Investigating New Essential Oils: Rationale, Results and Limitations

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Research in new essential oils may provide benefits (missing aroma notes, new sources of isolates, new chiral compounds), but it must reassert its originality and vigor and it must recognize the constraints of economics and regulations.

Rationale for Searching for New Essential Oils

Why is research carried out on essential oils? In the perfume and flavor industry, one might search for a new essential oil for one or more of the following reasons:

- To find new fragrant or aromatic raw materials able to be used as such for their organoleptic properties.
- To find new sources of isolates to be used as such or to serve as intermediates in the production of other substances.
- To identify new fragrant substances in order to carry out their synthesis, or to prepare structural analogues provided with similar properties.
- To find new essential oils or isolates with other properties.

Some examples will help us understand these principles.

Find New Fragrant or Aromatic Raw Materials Able To Be Used as Such

In the case of perfumery applications, there are numerous essential oils (as well as solvent extracts such as absolutes and resinoids) that already effectively provide the base notes. These notes (with examples of their occurrence) include floral (rose, geranium, neroli), woody (cedar, sandalwood, cypress), herbaceous (lavender), green (galbanum), spicy (clove, pepper), fruity (citrus, davana) and balsamic.

In addition, these natural products already suffer from overwhelming competition due to numerous synthetic products. The synthetic products typically compete well in performance and stability in the most diverse applications, as well as in cost.

The only perfumery notes that are not presently available from clearly defined plant sources in the world of essential oils are these:

- The amber note, although certain products derived from labdanum or from cypress can make a contribution.
- The musky note. Even if one considers that the ambrette essential oil provides a floral-fruity and musky odor, the intensity of the musky character (macrocyclic type) is too weak to meet the demands of modern perfumery. At the very most, the ambrette essential oil can find limited application in natural blackberry flavors. However, the weak musky character barely manages to justify the high cost of this raw material.

Taking into account the knowledge acquired in the area of structure-odor relationships, it is very unlikely that any essential oil contains a significant proportion of compounds possessing musky or amber odors. It is well established that, with few exceptions, molecules of this type generally contain 14 or more carbon atoms, which are rare in the plant kingdom. Also, if a plant raw material is found to contain a substance of this kind, it would be preferable to prepare an extract rather than an essential oil, since steam distillation is less apt to recover such substances. With respect to the possible screening of plant families based on biogenetic and chemotaxonomic considerations, it is interesting to note that the plant world has not provided significant sources of amber and musky odors. These odors both originate from the animal world.

The increased use of green and fresh notes in the formulations of actual perfumes is a trend that can boost the interest in essential oils possessing original nuances of this kind. Unfortunately, the raw materials available with this note are very limited.

In the area of food flavorings, essential oils have already

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found wide application. Mint and various citrus fruits (e.g., orange, lemon, grapefruit and mandarin) represent the largest volume of essential oils produced. The citrus oils are used largely in soft drink applications. In this field, there will, nevertheless, continue to be considerable interest in the development of new citrus essences stemming from novel hybrids, or obtained by physical processes which present a more faithful aromatic resemblance to the fruit. Although 120 essential oils are registered in the United States on the FEMA/GRAS list, there still exists a need for new essential oils that will complete the range of desired aromatic notes. This is the case, for example, for the green notes essential to the formulation of various vegetable flavors, as well as tropical fruit, and red and yellow fruit notes.

New essential oils possessing a sulfur note will certainly be welcomed, for the bucchu essential oil is practically the only one with this character.[a] A sulfur note is desirable in tropical fruit flavors such as passion fruit. For the formulation of raspberry flavors, the characteristic note of ionone can be provided by the essential oil of iris rhizomes. However, its high price is a severe limitation. For this reason, the systematic research on all new essential oils containing significant quantities of ionone isomers is largely justified. One can also apply this statement to damascenone and the damascones. One must be aware that these carotenoid derivatives are formed from different biogenetic schemes than those of the terpenoids or phenylpropanoids that occur commonly in essential oils. Other specific biosynthetic processes prevail for the generation of lactones of linear unsubstituted 4- or 5-hydroxy acids, indispensable to the formulation of yellow fruit flavors, among others. The only commercial essential oil that actually contains a large proportion of such lactones is massoia. This leaves a strong incentive to implement systematic searches leading to the discovery of additional or alternate natural sources. Recall that an additional interest in the massoia essential oil is the conversion of its lactones to the corresponding naturally saturated δ-lactones by bioreduction.

Find New Sources of Isolates

For a long time, scientists have attempted to isolate individual components from essential oils. Substances such as anethole, cineole, menthol, eugenol and safrole are already very elaborate molecules that nature puts at our disposal. They would be difficult and sometimes impossible to duplicate economically. Many of these compounds serve as building blocks for other needed components. For example, the pinenes and limonene enantiomers are substances whose interest vs. cost ratio is amazing. In fact, there is more interest in these two common flavor compounds than there is in the majority of basic raw materials derived from petrochemistry. A considerable amount of work over the last 100 years has been performed by chemists to add value to essential oil components. While this aspect of organic chemistry is often overlooked in chemical education, it is a fact that these works are now considered classics and are part of textbooks. It is, therefore, preferable not to discuss these well-known chemical transformations but rather to draw attention to the less evident uses of essential oil isolates.

Tremendous progress has been made in the last few years in understanding natural product enantiomers, in particular the relationship between enantiomeric purity and biological properties. This knowledge has been accompanied and strengthened by a rapid growth of enantioselective synthetic methods and analytical techniques permitting the evaluation of enantiomeric purity. In asymmetric synthesis, whenever one chooses to resort to a chiral building block (resident chiron), or to induction using a chiral auxiliary (auxiliary chiron), it is obviously

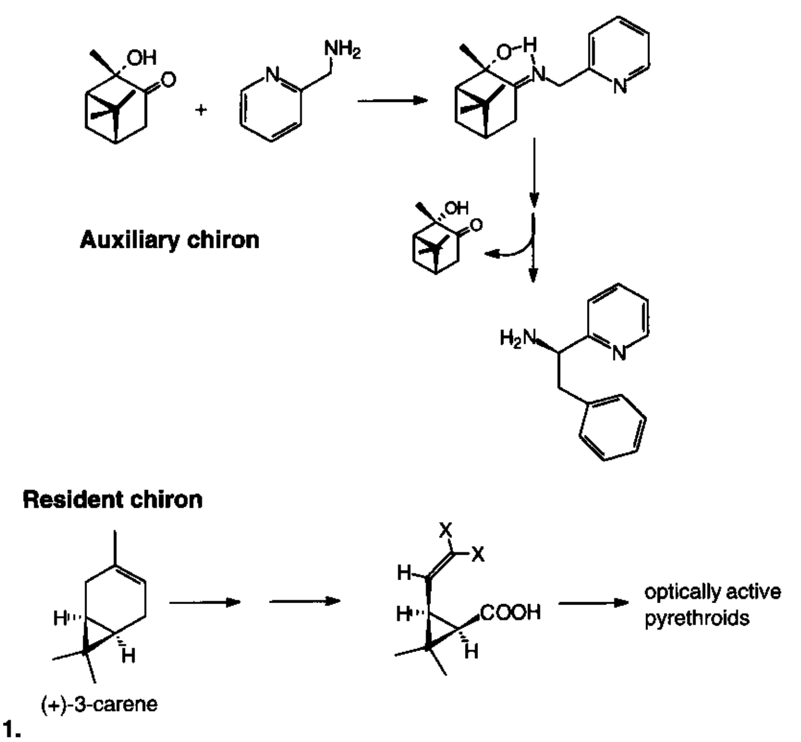

Figure 1.

[a]To a limited extent, asafetida and garlic oils may also find some uses.

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preferable that these elements be as enantiomerically pure as possible. As an example of auxiliary chiron, we can mention (–)-2-hydroxy-isopinocamphone for the preparation of (R)-2-pyridyl-benzylamine of high enantiomeric purity, an intermediate in drug synthesis. As an example of resident chiron, we can cite car-3-ene for preparing a variety of pyrethroids used as insecticides (Figure 1).

Essential oils can be particularly valuable sources of chiral auxiliaries and building blocks. One can cite camphor enantiomers as precursors of chiral auxiliaries (developed by Oppolzer in the 1980s), α-pinene derivatives for chiral boron reagents (still actively being developed by H. C. Brown) or for the preparation of 2-hydroxy-isopinocamphone (used as auxiliary), and β-pinene for preparing nopinone (used as a building block). Terpenic ketones, such as fenchone, pulegone and piperitone, as well as some alcohols, such as citronellol, are assets that still remain relatively rarely used as precursors of chiral building blocks. Because these natural substances should not be scalemic,[b] as is the case in many essential oils which contain them, the systematic screening of chiral essential oil components by gas chromatography can become a profitable activity. It is, indeed, possible that the examination of a new essential oil is this light can reveal an interest that otherwise would have seemed merely academic. This consideration obviously also applies to other known essential oils whose use may have declined over time for various reasons.

[b] Scalemicity may be used to define macroscopic mixtures of enantiomers that are not racemic. However, the precise use of this term is still controversial.

Identify New Fragrant Substances

The importance of certain minor compounds in essential oils has been recognized for a long time. In this regard, Ohloff[1] and, more recently, Mookherjee,[2] among others at past congresses, have presented brilliant contributions to the research of our industry. Can one still believe today that this area of research has been exhausted? Without a doubt, the most important essential oils (such as patchouli, vetiver, sandalwood, rose and others, without which the creation of major perfumes would be impossible) have been the subject of the most detailed investigations. Can it be said that all of their secrets have been revealed? To be convinced of the contrary, it suffices to use the example of β-damascone [**1**], identified for the first time in the essential oil of Bulgarian *Rosa damascena* by researchers at Firmenich around 1970. Although the concentration of this ketone in the oil does not exceed 3 ppm, it is still more than 10,000 times greater than its detection threshold.[3]

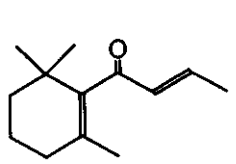
In order to unmask the secrets of trace compounds in essential oils, the chemist must show intelligence and rigorous tenacity. Unfortunately, the recent advent of sophisticated analytical techniques has progressively diverted many analytical chemists from these difficult roads to a path at the end of which the same rewards are not always granted. Indeed, isn't it quite easy today to identify, or rather recognize, several dozen compounds in one essential oil in less than one hour, a task that not too long ago would have required years? We can consider ourselves to be placed in the same situation today as those who preceded us by 50 years or more. They were successful in isolating and identifying, with the available technology of the time period, substances present at 1,000 ppm (for example) in a complex natural mixture. With extraordinary spectroscopic and separative techniques which are presently at our disposal, and by agreeing to dedicate an appropriate amount of time, we can assuredly complete the work of our predecessors, and continue to offer new perspectives to synthetic chemists and then to perfumers and flavorists. Over the past few years, this approach has been successfully adopted by a certain number of analytical chemists in the area of flavors in a particularly active hunt for new substances possessing high flavor unit numbers. Yet, when one reads about 500 publications or more that appear each year in the field of essential oils, it seems that the same efforts are not being made on a comparable level. Why?

Discover New Essential Oils and Isolates Endowed with Other Properties

A lot of effort has been devoted to the study of essential oils for their application in the perfume and flavor industry because of their aromatic properties. Scientists were (and still are) just as concerned with analytical aspects as agronomics (including answering questions dealing with variety selection), phytosanitary problems and harvesting techniques. Each of these is influenced by the technology of obtaining essential oils.

Since time immemorial, essential oils have been used for their health benefits. Their biological effects and possible therapeutic applications have clearly been discussed by Brud in New Delhi[4] and Buchbauer in Vienna[5] during the past two congresses. Aromatherapy and the recent aromachology are presently fields of increased interest. This interest may be justified insofar as these sciences are based on objective and rigorous work.[6] In the perfume industry, the psychophysiological effects of fragrant essential oils (for example, rose) have begun to find commercial applications. Of all the biological properties, the biocide properties (antibacterial, antifungal) have been the most studied in recent years. For the most part, this work has been carried out in developing countries where there is a vital need to control the sanitary environment while adding value to local natural resources. This is, at least, the officially stated motivation.

For other reasons, in advanced countries there exists a growing interest in natural products, not only in the flavor industry but also in the cosmetic industry. As consumers are becoming more aware of the incidence of allergic reactions, adverse side effects and increasing resistance by pathogenic organisms to synthetic disinfectants, they are turning toward natural products in hope of finding safer and milder products. An increased awareness of environmental protection has further strengthened the preference for plant-derived ingredients which are considered environmentally friendly because of their biodegradability and renewability. In this context, the cultivation of *Melaleuca alternifolia* (tea tree) has been undertaken in Australia in order to respond to the growing demand for an essential oil with a high content of terpin-1-en-4-ol and low content of cineole. It has been established that this essential oil displays powerful antimicrobial properties. Although used in cosmetic formulations, the intense and characteristic odor of this type of product is often a handicap for wider uses, such as in body care products. This problem also exists, albeit to a lesser extent, for the essential oil of *Leptospermum scoparium* (Manuka), recently developed in New Zealand for the same purpose.[7] In this case, it may be preferable to isolate the much less odorous polyketones [**2**]-[**4**] (as a mixture) from this oil. The search for essential oils possessing the desired biological properties and a low odor level is still justified even if this appears to be a difficult objective to reach. (See Figure 2.)



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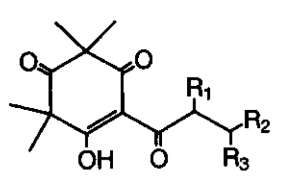

2: R_1=Me, R_2=R_3=H (flavesone)

3: R_1=H, R_2=R_3=Me (leptospermone)

4: R_1=R_2=Me, R_3=H (iso-leptospermone)

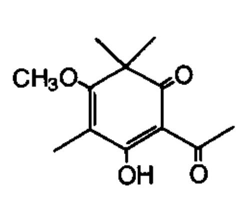

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Figure 2.

The same requirement exists for essential oils which possess the ability to strongly absorb ultraviolet radiation. These oils can find applications in cosmetic formulations such as sunscreens. While the effectiveness of essential oils with antimicrobial properties is often due to a synergy between various components, one may be able to isolate a single substance in an essential oil which will act as a natural UV absorber. As an example, we have identified triketone [**5**] (enol form) in the essential oil of the leaves of a *Melaleuca cajeputi* species.[8] Once isolated and purified, this substance is practically odorless, and has a UV absorbing power comparable to the most widely used synthetic products in sunscreens. This component also presents the advantage of significantly absorbing both UVA and UVB radiations, both considered today to be dangerous to the skin.

There exists an increasing demand for fragrances endowed with the ability to repel insects, and even some arthropods. In addition to marketing interest, the promotion of such products presents an undeniable advantage in areas where mosquitoes and flies are nuisances. Since certain synthetic fragrant substances presently used in perfumery are known to function in this manner, essential oils can also be used for the same purpose. A promising research area lies in the screening of oil-bearing plants traditionally known for insect repellent properties, testing them for repellent activity using appropriate protocols.

The list of areas in which essential oils, whether new or old, remain relatively unexplored is far from complete. As an example, Brud was already pointing out six years ago at the New Delhi Congress that "...allelopathy of oil-bearing plants is still an underinvestigated area with enormous potential. Possible uses of plants or (essential) oils as safe natural herbicides, growth boosters and other agents in agriculture are still open to research chemists."[4] This is a vigorous invitation for the entire scientific community to diversify its activities into these areas.

Results

The results of work carried out on essential oils are regularly presented at symposiums and in specialized scientific journals. In Europe, the 26th Annual International Symposium, which took place in 1995 in Hamburg, Germany, is certainly one of the best worldwide meetings. The TEAC, which held its 39th meeting in 1995 in Utsunomiya, Japan, is also an excellent congress on natural products and interesting terpene derivatives of essential oils. These two scientific congresses have high standards and are attended by scientists from both industry and academia, thereby offering a rare occasion for an exchange of ideas. In 1996, these symposia will be held in Vienna (Austria) and Saga, Kyushu (Japan), respectively. One must deplore the limited Asian and American participation in the European symposium (due probably to reasons of cost) and the virtually exclusive participation by Japanese scientists in the TEAC (for reasons of language).

Some of the problems that have affected scientific congresses on essential oils, or natural products in general, have also become a problem at this ICEOFF '95 Congress in Istanbul. For example, high registration costs for this congress explain the poor participation by our academic colleagues, particularly from India, China and Southeast Asian countries, and from countries formerly a part of the USSR. This is very regrettable, for these countries are either important producers of essential oils or possess an immense potential. This situation, therefore, poses a serious problem for the credibility and the future survival of the scientific program of this congress.

Today, there are numerous scientific journals that publish research on essential oils. In the majority of cases, these publications are of good scientific level, but this is dependent upon the editorial boards and the rigor of the reviewers. Certain negative aspects nevertheless appear frequently in these scientific papers.

- There seems to be far too much research which does not deserve to be published as such. For example, is it useful to publish analyses on essential oils already well documented, under the pretense that they have been experimentally produced in a different location? Reports of known essential oils should not be accepted for publication unless they have real chemotaxonomic or other biological significance.

- Too many publications report on essential oils which present no shred of originality in their composition. For example, is it useful to publish that an essential oil contains 70% pinenes or 20% b-selinene, for example, if this is of no taxonomic significance (unless enantiomeric excesses of these substances are reported as discussed above)? Before claiming that new essential oils are potential sources of an isolate already available elsewhere, it would be wise to be aware of the reality of the market, as we will later see.
- Too many publications mention compounds tentatively identified without this being supported by reliable data. This point was raised in Vienna during the last congress.[9] The possibilities and limitations offered by GC/MS instrumentation for the analysis of essential oils were discussed in 1993 during the 24th International Symposium on Essential Oils in Berlin.[10] This is certainly a most disturbing aspect, for it can endanger our credibility in the scientific community. The editorial boards of specialized journals and the bulk of our community should be conscious that such a situation would be judged intolerable in other areas such as analytical, physical or organic chemistry. Works which border on the edge of scientific misconduct should be severely rejected.
- Too much work is hastily published without a valid reason. Moreover, it is curious that journals practically never insist on justification when a preliminary note is submitted to them for an accelerated publication. Is there competition with other scientists? Is the importance of the work so significant that one publishes partial results without waiting to validate them by complementary observations or measurements? Generally speaking, it is never desirable to publish results from a small number of samples, and certainly not from a single sample! To cite an example, we have examined more than ten essential oil samples from *Teucrium* spp., prepared by ourselves from perfectly identified plant material collected in Madeira. It was impossible for us to confirm previously published results.[11] The same applies when new techniques are applied to the analysis of essential oils, which are indeed excellent models to validate these techniques. A new separation method and quantitation of enantiomers of a given essential oil component, or any measurement of this type, is certainly interesting and deserves to be published. On the other hand, it is an abuse if this preliminary result is taken as valid and characteristic of the substance being considered. For example, the massoia-lactone in massoia essential oil was proposed to be enantiomerically pure. However, after having analyzed more than a hundred authentic essential oil samples (prepared by ourselves), we can state that this result is not accurate.[12]

Limitations

There are a number of reasons not to continue research on some essential oils. These reasons may be political, regulatory, economic, ecological or simple need. Many essential oils can be confirmed to be interesting *a priori*, either by reason of their odor or other biological properties, or as a source of an isolate. Moreover, when one inquires about the motivations for conducting research on essential oils by university research groups, these reasons are always presented first, while motivations related to natural product chemistry or to the discovery of new chemical structures are infrequent. Rarely is the rather crucial consideration of economic interest taken into account. However, this interest can be quickly destroyed by two factors:

- Below minimal yield of essential oil from the plant material. The minimum yield lies at about 0.1% (with the exceptions of rose and lemon balm oils, among a few others).
- A limited availability of the plant material, depending on cultivable or wild growing plants. The risks associated with supply, climatic origin, politics, phytosanitary problems and other considerations have been sufficiently studied and will not be dealt with here.[13] Regarding rare and endemic species, the time and cost to ensure their renewal should also be taken into account.

National, supranational and international regulations can generate insurmountable barriers to the development and utilization of new essential oils. In certain countries, current regulations require notification about all new chemical products, synthetic or natural, that are subject to commercial transactions (such as handling, shipment, final uses and disposal). These regulations concern among other things the toxicological data, some of which relate to environment. For example, in North America, Australia and the EEC, strict regulations limit the uncontrolled proliferation of new chemical products. In Europe, the notification of a new substance is regulated by the seventh amendment of the 67/548/EEC guideline on dangerous substances. Depending on the yearly production and commercialization of a new substance, the cost of the physicochemical, biological (toxicological) and ecotoxicological testing can be considerable. It may vary from approximately $1,500 for 10 kg/year products to $150,000 for products up to 1 ton/year. Beyond 1 ton/year, using proper manufacturing procedures, the costs can become intolerable!

In the United States, only the essential oils found on the GRAS list can be used in food applications, which therefore is a positive list. In addition, by strict definition of essential oils, most of them can be considered Kosher. As of today, 120 out of 1,800 substances on this list are essential oils. It is interesting to note that since the release of the 13th FEMA/GRAS list (published in 1984), only one essential oil has been added: massoia. During the same period, only one essential oil has been withdrawn: calamus. More significantly, out of the 146 new items that have been added since 1979, only three are natural complex mixtures: massoia essential oil, osmanthus absolute and jambu oleoresin. Today, it is very difficult to get an essential oil approved. The main reason lies in the necessity to develop methods and define proper criteria for reviewing these products. These tasks are under the complete control of the FEMA expert panel. Such procedures are still under study. Some essential oils that are approved for use may nevertheless be subject to restriction because they contain a compound that is controlled by a particular regulation. Some examples in the EEC include essential oils that contain substances such as β-asarone, coumarin, pulegone, safrole, thujone and hydrogen cyanide. The International Organization of Flavor Industry (IOFI) is currently working to define analytical protocols to determine the concentrations of these substances allowable in the final products that reach consumers. These methods are taken into account by the Council of Europe Committee of Experts on Flavoring Substances.

University researchers should therefore be aware, at least to a certain extent, of the constraints on existing essential oils before engaging in investigations of new ones.

Likewise, national and international sponsoring organizations should also review these aspects before approving research programs in this domain.

Regulations or principles concerning the preservation of natural resources also must be taken into account prior to commercialization of a new essential oil. Significant moral guidelines are expressed in the Convention on Biodiversity and Action 21, declaration of principles related to forests, which were issued after the United Nations Conference on Environment and Development, which was held in Rio de Janeiro in June 1992. In the EEC, the 92/43/CEE guideline of 21 May 1992 defines responsibilities and methods for the protection of natural stands of endangered plant species.

Conclusion

Research on essential oils is unquestionably a very promising area for continued research. While one must question some of the work that is currently being published on essential oils because there is little originality or the work lacks rigor, there are numerous reasons to continue study. Some of these reasons are traditional in scope, such as searching for aroma notes missing in the flavor and fragrance field, new sources of isolates or new chiral compounds which may serve as building blocks for further compounds of interest. Other reasons are less traditional, such as finding natural sources of antimicrobial agents, UV blockers for skin care or even aromatherapy. The great diversity of compounds provided by essential oils and their natural status makes them ideal candidates to serve in these new applications.

There are, unfortunately, numerous barriers to the exploration and commercialization of new essential oils. These include political, economic, ecological and regulatory issues. Despite these problems, there is little question that we must continue to support research on essential oils and the dissemination of this research to the scientific community.

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