ELSEVIER

Current progress in the use of traditional medicines and nutraceuticals

Stephen Barnes[1,2,3] and Jeevan Prasain[1,3]

Traditional medicines in the form of botanical dietary supplements and nutraceuticals have found a place in 21st century healthcare. They nonetheless all contain compounds that are foreign to humans (i.e. xenobiotics) and that are subject to the same pharmacological issues encountered by synthetic therapeutic agents. It is crucial therefore for all parties, the medical profession, investigative scientists, the regulatory agencies and the public, to understand the particular characteristics of botanicals and nutraceuticals and their potential for success and failure in preventing and confronting disease.

Addresses
[1] Department of Pharmacology and Toxicology, McCallum Research Building, University of Alabama at Birmingham, 1918 University Boulevard, Birmingham, Alabama 35294, USA
[2] Center for Nutrient–Gene Interaction, University of Alabama at Birmingham, Alabama 35294, USA
[3] Purdue University–University of Alabama Botanicals Center for Age-Related Disease, Birmingham, Alabama 35294, USA

Corresponding author: Barnes, Stephen (sbarnes@uab.edu)

Current Opinion in Plant Biology 2005, **8**:324–328

This review comes from a themed issue on
Physiology and metabolism
Edited by Toni Kutchan and Richard Dixon

Available online 9th April 2005

1369-5266/$ – see front matter

DOI 10.1016/j.pbi.2005.03.010

Introduction

Botanicals have had a long history of use in traditional medicine. In many countries, they have been and remain the major source of medication for a wide range of ailments. The development of synthetic organic chemistry in the late 19th century, combined with the arrival of chromatographic separation methods in the first half of the 20th century, led to the isolation and identification of the bioactive principles in botanicals [1–4]. Nonetheless, despite the sophistication of modern organic chemistry, the ability of plants to make a particular stereoisomer of a bioactive compound has ensured that, in many cases, they remain the source of certain medicinal compounds. Even in the USA, 50% of the chemotherapeutic drugs used in the treatment of cancer in 2004 have their origin in plants [5]. Indeed, the relative ineffectiveness of combinatorial chemistry in the search for compounds that are both efficacious and non-toxic has led some investigators (and particularly the public) back towards botanicals. Three excellent reviews on the importance of plant-derived compounds to the discovery of new therapeutics appeared in 2004 [6–8]. One of these examines whether natural-product scaffolds might restore the value of the combinatorial approach [8]. Finally, we strongly recommend the 2003 review by Surh [9] because it is crucial to understand the mechanism of action of phytochemicals. In this opinion, we present a history of the introduction of these plant and food-derived products, and discuss the major issues, excitement and controversies associated with their current use.

Plants are chemical engines: they have more genes than mammals, including humans. They need this biosynthetic capability to defend themselves against a large number of environmental enemies. It's good that plants are so successful, otherwise how would CO_2 be converted to oxygen or nitrogen fixed to make this planet inhabitable? Because plants produce bioactive compounds in natural environments, their relationship to their surroundings has been a guide to the likelihood of identifying a useful bioactivity. For instance, plants or organisms that flourish in hostile microbial environments do so by releasing anti-microbial compounds. Fleming's observation of the anti-bacterial effect of penicillium molds [10], and the later isolation and identification of penicillin by Florey and colleagues [11], had an enormous impact on the treatment of infectious diseases, albeit with unprecedented social consequences.

Many plants are toxic to those who eat them. However, man (or perhaps more likely woman) had the wit to apply fire (and latterly cuisine) to degrade the harmful effects of plant toxins. During the ascent of man, societies determined those plants that were edible, those that appeared to have medicinal properties and those that were simply toxic. Many of the plants that had medicinal properties were hallucinogens, which provided the giver with the power to entrance, but not necessarily to cure or treat, the patient.

Diet and chronic disease

In the past 20 years, biomedical research has revealed that diet plays important roles in the prevention and progression of many of the major contemporary chronic diseases (e.g. atherosclerosis and cancer) [12–16]. This appreciation of the role of diet in the prevention of disease was not actually new, rather freshly rekindled. In the 16th, 17th and 18th centuries, many crewmen on long voyages across the South Pacific suffered, and often died, from scurvy. In

what was, in effect, a set of government-ordained clinical trials, 18th century sea captains (under the direction of the British Admiralty) explored the role of foods and food practices in maintaining the health of seamen. Some foods provided the missing (and yet-to-be-determined) vitamins B and C, whereas others reduced the antiscorbutic effects of the seamen's diet.

Epidemiological associations

Epidemiological studies conducted on populations in individual countries, as well as on migrants moving between nations with very different disease risks, have teased out connections between diet and chronic disease risk. In 1991, the National Cancer Institute in the US, along with several non-federal organizations, began the '5-a-Day' program to promote the benefits of a diet that is enriched in fruits and vegetables for the reduction of cancer risk. These types of foods contain substantial amounts of vitamins and other phytochemicals. This move reinvigorated research on the bioactive properties of phytochemicals. The program has since been expanded to recommend 5–9 servings of fruit and vegetables a day.

It was in this environment that the 1994 Dietary Supplements Health and Education Act (DSHEA) was born in the USA. This act was driven by the dissatisfaction of many patients with the slow development of synthetic therapeutic agents to treat or prevent their diseases. They argued that the legislation under which the Federal Drug Administration (FDA) operated for evaluating new drugs was too restrictive. DSHEA enabled materials that had been used or were being used in traditional medicine (and whose toxicities were 'known') as of October 15th 1994, or materials that were classified as dietary supplements, to be exempt from FDA regulations. New dietary-supplement preparations that were made up of these exempt materials could be brought to market without clinical trials. Indeed, the only safety profile that is needed is one that has to be provided by the manufacturer within 75 days before starting to sell the dietary supplement commercially. The DSHEA legislation gave birth to a large industry, with annual sales of dietary supplements in the USA rising to US$18 billion in 2002.

Botanical dietary supplements deliver a concentrated form of presumed bioactive agents from plants that are not generally part of the food supply. The term nutraceutical has no regulatory definition. Nutraceuticals represent products that are isolated or purified from foods, although they are generally sold in medicinal forms that are not usually associated with the original form of the food. They have some demonstrable physiological benefit or properties that contribute to the prevention of chronic disease and are used in dosages that exceed those that could be obtained from normal foods. Vitamins and their relatives are good examples of this class of product. Several bioactive phytochemicals have been reported from herbal medicines used in Traditional Chinese Medicine and Ayurvedic Medicine [17–19].

Many phytochemicals in edible plant materials (e.g. genistein in soybeans and curcumin in turmeric) and plant extracts that are used in traditional medicine or in dietary supplements are freely available to the public [3,17,20]. During processing, it is not always known which compounds to keep and which to throw away. Strictly speaking, a dietary supplement is the result of relatively simple procedures (i.e. extraction with water or tincture of alcohol).

Successes and failures of dietary supplements and nutraceuticals

Metabolism, enzyme induction and competition

The current top-ten botanical dietary supplements (Table 1) contain a wide variety of chemicals. They are all xenobiotics and, just like many conventional therapeutics, they are subject to metabolic processing by the phase I and phase II enzymes in the small intestine and liver [21–24]. This represents some concern. The amounts of a drug that are delivered to its site of action are determined, in many cases, by the rate of its metabolism.

Table 1

Top ten botanical dietary supplements in the USA.

Herbal	Claimed benefit	Bioactive principle(s)
Ginkgo biloba	Enhancement of memory, Alzheimer's disease, glaucoma	Flavone glycosides, terpene lactones
Garlic	Fights infection, cardiovascular, boosts immunity	Allicin
Echinacea	Boosts immunity	Inulin, echinacoside
Ginseng	Male infertility, diabetes, epilepsy, immune function	Gingsenosides
Saw Palmetto	Prostatitis, benign prostatic hyperplasia	Liposterols
St. John's Wort	Depression, anxiety, infection in wounds and burns	Hypericin, hyperforin, flavonoids
Feverfew	Migraine headaches	Sesquiterpene lactones (parthenolide)
Ginger	Motion sickness, osteoarthritis, indigestion, irritable bowel syndrome, vertigo, early morning sickness	Zingiberene and bisabolene, gingerols and shogaols
Valerian	Insomnia, anxiety	Many, GABA receptor agonists
Ephedra[a]	Coughing, weight loss	Ephedrine, pseudoephedrine

[a] Ephedra is now banned as a dietary supplement by the FDA.

One of the effects of the botanical compounds can be to compete with another (often conventional) drug for a particular metabolic step, thereby raising the drug concentration for a given dose that reaches the site of action. Conversely, a botanical compound might induce an enzyme and so increase the rate of metabolism of a drug and hence lower its effective concentration. The interaction between St. John's Wort and indinavir (a protease used in HIV therapy) is believed to be due to increased CYP3A4 activity, which metabolizes the drug and so reduces its effectiveness [25]. Other herb–drug interactions have been predicted from this study [26–28].

Toxicities

In many respects, the reported toxicities of botanical dietary supplements are an artificial problem created by the junction of traditional medicine and modern pharmacology. A patient in a society where only one of these medical practices is used will be treated by a physician who is knowledgeable in that group of medications. The problem lies in that the American or European (patient or doctor) has little information about traditional medicines, or the dietary supplements that they are made into. A good example is Ephedra (or *Ma Huang*), which is used in Chinese traditional medicine at doses that are sufficiently low that toxic effects associated with higher doses have not been observed. As a consequence, Ephedra qualified as a dietary supplement under the DSHEA legislation. Ephedra contains the alkaloid ephedrine, which is a bronchodilator. Because it is a stimulant, and is related in its effects to the previously banned amphetamines, Ephedra was used legally by segments of the public to reduce body weight. The young, including athletes, were the targets of advertising by the manufacturers of Ephedra products and, because of their inexperience, began consuming doses that were outside the range used by traditional medicine practitioners. Ephedra became linked to many cases of serious clinical complications or death and, consequently, the FDA issued a rule in 2004 that led to the ban of Ephdra as a dietary supplement, although its use in Chinese traditional medicine was left untouched.

Experimental paradigms and research on traditional medicine and nutraceuticals

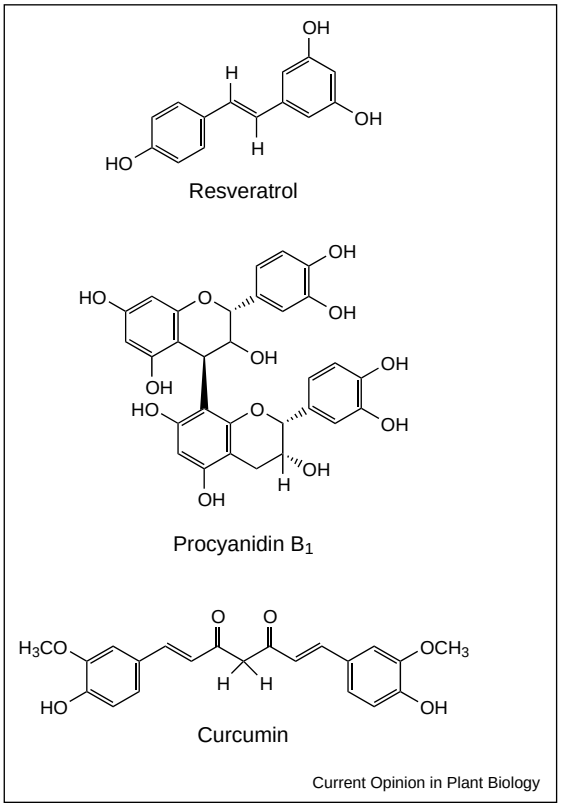
One of the limitations of the research carried out on botanicals has been the use of the paradigm in which each compound is studied in isolation to determine its intrinsic activity and mode of action. This approach is relevant to the evaluation of synthetic therapeutics but is not appropriate for botanicals that are a mixture of compounds. *A priori* it is not intended that they should be prepared as isolated compounds: in that case, they would be more like drugs and should be subject to normal FDA drug regulations. When analyzed in isolation, the activities of compounds that are purified from botanicals are often disappointing or even opposite when compared to those suggested by previous research. An example of such an 'opposite' effect was revealed by trials of β-carotene in the prevention of lung cancer. Instead of providing protection, as predicted by epidemiological studies and pre-clinical studies, an increase in the rate of cancer was observed in the β-carotene intervention trial [29,30]. There is a basis for explaining these data: β-carotene, like several other phytochemicals, is believed to react with radicals that are created by cellular oxidants. This reaction slows the rate of radical-induced damage to DNA and proteins because the β-carotene radical is chemically less reactive than other radicals produced in cells. In the presence of an excess of β-carotene, however, there will be large concentrations of the β-carotene radicals and these will cause just as much or more damage than occurs in the absence of β-carotene. In patients whose diets were non-supplemented but rich in phytochemical, the various phytochemicals can exchange the radicals until they eventually encounter radical-terminating anti-oxidants such as vitamin C. Under those circumstances, the combination of phytochemicals is more powerful than the sum of the components [31].

Excitement in dietary supplements and nutraceuticals research

Two polyphenols (resveratrol and the proanthocyanidins) that are present in grapes have generated much excitement in the past couple of years for those wanting to increase their life span and brain power (Figure 1). It has been long known that a 30% reduction of normal caloric intake in mice causes them to live longer [32]. A similar result has been observed in other model organisms (yeast, *Caenorhabditis* and *Drosophila*) [33]. Using the yeast model, investigators searched for (and found) a yeast gene (Sir2, a member of the sirtuin family) whose absence eliminated the effects of caloric restriction [34]. Sir2 is a histone deacetylase. It is NAD-dependent and increases in activity under the conditions of caloric restriction because of elevated levels of NAD. This precipitated an intense search for compounds that increased Sir2 activity. Rather than compounds from patented pharmaceutical libraries, the most active group is the polyphenols, in particular the grape polyphenol resveratrol (a stilbene) [35]. When included in the yeast growth medium, resveratrol extended the life of wildtype yeast, but not when Sir2 was deleted. Similar results were reported in *Drosophila* and *Caenorhabditis*[36].

The proanthocyandins are well known to be strong antioxidants *in vitro*. However, their polymeric nature and high molecular weight suggests that they would be unlikely to be absorbed either through the intestinal wall or across the blood–brain barrier. Nonetheless, animals on a high proanthocyanidin diet, such as one that is rich in blueberries, have a better short-term memory than those on a control diet [37,38]. A recent proteomics study showed that grape-seed extract that contains proantho-

Figure 1



Chemical structures of three polyphenols identified as important bioactives in 2003–2004. Resveratrol is a stilbene found in grapes; procyanidin B_1 is a proanthocyanidin in grape seed extract; and curcumin is a part of turmeric, an important of Indian cuisine and Ayervedic medicine.

cyanidins is able to systematically and reproducibly alter the expression of brain proteins in young rats [39]. It was interesting that these changes in protein expression were opposite to those observed in patients with neurodegenerative disease or in animal models of these diseases. Thus, the development of seedless grapes might have an unexpected detrimental effect. Grape-seed extract also reduced the number of mammary tumors in a carcinogen-induced adult rat model of breast cancer [13]. It was necessary, however, that the animals also consumed a laboratory chow diet; neither added genistein nor grape-seed extract had any effect on tumor number when the rats were fed a semi-purified soy-free diet. These results stress the importance of interactions between components of the diet over the lifetime of the animal.

Finally, an exciting role for curcumin, which is present in turmeric, has been identified in mice that carry the ΔF508 mutant CFTR gene for cystic fibrosis [40]. Although the mutant protein is expressed, it accumulates in the endoplasmic reticulum as a mis-folded protein. When administered in the diet, curcumin resulted in the transfer of the ΔF508 mutant CFTR protein to the plasma membrane as well as normalization of the nasal potential difference caused by defective chloride ion transport in mutant CFTR mice. This result has been disputed by a later study [41]; however, in this study curcumin was administered directly to cell preparations rather than to the animals. This suggests that curcumin might be a prodrug that undergoes metabolic activation in the mouse but not in cell-culture preparations.

Conclusions

Research on the materials of traditional medicine and on dietary supplements is encountering many of the mechanisms and challenges frequently encountered in mainstream pharmacology. The optimal use of these materials requires a greater knowledge of the practices of traditional medicine than is currently taught to the medical profession, or understood by the public. Nonetheless, such materials continue to provide an exciting interplay between the needs of plants and man.

Acknowledgements

Financial support for research on dietary supplements has been provided by Center grants from the National Center for Complementary and Alternative Medicine to the Purdue University-University of Alabama at Birmingham Botanicals Center for Age-related Disease (CM Weaver, Principal Investigator – P50 AT00477) and by the National Cancer Institute to the University of Alabama at Birmingham Center for Nutrient-Gene Interaction (S Barnes, Principal Investigator – U54 CA100949), as well as matching funds from the University of Alabama at Birmingham School of Medicine.

References

1. Drasar P, Moravcova J: **Recent advances in analysis of Chinese medical plants and traditional medicines**. *J Chromatogr B Analyt Technol Biomed Life Sci* 2004, **812**:3-21.
2. Fuzzati N: **Analysis methods of ginsenoside**. *J Chromatogr B Analyt Technol Biomed Life Sci* 2004, **812**:119-133.
3. Prasain JK, Jones K, Kirk M, Wilson L, Smith-Johnson M, Weaver C, Barnes S: **Profiling and quantification of isoflavonoids in kudzu dietary supplements by high-performance liquid chromatography and electrospray ionization tandem mass spectrometry**. *J Agric Food Chem* 2003, **51**:4213-4218.
4. Ying T, Luhua Z, Lin Z, Guangji W, Binren X: **Separation and identification of 20 chemical constituents in the traditional Chinese medicinal preparation Shenbao tablet by LC-ESI-MS3**. *J Chromatogr Sci* 2004, **42**:177-183.
5. Boon H, Wong J: **Botanical medicine and cancer: a review of the safety and efficacy**. *Expert Opin Pharmacother* 2004, **5**:2485-2501.
6. Lee KH: **Current developments in the discovery and design of new drug candidates from plant natural product leads**. *J Nat Prod* 2004, **67**:273-283.
7. Clardy J, Walsh C: **Lessons from natural molecules**. *Nature* 2004, **432**:829-837.
8. Ortholand JY, Ganesan A: **Natural products and combinatorial chemistry: back to the future**. *Curr Opin Chem Biol* 2004, **8**:271-280.
9. Surh YJ: **Cancer chemoprevention with dietary phytochemicals**. *Nat Rev Cancer* 2003, **3**:768-780.
10. Fleming A: **On the antibacterial action of cultures of a *Penicillium*, with special reference to their use in the isolation of *B. influenzae***. *Br J Exp Pathol* 1929, **10**:226-236.

11. Chain E, Florey HW, Gardner AD, Heatley NG, Jennings MA, Orr-Ewing J, Sanders AG: **Penicillin as a chemotherapeutic agent**. *Lancet* 1940 (ii):226-228.

12. Majumdar AP, Kodali U, Jaszewski R: **Chemopreventive role of folic acid in colorectal cancer**. *Front Biosci* 2004, **9**:2725-2732.

13. Kim H, Hall P, Smith M, Kirk M, Prasain JK, Barnes S, Grubbs C: **Chemoprevention by grape seed extract and genistein in carcinogen-induced mammary cancer in rats is diet-dependent**. *J Nutr* 2004, **134**:3445S-3452S.

14. Bellido C, Lopez-Miranda J, Blanco-Colio LM, Perez-Martinez P, Muriana FJ, Martin-Ventura JL, Marin C, Gomez P, Fuentes F, Egido J, Perez-Jimenez F: **Butter and walnuts, but not olive oil, elicit postprandial activation of nuclear transcription factor kappaB in peripheral blood mononuclear cells from healthy men**. *Am J Clin Nutr* 2004, **80**:1487-1491.

15. Register TC, Cann JA, Kaplan JR, Williams JK, Adams MR, Morgan TM, Anthony MS, Blair RM, Wagner JD, Clarkson TB: **Effects of soy isoflavones and conjugated equine estrogens on inflammatory markers in atherosclerotic, ovariectomized monkeys**. *J Clin Endocrinol Metab* 2005, in press.

16. Ravindranath MH, Muthugounder S, Presser N, Viswanathan S: **Anticancer therapeutic potential of soy isoflavone, genistein**. *Adv Exp Med Biol* 2004, **546**:121-165.

17. Giri RK, Rajagopal V, Kalra VK: **Curcumin, the active constituent of turmeric, inhibits amyloid peptide-induced cytochemokine gene expression and CCR5-mediated chemotaxis of THP-1 monocytes by modulating early growth response-1 transcription factor**. *J Neurochem* 2004, **91**:1199-1210.

18. Prasain JK, Jones K, Brissie N, Moore R, Wyss JM: **Barnes. Identification of puerarin and its metabolites in rats by liquid chromatography-tandem mass spectrometry**. *J Agric Food Chem* 2004, **52**:3708-3712.

19. Kadota S, Tezuka Y, Prasain JK, Ali MS, Banskota AH: **Novel diarylheptanoids of *Alpinia blepharocalyx***. *Curr Top Med Chem* 2003, **3**:203-225.

20. Penalvo JL, Heinonen SM, Nurmi T, Deyama T, Nishibe S, Adlercreutz H: **Plant lignans in soy-based health supplements**. *J Agric Food Chem* 2004, **52**:4133-4138.

21. Liu Y, Li W, Li P, Deng MC, Yang SL, Yang L: **The inhibitory effect of intestinal bacterial metabolite of ginsenosides on CYP3A activity**. *Biol Pharm Bull* 2004, **27**:1555-1560.

22. He N, Edeki T: **The inhibitory effects of herbal components on CYP2C9 and CYP3A4 catalytic activities in human liver microsomes**. *Am J Ther* 2004, **11**:206-212.

23. Cantoni L, Rozio M, Mangolini A, Hauri L, Caccia S: **Hyperforin contributes to the hepatic CYP3A-inducing effect of *Hypericum perforatum* extract in the mouse**. *Toxicol Sci* 2003, **75**:25-30.

24. Ameen M, Musthapa MS, Abidi P, Ahmad I, Rahman Q: **Garlic attenuates chrysotile-mediated pulmonary toxicity in rats by altering the phase I and phase II drug metabolizing enzyme system**. *J Biochem Mol Toxicol* 2003, **17**:366-371.

25. Zhou S, Chan E, Pan SQ, Huang M, Lee EJ: **Pharmacokinetic interactions of drugs with St. John's wort**. *J Psychopharmacol* 2004, **18**:262-276.

26. Zhou S, Chan E, Li SC, Huang M, Chen X, Li X, Zhang Q, Paxton JW: **Predicting pharmacokinetic herb–drug interactions**. *Drug Metabol Drug Interact* 2004, **20**:143-158.

27. Jang EH, Park YC, Chung WG: **Effects of dietary supplements on induction and inhibition of cytochrome P450s protein expression in rats**. *Food Chem Toxicol* 2004, **42**:1749-1756.

28. Anke J, Ramzan I: **Pharmacokinetic and pharmacodynamic drug interactions with Kava (*Piper methysticum* Forst. f.)**. *J Ethnopharmacol* 2004, **93**:153-160.

29. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, Keogh JP, Meyskens FL, Valanis B, Williams JH, Barnhart S, Hammar S: **Effects of a combination of β-carotene and vitamin A on lung cancer and cardiovascular disease**. *N Engl J Med* 1996, **334**:1150-1155.

30. Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, Belanger C, LaMotte F, Gaziano JM, Ridker PM *et al.*: **Lack of effect of long-term supplementation with β-carotene on the incidence of malignant neoplasms and cardiovascular disease**. *N Engl J Med* 1996, **334**:1145-1149.

31. Ward NC, Hodgson JM, Croft KD, Clarke MW, Burke V, Beilin LJ, Puddey IB: **Effects of vitamin C and grape-seed polyphenols on blood pressure in treated hypertensive individuals: results of a randomised double blind, placebo-controlled trial**. *Asia Pac J Clin Nutr* 2003, **12(Suppl)**:S18.

32. McCay CM, Crowel MF, Maynard LA: **The effect of retarded growth upon the length of the life span and upon the ultimate body size**. *J Nutr* 1935, **10**:63-79.

33. Klass MR: **A method for the isolation of longevity mutants in the nematode *Caenorhabditis elegans* and initial results**. *Mech Ageing Dev* 1983, **22**:279-286.

34. Wood JG, Rogina B, Lavu S, Howitz K, Helfand SL, Tatar M, Sinclair D: **Sirtuin activators mimic caloric restriction and delay ageing in metazoans**. *Nature* 2004, **430**:686-689.

35. Horwitz KT, Bitterman KJ, Cohen HY, Lamming DW, Lavu S, Wood JG, Zipkin RE, Chung P, Kisielewski A, Zhang LL *et al.*: **Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan**. *Nature* 2003, **425**:191-196.

36. Bauer JH, Goupil S, Garber GB, Helfand SL: **An accelerated assay for the identification of lifespan-extending interventions in *Drosophila melanogaster***. *Proc Natl Acad Sci USA* 2004, **101**:12980-12985.

37. Joseph JA, Denisova NA, Arendash G, Gordon M, Diamond D, Shukitt-Hale B, Morgan D: **Blueberry supplementation enhances signaling and prevents behavioral deficits in an Alzheimer disease model**. *Nutr Neurosci* 2003, **6**:153-162.

38. Goyarzu P, Malin DH, Lau FC, Taglialatela G, Moon WD, Jennings R, Moy E, Moy D, Lippold S, Shukitt-Hale B, Joseph JA: **Blueberry supplemented diet: effects on object recognition memory and nuclear factor-kappa B levels in aged rats**. *Nutr Neurosci* 2004, **7**:75-83.

39. Deshane J, Chaves L, Sarikonda KV, Isbell S, Wilson L, Kirk M, Grubbs C, Barnes S, Meleth S, Kim H: **Proteomics analysis of rat brain protein modulations by grape seed extract**. *J Agric Food Chem* 2004, **52**:7872-7883.

40. Egan ME, Pearson M, Weiner SA, Rajendran V, Rubin D, Glockner-Pagel J, Canny S, Du K, Lukacs GL, Caplan MJ: **Curcumin, a major constituent of turmeric, corrects cystic fibrosis defects**. *Science* 2004, **304**:600-602.

41. Song Y, Sonawane ND, Salinas D, Qian L, Pedemonte N, Galietta LJ, Verkman AS: **Evidence against the rescue of defective DeltaF508-CFTR cellular processing by curcumin in cell culture and mouse models**. *J Biol Chem* 2004, **279**:40629-40633.