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Unconventional natural sources for future drug discovery

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'There are more things between heaven and earth... ' **Despite the progress of science during the past four centuries, Shakespeare's words did not lose their actuality. Knowledge about the etiology of diseases is still limited, and for many life-threatening illnesses no effective treatments exist. Nature always has been a valuable source of drugs and, despite the unprecedented opportunities afforded by medicinal chemistry, continues to deliver lead compounds. Traditionally, research on natural sources was focused on terrestrial plants and microorganisms. More recently, however, organisms of marine origin are also being investigated. Here, the possibilities of unconventional and hardly explored sources are discussed.**

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▼ Natural products used as food or drinks, clues from the fascinating science of zoopharmacognosy, terrestrial animals and their excreta, and many other NPs not primarily known for their medical use, seem to have, to a great extent, escaped the attention of natural product research. It is nevertheless highly probable that these sources could contain biologically active compounds, some of which will prove to be valuable lead candidates for novel drugs.

Natural products have been the most successful source of drugs ever [1,2]. Historically, the most important natural sources have been plants. Research progressed along two major lines: ethnopharmacology (medicinal herbs, substances of abuse, ordeal poisons) and toxicology (poisonous plants, venomous animals, arrow and fish poisons) [3]. These strategies have produced many valuable drugs and are likely to continue to produce lead compounds [4]. It must be stated that traditional medicines have not been found by systematic research but by a combination of coincidence and observation, and at best by trial and error. Until the beginning of the 20th century, knowledge about receptors, bacteria and viruses was virtually nil [5]. As a consequence, many valuable natural compounds have escaped discovery. Due to the inability to diagnose disease accurately in ancient times, it is unlikely that in depth investigations of, for example, traditional Chinese Medicine and Ayurveda will directly lead to treatments for life-threatening diseases, although this can not be excluded.

Fleming's serendipitous discovery of penicillin was the start of the exploration of the second most investigated and, consequently, the second most prolific natural source: fungi. From those organisms, breakthroughs in the area of antibiotics, immunosuppressants and anticancer drugs have been realized. More recently, there has been a trend to explore marine environments. Already this has resulted in several marketed drugs and more are currently in clinical trials. Research on marine organisms has been the subject of several excellent reviews [6–10].

Ethnopharmacological, microbiological and marine sources must not be regarded as exhausted. The intention of this paper is to draw attention to other, unconventional sources that have never been investigated systematically in pharmacological assays. The first and most important step in drug discovery is the finding of leads. To facilitate that process, there are now a great variety of mechanism-based HTS assays. Traditionally, the natural sources investigated were well-determined individual species: mostly plants and fungi. Many of the sources discussed here are different: they are not individual species, and botanical or zoological identification in some cases is impossible.

Natural compounds from drink

Alcoholic beverages as sources of natural compounds

Myrica gale ('Gagelstrauch') has been used in beer brewery from the 10th century until

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early in the 18th century when it became forbidden because it made people who drank it become aggressive. This effect has been attributed to cineol [Figure 1; **(1)**], the main component of the essential oil of *Myrica gale*. A similar story is that of 'Porstbier', which was forbidden for the same reason by Kurfurst Georg von Hannover in 1723. This beer was brewed with 'Brauerkraut': *Ledum palustre*, the essential oil of which contains ledol **(2)**, which is structurally related to cineol. Around the turn of the 20th century, most European countries had outlawed absinth because of its mind-altering properties. The herb from which this liquor was extracted is *Artemisia absinthium* and its active substance is thujone **(3)**, which is chemically related to cineol. The mechanism-of-action of these compounds is still unknown. Alcoholic beverages can be regarded as extracts of specific plants or plant products that microorganisms have metabolically modified to produce compounds that are not present in the original sources. A subgroup is that of the 'bitters', alcoholic extracts of many different herbs. Superficially, alcoholic beverages can be considered mixtures of water and alcohol in different proportions. However, the examples indicate clearly that not all of the pharmacological effects of these drinks are alcohol related.

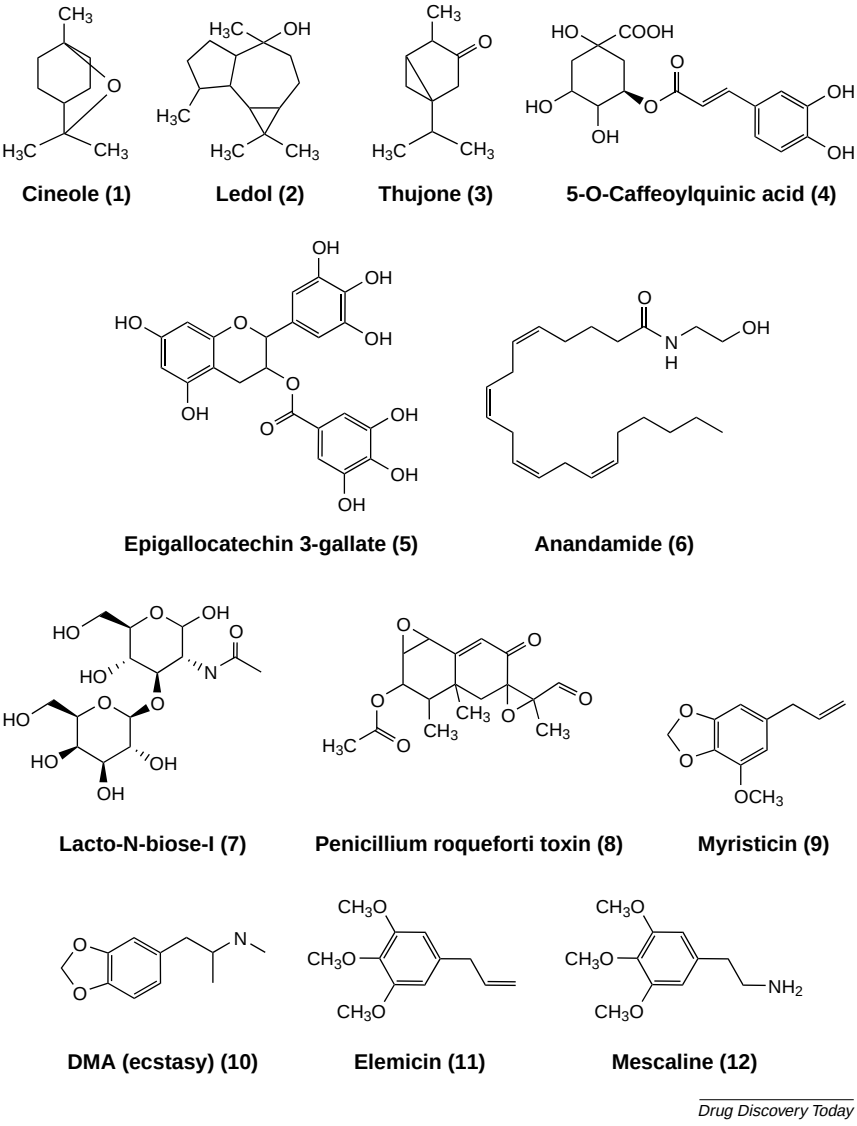

Figure 1. Structures of some intriguing compounds isolated from food and drinks. Most of the compounds are biologically active but in most cases their mechanism-of-action is unknown.

Non-alcoholic beverages as sources of natural compounds

Non-alcoholic beverages can be subdivided into pure natural substances like grapefruit juice and maple syrup, diluted extracts from natural sources such as 'soft drinks', and extracts of processed products like coffee, tea and cacao. Only the processed products have been investigated in detail. This resulted in the identification of not only caffeine and theobromine, responsible for the main pharmacological effects of these drinks, but also of compounds such as feruloyl quinic acid lactones **(4)** (with opiate receptor antagonistic activity) from coffee [11], epigallocathechins **(5)** (anti-tumor activity) from tea [12] and anandamide **(6)** (the endogenous ligand for cannabinoid receptors) from cacao [13].

All mammals produce milk, as nutrients for their offspring. Milk contains a large number of substances for which no biological activity has been established. A few examples from human milk are the amino acid furosine, the peptide α-lactorphin, the amino sugar lacto-N-biose-I **(7)**, the fatty acid 2,6-dihydroxy-4-pyrimidinecarboxylic acid and the aldehyde 2-dodecanal [14].

Analogous with the production of the previously mentioned metabolic products produced by fermentation, there is a enormous variety of potential products to be found from cheeses, based on milk from a wide variety of herbivores, which feed on an even wider variety of plant and animal species, and are fermented by a yet wider variety of bacteria

and fungi. Cheeses should therefore contain a staggering diversity of compounds (see Table 1). To date, only a few of these have been identified and, even for a specific example such as *Penicillium roquefortii* toxin **(8),** no mechanism-of-action is known. Whey is mostly water, lactose and proteins but it also contains many 'unknowns'. Whey powder and paste are easily obtained in large quantities and, just like other dairy products like yoghurt, quark, butter and buttermilk, are likely sources of pharmacologically active compounds.

Natural compounds from food of plant origin

Spices

Apart from salt, pepper is the most commonly used spice and its widespread use is probably due to it containing

Table 1. A Comparison of unconventional with well-established natural sources

Conventional and recently established sources	🗍	**!**	**B**	**L**	**®**
(Ethnopharmacological) plants	+++	+++	+++	+++	+++
Microorganisms	+++	+++	+++	+++	+++
Marine organisms	+++	++	++	+	+
Venomous animals	++	++	++	+	+
Genetically modified organisms/cells	++	+	+	?	-
Combinatorial chemistry on natural products	++	+	+	?	-
Insects	++	+	+	?	-
Unconventional sources					
Man and other mammals	+++	++	+	+	+
Hay	+++	+	+	+	+
Fruits, nuts, seeds	+++	+	+	+	-
Vegetables	+++	+	+	+	-
Birds	+++	+	+	?	-
Invertebrates	+++	+	+	?	-
Spices	+++	+	+	?	-
Crops and plant waste products	+++	+	?	?	-
Processed food products	+++	+	?	?	-
Silage	+++	?	?	?	-
Compost	+++	?	?	?	-
Flavors, fragrances, essential oils	++	++	+	+	-
Resins (including oleoresins, balsams and solids)	++	+	+	+	-
Wood & bark (excluding ethnopharmacology)	++	+	+	?	-
Dairy products (milk, cheese, etc)	++	+	+	?	-
Human/animal faeces	++	+	?	?	-
Other excreta (saliva, sweat, tears, etc)	++	+	?	?	-
Fatty, vegetable, fish and fossil oils	++	+	?	?	-
Mammalian, vegetable, insect and mineral waxes	++	+	?	?	-
Gums	++	?	?	?	-
Fibers	++	?	?	?	-
Human/animal urine	+	+	+	+	+
Alcoholic beverages	+	+	+	?	-
Non-alcoholic beverages	+	+	+	?	-
Hints from zoopharmacognosy	+	+	+	?	-

Arranged by the speculative number of compounds expected to be present in the different sources, and to be regarded as qualitative rather than quantitative. In the first column (🗍) an estimation of the potential of each source in terms of different organic compounds is given. The next column (!) provides an indication of the number of distinct compounds actually isolated. Facts on whether or not any of the isolated compounds were already found to be biologically active are given in the column headed "B". When any of the latter compounds qualified as leads or ultimately became drugs is presented in the columns marked "L" and ® respectively. +++ very many; ++ many; + few; ? unknown; - none

piperine, a slightly less pungent relative of capsaicin, the 'hot' substance from chili-pepper. Both compounds are thought to be agonists at the newly identified vanilloid receptors [15]. Thus, even the most common spices contain biologically active compounds. Apart from some spices that are also medicinal herbs, for example, garlic, ginger and onions, few have been investigated pharmacologically. An exception is *Myristica fragrans*, the plant from which nutmeg and mace are obtained. At high doses these spices are hallucinogenic; they have been shown to contain myristicin **(9)** and elemicin **(11)**, compounds resembling ecstasy **(10)** and mescaline **(12)**, respectively. Further support for the suggestion that spices might contain a wealth of biologically active molecules is the inhibition of multi-drug resistance in tumor cells by extracts of rosemary [16].

Vegetables, fruits and nuts

Nature provides mankind with a great variety of edible fruits, nuts and seeds**.** Although, in many cases, comparable parts of medicinal plants have been investigated, this applies only to a few plants commonly used as food. To emphasize the potential of these sources, recent patent applications claim antibiotic activity of grapes (*Vitis vinifera*) and cranberry (*Vaccinium macrocarpum*), attributed to the proanthocyanidins they contain [17]; wound healing properties of extracts of the flesh and seeds of grapefruit, *Citrus x paradisiaca* [18], and antitumor activity of extracts of orange peel, attributed to the poly-methoxy flavonoids it contains, specifically 3′,4′,5,6,7,8-hexamethoxy-flavone [Figure 2; **(13)**] [19].

Common vegetables**,** known to be 'healthy' because they contain carbohydrates, vitamins and minerals have been underinvestigated as a source of pharmacologically active molecules. Corroborating the suggestion that food plants deserve attention are patent applications claiming prevention of stomach- and lung-cancer by extracts of species from the Cruciferae and Scrophulariaceae families, including winter rape, mustard, radish and purslane [20]; and tumor reduction by an extract of beetroot (*Beta vulgaris*), attributed to betanin **(14)**, the purple pigment of this plant [21]. Vegetables are usually grown on a large scale and, apart from the parts used as food, these crops also result in large quantities of waste products, for example, sugar beet leaves, potato plant leaves, maize plants and so on. In general terms, crops (not just vegetables but also animal feed, flowers and fertilizers) offer the advantages of being unexplored, abundant and cheap sources of natural compounds. Yet another intriguing one is compost, which is available in large quantities, and likely to contain an added variety of different compounds due to fermentation by microorganisms (Table 1).

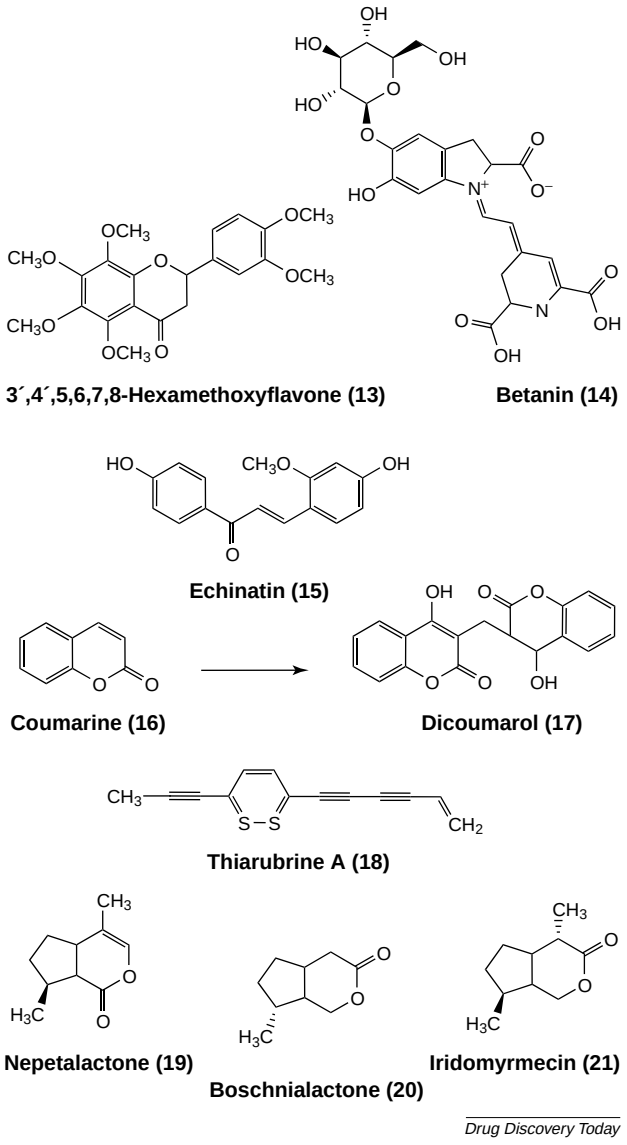

Figure 2. Biologically active compounds isolated from (processed) food or from plants based on zoopharmacological clues.

Processed food products

Processed food products form a large group of different products obtained by a variety of processes: fried, grilled, roasted, dried or smoked; muesli, cornflakes and other cereals, confectionaries, pastries, liquorice, peppermint, chocolate; fermentation products like ketjap and sambal, Worcester sauce, chutney, ketchup, and so on. Food products are processed for a variety of reasons – conservation, ease of digestion, palatability. However, only a few have been investigated for the presence of biologically active molecules. One example is liquorice (*Glycyrrhiza glabra*), which has been shown to contain echinatin **(15)** and other chalcones such as isoliquiritgenin and licochalcone B,

compounds proven to inhibit epidermal thickening and thus potentially useful to treat psoriasis [22]. Processed food products are worthwhile for consideration for pharmacological screening because processing almost certainly results in the formation of compounds that would not naturally occur in the original source.

From animal food to zoopharmacognosy

How often has drug discovery been compared with looking for the proverbial needle in the haystack? Why not try literally? Hay, as is silage, is a mixture of dried grasses and other plants, ready to be extracted. As a result of metabolism by microorganisms, both are bound to contain compounds that are not present in the original plants. A famous example of this is dicoumarol **(17),** which was isolated from hay in 1938. This compound does not occur in the original plant (*Melilotus alba*), but is formed by fermentation of its naturally occurring component, coumarin **(16)**. It became the first of the oral anticoagulants [23] (Table 1). Other possible sources are plants and other organisms on which wild animals feed. After millions of years of evolution these sources can be considered not only safe but also healthy. It is possible that they not only contain well-known classes of nutrients but also compounds of unknown pharmacological benefit. The reverse of this strategy has proven to be of value: the toxicity of many plants was noted because they were either avoided by animals, or they made animals feeding on them sick. Subsequent investigation resulted in the identification of many toxic compounds, some of which were developed into drugs: Dicoumarol, mentioned previously, is one example.

There is much more that can be learned from animal behavior. Zoopharmacognosy is the fascinating science involving the study of plants presumably consumed by animals for medicinal value. Chimpanzees for instance, occasionally feed on *Aspilia mosambicensis*, a plant containing thiarubrine A **(18)**, which is a strong nematocidal and antifungal compound [24]. Recreational drug use is a phenomenon not restricted to *Homo sapiens*. Every domestic cat-owner is familiar with the spectacular effects of catnip (*Nepeta cataria)*. Less well known is that this plant, as well as several other species (e.g. *Boschniakia rossica* and *Actinidia polygama)*, has similar effects on wild felines, including lions and jaguars. Nepetalactone **(19)**, boschnialactone **(20)** and iridomyrmecin **(21)** were isolated as active principles from these plants, and nepetalactone was already shown to possess intriguing pharmacological properties, to a certain extent resembling those of the opiates [25,26]. **'***There may be superior potential therapeutic value in plant products which evolved to attract rather than repel animals, including man.*' This hypothesis, reported by Perry *et al.* [27], certainly deserves attention!

Animals as sources of natural compounds

Animals have been sources of several fascinating 'drugs' like bezoar stones, castor, theriac and pearl [28]. Despite that, the only compounds from animal origin that are currently used as drugs are certain enzymes and hormones, and cytarabine and vidarabine, two mycalamides isolated from the marine sponge genus *Mycale* [29]. Potential new examples are the nicotinic agonist epibatidine [Figure 3; **(22)**], isolated from the tree frog *Epipedobates tricolor*, and several compounds isolated from marine animals [10], which are becoming established sources of new drugs (Table 1). However, does the paucity of examples from terrestrial animals mean that they are of little value in drug discovery?

Man and other mammals

What is the most promising source for the initial search for compounds that might prove to be useful as leads for novel drugs? The human body! Screening the literature for compounds known to occur in human tissues, but without any known biological function, results in an amazing array of hundreds of different molecules [14]. Ergothioneine **(24)**, ophidine **(25)** and trichochrome B **(26)** are just some examples. Screening of extracts of different human tissues for activity in mechanism- based pharmacological assays is bound to produce surprises.

Apart from man, more than 4000 species of mammals have been catalogued. Given the fact that the human body contains large numbers of compounds for which no biological function is known, it is not a logical choice to start a systematic investigation of other species instead. However, it might prove worthwhile to explore certain pertinent differences between man and other mammals. Although during evolution our olfactory organs have become less important, many mammals heavily rely on chemical communication. Perfumery has paid ample attention to the excretions of animals such as musk deer, civet cats and muskrats, but have these substances, or the appalling odors used by ferrets and skunks for defensive reasons, ever been investigated for their pharmacological activity?

Animals other than mammals

The only animals that have been subjected to intense scientific investigation in terms of biologically active compounds are those that are venomous [30] and, to a certain extent, those from marine environments [10]. Invertebrates are a large phylum comprising many different species,

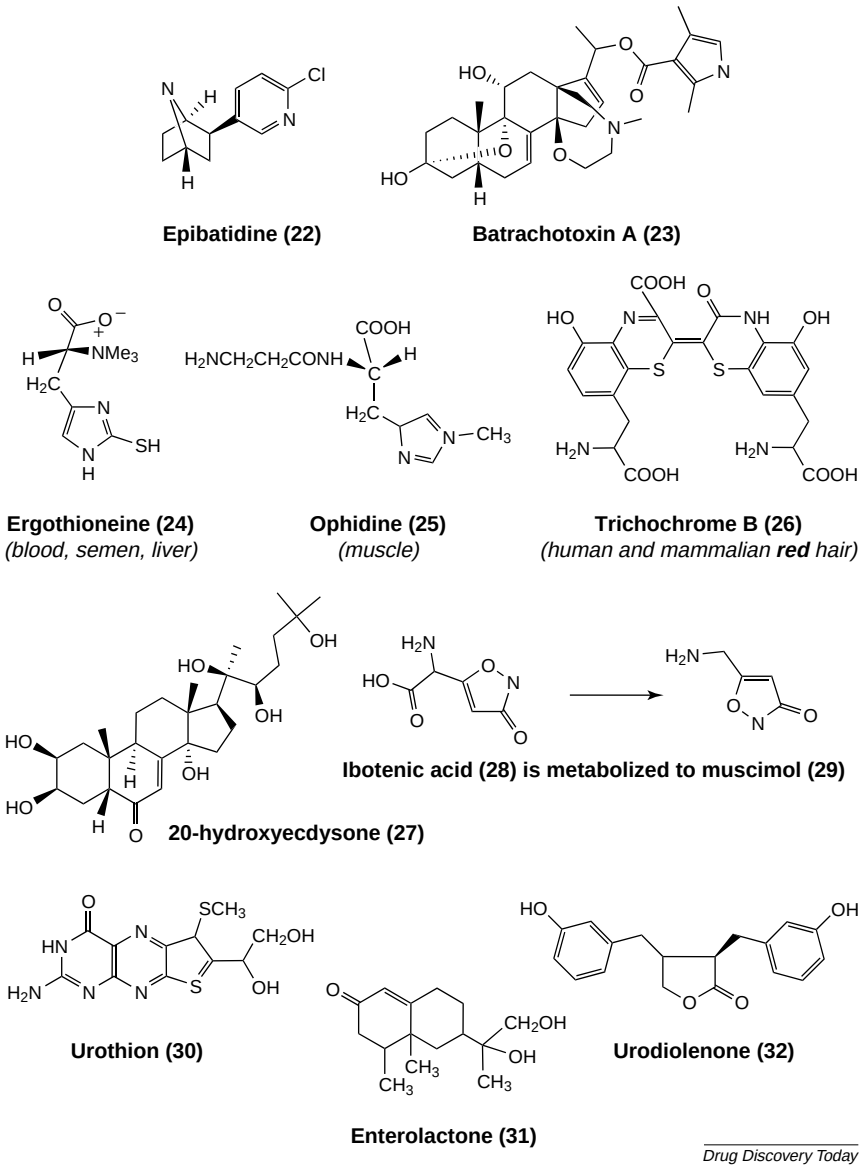

Figure 3. A glimpse of the chemical diversity of compounds isolated from man and other animals. Among these compounds are potential drugs, pharmacological tools and compounds of which little more than their structure is known.

including snails, mollusks, caterpillars and insects. As already pointed out by Harvey [1], insects certainly deserve attention. Larvae are also of interest as exemplified by the !Kung bushmen from the Kalahari desert, who use the pupae of the beetles *Diamphidia nigro-ornata* to obtain a lethal arrow poison. This was shown to contain the lethal polypeptide diamphotoxin [31].

Finally, what can we learn from birds? There are obvious differences compared with mammals, not least in that they have feathers, make nests and lay eggs. Feathers constitute birds' first line of defense against predators; nevertheless, the discovery of batrachotoxin alkaloids **(23)** in bird feathers [32] came as a surprise to the scientific community [33]. Some birds use the contents of their gizzards in the construction of their nests. What kind of compounds do these nests contain? Birds have special glands to treat their feathers and who knows the spectrum of compounds that might be contained within such secretions?

Excreta as sources of natural compounds

Faeces are derived from the physical digestion of food by animals and its subsequent fermentation by intestinal microflora. It is just about the least attractive natural source for screening of compounds for pharmacological activity. Nevertheless, in history there are several examples of the use of faeces for medicinal purposes. Under the name *Graecum album*, dog faeces is listed in old pharmacopoeias as a remedy for various illnesses [34]. In traditional Chinese Medicine, excreta of the silkworm, *Bombyx mori*, are used to treat infectious diseases, headaches and abdominal pain. The excreta were later shown to contain ecdysterones **(27)**, which are known to have analgesic effects in man. A substantial number of different substances have been isolated from human faeces, among them porphyrin derivatives, steroids and unusual fatty acid derivatives [14]. None of these compounds has been investigated for pharmacological activity. With urine, however, the situation is different. The biological activities of some substances from urine are known, and several are used as drugs, for example, chorionic gonadotropin, obtained from the urine of pregnant women, and conjugated oestrogens isolated from the urine of pregnant mares (Table 1). Some 'medicinal' uses are known for urine itself: some fakirs apparently drink their own morning urine, the scientific rationale behind which is speculated to be its high melatonin content [35]. Another fascinating story is the habit of drinking the urine of people who have eaten certain *Amanita* species, for its hallucinogenic properties. The explanation offered by modern science is that these mushrooms contain ibotenic acid **(28)**, which is metabolized

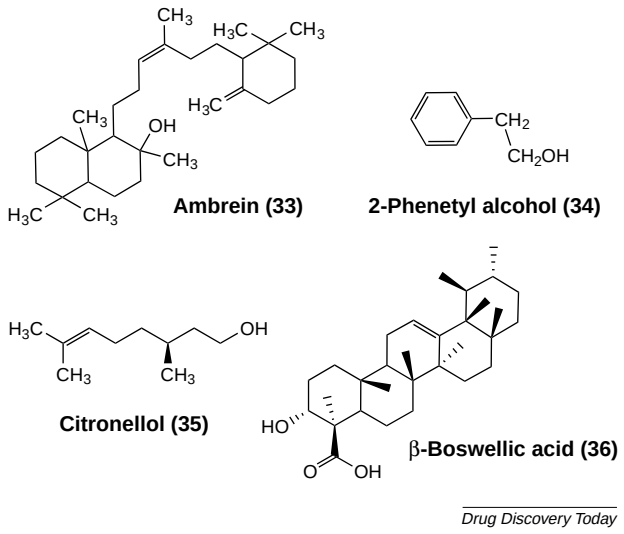

Figure 4. Simple and complex structures isolated from unconventional natural sources: not all interesting natural molecules have a complicated structure.

to the hallucinogenic muscimol **(29)**, which is then excreted in the urine. These examples show that urine can contain biologically active substances in concentrations high enough to become manifest after oral consumption. Thus, even unconcentrated urine would show activity in certain *in vitro* assays. Just as with faeces, human urine contains many compounds for which no pharmacological activity has been determined [14]. Urothion **(30)**, enterolactone **(31)** and urodiolenone **(32)** are some examples. Thus, there is evidence to support the hypothesis that urine of man and other animals is a likely source of biologically active substances. The same holds true for other types of excreta such as saliva, sweat, tears, sperm, frogspawn and ambergris [contains ambrein; Figure 4, **(33)**].

Natural products classified by non-medical use

Despite the serious tone of terms like 'aromatherapy' and 'aromacology', these 'sciences' are frowned upon by the scientific community. Lack of evidence is a justification for this reservation but it also offers a challenge. Odours and flavours elicit immediate reactions, mediated by olfactory receptors. It remains an open question whether or not flavors and fragrances have any therapeutic effect. Since ancient times, such effects have been claimed, for example, for musk, frankincense and myrhh [36]. In recent times, aromatherapy and Bach's flower remedies are becoming increasingly popular 'alternative' therapies. How likely is it that such therapies will ultimately prove to have a scientific basis? The fact that rose oil was shown recently to have a distinct anti-conflict activity by a mechanism other than that of the benzodiazepines [37] indicates that Bach's flower remedies contain at least one serious note! Or even more than one, because a similar effect was later demonstrated for lavender oil but not for many others [38]. The active components from rose oil were isolated and shown to be 2-phenethyl alcohol **(34)** and citronellol **(35)** [39]. Apart from the volatile 'essential oils', there are several other well-defined categories of oils. All natural oils contain countless minor components, often of unknown structure. Hardly explored, commercially available sources of potential lead compounds are, therefore, fatty oils such as castor oil, vegetable oils (e.g. olive oil), fish oils (e.g. herring oil) and fossil oils. Major constituents of natural waxes are not particularly interesting but all contain varying amounts of 'unknowns'. There is a substantial variety of waxes from different origins, ranging from mammalian (e.g. spermaceti from the head of the sperm whale and wool grease, an important source of vitamin D precursor), vegetable (e.g. palm wax), insect (e.g. bees wax) to mineral waxes (consisting of decaying plant and animal tissues). Natural resins contain many different compounds, most of which have never been analyzed, let alone screened. Resins vary enormously: from volatile 'oleoresins' via balsams to solids like the fossil amber and copal. Most resins are of vegetable origin but some are produced by insects, for example, *Kerria lacca*, the source of shellac. A recent patent application describes the use of extracts of resins of *Boswellia* species to treat inflammation and irritation of the oral cavity, an effect attributed to β-boswellic acid **(36)** [40]. Natural gums consist mainly of polymeric sugar molecules but their minor components are of potential interest. Major classes of natural gums are: plant exudates (e.g. tragacanth), plant seed components (e.g. guar), seaweed extracts (e.g. agar) and 'miscellaneous', such as the microbial xanthan. The term 'fibers' embraces raw, unprocessed material either of plant origin (e.g. cotton, flax, jute, hemp, kapok and sisal) or of animal origin (e.g. wool, silk, mohair, cashmere and camel). Bark of trees with an ethnopharmacological or toxicological history has had significant attention. Salicylic acid from the bark of the willow tree *(Salix alba)* is the most famous example. Quinine from the bark of *Cinchona spp.* is another, and ouabaine was isolated from the wood of *Acokanthera ouabaio*, used for the preparation of arrow poisons. These examples are all based on ethnopharmacology. Numerous other types of wood and bark remain to be explored.

Discussion

The intention of this paper is to draw attention to unconventional and hardly explored sources of natural compounds (see Table 1). It is neither a criticism on the traditional

roads followed by NP scientists, nor an attempt to divert attention from paths proven to be successful. Of a large variety of unconventional sources of NPs, several examples of compounds isolated from them are given. This number is limited by the fact that, indeed, the sources are unconventional, and only a few examples exist. Of some of the compounds mentioned, their mechanism-of-action is known. Epibatidine, for instance, is an agonist on nicotinic cholinergic receptors; feruyl quinic acid lactones are opiate receptor antagonists and dicoumarol is a vitamin K antagonist. However, for most of the examples with a distinct biological activity their mechanism-of-action is unknown. Examples of these include thujone, nepetalactone, citronellol and β-boswellic acid. It is possible that these compounds will ultimately be shown to act via known receptors, but there is a distinct possibility that they act on hitherto unknown molecular targets.

It is easier said than done to include the unconventional sources discussed in this paper in screening programs. To start with, all of them are more or less complex mixtures of natural compounds and it will often prove necessary to start with extraction procedures before samples are obtained that can be tested. A complicating factor is that when a reproducible 'hit' is identified, it will be necessary to isolate the active compound and to elucidate its structure. A decade ago this was often used as an argument not to include mixtures of natural origin in screening operations, but the unprecedented analytical possibilities of the 21st century have overcome that objection. Another argument used against natural compounds is that their structures are too complex to enable QSAR or synthesis on a commercial scale. In reality, the structural complexity of natural compounds covers the entire spectrum from very simple to extremely complex. It is possible that a lead with a simple structure is identified, but also that a compound will be identified with a structure of the caliber of Taxol®, which, its structure notwithstanding, became one of the best selling drugs ever. Nevertheless, it is a good and complementary strategy to first concentrate on the sources that are plentiful and easy to re-supply. As discussed previously [4], there is no need to select endangered species in pursuit of lead compounds. Finally, there is the matter of reproducibility. Every natural product scientist is aware of even seasonal variations in the chemical content of, for instance, well-determined individual plant species. Then why do we even think about suggesting compost or faeces as potential sources? It will be hard to find less reproducible ones. Reasons are simple: the sources in question are plentiful and, when a hit is found, there will be enough of the original material to isolate the active compound and to elucidate its structure. Then there is no guarantee that the compound will be found in the next sample but when that is the case, it is at least known that the compound exists and, when it is important enough, it certainly will be retrieved again. Thus, in addition to traditional sources, there are now possibilities to explore less conventional sources of NPs. This is based on the well-proven fact that nature until this day has proven to be superior to the combined efforts of medicinal chemists in terms of synthesizing useful molecules. This article started with a quote from a famous writer, it ends with one, too: '*The reasonable man adapts himself to the world, the unreasonable one persists in trying to adapt the world to himself. Therefore, all progress depends on the unreasonable man*' (Bernard Shaw).

References

1 Harvey, A. (2000) Strategies for discovering drugs from previously unexplored natural products. *Drug Discov. Today* 5, 294–300
2 Newman, D.J. *et al.* (2003) Natural products as sources of new drugs over the period 1981 – 2002. *J. Nat. Prod.* 66, 1022–1037
3 Heinrich, M. and Gibbons, S. (2001) Ethnopharmacology in drug discovery: an analysis of its role and potential contribution. *J. Pharm. Pharmacol.* 53, 425–432
4 Tulp, M. and Bohlin, L. (2002) Functional versus chemical diversity: is biodiversity important for drug discovery? *Trends Pharmacol. Sci.* 23, 225–231
5 Prous, J.R. (1999) A century of progress in drug therapy. *Drugs News Perspect.* 12, 581–621
6 Kerr, R.G. and Kerr, S.S. (1999) Marine natural products as therapeutic agents. *Expert Opin. Ther. Pat.* 9, 1207–1222
7 Mayer, A.M.S. and Lehmann, V.K.B. (2000) Marine pharmacology. *Pharmacologist* 42, 62–69
8 Proksch, P. *et al.* (2002) Drugs from the sea – current status and microbiological implications. *Appl. Microbiol. Biotechnol.* 59, 125–134
9 Jensen, P.R. *et al.* (2003) The true potential of the marine microorganism. *Curr. Drug Discov.* January, 17–19
10 Haefner, B. (2003) Drugs from the deep: marine natural products as drug candidates. *Drug Discov. Today* 8, 536–544
11 Wynne, K.N. *et al.* (1987) Isolation of opiate receptor ligands in coffee. *Clin. Exp. Pharmacol. Physiol.* 14, 785–790
12 Jankum, H. *et al.* (1997) Why drinking green tea could prevent cancer. *Nature* 387, 561
13 Di Tomaso, E. *et al.* (1996) Brain cannabinoids in chocolate. *Nature* 382, 677–678
14 Dictionary of Natural Products (2001) http://www.chemnetbase.com, Chapmann & Hall/CRC Press
15 Kress, M. and Zeilhofer, H.U. (1999) Capsaicin, protons and heat: new excitement about nociceptors. *Trends Pharmacol. Sci.* 20, 112–118
16 Plouzek, C.A. *et al.* (1999) Inhibition of P-glycoprotein activity and reversal of multidrug resistance *in vitro* by rosemary extract. *Eur. J. Cancer* 35, 1541–1545
17 Nicholi, V. and Howell, A.B., Rutgers University (1999) Plant proanthocyanidin extract effective at inhibiting adherence of bacteria with P-type fimbriae to surfaces. Patent Cooperation Treaty (PCT) publication number WO 99/12541
18 Haering, L. and Steinhauser, T. (2000) Wound dressing containing dilute solution of grapefruit flesh or seed extract as active ingredient having e.g. bactericidal, anti-inflammatory and healing promoting action. DE 19929298
19 Chen, K.Y. *et al.*, Rutgers University (2001) Extract of orange peel for prevention and treatment of cancer. Patent Cooperation Treaty (PCT) publication number WO 01/21137

20 Zheng Tao (1999) Auxiliary method for curing tumor, its preparation method and application. CN1237423
21 Kapadia, G. (2000) Inhibitory effect of synthetic and natural colorants on carcinogenesis III. 6,080,411
22 Taylor, E.J. and Evans, F.J., University of London Pharmacy (2000) Chalcone plant extracts for use in therapy. European patent application number EP/0998939
23 Silverman, R.B. (1981) Models studies for a molecular mechanism of action of oral anticoagulants. *J. Am. Chem. Soc.* 103, 3910–3915
24 Robles, M. *et al.* (1995) Recent studies on the zoopharmacognosy, pharmacology and neurotoxicology of sesquiterpene lactones. *Planta Med.* 61, 199–203
25 Osterhoudt, K.C. *et al.* (1997) Catnip and the alteration of human consciousness. *Vet. Hum. Toxicol.* 39, 373–375
26 Aydin, S. *et al.* (1998) Nepetalactone: a new opioid analgesic from Nepeta caesarea Boiss. *J. Pharm. Pharmacol.* 50, 813–817
27 Perry, E.K. *et al.* (1999) Medicinal plants and Alzheimer's disease: from ethnobotany to phytotherapy. *J. Pharm. Pharmacol.* 51, 527–534
28 Sneader, W. (1989) Medicines derived from animals. *Drug News & Perspect.* 2, 434–436
29 Rayl, A.J.S. (1999) Oceans: medicine chests of the future? *Scientist* 13, 1
30 Habermehl, G.G. (1981) *Venomous Animals and their Toxins*, Springer Verlag
31 De la Harpe, J. *et al.* (1983) Diamphotoxin. The arrow poison of the !Kung bushmen. *J. Biol. Chem.* 258, 11924–11931
32 Dumbacher, J.P. *et al.* (2000) Batrachotoxin alkaloids from passerine birds: a second toxic bird genus (*Ifrita kowaldi*) from New Guinea. *Proc. Natl. Acad. Sci. U. S. A.* 97, 12970–12975
33 Weldon, P.J. (2000) Avian chemical defense: toxic birds not of a feather. *Proc. Natl. Acad. Sci. U. S. A.* 97, 12948–12949
34 Lewin, R. (1999) *Merde*, Aurum Press
35 Mills, M.H. and Faunce, T.A. (1991) Melatonin supplementation from early morning auto-urine drinking. *Med. Hypotheses* 36, 195–199
36 Michie, C. (1989) Pharmaceutical magic from the Magi. *New Sci.* 23/30, 26–28
37 Umezu, T. (1999) Anticonflict effects of plant-derived essential oils. *Pharmacol. Biochem. Behav.* 64, 35–40
38 Umezu, T. (2000) Behavioural effects of plant-derived essential oils in the Geller type conflict test in mice. *Jpn. J. Pharmacol.* 83, 150–153
39 Umezu, T. *et al.* (2002) Anticonflict effects of rose oil and identification of its active constituents. *Life Sci.* 72, 91–102
40 Watkins, S.D., Quest International (2000) Compositions containing boswellia extracts. Patent Cooperation Treaty (PCT) publication number WO 00/62751