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Nutraceuticals

Second edition

Brian Lockwood

Nutraceuticals

A guide for healthcare professionals

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Preface

This book was written in response to the obvious need for a scientifically based text on the evidence for the use of nutraceuticals for the prevention and treatment of important disease states. The use of nutraceuticals is by now an established complementary therapy, with a few being used as if they were conventional pharmaceuticals, and a number of others being purchased and used by the general public as self-medication. Although nutraceuticals are constantly discussed in the media and freely available, comprehensive knowledge concerning their activities, mode of action and safety is not yet widely available. The main aim of this book was, therefore, to explore, discuss and possibly substantiate claims that a number of nutraceuticals can actually treat or prevent the underlying causes of disease.

Consumers clearly hope that they will benefit from intake of these products either through long-term use or via a conscious decision to change lifestyle. That is why I have decided here, unlike a number of other books on the subject, to organise the information according to disease states. In addition, any evidence quoted should be of understandable quality. The inclusion of directly attributable information sources was considered vital for this, producing a usable text for both patient, consumer and healthcare practitioners wanting to find further details by checking the original publications. Wherever possible, I have tried to focus on clinical and human research, although results from animal studies are included, particularly for the chapter on animal health, but also when there are major findings or there are insufficient human data.

Previous books have either focused on the individual chemical entities and their applications, or consist of information in therapeutic areas which is not directly attributed to published data, hence not allowing easy access to original material. In contrast, this text aims to cover a wide range of nutraceuticals, specifically focusing on their use in specific therapeutic categories. Although the book was designed as a text to inform readers as to the claimed benefits of specific nutraceuticals in

various therapeutic contexts, it was still thought necessary to include monographs on individual compounds. This gives us the opportunity to describe their properties and to define the characteristics that are often important in a number of disease states, either due to a particular activity that results in applications in more than one therapeutic area, or because they possess a number of attributes with wide-ranging applications. The monographs include information on biological sources, which are important for those wishing to supplement their diets with specific foods containing nutraceuticals, manufacturing and analytical details, metabolism, bioavailability and pharmacokinetics. Much of this information has been compiled into tables to allow easy comparison between the entities discussed.

The major change in this text with respect to the previous book is the inclusion of soy and tea. Over the last 10–20 years a body of scientific and medical literature has been published concerning the proposed health benefits of soy and tea products. This weight of evidence, still increasing annually, has determined that any text on the subject of nutraceuticals takes into account commercially available products from these two sources. At the time of writing (2006) it can be said that roughly 20–30% of all studies and reviews on nutraceuticals are derived from these two supplements.

In addition to the growth in evidence for these two supplements, there is now also more evidence concerning, for example, flax lignans and resveratrol, which justifiably warrants their inclusion in any relevant text. Looking to the future, we can also see more evidence being published on minor or new nutraceuticals, such as theanine and NADH, which have been the subject of clinical trials.

Since 2002 there has been rapid expansion of publications in the overall area of nutraceuticals, and this book attempts to reflect this new material, particularly in reporting more detailed pharmacological profiling of the nutraceuticals. Chapters on a number of pertinent aspects of nutraceutical use have been included, apart from their applications in specific therapeutic categories, namely combination therapy and synergy, safety, adverse effects and quality issues, along with a section on minor nutraceuticals.

Increasing evidence that health is related to diet have resulted in a range of government initiatives designed to encourage healthy eating, and positive steps are being taken by an increasing number of individuals. However, for many people living in an increasingly sophisticated world, supplementation with formulated nutraceuticals is a more realistic solution than making major modifications to the diet.

It is hoped that this work will be useful to pharmacists, medical practitioners and nursing staff, as well as respective students. A chapter on veterinary nutraceuticals specifies particular applications for domesticated animals, but many of the included human nutraceuticals are now also being used for animals.

Most information is summarised to allow readers to refer to data on the large number of nutraceuticals currently available; some are the subject of vast numbers of clinical trials and scientific publications, while others have only been described in limited published data. Some of the information has been published recently in peer-reviewed articles (for example in *Nutrition* or the *Pharmaceutical Journal* and business-related science journals) along with chapters in books, and a chapter in the *Encyclopedia of Pharmaceutical Technology*. These publications were often in association with co-authors, and are referenced in relevant sections. Over the last 3–4 years numerous publications have appeared on the subject of nutraceuticals, and it has been an ongoing task to keep updating sections in this book, with references up to mid-2006 being incorporated. Inevitably a number of articles will have been superseded by more up-to-date studies during the publication process.

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daidzein and genistein to the non-acylated form,[75] allowing absorption in the gut. Once in the plasma, the compounds can be taken up by the liver and excreted in the bile as conjugates, mainly as 7-*O*-β-glucuronide.[73]

The isoflavones become highly bound to proteins in the plasma, and less than 3% will circulate as the free aglycone form.[76] A study conducted on subjects fed a soy beverage for two weeks reported plasma levels of genistein and daidzein to range between 0.55 and 0.96 μmol, mostly as glucuronide and sulfate conjugates.[77]

The metabolism of genistein and daidzein occurs mainly in the liver, and these metabolites are excreted via the biliary, urinary or faecal routes. Only 1–2% of genistein is excreted faecally, the biliary and urinary routes are of greater significance when considering clearance.[78] Genistein and daidzein both undergo extensive first-pass metabolism, removing them from the plasma.[77] The genistein 7-*O*-β-glucuronide can be excreted in the bile duct, where reabsorption may occur. It was suggested that daidzein is less bioavailable than genistein due to its more rapid excretion in the urine. This may be due, however, to the less hydrophobic nature of daidzein.[71]

Therapeutic areas: Cardiovascular, mental, bone, women's and skin health, cancer prevention (antioxidant and oestrogenic)
Legal classification: No restriction
Recommended dose: 30–50 mg/day
Formulations available: Tablet, powder

Tea

Structure and properties

Tea is obtained from *Camellia sinensis*, an evergreen shrub native to South-East Asia but cultivated in over 30 countries worldwide.[79] Tea is derived from the leaves of the plant, with the top two leaves and the bud producing the finest tea.[80] The leaves contain polyphenols (approximately a third of the dry weight)[81] together with an enzyme called polyphenol oxidase.

Approximately 3 billion kg of tea are produced and consumed each year[82] and of the three main types of tea produced – black, green and oolong – black tea accounts for approximately 78% of the total consumed worldwide, with green tea representing 20% and oolong tea less than 2%.[79]

Green tea is produced by steaming or heating the freshly harvested leaves; this inactivates the enzyme polyphenol oxidase, and prevents

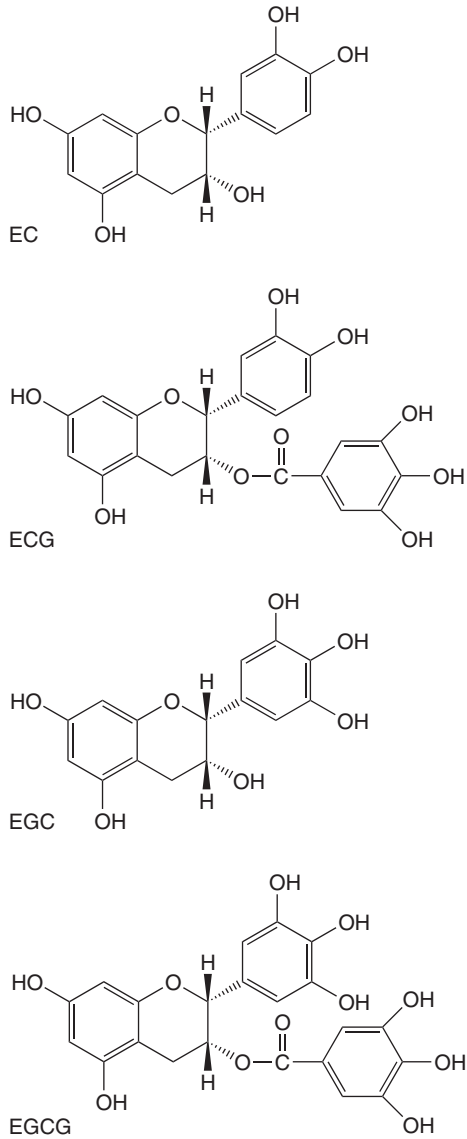


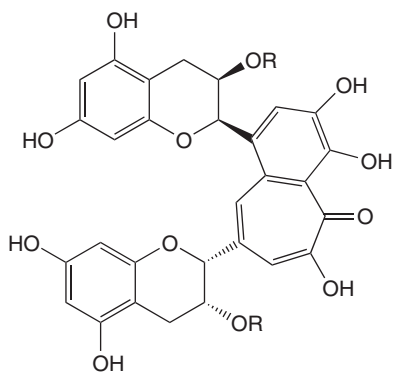
Figure 2.26 The major catechins in tea: (—)-epicatechin (EC), (—)-epicatechin gallate (ECG), (—)-epigallocatechin (EGC) and (—)-epigallocatechin gallate (EGCG).

fermentation of the polyphenols such as catechins. To produce black tea the leaves are left to wither, which allows the moisture content to decrease. The leaves are then rolled and crushed, which permits the release of polyphenol oxidase and the oxidation of the polyphenols. The

catechins (polyphenols) are converted into theaflavins and thearubigins. After 60–90 minutes the product is dried using a stream of hot air.[79,83–85] Oolong tea is produced via the same process as black tea but the leaves are dried with hot air after only 30 minutes, and therefore only partial fermentation occurs.[81]

The polyphenols (proanthocyanidins) include catechins, quercetin, myricetin and kaempferol and they account for 30–42% of the dry weight of tea. Catechins are the main components and the four principal ones found in tea are (—)-epicatechin (EC), (—)-epicatechin gallate (ECG), (—)-epigallocatechin (EGC) and (—)-epigallocatechin gallate (EGCG),[86] of which EGCG is the most abundant, accounting for 50–80% of the catechins.[83] A typical brewed cup of green tea, approximately 240 mL, can contain up to 200 mg of EGCG.[79] Figure 2.26 shows the structures of the major catechins in tea.

In addition to gallic acids and theanine, green tea contains approximately 3–6% of caffeine, and theophylline and theobromine.[83] Black tea also contains catechins but to a lesser extent – only 3–10% of the dry weight compared with 30–42% in green tea. Black tea also contains theaflavins, including: theaflavin, theaflavin-3-gallate, theaflavin-3′-gallate and theaflavin-3,3′-digallate. Theaflavins only account for 2–6% of the dry weight of black tea; thearubigins are the major components accounting for over 20% of the dry weight.[85] Thearubigins have a higher molecular weight than theaflavins and are presently poorly defined chemically.[85] Black tea contains slightly less caffeine than green tea, on average 2–4% of the dry weight. Oolong tea also contains thearubigins, theaflavins and catechins.[83] Figure 2.27 shows the basic structures of theaflavins.



Theaflavins (R = H or gallate–all combinations possible)

Figure 2.27 The structure of the theaflavins.

Catechins are the main polyphenolic component of green tea and EGCG has been claimed to be the most biologically active.[87]

Metabolism and pharmacokinetics

Following the administration of decaffeinated green tea (1.5, 3.0 and 4.5 g tea solids) to human volunteers, peak plasma concentrations of 326, 550 and 190 μg/L were observed for EGCG, EGC and EC, respectively 1.4–2.4 hours after ingestion. The half-life of EGCG (5.0–5.5 hours) was higher than the half-lives of EGC or EC (2.5–3.4 hours). Over 90% of total EGC and EC were excreted in the urine within 8 hours, but EGCG was not, only appearing in faeces.[88]

Following consumption of 2–3 cups of green tea, peak saliva levels of 4.8–22, 11.7–43.9 and 1.8–7.5 mg/L were observed respectively for EGCG, EGC and EC. After volunteers held a solution of EGCG in their mouths for a few minutes, both EGCG and EGC were detected in saliva. EGCG was converted to EGC via an enzyme, catechin esterase, and both compounds were absorbed through the oral mucosa.[88] These results suggest that drinking tea slowly is very effective in delivering high concentrations of catechins to the oral cavity and oesophagus.[85]

In another study in humans, single oral doses of 200–800 mg EGCG were administered, and the mean area under the plasma concentration time curves of EGCG was from 22.5 to 167.1 min × μg/mL for the 200–800 mg doses. EGC and EC were not detected in the plasma, and the availability of EGCG increased over the dosage range, possibly due to the presence of saturable presystemic elimination.[89] Later work using multiple-dose administration of EGCG revealed a >60% increase in the plasma concentration time curves after four weeks of administration at the 800 mg doses.[90] A study using 195 mg EGCG found similar pharmacokinetic data, but considerable interindividual variability was noted.[91]

Catechin bioavailability from 28 studies has been reviewed.[92] It was noted that the bioavailability differed markedly between the different catechins. EGCG was seen to be methylated in a number of studies, at either the 4′-*O*- or 4′,4′′-di-*O*-positions, and these were often the major metabolites of EGCG. EGCG is also the only polyphenol present in plasma as a major proportion of the ingested dose. Other catechins have been found as glucuronide and sulfate conjugates.[92] A range of hydroxyphenyl valerolactone analogues have been identified in plasma and urine, mainly as conjugates, and these account for high levels

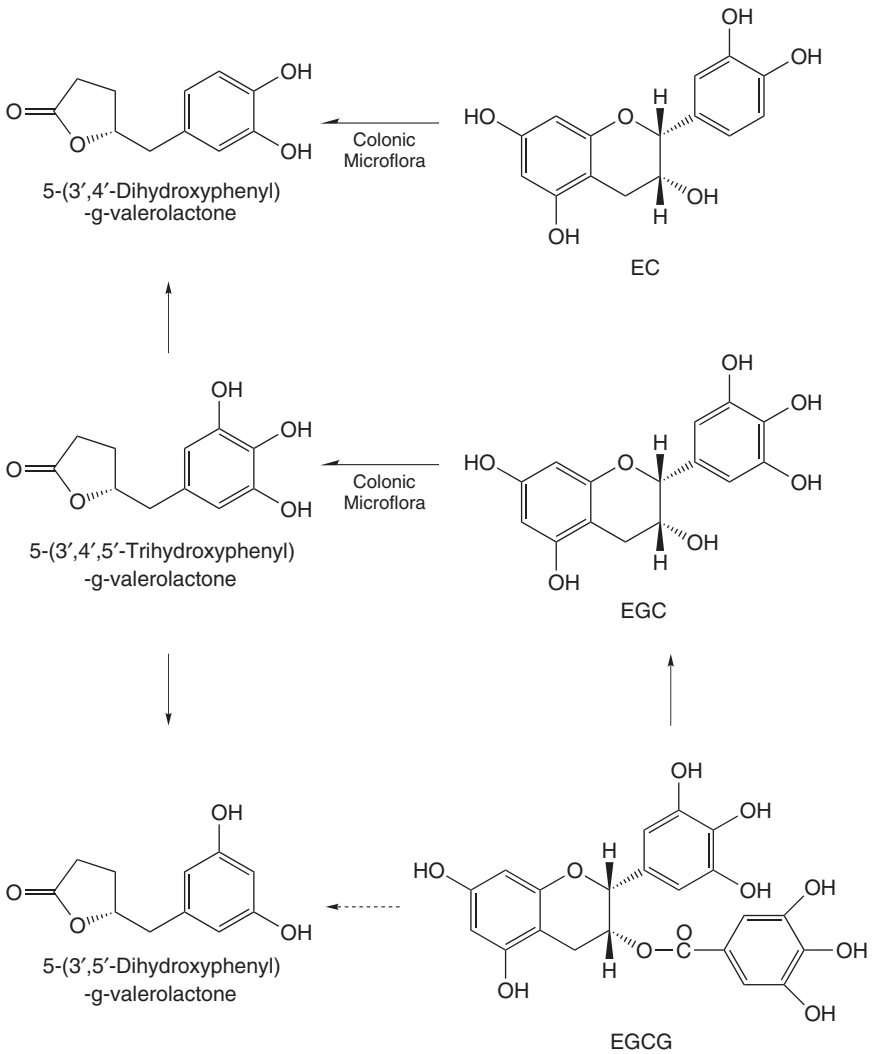


Figure 2.28 Biotransformation of catechins. Reprinted from Lambert J D, Yang Chung S. Cancer chemopreventive activity and bioavailability of tea and tea polyphenols. *Mutat Res* 2003; 523–524: 201–208, with permission.

of EGC and EC, 8–25 times the levels detected of the unchanged compounds.[92]

Tea polyphenols have low bioavailability due to their high molecular weights and polarity. The large number of hydroxyl substituents may hinder absorption of the compounds across the gut lumen.[93]

Figure 2.28 outlines a number of human metabolites from catechins catalysed by colonic microflora. A number of methylations of EC, EGC and EGCG catalysed by catechol-*O*-methyltransferase (COMT) have also been shown to give rise to mono- and di-methyl forms.[93]

Human colonic microflora, *in vitro*, have also been shown to degrade exogenous catechin polymers into monohydroxylated phenylacetic, phenylpropionic and phenylvaleric acids, over 48 hours of incubation in anoxic conditions.[94] Catechins themselves are rapidly eliminated, but galloylated catechins such as ECG and EGCG have not been detected in the urine, due to their preferential excretion in the bile.[91]

Tea polyphenols have low bioavailability due to their high molecular weights and a high number of hydroxyl substituents. This makes them susceptible to phase II enzymes, resulting in their biotransformation. Also, the hydroxyl groups may hinder absorption of the compounds across the gut lumen.[95] The theaflavins are still less bioavailable.[84]

Therapeutic areas: Cardiovascular, bone, skin and oral health, cancer prevention and weight management (antioxidant)
Legal classification: No restriction
Recommended dose: 5–100 mg/day of tea polyphenols
Formulations available: Tablet, capsule, powder, tea

Creatine

Structure and properties

Creatine (Figure 2.29) is distributed throughout the human body, with 95% found in skeletal muscle.[96] It occurs naturally in the human diet, as red meat and fish contain 4–10 g/kg. It is also synthesised in the kidney, liver and pancreas. Creatine supplementation gives rise to higher levels of phosphocreatine, which is used to produce and regenerate ATP, resulting in cells being better able to deal with energy requirements in health and disease.[96]

Metabolism and pharmacokinetics

Creatine and phosphocreatine are catabolised to creatinine, which is eliminated in the urine. Creatine pharmacokinetics are non-linear, as skeletal muscle which acts as a depot for creatine, has a finite capacity

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Weight management

Obesity

In the UK, as in many other developed countries, there is an increasing obesity epidemic. Between 1993 and 2003 the number of clinically obese individuals almost doubled. Numbers of clinically obese men rose from 13% to 23%, and women from 16% to 23%.[1] A further 44% of men and 33% of women in the UK are classed as clinically overweight.[1] Childhood obesity has also become a major issue, prompting the UK government to aim new policies at curbing the increase of unhealthy children[2] following a recent TV series highlighting the role of convenience food in the growing childhood obesity epidemic.[3]

Obesity is not only a major health problem, it also causes concern for individuals for cosmetic reasons, and the enormous variety of dieting supplements and popularity of weight loss clubs show how weight loss has become a multimillion pound industry. In the USA, the number one health issue (as reported by 40% of the population) is the need to lose weight for reasons of appearance.[4] Two-thirds of Americans (representing 138 million adults) also report that they have used some method to maintain or manage their weight during 2004.[4]

Strategies for weight loss

Low carbohydrate diets are just one example from the long list of diets on offer for those wanting to lose weight. The popularity of the Atkins diet, the Glycaemic Index (GI) diet and meal replacement diets such as Slimfast, are examples of the many routes people are willing to try in order to achieve weight loss.

Clubs and organisations where group support and encouragement are available alongside a diet regime are also popular. Weight Watchers, an international slimming organisation that has 6000 classes weekly in the UK and claims to have helped around 30 million dieters to lose weight,[5] and Slimming World, which has recently joined forces with

NHS Primary Care Trusts to aid dieters,[6] are examples of such organisations.

Supplements for weight loss are numerous. People generally prefer to seek a shortcut to weight loss, so the demand for such supplements, which often claim to give fast results, is huge. Coupled with the fact that many of these products can be marketed as food supplements with relatively little regulatory controls, the market is rapidly expanding.[7]

The universally acknowledged way to lose weight is a calorie controlled diet with increased physical activity, as most healthcare professionals advise.[8] Diet alone is useful, but for long-term maintenance of body weight, exercise is critical, helping prevent the cyclical effect of rapid weight gain after a period of dieting.[9] Self-monitoring and other behavioural interventions can also enhance weight loss.[8]

Conventional pharmaceutical treatments such as the lipase inhibitor orlistat are also available for weight loss, but only on prescription. Orlistat works by blocking fat absorption but has unpleasant and common side-effects of faecal incontinence and flatulence.[10]

Nutraceuticals

Nutraceuticals are a growing sector of the supplements market for weight loss, and there are a wide variety of products, formulated into capsules or tablets, or even incorporated into foods or convenience style foods such as snack bars. Several nutraceuticals currently being marketed as aids to weight loss have been the subject of scientific and medical research. The major examples include L-carnitine and acetyl-L-carnitine, dehydroepiandrosterone (DHEA), green tea and conjugated linoleic acid (CLA).

L-Carnitine and acetyl-L-carnitine

L-Carnitine is an endogenous product found in the kidneys and liver that can also be obtained by intake of dairy products and red meat in the diet. It is a co-factor in the process of fat oxidation for cellular energy production.[11] Fat oxidation in muscle tissue is reduced in obesity due to a reduction of L-carnitine-mediated enzyme activity.[12] It is for this reason that carnitine is purported to be of benefit in obese people by increasing fat oxidation,[13] and explains why it is often promoted as a 'fat burner'. However, it has not been tested for its effectiveness or safety over prolonged periods of time.

One study found that rats fed L-carnitine supplementation in combination with an energy-restricted diet had the same weight loss and

body composition as rats fed an energy-restricted diet alone.[14] Results showed both groups lost considerable amounts of weight and had a marked reduction in body fat, but there were no significant differences between the control group and the treated group.

L-Carnitine was shown to drastically reduce body fat in a study of basketball players, although it did not cause a significant fall in overall body mass.[15] The study was investigating L-carnitine as an ergogenic aid for reducing body fat in already lean athletes. A cohort of 12 basketball players were supplemented with L-carnitine for eight weeks and compared with a control group. In the supplemented group there were significant improvements in speed, jumping ability and VO_2 max (maximal oxygen uptake), and an average 21% fall in body fat. However, there was no significant difference in overall reduction of body mass between the two groups.

A review of common dietary supplements for weight loss concluded that there was insufficient or conflicting evidence for L-carnitine, and that despite no evidence of adverse effects, no trials demonstrated L-carnitine's effectiveness as a supplement for weight loss. The review suggested that doctors should caution patients that L-carnitine has so far not been proven useful for weight loss, but if a patient wanted to use the supplement, then doctors should monitor them for any positive or negative effects.[16]

Acetyl-L-carnitine has similar roles to L-carnitine, and is used by athletes as a metabolic source of L-carnitine. It is synthesised by mitochondria and found in the brain, kidney and liver. Claims have been made that supplementation with acetyl-L-cartinine can increase energy and help weight loss.[17] Acetyl-L-carnitine is capable of restoring mitochondrial energy production, so it is believed to increase general metabolic activity as well. It is for these reasons that acetyl-L-carnitine is purported to increase ambulatory activity and increase metabolism, although animal studies show mixed results, with one study showing an improvement in metabolic function of rats supplemented with acetyl-L-carnitine,[17] and another study showing that acetyl-L-carnitine prevented weight loss in rats.[18] There is no scientific evidence for weight loss in humans with acetyl-L-carnitine.

Dehydroepiandrosterone

DHEA is an adrenal hormone found naturally in the body. Blood levels of DHEA in humans peak at around the age of 20, and decrease rapidly after 25 years of age. DHEA plays a role in receptor and enzyme adaptations that are thought to favour increased fat oxidation and decreased

fat deposition.[19] Administration of DHEA to rats has led to a decrease in their visceral fat accumulation, and also resulted in a lower increase of body fat with advancing age.[19] For human consumption DHEA is only available on prescription in the UK, but is widely available for sale on the Internet. It is marketed as a 'thermogenic' compound with the ability to burn fat and also to help maintain fat loss.[18]

One study concluded that inefficient energy utilisation and obesity in rats was corrected with DHEA treatment.[20] DHEA was administered to obese prediabetic OLETF rats for a 17-day period, during which the rats sustained significant weight loss. This loss was partly attributed to enhanced utilisation of energy ingested. It was suggested that DHEA corrected deficient expression levels of uncoupling protein 1 (UCP-1) in brown adipose tissue in these rats, which contributed to more efficient energy utilisation and hence weight loss.

A study of the effects of DHEA in humans concluded that compared with a placebo, DHEA induced significant decreases in abdominal fat in elderly men and women.[19] In a randomised, double-blind, placebo-controlled six-month trial of men and women over 65 years, a daily dose of 50 mg DHEA reduced visceral and subcutaneous fat significantly. The volunteers in this study were included if their weight had been stable for the previous year. During the study volunteers were asked not to alter their usual diet or activity levels. No significant adverse effects were reported with the DHEA supplements. It was suggested that DHEA acts as a peroxisome proliferator-activated receptor α (PPARα) agonist, which have been shown to reduce fat stores in muscle and reduce obesity. DHEA also increased the concentration of circulating insulin-like growth factor I (IGF-I) within the body, which has been shown in previous studies to reduce abdominal fat.

More research is needed to assess the side-effect profile of DHEA, and there are inherent dangers involved in unsupervised use of these steroids. Long-term studies are also needed with DHEA to assess the effects of increased IGF-I levels, and the effect of changes in oestradiol and testosterone levels on the body, as this supplement could be taken for long periods of time if found to be effective.

Green tea

The claimed benefits of drinking green tea and taking green tea supplements are becoming more widely discussed, with the lay media and articles on the Internet extolling their claimed health benefits. Green tea contains catechin polyphenols, which have been shown to inhibit

catechol-*O*-methyltransferase (COMT), an enzyme responsible for the degradation of noradrenaline, which itself has an important role in the control of thermogenesis and fat metabolism.[21]

Tea catechins have been shown to cause loss of appetite, which might involve neuropeptides other than leptins, since (—)-epigallocatechin gallate (EGCG) is effective in reducing the body weight of both lean and obese (leptin receptor-negative) rats. However, the body weight loss has been found to be reversible, and the animals regain body weight when EGCG administration is stopped. The *in vitro* thermogenic effect of green tea extract on adipose tissue can be mimicked by EGCG, giving credence to the belief that EGCG is the important component of green tea.[22]

It has been recommended that the use of green tea for weight loss should be cautioned and closely monitored in patients that choose to take it, as product quality and efficacy is uncertain, although adverse effects are not likely if the equivalent of five cups daily is not exceeded.[16]

A small study of ten male adults indicated that green tea extract significantly increased 24-hour energy expenditure, measured by indirect calorimetry while in a respiratory chamber.[21] This was a crossover study in which the ten volunteers were assigned one of three treatments (a placebo, green tea extract or the equivalent amount of caffeine to that in the green tea extract) on three occasions. Treatment with the placebo or the caffeine did not have any significant effects on energy expenditure. These results rule out the hypothesis that caffeine alone is responsible for the increased energy expenditure. The major limitation of this study, aside from its small sample size, is that it did not actually measure body weight as a parameter, as it was only carried out for a period of 24 hours at any one time. However, the authors do suggest that green tea extract has good potential to influence body weight and body composition due to its promotion of fat oxidation and thermogenic properties. An important observation of the study was that there was no increase in heart rate, as is seen with other substances that increase energy expenditure such as ephedrine and other sympathomimetic drugs. This means that the risk of adverse cardiovascular effects is greatly reduced.

Another study on the effects of green tea for weight maintenance after weight loss showed that weight maintenance over a 13-week period, after a 7.5% body weight loss, was not affected by green tea consumption.[23] This randomised, parallel and placebo-controlled trial included 104 participants and was undertaken over a four-week weight loss period, followed by a 13-week weight maintenance period. Overweight and moderately obese men and women volunteers were recruited. The study attempted to try to find a solution to the common

problem of cyclical weight loss and regain, and the issue of long-term weight maintenance that is obviously required if patients are to maintain the benefits of their initial weight loss. Overall results showed that the body weight regained (as a percentage of body weight lost) by the green tea and placebo groups was not significantly different. Hunger and satiety were also the same in the two groups, and there were no metabolic differences. The same study[23] showed that the high habitual caffeine consumers had higher weight gain in the 13 weeks than low habitual caffeine consumers. Habitual caffeine consumption did not differ between the green tea and the placebo group. This result could indicate that the green tea supplement was only effective when habitual caffeine intake was low (or that a much increased dose was needed if caffeine intake was high). The authors suggested that saturation of the ability of green tea to further stimulate noradrenaline-related mechanisms of weight loss may be important, as caffeine and green tea both produce some of their effects through this mechanism. This seems to contradict the previous study[21] that claimed it was the catechins exerting the effect on fat metabolism and thermogenesis, not the caffeine. However, caffeine may be exerting its effect via a different mechanism.

No side-effects were reported in any of the studies. As green tea is consumed by a large number of people worldwide with few reported adverse effects, it would appear to be relatively safe. Green tea could be incorporated into an everyday Western lifestyle without necessitating the trouble of buying and taking tablets and capsules. However, some people may be unable to palate the astringent taste of green tea, in which case supplements may be preferred.

Conjugated linoleic acid

CLA is a collective term used to describe a mixture of positional and geometric dienoic linoleic acid isomers with conjugated double bonds. In dietary supplements, various combinations of the different isomers are found. CLA isomers can be obtained from normal dietary components such as dairy and meat products.

A review of 13 randomised, placebo-controlled trials in humans concluded that there was little evidence to support the proposition that CLA reduced body weight or promoted repartitioning of body fat in humans.[24] It only reviewed trials that had lasted for longer than four weeks, and concluded that the CLA isomer *trans*-10, *cis*-12 may produce liver hypertrophy and insulin resistance. The authors recommended that

CLA supplementation should be cautioned before studies with further data to clarify this situation were published.

Studies in rodents have shown that adminstration of CLA can significantly reduce body fat and lower body weight.[24–27] However, in human studies, results have been mixed. One review article found that of all the 13 studies reviewed, none showed any evidence for significant reduction in body weight and only two showed significant fat-lowering effects.[25] It has been noted that the body fat-lowering effect of CLA is due to the *trans*-10, *cis*-12 isomer[25,26] (but that over 90% of human CLA intake from food is from the *cis*-9, *trans*-11 isomer[25]).

A further review concluded that although CLA reduced weight gain and fat deposition in rodents, the effects in humans are less significant and often inconsistent.[26] The different mechanisms thought to be responsible for the activity of CLA are increasing energy expenditure, reduced fat cell size, increasing apoptosis of fat cells, and the inhibition of lipogenesis in the liver or increasing fat oxidation. Side-effects of CLA that have been found are the negative effect on insulin sensitivity and glycaemic control, and the development of fatty liver and spleen. However, these side-effects have so far only been shown in rodents.[27] This indicates that further reliable data are required before a clear judgement can be made on the use of CLA for weight management in humans. The safety of CLA was investigated in a trial on rats in which the equivalent of 30 times the human dose was used, and no adverse effects were observed.[27] Several human trials have been reported in which no adverse effects occurred when high-quality CLA was taken at doses of 3–6 g per day.

One year-long study into the effects of CLA on body fat mass concluded that long-term supplementation of CLA in healthy overweight adults significantly reduced body fat mass.[28] This randomised, double-blind, placebo-controlled study, with no diet or lifestyle restrictions placed on the volunteers, showed a slight reduction in body mass index and body weight in the CLA group, whereas there was no change in the placebo group. Adverse effects were mainly mild or moderate gastrointestinal symptoms. A high compliance and low dropout rate of volunteers also showed CLA was well tolerated. A later trial by the same team assessed the effect of CLA supplementation at 3.4 g/day over 12 months, and found a 6–8% reduction in body fat mass.[29]

A further review found that there were insufficient data to support the use of CLA for weight loss in humans, and that overall quality, safety and efficacy of CLA is uncertain.[16] It recommended that doctors should

caution patients about the use of CLA, and closely monitor those who took the supplement, as efficacy and safety have not been proven.

A further recent study concluded that the metabolic effects of CLA are complex and still not well understood.[30] This is partly due to the lack of knowledge regarding the mechanisms of CLA at a molecular level, and the lack of controlled studies on the different isomers of CLA. Another study found that there was no effect on body weight and body mass index in volunteers taking CLA for a 12-week period, but that CLA in a dose of 3.4 g per day was safe.[31] The most recent trial involving 122 obese subjects and the same daily dose over a period of one year concluded that CLA did not prevent weight or fat mass regain.[32] Further studies are required in order to make a clear judgement on the efficacy of CLA as a weight loss aid.

Conclusions

Of all the nutraceuticals reviewed, DHEA seems the most likely candidate for producing actual weight loss, as opposed to alteration of body composition. It has shown weight loss effects in both animal and human studies. In some countries, however, supply is restricted as is the case in the UK, and consequently it is not legally available for self-medication. L-Carnitine has demonstrated potential as an ergogenic aid, but there is little firm evidence to support its use for weight loss. Green tea has also shown little evidence for ability to cause weight loss, although studies have shown it can increase energy expenditure, so further long-term trials are needed to assess whether it can have effects on body weight over an extended period of time. Green tea also seems to have a better safety profile than the other nutraceuticals reviewed. CLA has been shown to have variable ability to reduce body fat in humans. Although it has shown weight loss effects in rodents, it has not yet been demonstrated to cause weight loss in humans.

So far, the studies that have been published do not go far enough in establishing the long-term safety and efficacy of these nutraceuticals. It is critically important in supplements that are likely to be taken long term that safety is established. It is also important that the efficacy of these nutraceuticals is established in large human studies with actual body weight loss as a parameter, as opposed to energy expenditure or body fat loss with no overall weight loss.

Despite the promise and lure of nutraceutical supplements and crash diets, consumers can never expect dramatic weight loss and long-term maintenance of a lower body weight unless they reduce their calorie

intake and take some form of exercise. For those individuals with a body mass index indicative of clinical obesity (30 kg/m^2 and above), medical intervention for weight loss must be considered to reduce the risk of weight-related health problems such as type 2 diabetes and cardiovascular disease.

Even if nutraceutical supplementation is only a psychological prop or placebo to aid weight loss, alongside diet or lifestyle changes, it may be helpful because if there is an overall weight loss then that will be beneficial to the patient's health. One argument frequently claimed for the use of supplements is that when patients have tried and failed on other weight-loss programmes and various diets, their weight may have become a serious health threat, so that any possible aid to weight loss becomes worth trying. The risks of any dieting aids must obviously be balanced against the benefits of weight loss and the reduction of the health risks of remaining overweight.

With the huge range of products available, pharmacists and nutritionists are at the forefront when it comes to explaining and justifying the relative merits of the various weight loss supplements available, alongside offering basic diet and lifestyle advice to customers, and knowing when to direct them to their GP if medical intervention is required. Such professional advice is necessary to weigh up and evaluate the clinical evidence of different products, as opposed to the possibility of inaccurate and often unreliable information supplied by the media and on the Internet. However, a lack of quality data obviously impacts on the ability of the pharmacist to offer good quality advice. Further trials are needed for these nutraceuticals to establish a greater degree of knowledge on their potential contribution to weight loss.

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22

Safety, adverse effects and interactions of nutraceuticals

Although many of the nutraceuticals discussed in this book are natural components of body tissues and dietary constituents, evidence is starting to appear concerning adverse effects and interactions. This chapter will discuss examples of published safety data on nutraceuticals, general adverse effects and drug interactions, examining in particular, carnitine, acetyl-L-carnitine, soy isoflavones, tea catechins and wine polyphenols, melatonin and glucosamine, and studies of specific adverse effects and toxicity of these products. Compared with pharmaceuticals there is still little evidence available, although information is slowly increasing, due partly to increasing usage, but also due to interest from clinicians and nutraceutical manufacturers.

Safety data

Safety data derived from animal studies after single-dose treatment with a number of nutraceuticals has been collated.[1] LD_{50} values and safe doses are available for glucosamine,[2] chondroitin,[3] carnitine,[4] melatonin,[5] Pycnogenol,[6] grape seed proanthocyanidin extract (GSPE),[7] methylsulfonylmethane (MSM),[8] lutein,[9] policosanol,[10] lycopene[11] and daidzein.[12] These examples of nutraceuticals would appear to be very safe at therapeutic levels, but long-term usage may show further adverse effects than these data shown for single-dose treatment.

General adverse effects

Since 1999, the Natural Standard Research Collaboration has graded complementary medicines, including nutraceuticals, according to their efficacy. Importantly, they also collate data on adverse effects and interactions with medicines, which until recently were only sporadically reported. A number of their data-retrieval protocols have uncovered possibly serious associations, a few of which are documented in this chapter.[13] US Poison Control Centers have also reported problems with

Table 22.1 Incidence of adverse effects of a number of nutraceuticals

Symptom	*Nutraceutical*	*Incidence cases (single ingredients)*
Drowsiness/lethargy	Melatonin	26 (22)
Headache	Creatine	35 (16)
Peripheral numbness or weakness, possible neuropathy or ischaemia	Glucosamine/chondroitin	1
Coma	Melatonin	1 (1)
Ataxia	Melatonin	1 (1)
Tachycardia	Melatonin	2 (2)
Hypertension	Melatonin	1 (1)
Conduction disturbances and dysrhythmias	DHEA	1
Anaemia	Glucosamine/chondroitin	1
Anaemia with bleeding	Melatonin	1
Anaemia with hepatotoxicity	Melatonin	1
Electrolyte abnormalities	Creatine	1
Dyspnoea/shortness of breath	Melatonin	1 (1)
Urinary retention	Creatine	1 (1)

Data collated from Palmer M E, Haller C, McKinney P E *et al.* Adverse events associated with dietary supplements: an observational study. *Lancet* 2003; 361: 101–106, with permission of Elsevier.

the increasing use of nutraceuticals. The most commonly cited adverse effects were drowsiness, lethargy and headaches. Symptoms from moderate to severe were seen in a number of entities and the authors warned that it was difficult to identify the cause in multicomponent formulations or if the product was incompletely labelled. Table 22.1 summarises the incidence of life-threatening or potentially serious adverse effects of nutraceuticals found in the survey.[14] Melatonin accounted for 4% of the total adverse effects reported (also included were herbal remedies). These results were perhaps unexpected, but may be a reflection of the popularity of supplementing with melatonin and creatine in the population surveyed.

Nutraceuticals are frequently involved in basic metabolic pathways in the body, and the presence and levels of a particular nutrient may impair or enhance the action of another. This interaction has been reported for nutrients such as dietary fatty acids and vitamin A,[15] other examples being depression of glucose levels by coenzyme Q10 (Co Q10) and levels of thyroid hormone depressed by carnitine or soy products.[16] Nine oral prescription medicines have been shown to have reduced

absorption after administration with flaxseed products.[17] However, most adverse effects are mild and experienced by a small proportion of consumers.

Some patients have experienced mild gastrointestinal effects after taking Pycnogenol,[6] *S*-adenosyl methionine (SAMe),[18] carnitine,[4] chondroitin[19] or glucosamine.[20] In addition, it has been claimed that there is a possible risk of significant psychiatric and cardiovascular adverse effects with SAMe; this is unsurprising with such an important endogenous metabolite.[18] The incidence of hypomania caused by SAMe in a number of studies has been reviewed.[21] α-Lipoic acid has been found to cause allergic skin reactions and possible hypoglycaemia in diabetic patients as a consequence of improved glucose utilisation.[21]

Daily intakes of carotenoids greater than 30 mg per day have been found to cause hypercarotenaemia (yellowing skin).[19] Slightly more serious effects have been reported with creatine, and include weight gain, typically 1–2 kg, muscle cramps, and isolated cases of renal dysfunction, and also the possibility of cytotoxicity.[23] Chronic creatine supplementation has been reported to increase the bodily production of potentially dangerous formaldehyde, which is known to cross-link proteins and DNAs.[24] There is also now mounting evidence that both creatine and creatinine are precursors of mutagenic amino-imidazoazaarenes. This is of significance in the light of the increasing prevalence of diet supplementation with several hundred times the levels of creatine naturally present in food.[25]

Dehydroepiandrosterone (DHEA) has been postulated to have a number of potential side-effects including hair loss and menstrual irregularities in women, and increased risk of prostate cancer in men.[19] As DHEA is a hormone, masculinisation may occur in women, and gynaecomastia and breast tenderness in men may become evident.[13] DHEA may also be responsible for causing an increase in blood sugar levels.[13] An increased risk of prostate cancer is reported in individuals being treated with α-linolenic acid to reduce the risk of heart disease,[26] and increased cell damage during intense exercise has been reported after use of Co Q10.[27]

Potential adverse effects of conjugated linoleic acid (CLA) have been reported, based mainly on evidence obtained from animals. Rats given 1% CLA in their diets showed decreased mineral apposition rate and bone formation in the tibia. The authors also questioned the wisdom of using CLA isomers that do not exist in foods in commercial preparations.[28] There is increasing evidence from both animal and human work that the CLA isomer *trans*-10, *cis*-12 may produce liver hypertrophy and

insulin resistance, using a mechanism resembling lipodystrophy that redistributes fat.[29] Both black and green teas contain caffeine, from which multiple adverse effects have been reported, mainly due to its activity as a CNS stimulant.[13]

Drug interactions

A number of interactions have been reported both between nutraceuticals and with prescribed medicines.

Work in rats has shown policosanol to increase the anti-ulcer effects of cimetidine.[30] Interactions between the two antidepressants SAMe and clomipramine have been reported,[31] and it is possible that there are interactions between SAMe and tyramine and other centrally acting pharmaceuticals. Prostaglandin excretion has been shown to be lowered after supplementation with *n*-3 fatty acids and α-linolenic acid, in combination with indometacin.[32] The anticoagulant activity of warfarin is decreased after Co Q10 administration,[33] but raised when taken in conjunction with policosanol.[16] Increased anticoagulant effects have been reported with nicoumalone taken in combination with carnitine, and gastrointestinal bleeding was also noted.[34]

Many of the effects of CLA in the hepatic activity of lipogenic enzymes and gene expression have been reported to be reversed by fish oil containing docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).[35] γ-linolenic acid (GLA) is known to inhibit *in vitro* the activity of a number of CYP enzymes, suggesting a clinical interaction with phenothiazines, and theoretical considerations suggest a possible interaction with tamoxifen.[36] There have been multiple reports of seizures occurring in patients taking evening primrose oil in combination with phenothiazine neuroleptics such as chlorpromazine, trifluoperazine and thioridazine. *n*-3 Fatty acids may reduce blood pressure and enhance the effects of medications used for this purpose, and flaxseed, but not the oil, may reduce the absorption of oral medication. To prevent this latter problem, medication should be taken 2 hours after flaxseed consumption. The use of creatine with diuretics such as furosemide should be avoided due to the risks of dehydration, and kidney damage may be greater when creatine is used with medicines that may damage kidneys, such as anti-inflammatories (e.g. ibuprofen) or cimetidine. Finally, the caffeine content of teas has been documented as causing severe cardiovascular events when used in conjunction with ephedrine, and it is also thought to be synergistic in combination with other stimulants.[13]

A number of reports have highlighted the possibility of prescription medicines depressing levels of nutraceuticals. Acetohexamide,

propranolol, phenothiazine and tricyclic antidepressants have lowered levels of Co Q10, and valproic acid has been shown to lower levels of carnitine and acetyl-L-carnitine. It has been recommended that increased Co Q10 supplementation is required when taking statins.[1] This advice is particularly important as statins are available without prescriptions in the UK, and consequently require pharmaceutical intervention for safe use. Although Co Q10 depletion may be tolerated by young patients in the short term, higher doses over longer periods of time and to elderly patients with chronic conditions may be dangerous.[37]

Carnitine and acetyl-L-carnitine

Carnitine and acetylcarnitine are endogenous constituents in human metabolism, but only the L-carnitine and acetyl-L-carnitine occur naturally; the synthetic D-isomers show more serious adverse effects.

Drug interactions

Sodium valproate, pivampicillin and isotretinoin have been reported to induce carnitine deficiency.[38] Sodium valproate interferes with carnitine uptake by forming valproyl-CoA and valproyl carnitine, which results in direct competitive inhibition of carnitine uptake at the transport site, and reduction in efficiency of carnitine transporters.[1] Valproate-induced hepatotoxicity, overdose and other acute metabolic crises linked with carnitine deficiency require intravenous supplementation, while non-emergency situations (e.g. infants and young children taking valproate) may need oral supplementation.[39]

Pivampicillin has been found to lower carnitine levels, suggesting the need for carnitine supplementation, and zidovudine has been reported to be less effective when administered with carnitine.[38]

A positive effect has been reported in cystic acne patients on isotretinoin therapy concurrently taking L-carnitine. Isotretinoin elicits some of the adverse effects associated with carnitine deficiency, but patients taking L-carnitine along with isotretinoin found that the adverse effects disappeared without the need to discontinue or reduce the isotretinoin.[40]

Adverse effects and toxicity

Both L-carnitine and acetyl-L-carnitine have been shown to have very low toxicity with rare and generally minor side-effects.[1]

The adverse effects have recently been reviewed. They include sporadic reports with the use of carnitine, such as pungent skin odour and a fishy body or urine odour following administration. Nausea and vomiting, as well as diarrhoea and muscle cramping have been reported with both carnitine and acetyl-L-carnitine supplementation. Aggression and agitation have been reported in some patients following administration of acetyl-L-carnitine.[1]

D-Carnitine

Most dietary supplements contain L-carnitine or a DL-carnitine mixture, which is a result of chemical synthesis. D-Carnitine is a competitive inhibitor of L-carnitine uptake, and this delays mitochondrial fatty acid oxidation and energy formation. D-Carnitine administration results in a depletion in L-carnitine in cardiac and skeletal muscle, which can cause cardiac arrhythmias and muscle weakness. Toxicity has been seen following administration of DL-carnitine, and D-carnitine has been classed as not safe for human consumption in the USA.[41]

Soy isoflavones

A few isolated adverse effects have been reported with soy isoflavones. An epidemiological study revealed a relationship between soy intake and an increased risk of bladder cancer.[42] Work carried out in animals has demonstrated the possibility of reproductive problems, but no human data have been published. Healthy postmenopausal women were administered 150 mg soy isoflavones daily for 5 years, and they exhibited an increased occurrence of endometrial hyperplasia.[43] One report has found that low-dose genistein stimulates proliferation of breast cancer cells *in vitro*, and high tofu consumption in men has been claimed to be responsible for lower brain weights and reduced scores on cognitive tests.[44] Asthma has been reported in young adults after drinking soy beverages.[45]

Toxicity

Studies in animals have revealed potentially mutagenic, carcinogenic and teratogenic properties of phytoestrogens,[46] and an influence on reproductive physiology has been associated with production of equol from daidzein. Equol is thought to be responsible for permanent histological damage to the reproductive organs of the ewe.[47]

Possible toxic effects of genistein related to its ability to inhibit tyrosine kinase and topoisomerase have been reported in animal studies.[1] The relevance of these findings has yet to be reported in humans. Genistein and daidzein have been investigated to examine their ability to induce chromosomal aberrations in cultured human peripheral blood lymphocytes, and chromatid aberrations have been observed, but *in vivo* data have not been reported.[1]

Adverse effects

A study into the effects of individual soy isoflavones in women found cases of loss of appetite, pedal oedema, nausea and breast tenderness, possibly caused by the isoflavones. Reductions of blood pressure and neutrophil count have also been reported.[48] Genistein administration causes hypophosphataemia, and may affect phosphorous deposition in the bone, leading to inhibition of bone formation over an extended period of time.[49]

Caution should be taken with excessive consumption of the isoflavones. At present although there is little evidence on the effects of chronic or high dosage on toxicity in humans, high mid-life tofu consumption has been linked to cognitive impairment and brain atrophy in late life.[50] Soy allergy has also been documented from skin tests, and is reported to occur in up to 6% of all children.[13]

Catechins

Catechins, which are a class of proanthocyanidins, are present in many plant food products, particularly wine and tea, and are generally thought to be safe.[1]

Toxicity and adverse effects

High levels of antioxidants such as catechins may cause pro-oxidation in some individuals, potentially worsening cardiovascular damage and atherosclerosis.[38]

A range of adverse effects have been reported with teas, and some with specified tea constituents. The first rather unexpected effect is the erosive effect of black tea on dental enamel, even though the effect is only 20% of that recorded for a number of herbal teas.[51] One case report detailed the inhibition of efficacy of oral iron treatment in iron-deficiency anaemia with excessive tea consumption, and it has been

recommended that oral iron medications should not be taken with tea.[52] However, work carried out on the inhibitory action of (—)-epigallocatechin gallate (EGCG) at doses up to 300 mg on non-haem iron absorption was found to be much lower than that for black tea itself.[53] The possible pro-oxidant effects of tea catechins have been considered, and it is known that they can be both pro- and antioxidant, being capable of causing damage to biological molecules and tissues.[54] Allergies have also been reported with teas, for example the widely quoted induction of asthma in workers in a green tea factory, probably caused by airborne inhalation,[55] which is probably irrelevant to tea drinkers. Another symptom is activation of hypoxia-inducible factor 1, which can be a serious effect in cases of consumption of high doses of tea catechins.[56]

A recent review discussed adverse effects of catechin derivatives, and reported them to inhibit most digestive enzymes, including pectinase, amylase, lipase and proteolytic enzymes. They are said to interfere with the digestion and absorption of carbohydrates, and also to interfere with iron metabolism. Despite being investigated for anti-carcinogenic effects, catechins have also been suspected to cause cancers, although it is thought that this carcinogenic activity may be due to the irritation and cellular damage that they cause rather than direct mutation of DNA. *In vitro*, epicatechin-(4β-8)-catechin and catechin have been shown to possess a strong inhibitory effect on sperm motility, showing a dose–response relationship. However, it is not known whether these effects are exerted *in vivo*.[1]

Melatonin

During the chemical synthesis of melatonin L-kynurenine is produced, which has been reported to have a convulsant effect. Another side-product, quinolinic acid, has been reported to be neurotoxic.[57]

Adverse effects

Side-effects of melatonin that have been demonstrated include inhibition of reproductive function, delayed timing of puberty and influence (when taken during pregnancy and lactation) on the circadian status of the fetus and neonate and on future development.[58]

Melatonin administration has been reported to cause residual drowsiness the following morning, sleep disturbance and excitement after wakening and before going to sleep.[59] It has also been reported

that asynchronous supplementation disrupts sleep and alters the circadian rhythm.[60]

A large number of wide-ranging adverse effects have been noted, and it is obviously safer to take the minimum effective dose on the minimum of occasions.[1] One report of the formation of secondary oxidation products, such as the endoperoxides, has been published, which may explain the pro-oxidant property of melatonin.[61]

Few studies have been carried out to determine the effect of melatonin on the human reproductive system, although in one interesting experiment in young women a large dose of 300 mg daily for four months was found to suppress the midcycle surge in luteinising hormone and to partially inhibit ovulation. This effect was increased by the addition of a progestin mini-pill. Side-effects with this contraceptive use of melatonin included abnormal bleeding and headaches, but interestingly, no effect on sleep was reported.[62,63] Most studies on reproduction and melatonin have been carried out in animals, as many animals have a seasonal reproduction cycle, which may be affected by melatonin levels. The role of melatonin in non-seasonal breeders, such as humans, has not been defined but should be considered when starting melatonin therapy.[64]

Toxic effects and drug interactions

Melatonin has been reported to interact with a number of prescription drugs, for example, serum melatonin levels have been shown to increase after taking fluvoxamine due to fluvoxamine reducing the metabolism of melatonin by inhibiting P450CYP enzymes. Certain sedative medications may have a similar effect, which could lead to exaggerated enhancement of their sedative effects.[65] Melatonin interacts with nifedipine, increasing the blood pressure and heart rate of patients taking the two products concurrently.[66] It should not be given to children or pregnant or lactating women, as it crosses the placenta and has been responsible for rhythmic variations in milk in both humans and goats. Furthermore, it has been shown that melatonin interferes with glucose metabolism.[67]

Glucosamine

Glucosamine is generally safe, but gastrointestinal side-effects occur in up to 12% of consumers. These effects included upset stomach, nausea, heartburn and diarrhoea.[20]

Adverse effects

Glucosamine has been reported to produce an immediate-hypersensitivity reaction (urticaria) in one case study,[68] and asthma exacerbation[69] and renal toxicity[70] have been reported when used in combination with chondroitin. Animal studies have shown that high levels of glucosamine administration can raise plasma glucose levels, and this may also happen in humans.[71] This is of particular significance in elderly populations where there is an high risk of both type 2 diabetes and rheumatoid arthritis occurring, the latter often being treated with glucosamine. It has been claimed that glucosamine affects insulin secretion and/or action in humans due to its involvement in the hexosamine pathway.[72] However, in a recent study it was reported that oral glucosamine did not cause significant alterations in glucose metabolism in patients with type 2 diabetes.[71]

One report has suggested that a number of glycosaminoglycans, including chondroitin (but glucosamine has not been investigated) provoke autoimmune dysfunction, thereby promoting inflammation. These data were obtained both in a murine model and in patients with rheumatoid arthritis.[73] A recent publication by the Committee on Safety of Medicines (CSM) and the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK has highlighted an interaction with warfarin. Seven incidences of increased prothrombin times in patients with previously stable levels have been reported.[74]

Conclusions

Carnitine, soy isoflavones, teas and proanthocyanidins are safely consumed routinely by many populations in their habitual diets, however, as they are increasingly being used as nutraceuticals, further investigations must be made concerning their possible toxicity, as supra-normal levels may be consumed. Melatonin and glucosamine are normal components of human metabolism, but in unusual dosages and with chronic administration they may show side-effects.

Nutraceuticals show fewer adverse effects and interactions with medicines than prescription medicines and herbal remedies; however, the absence of documented effects does not indicate that these products are necessarily safe. In the interests of patient safety all use of nutraceuticals should be made available to healthcare prescribers to ensure that precautions are explained and acted upon.

Although many nutraceuticals are present as components of food or as molecules in human metabolism, a number of adverse effects and

toxicities have been reported. Increasing use of these compounds by consumers at higher doses and chronic administration may reveal further adverse effects in the future.[1]

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