grimes JA, Fraser SP, Stephens GJ, Downing JE, Laniado ME, Foster CS, Abel PD, Djamgoz MB. (1995) Differential expression of voltage-activated Na+ currents in two prostatic tumour cell lines: contribution to invasiveness in vitro. FEBS Lett. 369 (2-3), 290-4.

[12] Laniado ME, Lalani EN, Fraser SP, Grimes JA, Bhangal G, Djamgoz MD, Abel PD. (1997) Expression and functional analysis of voltage-activated Na+ channels in human prostate cancer cell lines and their contribution to invasion in vitro. Am. J. Pathol. 150 (4), 1213-21.

[13] Bennett ES, Smith BA, Harper JM. (2004) Voltage-gated Na+ channels confer invasive properties on human prostate cancer cells. Pflugers Arch. 447 (6), 908-14.

[14] Roger S, Besson P, Le Guennec JY. (2003) Involvement of a novel fast inward sodium current in the invasion capacity of a breast cancer cell line. Biochim. Biophys. Acta. 1616 (2), 107-11.

[15] Fraser SP, Diss JK, Chioni AM, Mycielska ME, Pan H, Yamaci RF, Pani F, Siwy Z, Krasowska M, Grzywna Z, Brackenbury WJ, Theodorou D, Koyuturk M, Kaya H, Battaloglu E, De Bella MT, Slade MJ, Tolhurst R, Palmieri C, Jiang J, Latchman DS, Coombes RC, Djamgoz MB. (2005) Voltage-gated sodium channel expression and potentiation of human breast cancer metastasis. Clin. Cancer Res. 11 (15), 5381-9.

[16] Pancrazio JJ, Tabbara IA, Kim YI. (1993) Voltage-activated K+ conductance and cell proliferation in small-cell lung cancer. Anticancer Res. 13 (4), 1231-4.

[17] Blandino JK, Viglione MP, Bradley WA, Oie HK, Kim YI. (1995) Voltage-dependent sodium channels in human small-cell lung cancer cells: role in action potentials and inhibition by Lambert-Eaton syndrome IgG. J. Membr. Biol. 143 (2), 153-63.

[18] Onganer PU, Djamgoz MBA (2005) Small-cell lung cancer (human): potentiation of endocytic membrane activity by voltage-gated Na+ channel expression in vitro. J. Membr. Biol. 204 (2), 67-75.

[19] Champigny G, Verrier B, Lazdunski M. (1991) A voltage, calcium, and ATP sensitive non selective cation channel in human colonic tumor cells. Biochem. Biophys. Res. Commun. 176 (3), 1196-203.

[20] Lepple-Wienhues A, Berweck S, Bohmig M, Leo CP, Meyling B, Garbe C, Wiederholt M. (1996) K+ channels and the intracellular calcium signal in human melanoma cell proliferation. J. Membr. Biol. 151 (2), 149-57.

[21] Fraser SP, Diss JK, Llyod LJ, Pani F, Chioni AM, George AJ, Djamgoz MB. (2004) T-lymphocyte invasiveness: control by voltage-gated Na+ channel activity. FEBS Lett. 569 (1-3), 191-4.

[22] Onganer PU, Seckl MJ, Djamgoz MB. (2005) Neuronal characteristics of small-cell lung cancer. Br. J. Cancer. 93 (11), 1197-201.

[23] Hoang BX, Levine SA (2006) Hypothesis of the cause and development of neoplasms. Eur. J. Cancer Prevent. In the press.

[24] Diss JK, Fraser SP, Djamgoz MB. (2004) Voltage-gated Na+ channels: multiplicity of expression, plasticity, functional implications and pathophysiological aspects. Eur. Biophys J. 33 (3), 180-93.

[25] O'Grady S, Lee SY. (2005) Molecular diversity and function of voltage-gated (Kv) potassium channels in epithelial cells. Int. J. Biochem. Cell Biol. 37 (8), 1578-94.

[26] Fraser SP, Ding Y, Liu A, Foster CS, Djamgoz MB. (1999) Tetrodotoxin suppresses morphological enhancement of the metastatic MAT-LyLu rat prostate cancer cell line. Cell Tissue Res. 295 (3), 505-12.

[27] **Djamgoz MBA, Mycielska M, Madeja Z, Fraser SP, Korohoda W. (2001)** Directional movement of rat prostate cancer cells in direct-current electric field: involvement of voltage-gated Na+ channel activity. **J.** *Cell Sci.* 114 (14), 2697-705.

[28] Fraser SP, Salvador V, Manning EA, Mizal J; Altun S, Raza M, Berridge RJ, Djamgoz MB. (2003) Contribution of functional voltage-gated Na+ channel expression to cell behaviors involved in the metastatic cascade in rat prostate cancer: I. Lateral motility. J. Cell Physiol. 195 (3), 479-87.

[29] **Mycielska M, Fraser SP, Szatkowski M, Djamgoz MB.** (2003) Contribution of functional voltage-gated Na+ channel expression to cell behaviors involved in the metastatic cascade in rat prostate cancer: II. Secretory membrane activity. J. Cell Physiol. 195 (3), 461-9.

[30] Krasowska M, Gryzwna ZJ, Mycielska ME, Djamgoz MB. (2004) Patterning of endocytic vesicles and its control by voltage-gated Na+ channel activity in rat prostate cancer cells: fractal analyses. Eur. Biophys. J. 33 (6), 535-42.

[31] Mycielska ME, Dye, J, Stepien, E, Djamgoz, MBA. (2004) Substrate influences voltage-gated Na+ channel expression in strongly metastatic rat prostate cancer cell line. J. Physiol. **557P,** C85.

[32] Diss JK, Stewart D, Pani F, Foster CS, Walker MM, Patel A, Djamgoz MB. (2005) A potential novel marker for human prostate cancer: voltage-gated sodium channel expression in vivo. Prostate Cancer Prostatic Dis. 8 (3), 266-73.

[33] Abdul M, Hoosein N. (2002) Expression and activity of potassium ion channels in human prostate cancer. Cancer Lett. 186 (1), 99-105.

[34] Anderson JD, Hansen TP, Lenkowski PW, Walls AM, Choudhury IM, Schenck HA, Friehling M, Holl GM, Patel MK, Sikes RA, Brown ML. (2003) Voltage-gated sodium channel blockers as cytostatic inhibitors of the androgen-independent prostate cancer cell line PC-3. Mol. Cancer Ther. 2 (11), 1149-54.

[35] Park EJ, Pezzuto JM. (2002) Botanicals in cancer chemoprevention. Cancer Metastasis Rev. 21 (3-4), 231-55.

[36] Dong Z. (2000) Effects of food factors on signal transduction pathways. Biofactors. 12 (1-4), 17-28.

[37] Kroenke CH, Fung TT, Hu FB, Holmes MD. (2005) Dietary patterns and survival after breast cancer diagnosis. J. Clin. Oncol. 23 (36), 9295-303.

[38] Langcake P, Pryce RJ. (1997) A new class of phytoalexins from grapevines. Experientia. 33 (2), 151-2.

[39] Wolter F, Ulrich S, Stein J. (2004) Molecular mechanisms of the chemopreventive effecs of resveratrol and its analogs in colorectal cancer: key role of polyamines. J. Nutr. 134 (12), 3219-22.

[40] Stewart JR, Artime MC, O'Brian CA. (2003) Resveratrol: a candidate nutritional substance for prostate cancer prevention. J. Nutr. 133 (7 Suppl), 2440S-3S.

[41] Ulrich S, Wolter F, Stein JM. (2005) Molecular mechanisms of the chemopreventive effects of resveratrol and its analogs in carcinogenesis. Mol. Nutr. Food Res. 49 (5), 452-61.

[42] Wu YL, Ohsaga A, Oshiro T, Iinuma K, Kondo Y, Ebihara S, Sasaki H, Maruyama Y. (2005) Suppressive effects of red wine polyphenols on voltage-gated ion channels in dorsal root ganglionic neuronal cells. Tohoku J. Exp. Med. 206 (2), 141-50.

[43] Kim HI, Kim TH, Song JH. (2005) Resveratrol inhibits Na+ currents in rat dorsal root ganglion neurons. Brain Res. 1045 (1-2), 134-41.

[44] Orsini F, Verotta L, Lecchi M, Restano R, Curia G, Redaelli E, Wanke E. (2004) Resveratrol derivates and their role as potassium channels modulators. J. Nat. Prod. 67 (3), 421-6.

[45] Granados-Soto V, Arguelles CF, Ortiz MI. (2002) The peripheral antinociceptive effect of resveratrol is associated with activation of potassium channels. Neuropharmacology. 43 (5), 917-23.

[46] Zhang Y, Liu Y, Wang T, Li B, Li H, Wang Z, Yang B. (2006) Resveratrol, a natural ingredient of grape skin: antiarrhythmic efficacy and ionic mechanisms. Biochem. Biophys. Res. Commun. 340 (4), 1192-9.

[47] Shimizu T, Nakazato T, Xian MJ, Sagawa M, Ikeda Y, Kizaki M. (2006) Resveratrol induces apoptosis of human malignant B cells by activation of caspase-3 and p38 MAP kinase pathways. Biochem. Pharmacol. 71 (6), 742-50.

[48] Blumenstein I, Keseru B, Wolter F, Stein J.(2005) The chemopreventive agent resveratrol stimulates cyclic AMP-dependent chloride secretion in vitro. Clin. Cancer Res. 11 (15), 5651-6.

[49] Tang XQ, Bi H, Feng JQ, Cao JG. (2005) Effect of curcumin on multidrug resistance in resistant human gastric carcinoma cell line SGC7901/VCR. Acta Pharmacol. Sin. 26 (8), 1009-16.

[50] Siwak DR, Shishodia S, Aggarwal BB, Kurzrock R. (2005) Curcumin-induced antiproliferative and proapoptotic effects in melanoma cells are associated with suppression of IkappaB kinase and nuclear factor kappaB activity and are independent of the B-Raf/mitogen-activated/extracellular signal-regulated protein kinase pathway and the Akt pathway. Cancer. 104 (4), 879-90.

[51] Dorai T, Cao YC, Dorai B, Buttyan R, Katz AE. (2001) Therapeutic potential of curcumin in human prostate cancer. III. Curcumin inhibits proliferation, induces apoptosis, and inhibits angiogenesis of LNCaP prostate cancer cells in vivo. Prostate. 47 (4), 293-303.

[52] Shishodia S, Amin HM, Lai R, Aggarwal BB. (2005) Curcumin (diferuloylmethane) inhibits constitutive NF-kappaB activation, induces G1/S arrest, suppresses proliferation, and induces apoptosis in mantle cell lymphoma. Biochem. Pharmacol. 70 (5), 700-13.

[53] Aggarwal BB, Shishodia S, Takada Y, Banerjee S, Newman RA, Bueso-Ramos CE, Price JE. (2005) Curcumin suppresses the paclitaxel-induced nuclear factor-kappaB pathway in breast cancer cells and inhibits lung metastasis of human breast cancer in nude mice. Clin. Cancer Res. 11 (20), 7490-8.

[54] Keller DI, Rougier JS, Kucera JP, Benammar N, Fressart V, Guicheney P, Madle A, Fromer M, Schlapfer J, Abriel H. (2005) Brugada syndrome and fever: genetic and molecular characterization of patients carrying SCN5A mutations. Cardiovasc. Res. 67 (3), 510-9.

[55] Kunzelmann K. (2001) CFTR: interacting with everything? News Physiol. Sci. 16, 167-70.

[56] Dyer JL, Khan SZ, Bilmen JG, Hawtin SR, Wheatley M, Javed MU, Michelangeli F. (2002) Curcumin: a new cell-permeant inhibitor of the inositol 1,4,5-triphosphate receptor. Cell Calcium. 31 (1), 45-52.

[57] Shishodia S, Sethi G, Aggarwal BB. (2005) Curcumin: getting back to the roots. Ann. N. Y. Acad. Sci. 1056, 206-17.

[58] Kim JH, Xu C, Keum YS, Reddy B, Conney A, Kong AN. (2006) Inhibiton of EGFR signalling in human prostate cancer PC-3 cells by combination treatment with beta-phenylethyl isothiocyanate and curcumin. Carcinogenesis. 27 (3), 475-82.

[59] Sashihara S, Tsuji S, Matsui T. (1998) Oncogenes and signal transduction pathways involved in the regulation of Na+ channel expression. Crit. Rev. Oncog. 9 (1), 19-34.

[60] Tuoya, Baba N, Shimoishi Y, Murata Y, Tada M, Koseki M, Takahata K. (2006) Apoptosis induction by dohevanil, a DHA substitutive analog of capsaicin, in MCF-7 cells. Life Sci. 78 (13), 1515-9.

[61] Kim CS, Park WH, Park JY, Kang JH, Kim MO, Kawada T, Yoo H, Han IS, Yu R. (2004) Capsaicin, a spicy component of hot pepper, induces apoptosis by activation of the peroxisome proliferator-activated receptor gamma in HT-29 human colon cancer cells. J. Med. Food. 7 (3), 267-73.

[62] Lo YC, Yang YC, Wu IC, Kuo FC, Liu CM, Wang HW, Kuo CH, Wu Jy, Wu DC. (2005) Capsaicin-induced cell death in a human gastric adenocarcinoma cell line. World J. Gastroenterol. 11 (40), 6254-7.

[63] Mori A, Lehmann S, O'Kelly J, Kumagai T, Desmond JC, Pervan M, McBride WH, Kizaki M, Koeffler HP. (2006) Capsaicin, a component of red peppers, inhibits the growth of androgen-independent, p53 mutant prostate cancer cells. Cancer Res. 66 (6), 3222-9.

[64] Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. (1997) The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature. 389 (6653), 816-24.

[65] Su X, Wachtel RE, Gebhart GF. (1999) Capsaicin sensivity and voltage-gated sodium currents in colon sensory neurons from rat dorsal root ganglia. Am. J. Physiol. 277 (6), G1180-8.

[66] Liu L, Oortgiesen M, Li L, Simon SA. (2001) Capsaicin inhibits activation of voltage-gated sodium currents in capsaicin-sensitive trigeminal ganglion neurons. J. Neurophysiol. 85 (2), 745-58.

[67] Milesi V, Rebolledo A, Alvis AG, Raingo J, Grassi de Gende AO. (2001) Voltage-activated sodium current is inhibited by capsaicin in rat atrial myocytes. Biochem. Biophys. Res. Commun. 282 (4), 965-70.

[68] Kohane DS, Kuang Y, Lu NT, Langer R, Strichartz GR, Berde CB. (1999) Vanilloid receptor agonists potentiate the in vivo local anesthetic activity of percutaneously injected site 1 sodium channel blockers. Anesthesiology. 90 (2), 524-34.

[69] Lundbaek JA, Birn P, Tape SE, Toombes GE, Sogaard R, Koeppe RE 2nd, Gruner SM, Hansen AJ, Andersen OS. (2005) Capsaicin regulates voltage-dependent sodium channels by altering lipid bilayer elasticity. Mol. Pharmacol. 68 (3), 680-9.

[70] Bielefeldt K. (2000) Differential effects of capsaicin on rat visceral sensory neurons. Neuroscience. 101 (3), 727-36.

[71] Baker MD, Ritchie JM. (1994) The action of capsaicin on type I delayed rectifier K+ currents in rabbit Schwann cells. Proc. Biol. Sci. 255 (1344), 259-65.

[72] Kehl SJ. (1994) Block by capsaicin of voltage-gated K+ currents in melanotrophs of the rat pituitary. Br. J. Pharmacol. 112 (2), 616-24.

[73] Park K, Brown PD, Kim YB, Kim JS. (2003) Capsaicin modulates K+ currents from dissociated rat taste receptor cells. Brain Res. 962 (1-2), 135-43.

[74] Liu L, Simon SA. (2003) Modulation of IA currents by capsaicin in rat trigeminal ganglion neurons. J Neurophysiol. 89 (3), 1387-401.

[75] Yeon D, Kwon S, Lee Y, Leem J, Nam T, Ahn D. (2001) Capsaicin-induced relaxation in rabbit coronary artery. J. Vet. Med. Sci. 63 (5), 499-503.

[76] Santell RC, Kieu N, Helferich WG. (2000) Genistein inhibits growth of estrogen-independent human breast cancer cells in culture but not in athymic mice. J. Nutr. 130 (7), 1665-9.

[77] Sarkar FH, Adsule S, Padhye S, Kulkarni S, Li Y. (2006) The role of genistein and synthetic derivates of isoflavone in cancer prevention and therapy. Mini Rev. Med. Chem. 6 (4), 401-7.

[78] Ju YH, Allred CD, Allred KF, Karko KL, Doerge DR, Helferich WG. (2001) Physiological concentrations of dietary genistein dose-dependently stimulate growth of estrogen-dependent human breast cancer (MCF-7) tumors implanted in athymic nude mice. J. Nutr. 131 (11), 2957-62.

[79] Hilborn MD, Vaillancourt RR, Rane SG. (1998) Growth factor receptor tyrosine kinases acutely regulate neuronal sodium channels through the src signaling pathway. J. Neurosci. 18 (2), 590-600.

[80] Bouron A, Becker C, Porzig H. (1999) Functional expression of voltage-gated Na+ and Ca2+ channels during neuronal differentiation of PC12 cells with nerve growth factor or forskolin. Naunyn Schmiedebergs Arch. Pharmacol. 359 (5), 370-7.

[81] Liu L, Yang T, Simon SA. (2004) The protein tyrosine kinase inhibitor, genistein, decreases excitability of nociceptive neurons. Pain. 112 (1-2), 131-41.

[82] Kusaka M, Sperelakis N. (1996) Genistein inhibition of fast Na+ current in uterine leiomyosarcoma cells is independent of tyrosine kinase inhibition. Biochim. Biophys. Acta. 1278 (1), 1-4.

[83] Paillart C, Carlier E, Guedin D, Dargent B, Couraud F. (1997) Direct block of voltage-sensitive sodium channels by genistein, a tyrosine kinase inhibitor. J. Pharmacol. Exp. Ther. 280 (2), 521-6.

[84] Watson CL, Gold MR. (1997) Lysophosphatidylcholine modulates cardiac I(Na) via multiple protein kinase pathways. Circ. Res. 81 (3), 387-95.

[85] Wang Y, Wagner MB, Kumar R, Cheng J, Joyner RW. (2003) Inhibition of fast sodium current in rabbit ventricular myocytes by protein tyrosine kinase inhibitors. Pflugers Arch. 446 (4), 485-91.

[86] Washizuka T, Horie M, Obayashi K, Sasayama S. (1998) Genistein inhibits slow component delayed-rectifier K currents via a tyrosine kinase-independent pathway. J. Mol. Cell. Cardiol. 30 (12), 2577-90.

[87] Peretz A, Sobko A, Attali B. (1999) Tyrosine kinases modulate K+ channel gating in mouse Schwann cells. J. Physiol. 519 (2), 373-84.

[88] Teisseyre A, Michalak K. (2005) Genistein inhibits the activity of Kv1.3 potassium channels in human T lymphocytes. J. Membr. Biol. 205 (2), 71-9.

[89] Zhang ZH, Wang Q. (2000) Modulation of a cloned human A-type voltage-gated potassium channel (hKv1.4) by the protein tyrosine kinase inhibitor genistein. Pflugers Arch. 440 (5), 784-92.

[90] Radad K, Gille G, Liu L, Rausch WD. (2006) Use of ginseng in medicine with emphasis on neurodegenerative disorders. J. Pharmacol. Sci. 100 (3), 175-86.

[91] Liu WK, Xu SX, Che CT. (2000) Anti-proliferative effect of ginseng saponins on human prostate cancer cell line. Life Sci. 67 (11), 1297-306.

[92] Shin HR, Kim JY, Yun TK, Morgan G, Vainio H. (2000) The cancer-preventive potential of Panax ginseng: a review of human and experimental evidence. Cancer Causes Control. 11 (6), 565-76.

[93] Fukushima S, Wanibuchi H, Li W. (2001) Inhibition by ginseng of colon carcinogenesis in rats. J. Korean Med. Sci. 16 Suppl, S75-80.

[94] Lee JH, Jeong SM, Kim JH, Lee BH, Yoon IS, Lee JH, Choi SH, Kim DH, Rhim H, Kim SS, Kim JI, Jang CG, Song JH, Nah SY. (2005) Characteristics of ginsenoside Rg3-mediated brain Na+ current inhibition. Mol. Pharmacol. 68 (4), 1114-26.

[95] Liu D, Li B, Liu Y, Attele AS, Kyle JW, Yuan CS. (2001) Voltage-dependent inhibition of brain Na+ channels by American ginseng. Eur. J. Pharmacol. 413 (1), 47-54.

[96] Kang DI, Lee JY, Yang JY, Jeong SM, Lee JH, Nah SY, Kim Y. (2005) Evidence that the tertiary structure of 20(S)-ginsenoside Rg(3) with tight hydrophobic packing near the chiral center is important for Na+ channel regulation. Biochem. Biophys. Res. Commun. 333 (4), 1194-201.

[97] Jeong SM, Lee JH, Kim JH, Lee BH, Yoon IS, Lee JH, Kim DH, Rhim H, Kim Y, Nah SY. (2004) Stereospecificity of ginsenoside Rg3 action on ion channels. Mol. Cells. 18 (3), 383-9.

[98] Kim CS, Son SJ, Kim HS, Kim YD, Lee KS, Jeon BH, Kim KJ, Park JK, Park JB. (2005) Modulating effect of ginseng saponins on heterologously expressed HERG currents in Xenopus oocytes. Acta Pharmacol. Sin. 26 (5), 551-8.

[99] Bai CX, Takahashi K, Masumiya H, Sawanobori T, Furukawa T. (2004) Nitric oxide-dependent modulation of the delayed rectifier K+ current and the L-type Ca2+ current by ginsenoside Re, an ingredient of Panax ginseng, in guinea-pig cardiomyocytes. Br. J. Pharmacol. 142 (3), 567-75.

[100] Kim ND, Kang SY, Park JH, Schini-Kerth VB. (1999) Ginsenoside Rg3 mediates endothelium-dependent relaxation in response to ginsenosides in rat aorta: role of K+ channels. Eur. J. Pharmacol. 367 (1), 41-9.

[101] Duan Y, Zheng J, Law V, Nicholson R. (2006) Natural products from ginseng inhibit [3H]batrachotoxinin A 20-alpha-benzoate binding to Na+ channels in mammalian brain. Eur. J. Pharmacol. 530 (1-2), 9-14.

[102] Rawat DS, Joshi MC, Joshi P, Atheaya H. (2006) Marine peptides and related compounds in clinical trail. Anticancer Agents Med. Chem. 6 (1), 33-40.

[103] Simmons TL, Andrianasolo E, McPhail K, Flatt P, Gerwick WH. (2005) Marine natural products as anticancer drugs. Mol. Cancer Ther. 4 (2), 333-42.

[104] Davis BC, Kris-Etherton PM. (2003) Achieving optimal essential fatty acid status in vegetarians: current knowledge and practical implications. Am. J. Clin. Nutr. 78 (3 suppl) 640S-46S.

[105] Jude S, Roger S, Martel E, Besson P, Richard S, Bougnoux P, Champeroux P, Le Guennec JY. (2006) Dietary long-chain omega-3 fatty acids of marine origin: A comparison of their protective effects on coronary heart disease and breast cancers. Prog. Biophys. Mol. Biol. 90 (1-3), 299-325.

[106] Tsujita-Kyutoku M, Yuri T, Danbara N, Senzaki H, Kiyozuka Y, Uehara N, Takada H, Hada T, Miyazawa T, Ogawa Y, Tsubura A. (2004) Conjugated docosahexaenoic acid suppresses KPL-1 human breast cancer cell growth in vitro and in vivo: potential mechanisms of action. Breast Cancer Res. 6 (4), 291–9.

[107] Connolly JM, Coleman M, Rose DP. (1997) Effects of dietary fatty acids on DU-145 human prostate cancer cell growth in athymic nude mice. Nutr. Cancer. 29 (2), 114-9.

[108] Iigo M, Nakagawa T, Ishikawa C, Iwahori Y, Asamato M, Yazawa K, Araki E, Tsuda H. (1997) Inhibitory effects of docosahexaenoic acid on colon carcinoma 26 metastasis to the lung. Br. J. Cancer. 75 (5), 650-5.

[109] Albino AP, Juan G, Traganos F, Reinhart L, Connolly J, Rose DP, Darzynkiewicz Z (2000) Cell cycle arrest and apoptosis of melanoma cells by docosahexaenoic acid: association with decreased pRb phosphorylation. Cancer Res. 60 (15), 4139-45.

[110] Hooper L, Thompson RL, Harrison RA, Summerbell CD, Ness AR, Moore HJ, Worthington HV, Durrington PN, Higgins JP, Capps NE, Riemersma RA, Ebrahim SB, Davey Smith G. (2006) Risks and benefits of omega-3 fats for mortality, cardiovascular disease, and cancer: systematic review. Br. Med. J. 332 (7544), 752-60.

[111] Siddiqui RA, Zerouga M, Wu M, Castillo A, Harvey K, Zaloga GP, Stillwell W. (2005) Anticancer properties of propofol-docosahexaenoate and propofol-eicosapentaenoate on breast cancer cells. Breast Cancer Res. 7 (5), R645-54.

[112] Maheo K, Vibet S, Steghens JP, Dartigeas C, Lehman M, Bougnoux P, Gore J. (2005) Differential sensitization of cancer cells to doxorubicin by DHA: A role for lipoperoxidation. Free Radic. Biol. Med. 39 (6), 742-51.

[113] Jo T, Iida H, Kishida S, Imuta H, Oonuma H, Nagata T, Hara H, Iwasawa K, Soma M, Sato Y, Nagase T, Nagai R, Nakajima T. (2005) Acute and chronic effects of eicosapentaenoic acid on voltage-gated sodium channel expressed in cultured human bronchial smooth muscle cells. Biochem. Biophys. Res. Commun. 331 (4), 1452-9.

[114] Xiao YF, Gomez AM, Morgan JP, Lederer WJ, Leaf A. (1997) Suppression of voltage-gated L-type Ca2+ currents by polyunsaturated fatty acids in adult and neonatal rat ventricular myocytes. Proc. Natl. Acad. Sci. 94 (8), 4182-7.

[115] Xiao YF, Kang JX, Morgan JP, Leaf, A. (1995) Blocking effects of polyunsaturated fatty acids on Na+ channels of neonatal rat ventricular myocytes. Proc. Natl. Acad. Sci. 92 (24), 11000-4.

[116] Leifert WR, McMurchie EJ, Saint DA. (1999) Inhibition of cardiac sodium currents in adult rat by n-3 polyunsaturated fatty acids. J. Physiol. 520 (3), 671-9.

[117] Isbilen B, Fraser SP, Djamgoz MBA. (2006) Docosahexaenoic acid (omega-3) and migration of mda-mb-231 human breast cancer cells: role of voltage-gated sodium channel expression. MS submitted for publication.

[118] Honore E, Barhanin J, Attali B, Lesage F, Lazdunski M. (1994) External blockade of the major cardiac delayed-rectifier K+ channel (Kv1.5) by polyunsaturated fatty acids. Proc. Natl. Acad. Sci. 91 (5), 1937-41.

[119] Singleton CB, Valenzuela SM, Walker BD, Tie H, Wyse KR, Bursill JA, Qiu MR, Breit SN, Campbell TJ. (1999) Blockade by N-3 polyunsaturated fatty acis of the Kv4.3 stably expressed in Chinese hamster ovary cells. Br. J. Pharmacol. 127 (4), 941-8.

[120] Xiao YF, Morgan JP, Leaf A. (2002) Effects of polyunsaturated fatty acids on cardiac voltage- activated K+ currents in adult ferret cardiomyocytes. Sheng Li Xue Bao. 54 (4), 271-81.

[121] Leifert WR, Jahangiri A, McMurchie EJ. (2000) Membrane fluidity changes are associated with the antiarrhythmic effects of docosahexaenoic acid in adult rat cardiomyocytes. J. Nutr. Biochem. 11 (1), 38-44.

[122] Jude S, Bedut S, Roger S, Pinault M, Champeroux P, White E, Le Guennec JY. (2003) Peroxidation of docosahexaenoic acid is responsible for its effects on Ito and Iss in rat ventricular myocytes. Br. J. Pharmacol. 139 (4), 816-22.

[123] Guizy M, Arias C, David M, Gonzalez T, Valenzuela C. (2005) **ω-3 and ω-6 polyunsaturated fatty acids block HERG channels. Am. J. Physiol. Cell Physiol. 289 (5), C1251-60.**

[124] **Doolan GK, Panchal RG, Fonnes EL, Clarke AL, Williams DA, Petrou S. (2002) Fatty acid augmentation of the cardiac slowly activating delayed rectifier current (IKs) is conferred by hminK. FASEB J.** 16 (12), 1662-4.

[125] Huang JM, Xian H, Bacaner M. (1992) Long-chain fatty acids activate calcium channels in ventricular myocytes. Proc. Natl. Acad. Sci. 89 (14), 6452-6.

[126] Xiao YF, Ke Q, Wang SY, Auktor K, Yang Y, Wang GK, Morgan JP, Leaf A. (2001) Single point mutations affect fatty acid block of human myocardial sodium channel alpha subunit Na+ channels. Proc. Natl. Acad. Sci. 98 (6), 3606-11.

[127] Andersen OS, Nielsen C, Maer A, Lundbaek JA, Goulian M, Koeppe RE. (1999) Ion channels as tools to monitor lipid bilayer-membrane protein interactions: gramicidin channels as molecular force transducers. Methods. Enzymol. 294, 208-24.

[128] Whiteside MA, Heimburger DC, Johanning GL. (2004) Micronutrients and cancer therapy. Nutr. Rev. 62 (4), 142-7.

[129] Leone N, Courbon D, Ducimetiere P, Zureik M. (2006) Zinc, copper, and magnesium and risks for all-cause, cancer, and cardiovascular mortality. Epidemiology. 17 (3), 308-14.

[130] Watanebe R, Hanamori K, Kadoya H, Nishimuta M, Miyazaki H. (2004) Nutritional intakes in community-dwelling older Japanese adults: high intakes of energy and protein based on

high consumption of fish, vegetables and fruits provide sufficient micronutrients. J. Nutr. Sci. Vitaminol. 50 (3), 184-95.

[131] Ozmen H, Erulas FA, Karatas F, Cukurovali A, Yalcin O. (2006) Comparison of the concentration of trace metals (Ni, Zn, Co, Cu and Se), Fe, vitamins A, C and E, and lipid peroxidation in patients with prostate cancer. Clin. Chem. Lab. Med. 44 (2), 175-9.

[132] Gilly WF, Armstrong CM. (1982) Slowing of sodium channel opening kinetics in squid axon by extracellular zinc. J. Gen. Physiol. 79 (6), 935-64.

[133] Hanck DA, Sheets MF. (1992) Extracellular divalent and trivalent cation effects on sodium current kinetics in single canine cardiac Purkinje cells. J. Physiol. 454, 267-98.

[134] Sheets MF, Hanck DA. (1992) Mechanisms of extracellular divalent and trivalent cation block of the sodium current in canine cardiac Purkinje cells. J. Physiol. 454, 299-320.

[135] Ravindran A, Schild L, Moczydlowski E. (1991) Divalent cation selectivity for external block of voltage-dependent Na+ channels prolonged by batrachotoxin. Zn2+ induces discrete substates in cardiac Na+ channels. J. Gen. Physiol. 97 (1), 89-115.

[136] Schild L, Moczydlowski E. (1994) Permeation of Na+ through open and Zn2+-occupied conductance states of cardiac sodium channels modified by batrachotoxin: exploring ion-ion interactions in a multi-ion channel. Biophys. J. 66 (3), 654-66.

[137] Schild L, Moczydlowski E. (1991) Competitive binding interaction between Zn2+ and saxitoxin in cardiac Na+ channels. Evidence for a sulfhydryl group in the Zn2+/saxitoxin binding site. Biophys. J. 59 (3), 523-37.

[138] Harrison NL, Radke HK, Tamkun MM, Lovinger DM. (1993) Modulation of gating of cloned rat and human K+ channels by micromolar Zn2+. Mol. Pharmacol. 43 (3), 482-6.

[139] Teisseyre A, Mozrzymas JW. (2002) Inhibition of the activity of T lymphocyte Kv1.3 channels by extracellular zinc. Biochem. Pharmacol. 64 (4), 595-607.

[140] Kehl SJ, Eduljee C, Kwan DC, Zhang S, Fedida D. (2002) Molecular determinants of the inhibition of human Kv1.5 potassium currents by external protons and Zn2+. J. Physiol. 541 (1), 9-24.

[141] Gruss M, Mathie A, Lieb WR, Franks NP. (2004) The two-pore-domain K+ channels TREK-1 and TASK-3 are differentially modulated by copper and zinc. Mol. Pharmacol. 66 (3), 530-7.

[142] Clarke CE, Veale EL, Green PJ, Meadows HJ, Mathie A. (2004) Selective block of the human 2-P domain potassium channel, TASK-3, and the native leak potassium current, IKSO, by zinc. J. Physiol. 560 (1), 51-62.

[143] Kim JS, Park JY, Kang HW, Lee EJ, Bang H, Lee JH. (2005) Zinc activates TREK-2 potassium channel activity. J. Pharmacol. Exp. Ther. 314 (2), 618-25.

[144] Prost AL, Bloc A, Hussy N, Derand R, Vivaudou M. (2004) Zinc is both an intracellular and extracellular regulator of KATP channel function. J. Physiol. 559 (1), 157-67.

[145] Bancila V, Cens T, Monnier D, Chanson F, Faure C, Dunant Y, Bloc A. (2005) Two SUR1-specific histidine residues mandatory for zinc-induced activation of the rat KATP channel. J. Biol. Chem. 280 (10), 8793-9.

[146] Bancila V, Nikonenko I, Dunant Y, Bloc A. (2004) Zinc inhibits glutamate release via activation of pre-synaptic K channels and reduces ischaemic damage in rat hippocampus. J. Neurochem. 90 (5), 1243-50.

[147] Jahng AW, Strang C, Kaiser D, Pollard T, Pfaffinger P, Choe S. (2002) Zinc mediates assembly of the T1 domain of the voltage-gated K+ channel 4.2. J. Biol. Chem. 277 (49), 47885-90.

[148] Strang C, Kunjilwar K, DeRubeis D, Peterson D, Pfaffinger PJ. (2003) The role of Zn2+ in Shal voltage-gated potassium channel formation. J. Biol. Chem. 278 (33), 31361-71.

[149] Mathie A, Sutton GL, Clarke CE, Veale EL. (2006) Zinc and copper: Pharmacological probes and endogenous modulators of neuronal excitability. Pharmacol. Ther. Epub ahead of print.

[150] Pantel K, Brakenhoff RH. (2004) Dissecting the metastatic cascade. Nat. Rev. Cancer. 4 (6), 448-56.

[151] Limpens J, Schroder FH, de Ridder CM, Bolder CA, Wildhagen MF, Obermuller-Jevic UC, Kramer K, van Weerden WM. (2006) Combined lycopene and vitamin E treatment suppresses the growth of PC-346C human prostate cancer cells in nude mice. J. Nutr. 136 (5), 1287-93.

[152] Kucuk O, Sarkar FH, Sakr W, Djuric Z, Pollak MN, Khachik F, Li YW, Banerjee M, Grignon D, Bertram JS, Crissman JD, Pontes EJ, Wood DP Jr. (2001) Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. Cancer Epidemiol. Biomarkers Prev. 10 (8), 861-8.

[153] Khan N, Afaq F, Saleem M, Ahmad N, Mukhtar H. (2006) Targeting multiple signaling pathways by green tea polyphenol (-)-epigallocatechin-3-gallate. Cancer Res. 66 (5), 2500-5.

[154] Oak MH, El Bedohui J, Schini-Kerth VB. (2005) Antiangiogenic properties of natural polyphenols from red wine and green tea. J. Nutr. Biochem. 16 (1), 1-8.

[155] Nilius B, Droogmans G. (2001) Ion channels and their functional role in vascular endothelium. Physiol. Rev. 81 (4), 1415-59.

[156] Van den Bemd GJ, Chang GT. (2002) Vitamin D and vitamin D analogs in cancer treatment. Curr. Drug. Targets. 3 (1), 85-94.

[157] Wang WX, Ji YH. (2005) Scorpion venom induces glioma cell apoptosis in vivo and inhibits glioma tumor growth in vitro. J. Neurooncol. 73 (1), 1-7.

[158] Zuo XP, Ji YH. (2004) Molecular mechanism of scorpion neurotoxins acting on sodium channels: insight into their diverse selectivity. Mol. Neurobiol. 30 (3), 265-78.

[159] Asaga S, Ueda M, Jinno H, Kikuchi K, Itano O, Ikeda T, Kitajima M. (2006) Identification of a new breast cancer-related gene by restriction landmark genomic scanning. Anticancer Res. 26 (1), 35-42.

[160] Debes JD, Roberts RO, Jacobson DJ, Girman CJ, Lieber MM, Tindall DJ, Jacobsen SJ. (2004) Inverse association between prostate cancer and the use of calcium channel blockers. Cancer Epidemiol. Biomarkers Prev. 13 (2), 255-9.

[167] Prommer EE. (2005) Ziconotide: can we use it in palliative care? Am. J. Hosp. Palliat. Care. 22 (5), 369-74.

[162] Lao CD, Ruffin MT 4th, Normolle D, Heath DD, Murray SI, Bailey JM, Boggs ME, Crowell J, Rock CL, Brenner DE. (2006) Dose escalation of a curcuminoid formulation. BMC Complement. Altern. Med. 6:10.