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NATURAL AND SYNTHETIC SUBSTANCES RELATED TO HUMAN HEALTH

(IUPAC Technical Report)

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Natural and synthetic substances related to human health

(IUPAC Technical Report)

Abstract: There is a widespread belief on the part of the general public that natural substances are inherently superior to synthetic substances with regard to efficacy and safety in matters related to human health. This question is examined by reviewing the therapeutic use of drugs and herbal medicine preparations, the role of vitamins and nutrients, and the effects of toxic substances. A comparison of the characteristics of natural and synthetic substances within these categories shows a similar range of favorable and unfavorable effects. It is apparent that molecular structure and dose determine the effect of substances on human health, not whether they are of natural or synthetic origin.

INTRODUCTION (J. G. Topliss)

Chemical substances can be characterized in many ways, one of which is whether they occur in nature or not. Human health is impacted by a wide variety of chemical substances, including those essential to human life, such as vitamins and nutrients, medicines, and toxic materials. Understandably, there is a vital interest in this subject on the part of the general public. A popular view holds that natural substances are innately superior to man-made or synthetic substances with respect to their effects, good or bad, on human health. This can extend to so-called nature-identical materials that are natural substances produced synthetically in an identical molecular form. The purpose of this article is to explore the subject by reviewing, in an illustrative manner, drug substances, herbal medicinal preparations, vitamins and nutrients, and toxic substances, with a view to providing an informed, rational perspective.

DRUG SUBSTANCES (A. M. Clark, C. D. Hufford, and J. M. Rimoldi)

Introduction

Natural products continue to play an important role in the discovery and development of new pharmaceuticals, as clinically useful drugs, as starting materials to produce synthetic drugs, or as lead compounds from which a totally synthetic drug is designed [1]. At the same time, synthetic compounds, unrelated to natural products, have played an increasingly progressive role in new drug discovery. Continuous improvements in synthetic methodology have provided practical access to a vast array of synthetic substances, most recently in the form of combinatorial synthesis.

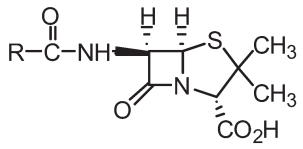
Natural compounds and synthetic compounds are, in many respects, complementary as avenues for new drug substances since natural products often possess complex structural features not easily accessible by total synthesis. In this brief overview, some selected examples will be provided from the categories of natural, semisynthetic, and synthetic drugs in relation to the central theme of this article. Semisynthetic drugs produced by modifying natural products are man-made substances, although they may be regarded as intermediate in character between natural and synthetic substances.

Natural product-related drugs

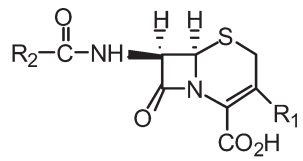
Antibiotics and other anti-infectives

Antibiotics are, by definition, natural products or derivatives of natural products. Since the discovery of penicillin, a large number of antibiotics have been isolated from scores of microorganisms [2], and several new antibiotics make it to the clinic each year. The antibiotics are important, life-saving drugs. Major classes include β-lactams, tetracyclines, macrolides, and aminoglycosides. Additionally, explorations into the mechanisms by which both the clinically used antibiotics and those that are not used clinically exert their action have led to an understanding of the biology of the target pathogens that would not likely have been possible without these important biochemical probes. Further advances will surely be forthcoming with the application of more advanced molecular biology techniques.

Among the most important antibiotics, both from a historical and a clinical utility perspective, are the β-lactams, which are predominated by the penicillins and cephalosporins. The naturally occurring penicillin first isolated from cultures of *Penicillium* in the middle of the last century were extraordinary discoveries, yet suffered certain shortcomings as therapeutic agents. While the β-lactam nucleus is required for the desired antimicrobial action, the early natural penicillins had a very narrow spectrum of activity, poor pharmacokinetics and chemical stability, and were easily destroyed by the action of penicillinase, which conferred resistance to bacterial strains capable of producing this enzyme. These shortcomings were overcome when it was discovered that 6-aminopenicillanic acid, the biosynthetic precursor to the natural penicillins, could be synthetically modified to introduce varying side chains (R) that determined the properties of the modified product. Thus began an era of developing semisynthetic and synthetic analogs of β-lactams with much improved properties, including better stability and pharmacokinetics (especially oral bioavailability), extended antimicrobial spectrum, and resistance to the action of penicillinase. Presently, there are more than a dozen penicillin antibiotics in clinical use, but only two are produced without synthetic modification: penicillin G and penicillin V.



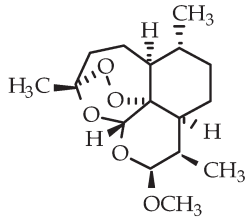
Penicillins



Cephalosporins

Similarly, the first cephalosporin (cephalosporin C) lacked potency, spectrum, and other desirable pharmaceutical properties. With the discovery of synthetic methodology to replace the side-chain of the naturally occurring cephalosporins with side-chains designed to confer more desirable properties, the door was opened to improve semisynthetic analogs. Currently, there are more than 25 cephalosporins in clinical use today, all of which are produced through semisynthesis or total synthesis.

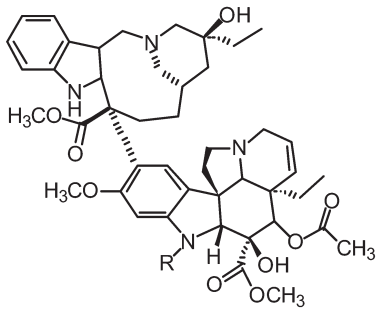
The discovery of new important anti-infectives is not limited to searching the microbial kingdom, but includes plant and animal sources as well. Artemisinin, a sesquiterpene with an unusual endoperoxide moiety, was isolated from the Chinese medicinal plant commonly known as Qinghaosu (*Artemisia annua*), an herbal remedy that had been used in China for centuries for the treatment of malaria. Isolated in 1972 as the active constituent, artemisinin was discovered to be particularly effective for the deadly cerebral malaria. Subsequent efforts to develop artemisinin derivatives with more desirable pharmaceutical properties included many synthetic and semisynthetic studies, microbial transformations, biological evaluations, mechanism of action studies, and pharmacological studies of artemisinin and a number of related analogs [3–5]. From these efforts, the semisynthetic derivative artemether was developed and is now approved for the treatment of malaria in much of the world. Thus, a natural substance was transformed into a related semisynthetic substance with superior drug properties.



Artemether

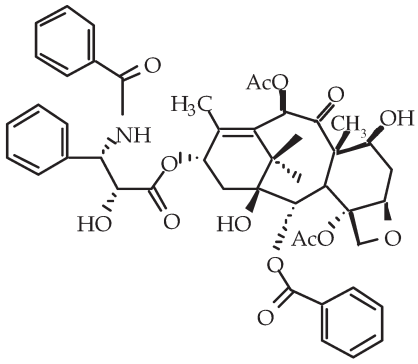
Anticancer drugs

Natural products have provided the most important successes in the chemotherapy of cancer. Most of the major anticancer drugs are unmodified natural products obtained from plants or microorganisms [6], and include such important anticancer drugs as bleomycin, doxorubicin, daunorubicin, vincristine, vinblastine, mitomycin, streptozocin, and paclitaxel (Taxol™). Ironotecan (a camptothecin derivative), and etoposide and tenoposide (podophyllotoxin derivatives) are examples of semisynthetic derivatives of natural products that are important anticancer drugs. Vincristine and vinblastine are complex, dimeric indole-indolines obtained from the rosey periwinkle (*Catharansus rosea*), and are among the most important therapies for the treatment of childhood leukemia, Hodgkin's disease, and metastatic testicular tumors. These unmodified natural products continue to be produced today by mass cultivation and processing of the plant material [7]. Vinorelbine is a semisynthetic analog and has been reported to have decreased hematological toxicity.

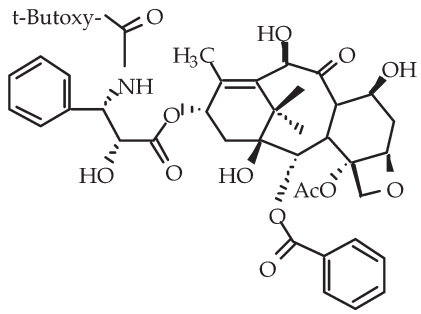


Vincristine, R = CHO
Vinblastine, R = CH_3

As part of a program undertaken over 40 years ago by the National Cancer Institute, which was aimed at examining higher plants as a source of anticancer agents, one of the most important discoveries of this century occurred. Wall and Wani reported that a complex diterpene, which they isolated from the bark of the Pacific yew tree and named taxol, was reported to possess significant cytotoxicity for cancer cells [8]. Although it took some 15 years for the potential of paclitaxel to be realized, it is now recognized as a breakthrough in the treatment of ovarian breast cancers and one of the most exciting new drugs in recent history. Currently, both a semisynthetic derivative with improved water solubility, docetaxel (Taxotere®), and paclitaxel (Taxol®) are approved and used clinically. Paclitaxel also serves as a vivid example of the utility of bioactive natural products as biochemical probes. Studies on the paclitaxel's mechanism of anticancer action revealed a previously unknown mechanism (stabilization of microtubules [9]). Using bioassays to detect this type of activity, two new structurally unrelated classes of natural products have now been discovered and shown to act by the same mechanism [10], and intense efforts are underway to identify drug candidates from these classes. Since paclitaxel was the



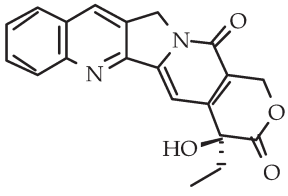
Paclitaxel



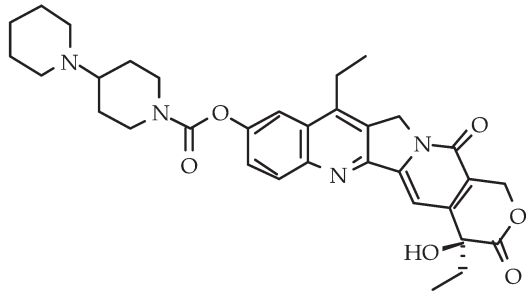
Docetaxel

only known compound to exhibit this activity, without its discovery and development this new target for anticancer drug discovery and development would likely not have been identified.

Camptothecin, an alkaloid from the Chinese tree, *Camptotheca acuminata* Descne [11], was also discovered by Wall and Wani. Although showing promising antitumor activity, clinical studies were discontinued due to unpredictable side effects. Subsequent semisynthetic modifications led to the development of Ironotecan (Topotecin™, Campto™), a derivative of camptothecin that is now clinically available [12]. The camptothecins act by inhibition of the topoisomerase I.

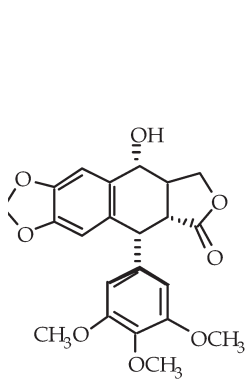


Camptothecin

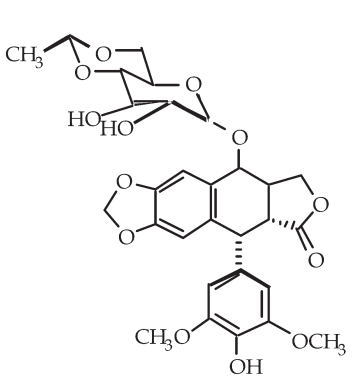


Ironotecan

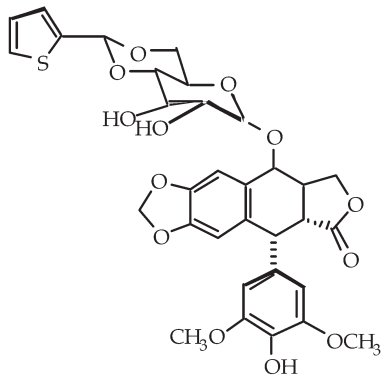
Podophyllin is a crude resin derived from *Podophyllum peltatum* and is used topically to treat condylamata acuminata (warts). Podophyllin contains, among other things, the lignan, podophyllotoxin, which is the chemical precursor to two important semisynthetic anticancer drugs, etoposide and tenoposide [13]. These drugs inhibit topoisomerase II, a mechanism quite different from that of podophyllotoxin (spindle poison), thus illustrating that structural similarity alone is not always a reliable predictor of similar biological effect.



Podophyllotoxin



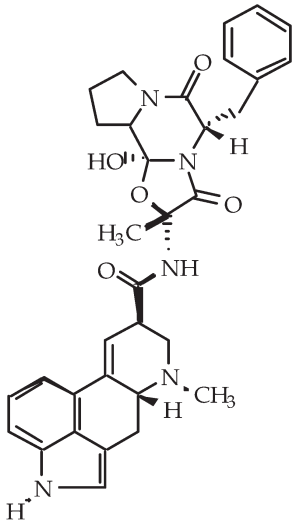
Etoposide



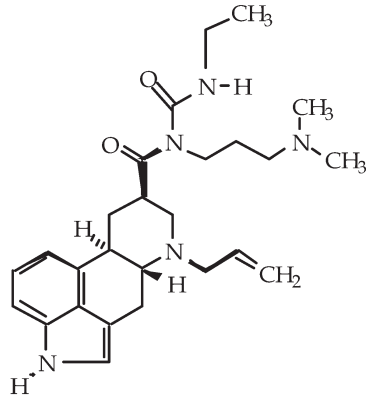
Teniposide

Cardiovascular drugs

It was known as early as 1776 that extracts of *Digitalis* were effective in controlling heart disease. However, the active constituents, complex glycosides such as digoxin, digitoxin, and the lanatosides, were not isolated and structurally characterized until almost a century later. These compounds exert a powerful and selective positive inotropic action on the cardiac muscle, and are important drugs in the treatment of congestive heart failure. Perhaps due to the complexity of their structures, which include numerous chiral centers, the unmodified natural products continue to be used clinically, and also continue to be produced by mass cultivation and extraction of foxglove [7]. In addition to the cardiac glycosides, a number of naturally occurring alkaloids are important drugs in the control of various cardiovascular conditions. For example, the alkaloid quinidine, from the bark of the *Cinchona* tree, is an important anti-arrhythmic drug. Other important natural products active as cardiovascular drugs include papaverine, a non-narcotic peripheral vasodilator, theophylline, an important bronchodilator used to control asthma in children, and the vasoconstrictive alkaloid ergotamine, which is obtained from a fungus that infects rye grass and is used clinically to treat migraine headaches. Cabergoline, a semisynthetic derivative of the ergot alkaloids, is a dopamine D_2 receptor agonist that is used as an antiprolactin [14].



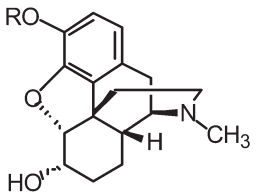
Ergotamine



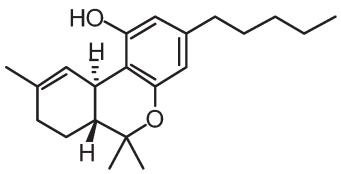
Cabergoline

Central nervous system (CNS) drugs

One of the oldest CNS drugs in use is *d*-tubocurarine, a neuromuscular blocker derived from a plant (curare) used as an arrow poison by South American Indians [7]. Also, the opium alkaloids codeine and morphine are important analgesic drugs, and continue to be manufactured by processing opium exudate and extract [7]. Delta-9-tetrahydrocannibinol (THC), the component of *Cannibas sativa* responsible for its CNS effects, is an important drug (Marinol®) used to reduce nausea associated with cancer chemotherapy. Although prepared commercially using synthetic methodology, Marinol® is identical to natural THC.

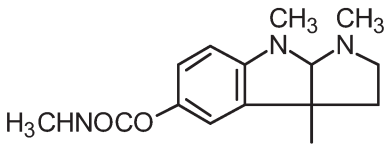


Morphine, R = H
Codeine, R = CH_3

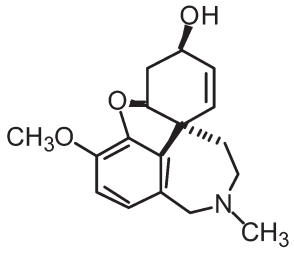


Δ^9-THC

Physostigmine, a naturally occurring alkaloid, and its carbamate ester, neostigmine, are acetylcholinesterase inhibitors used for the treatment of myasthenia gravis and as antagonists to neuromuscular blockade by nondepolarizing blocking agents. Galanthamine, an alkaloid that occurs in the bulbs of daffodils, is also an acetylcholinesterase inhibitor and is currently in clinical trials as a possible therapy for cognitive impairment in Alzheimer's disease [19].



Physostigmine

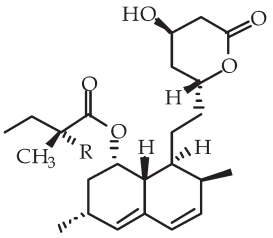


Galanthamine

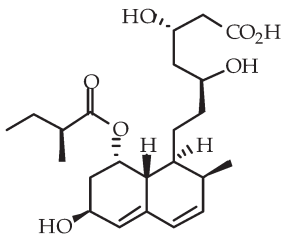
Cholesterol-lowering agents

The clinically useful cholesterol-lowering agents known as the "statins" were derived from natural products isolated from a fungus. These drugs inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), an enzyme critical in the biosynthesis of cholesterol. The first such agent, compactin, was initially reported as an antifungal agent [16]; however, once its mechanism of action was determined, a search for other naturally occurring HMG-CoA reductase inhibitors led to the discovery of lovastatin, a metabolite of the fungus *Aspergillus terreus* [17] that was first introduced to the market in 1989 followed by pravastatin in 1991. Many analogs, both semisynthetic and totally synthetic, were later prepared, and from these several have become important drugs, including simvastatin (launched 1991), pravastatin (1991), and atorvastatin (1997). The latter, a chiral totally synthetic compound, has become the drug of choice in this therapeutic category based on its superior ability to reduce cholesterol at low doses. The development of the statins is a very good example of a natural product-based discovery of an important new drug class followed by optimization of properties yielding improved drugs. It illustrates the interconnection between a natural product and its semisynthetic and

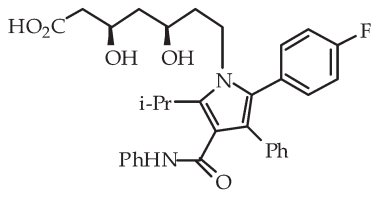
totally synthetic analogs and the determining role of molecular structure, whether constructed by nature or humans, with respect to drug properties.



Lovastatin, R = H
Simvastatin, R = CH_3



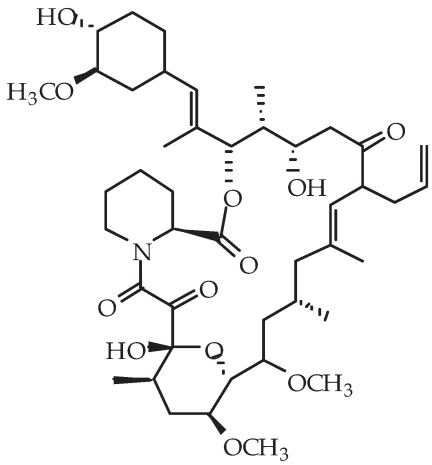
Pravastatin



Atorvastatin

Immunomodulators

The immunomodulators cyclosporin, originally isolated from the soil fungus *Trichoderma polysporum* [18] and tacrolimus (FK-506), a secondary metabolite of *Streptomyces tsukabaensis*, are used to suppress immunological rejection of the transplanted organs [14]. These unmodified natural products represent major breakthroughs for organ transplantation.



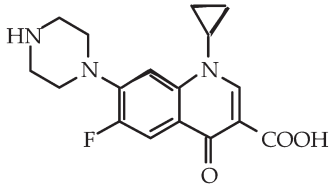
Tacrolimus

Drugs of synthetic origin

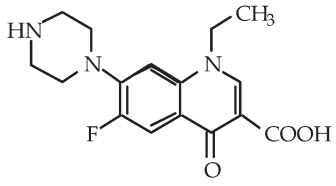
Anti-infectives

The important antimalarial drugs primaquine, chloroquine, and mefloquine were all patterned after the alkaloid quinine, the active constituent of the "fever tree" *Cinchona succiruba*, known for centuries by South American Indians to be effective in controlling malaria [7]. When the natural source of quinine was threatened during World Wars I and II, massive programs to synthesize multitudes of quinoline derivatives based on the quinine prototype ensued, and the aminoquinolines cited above were among some of the successful drugs to emerge from this extensive effort. The effort to design better antimalarial agents has also led to the discovery of other important anti-infectives, including a class of synthetic antibacterials that is among the most prescribed in clinical use today—the fluoroquinolones. The first of the quinolones to be used clinically, nalidixic acid, was synthesized as part of a large program

by the Sterling Drug Company to synthesize new antimalarials based on the quinine nucleus [19]. The 1,8-naphthyridines were observed to be antibacterial, and in 1964, nalidixic acid became available for use in the United Kingdom for urinary tract infections. However, its limited spectrum of activity and poor pharmaceutical properties led to programs to prepare thousands of other quinolone derivatives with improved features. More than 15 years later, in 1980, Koga and coworkers [20] reported that structural analogs modified at C6 and C7 demonstrated certain improved properties. In particular, it was noted that analogs carrying a fluorine at position 6 showed broader and more potent antimicrobial activity, and the class of fluoroquinolones subsequently became one of the most studied structural classes of antimicrobials. Ciprofloxacin and norfloxacin are examples of currently available fluoroquinolone antibacterials that are used extensively in both community and hospital settings.

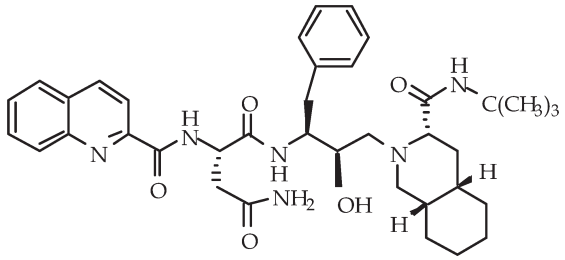


Ciprofloxacin



Norfloxacin

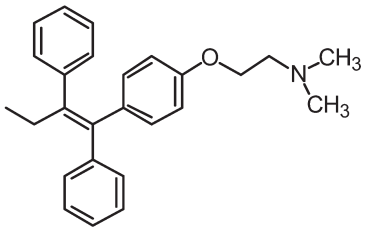
The HIV-1 protease inhibitors are another example of synthetic anti-infectives, but these agents have resulted from the rational design of inhibitors based on an understanding of the role of the aspartic protease enzyme in the life cycle of the virus. Results of early studies to design inhibitors of human renin (also an aspartic protease) for potential use in antihypertensive therapy were applied to the design of inhibitors of HIV protease [21]. Saquinavir was the first HIV protease inhibitor to be introduced for clinical use.



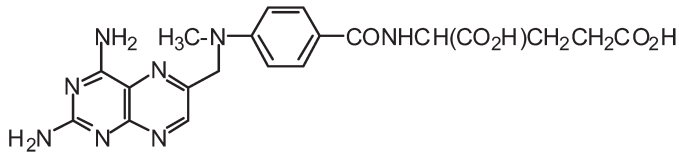
Saquinavir

Anticancer drugs

Included among the most important anticancer drugs in use today are tamoxifen and methotrexate, which are both synthetic drugs. Tamoxifen was derived from the diethylstilbesterol nucleus, which itself was patterned after estradiol. First reported for its contraceptive activity in rats [22], tamoxifen was later found to bind to human estrogen receptors, thus paving the way for its use in the treatment of breast cancer. Tamoxifen is now one of the most widely used and successful drugs in the treatment of breast cancer [23]. Methotrexate is an antifolate, patterned after physiological folate, is one of the most widely used antineoplastic drugs available, and shows efficacy in the treatment of a variety of neoplasms [24].



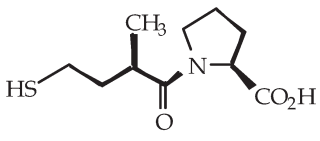
Tamoxifen



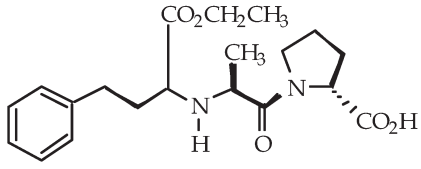
Methotrexate

Cardiovascular drugs

An examination of the pharmacological activity of tetropide, a component of the venom of the pit viper (*Bothrops jararaca*), led to the discovery of the role of angiotensin-converting enzyme (ACE) in hypertension [25–27]. Using a model system for the interaction of small peptides with the enzyme [28], captopril was designed as a specific, orally effective ACE inhibitor. Following the success of captopril for the control of hypertension [28], many additional ACE inhibitors, such as enalapril, were designed and synthesized. The ACE inhibitors now constitute one of the most important classes of cardiovascular drugs [29].

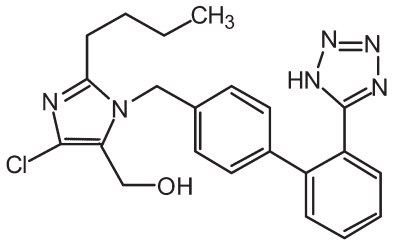


Captopril



Enalapril

The development of specific agents that interfere with the renin-angiotensin system have defined the contribution of this system to blood pressure regulation and to the pathogenesis of hypertension, congestive heart failure, and chronic renal failure. This was first realized in the 1970s with the discovery of saralasin, a peptide antagonist of angiotensin II receptors [30]. However, saralasin lacked oral activity, and at higher doses, exhibited partial angiotensin II agonist profiles. The development of losartan, the first orally active angiotensin II receptor antagonist, derived from 1-benzylimidazole-5-acetic acid pharmacophores, represented a breakthrough in angiotensin II blockade [31]. To date, six orally angiotensin II receptor antagonists are marketed in the United States, including, valsartan, irbesartan, candesartan, telmisartan, and eprosartan. All of these agents have identical mechanisms of action but differ in their pharmacokinetic profiles, which account for their differences in efficacy [32].

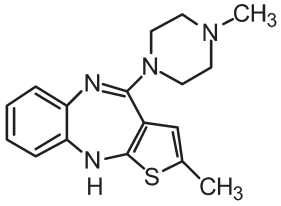


Losartan

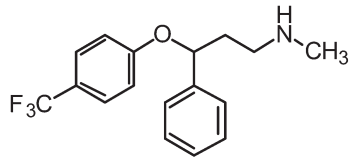
CNS drugs

Totally synthetic drugs have been of the utmost importance in the CNS arena since the accidental discovery of the powerful analgetic properties of meperidine in 1937 and continuing through the synthesis of the currently widely used selective serotonin reuptake inhibitors as antidepressants. Along the way, the treatment of mental illness has been revolutionized through the discovery of CNS drugs such as the phenothiazines (chlorpromazine) and the butyrophenones (haloperidol) for psychotic disorders, the tricyclic antidepressants (imipramine) for depression, and the benzothiadiazines (diazepam) for anxiety. Of the numerous synthetic CNS drugs that are now available in medicine, just two of the newer ones will be briefly discussed for illustrative purposes.

Fluoxetine (Prozac™) was the first of the specific 5-HT reuptake inhibitors, also known as the selective serotonin reuptake inhibitors (SSRIs), to be discovered. A number of others have subsequently been introduced. The synthesis and pharmacological activity of fluoxetine was first described by Wong and coworkers [33] in 1975. Since its discovery, more than 5000 research papers have appeared on fluoxetine [34], and in her review of the pharmacology and uses of fluoxetine, Scott [34] notes that the development of the SSRIs is one of the most significant milestones to take place with regard to the progress of psychopharmacology.



Olanzapine

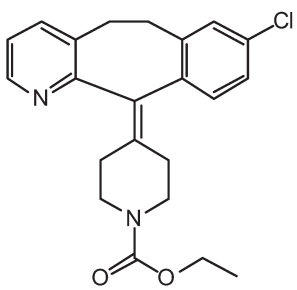


Fluoxetine

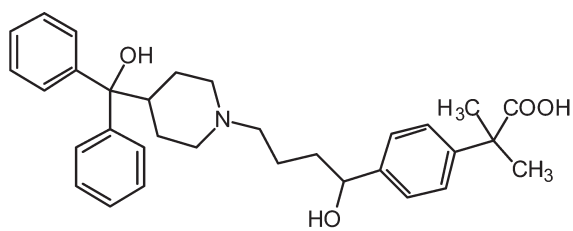
Olanzapine (Zyprexa®) is a recently introduced atypical antipsychotic agent with a high affinity for dopaminergic and serotonergic receptors, and it also has high anticholinergic activity. A key advantage over older agents is that it is less likely to produce extra pyramidal side effects and does not produce granulocytopenia.

Histamine antagonists and proton pump inhibitors

H1 histamine receptor antagonists are used worldwide for the treatment of allergic rhinitis, conjunctivitis, and urticaria. Since the first clinically useful antihistamines were introduced in the 1940s [35], over 40 first-generation H1 receptor antagonists have been marketed [36]. Adverse CNS effects and poor receptor specificity resulting in marked sedation and anticholinergic effects, have led to the development of second-generation H1 receptor antagonists largely devoid of these adverse effects. Loratidine and fexofenadine represent two of the more common second-generation agents prescribed. Other second-generation drugs of this class include acrivastine, astemizole, azelastine, cetirizine, ebastine, and mizolastine.

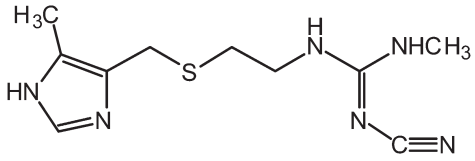


Loratidine



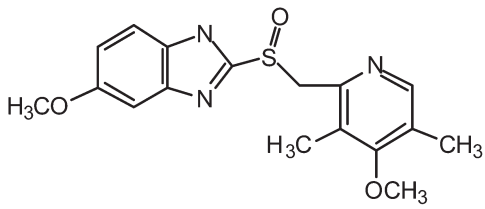
Fexofenadine

The development of cimetidine, the first clinically useful H2 histamine receptor antagonist indicated for the treatment of peptic ulcer disease approved by the U.S. Food and Drug Administration (U.S. FDA) in 1977, clearly defined the role of medicinal chemistry in rational drug design [37]. Cimetidine was constructed using histamine as the lead pharmacophore, and structural optimization was accomplished by modulation of physicochemical parameters including partition coefficients and ionization constants. Separation of agonist and antagonist properties initially led to the development of burimamide, metiamide, and finally cimetidine. Additional H2 receptor antagonists introduced later include ranitidine, famotidine, and nizatidine.



Cimetidine

Proton pump inhibitors represent a class of antisecretory compounds, the substituted benimidazoles, that are devoid of anticholinergic or histamine H2 receptor antagonist proprties, but suppress gastric acid secretion by specific inhibition of the (H^+,K^+)-ATPase enzyme system at the secretory surface of gastric parietal cells. The proton pump inhibitors have emerged as a therapeutic alternative to H2-antagonists for the treatment of gastric disorders, including gastric esophageal reflux disease (GERD) [38]. Omeprazole and related proton pump inhibitors (lansoprazole, pantoprazole, and rabeprazole) all share a benzimidazole framework, and are considered pro-drugs, since they are stable at neutral pH but rearrange in the presence of acid to form tetracyclic sulphenamides, which covalently inhibit the enzyme [39].



Omeprazole

Conclusions

Although most of the drugs in use today are synthetic drugs, many (perhaps half or more) had their beginnings as natural products. Only a few have been cited here for illustrative purposes. Safety, efficacy, pharmacokinetics, metabolic or chemical stability, and other important characteristics of a drug are functions of the chemical structure of the molecule, not its origin. The molecular structure of a compound, which defines its interactions with other molecules in the body, is the prime reason it exhibits desirable and/or undesirable biological activities. Whether the compound is of natural or synthetic origin is irrelevant. To correlate origin with an expected greater or lesser safety profile or desirable features is unfounded, and can be dangerously misleading. Many of the most toxic chemical substances known are natural products, and some of the safest, most effective, and widely used drugs are of synthetic origin. In fact, structure–activity relationship (SAR) studies and synthetic modifications of bioactive natural products are usually done in an effort to produce an improved drug substance with a better therapeutic index. Thus, many of the most successful and important drug substances are derived through a *combination* of natural product chemistry and synthetic chemistry.

Natural products will continue to serve as lead compounds for drug development and as biochemical probes for the discovery of pharmacological and biochemical processes. Many exciting developments are occurring in the general arena of drug discovery. Combinatorial chemistry will provide an ever-increasing pool of compounds for evaluation of therapeutic potential, and advances in molecular biology will provide insights into the biological processes, and hence possible targets, of diseases. Bioactive natural products can serve as probes to help unravel these molecular and pharmacological processes and to serve as molecular scaffolds for combinatorial synthesis of tens of thousands of derivatives for rapid and more efficient SAR studies to identify the most exciting new lead compounds for drug development. Clearly, both natural and unnatural products have a vital role in improving the human condition.

HERBAL MEDICINE PREPARATIONS (E. Ernst)

Introduction

Herbal medicine preparations (HMPs), as they are generally known in most countries, are classified as botanical dietary supplements (BDSs) in the United States, where they are not subject to the same safety and efficacy regulations that apply to prescription and over-the-counter drugs. The United States is presently experiencing an unprecedented boom in their use. Between 1990 and 1997, purchases by the general population increased by 380 % [40]. In 1998, the total market was worth USD 3.87 billion, and the herb with the highest annual percentage increase (2801 %) was St. John's wort [41].

Efficacy

St. John's wort will be used as an example of an HMP for which efficacy and safety have been investigated fairly rigorously. Its main indication is mild to moderate depression. Depression responds extremely well to placebo medications. Thus, it is particularly important to account for this phenomenon when testing the efficacy of St. John's wort for depression. Numerous placebo-controlled trials have been carried out, almost all in Germany where this herbal preparation now outsells Prozac® by about 2:1.

There is much debate about which are the active ingredients of St. John's wort. Even though no final conclusions can be drawn as yet, it is clear that more than one family of active principles is responsible. It seems certain that hypericin and hyperforin both contribute to the antidepressant action. The relative size of these contributions to the total pharmacological action remains uncertain.

A systematic review of all trials available by 1996 located 23 placebo-controlled trials [42]. Collectively, these studies included 1757 patients. A meta-analysis of their results showed that St. John's wort was significantly more efficacious than placebos in treating depression. The chances of benefiting from the herbal remedy were about 2.5 times higher than those for placebo.

Eight studies were found where St. John's wort was tested against conventional antidepressants [42]. A meta-analysis of these data suggested that the herbal medicine is equally as effective as imipramine, maprotiline, bromazepam, amitriptyline, or diazepam.

Even though this sounds highly encouraging, several important caveats ought to be pointed out:

- All of these studies were on mild to moderate depressions, and experts are not unanimous about whether these required medication in the first place.
- All of the studies were of relatively short duration (usually 4–6 weeks), and long-term effects remain uncertain.
- There is insufficient information as to relapse rates of patients treated with St. John's wort.
- In the comparative trials, the conventional antidepressants were usually underdosed; thus therapeutic equivalence has not been established beyond reasonable doubt.
- No trials exist that compare St. John's wort against the newer synthetic antidepressants like Prozac®.

Since the publication of this meta-analysis, six further studies have been published. These new data have been recently reviewed [43]. Essentially, the new trials confirm the previous results. Some evidence emerged that St. John's wort is as effective as the newer synthetic antidepressants and that it also works in the more severe types of depression. Yet, so far, this evidence is not fully convincing. A large U.S. study organized by the National Institutes of Health (NIH) is on its way, which is expected to provide a definitive answer.

St. John's wort was chosen here as an example. Other HMPs for which similarly compelling evidence of efficacy (i.e., systematic reviews) has been published include the following:

- ginkgo biloba for cerebral insufficiency [44] and dementias [45,46]
- saw palmetto for benign prostate hyperplasia [47]
- horse chestnut seed extract for primary varicosis [48]
- peppermint oil for irritable bowel syndrome [49]

Ginseng is a good example of a widely used HMP that is not backed up by convincing evidence of efficacy. It achieved retail sales of USD 96 million in the United States in 1998 as a BDS, placing it third in this category [50]. Considerable confusion has been caused by not distinguishing between Siberian ginseng (*Eleutherococcus senticosus*), Asian ginseng (*Panax quinquefolius*), and Japanese ginseng (*Panax japonicus*). *Panax ginseng* species have been in traditional use for alleged sedative, hypnotic, demulcent, aphrodisiac, antidepressant, and diuretic activity. Moreover, it is often recommended to improve stamina, concentration, vigilance, and well-being [51].

The pharmacological activities of the *Panax ginseng* species range from stimulation of the central nervous system to modulation of the immune defense and anabolic effects [48]. The effects of Siberian ginseng are less well researched but claimed to be similar to those of *Panax ginseng*. A systematic review of all randomized, placebo-controlled, double-blind trials [53] included 16 studies of all types of ginseng relating to enhancement of physical or mental performance and immunomodulation. Most trials were methodologically poor, with many studies using healthy volunteers rather than patient populations. The results were, in general, contradictory, and none of the above-named indications were supported by evidence from sound clinical trials. A further review of animal and human studies of ginseng as an erogogenic aid to physical performance [54] concluded that there is an absence of compelling research evidence regarding the efficacy of ginseng for this indication.

Safety

Consumers turn to HMPs because they (are made to) believe that they are inherently free of adverse events. Natural is all too often and all too quickly equated with harmless. This notion is misleading at best and dangerous at worst [55]. The argument of the "test of time" is often used: anything that has been used for hundreds of years has to be safe. There are, however, numerous reasons why this argument is a fallacy [56].

The only HMP that has been systematically reviewed in relation to adverse drug reactions (ADRs) is St. John's wort [57]. Searches of four computerized literature databases were performed for records of ADRs. Manufacturers of hypericum products, the international drug-monitoring center of the World Health Organization (WHO), and the national drug safety monitoring bodies of Germany and the United Kingdom were also contacted for information. Information on ADRs originated from case reports, clinical trials, post-marketing surveillance, and drug-monitoring studies. Collectively, these data suggest that hypericum is well tolerated, with an incidence of adverse reactions similar to that of placebo. The most common adverse effects are gastrointestinal symptoms, dizziness/confusion, and tiredness/sedation. A potential serious ADR is photosensitivity, but this appears to occur extremely rarely. This review concluded that hypericum has an encouraging safety profile. However, as most of the current data originate from short-term investigations, more long-term studies would be desirable.

An analysis was carried out to compare the nature and frequency of ADRs of St. John's wort to a range of synthetic antidepressants [58]. This confirmed the safety of this HMP and suggested that ADRs of St. John's wort have an incidence rate that is 50 % or less than that associated with conventional antidepressants. Similarly positive, albeit less thoroughly researched, evidence exists for the other above-mentioned HMPs.

A number of relatively serious adverse effects of *Panax ginseng* have been reported [59], ranging from insomnia, diarrhea, vaginal bleeding, and mastalgia to severe headache, schizophrenia, and Stevens–Johnson syndrome. The incidence of these adverse effects seems to be low. Also, a recent study suggested that an oral dose of 3 g of American ginseng attenuated the postprandial glycemic response to a 25 g oral glucose challenge [60]. The effect was notable both in nondiabetic subjects and in individuals with Type 2 diabetes. The authors therefore caution that American ginseng could cause hypoglycemia in nondiabetic subjects.

Yet, other HMPs are clearly burdened with serious ADRs. Examples from this category include: aconite, aristolochia, broom, chaparall, comfrey, germander, liquorice root, and pennyroyal. Plants belonging to the *Aristolochia* species are rich in aristolochic acids and aristolactams. Aristolochic acids I and II have been demonstrated to have mutagenic potential in several test systems [61].

A 49-year-old woman was admitted to hospital with clinical signs of hepatitis where this diagnosis was confirmed [62]. The usual causes for hepatitis were ruled out. The medical history revealed that she had recently started to use a Chinese herbal tea to treat her eczema. Examination of the herbal mixture showed that it contained *Aristolochia debilis* root and seven other medicinal plants. Like *Aristolochia fangchi, Aristolochia debilis* contains aristolochic acid and is therefore the likely cause of the toxic hepatitis.

In Belgium, nephropathy in about 100 individuals has been attributed to an herbal slimming preparation that included the Chinese herbs *Stephania tetranda* and *Magnolia officinalis.* In the preparation, the root of *Stephania tetranda* (Chinese name "Fangji") was, in all probability, substituted for or contaminated with the root of *Aristolochia fangchi* (Chinese name "Guang fangji") [63]. The nephropathy was characterized by extensive interstitial fibrosis with atrophy and loss of the tubules [64]. Several patients showed evidence of urothelial malignancy [64]. The preparation was also distributed in France, and two cases have been reported from Toulouse and one possible case from Nice [65].

Contamination is an important safety issue with HMPs. This is especially relevant for Asian HMPs, which have been shown to be contaminated with synthetic drugs and/or heavy metals with an alarming degree of regularity, e.g., ref. [66]. These reports stress the importance of proper quality control of these preparations.

Another issue is herb/drug interactions. This area is grossly under-researched, yet it is important, particularly since we know that users of HMPs tend to belong to that fraction of society that would employ them alongside prescribed drugs [40]. Judging from what we know to date, it is certain that such interactions exist, e.g., ref. [55]. This is perhaps the most urgent issue for future research. For example, important herb/drug interactions are possible if St. John's wort is administered concomitantly with other medications. It acts as a hepatic enzyme inducer via an interaction of the cytochrome P450 system [67]. In addition, it probably activates P-glycoprotein, which further increases the elimination of synthetic drugs [68]. Through these mechanisms, it can decrease the plasma level of a range of prescribed drugs (e.g., anticoagulants, oral contraceptives, and antiviral agents), which can have clinically serious consequences [69–71].

Conclusions

HMPs are popular but largely unregulated as drugs. Some of them constitute highly active medicines that therefore have the potential for doing good *and* harm. Generalizations about the balance of risk and benefit are not possible as each HMP has to be judged on its own merit. The challenge for the future is

to generate sufficiently reliable data to render reasonable risk/benefit evaluations in all cases. Perhaps the most urgent issue for future research is herb/drug interactions.

VITAMINS AND NUTRIENTS (B. J. Weimann)

Introduction

Because of the enormous increase of the world population, in particular in the developing countries, the problem of providing people with sufficient food of balanced composition presents a major challenge. Besides the major constituents, fats, carbohydrates, and proteins, other food components such as vitamins, carotenoids, essential fatty acids, dietary fibers, and others play an important role. On the other hand, serious health problems arise nowadays among populations of industrialized countries due to excessive consumption of food with a high-fat and/or -sugar content. The modern trend toward new types of food (health food, fast food, low-calorie food, etc.) in affluent societies requires special methods of processing, supplementation with essential nutrients, and storage to assure good quality and the consumer's acceptance. For example, many food products have added vitamins to increase nutritive value, protect from oxidative degradation, and serve as colorants.

Vitamins

Vitamins are essential nutritional factors that are contained in food as small organic compounds and are required for the normal growth, maintenance, and functioning of the human body. Historically, they have been divided into water-soluble (B_1, B_2, B_6, B_{12}, biotin, C, folic acid, nicotinamide, pantothenic acid) and fat-soluble (A, D, E, K_1) vitamins. The water-soluble vitamins except vitamin C are coenzymes or precursors of coenzymes that catalyze, in the presence of specific enzymes, many biochemical reactions in the metabolism of carbohydrates, proteins, lipids, and nucleic acids. Others do not function as coenzymes, but are involved in the visual process, growth, and cell differentiation (vitamin A and the derivative retinoic acid, β-carotene as provitamin A), intestinal absorption of calcium and bone mineralization (vitamin D). They also serve as antioxidants by scavenging free radicals to protect the organism from oxidative damage (vitamin E). Water-soluble vitamins are poorly stored, and high intake levels lead to excretion in urine, while fat-soluble vitamins can be stored in the body. Therefore, hypervitaminosis, mainly of vitamins A and D, can lead to toxic manifestations caused by excessive intake.

Throughout the history of mankind, deficiencies of nutritional factors—especially vitamins (hypovitaminosis)—and hence disturbance of many metabolic functions, have been a major cause of diseases (e.g., scurvy, pellagra, beriberi, pernicious anemia, blindness, etc.) and death. In fact, vitamins were originally recognized by signs of deficiency. Administration of vitamins reverses the majority of the clinical symptoms. In humans, levels of recommended dietary allowances (RDAs) [72] have been established based on the estimated needs of healthy people. These levels are thought to prevent signs of clinical deficiency, however, they may not be adequate to cover the increased vitamin requirements in humans that smoke, suffer from diseases, or have metabolic or genetic disturbances.

Vitamin C

There have been many clinical studies on the effect of vitamin C on the common cold and the reported results have shown wide variation, most likely due to the different protocols used [73]. However, a decrease in the duration and severity of cold symptoms has been consistently observed for large doses of vitamin C (1–3 g/d, USA RDA for adults is 60 mg/day). Vitamin C is the most efficient antioxidant in human blood [74]. Since the concentration of vitamin C decreases in plasma and leukocytes in episodes such as infections, vitamin C acts as an antioxidant by inactivating excessive amounts of radicals formed during the oxidative burst of phagocytes. These radicals destroy viruses and bacteria in the host, but also induce inflammatory processes that are reduced by vitamin C. The importance of vitamin

C as part of the defense system is also shown by the very low concentrations of vitamin C in the plasma of critically ill patients [75].

Vitamin E

There is experimental evidence that the oxidative modification of low-density lipoproteins (LDLs) is a key process in initiating atherosclerosis. Lipid-laden macrophages (foam cells) containing oxidized LDLs are found in early lesions called fatty streaks. These findings led to the formulation of the antioxidant hypothesis of atherosclerosis. LDL particles carry natural antioxidants (vitamin E, β-carotene, lycopene, ubiquinol), which can inactivate free radicals and hence protect LDLs from oxidative damage. Epidemiological studies have shown a correlation between high levels of vitamin E in plasma and a lower risk of coronary heart disease. In randomized, placebo-controlled trials of α-tocopherol (vitamin E) in relation to cardiovascular mortality, different results have been reported. In the Alpha-Tocopherol Beta Carotene study [76], no effect was seen. The dose of 50 mg of vitamin E per day may have been too low to give treatment effects. However, in the GISSI-Prevenzione trial [77], using higher doses of vitamin E (300 mg/d), the mortality group was similar to the placebo group. In contrast, the rate of nonfatal myocardial infarctions was significantly reduced in the CHAOS study using 400 and 800 IU of vitamin E per day [78]. Vitamin E is nontoxic [79] and in animal experiments has been shown to be neither mutagenic, teratogenic, nor carcinogenic.

B-vitamins

In the early 1960s, a new, rare disease, homocystinuria, was found to be associated with an inborn error of metabolism due to the absence or reduced activity of the enzyme cystathionine β-synthase. Elevated levels of homocysteine are found in the plasma and urine of these patients. Characteristic features of patients with homocystinuria are premature vascular disease and death. Homocysteine is formed as an intermediate in the transsulfuration pathway where methionine is converted to cysteine. B-vitamins are involved in many of these enzymatic reactions, and a low intake of these vitamins is correlated with elevated homocysteine levels, especially in the elderly [80]. From these observations, it was hypothesized that homocysteine might be involved in the pathogenesis of arteriosclerosis [81]. The analysis of many studies on homocysteine and cardiovascular diseases led to the conclusion that a moderate level of homocysteine in blood is an independent, graded risk factor for atherosclerotic disease in coronary, cerebral, and peripheral vessels [82]. Results from the recently published European Concerted Action Project [83] show a dose–response effect between the increase of total homocysteine and the risk of coronary disease. In addition, an inverse relationship could be shown between levels of homocysteine in plasma and mortality of patients with coronary artery disease [84].

Vitamin production

Vitamins are produced on an industrial scale either by chemical synthesis, fermentation, or extraction from natural sources. There has been public concern that vitamins produced either by chemical synthesis or fermentation may be different from vitamins present in fruit or vegetables. However, the majority of industrially produced vitamins are chemically identical, "nature-identical", with the corresponding substances isolated from plants. Generally, the industrially produced vitamins are either nature-identical compounds, derivatives that are transformed into nature-identical forms after hydrolysis in tissues, or they consist of several stereoisomers.

A typical example of a nature-identical vitamin is vitamin C with the official designation L-ascorbic acid, which is produced worldwide on a scale approximating 60 000 tons per year. It is completely identical with the compound isolated from natural sources such as citrus fruits and is widely used in the food and pharmaceutical industries. Vitamin C has two chiral centers at C-4 and C-5. The stereoisomer erythorbic acid (D-araboascorbic acid or D-isoascorbic acid) has a negligible vitamin C activity but similar antioxidant properties to L-ascorbic acid. Erythorbic acid does not occur in nature and is nontoxic. Worldwide, about 5500 tons of erythorbic acid/sodium erythorbate are produced annually. It is used as

a substitute for vitamin C as an antioxidant, for instance, to inhibit the formation of nitrosamine in cured meat.

The stability of some vitamins is unsatisfactory when stored over extended periods of time. However, a dramatic increase of stability can be achieved by transforming certain vitamins into their appropriate derivatives. These modifications protect the active molecules from degradation, e.g., by atmospheric oxygen and moisture. Examples of commercially available synthetic derivatives are all-*trans*-retinyl acetate or RRR-α-tocopheryl acetate. When ingested, these compounds are hydrolyzed by enzymes such as pancreatic lipase and retinyl ester hydrolase in the gastrointestinal tract producing nature-identical compounds.

An intense discussion concerning natural vs. synthetic vitamins has been focused on α-tocopherol, which is the most active and most important member of the vitamin E group. Vitamin E is a general term employed for tocopherols and the structurally related tocotrienols [85]. They are highly lipophilic and protect membranes and lipoproteins from oxidative damage. α-Tocopherol is used in large quantities in humans for medical purposes, in animal husbandry, and to protect food from oxidative degradation. The homologs, β-, γ-, and δ-tocopherol, having a lower degree of methylation of the chromanol ring system, are less biopotent. These mixed tocopherols occur in substantial quantities in vegetable oils such as soybean oil or palm oil distillates and can be isolated from the residues, which are available on a large scale from refining processes. From these β-, γ-, and δ-tocopherol homologs, nature-identical RRR-α-tocopherol can be obtained by chemical transformation.

The naturally occurring α-tocopherol (RRR-α-tocopherol or d-α-tocopherol) has three chiral centers. The chemically synthesized all-rac-α-tocopherol (d,l-α-tocopherol) is racemic at all three chiral centers and is, therefore, a mixture of eight stereoisomers. The usual synthetic process is condensation of racemic isophytol with 2,3,6-trimethylhydroquinone and is carried out on a scale of about 20 000 tons per year worldwide. Using the rat gestation-resorption test, the activity ratio of the biopotencies of all-rac-α-tocopherol and RRR-α-tocopherol amounted to 1:1.36. All eight stereoisomers have been synthesized [86] and tested for their biological activity [87]. The RRR form is the most active (100 %), and the SSR form is the least active (21 %). It appears that the natural form, RRR-α-tocopherol, is preferentially bound and retained in the human body, whereas the synthetic vitamin E, all-rac-α-tocopherol, is metabolized at a higher rate, and the metabolites are more rapidly excreted in the urine [88].

Carotenoids

The term carotenoid includes both pure hydrocarbons and oxygenated derivatives. Carotenoids are synthesized by photosynthetic bacteria, yeasts, and plants, where they function as accessory pigments in photosynthesis and photoprotection. Because of the enormous variety of chemical structures, they are the most important group of pigments in nature. Most of the naturally occurring carotenoids exist as all-*trans* isomers.

Due to their conjugated polyene structures, carotenoids can absorb light and quench various energetically excited molecules and inactivate free radicals, particularly in lipid peroxidation by inhibiting the propagation steps [89]. β-Carotene can be enzymatically transformed by reduction to retinol (vitamin A) or oxidized to retinoic acid, which is important for growth and cell differentiation. Carotenoids capable of yielding vitamin A are termed provitamin A carotenoids. This conversion of β-carotene to vitamin A is regulated by the vitamin A status of humans, and, therefore, consumption of large doses of β-carotene does not cause vitamin A hypervitaminosis and toxicity. A very interesting development with far-reaching health consequences is the genetic manipulation of staple foods such as rice to express β-carotene [90]. Insufficient supply of either vitamin A or β-carotene results in eye diseases such as night-blindness, xerophthalmia, and eventually blindness. In addition, diarrhea, respiratory diseases, and viral infections (measles) have been observed in vitamin A-deficient subjects. Particularly in Southeast Asia, where rice represents the main staple food, this project could have enormous impact on the health of the population.

At present, partial and total chemical synthesis are the main manufacturing methods to synthesize the many carotenoids. To produce these on an industrial scale, sophisticated technical syntheses have been worked out yielding nature-identical products [91]. Carotenoids are used for the coloration of various food products such as margarine to achieve the level of pigmentation demanded by consumers. Naturally occurring carotenoids can be extracted from various sources, but the high production cost of natural β-carotene, for example, limits its use as a colorant to health foods and related products.

Although many in vitro and in vivo studies claim beneficial health effects of carotenoids (e.g., on ischemic heart disease, stroke, immunomodulation, cancer, cataracts, macular degeneration), the biological functions of carotenoids in humans are not yet fully understood. β-Carotene and/or canthaxanthin have been used successfully to treat certain genetically inherited diseases in humans such as erythropoietic protoporphyria [92]. No serious toxicological problems were found in these patients after long-term use of high doses of β-carotene (180 mg/d). The carotenoids lutein and zeaxanthin appear to be important in the prevention of age-related ocular diseases such as macular degeneration and senile cataracts. They may absorb blue light, the most energetic part of sunlight, thus protecting photoreceptors and the retinal pigment epithelium [93] and function as antioxidants limiting oxidative damage [94]. Several commercial products containing lutein are available as supplements on the American market to lower the risk of macular degeneration. Epidemiological observations have shown an inverse relationship between intake of green/yellow vegetables containing β-carotene and the incidence of certain types of cancers [95]. However, in two randomized, placebo-controlled intervention trials, β-carotene supplements unexpectedly caused a higher incidence of lung cancer in smokers and/or asbestos-exposed workers [76,96]. In contrast, the results of a study involving a large group of male U.S. physicians showed no effect of β-carotene on cancer or cardiovascular diseases. As a consequence, the use of β-carotene to limit these diseases remains questionable.

Fats

The excessive energy consumption (fat and sugar) in the affluent societies of Europe and North America and, hence, the increasing incidence of overweight and obesity causes many health problems. Chronic diseases related to obesity are diabetes mellitus, arthritis, hypertension, some types of cancer, and coronary heart disease with increased mortality [97]. Furthermore, childhood obesity is the beginning of chronic diseases that become apparent later in the adult population [98]. Among the many risk factors of coronary heart disease and stroke identified so far, is a high intake of saturated fatty acids (animal fats) which raises the level of blood lipids, low-density lipoproteins, and triacylglycerides. This is associated with atherosclerosis (formation of fatty streaks and fibrous plaques in blood vessels supplying the heart and brain) and increased prothrombotic tendency for platelet aggregation (thrombus formation). The current Western diet contains high amounts of total fat, *trans* fatty acids and the *n*-6 and *n*-3 essential fatty acids in an unbalanced composition [99]. As recommended by health authorities, dietary intake of total fat should not exceed 30 % of the total daily calorie intake, but Americans, for example, obtain about 35–40 % of their energy from fat. The energy per gram of dietary fat is 9 kcal. Although recommended daily allowance (RDA) values for *n*-3 and *n*-6 polyunsaturated fatty acids (PUFAs) have not yet been established, the advised intake of PUFAs should be below 8 % with a ratio of *n*-6 to *n*-3 PUFAs between 5–3:1. Since foods that combine fat and sugar are universally preferred by humans of all ages, it seems to be necessary either to reduce, balance the components of, or partially substitute dietary fat intake. In response to consumer demand and the perceived health benefits of lower fat consumption, products containing naturally occurring PUFAs or fat replacers are being developed and marketed.

Generally, fats (lipids, triglycerides) are composed of one molecule of glycerol and three chains of either saturated, monounsaturated, or polyunsaturated fatty acids differing in chain length. PUFAs are grouped into classes depending on the position of the first double bond from the methyl end of the molecule. Accordingly, they belong to the *n*-3, *n*-6, or *n*-9 class of PUFAs with *n*-3 and *n*-6 as the main

classes. Linoleic acid (*n*-6) and α-linolenic acid (*n*-3) are essential fatty acids, which have to be provided by the diet as in the case of vitamins. Others can be enzymatically synthesized in tissues using elongases and desaturases to obtain the desired chain length and number of double bonds. The main members of the *n*-3 PUFAs, eicosapentanoic acid, and docosahexanoic acid, are derived from α-linolenic acid, while the *n*-6 PUFA, γ-linolenic acid, dihomo-γ-linolenic acid, and arachidonic acid, are synthesized from linoleic acid. They are structural components of phospholipids in cell membranes and serve as precursors for prostaglandin, eicosanoid, and leukotriene biosynthesis. A number of studies have shown that ingestion of *n*-3 PUFAs reduces cardiovascular morbidity and mortality [77,100]. Greenland Eskimos and Japanese consuming high amounts of fish and hence *n*-3 PUFA have an increased incidence of hemorrhagic stroke. However, moderate fish oil intake does not reduce platelet aggregation and therefore does not enhance bleeding tendency [101]. Generally, animal fats contain mainly saturated fatty acids. Vegetable oils (sunflower, linseed, rapeseed, soybean, corn) are rich in *n*-6 PUFA, while green leafy vegetables (e.g., lettuce, spinach, cabbage) and fish liver oils or fish (e.g., herring, salmon, sardine) are relatively rich in *n*-3 PUFA. A wide range of processed foods such as margarine, fat spreads, salad dressings, yogurt, and milk drinks are based on vegetable oils containing PUFAs or are fortified with a single isolated PUFA. The recommended daily intake of *n*-3 PUFA is about 1.2 g.

Fat replacers

Generally, fat is important both for the consistency and texture of food and as a carrier and conveyer of flavor because many flavor and aromatic components are lipid-soluble. Fat replacers should, therefore, have similar organoleptic characteristics. These products should be safe and physiologically inert, while maintaining functional (appearance, hydrophobicity, temperature behavior), and sensory properties of common high-fat products. They mainly stimulate sensory properties. Influences on other nutrients in the gastrointestinal tract are generally minimal. However, some materials (cellulose, certain gums) are resistant to digestion and may affect absorption of micronutrients such as minerals, fat-soluble vitamins, and carotenoids. Based on their chemical type, fat replacers can be grouped in three classes of products: (1) lipid-based compounds (e.g., fatty acid esters of sugars and sugar alcohols such as Olestra®, branched and asymmetric triglycerides, polycarboxylic acid and propoxylated glycerol esters, retrofats, specific naturally occurring lipids); (2) proteins (whey protein concentrate, microparticulated proteins, e.g., Simplesse®); and (3) carbohydrates (modified starches, inulins, water-binding and jelling substances, dextrins, polydextrose, modified glucose polymers, dietary fibers such as gums, pectin carrageenan).

Many of the lipid-based substances are resistant to hydrolysis by pancreatic lipases in the gut and are excreted intact. Therefore, they have no metabolizable energy. Examples are retrofats (inverse fats), which are esters of carbonic acids such as citric acid and long-chain alcohols. Asymmetric triglycerides such as Caprenin® and Saltrim®, containing medium- and long-chain fatty acids, are fat-like in their functional properties with diminished energy values. They are hydrolyzed in the gastrointestinal tract, but only partially absorbed due to their extended chain lengths. The caloric value of Caprenin® is 20 kJ/g (5 kcal/g) compared with 36 kJ/g (9 kcal/g) for common dietary triglycerides [102]. It has GRAS (generally regarded as safe) status and is on the U.S. market.

Other products derived from natural food sources are carbohydrate- and protein-based materials that are partially or fully digested and absorbed. Examples are gums (carrageenan, xanthan, alginates, guar) that are used in cream toppings and candies. Derivatives of starches from potatoes, tapioca, and corn obtained by enzymatic or acid hydrolysis are used in salad dressings, frozen desserts, table spreads, dips, or confections. In addition, products derived from hemicellulose and soluble fibers are used as water-soluble bulking agents. Gelatin and whey products provide stability and improve mouth feel. Polydextrose is produced by polymerization from glucose and has no effect on absorption and metab-

olism of essential nutrients. It is used for salad dressings, confections, frostings, and frozen dairy deserts.

Carbohydrate fatty acid polyesters are synthetic fat substitutes that can be obtained by esterification of fatty acids and mono-, oligo-, or polysaccharides with a wide range of physical and biological properties. Sucrose polyesters lower levels of blood cholesterol in hypercholesterolemic patients and also cause reduction of body weight. The product Olestra® is a sucrose polyester of naturally occurring fatty acids of short to medium chain lengths. Approximately six to eight fatty acids are attached to one molecule of sucrose. Olestra® is neither hydrolyzed nor absorbed in the gastrointestinal tract and hence is a noncaloric fat replacer. It is registered in the United States and used for deep-frying and for the production of potato chips and snacks.

Microencapsulated proteins are usually prepared from milk, egg white, or whey proteins. The uniform particle size of 0.1–3 μm results in the smooth texture of fat. Products containing microencapsulated proteins have a creamy texture similar to products with a full fat content. They are used in many applications such as frozen and refrigerated products, salad dressings, mayonnaise, sour cream, and cheese spreads.

Conclusions

Natural and synthetic substances appear to be one of the most often discussed themes in connection with human nutrition by the general public. Vitamins, carotenoids, some polyunsaturated fatty acids, and trace elements are essential nutrients that cannot be synthesized by the human body. Insufficient intake leads to nutritional deficiency resulting in diseases and eventually death. As a consequence, it is common practice nowadays to enrich various types of food with these substances (food additives). Upper limits of the amounts are stipulated by governmental authorities (RDA, recommended dietary allowances; ADI, accepted daily intake, and other guidelines). The huge amounts of these compounds needed throughout the world are mainly produced chemically or by fermentation. The chemical structures of the majority of these compounds are identical with the corresponding natural substances (nature-identical) or derivatives that are hydrolyzed to nature-identical compounds in the body. As in the case of chemically synthesized vitamin E, where eight stereoisomers exist in the mixture, some stereoisomers express lower biological activity but do not exert any toxic side effects. In this context, it appears that efficacy, chemical stability, cost-efficiency, safety, and purity of these nutritive ingredients are all important criteria.

Obesity is the most common nutritional disorder in the industrialized countries. When components of traditional foods are replaced by artificial substances, the aim is to remove the undesirable properties of fat (high calorie value), but to maintain physical and organoleptic properties. The long-term effects of fat replacers on the energy value of food supply and human health have yet to be determined. They may provide a health benefit to certain subpopulations, but they may also reduce the bioavailability of other nutrients such as fat-soluble vitamins, have adverse effects on the function of the gastrointestinal tract, or interfere with the microflora of the gastrointestinal tract.

TOXIC SUBSTANCES (G. A. R. Johnston)

Introduction

Toxic substances have the ability to damage living organisms—they are poisons. Everyday household products, such as bleaches, disinfectants, and detergents, contain toxic substances. These products are useful to us, and we have learned to minimize the risks that they present. The better we understand such substances, the more we are able to benefit from them. Toxic substances are potentially dangerous, but many perform useful roles in the modern world. If we are to live safely with them, we need to minimize the risks they present.

The importance of dose must be emphasized when considering toxic substances. The dose makes the poison. Even the most toxic substance known is now used in medicine in carefully controlled doses. Too little of a substance can be just as toxic as too much. Oxygen and water are examples of substances essential to life that can be toxic to humans if we have either too little or too much.

Toxicity is not a function of whether or not a substance is of natural or synthetic origin. The toxins most lethal to humans are mostly natural substances and are often part of a chemical defense strategy to protect against predators. Highly toxic synthetic substances are most likely to be nerve gases or pesticides. A representative list of toxic substances is shown in Table 1.

Table 1 A representative list of toxic substances from the chemistry.about.com web pages (http://chemistry.about.com/education/chemistry/library/blpoison.htm).

Name	Fatal adult human dose in milligrams
Botulinum toxin A	0.001
Ricin	0.07
Saxitoxin	1
VX (nerve gas)*	10
Hydrogen cyanide	50
Nicotine	60
Arsenic	70
Soman (nerve gas)*	350
Strychnine	350
Dieldrin (pesticide)*	3500
Caffeine	10 000
Pyrethrins (pesticide)	15 000
Ethanol	386 000

*Synthetic substance

The most powerful toxic substance

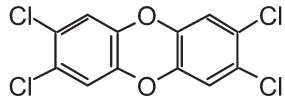
The dubious honor of being the most powerful toxic substance goes to a protein produced by the bacterium, *Clostridium botulinum.* This protein is responsible for fatal food poisoning—botulism—being produced when the bacterium grows in the absence of oxygen in canned or preserved food. There are seven closely related proteins produced by the bacterium, and they are named botulinum toxins A to G.

Botulinum toxin A, the most widely studied, is fatal to humans in doses as low as 0.001 mg. This makes it the most powerful toxic substance known. Like its close relative, tetanus toxin, botulinum toxin is a neurotoxin that prevents the release of neurotransmitters from nerve terminals. Botulinum toxin A is a protein made up of 1285 amino acids, and its structure, which has been determined by X-ray analysis, has given us great molecular understanding of its neurotoxic action [103].

Despite its extreme toxicity, botulinum toxin A is finding increasing use in medicine for certain conditions that involve involuntary muscle contractions. This is a result of pioneering work of scientists at the University of Wisconsin in the early 1980s. In 1989, the U.S. FDA granted approval for its use in the treatment of the eye disorders, blepharospasm and strabismus, that are characterized by excessive muscle contractions. Very small doses of the toxin are injected into the affected muscles. The toxin paralyses or weakens the injected muscle by blocking the release of acetylcholine, but leaves other muscles unaffected. There is an extensive literature on the therapeutic uses of botulinum toxin A and numerous Web sites, including Botulinum-Toxic.Net (http://www.bu.edu/cohis/nphram/) by Eric First at the Boston University School of Medicine. The medical use of botulinum toxin A, a natural substance, illustrates that a good understanding of the chemistry and biology of the substance can make even the most toxic substance known useful to humans.

The most publicized toxic substances

Dioxin is the name given to a family of polychlorinated substances, the most widely studied and the most toxic of which is TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.



TCDD

Dioxins are undesirable impurities derived from the combustion of substances that contain chlorine. Forest fires, paper manufacture, municipal waste combustion, motor vehicle emissions, and chemical manufacturing plants all produce dioxins. Dioxins are, thus, natural substances, whose production is increased by human activity.

There is great public interest in dioxins as toxic substances in the food chain and in the environment. Serious concerns about dioxins were first raised in 1970 when they were found in significant concentrations in Agent Orange, used as a defoliant in the Vietnam War and suspected of being responsible for birth defects. When most people think of toxic substances they think of dioxins.

In laboratory animals, dioxins have been shown to cause a variety of abnormalities. The LD50 (lethal dose) for TCDD in rats is 0.022 mg/kg. This would translate to an LD of 1.54 mg for a 70-kg human (making it some 1500 times less potent than botulinum toxin A), but very little human toxicity data is available for TCDD.

Most human data has been obtained from occupational settings where workers have been exposed to chemicals containing TCDD [104]. The signs and symptoms of poisoning of humans with chemicals containing TCDD are similar to those seen in animals. Initially, these were severe skin lesions—chloracne—that provided most cause for concern, but major worries about cancer and birth defects created alarm in the community.

Fears concerning the threat of dioxins to human health are much stronger than are justified solely on the basis of the available scientific data. There continues to be extraordinary publicity in the popular press given to dioxins and their threat to public health. No comprehensive studies have been conducted to determine possible adverse effects to the general population from exposure to dioxins in the environment [104].

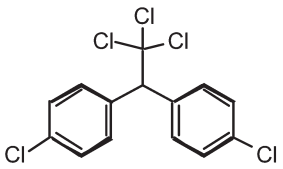
There are numerous Web sites on the dangers of dioxins, for example, Dioxin Alert! (http://members.tripod.com/dioxinalert/index.html) documents the dioxin scare in Belgium that resulted in June 1999 in the ban of many Belgium foodstuffs in the European Union and in many Asian countries. As a result, Malaysia ordered the recall of all meat, eggs, dairy products, and infant formula produced in the European Union. The source of the dioxins was identified as a storage tank of oils and fats in a Belgium processing company that sold the fat for use in animal foodstuffs. The origin of the dioxins in the storage tank is unknown. Worries about dioxin contamination also led to the withdrawal of Coca Cola produced in Belgium. A letter to *The Lancet* said that the widespread reports of Coca-Cola "poisoning" were in fact symptoms of mass sociogenic illness (MSI)—brought about by society's heightened sense of anxiety over the safety of food products [105]!

Unlike botulinum toxin, dioxins currently have no medically useful properties. The unwanted production of these substances is being reduced in line with the overall "greening" of chemical manufacture.

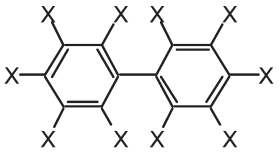
Endocrine-disrupting substances

Endocrine disrupters have a chemical similarity to natural hormones and are able to interact with receptors for these hormones and thus to disrupt the natural function of the hormones. These substances occur widely in the environment being derived from both natural and synthetic sources.

Public concern about endocrine disrupters in the environment was stimulated by the publication of a book entitled *Our Stolen Future: Are We Threatening Our Fertility, Intelligence and Survival?*—a scientific detective story in 1996 by Colborn, Dumanoski, and Myers. This issue began with research in the 1970s that indicated that the insecticide DDT and a group of industrial substances known as PCBs (polychlorinated biphenyls) were reducing the fertility of seals. Much scientific work has been carried out subsequently on the mechanisms of action of these substances, which are clearly associated with their chemical similarities to human estrogens [106].



DDT



PCBs

X = H or Cl

It is now apparent that a range of natural and synthetic substances are capable of acting as endocrines in a wide variety of animals. In addition to DDT and PCBs, synthetic substances that can act as endocrine disrupters include phthalate plasticizers used to soften poly(vinyl chloride) (PVC) and synthetic estrogens used in contraceptive pills and in hormone replacement therapy. Natural substances known to interact with hormone receptors include phytoestrogens (mainly isoflavones such as genistein that are widely distributed in plants) and, of course, the hormones excreted by humans and other animals.

Considerations of the risks associated with endocrine disrupters must include assessment of the possible exposure of these substances to humans and animals, that is, the dose of the substance. Clearly, most people consume phytoestrogens in their normal diet. For example, genistein is found in high concentration in soy products, including tofu. There is no evidence to suggest that people consuming substantial quantities of soy products have disrupted endocrine function.

Current studies on endocrine disrupters focus on the development of accurate, sensitive, and selective methods for monitoring these substances in the environment, and a much more detailed understanding of the effects of these substances on biological systems. Assessing the overall toxicity of endocrine disrupters requires more information on environmental levels, dietary intakes, target organ exposures, mechanisms of action, and interactive effects of mixtures [107].

Assessing toxicity

We are all familiar with the concept of "risk". Just about everything we do involves risk. Every day we make choices amounting to risk assessment. When dealing with potentially toxic substances, however, risk assessment takes on a more formal role.

A variety of government agencies regulate the manufacture, availability, and use of chemical substances in foods, medicines, agricultural and veterinary products, and industrial chemicals. In this context, risk and hazard have different meanings. A hazard is an intrinsic property of a substance to do harm, while the concept of risk has two elements—the likelihood of an event occurring and the consequence of the event if it does occur. For example, to assess the risk of nicotine in cigarettes, we must consider the toxic substance nicotine as the hazard, the act of smoking cigarettes as the event, and the consequences may include lung cancer and heart disease.

Governments have been urged by organizations, such as Greenpeace, to adopt a precautionary approach to substances that may harm the environment. They are being encouraged to take action to avoid the threat of harm even when firm evidence of cause–effect relationships is unavailable. There is increasing pressure on government agencies to adopt what has become known as the "Precautionary Principle" when assessing substances [108].

Thus, assessing the likely risk of toxic substances is a complex issue involving data from a variety of scientific disciplines and consideration of both short- and long-term effects on all living organisms. With toxic substances, we must balance any social benefit associated with a particular substance against the risks posed by its use, manufacture, and disposal.

Conclusions

The above discussion of toxic substances illustrates a number of important points:

- We commonly encounter toxic substances in everyday life.
- Dosage must always be taken into account; even the most toxic substance known can be used safely in suitably low doses.
- Public perception of toxic substances is not always supported by scientific facts.
- The more we know about the chemistry and biology of toxic substances the better.
- There are different types of toxic substances. Some are lethal to humans, while others have insidious effects such as disrupting endocrine function. Substances may be toxic to farm animals, wildlife, and the environment.
- Toxicity is not a function of whether a substance is natural or synthetic.
- We must balance any social benefit associated with a particular substance against the risks posed by its use, manufacture, and disposal.

SUMMARY (J. G. Topliss)

Substances produced in nature exhibit a variety of properties with respect to their effects on human health. These range from the control of regulatory processes essential for human life, serving as nutrients, acting as medicinal agents to cure or alleviate disease either as single substances or mixtures as in herbal preparations, all the way to producing extreme toxicity. Many have both favorable and unfavorable effects, often dose-dependent. Even some vitamins can have untoward effects at very high doses, and the most potent natural toxin of all, botulinum, is used as a drug in minute doses to treat some conditions involving involuntary muscle contractions.

Natural substances originate from a wide variety of living organisms and serve different purposes. In addition to those acting in essential roles in human life, such as vitamins and nutrients, some are noxious and act as defense mechanisms against predators, while others paralyze prey. Yet others may have no obvious purpose but are metabolic end-products that may possess all manner of properties from useful to harmful. These include genistein, widely distributed in plants, which in animal tests can disrupt endocrine function, and the botulinum toxins. Herbal products used as medicinal agents may have harmful effects in humans as well as beneficial ones, and they have not been subjected to the same rigorous standards of efficacy, safety, and purity accorded single chemical entities approved as drugs by regulatory agencies. The chemical structures of natural products are diverse and complex. Natural products provided the earliest medicinal agents as complex mixtures from botanical preparations and as single drug substances long before synthetic organic chemistry developed to the stage where it could be an important route to new drugs, and they continue to be important today as sources of new drugs.

Synthetic substances, produced by chemical synthesis from basic chemical building blocks and utilized for a variety of purposes, have proliferated over the last half-century as synthetic methodology and production technology have developed to highly sophisticated levels. Modern drug research is now

predominantly based on substances produced by chemical synthesis, including the use of computer-aided drug design, combinatorial libraries, and structural optimization of lead compounds of both natural and synthetic origin to maximize the benefit–risk ratio. However, the discovery of bioactive natural products, which serve as leads for new drugs, remains an important drug discovery strategy. On the other hand, herbal products, for better or worse, remain essentially as the plant produced them: complex multicomponent mixtures that are often not well characterized or understood. Greater understanding will only be achieved as rigorous and well-designed scientific studies are conducted to examine the properties of these products that are consumed by millions of people each year.

The introduction and use of synthetic substances for various industrial purposes, and impurities arising from industrial processes, has led to some exposure to toxicity risk. Of course, a high level of toxicity is the intended purpose of a nerve gas. Pesticides can be toxic to humans, and dioxins are toxic substances, products of combustion, which can be generated through natural events such as forest fires or industrial processes. DDT, PCBs, and phthalate plasticizers are synthetic substances that pose risks as disruptors of endocrine function.

Another type of substance is a natural one that has been modified by a chemical synthesis process to a semisynthetic derivative in order to improve its properties. Examples are the numerous antibiotic semisynthetic penicillin and cephalosporin drugs and vitamin derivatives that improve stability. Natural substances that are also available in an identical molecular form by synthesis, represent another distinct category. A typical example is vitamin C, which is produced commercially by synthesis, and the synthetic substance is referred to as a nature-identical vitamin.

In conclusion, from the examples presented in this article, it is clear that natural and synthetic substances have a similar overall range of properties with regard to efficacy and safety, in terms of their impact on human health. The actions of individual substances are determined by their molecular structures and dose, not whether they are of natural or synthetic origin.

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