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Rediscovery of known natural compounds: Nuisance or goldmine?

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Abstract—Do all natural compounds have a distinct biological activity, or are most of them merely biosynthetic debris? Many natural compounds have important biological functions, and certainly many more of the ample 200,000 currently known will ultimately prove to be more than just 'secondary metabolites'. The question is how to select the most promising candidates for potential new drugs. 'Rediscovery' of known natural compounds is regarded as a nuisance or disappointment by scientists involved with the identification of novel compounds. The other side of the coin, however, is that the discovery that a particular compound occurs in unrelated species can be a valuable clue toward the identification of a novel receptor or enzyme. Here, we put forward the hypothesis that when a natural compound occurs in unrelated species, it must have an important biological function by interacting with a specific molecular target. This is because it is extremely improbable that in nature one particular compound is synthesized in totally unrelated species for no reason at all. For many compounds occurring in unrelated species, it is already known that they act on specific molecular targets. For others, it is just known that they occur in different species. In some cases, biological activities are known but not the underlying mechanisms of action. It is from this category of compounds that important discoveries are likely to be made. Some (around 70) of them were identified. They represent important clues from nature offering an alternative approach to the classical screening of large numbers of compounds.

1. Introduction

It is a rule rather than exception that natural compounds occur in more than one species, but in most cases, those species are related.[1] The protagonists of this article are compounds occurring in unrelated species, for example, animals and plants, and not those that 'just' occur in unrelated plant species.

There are many examples of compounds naturally occurring in unrelated species which have very important mechanisms of action. Evidently, virtually all neurotransmitters, such as acetylcholine, dopamine, serotonin, γ-aminobutyric acid, adrenaline, histamine, etc., are present in the human body and—apart from other mammalian species—also in a variety of plant species. The same is true for a number of peptide and steroid hormones. Bombesin, for instance, was originally isolated from toads of the genus *Bombina*, and later shown to occur in humans and other animals as well; the androgen testosterone also occurs in the pollen of the Scots pine, *Pinus sylvestris*; estrone and estradiol not only occur in mammals but also in some plants, notably apple, date, and apricot; cholesterol is also found in the date palm (*Phoenix dactylifera*) and in marine red algae. All essential amino acids occur in mammals as well as in different plant species, and the same holds true for essential purines like adenine, cytosine, guaninine, thymine, and uracil; for essential sugars like D-glucose, D-fructose, D-galactose, and glucuronic acid; for amino sugars; for many essential fatty acids, including the hydroxylated furanoid and tetrahydrofuran fatty acids; and for coenzymes (ubiquinones). Prostaglandins are found in mammalian and human tissue, and some are detected also in coral and insects. More examples can be found among the vitamins: ascorbic acid occurs in a wide variety of different species, and so do most of the A and B vitamins.

Apart from the compounds mentioned above, all of vital importance for human, there are a number of compounds which are now registered drugs. L-DOPA,

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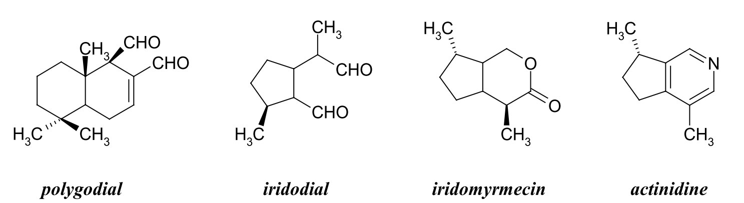
for instance, occurs in plants as well as in fungi; emodine occurs in plants, fungi, and lichen species; 4-hydroxy-coumarin not only occurs in many plant species but also in *Penicillium* spp.; paclitaxel was not only isolated from certain plant species but also from a fungus (*Seimatoantlerium tepuiense*). Finally, there are several important pharmacological tools. Examples of the latter are tetrodotoxin, one of the most toxic substances known, isolated from an astonishing array of different species,[2] and bathrachotoxin, first discovered in the skin of poison arrow frogs and surprisingly also in birds.[3] The fact that such pharmacological tools may develop into drugs is exemplified by deoxynojirimycin, a polyhydroxy alkaloid isolated from the mulberry tree (*Morus*) and *Streptomyces* spp., shown to be a potent glycosidase inhibitor. Derivatives of this compound are on the market as oral antidiabetic drugs (Miglitol®, Emiglitate®).

The examples given above support the statement that many compounds isolated from unrelated species have important biological activities. For all of them, their mechanism of action is known. Protagonists of this article are compounds identified in unrelated species of which no mechanism of action is known. The compounds discussed below were identified as being isolated from more than one species by studying literature sources.[1,4,5] It is possible that some of the examples actually are not synthesized in all species, but are sequestered through the food chain.[6] This phenomenon is, for instance, known to occur in insects that store certain plant chemicals. But this must be for a reason.

2. Insect antifeedants attractive to cats

The sesquiterpenoid polygodial is responsible for the hot peppery taste of the water pepper, *Polygonium hydropiper*. It occurs in many different species of plants, ferns, and liverworts, and surprisingly also in marine nudibranch snails (*Ophistobranchia*). The compound is known to be an insect antifeedant, it has antimicrobial activity, inhibits plant growth, and is cytotoxic and poisonous to fish. In mammals, it has an antinociceptive activity and protective effects on gastric mucosal lesions. Its' mechanism of action has not been elucidated.[10,11] Another dialdehyde is iridodial, a simple iridoid first isolated from the Australian ant *Iridomyrmex detectus* and the hunting beetle *Staphylinus olens*, and later from a tree (*Myoporum*) as well. This compound is an insect repellant and additionally has antifungal activity. In equilibrium with its dialdehyde-lactol form, it is easily oxidized to nepetalactone, a compound that potently attracts cats and other Felidae such as lions and jaguars. The latter property is shared by another iridoid: iridomyrmecin, isolated from *Actinidia polygama* and related plant species, as well as from ants (*I. humilis*). This compound also is an antibiotic and insect antifeedant. In addition, the monoterpene alkaloid actinidine is known to be strongly attractant to cats. With iridodial, it shares a potent antifungal activity. It occurs in many plant species and furthermore in the defensive secretions of black beetles, ants, grasshoppers, and flies. In none of these compounds is the mechanism of action is known.



This article is not meant to be an exhaustive survey, but only to serve as a trigger to investigate these and similar compounds in more detail, because we are convinced that when a natural compound occurs in unrelated species it must have an important biological function by interacting with a specific molecular target. In this article, about 70 compounds occurring in at least two unrelated species, and their names, structures, and natural sources are given. They are grouped together, primarily based on structural resemblance, thereby not suggesting that these compounds necessarily share biological targets.

A short version of this article was published as a letter earlier this year,[7] as a continuation of two earlier publications with emphasis on natural products and drug discovery.[8,9]

3. Acids with more than a sour taste

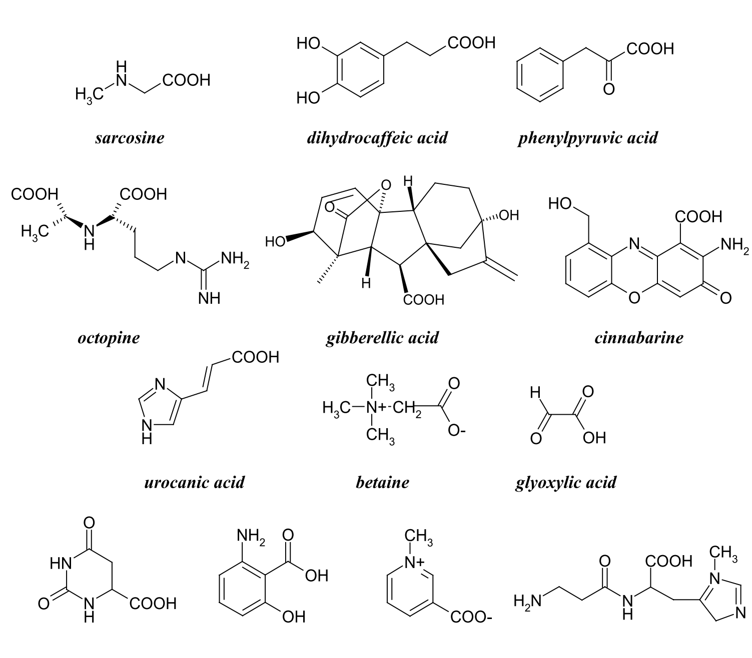
A number of acids, with structures ranging from very simple to very complicated, occur in unrelated species. Sarcosine is a very simple one, found in sea stars, sea urchins, red algae, crabs and lobsters. Dihydrocaffeic acid was isolated from *Lycopodium clavatum*, and also occurs in many higher plants. It has a blood pressure lowering effect in animals. Phenylpyruvic acid occurs in plants and microorganisms and in the urine of patients suffering from phenylketonuria. Octopine is present in the muscles of mollusks (scallops) and octopodes (*Eledone moschate*) and also in the root neck galls of dicotyledonous plants, probably following bacterial infections. Gibberellic acid, the best studied plant hormone, was likewise shown to be present in fungi, algae, and bacteria. Cinnabarine occurs in the ubiquitous cinnabar polypore and in human red hair. Apart from having a red color, the compound also is an antibiotic and antiviral.[12] Betaine was originally isolated from *Atriplex spongiosa*, and later found in many other plant species, especially in Compositae and Gramineae. It also occurs in mammalian brain, muscle, and blood. The compound may play a role in the therapy of alcoholic liver disease.[13] Glyoxylic acid is present in many mammalian tissues and also in several plant species, particularly in unripe grapes, apples, and pears. Urocanic acid occurs in the human epidermis and in many *Bacillus* spp. It has antitumor activity and is used as sun-blocking agent. Orotic acid occurs in cow milk, but not in human milk, and in different fungi and plants. The compound has bacteriostatic and cytostatic properties. The radical scavenger 3-hydroxy anthranillic acid was isolated from humans, rats, fungi (*Claviceps purpurea*), plants (*Brassica* spp.), and bacteria. Trigonelline has been detected in a variety of mammalian tissues and in many plants, for instance, in the seeds of fenugreek and alfalfa, in coffee beans, and seeds of *Cannabis sativa*. The compound was found to be hypoglycemic in animal models.[14] As the name says, anserine was first detected in geese muscle, and later also in human muscle, other birds, and even crocodiles. Nothing is known about the biological function. Finally, two very long chain saturated fatty acids were detected in several species: cerotic acid ($H_3C–(CH_2)_{24}–COOH$) is found in bee and other insect waxes, carnauba and other palm leaf and grass waxes, and *Mycobacterium tuberculosis*, whereas melissic acid ($H_3C–(CH_2)_{28}–COOH$) was detected in plant waxes, bee wax, and wool.

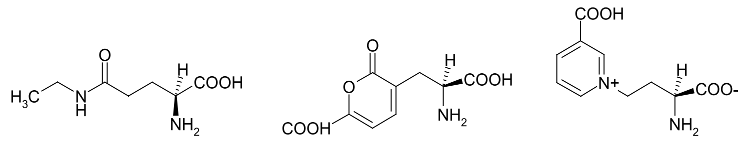
4. Nonproteinogenic amino acids

A small group of nonproteinogenic amino acids occurs in unrelated nonmammalian species. Of these, theanine is the best known. This compound occurs in high concentrations in tea as well as in certain fungi. It has neuroprotective properties,[15] and was the subject of a substantial number of studies. Yet its mechanism of action remains to be elucidated. Stizolobic acid, occurring in plants and toadstools, possibly interacts with excitatory amino acid receptors,[16] but its precise mechanism of action is unknown. Nicotianine was first isolated from tobacco leaves and also from the edible fungus *Lentinus edodes* (Shii-take). Saccharopin occurs in plants, yeast, and fungi. Baikiain was isolated from Rhodesian teakwood (*Baikiaea plurijuga*), other plants, and red algae. Hernycin is isolated from the rubber tree, fungi (*Boletus edulis*), fly agaric (*Amanita muscaria*), and the king crab (*Limulus polyphemus*). The latter compound is closely related to ergothioneine, a nonprotogenic amino acid occurring in human blood, semen, liver, and kidney, a fungus (*Claviceps purpurea*), and the king crab. This compound has antiapoptotic activity and could become of therapeutic value in Alzheimer's disease.[17] Cystathionine occurs in many plant species and human urine.

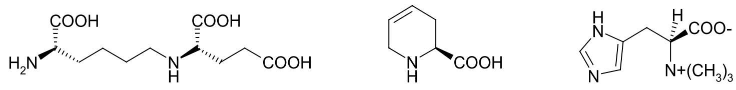
5. Quinones from unrelated species

In the plant kingdom, large numbers of quinones occur. A number of them can be found in unrelated species. Well known is hypericin, occurring in St. John's wort and other *Hypericum* spp., as well as in mealy bugs (*Nipaecocus aurilanatus*). The compound is assumed to be at least partly responsible for the antidepressant activity of St. John's wort. Physcion is an anthraquinone occurring in plants and fungi. Islandicin, originally isolated from *Penicillium islandicum*, was later also found in several plant species and lichens. The same applies to the anthrone chrysarobin, a compound known to be a tumor promotor. The naphthoquinone phthiocol

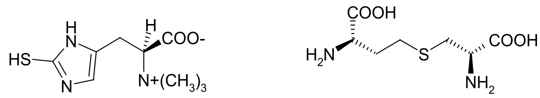




theanine *stizolobic acid* *nicotianine*



saccharopin *baikiain* *hernycin*

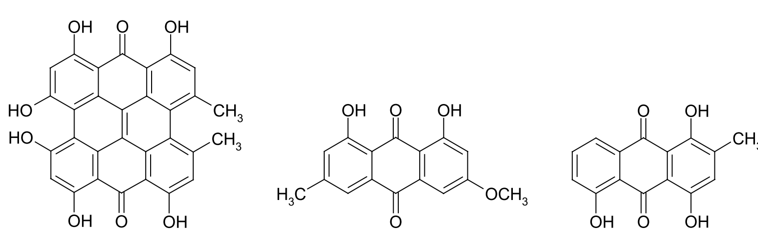


ergothioneine *cystathionine*

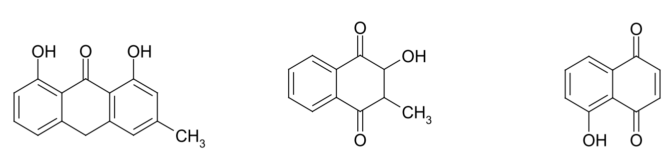
occurs in plants and bacteria (*M. tuberculosis*), whereas juglone is not restricted to the black walnut (*Juglans regia*), and also found in several *Penicillium* spp. as well. This reactive oxygen-generating compound is phytotoxic. Of most of the quinones mentioned above, some biological activities are known: antimicrobial, antifungal, and antiviral. But what they also have in common is that for none the mechanism of action is known. The same applies to canthin-6-one; this compound occurs in plants (Rutaceae and Simaroubaceae spp.) and a fungus (*Boletus curtisii*). It has strong antimicrobial activity, especially against *Staphylococcus aureus*. Mellein was first isolated from fungi (*Aspergillus* spp.), and later shown to occur in the wax moth, ants, and termites. In the latter two it is part of their defense secretions. In the ant *Lasius fuliginosus* mellein is the trail pheromone; mimosamycin occurs in sponges and *Streptomycetes* spp., and is an antibiotic.

6. Trace amines: More than metabolic by-products?

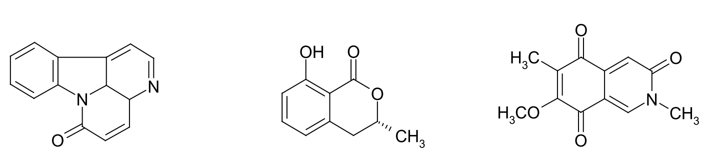
Phenethylamine occurs in human brain and many plant species, such as in oil of almonds, many types of fruit (e.g., prunes and bananas), and algae (Rhodophyceae). Tryptamine is present in mammalian tissues, higher plants, and fungi. Tyramine and octopamine occur in mammals, insects, and numerous plant species. The presence of these so-called trace amines in the mammalian central nervous system has been known for decades. Despite much initial interest, these compounds have largely been thought of as little more than metabolic by-products. The recent description of a family of mammalian trace amine receptors, however, has seen a resurgence of interest in the physiological role of this class of compounds.[18] Skatole occurs in human feces and is responsible for its characteristic odor. With a detection threshold of 7.2×10^{-13} Mol/l it is one of



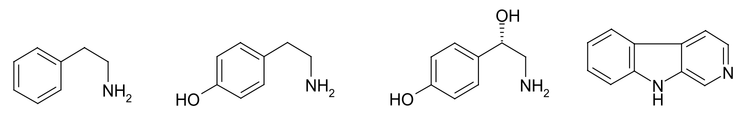
hypericin *physcion* *islandicin*



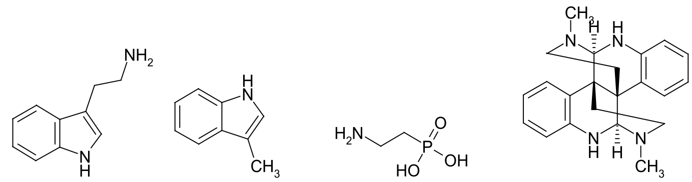
chrysarobin *phthiocol* *juglone*



canthin-6-one *mellein* *mimosamycin*



phenethylamine ***tyramine*** ***octopamine*** ***β-carboline***



tryptamine ***skatole*** ***ciliatine*** ***calycanthine***

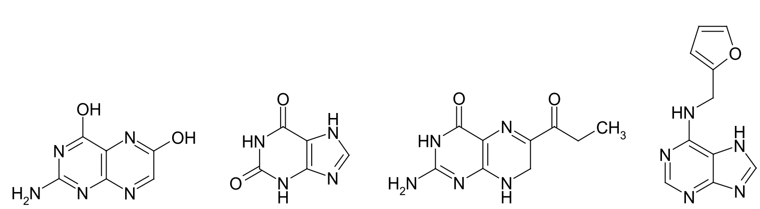
the most powerful stinking chemicals.[19] The compound also occurs in civet cat excretions, in the blood of boars (but not in humans), in beetroot, and in several other plant species. For different insects, it functions as oviposition pheromone. Ciliatine was isolated from sources as diverse as bovine brain, sea anemones, protozoa, and mycobacteria, β-carboline from several plant species (a.o. *Cataranthus roseus*) and microorganisms (*Streptomyces*), and calycanthine from several plant species, particularly in the seeds of *Calycanthus* spp., and the South American arrow poison frog *Phyllobates terribilis*.

7. Pteridins and xanthines: Just colorants, or . . .?

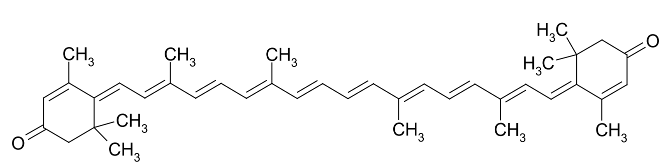
Xanthopterin is the yellow pigment in butterfly wings, wasps, and other insects as well as in mammalian urine. Xanthine occurs in human muscle and liver and also in many plants and mushrooms. Isosepiaptenin is the eye pigment of the fruit fly *Drosophila melanogaster* and additionally occurs in cyanobacteria (*Anaceptis nidulans*). Kinetin is a plant cytokine occurs in yeast. It is a plant growth regulator and induces callus formation in plant cell cultures. But it is not inert in humans and this was recently discovered: the compound could be of therapeutic value in diseases caused by defective splicing of pre-mRNA.[20] Rodoxanthin occurs in plants (*Taxus baccaa*), fungi, bacteria, and feathers of different birds, for instance, the Australian dove (*Megaloprepia magnifica*). Rubixanthin occurs in plants (sunflower) and microorganisms. Zeaxanthin is found in very diverse species: corn, eggs, fish, crustaceans, birds, fungi, bacteria, and algae.

8. In favor of flavor: Aldehydes

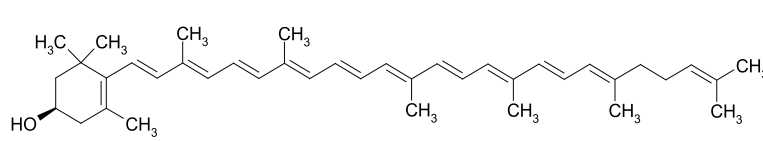
Several aldehydes are found in unrelated species. 2,6-Nonadienal, the compound responsible for the



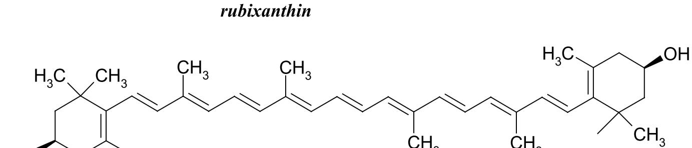
xanthopterin ***xanthine*** ***Isosepiaptenin*** ***kinetin***



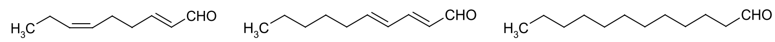
rhodoxanthin



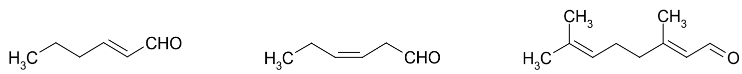
rubixanthin



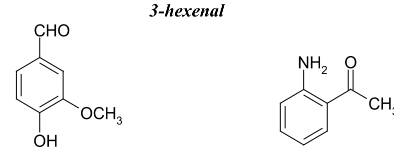
zeaxanthin



2,6-nonadienal *2,4- decadienal* *2-dodecanal*



2-hexenal *3-hexenal* *citral*



vanillin *2-aminoacetophenone*

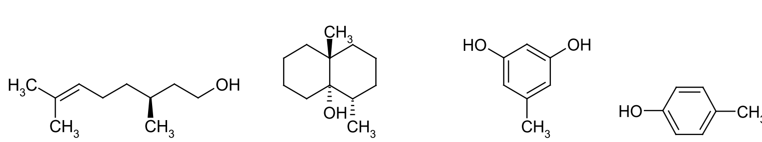
characteristic odor of cucumber, additionally occurs in other types of fruit such as melon and mango, and it is also found in mammals and fish. The same is true for 2,4-decadienal. This aldehyde was isolated from mammals and fish, and it is also known to be the major contributor to the flavor of citrus oils. 2-Dodecanal is present in human milk, coriander, and peanuts. 2-Hexenal and 3-hexenal occur in the essential oils of many plants and are main constituents of the characteristic flavor of apple juice. Besides that the compounds are alarm pheromones of certain insects. Citral is the main constituent of lemon grass oil, and it occurs also in the essential oils of many other plants. The compound was also detected in mites. It has antiseptic activity but likewise known to be a fragrance allergen and irritant.[21] Vanillin with its famous odor and flavor occurs in *Vanilla planifolia*, and in many other plants as well; the bug *Eurygaster integriceps* uses it as insect attractant. Vanillin is a flavoring agent and has antifungal, antimutagen, and anticarginogen activities. Knowledge about the mechanisms behind these properties is increasing.[22] 2-Amino-acetophenone is the impact compound in grape flavor, and it also occurs in human milk. The compound is a pheromone produced by virgin honeybee queens and released with feces. In small social groups, the pheromone repels and is used to terminate agonistic interactions between queens and workers.[23]

9. Nonintoxicating alcohols

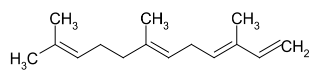
β-Citronellol is abundant in the essential oils of many plants, for instance, in *Java citronella* oil and rose oil. From the latter source, it was isolated as the active principle having an anticonflict activity by a mechanism other than that of benzodiazepines.[24] The compound also occurs in glandular secretions of alligators. Geosmine is responsible for the characteristic odor of freshly plowed soil. It was first isolated from different *Streptomyces* spp. and later also from myxobacteria and beet juice and roots. Orcinol occurs in plants, lichen (*Evernia prunastri)*, oak moss, and fungi (*Aspergillus fumigatus*). *p*-Cresol is present in human urine, the leaves of murus species and many other plants. It is antiseptic and has paraciticide activity as well.

10. On the right trail: Alkanes and alkenes

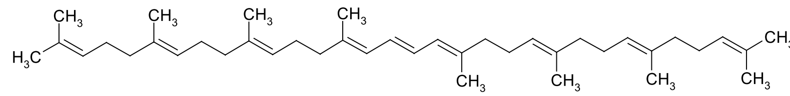
α-Farnesene is attractant to larvae of the apple moth and it is the alarm pheromone of certain aphid species and it occurs in ants, moths, and in the essential oils of many plants. Pristane is present in shark liver, fish oil, ambergris, plankton, and anise fruits. The compound induces arthritis in laboratory animals. Phytoene occurs in plants and bacteria. Neurosporene in plants (pineapple) and microorganisms. Germacrene B was first isolated from the essential oil of *Citrus junus*, and later from several other plants. It is also present in the volatile secretions of certain insects and in the larvae of the butterfly *Papilio protenor*. It has antibacterial activity. Neocembrene is the trail pheromone of the termite *Nasutitermis exitiosus* and also present in essential oils of *Pinus spp*. and the cloacla gland of Chinese alligator (*Alligator sinensis*); it attracts females of that species. Squalene is found in human body fat, fish, olive oil, and yeast. It has antibacterial, antitumor and immunosuppressant activity. Recently, it was found to be cardioprotective.[25] Lycopene occurs in plants (tomatoes), many fruits and berries, bacteria, and in human blood and liver. The 'elephant pheromone' is excreted by the female of the Asian elephant, to indicate her readiness to mate. Likewise, it is also the sex pheromone of well



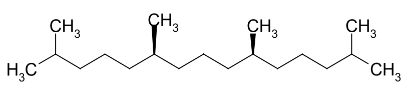
β-citronellol *geosmine* *orcinol* *p-cresol*



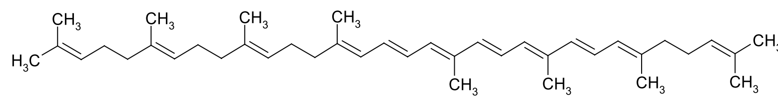
α-farnesene



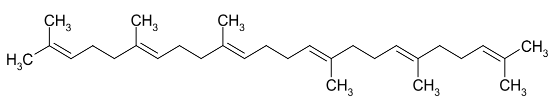
phytoene



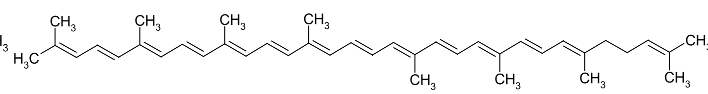
pristane



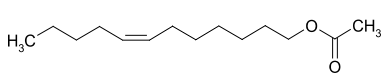
neurosporene



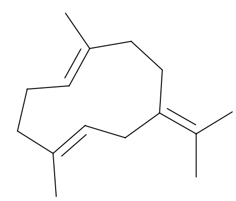
squalene



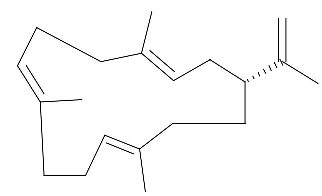
lycopene



elephant pheromone



germacrene B



neocembrene

over 100 different insect species. It is intriguing to observe that organisms as diverse as elephants and butterflies are affected by pheromones with identical or similar structures.[26]

11. Concluding remarks

The examples summarized in Table 1 offer an alternative to the classical screening of large numbers of compounds. Where nowadays it is easy to screen 100,000 or more compounds on a novel target, it is easier said than done with natural compounds. By far most of them are simply not generally available. Therefore, selections will have to be made. The hypothesis put forward in this article: 'when a natural compound occurs in unrelated species, it must have an important biological function by interacting with a specific molecular target', offers an alternative which is very likely to produce results.

The compounds discussed are all likely to act via specific molecular mechanisms, mechanisms that 'just' need to be elucidated. In some cases, those may turn out to be already known. The result is a new pharmacological tool, and possibly also a lead toward a drug candidate. It is also likely that hitherto unknown mechanisms will be discovered. Because from the start, it is already known that if such a mechanism plays an important role in nature in more than one unrelated species, such a discovery could easily turn out to be a breakthrough, especially because the first lead already is at hand. And sure enough, there is also the possibility that certain compounds present in unrelated nonmammalian species will prove to have no activity at all in mammals. Those are of no interest in drug discovery, but may attract interest in other branches of science.

Some of the compounds discussed here most certainly are potential new pharmacological tools, and perhaps even leads for novel drugs. But this list was not meant to be exhaustive. Very likely further investigations of the literature will reveal more compounds. And certainly, many research groups around the world are continuously investigating diverse natural sources for new compounds. Invariably, at times they will 'rediscover' known compounds. When those are compounds of which the mechanism of action is known, such discoveries are a nuisance or disappointment. The discovery of a known compound with an unknown mechanism of action is always of scientific interest. However, the discovery of such a compound in a species unrelated to that from which the compound was first isolated, could be a veritable goldmine.

Table 1. Compounds occurring in unrelated species

Compound	Species					Biological activity
	Man	Animal	Insects	Plants	Micro	
Polygodial		X		X		Antinociceptive
Iridodial			X	X		Antifungal
Iridomyrmecin			X	X		Antibiotic
Actinidine			X	X		Antifungal
Sarcosine		X		X		?
Dihydrocaffeic acid				X	X	Hypotensive
Phenylpyruvic acid	X	X		X	X	?
Octopine		X		X		?
Gibberellic acid				X	X	?
Cinnabarine	X	X			X	Antibiotic
Betaine	X	X		X		?
Glyoxylic acid	X	X		X		?
Urocanic acid	X	X			X	Antitumor
Orotic acid		X		X	X	Cytostatic
3-OH anthranillic acid	X	X		X	X	?
Trigonelline		X		X		Hypoglycaemic
Anserine	X	X				?
Cerotic acid			X	X	X	?
Melissic acid		X	X	X		?
Theanine				X	X	Neuroprotective
Stizolobic acid				X	X	?
Nicotianine				X	X	?
Saccharopin				X	X	?
Baikiain				X	X	?
Hernycin		X		X	X	?
Ergothioneine	X	X			X	Anti-apoptotic
Cystathionine	X	X		X		?
Hypericin			X	X		Antidepressant
Physcion				X	X	Antimicrobial
Islandicin				X	X	Antimicrobial
Chrysarobin				X	X	Antifungal
Phthiocol				X	X	Antifungal
Juglone				X	X	?
Canthin-6-one				X	X	Antimicrobial
Mellein			X		X	?
Mimosamycin		X			X	Antibiotic
Phenethylamine	X	X		X		?
Tryptamine	X	X		X	X	?
Tyramine	X	X	X	X		?
Octopamine		X	X	X		?
Skatole		X		X		?
Ciliatine		X	X	X	X	?
β-Carboline				X	X	?
Calycanthine		X		X		?
Xanthopterin		X	X			?
Xanthine	X	X		X	X	?
Isosepiaptenin			X		X	?
Kinetin				X	X	Antitumor
Rodoxanthin		X		X	X	?
Rubixanthin				X	X	?
Zeaxanthin		X		X	X	?
2,6-Nonadienal		X		X		?
2,4-Decadienal		X		X		?
2-Dodecanal	X	X		X		?
2-Hexenal			X	X		?
3-Hexenal			X	X		?
Citral			X	X		?
Vanillin			X	X		Antifungal
2-Amino-acetophenone	X	X	X	X		?
β-Citronellol		X		X		Anti-conflict
Geosmine				X	X	?
Orcinol				X	X	?
p-Cresol	X	X		X		Antiseptic
α-Farnesene			X	X		?
Pristane		X		X		?

(*continued on next page*)

Table 1 (*continued*)

Compound	Species					Biological activity
	Man	Animal	Insects	Plants	Micro	
Phytoene				X	X	?
Neurosporene				X	X	?
Germacrene B			X	X		Antibacterial
Neocembrene		X	X	X		?
Squalene	X	X		X	X	Cardioprotective
Lycopene	X	X		X	X	?
Elephant pheromone		X	X			?

Compounds of which no mechanism of action is known.

All of the compounds listed in the table are described in at least one of the literature sources given in the introduction.[1,4,5] All of the compounds listed as occurring in human also occur in other mammals, but the reverse is not (known to be) true.

'Micro' embraces bacteria, fungi, and viruses.

'Biological activity' is known for some compounds, but for none a mechanism of action (receptor or enzyme) is known.

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