JPP Journal of Pharmacy and Pharmacology
ROYAL PHARMACEUTICAL SOCIETY

JPP Journal of Pharmacy and Pharmacology

JPP 2011, 63: 3–10

Received March 22, 2010
Accepted June 7, 2010
DOI
10.1111/j.2042-7158.2010.01159.x
ISSN 0022-3573

Review

The quality of commercially available nutraceutical supplements and food sources

G. Brian Lockwood

School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, UK

Abstract

Objectives Nutraceuticals are components of dietary origin, with claimed beneficial therapeutic activities. The quality of nutraceuticals is paramount for efficacy and safety, and it includes quality of raw materials, different available chemical forms, complex products, lack of substitution of inappropriate materials, and the absence of contaminants. The aim of this review is to investigate the extent of substandard formulated and raw material nutraceuticals, and to highlight any consequent health concern.

Key findings Reports of the quality of raw materials have revealed wide variations, often as a result of lack of clear regulatory definitions with respect to size of polymeric entities and also presence of glycosidic and salt forms. Published evaluations of over 70 formulations of 25 different nutraceuticals revealed variable quality; no nutraceutical showed consistent high quality, but a number revealed consistent low quality, thereby making the case for closer regulation of manufacturers. Whole food sources have also been shown to be widely variable in constituent levels. The effect of different formulations requires consideration, as the different types have been shown to have marked effects on bioavailability.

Summary The poor quality of commercially available nutraceuticals has been highlighted. In addition, incidences of side effects and drug interactions are increasing, as consumption of nutraceuticals rises. Pharmacists and health practitioners need to be aware of the scientific literature to advise accordingly.

Keywords nutraceutical supplements; quality evaluations

Introduction

Nutraceuticals are a relatively recent class of complementary medicine, defined as a 'food, or parts of a food, that provide medical or health benefits, including the prevention and treatment of disease'. The major groups of nutraceuticals are either normal human metabolites such as carnitine, coenzyme Q10, creatine, lipoic acid, melatonin, dehydroepiandrosterone (DHEA) and *S*-adensoylmethionine (SAMe), responsible for healthy activity, or bioactive plant dietary components. Their mode of action is often well documented and they are used to supplement endogenous levels, often in perceived deficiency states. n-3-Fatty acids and carotenoids are endogenous constituents, but are also widely available in the diet. Other nutraceuticals may be found in specific foods such as soy isoflavones, the glycoaminoglycans, glucosamine and chondroitin, are derived from various animal materials, and methylsulfonyl methane (MSM), which only occurs in miniscule levels in particular foods, is commercially obtained from synthesis, however, most are available from a range of dietary components.

Efficacy of medicine based complementary therapies is now routinely addressed by publication of clinical trials, meta-analyses, and by systematic reviews such as the Cochrane Database. There is now a vast amount of data which has been comprehensively reviewed by the latter two, both in the area of herbal remedies and nutraceutical supplements. Collated data for nutraceuticals has been reviewed previously.[1] Although there is variability in the quality of evidence for efficacy, these products are widely used. One demographic survey from Washington State, USA, supplied detailed evidence from over 60 000 (males and females of roughly even numbers) 50–76-year olds, which revealed that 29.7% of respondents used glucosamine, chondroitin or MSM for treating osteoarthritis, 25.3% for treating neck, back or joint pain, and 20% used melatonin for insomnia. There was also a high incidence in the use of lycopene, DHEA, lutein, soy products, fish oil and coenzyme Q10.[2] Increasing levels of usage have been confirmed by recent commercial data.[3] Although

Correspondence: G. Brian Lockwood, School of Pharmacy & Pharmaceutical Sciences, University of Manchester, Oxford Road, Manchester M13 9PT, UK.
E-mail: brian.lockwood@manchester.ac.uk

nutraceutical supplements may appear to be useful for numerous health problems and age related diseases, it is important to address the problems which may be encountered with a largely unregulated source of supply. This review attempts to address these issues.

The perennial problem with natural product based complementary therapies is their efficacy, safety, and quality. Quality is complicated by a number of parameters not so readily seen in conventional pharmaceuticals, such as the presence of complex, multi-component raw materials, which includes clear identification of the main active components, origin of material, level of active constituents and bioavailability. Rigorous quality control and quality assurance of conventional medicines ensures that they are, as expected to be, fit for their purpose, containing the stated dose of active constituents, and also ensures that they have suitable disintegration characteristics, and bioavailability, allowing for absorption in the gastrointestinal tract. The composition of complementary medicines is increasingly being analysed, and examples have been found to fail the relevant standards, or be noncompliant with label claims. A number of herbal products have been banned by regulatory authorities for misleading label information, relating to source and content of actives, and for containing totally unsuitable components and contaminants. Monographs for quality control are being introduced, and dangerous products are increasingly removed from the marketplace. Similar control is now being carried out with nutraceutical supplements, where their use is not in the interest of the general public. In 2002, the UK Food Safety Agency banned a number of n-3-polyunsaturated fatty acid (PUFA)-containing fish oils and issued a warning concerning products containing low levels of dioxins and polychlorinated biphenyls.[4] Monographs, which include analytical standards for active constituents of nutraceutical supplements, are now available and further being introduced. The Handbook of Analytical Methods for Dietary Supplements lists monographs on five nutraceuticals: chondroitin, coenzyme Q10, glucosamine, melatonin and soy.[5] The United States Pharmacopeia/National Formulary has seven monographs: chondroitin, coenzyme Q10, glucosamine, lipoic acid, lutein, lycopene, and Maritime Pine extract (pycnogenol).[6]

The Office of Dietary Supplements of the National Institute of Health in the USA plan monographs for up to 20 nutraceuticals, and the Association of Official Analytical Chemists (AOAC) is likewise planning eight further monographs after publishing standards on glucosamine.[7,8]

The aim of this review is to investigate the extent of substandard formulated and raw material nutraceuticals, and to highlight any consequent health concern.

Raw Material

Analyses of raw materials are rarely published, but limited data exists for chondroitin and glucosamine. Twelve samples of chondroitin were evaluated and results ranged from 39.5 to 105.6% of content.[9] Analysis of glucosamine showed good quality conformity in one survey, where all four samples were found to contain 100%.[10] Commercially available chondroitin raw materials often vary in size with molecular weights ranging widely, between 50 to below 1 kDa, and a recent survey revealed levels from 9.3–28.7 kDa in samples of raw material.[9,11] There has been some concern that chrondroitin samples may be contaminated with bovine spongiform encephalitis (BSE). Sourcing of material from disease free animals and deproteination of raw material are techniques used to limit the risk. It is thought that the risk is extremely low but no reports of testing for BSE prion contamination in supplements have been published.

Problems relating to the precise chemical form of the named nutraceutical in the products exist for some materials. The isoflavones are an example of products which exist in nature in the form of glycosides and the sugar content of the molecule may constitute up to 40–50% of the total. Consequently, the isoflavone aglycone levels will be much lower than the claimed levels for the glycoside.[1]

Glucosamine exists in a number of different forms, usually the sulphate or hydrochloride, and the N-acetyl form is also available. Dependent upon which form is in use, the level of glucosamine base will vary as a proportion of the whole molecule, and therefore different products may have wide variations in levels of the glucosamine base, which may not necessarily be outlined on the label. In addition to this complication, either potassium or sodium chloride may be added as a stabilising agent. Again, the presence of this may not be outlined on the label, and if the weight of total glucosamine salt plus stablising agent is quoted on the label, the actual weight of glucosamine is even further reduced.[12]

SAMe is prone to degradation, consequently the toluenedisulfonate, 1,4-butanedisulfonate, and disulfate tosylate forms are widely used. Use of the latter form would, for example, effectively double the molecular weight, consequently halving the level of actual SAMe in products using this as a source of raw material.

Actual Levels of Active Ingredients in Formulated Nutraceutical Products

Specifications for pharmaceuticals normally require 95–105% content of claimed active constituent, and nutraceuticals should now be assessed to this standard.[13] Published reports have appeared for over 20 nutraceuticals, and an internet site, ConsumerLab.com, has released evaluation reports for a subscription fee of $29.95 per year, over the last few years.[14] These reports list named products and levels of contents of constituents, enabling consumers to choose products on this basis. ConsumerLab data has been produced for MSM, coenzyme Q10, SAMe, docosahexaenoic (DHA)/eicosapentaenoic (EPA), DHEA, lutein/zeaxanthin, creatine, sterols, amongst other nutraceuticals.[1] Although products have been named, varying levels of constituents used for assessment of ‘passing’ are no doubt confusing to subscribers. The European Pharmacopoeia standard designation of good quality (95–105%) has not been used, and variable parameters for the different entities employed.

Available data published up to 2007 shows wide variability in quality of products available to consumers, and is continually evolving.[1] Studies on uniformity of products between batches are now appearing, but few bioavailability studies have been published. Data freely available in the public domain is collated below.

Table 1 lists examples of evaluations of content levels compared with stated label contents, of a range of nutraceuticals, by research laboratories.[15–56]

Table 2 lists examples of evaluations of content of chondroitin and glucosamine by research laboratories.[57–65]

The majority of analyses employ high performance liquid chromatography (HPLC), which is the best method for water soluble entities. However, newer methods such as capillary electrophoresis (CE), micellar electrokinetic chromatography (MEC), and high performance size exclusion chromatography (HPSEC) are being used for nutraceutical analysis. Increasing use of newer methods has been reported for analysis of components and metabolites of soy, teas, glucosamine and coenzyme Q10, but no further reports on quality assessment have been published.[66–68]

Carnitine samples showed good compliance in two surveys, but not in two further reports. Creatine products conformed poorly, as did n-3-PUFAs and γ-linolenic acid, lutein and zeaxanthin, lycopene and α-tocopherol. Complex materials such as soy and tea extracts were also found to have poor compliance.

A few individual nutraceuticals may be classed as medicines in certain countries, and as such are subject to medicine regulations. Evaluation of 10 Japanese pharmaceutical grade coenzyme Q10 products showed complete compliance with standards, and in one survey of US products also, but not in three other surveys.[20,22] Variability has been reported for other examples of products often classed as medicines, such as DHEA.

Examples of most of the formulated nutraceutical products have been tested over the last 15 years, although no examples of acetylcarnitine, or pycnogenol have been reported. The latter product is a branded formulation made by a single manufacturer, consequently subject to internal standards. Relatively high quality was found for melatonin products, but poor quality was found with soy isoflavones, proanthocyanidins, and α-tocopherol. Other reports on the quality of nutraceuticals recorded data on lutein, SAMe, and DHEA products, but they showed a similar picture of low quality products available. [28,29,43] Lack of label compliance for single entity products is evident, but is even more pronounced for complex materials such as soy.

Two of the most popular products, chondroitin and glucosamine, showed variable content compliance (Table 2), probably caused by use of a range of sources for starting materials and chemical forms used. No publications have reported on MSM levels in formulated products. Analysis of chondroitin demonstrates a range of problems not seen in the majority of nutraceuticals; the molecular mass of the molecule is variable, dependent upon biological origin, varying from 14–70 kDa (bovine, porcine, chicken, shark or skate cartilage). Within the chondroitin samples the specific ratio of different disaccharides varies and is further complicated by admixtures and other sources such as avian material.[69] Disaccharide compositional analysis of 12 Japanese chondroitin supplements showed two products falsely labelled, as being from shark as opposed to their actual bovine origin.[70] Another study revealed that commercially available chondroitin may actually consist of hyaluronic acid.[71] Overall, published studies have shown that the quality of chondroitin sulphate in commercially available products is often poor. Pharmaceutical grade chondroitin should be used for the manufacture of formulated products to guarantee standardised molecular structure, which will affect both pharmacokinetics and overall activity of the product.[72]

Contents of Active Constituents of Ranges of Nutraceuticals of Complex Composition

Complex mixtures of natural products are increasingly being sold on the basis that individual components or the complete material may have health benefits. Six examples of these include flaxseed, teas, soy, resveratrol, conjugated linoleic acid (CLA) and grape seed extracts.

There has been solid growth in interest in the medicinal properties of flaxseed over recent years, and the long established historical use of it under the name of linseed has largely been forgotten. Much work has been published on the health benefits of the active components, namely α-linoleic acid and the lignans. The effect of three flaxseed cultivars with varying levels have been reported to demonstrate different levels of activity on a number of biomarkers for atherosclerosis and mental stress, showing the importance of their composition on biological activity.[73] A few surveys of the composition of proprietary breads and cereals containing flax have been published, and show extremely wide ranges of constituents to be present. However, some of the products have been named, allowing consumers to select specific brands for high levels.

Both green and black (to a lesser extent) teas are popular as a source of antioxidants, but variability of levels of claimed active compounds depends upon the method of preparation of the infusion, as well as choice of tea type. Surveys of teas and their preparation have been reported to exhibit differences in their theanine levels and wide variations in the catechin derivatives. As with flaxseed constituents, extreme variations have been reported in catechin levels.[54] The catechins have been shown to be remarkably stable during normal tea making procedures, but long-term storage in aqueous media at extreme pH may cause greater degradation, as may be the case with convenience products.[74] Levels of theanine, caffeine and catechins were compared in a range of six teas from Taiwan. Although caffeine levels were similar, wide variations were reported for theanine (20–92 mg/g) and the catechins.[75]

Similar wide variations in levels of isoflavones have been reported in other products. Levels of glycosides and aglycones have been reported for soymilk products, tofu products, fermented soy food products, including soy sauce, miso and tempeh, and meat analogue/hamburger products, and variations in individual isoflavone levels were found. A number of evaluations of soy supplements have been reported (Table 1). One detailed analysis of 12 products surveyed the levels of the three most prevalent glycosides and their aglycones, and as expected revealed extreme variations, notably from 0.4 to 57 mg/g. Where actual levels of isoflavones were claimed, levels were found to be low.[76] In addition to the data in Table 2, detailed analysis of the individual isoflavone contents of 13 soy supplements from south east Asia have been reported.[76] In addition to major differences in individual levels of isoflavones, some products had lower total levels

Table 1 Proportion of products shown to comply with accepted quality standards from a range of nutraceutical supplements (tablets unless stated otherwise)

Nutraceutical	Origin	Analysis technique	Proportion passed (95–105% label claim)	Range of contents (% of label claim)
Branched-chain amino acids[15]	Italy	MEC	3/3	97–104%
Carnitine[16]	Czech†	CE	1/3	50–104%
Carnitine[16]	USA†	CE	0/1	35%
Carnitine[17]	Greece†	HPLC	2/2 capsules	98% each
Carnitine[17]	Greece†	HPLC	5/5 oral solutions	96–100%
β Carotene[18]	Germany†	HPLC	1/11	61–137%
β Carotene[19]	Canada	HPLC	2/6	86–111%
Coenzyme Q10[20]	Japan	HPLC	10/10	96–106%
Coenzyme Q10[21]	New Zealand	HPLC	1/7	100–130%
Coenzyme Q10[22]	USA	HPLC	100%, number not stated	95–105%
Coenzyme Q10[23]	USA	HPLC	4/4	98–103%
Coenzyme Q10[24]	Japan	HPLC	36/61	5–123%
Creatine[25]	USA	TLC	1/8	83–106%
Creatine[26]	USA†	HPLC	2/2	Effervescent powders 99–100%
Creatine[26]	USA†	HPLC	0	'Serum' formulation, 1.7% of claimed level
Creatine[27]	USA†	HPLC	4/6	94–126%, 100% in four
DHEA[28]	USA	HPLC	6/16	Three contain 0%, and one 150%
DHEA[29]	USA	HPLC	14/45	74–110%, plus one of 0%
Docosahexaenoic acid[30]	USA†	GLC	1/8	57–115%
Eicosapentanoic acid[30]	USA†	GLC	0/8	75–94%
γ-Linolenic acid[31]	Germany†	GLC	5/19	73–107%
γ-Linolenic acid[32]	Australia†	GLC	12/16	36–109%
Lipoic acid[33]	Austria	CE	3/5	87–110%
Lipoic acid[34]	Austria	HPLC	1/6	40–97%
Lutein[35]	USA	HPLC	0/3	134–194%
Lutein/zeaxanthin[36]	German	HPLC	0/7	16–136%
Lutein/zeaxanthin[36]	USA	HPLC	2/7	11–22%
Lutein[19]	Canada†	HPLC	0/2	109–125%
Lycopene[37]	Canada	HPLC	1/6	6–143%
Melatonin[38]	Italy	HPTLC	5/6	93–102%
Oxyresveratrol[39]	USA	HPLC	–	Three of four contained 0%
Policosanol[40]	USA	GC-MS	Tablet 53%	Octacosanol 58%
			Capsule 54%	16%
			Capsule 40%	24%
Proanthocyanidins[41]	Japan grape seed oil	HPLC	0/2	ND
Resveratrol[42]	USA	HPTLC	2/4	94–97%
SAMe[43]	USA	NS	4/12	Levels from 40–120%
Soy isoflavones[44]	31 USA/1 UK	HPLC	4/32	10%–383%
Soy isoflavones[45]	Australia†	HPLC	2/10	<1–100%
Soy isoflavones[46]	Finland	HPLC	1/7	37–99%
Soy isoflavones[47]	Various	HPLC	2/14*	30–99%
Soy isoflavones[48]	USA†	Gradient HPLC	2/13*	47–99%
Soy isoflavones[49]	Austria	Gradient HPLC	NS	91–109%
Soy isoflavones[50]	Germany	HPLC	2/11	51–139%
Soy isoflavones[51]	UK	HPLC-MS/MS	2/19	40–130%
Soy isoflavones[51]	UK	HPLC-MS/MS	1/17	5–133%
Sterol/stanols[52]	S. Africa	HPLC	0/5	73–106%
Sterols[53]	USA	HPTLC	0	2%
Green tea extracts[54]	USA	Gradient HPLC	0/4	9–48% catechin content stated on labels
Green tea extracts[55]	USA†	MEC	0/3	92–141%
α-Tocopherol[37]	Canada	HPLC	0/7	59–149%
α-Tocopherol[56]	USA	LC-MS	4/14	0–119%

*Products specifying levels of particular isoflavones, genistein and daidzein, all failed to meet claims. †Disclosure of product identity. CE, capillary electrophoresis; HPLC, high performance liquid chromatography; LC-MS, liquid chromatography-mass spectroscopy; MEC, micellar electrokinetic chromatography; ND, not detected; NS, not stated; TLC/HPTLC, thin layer chromatography/ high performance thin layer chromatography.

Table 2 Proportion of chondroitin and glucosamine products shown to comply with accepted quality standards (tablets unless stated otherwise)

Nutraceutical	Origin	Analysis technique	Proportion passed (95–105% label claim)	Range of contents (% of label claim)
Chondroitin[57]	USA	HPSEC	1/3	101–103%
Chondroitin[57]	USA	HPSEC	2/4*	32–99%
Chondroitin[12]	Canada	HPLC	2/7	33–109%
Chondroitin[58]	USA	NS	0/3	80–90%
Chondroitin[58]	USA	NS	3/12*	80–120%
Chondroitin[59]	USA	HPLC	4/11	9–112%
Chondroitin[9]	S. Korea	SAX-HPLC	6/12	40–106%
Chondroitin[60]	S. Korea	SAX-HPLC	0/7	1–21%
Glucosamine[57]	USA	HPLC	2/6	77–117%
Glucosamine[57]	USA	HPLC	2/4*	90–108%
Glucosamine[61]	USA	HPLC	CosaminDS	101%
Glucosamine[58]	USA	NS	3/4	95–135%
Glucosamine[12]	Canada	HPLC	0/15	89–117%
Glucosamine[58]	USA	NS	9/12*	75–120%
Glucosamine[62]	USA	HPLC	6/6	99–103%
Glucosamine[63]	USA	HPTLC	0/6	55–87%
Glucosamine[59]	USA Capsule	HPLC	0/3	41–87%
Glucosamine[59]	USA	HPLC	4/14	35–117%
Glucosamine[64]	Iran	HPLC	2/10	13–139%
Glucosamine[65]	USA	CE	6/6	97–105%

*Combination product, chondroitin + glucosamine. CE, capillary electrophoresis; HPLC, high performance liquid chromatography; HPTLC, high performance thin layer chromatography; HPSEC, high performance size exclusion chromatography; NS, not stated; SAX-HPLC, strong anion exchange HPLC.

than claimed on their labels, and there was a fivefold difference in the range of this parameter over the 13 products. Commercial examples of 12 soy foods have been investigated and found to contain widely differing levels of daidzein, glycetein, and genistein.[77]

The resveratrol content of grape products has been investigated, again showing a wide range of levels. Juices from white grapes are known to contain lower levels than those from red grapes, and levels also depend on the variety of the plant, with these different types again showing extreme variations in levels.[78]

Individual and total CLA isomer levels in four US formulated supplements have been assessed, and found to vary widely, probably due to the variability of fixed oil source, and the conditions of isomerisation.[79]

Sixteen Spanish grape seed products have been studied and shown to have widely differing antioxidant activity as assessed by standard techniques, coupled with assessment of gallic acid and cyanidin levels. Unfortunately no comparison was made with labelled constituent levels.[80] A further 10 products derived from grape seed skins were evaluated, and detailed quantitative data was shown for the levels of 13 cyanidins.[81]

The Effect of Formulation

Although the most common forms of commercially available nutraceuticals are tablets and capsules, there is increasing use of more novel dosage forms, including soft gels, various controlled release preparations, chewable tablets, liquids, chewing gum, patch, dissolving strips, oral sprays, and fizzing tablets. One of the most popular nutraceutical supplements, glucosamine is now available as a gel rub, gel patch, effervescent and liquid, as well as tablets.[1]

In addition to modifying the stability of the active component particularly with liquid formulations, there is every chance that the bioavailability will be affected.

Detailed comparative data for formulations of individual nutraceuticals has been reported e.g. for coenzyme Q10, and creatine.[82,83] The bioequivalence of four coenzyme Q10 formulated products has been studied, 180 mg doses of four products evaluated. The absolute bioavailability of coenzyme Q10 is unknown as it is strongly lipophilic and practically insoluble in aqueous solution, and has poor bioavailability. A range of products formulated with emulsifying agents and oil based vehicles, as well as fully solubilised formulations were studied, in an attempt to improve bioavailability. Improved bioavailability was recorded for the oil suspension in a soft gelatin capsule when compared with a standard dry formulation.[84] Research into the variability of 10 coenzyme Q10 products available in New Zealand, showed that there was at least fourfold variation in the increase in plasma coenzyme Q10 levels achieved by the different products, and patients showed no increase in levels with the least effective products.[21]

The pharmacokinetic data of 17 formulated creatine products taken from six published studies, showed a wide range in levels of quoted pharmacokinetic parameters, maximum concentration (blood concentration–time profile) (C_{max}), area under the curve (AUC), half life ($t^1/_2$), clearance, and the volume of distribution. Overall, these levels showed variations of the order of 100%, even comparable data from a single study using different volunteer groups (young or elderly) exhibited variation of up to 50%.[83]

Other Indicators of Quality

The results of evaluation of levels of constituents in formulated or compounded products give some insight into the quality of products commercially available. However, until analytical methods for individual entities are standardised and compliance mandatory, there is no way of comparing results between research groups, or comparing the accuracy of individual methods. One published example of method comparison evaluated four electrophoretic methods for assaying of carnitine, and found levels ranging from 19.3 to 25.3 g/100 g.[6] A number of other examples have been published. The researchers of a soy quality/price survey also noted that different batches of the same product contained different levels of constituents, demonstrating little or no control of the production process.[48]

Manufacturers often supply formulations in dosages not usually employed in clinical trials, and often lower, therefore unless consumers are aware of the levels used for the reported effects, they may be taking dosage levels below the stated label claim.

One further problem which has been reported is that some manufacturers use label instructions advising the use of doses below those used in clinical trials, for example five of 12 combination glucosamine and chondroitin products, two of four glucosamine products, and three of three chondroitin products were found to be labelled with low recommended doses advised.[15] To add to the confusion, suggested daily doses of lutein have been reported to range from 0.25 to 22.5 mg, a factor of 90-fold difference.[14] Manufacturers have not yet followed the route of pharmaceutical companies who usually include detailed patient information leaflets with their products, enabling patients to take a recommended dosage schedule, study side effects, and possible interactions with prescription medicines.

A look at a range of commercial nutraceuticals will show that there is a marked difference in price. Numerous examples of wide price variations can be found. The costs of a number of ranges have shown wide variations. The price variations for these nutraceuticals are wide, particularly when the differential for formulated soy isoflavones is shown to be a factor of nearly 22-times! There is however, no evidence that quality is responsible for these variations.[1]

Conclusions

There are a number of nutraceuticals with applications in a number of therapeutic areas. Some of them show comparable efficacy to conventionally prescribed pharmaceuticals, but as consumption rises, so does incidence of poor quality of formulated commercial products. The quality issue includes raw materials, different chemical forms, complex products, substitution of inappropriate materials, the presence of contaminants, and different formulations. The number of formulated products exhibiting extreme deviation from label claims is particularly worrying. Side effects and drug interactions have been reviewed, and these are also indicators of overall quality.[85] Overall quality determinations on commercial formulated products reveal a situation lacking integrity on behalf of many manufacturers. Compared with both conventional pharmaceuticals and complementary medicines, nutraceuticals show lower incidences of adverse effects and drug interactions, but this is rising with increasing use. It has been suggested that only clear government regulation will eradicate quality problems and limit adverse effects and drug interactions.[3]

Overall, the impact of these findings on practice are clear: patients are increasingly using nutraceuticals for general health and age-related diseases; quality is not satisfactorily regulated; poor products have been identified; pharmacists and health practitioners need to be aware of the scientific literature to advise accordingly.

Declarations

Conflict of interest

The Author(s) declare(s) that he has no conflicts of interest to disclose.

Funding

This review received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Lockwood GB. *Nutraceuticals: A Balanced View for Healthcare Professionals*. London: Pharmaceutical Press, 2007.
2. Gunther S *et al*. Demographic and health-related correlates of herbal and specialty supplement use. *J Am Diet Assoc* 2004; 104: 27–34.
3. Lockwood GB. The hype surrounding nutraceutical supplements: do consumers get what they deserve? *Nutrition* 2007; 23: 771–772.
4. Anon. Survey of dioxins and dioxin-like PCBs in fish oil supplements. 2010. http://www.food.gov.uk/science/surveillance/fsis-2002/26diox (accessed 17 March 2010).
5. Jaksch F *et al*. *Handbook of Analytical Methods for Dietary Supplements*. Washington, DC: American Pharmacists Association, 2005.
6. Anon. *United States Pharmacopeia/National Formulary*. Rockville, MD: USP Convention, 2007.
7. Wechsler J. Standards for supplements. *Pharm Technol Eur* 2003; 18–20.
8. Anon. Dietary supplements methods. 2009. http://www.aoac.org/dietsupp6/Dietary-Supplement-web-site/DSMethods.html (accessed 17 March 2010).
9. Sim J-S *et al*. Quantitative analysis of chondroitin sulfate in raw materials , ophthalmic solutions, soft capsules, and liquid preparations. *J Chromatogr B* 2005; 818: 133–139.
10. Liang Z *et al*. Determination of the nutraceutical, glucosamine hydrochloride, in raw materials, dosage forms and plasma using pre-column derivatization with ultraviolet HPLC. *J Pharm Biomed Anal* 1999; 20: 807–814.
11. Green R. The laboratory notebook. *Nutraceuticals World* 2004; 24–25.
12. Russell AS *et al*. Active ingredient consistency of commercially available glucosamine sulfate products. *J Rheumatol* 2002; 29: 2407–2409.
13. Anon. Commission directive 2003/63/EC. *OJEU* 2003; L159/46.
14. ConsumerLab.com. 2004 (accessed 30 March 2004 (no longer available)).

15. Cavazza A *et al*. Rapid analysis of essential and branched -chain amino acids in nutraceutical products by micellar electrokinetic capillary chromatography. *J Agric Food Chem* 2000; 48: 3324–3329.
16. Prokoratova V *et al*. Capillary electrophoresis determination of carnitine in food supplements. *J Chromatogr A* 2005; 1081: 60–64.
17. Kakou A *et al*. Determination of L-carnitine in food supplement formulations using ion-pair chromatography with indirect conductimetric detection. *J Chromatogr A* 2005; 1069: 209–215.
18. Aman R *et al*. Determination of carotenoid stereoisomers in commercial dietary supplements by high-performance liquid chromatography. *J Agric Food Chem* 2004; 52: 6086–6090.
19. Humayoun M, Bryan M. Extraction and quantification of major carotenoids in processed foods and supplements by liquid chromatography. *Food Chem* 2008; 111: 255–261.
20. Nishii S *et al*. Quality test of commercial ubidecarenone tablets. *Byoin Yakugaku* 1983; 9: 14–18.
21. Molyneux S *et al*. The bioavailability of coenzyme Q10 supplements available in New Zealand differs markedly. *N Z Med J* 2004; 117: U1108.
22. Johnson C *et al*. Analysis of CoQ10 in nutraceuticals. Abstracts of Papers, 229th ACS National Meeting, San Diego, CA, United States, March 13–17, 2005.
23. Tang PH. Determination of coenzyme Q10 in over-the-counter dietary supplements by high – performance liquid chromatography with coulometric detection. *J AOAC Int* 2006; 89: 35–39.
24. Kettawan A *et al*. The quality control assessment of commercially available coenzyme Q10-containing dietary and health supplements in Japan. *J Clin Biochem Nutr* 2007; 41: 124–131.
25. Wagner SD *et al*. Quantification of creatine in nutrition supplements by thin layer chromatography-densitometry with thermochemical activation of fluorescence quenching. *J Liquid Chromatogr Rel Technol* 2001; 24: 2525–2530.
26. Dash AK, Sawhney A. A simple LC method with UV detection for the analysis of creatine and creatinine and its application to several creatine formulations. *J Pharm Biomed Anal* 2002; 29: 939–945.
27. Persky AM *et al*. Validation of a simple liquid chromatography assay for creatine suitable for pharmacokinetic applications, determination of plasma protein binding and verification of percent labelled claim of various creatine products. *J Chromatogr B* 2003a; 794: 157–165.
28. Parasrampuria J *et al*. Quality control of dehydroepiandrosterone dietary supplement products. *J Am Med Assoc* 1998; 280: 1565.
29. Thompson RD, Carlson M. Liquid chromatographic determination of dehydroepiandrosterone (DHEA) in dietary supplement products. *J AOAC Int* 2000; 83: 847–857.
30. Chee KM *et al*. Fatty acid content of marine oil capsules. *Lipids* 1990; 25: 523–528.
31. Ihrig M, Blume H. Preparations of evening primrose oil: a quality comparison. *Pharmazeutische Zeit* 1994; 139: 39–42.
32. Gibson RA *et al*. γ-Linolenic acid (GLA) content of encapsulated evening primrose oil products. *Lipids* 1992; 27: 82–84.
33. Sitton A *et al*. Determination of lipoic acid in dietary supplement preparations by capillary electrophoresis. *J Biochem Biophys Methods* 2004; 61: 119–124.
34. Durrani AI *et al*. alpha-Lipoic acid in dietary supplements: development and comparison of HPLC – CEAD and HPLC -ESI-MS methods. *J Pharm Biomed Anal* 2007; 45: 694–699.
35. Sechrist J *et al*. Quantification of lutein in dietary supplements by reversed-phase high-performance thin-layer chromatography with visible-mode densitometry. *Acta Chromatogr* 2002; 12: 151–158.
36. Breithaupt DE, Schlatterer J. Lutein and zeaxanthin in new dietary supplements -analysis and quantification. *Eur Food Res Technol* 2005; 220: 648–652.
37. Feifer AH *et al*. Analytical accuracy and reliability of commonly used nutritional supplements in prostate disease. *J Urol* 2002; 168: 150–154.
38. Costantini A, Paoli F. Melatonin: quantitative analysis in pharmaceutical oral dosage forms using thin-layer chromatography (TLC) densitometry. *Il Farmaco* 1998; 53: 443–447.
39. Bertram RM *et al*. High performance liquid chromatographic analysis: applications to nutraceutical content and urinary disposition of oxyresveratrol in rats. *Biomed Chromatogr* 2010; 24: 516–521.
40. Irmak S *et al*. Policosanol contents of beeswax , sugar cane and wheat extracts. *Food Chem* 2006; 95: 312–318.
41. Nakamura Y *et al*. Analysis of proanthocyanins in grape seed extracts, health foods and grape seed oils. *J Health Sci* 2003; 49: 45–54.
42. Babu SK *et al*. Estimation of trans-resveratrol in herbal extracts and dosage forms by high-performance thin-layer chromatography. *Chem Pharm Bull* 2005; 53: 691–693.
43. Anon. Emotional aspirin. *Consumer Reports* 2000; 60–62.
44. Setchell KDR *et al*. Bioavailability of supplements. *J Nutr* 2001; 131: 1362S–1375S.
45. Howes JB, Howes LG. Content of isoflavone–containing preparations. *Med J Aust* 2002; 176: 135–136.
46. Nurmi T *et al*. Isoflavone content of the soy based supplements. *J Pharm Biomed Anal* 2002; 28: 1–11.
47. Penalvo JL *et al*. Plant lignans in soy–based health supplements. *J Agric Food Chem* 2004; 52: 4133–4138.
48. Chua R *et al*. Quality, labeling accuracy , and cost comparison of purified soy isoflavonoid products. *J Altern Complement Med* 2004; 10: 1053–1060.
49. Krenn L, Poetsch V. An efficient HPLC method for the quantification of isoflavones in soy extract and soy dietary supplements in routine quality control. *Pharmazie* 2006; 61: 582–585.
50. Sturtz M *et al*. Quantitative determination of isoflavones in soy based nutritional supplements by high-performance liquid chromatography. *J Verbraucherschutz Lebensmittelsicherheit* 2008; 3: 127–136.
51. Clarke DB *et al*. Determination of phytoestrogens in dietary supplements by LC – MS / MS. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2008; 25: 534–547.
52. Nair VDP *et al*. Determination of stigmasterol, β-sitosterol and stigmastanol in oral dosage forms using high performance liquid chromatography with evaporative light scattering detection. *J Pharm Biomed Anal* 2006; 41: 731–737.
53. Halkina T, Sherma J. Determination of sterols and fatty acids in prostate health dietary supplements by silica gel high performance thin layer chromatography with visible mode densitometry. *J Liquid Chromatogr Rel Technol* 2007; 30: 2329–2335.
54. Manning J, Roberts JC. Analysis of catechin content of commercial green tea products. *J Herb Pharmacother* 2003; 3: 19–32.
55. Weiss DJ *et al*. Analysis of green tea extract dietary supplements by micellar electrokinetic chromatography. *J Chromatogr A* 2006; 1117: 103–108.
56. Remsberg CM *et al*. Ingredient consistency of commercially available polyphenol and tocopherol nutraceuticals. *Pharmaceutics* 2010; 2: 50–60.
57. Adebowale A *et al*. Nutraceuticals, a call for quality control of delivery systems: a case study with chondroitin sulfate and glucosamine. *J Nutraceuticals Funct Med Food* 1999; 2: 15–30.
58. Anon. Joint remedies. *Consumer Reports* 2002; 18–21.
59. Eddington ND. Design and results of a study to analyze the contents of glucosamine and chondroitin sulphate content in

marketed products: update and the need for industry standards. In: Augsburger L, ed. *Examining the Science behind Nutraceuticals*. Washington, DC. AAPS, 2005: 228–239.
60. Sim J-S *et al*. Evaluation of chondroitin sulfate in shark cartilage powder as a dietary supplement: raw materials and finished products. *Food Chem* 2007; 101: 532–539.
61. Way WK *et al*. Determination of glucosamine in nutritional supplements by reversed-phase ion-pairing HPLC. *J Liquid Chromatogr Rel Technol* 2000; 23: 2861–2871.
62. Shao Y *et al*. A stability-indicating HPLC method for the determination of glucosamine in pharmaceutical formulations. *J Pharm Biomed Anal* 2004; 35: 625–631.
63. Sullivan C, Sherma J. Development and validation of an HPTLC – densitometry method for assay of glucosamine of different forms in dietary supplement tablets and capsules. *Acta Chromatogr* 2005; 15: 119–130.
64. Nemati M *et al*. Development of a simple and sensitive high-performance liquid chromatography method for determination of glucosamine in pharmaceutical formulations. *J AOAC Int* 2007; 90: 354–357.
65. Volpi N. Capillary electrophoresis determination of glucosamine in nutraceutical formulations after labeling with anthranilic acid and UV detection. *J Pharm Biomed Anal* 2009; 49: 868–871.
66. Dentith S, Lockwood B. Development of techniques for the analysis of isoflavones in soy foods and nutraceuticals. *Curr Opin Clin Nutr Metab Care* 2008; 11: 242–247.
67. Kirrane M, Lockwood B. Developments in the analysis of tea. *Nutrafoods* 2008; 7: 11–20.
68. Adams J, Lockwood B. Development of techniques for analysis of nutraceuticals with particular reference to glucosamine and coenzyme Q10. In: Pathak Y, ed. *Handbook of Nutraceuticals*, Vol. 1. Boca Raton, FL: Taylor & Francis, 2009: 132–148.
69. Volpi N. Analytical aspects of pharmaceutical grade chondroitin sulfates. *J Pharm Sci* 2007; 96: 3168–3180.
70. Sakai S *et al*. Identification of the origin of chondroitin sulfate in 'health foods'. *Chem Pharm Bull* 2007; 55: 299–303.
71. Saad OM *et al*. Analysis of hyaluronan content in chondroitin sulfate preparations by using selective enzymatic digestion and electrospray ionization mass spectrometry. *Anal Biochem* 2005; 344: 232–239.
72. Volpi N. Quality of different chondroitin sulphate preparations in relation to their therapeutic activity. *J Pharm Pharmacol* 2009; 61: 1271–1280.
73. Spence JD *et al*. The effect of flax seed cultivars with differing content of alpha-linolenic acid and lignans on responses to mental stress. *J Am Coll Nutr* 2003; 22: 494–501.
74. Chen Z *et al*. Degradation of green tea catechins in tea drinks. *J Agric Food Chem* 2001; 49: 477–482.
75. Chen C-N *et al*. Capillary electrophoretic determination of theanine, caffeine, and catechins in fresh tea leaves and oolong tea and their effects on rat neurosphere adhesion and migration. *J Agric Food Chem* 2003; 51: 7495–7503.
76. Prabhakaran MP *et al*. Evaluation of the composition and concentration of isoflavones in soy based supplements, health products and infant formulas. *Food Res Int* 2006; 39: 730–738.
77. Preinerstorfer B, Sontag G. Determination of isoflavones in commercial soy products by HPLC and coulometric electrode array detection. *Eur Food Res Technol* 2004; 219: 305–310.
78. Nikfardjam MP *et al*. Investigation of pure grape juices on their content of resveratrols. *Deutsche Lebensmittel-Rundschau* 2000; 96: 319–324.
79. Yu L *et al*. Comparison of commercial supplements containing conjugated linoleic acids. *J Food Composit Anal* 2003; 16: 419–428.
80. Monagas M *et al*. Quality assessment of commercial dietary antioxidant products from *Vitis vinifera* L. grape seeds. *Nutr Cancer* 2005; 53: 244–254.
81. Monagas M *et al*. Commercial dietary ingredients from *Vitis vinifera* L. leaves and grape skins: antioxidant and chemical characterization. *J Agric Food Chem* 2006; 54: 319–327.
82. Miles MV *et al*. Bioequivalence of coenzyme Q10 from over-the-counter supplements. *Nutr Res* 2002; 22: 919–929.
83. Persky AM *et al*. Pharmacokinetics of the dietary supplement creatine. *Clin Pharmacokinet* 2003; 42: 557–574.
84. Weis M *et al*. Bioavailability of four oral coenzyme Q10 formulations in healthy volunteers. *Mol Aspects Med* 1994; 15: S273–S280.
85. Davies E *et al*. Adverse effects and toxicity of nutraceuticals. In: Preedy VR, Watson RR, eds. *Reviews in Food and Nutrition Toxicity*, Vol. 3. Boca Raton: CRC Press, 2005: 165–195.