Debunking Functional Group Theory: Not Supported by Current Evidence and Not a Useful Educational Tool

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EXECUTIVE SUMMARY

What is Functional Group Theory?

Since 1990, functional group theory (FGT) has been a recognized way of categorizing essential oils according to their main chemical constituents to explain—and predict—the effects of an essential oil on the body. Constituents are classified according to their functional group, or chemical family, in a quadrant "grid system."

About This Review

As knowledge of essential oil chemistry has grown considerably, the authors began to question whether FGT is still a useful tool for learning about the biological effects of essential oils. They looked at the published scientific literature for the majority of essential oil constituents. As a way of investigating FGT in depth, they reviewed reports of monoterpene alcohols (MAs), the most widely studied chemical family. They looked at what is known about the activity of MAs on the body, those essential oils with the highest proportion of MA constituents, and reviewed their categorization according to FGT.

Review Findings

The authors found very few instances where a biological effect was either limited to, or especially potent in, any one chemical family. They found that many of the known pharmacological effects of essential oils are not consistent with their FGT categorizations; therefore, they are listed as exceptions. After reviewing 19 MAs and 154 scientific reports, the authors found very little supporting data for FGT. A significant finding was that MAs, which are predicted by FGT to be stimulants, are in fact sedatives. The authors could find no supporting evidence that the FGT grid system has any relationship with pharmacological activity.

Conclusions

The authors concluded that FGT is often misleading and is too simplistic of a tool to be useful, because the categorizations often suggest relationships that are not supported by current knowledge. This may be because FGT does not identify many important molecular features of essential oil constituents. Rather than attempting to plug these into loosely defined categories with multiple exceptions, the authors suggest a more practical model: simply learn about the effects of individual essential oils and constituents, and why such effects occur.

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> *It is the peculiar and perpetual error of the human intellect to be more moved and excited by affirmatives than by negatives.*
> **-Francis Bacon (1620)**

Disclaimer

This article cites research relating to the constituents of essential oils. Some of it – a very small amount – is clinical research, but most of it is pre-clinical. As such, it may or may not indicate an actual therapeutic property for a specific constituent. If it does, the therapeutic property may or may not extrapolate to an essential oil containing the constituent. None of the information in this article should be read as indicating specific therapeutic properties for a whole essential oil.

Abstract

Functional Group Theory (FGT) proposes that a set of common properties can be ascribed to molecules found in essential oils that share the same functional group. The theory posits that pharmacological properties can be determined by their position on a grid system with electrical resistance as the vertical axis, and polarity as the horizontal axis. FGT is alleged to predict the pharmacological activities of essential oils based on their functional group content. FGT is widely referenced in Aromatherapy education and literature, and yet it has neither been subjected to scrutiny nor meaningfully updated since 1990 to reflect current knowledge.

The idea that the biological properties of a chemical are related to the presence of a certain functional group is not new and is not limited to essential oils. For example, phenolic compounds have long been known to be antioxidant, aromatic amines to be potentially carcinogenic, and thiols and sulfides to be toxic. However, the assumption that the properties of all molecules can be predicted simply by knowing their functional group is a massive leap.

We, therefore, decided to examine whether FGT is a valid tool to: (1) describe and categorize the pharmacological activities of essential oils with known properties, (2) predict new pharmacological activities for these essential oils, or (3) predict the pharmacological activities of essential oils with no known properties. In order to address these questions, we reviewed seven publications as representative of the FGT literature (i.e., that make use of FGT as a working theory). We then introduced the concept of structure–activity relationship (SAR) and its methods, comparing these with the theoretical contents and assumptions of FGT to see how tenable FGT is in theoretical terms.

Using a layered approach to evaluate the merits of FGT on empirical grounds, we first examined its claims in general terms and reviewed what we already know about the SAR of terpenes and terpenoids. We then compared this with FGT by reviewing the pharmacological activities of a selected functional group – monoterpene alcohols – and compared our findings with the predictions of FGT. Finally, we examined the issues involved in extrapolating properties from constituent to essential oil.

Our review of FGT literature revealed no attempt at systematic and statistical treatment of data. Hence, we did not attempt to build a predictive or descriptive model. In addition, none of the examined texts explain the methodology used to gather supporting data. In many instances, claims are not supported by evidence. Many of the activities assigned to chemical classes are based on practitioners' opinions of a very limited set of essential oils, and authors sometimes differ in the properties they ascribe to the same functional group.

Our analysis shows that FGT is a limited version of SAR, accompanied by unscientific references to a supposed role of electro-chemical parameters. We found that FGT is not able to perform its purported descriptive and predictive functions, its conclusions are too absolute, and many of its claims do not stand up to scrutiny. We conclude that FGT is not a useful tool for research because it is too simplistic, it fails to identify the most relevant molecular features linked to activity, and it is not useful for teaching because it suggests solid and fixed relationships that do not exist since they are not supported by the published data.

1 What is functional group theory?

People use essential oils for a variety of reasons, and essential oil users and health professionals alike look for evidence for the claims made about essential oils. Teachers of Aromatherapy and aromatic medicine are also keen to provide their students with a clear rationale and evidence base for what they teach. This drive for a scientific basis for essential oil use is not new and was given a boost in 1990, with the publication of *L'Aromathérapie exactemen*t by Pierre Franchomme and Daniel Pénöel. They evaluated two physicochemical aspects of essential oil constituents – polarity and electrical resistance – to create the "bubble chart" that describes functional group theory (Franchomme and Pénoël, 1990), recreated as figures 1 and 2. This was said to correlate with yin and yang, and Faucon (2012) added the "hot" and "cold" dimensions.

The chart separates a range of essential oil constituents on a grid based on their chemical structure, whether they were drawn to a cathode or anode when a vapor of the constituent was passed through an electric field, and whether they are polar or nonpolar as based on the presence or absence of polar functional groups. Readers should note that Faucon (2012) gives pH and Schnaubelt (1998) gives lipophilicity/hydrophilicity for the horizonal axis.

The functional groups are structures such as -OH groups, C=O groups, ester groups, $-OCH_3$ groups, and so on. These groups are attached to the carbon skeleton, either monoterpenoid or sesquiterpenoid in structure, or else have a benzene ring as the carbon framework. It is worth noting that biological and chemical properties are dependent not only on the functional group part of a molecule but also on the structural framework to which the functional group is attached.

The different chemical families, grouped by the presence of different functional groups, were then assigned therapeutic properties: esters were deemed to be antispasmodics, monoterpene alcohols and phenols were categorized as anti-infectious and immune stimulants, and monoterpenes were deemed cortisone-like and antiseptic (Franchomme and Pénöel, 1990). Many of these claims are not supported by references in the ensuing text, which calls into question their validity. In addition, the properties ascribed to oxides, for example, seem to be entirely based on one compound: 1,8-cineole.

Now almost thirty years later, research on the therapeutic effects of essential oil constituents has far surpassed what was available in 1990, and it is time for a review of functional group theory.

FGT is not a scientific theory in the technical sense, which is defined as: "an explanation of some aspect of the natural world that has withstood rigorous scrutiny and that can, in accordance with the scientific method, be repeatedly tested, using a predefined protocol of observations and experiments" (Zalta, 2016). FGT more resembles a working hypothesis, a heuristic tool that is proposed to predict the pharmacological activities of essential oils based on their constituent chemistry. A simplistic version of FGT was outlined, without being given a name, by René-Maurice Gattefossé in 1937 (Gattefossé, 1993).

> ***"Now almost thirty years later, research on the therapeutic effects of essential oil constituents has far surpassed what was available in 1990, and it is time for a review of functional group theory."***

FGT combines two similar but distinct fields of enquiry. One is quantitative structure–property relationships (QSPR), which studies the relationship between chemical structure and chemical properties (i.e., all molecules with an -OH group behave as an alcohol). The other is the structure–activity relationship (SAR) – the relationship between the chemical or 3-D structure of a molecule and its biological activity (e.g., all esters are antispasmodic). FGT also

assumes that data pertaining to an isolated constituent can be used to define the activity of the whole essential oil if said constituent dominates or characterizes the oil. However, there is no exploration of the issues surrounding this assumption, such as at what percentage a constituent can be said to dominate or whether synergistic phenomena can be discounted and in what circumstances.

This understanding prompted us to examine whether FGT is a valid tool to:

1. Describe and categorize the pharmacological activities of essential oils with known properties.
2. Predict new pharmacological activities for these essential oils.
3. Predict the pharmacological activities of essential oils with no known properties.

In order to address these questions, we will review the literature on FGT to explore its theoretical content, briefly introduce the concept of SAR and its methods, and then compare these with the theoretical contents and pre-assumptions of FGT to see how tenable FGT is in theoretical terms. We will then look at the empirical data for terpenoids to compare it with FGT. Finally, we will briefly examine the issues involved in extrapolation (i.e., to what extent we can predict the properties of an essential oil from the known properties of its constituents).

2 Review of functional group theory literature

Functional group theory was first named and clearly defined for essential oils in 1990 by Pierre Franchomme and Daniel Pénöel in their book, *L'Aromathérapie exactement.* It is based on the grid system shown in figure 2 with polarity and electrical resistance as the two axes. Subsequent authors, including Schanubelt (1998) and Faucon (2012), ascribed other activities for the axes. Depending on where a functional group is placed in the grid system, it is said to possess certain qualities. For example, chemical groups in the lower half of the grid are tonic and stimulant, while those in the upper half are sedative. "Stimulant" is not clearly defined, but since it lies opposite "sedative," we have assumed this includes central nervous system (CNS) stimulant.

Monoterpene alcohols (MAs), which are classed as electropositive, are tonic and stimulant. As evidence, borneol is said to be a gall bladder tonic, geraniol a uterine tonic, and menthol a liver stimulant; however, no rationale is given for why electropositivity would give rise to these so-called "tonic" properties. The alcohol group does not carry a formal positive charge unlike an ammonium group, for example. Other properties are ascribed to functional groups that have no apparent relationship with their grid placement.

In addition to the grid system, the basic tenets of FGT are:

- Essential oils show certain general activities in accord with the activity of the dominant chemical group present. Functional groups include alcohols, ketones, aldehydes, etc.
  Thus, an essential oil dominated by monoterpene alcohols should show a range of activity consistent with that of MAs.
- The biological activity (effect on the body) of a molecule can be described and predicted based on the functional group it presents, such as a monoterpene alcohol showing activities predicted for any -OH (alcohol) containing monoterpene (e.g., antiseptic, immunomodulatory, etc.).

The electrical resistivity of essential oils is entirely based on the work of Franchomme and Pénöel (1990). Their experimental method is described, and data are given for whole essential oils and individual constituents. To the best of our knowledge, their work has never been replicated, although there is one report for electrical resistivity in lavender oil and peppermint oil (Ismaili *et al.,* 2015). It is likely that specific molecules do possess measurable electrical resistivity. Whether they fall into neat categories as described by FGT is not known, however, as only 41 individual constituents were tested with some of the functional groups only represented by one compound.

The relationship between electrical resistivity and biological systems is based on the bioelectronic theory of Louis-Claude Vincent (1954), and this is acknowledged by Franchomme and Pénöel (1990) and by Faucon (2012). Vincent's theory is based on three parameters: pH (acidity/alkalinity), rH_2 (oxidation/reduction), and ρ (electrical resistivity) (Országh, 1992). There are three important issues to consider: (1) bioelectronic theory is based on systems that contain water and not lipophilic systems; (2) bioelectronic theory as it applies to medicine has never been accepted by the scientific community and was debunked by Point (2015); and (3) even if was true that we could classify essential oil constituents according to such a grid system, it still would not predict their specific pharmacological effects.

We have not been able to find evidence for why either polarity or electrical positivity/negativity would determine pharmacological action. When citations are given, they sometimes lead to a dead end due to authors citing each other with Franchomme and Pénöel (1990) as the ultimate root of the information. This is problematic as Franchomme and Pénöel (1990) often give no supporting citations for their claims. The issue of the "grid system" and related pharmacological properties is really the easiest to challenge as it simply has no basis. We can only class it as pseudo-science.
A more crucial point is that the FGT grid system/bubble chart claims specific related properties, i.e., that all negatively charged molecules (anions, or electron donors) are "calmants et relaxants," and all positively charged molecules (cations) are "tonique et stimulants" (Franchomme and Pénöel, 1990). (Pierre Franchomme did not reply to an email sent in November 2017 requesting clarification on this relationship). In a 2017 blog post about FGT, Petra Ratajc commented, "The basic problem of the theory is that it generalizes (sic) the physicochemical properties of the molecules to biological effects. Although this approach is often adopted as part of holistic Aromatherapy practice and education, it is – iron-

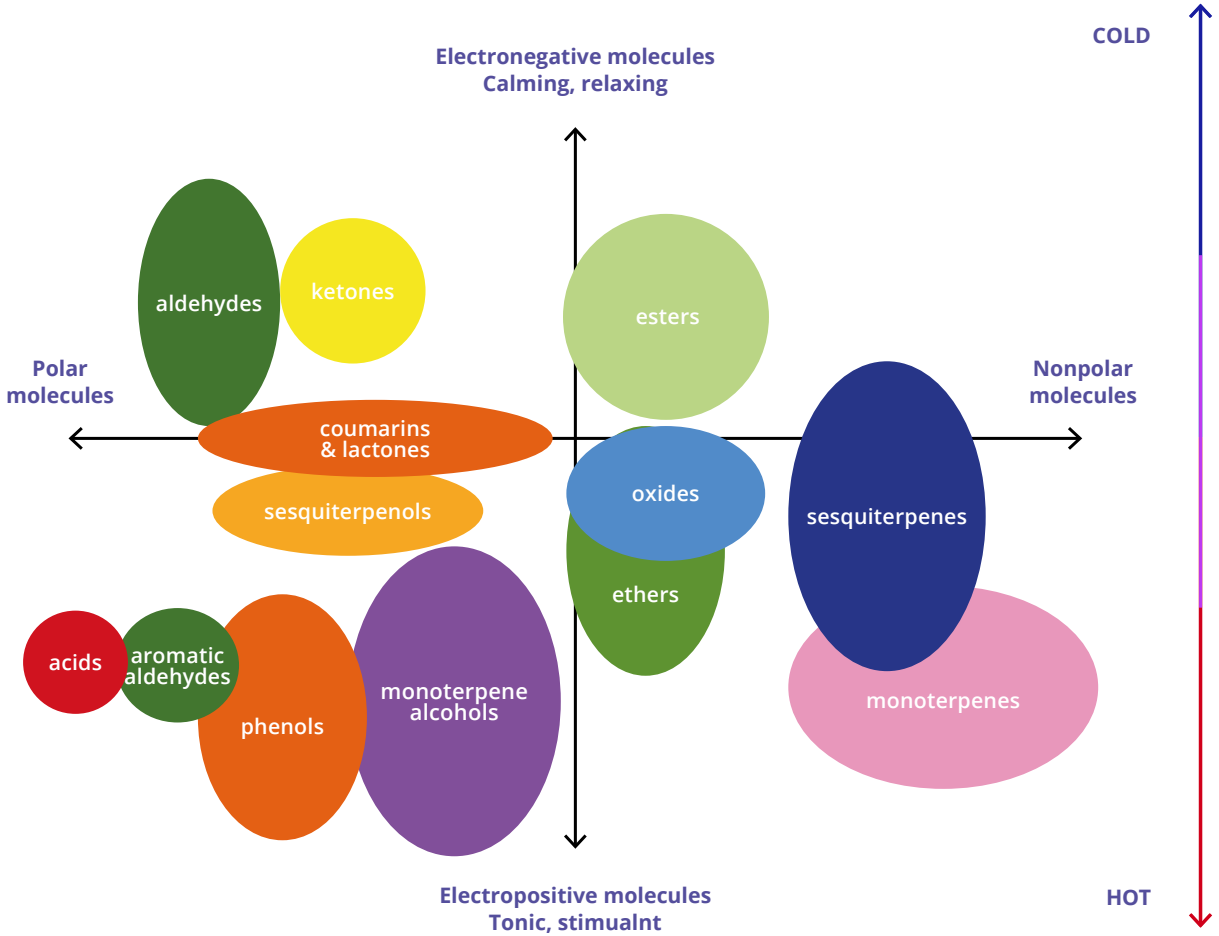

Figure 1.
The FGT grid, or bubble chart, showing functional groups, adapted from Franchomme and Pénoël (1990) and Faucon (2012).

ically – entirely reductionist. Why? Because it extrapolates properties at the lower domain of organization (physicochemical properties) to explain higher-level phenomena (biological effects). This is, by definition, reductionism in natural sciences (Felz *et al.*, 2006; Looijen, 1999)."

Several authors wishing to share functional group theory in English have taken the bubble chart and either reproduced it or modified it in their attempts to provide an evidence base for the therapeutic effects of essential oils. We looked at how FGT was presented in five books that have been widely used in Aromatherapy education over the last decades: Schnaubelt, 1998; Bowles, 2003 (also one of the authors of this article); Pengelly, 2004; Faucon, 2012; and Price and Price, 2012; and a journal article that espouses FGT (Djilani and Dicko, 2012).

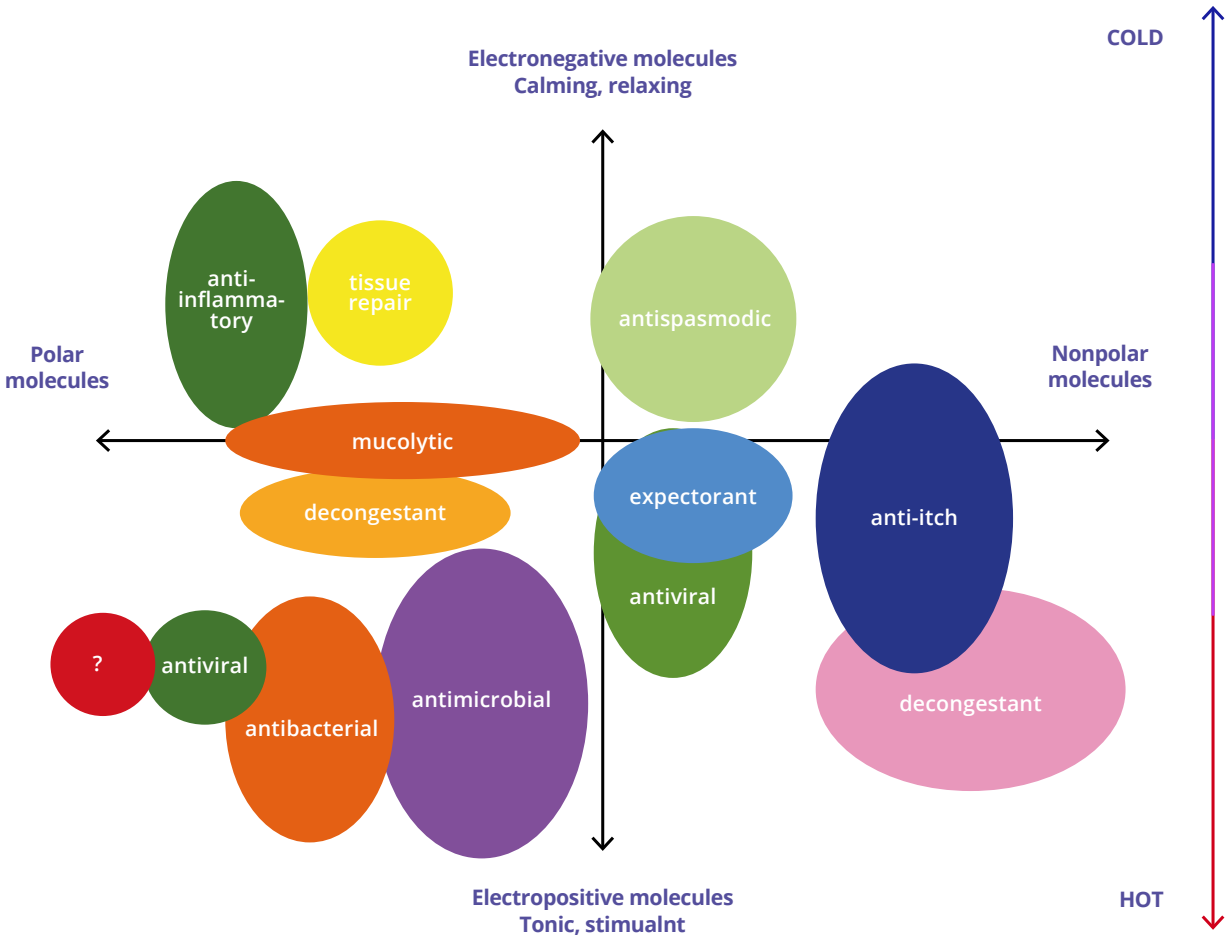

Figure 2.
The FGT grid, or bubble chart, showing some ascribed properties, adapted from Franchomme and Pénoël (1990) and Faucon (2012).

Consistency between these authors is noticeably lacking. Table 1 shows how they reported properties for the MA family. Some of the inconsistencies may be easy to explain (a "no" simply means that the author did not cite that property for MAs), but we believe that the overall picture reflects the fragility of FGT. The seven works cited in table 1 do not constitute an exhaustive list, but are representative of the general approach taken in FGT.

> *"The basic problem of the theory is that it generalizes the physicochemical properties of the molecules to biological effects. Although this approach is often adopted as part of holistic aromatherapy practice and education, it is – ironically – entirely reductionist."*

Three authors do not mention the grid system (bubble chart) at all (Bowles, 2003; Pengelly, 2004; Djilani and Dicko, 2012). This may explain why neither Bowles nor Pengelly cite MAs as being stimulant. Interestingly, when one of us met Michel Faucon in 2017 and asked him whether he believed that functional group theory was still valid, he stated that he did not.

Property	Pénöel & Franchomme 1990	Schnaubelt 1998	Bowles 2003	Pengelly 2004	Faucon 2012	Djilani & Dicko 2012	Price & Price 2012
Stimulant	yes	yes	no	no	yes	yes	yes
Immuno-stimulant	yes	yes	no	no	Immuno-modulatory	no	no
Antiseptic or anti-infectious	yes	yes	yes	yes	no	yes	yes
Anti-inflammatory	no	no	no	no	no	yes	no
Anesthetic	no	no	Analgesic	no	no	yes	Analgesic
Antispasmodic	no	no	yes	no	no	yes	no

Table 1. Examples of properties of monoterpene alcohols ascribed by various authors.

When challenged about the validity of FGT, proponents often respond with comments such as: "of course there are exceptions," or "it's not perfect but it's a useful teaching tool," or "it's a good starting point, and then you learn it's not that simple." One of our aims therefore is to answer the question: "is functional group theory a useful educational tool?"

3 Structure–activity relationships

The functional group is just one of many factors of structure–activity relationship (SAR) – the connection between a molecule's structure and its biological activity. In figure 3, we show nine molecular sub-categories to illustrate that FGT includes only the first three of these. We do not doubt that the structure of a molecule largely determines its activity, but this structure is not limited to the functional group.

Modern pharmacology is based on the assumption that "(t)he effects of most drugs result from their interaction with macromolecular components of the organism" and that "(b)oth the affinity of a drug for its receptor and its intrinsic activity are determined by its chemical structure" (Brunton *et al.,* 2011) and even minor changes in this structure can produce important changes in the pharmacological properties of the molecule, as shown for example in the selectivity of receptors for optical isomers of a molecule. This is also known as the lock-and-key principle: the structure of a molecule allows it to interact with a specific receptor site (figure 4). The nature of that interaction is not always the same; for example, a molecule may activate a receptor site (agonist), may block it (antagonist), or may be capable of doing both things (bimodal), depending for example on dose.

SAR modelling is the study of the relationships between the molecular structure and biological or physicochemical activity of a chemical (McKinney *et al.,* 2000). SAR reasoning derives from specific cases and then generalizes where possible. The aim is to understand what constitutes a class of active molecules, what determines that activity. and what determines the difference between active and inactive molecules. This is based on the premise that the structure

FGT vs. SAR
Levels of similarity

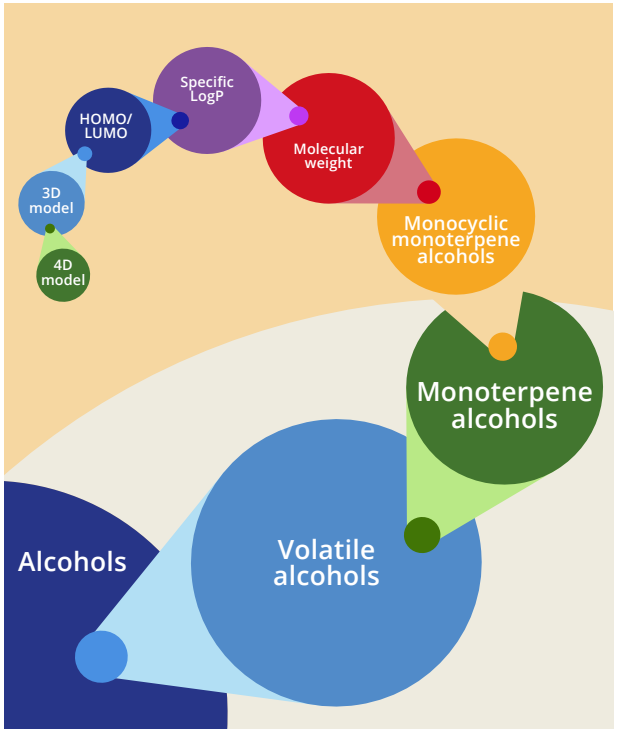

Figure 3. The functional group is just one aspect of the structure–activity relationship.

of a molecule determines its physical and chemical properties, and these, in turn, determine its biological properties – the effects it will have on the human body (McKinney *et al.,* 2000).

"Read-across" SAR is the approach that decides that the unknown property of a compound is the same as the known property of another compound if the two compounds are sufficiently similar (OECD, 2018). This approach is, however, not without problems, and it heavily depends on the subjective concept of "similarity." The "SAR paradox" refers to the fact that not all similar molecules demonstrate similar activities (Xu and Agrafiotis, 2002; Nikolova and Jaworska, 2003).

Lock and key principle

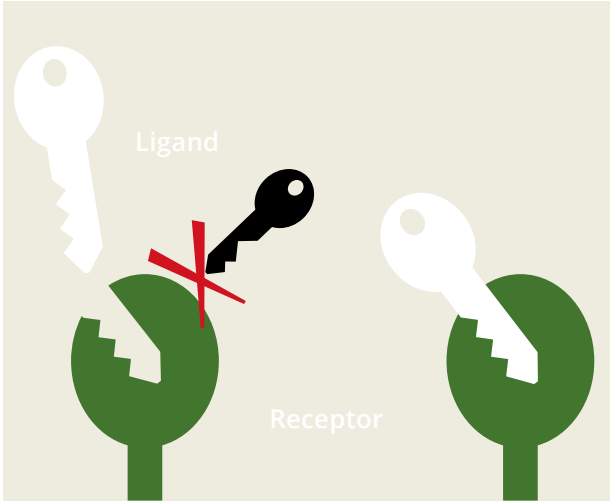

Figure 4. Lock and key principle: the idea that a molecule only interacts with a receptor site when there is a good fit between them.

"Classical" SAR is based on direct measure of "structural similarity," but it has been shown that structural similarity does not always imply similarity in activity (Martin *et al.,* 2002). Stereo-isomers are pairs of molecules that look very similar structurally, and that differ only in their 3-D orientation. However, many of the stereo-isomers (enantiomers – molecules that are mirror images of each other) found in essential oils have different activities. For example, S-(+)-carvone and R-(-)-carvone (figure 5) had opposite effects on bacterial quorum sensing, suggesting that they will have different antibacterial effects (Ahmad *et al.,* 2015). Similarly: S-(+)-carvone was anticonvulsant in mice, while R-(-)-carvone was not (de Sousa et al., 2007a); (-)-menthol was analgesic in mice, while (+)- menthol was not (Galeotti *et al.,* 2002); and in a human trial, (+)-linalool had a stimulating effect on heart rate, while (-)-linalool had a sedating effect on heart rate (Höferl *et al.,* 2006).

3.1 Quantitative SAR

Quantitative SAR (QSAR) improves on SAR by using a formal representation of similarity. It assigns numerical representations (descriptors) to various aspects of the chemical compounds. These mathematical descriptors can be very different and be based on different features of the molecules. They can be treated with statistical tools to measure their similarity, or their proximity in descriptor space, in a diagram. This analogy holds true only under the assumption that if two molecules are in the same region of a descriptor space then they are likely to have similar biological effects (the so-called "neighborhood principle"). In other words, QSAR is only useful if similar molecules do have similar activity. However, there is contradictory evidence for the neighborhood principle, because descriptor similarity does not always translate into similarity in activity (Martin *et al.,* 2002; Nikolova and Jaworska, 2003).

Carvone isomers

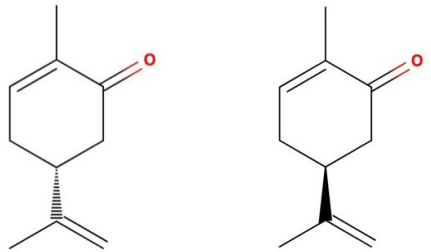

Figure 5. Carvone stereo-isomers.

A paper that uses a numerical approach to similarity is entitled: "Do structurally similar molecules have similar biological activity?" (Martin *et al.,* 2002). The authors look at four molecules: acetylcholine, nicotine, dopamine, and pergolide, which are used as classic examples of similarity in biological action. The results are that even pairs of molecules that are extremely close in activity (such as acetylcholine and nicotine as nicotine agonists; dopamine and pergolide as dopamine agonists) can be very dissimi-

lar in shape. In fact, calculating the chemical similarity of these four molecules, using a numerical method based on a 2-D description of the molecules ("Daylight fingerprint") evaluated with a statistical tool called the "Tanimoto coefficient," the highest score is between nicotine and pergolide (0.32), and the second highest is between acetylcoline and dopamine, not the pairs that show similar activity. The Tanimoto coefficient is one of the most sophisticated tools in QSAR and identifies molecules that are very similar from a chemical perspective.

In the same paper the authors classify a set of molecules using the Tanimoto coefficient. The conventional wisdom would be that a chemical similarity superior or equal to 0.85 would translate in an 80% chance of similarity in biological activity, but the paper finds that in reality the chance of similarity in biological activity is only 30%. This would mean that while similar molecules are more likely to have similar effects, the likelihood is far lower than assumed. And, this is a system that compares molecules that share many more similar traits than just a functional group.

Both Nikolova and Jaworska (2003) and Martin *et al.,* (2002) conclude that molecular similarity does not necessarily translate to similarity of action, and we need to be able to establish that there is a link between how similar molecules are in both shape and activity. Martin *et al.* (2002) also add that molecules that "look very similar to a chemist sometimes bind in very different orientations in the protein active site, bind to a different conformation of a protein, or bind to a different protein altogether." This means that similar molecules can demonstrate different pharmacological effects.

Similarity measures are more reliable if accompanied by a description of their mechanism of action: "If two molecules have the same effect via the same mechanism, then their similarity is more certain than it would be if the effect was achieved through different mechanisms" (Chockalingam *et al.,* 2007). This does not mean that similar molecules are likely to have a similar effect, but that molecules that have a similar effect through the same mechanism of action are likely to look similar.

Both medicinal chemists and pharmacognosy experts looking for new active molecules strive to find ways to predict activity without having to test a compound. Yet even with the most sophisticated tools to identify similar molecules, the result is only a slightly higher probability of similar activity.

> ***"This would mean that while similar molecules are more likely to have similar effects, the likelihood is far lower than assumed. And, this is a system that compares molecules that share many more similar traits than just a functional group."***

3.1.1 Types of descriptors used in QSAR

Structural descriptors such as molecular weight (MW) and H-bond acceptors or donors.

Physicochemical descriptors such as the partition coefficient (LogP) and the hydrophobicity constant, which is derived from this.

Topological descriptors such as Randic shape index, electro-topological state atom index (E-state index, measuring the important topological features and molecular fragments mediating a particular response).

Electronic descriptors like the highest occupied molecular orbital (HOMO) energy (which measures the nucleophilicity of a molecule), the lowest unoccupied molecular orbital (LUMO) energy (which measures the electrophilicity of a molecule), and the dipole/quadrupole moment (which describes strength and orientation behavior of a molecule in an electrostatic field) (Roy *et al.,* 2015).

The construction of a valid QSAR model is a complex and multistep process, and not a simple, unsystematic collection of data. The predictivity of the model depends on the quality of the data, especially on the identification of relevant chemical features, biological activities, and mechanism of action.

It also depends on thorough knowledge of the problems of induction when confronted with limited datasets and many parameters (Falkenauer, 1998) and the judicious use of computer simulations, statistical tools, and in general statistical models that allow for the reduction of noise (random error) and the identification of "real" strong trends. Data interpretation should be carried out by experts in QSAR analysis.

3.2 Structure and function – what we do know

If biological activity (function) does in fact derive from the structure of a molecule, surely something must be known about this by now? Indeed yes, but it is worth repeating that the functional group of a molecule is only one aspect of its structure. Here is what we can conclude about compounds possessing specific functional groups.

3.2.1 Phenols

Compared with most other functional groups, there are a relatively small number of phenols found in essential oils. In terms of percent concentration in commonly used essential oils, the principal three are eugenol, carvacrol, and thymol. As with other phenolic compounds not found in essential oils, these three possess certain properties (Hung, 2016). All of them demonstrate significant antioxidant activity (Delgado-Marin *et al.,* 2017). Carvacrol and thymol, two isomers of the same molecule, are notably antibacterial and skin irritant. Eugenol is also notably antibacterial but is less irritant (Miladi *et al.*, 2017; Tisserand and Young, 2014). The difference in skin irritation may be related to the fact that eugenol possesses both etheric and phenolic functional groups.

There are significant differences in the skin sensitizing potential of phenols (table 2), and this is shown in research on methyl salicylate, eugenol, isoeugenol, eugenol, and 1,4-hydroquinone, despite these molecules possessing some similar physicochemical features (Gerberick *et al.,* 2004).

Learning that "phenols are generally antioxidant, antibacterial, and skin irritant" does make sense, though it's also important to understand that the antioxidant effect of these phenols is dose-dependent and that it reverses to a pro-oxidant effect in higher doses (Llana-Ruiz-Cabello *et al.,* 2015).

Phenol	Sensitizing potential	Molecular weight	LogKp	Log-Ko/w
Methyl salicylate	Non -sensitizing	153.15	-2.74	1.27
Eugenol	Weak	164.2	-2.19	2.15
Isoeugenol	Moderate	164.2	-2.19	2.15
1,4-hydroquinone	Strong	110.12	-2.56	1.17

Table 2. Four phenols that are similar in some respects, but that show very different potential for skin sensitization

3.2.2 Ketones

There are many ketones found in commonly used essential oils (table 3). A minority are notably neurotoxic and may cause seizures in overdose. These are thujone, pinocamphone, and camphor. This activity has been seen in both rodent testing and human oral dosing from essential oil use, and we know that camphor is less toxic than the other two compounds (Tisserand and Young, 2014). However, many other ketones are either non-convulsant (unless given in a lethal dose) or they are anticonvulsant (de Sousa *et al.,* 2007a; Hosseinzadeh and Parvardeh, 2014; Orellana-Paucar *et al.,* 2013; de Melo *et al.,* 2017; Wenzel and Ross, 1957). Thymoquinone has even been used in a small clinical study as an anticonvulsant for intractable pediatric seizures (Akhondian *et al.,* 2011). Thus, the generalization designating ketones as neurotoxic is not helpful nor accurate; however, instruction that details specific information for camphor, thujone, and pinocamphone as potentially neurotoxic makes sense.
It is noteworthy that all three are bicyclic monoterpenoid ketones. Another bicyclic monoterpenoid ketone, verbenone, still attests to FGT as categorically unreliable as it is anticonvulsant in mice (de Melo *et al.,* 2017).

3.2.3 Aldehydes

We know that cinnamaldehyde and citral (geranial + neral) are among the high-risk skin allergens. These, along with cuminal,

Ketone	Rodent/Human	Structure	Citations
May be consulvant in oral dose			
α- & β- Thujone	R + H	Bicyclic monoterpenoid	1, 2, 3, 4, 5, 6, 7
Pinocamphones	R & H	Bicyclic monoterpenoid	4, 7
Camphor	R & H	Bicyclic monoterpenoid	7, 8, 9, 10, 11, 12, 13, 14, 15, 16
Consulvant in massive but sub-lethal oral dose			
Fenchone	R	Bicyclic monoterpenoid	7, 17
(R)-(+)-Pulegone	R & H	Monocyclic monoterpenoid	7, 18, 19, 20, 21
Non consulvant in sub-lethal dose			
(-)-Carvone	R	Monocyclic monoterpenoid	7, 22
Dihydrocarvone	R	Monocyclic monoterpenoid	7
α- & β- Ionone	R	Monocyclic monoterpenoid	7
(Z)-Jasmone	R	Monocyclic monoterpenoid	23
(-)-Menthone	R	Monocyclic monoterpenoid	7
Piperitone	R	Monocyclic monoterpenoid	7
Umbellulone	R	Bicyclic monoterpenoid	7
Anticonsulvant			
(+)-Carvone	R	Monocyclic monoterpenoid	7, 22
Thymoquinone	R & H	Bicyclic monoterpenoid	24, 25
ar-Turmerone	R & H	Benzenoid sesquiterpenoid	26
(-)-Verbenone	R	Bicyclic monoterpenoid	27

Table 3. Ketones, structure, type of research (rodent and/or human), and degree of neurotoxicity.
(See 10.2 Ketones and neurotoxicity references for table 3 for key to citations.)

also possess potent antifungal activity (Feyaerts *et al.,* 2018). There may be some SAR here, but we need to know more about the specific aspects of structure to determine the potency of these effects before concluding that all aldehydes – and there are many – are antifungal skin allergens (Morcia *et al.,* 2017). Anisaldehyde, benzaldehyde, cinnamaldehyde, cuminaldehyde, salicylaldehyde, and vanillin are all benzenoid aldehydes that demonstrate variable skin sensitizing potential. Vanillin is non-sensitizing (Natsch *et al.,* 2012).

3.2.4 Sesquiterpene lactones

The most notable skin allergens include several sesquiterpene lactones: costunolide, dehydrocostus lactone, alantolactone, and massoia lactone (Tisserand and Young, 2014). Sensitivity to sesquiterpene lactones has been widely reported and includes negative reactions to substances such as parthenolide, which is not found in essential oils. There is very likely some valid SAR here, though exactly what is not known (Paulsen and Andersen, 2017). However, allergenic activity has not been reported in lactones that do not have a sesquiterpene skeleton, including ambrettolide and nepetalactone.

3.2.5 Ethers (alkenylbenzenes)

This has never been addressed in the FGT literature, but the most notable carcinogens found in essential oils are all ethers: estragole, safrole, methyleugenol, and possibly α-asarone and β-asarone (Tisserand and Young, 2014). However, there are also ethers that are either not carcinogenic or are currently under ongoing research: eugenol, isoeugenol, dill apiole, parsley apiole, trans-anethole, elemicin, and myristicin (Martins *et al.,* 2018). The structure-activity determinants for the variation in carcinogenic activity has not yet been fully determined.

3.2.6 Furanocoumarins

Seemingly not addressed in the FGT literature is the association between a furanocoumarin structure and phototoxic activity despite the very close correlation. Almost all phototoxic constituents are furanocoumarins, and almost all furanocoumarins are phototoxic (Tisserand and Young, 2014).

3.2.7 Summary

Clearly there are some structure–function relationships that have been validated over time, notably for sesquiterpene lactones, phenols, and furanocoumarins. However, these few examples do not validate the totality of the original FGT claims. It's also worth noting that phenols and furanocoumarins generally act via non-specific mechanisms. They are generally reactive towards biological structures, and they do not need to bind to specific receptors (although they can do). The other functional groups, perhaps because of lesser reactivity, need a specific receptor-binding mechanism to exert their activity. For example, the antibacterial activity of carvacrol, thymol, and eugenol is primarily due to bacterial membrane disruption. This effect applies to cell membranes in general, so it likely also explains their skin irritant potential (Chauhan and Kang, 2014; Ferreira *et al.,* 2016; Gonçalves *et al.,* 2015; Khan *et al.,* 2017). The phenol and furanocoumarin examples do not seem to invalidate the general position that functional groups per se are not good predictors of biological activity. Contrary to FGT lore, we could find no evidence for any ester found in essential oils being antispasmodic.

It is nothing more than false inductive reasoning that leads to classifying all constituents within a functional group as a quality, such as all neurotoxic compounds as ketones. However, SAR in essential oil constituents does exist, but research on this is in its infancy (Owen *et al.,* 2018). The relevance of a molecule's functional group is only one aspect of a complex picture.

3.3 Comment on functional group theory as a structure–activity model

In our opinion, FGT is flawed as a structure–activity relationship model for these reasons:

- In many instances the authors do not support heir claims with scientific data. Many of the activities assigned to chemical classes by the authors are based on

a limited set of essential oils or constituents.

- Even when claims are supported with data, some of the ascribed properties are so general that their verification is problematic, or irrelevant.
- Although clearly belonging to the area of heuristic tools, FGT is described as if it has a more solid standing than it in fact does, and the authors use it to make absolute, or very strong, claims, such as: "ketones are neurotoxic" or "esters are antispasmodic" (Bowles, 2003; Franchomme and Pénoël, 1990; Pengelly, 2004; Djilani and Dicko, 2012).
  As we have seen before, such claims are unwarranted even in the field of QSAR since the SAR paradox is always present and conclusions are always tentative.
- Authors sometimes differ in the properties they ascribe to the same functional groups. For example, only Faucon (2012) refers to ketones as cholagogues, and only Djilani and Dicko (2012) refer to monoterpenes as hepatoprotective.
- When authors declare that "alcohols have activity X," what they really mean is that "all (or the great majority of) alcohols have activity X." They also mean that alcohols demonstrate activity X much more strongly than do other functional groups, either in terms of potency or in terms of number of compounds. This means that FGT is only useful if it can isolate a functional group which has specific activities that are common to its members, and that are more potent than the same activities in most other functional groups.

FGT has not fundamentally changed since 1990. In order to find out whether an SAR model based on functional groups is relevant in the light of what we know today, we decided to examine the data for monoterpene alcohols in detail.

> ***"Contrary to FGT lore, we could find no evidence for any ester found in essential oils being antispasmodic."***

4 Literature review of SAR and pharmacological activity for monoterpene alcohols

In order to examine the usefulness of FGT in describing how essential oil constituents work, we reviewed the research on terpenes and QSAR, focusing on monoterpene alcohols (MAs). MAs include some of the most extensively researched essential oil constituents and demonstrate a variety of pharmacological activities with enough mechanistic detail to make a deeper analysis possible.

Analgesic	Effects on contractility	Anticonvulsant	Antiinflammatory
Local anesthetic	Vasorelaxant	Antiepileptogenic	Antiobesity
Antihyperalgesic	Vasoprotective	Antidepressant	Antihyperglycemic
Cooling	Anti-diarrheal	Anxiolytic	Antihyperuricemic
Antinociceptive	Antiperistaltic activity	CNS depressant	Counter-irritative
Nerve conductive	Antiasthmatic	Neuroprotective	Cytoprotective
Antiarrhythmic	Cough inhibitor	Antidislipidemic	Duodenoprotective
Antihypertensive	Improve subjectively nasal airflow without decrease nasal resistance	Antioxidant	Gastroprotective

Table 4. Biological activities of monoterpene alcohols found in the literature (1980-2017)

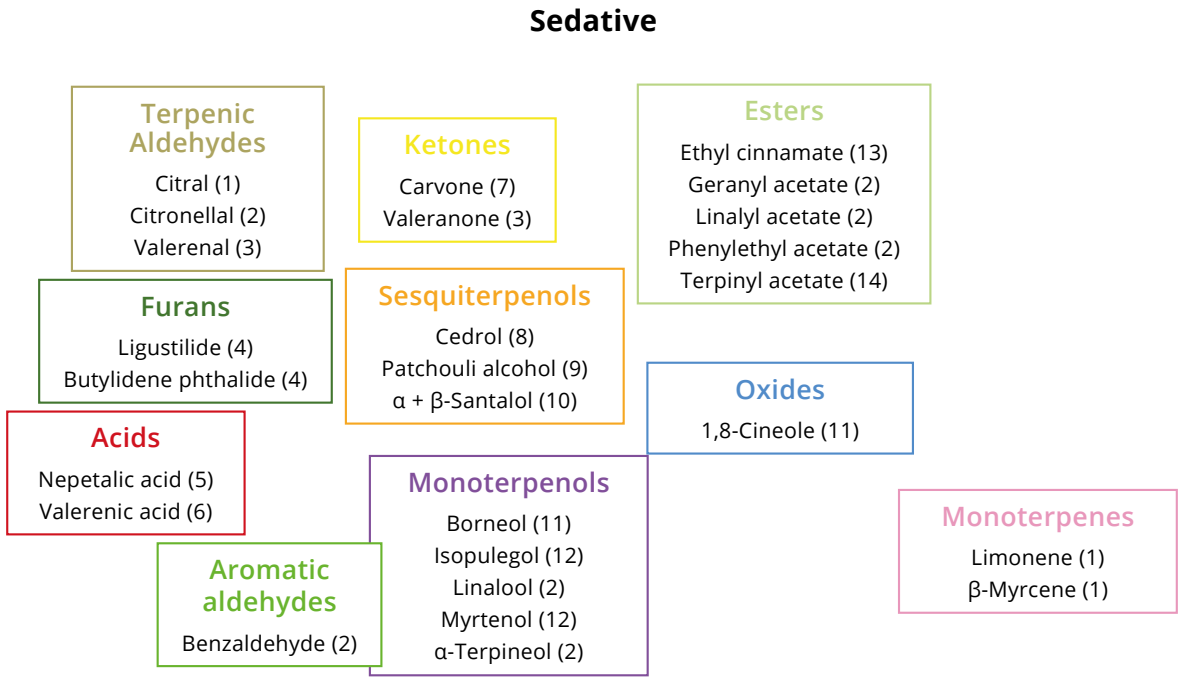

Figure 6. Constituents with sedative activity and where they would appear on the FGT grid.
(See 10.3 Sedative references for figure 6 for key to citations.)

These activities were compared to those predicted by FGT, and any other chemical family that shows these activities was noted. We wanted to answer the following questions: do all MAs show the same range of activities? Do these compare with those predicted by FGT? Do other functional groups also show the same or a similar range of activities? Finally, we isolated a specific activity shown by MAs, namely analgesia, and compared MAs to all the other terpenoids to evaluate how many functional groups also show analgesic activity.

4.1 Empirical data for monoterpene alcohols

Over 500 studies on the activities of monoterpene alcohols were evaluated, and 150 were selected for inclusion. We found evidence for 32 distinct activities for 17 different MAs: borneol, carveol (various isomers), citronellol, dihydrocarveol, fenchyl alcohol, geraniol, isoborneol, isopulegol, linalool, menthol, myrtenol, nerol, perillyl alcohol, *trans*-pinocarveol, terpinen-4-ol, α-terpineol, and (S)-*cis*-verbenol (table 4). (We treated neoisopulegol and isopulegol as a single molecule.) We decided not to distinguish between *in vitro* tests, animal tests, and human trials in this paper, as we were interested in collecting all available indications of possible therapeutic action. We then analyzed the data to check whether these activities were unique to MAs and whether they applied to all MAs, as would be expected from FGT.

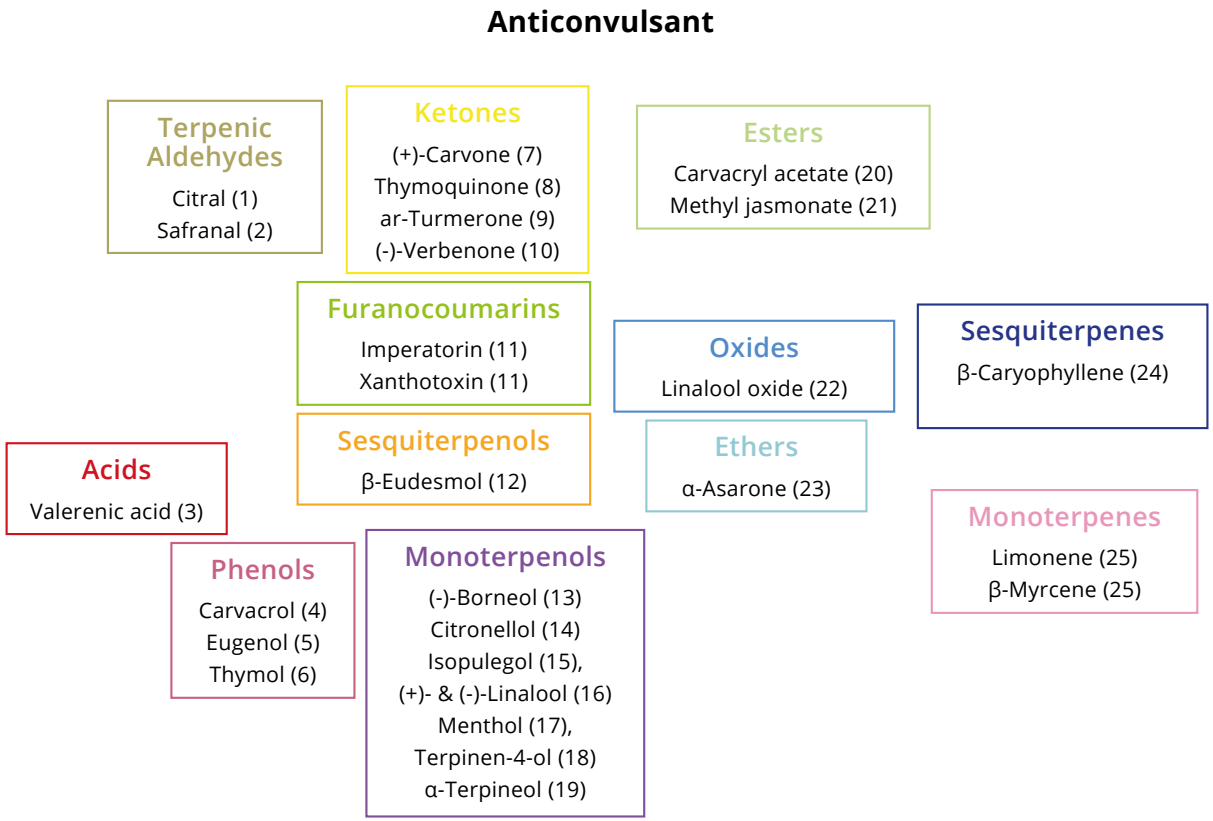

Figure 7. Constituents with anticonvulsant activity and where they would appear on the FGT grid.
(See 10.4 Anticonvulsant references for figure 7 for key to citations.)

4.1.1 The activities of monoterpene alcohols are not unique

We found that the main activities shared by most MAs, and reported in most studies, were also shared by many other functional groups. Figures 6, 7, 8, and 9 summarize the data for four activities of MAs: sedative, anticonvulsant, analgesic, and anti-inflammatory. These graphics show that the most salient activities of MAs are also shared by molecules of many other functional groups. This seems to especially apply to both analgesic and anti-inflammatory activity, and one possible reason is that there are multiple pathways and mechanisms through which these effects can take place in the body. Thus, it is useful to know mechanisms of action and the type of pain or inflammation that needs to be addressed so that more informed choices can be made. Simply labelling an essential oil or constituent as "anti-inflammatory" tells us very little since this property is so common.

4.1.2 Do monoterpene alcohols share properties?

But if these activities are not unique to MAs, are they at least possessed by all MAs? In this case the literature clearly shows that of the 32 activities studied over 17 MAs, only two activities are shared by a significant number of MAs. Anti-inflam-

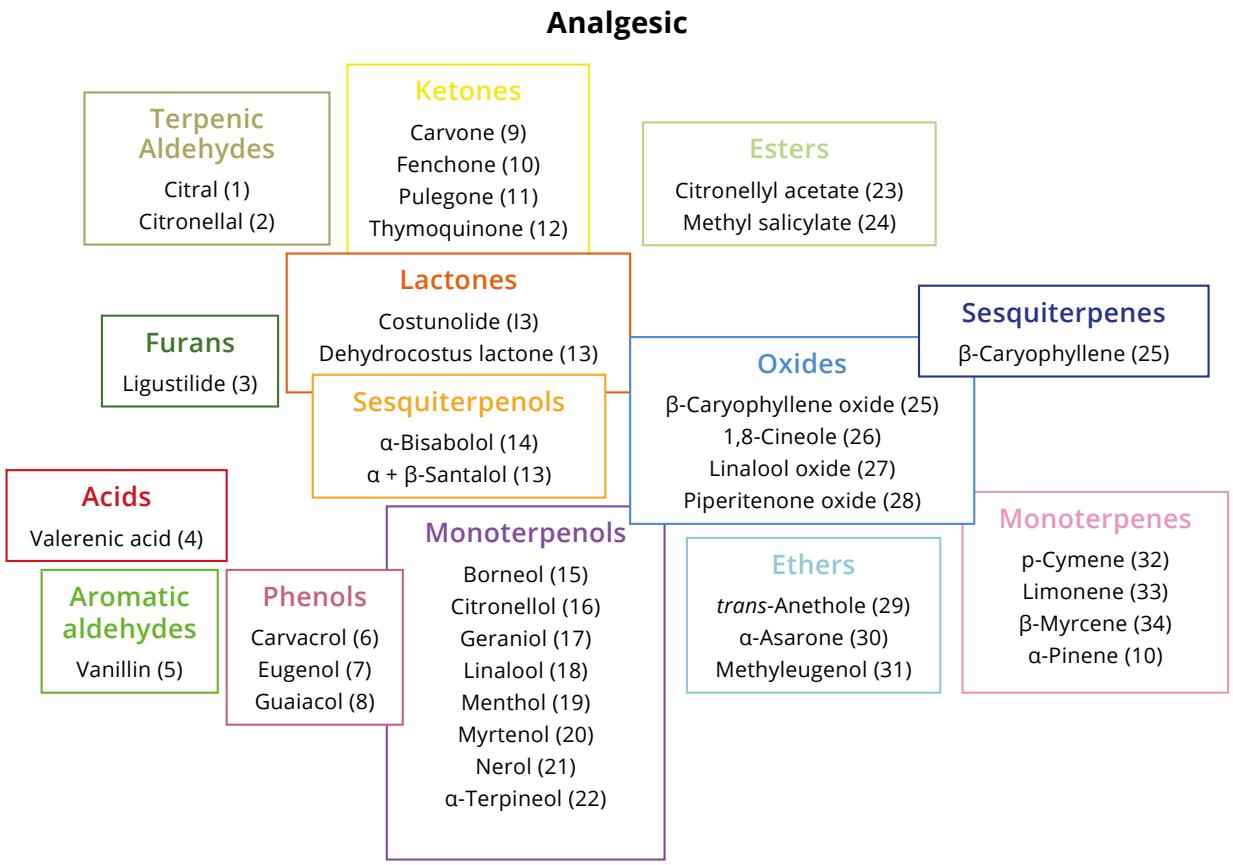

Figure 8. Constituents with analgesic activity and where they would appear on the FGT grid.
(See 10.5 Analgesic references for figure 8 for key to citations.)

matory activity (with 11 active molecules) and analgesic activity (with eight active molecules) are most commonly shared. We then have anticonvulsant and sedative activity shared by five molecules and all the others being shared by two, three, or four molecules, or not being shared at all (table 5). One of these activities, sedative, is not recognized as valid by FGT, which states that MAs are stimulants (Franchomme and Pénoël, 1990; Price and Price, 2012).

If we include mechanism of action as demonstrative of effect, 13 of the 17 MAs showed CNS depressant activity: borneol, carveol, dihydrocarveol, isoborneol, isopulegol, linalool, menthol, myrtenol, neoisopulegol, nerol, pinocarveol, terpinen-4-ol and verbenol in various isomeric forms. A detailed elaboration of these properties can be seen in table 8. This suggests the possibility that all these molecules are CNS sedatives.

Activity	Number	Activity	Number
Analgesic	**8/17**	Anticonvulsant	5/17
Local anesthetic	1/17	Antiepileptogenic	1/17
Antihyperalgesic	1/17	Antidepressant	1/17
Cooling	1/17	Anxiolytic	2/17
Antinociceptive	1/17	Sedative	5/17
Nerve conduction	4/17	Neuroprotection	3/17
Antiarrhytmic	1/17	Antidislipidemic	1/17
Antihypertensive	1/17	Antioxidant	3/17
Effects on contractility	1/17	**Anti-inflammatory**	**11/17**
Vasorelaxant	2/17	Antiobesity	1/17
Vasoprotective	1/17	Antihyperglycemia	1/17
Anti-diarrheal	1/17	Antihyperuricemia	1/17
Antiperistaltic activity	1/17	Counterirritation	1/17
Antiasthmatic	1/17	Cytoprotective	1/17
Cough inhibitor	1/17	Duodeno protection	1/17
Subjectively improve nasal airflow without decrease nasal resistance	1/17	Gastroprotection	4/17

Table 5. Numbers of monoterpene alcohols with similar therapeutic properties.

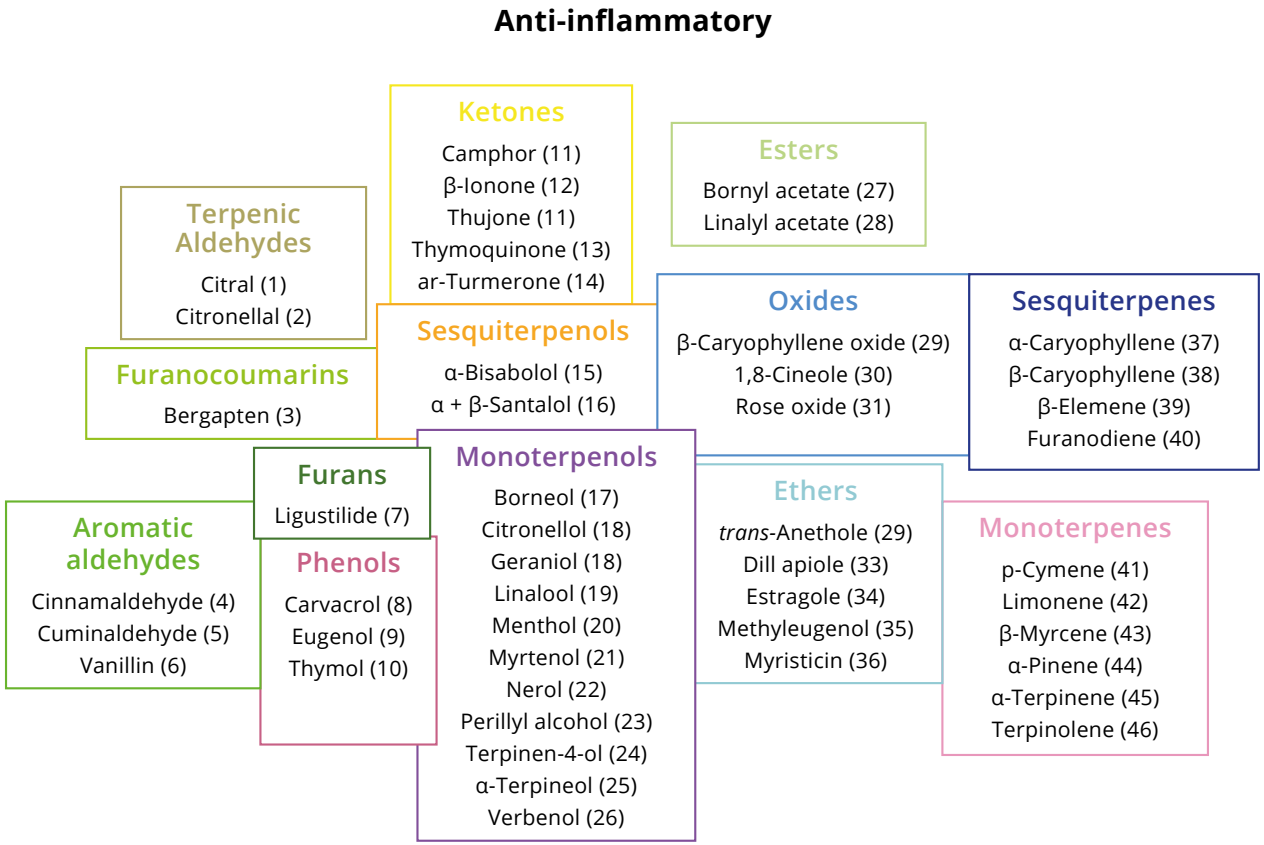

Figure 9. Constituents with anti-inflammatory activity and where they would appear on the FGT grid.
(See 10.6 Anti-inflammatory references for figure 9 for key to citations.)

4.2 Evaluation of structural details to improve the predictive power of functional group theory

Are there chemical features other than functional groups that might be more useful in describing/predicting the activity of MAs? We examined whether the analgesic, anesthetic, and nerve desensitization activities of MAs could be predicted by their 3-D structure, position of the hydroxyl group, and stereo-isomer properties. Table 6 shows the clustering of activities based on whether a molecule was linear, monocyclic, or bicyclic.

This shows that the addition of the descriptor of whether a molecule was linear, monocyclic, or bicyclic did not significantly add to FGT in terms of being able to predict a molecule's likely therapeutic function.

It must be stressed that in the literature we found investigations of general activity categories (analgesic, anti-inflammatory, sedative) or more specific investigations of the mechanisms responsible for the activity (i.e., receptor binding or modulation). Even though a general activity can and is shared by different chemical classes, it may derive from different mechanisms.

> *"This shows that the addition of the descriptor of whether a molecule was linear, monocyclic or bicyclic did not significantly add to FGT in terms of being able to predict a molecule's likely therapeutic function."*

4.2.1 Linear monoterpene alcohols

Linear monoterpene alcohols (LMAs) show evidence of stronger antioxidant and anti-inflammatory properties than other MAs, and this leads to a first cluster subdivision. Linalool, geraniol, citronellol, and nerol inhibit inflammation in different ways and at different stages of the inflammatory cascade (Su *et al.,* 2010; Huo *et al.,* 2013). Linalool decreases induced expression of NO and NFkB and other inflammatory mediators such as TNF-α and some interleukins such as IL-6 (Li *et al.,* 2015). Moreover, citronellol and geraniol increase the activity of antioxidant pathways (SOD, GST, CAT) and decrease COX-2 expression, possibly via PPAR modulation (Katsukawa et al., 2011). These different mechanisms of action suggest differences in the types and causes of inflammation that these molecules might address. For example, linalool decreases levels of inflammatory molecules, while citronellol and geraniol inhibit inflammatory pathways and increase antioxidant activity.

LMAs, specifically linalool (Peana *et al.* 2003), also exert an analgesic-like activity. Numerous papers offer evidence of this activity for these tertiary MAs and show how the final effect is obtained via interaction with different pathways and targets: opioid (Peana et al., 2003; Sakurada *et al.,* 2011), adenosine (Peana *et al.,* 2006a), glutamate (Batista *et al.,* 2008), dopamine, and acetylcholine (Peana *et al.,* 2004). It is also possible that a smaller contribution to the analgesic effect is due to interaction with transient receptor potential (TRP) channels (Batista *et al.,* 2011) – receptor sites that are often involved in sensations of heat, cold, irritation, or pain.

Linalool also has an anesthetic effect that can be linked with analgesic effect under the general category of effects on pain perception, but in this case the effect is weaker than the one shown by citronellol and geraniol (Ohtsubo *et al.,* 2015). This effect is mediated by a TRP-independent inhibition of compound action potentials (CAPs) that lead to nerve conduction impairment. This reduction of nerve excitability seems to be characteristic of linear MAs and a few others, such as borneol.

	Number of studies		
Property	**Linear MAs**	**Monocyclic MAs**	**Bicyclic MAs**
Analgesic*	Linalool (8) Citronellol (3)	Menthol (8)	
Anti-inflammatry**	Geraniol (9) Linalool (7) Citronellol (4)	Terpinen-4-ol (3)	
CNS-depressant/ sedative*	Linalool (7)	Menthol (3) Isopulegol (3)	Myrtenol (3) Verbenol (2)

Table 6. Biological activities of monoterpene alcohols according to carbon skeleton, and for which we found more than two citations
* For all the other molecules we could find only 1 study.
** For all the other molecules we could find only 1 or 2 studies

Linear monoterpenols

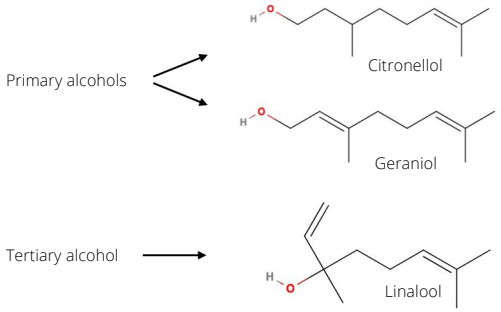

Figure 10. Linear monoterpene alcohols.

Finally, the literature shows that linalool also has a sedative effect in human and animal models (Höferl *et al.,* 2006; Gastón et al., 2016). Although it is difficult to draw conclusions from the limited data, it is apparent that linalool, a linear, tertiary monoterpene alcohol, has a unique activity pattern. This suggests that deeper analysis

of structural features beyond simple functional group is a better descriptor and perhaps predictor of pharmacological activity.

4.2.2 Monocyclic monoterpene alcohols

Although the monocyclic structure gives rise to a wider class of molecules compared with the linear one, most of the literature deals only with menthol and its isomers. Menthol is unique (Farco and Grundmann, 2013), in that it is the only monocyclic monoterpene alcohol (MMA) so far investigated that exerts its analgesic activity via opioidergic system interaction (Galeotti *et al.,* 2002). Nevertheless, the scientific literature is mainly concerned with its strong local anesthetic activity involving Na^+ and Ca^{2+} channels and marked TRP channel modulation (Swandulla et al., 1987; Haeseler *et al.,* 2002; Abe *et al.,* 2006). This activity probably explains menthol's cough

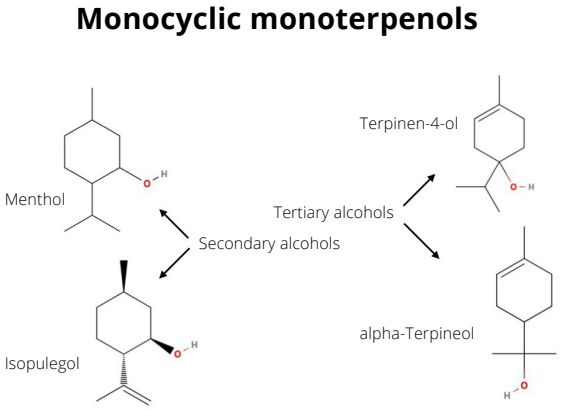

Figure 11. Monocyclic monoterpene alcohols.

inhibition (Buday *et al.,* 2012) and its effect on subjective nasal airflow (Lindemann *et al.,* 2015). Furthermore, it seems to explain the efficacy of menthol and menthol-rich essential oils in the treatment of different kinds of itch and local pain (Amjadi *et al.,* 2012; Elsaei *et al.,* 2016; Fallon *et al.,* 2015). Menthol also shows GABA receptor interaction, which implies a possible sedative effect (Zhang *et al.,* 2008).

It appears that chirality plays a role in the mechanism of action of the molecule. Although (-)-menthol and (+)-menthol show an equal local anesthesia (Galeotti *et al.,* 2001), (-)-menthol demonstrated central analgesic properties not shared by (+)-menthol (Galeotti *et al.,* 2002). (-)-Menthol is the isomer most commonly found in nature. Moreover, general TRP modulation can be broken down to show that menthol acts on specific subfamilies such as TRPM8, TRPV3, and TRPA1 (Farco and Grundmann, 2013) and that, in the case of TRPA1, it has a bimodal effect (can activate and/or deactivate) depending on dose and on human or mouse subtype (Karashima *et al.,* 2007).

Other MMAs interact strongly with the TRPV3 subfamily, though not in the same way as menthol; the literature shows lower effective concentrations (ECs) respectively for dihydrocarveol, carveol, and isopulegol compared to menthol (Vogt-Eisele *et al.,* 2007). The investigations on TRPV3 binding suggest that the -OH position on the carbon skeleton may be a key feature that predicts the type of TRP modulation; this probably explains why terpineol is not active.

It could be asserted that TRP modulation is much more common for MMAs than for other MAs. Linear MAs demonstrate only weak modulation of TRPA1 and TRPM8. Amongst bicyclic structures borneol alone exhibits relevant activity stronger on TRPV3 than on TRPM8 and TRPA1 (Takaishi *et al.,* 2014; Chen *et al.,* 2016). All other compounds that have been studied so far show a rather weak modulation on all three TRP subtypes.

Vogt-Eisele and colleagues and Sherkheli and colleagues analyzed and discussed SAR for MAs. They consider O and C=C position as critical features for the final effect while showing how these features are not unique to MAs and can be found in molecules with different functional groups (Vogt-Eisele *et al.,* 2007; Sherkheli *et al.,* 2009).

4.2.3 Bicyclic monoterpene alcohols

Bicyclic monoterpene alcohols (BMAs) seem to be the major class of compounds involved in CNS depressant activity. Compounds carrying a pinane type bicyclic skeleton strongly enhance GABA evoked currents via allosteric modulation of $GABA_AR$ (Kessler *et al.,* 2014). This positive allosteric

modulation, either at synaptic or extrasynaptic $GABA_A$ receptors, augments either phasic or tonic (respectively) GABAergic inhibition in the CNS (Jonas and Buszaki, 2007). Most of the tested MAs demonstrate only phasic GABAergic inhibition while two, myrtenol and verbenol, demonstrate both phasic and tonic inhibition (van Brederode *et al.,* 2016).

Granger and colleagues show how other bicyclic structures interact differently with $GABA_AR$ depending on GABA concentration – borneol enantiomers and the isomer isoborneol, for example (Granger *et al.,* 2005). At the same time, they underline how small structural differences lead to different mechanisms of interaction with the target. This bimodal effect is common in various well-studied enantiomers such as (+)- and (-)-menthol and (+)- and (-)-linalool and highlights the fact that FGT does not consider this subtle but fundamental dissimilarity (Galeotti *et al.,* 2002; Höferl *et al.,* 2006).

CNS depressant activity is less potent in LMAs than BMAs, except in the case of linalool. Although MMAs such as menthol isomers, isopulegol, dihydrocarveol, and carveol show an increased phasic GABAergic inhibition, the effect is weaker than that of BMAs (Kessler *et al.,* 2014). The comparison seems to suggest a critical role for the bicyclic skeleton and the -OH position in determining activity.

Byciclic monoterpenols

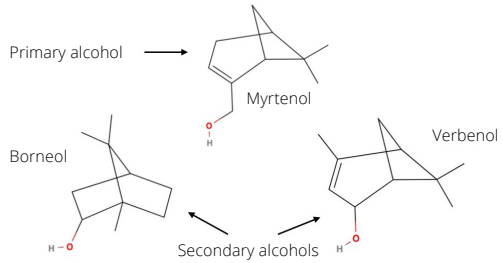

Figure 12. Bicyclic monoterpene alcohols.

4.2.4 Monoterpene alcohols – other effects and mechanisms

In (bicyclic) borneol and in (monocyclic) isopulegol and terpinen-4-ol, anticonvulsant activity is linked to the GABAergic system (Silva *et al.,* 2009a; Quintans-Júnior *et al.,* 2010; Nòbrega et al., 2014). Some studies demonstrate how the anti-inflammatory/antioxidant properties of these MAs increase their anti-seizure activity (Tambe *et al.,* 2016).

Gastro- and duodenoprotective effects (de Carvalho *et al.,* 2014; Rozza *et al.,* 2014; Viana *et al.,* 2016) and neuroprotection (Liu *et al.,* 2011; Sabogal-Guáqueta *et al.,* 2016) have also been observed. From the analysis of the underlying mechanism and pathways, the antioxidant and anti-inflammatory properties of all classes of MA are responsible for this final protective effect. This is also true for antidyslipidemic activities (those which counteract the imbalance of lipids, such as cholesterol). Moreover, geraniol, linalool, and perillyl alcohol show a cholesterol-reducing effect through inhibiting a key enzyme, HMG-CoA reductase (Peffley and Gayen, 2003; Cho *et al.,* 2011; Jayachandran *et al.,* 2015).

Continuing to analyze other emerged properties demonstrates once again that any attempt to categorize therapeutic potential based on 3-D shape alone would be pointless. Their activities or underlying mechanisms shared at least two of the three structures – linear, monocyclic, or bicyclic.

4.3 Empirical data on analgesic activity

As previously mentioned, any real predictive power of SAR depends on mechanistic knowledge. So, we need to go beyond the simple description of a final effect and investigate mechanisms. Although the test used to verify one activity on different molecules is always the same, it might not be able to discriminate between different mechanisms of action; is the analgesic activity secondary to an anti-inflammatory one, or is it a direct one? Is it central or peripheral? On which receptor does the molecule act? This kind of information can help practitioners make clinically relevant decisions.

In order to look at activities in a more specific way, mechanisms and targets need to be identified. Looking at the data on

the three main activities, we have clearly defined pathways and mechanisms for the anti-inflammatory one, but the specific primary target is often omitted in the literature. Even subdividing the data according to the different pathways doesn't necessarily help in isolating the target, since different targets can lead to similar cascades of molecular and cellular events. The CNS-depressant activity is often based on good clinical evidence, but most studies do not investigate mechanisms and primary targets. Except for myrtenol, verbenol, menthol, borneol, and isoborneol, which are known to modulate GABAAR, we don't have much detail on mechanisms. We know other molecules have GABA-like activity, but we don't know which receptor they bind to or whether they act via tonic or phasic modulation.

We therefore decided to focus on pain relief. In this case, mechanisms and targets are better identified: there is a direct central effect on the CNS through different neurotransmitters (opioid peptides, adenosine and glutamate), and there is a peripheral effect mediated by TRP channel modulation, CAP inhibition, or NO synthesis and release.

At this stage we can look at whether other descriptors are more useful to describe and predict analgesic activity and see whether there are other functional groups that are also active.

Our review of the literature shows that each molecule possesses a different mechanism of action, that not all MAs exert analgesic/antinociceptive activity, and that this activity is not limited to specific MAs but is rather widely shared by other molecules belonging to different functional groups. This includes monoterpenes, oxides, phenols, ketones, aldehydes, and ethers possessing either 10 or 15 carbon atoms (figure 8). Furthermore, the main and validated animal models of nociception considered here, rats and mice, show how analgesic activity is common both to hydrocarbon terpenes and to oxygenated ones. This strongly suggests that oxygenated functional groups are not necessary for this activity (de Sousa, 2011; Guimarães *et al.,* 2013).

Linear monoterpenoid molecules usually modulate the opioid system (de Sousa, 2011, Guimarães *et al.,* 2013; Peana *et al.,* 2003, 2006a; Brito *et al.,* 2012) and decrease the release of NO (Li *et al.,* 2015; Su *et al.,* 2010, Soubh *et al.,* 2015; Brito *et al.,* 2012). They bind likewise to TRP receptors, albeit less strongly than monocyclic MAs (Behrendt *et al.,* 2004; Vogt-Eisele *et al.,* 2007). CAP inhibition is also involved in the analgesic-like effect (La Rocca et al., 2016; Ohtsubo *et al.,* 2015; Leal Cardoso et al., 2010). Linear MAs seem to possess both analgesic and anti-inflammatory activities at the same time. In the case of linalool, several modulations contribute to its analgesic activity, including interactions with opioidergic, adenosinergic, dopaminergic, glutamatergic, and cholinergic systems (Guimarães *et al.,* 2013). Monocyclic monoterpenols seem to exert their analgesic effect without the participation of the opioid system, with the notable exception of (-)-menthol systems (Guimarães *et al.,* 2013; de Sousa, 2011).

A key for analgesic activity seems to be the involvement of different kinds of modulation (agonism/antagonism) on the TRP receptor family. In fact, menthol and its isomers modulate more TRP receptor family subgroups when compared to other molecules. It must be stressed that, excluding these molecules, few studies show a relationship between TRP modulation and pain relief.

Bicyclic monoterpenols do not appear to exert significant analgesic activity. Borneol shows a peripheral activity via CAP and TRPA1 inhibition (Ohtsubo *et al.,* 2015; Sherkheli *et al.,* 2015; Takaishi *et al.,* 2014). Even though BMAs as a class show a wide interaction with the GABAergic system (Kessler *et al.,* 2014; van Brederode *et al.,* 2016), only borneol exerts a central analgesic activity via a probable but unclear GABAAR modulation (Jiang *et al.,* 2015). Other bicyclic MAs inhibit only the inflammatory phase by blocking some components of the inflammatory cascade such as TNF-α or NO (Silva *et al.,* 2014).

> *"Our review of the literature shows that each molecule possesses a different mechanism of action, that not all MAs exert analgesic/antinociceptive activity, and that this activity is not limited to specific MAs but is rather widely shared by other molecules belonging to different functional groups."*

4.3.1 Position of the -OH functional group in addition to 3-D shape

Monoterpene alcohols can have their hydroxyl (-OH) groups attached in three different formats. The position of the alcohol group determines what types of chemical reactions can occur at that location and may affect therapeutic activity. See figure 13 for a generic illustration.

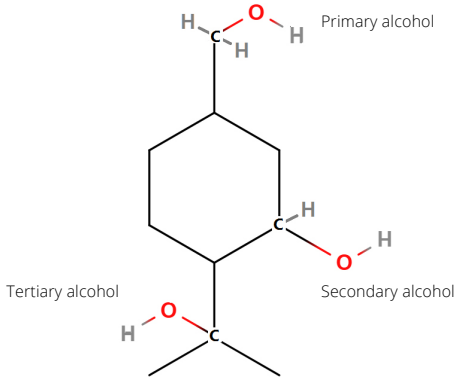

Figure 13. Three possible positions of the hydroxyl group in an alcohol molecule.

1. Primary alcohols have the hydroxyl group on a terminal carbon atom. They can oxidize to aldehydes. Geraniol, citronellol, and myrtenol are examples from figures 10 and 12.

Molecule	Structure	-OH position	Mechanism
Borneol	Bicyclic; camphane type	Secondary	Probable TRPA1 involvement* (Takaishi et al. 2014)
(+)-Borneol	Bicyclic; camphane type	Secondary	CAP inhibition (Ohtsubo et al. 2015) GABAAR involvement (Jiang et al. 2015)
(-)- Borneol	Bicyclic; camphane type	Secondary	CAP inhibition (Ohtsubo et al. 2015)
(-)-Myrtenol	Bicyclic; camphane type	Primary	Anti-inflammatory pathways# (Silva et al. 2014)
Geraniol	Linear	Primary	CAP inhibition. (La Rocca et al. 2016, Ohtsubo et al. 2015)
S-(-)-β-Citronellol	Linear	Primary	Opioid (Brito et al. 2012) CAP inhibition (Ohtsubo et al. 2015) Anti-inflammatory pathways# (Brito et al. 2012)
R-(-)-Linalool	Linear	Tertiary	TRPA1 (Batista et al. 2011), Opioid (Peana et al. 2003, Peana et al. 2004), Cholinergic (Peana et al. 2003, Peana et al. 2004), Dopaminergic (Peana et al. 2004), Adenosinergic (Peana et al. 2006), Glutamatergic (Batista et al. 2008, Batista et al. 2011), CAP inhibition (Venancio et al. 2016)
(±)-Linalool	Linear	Tertiary	Opioid (Sakurada et al. 2011) CAP inhibition (Leal-Cardoso et al. 2010)
Linalool	Linear	Tertiary	CAP inhibition (Leal-Cardoso et al. 2010)
(+)-Menthol	Linear	Secondary	No analgesic activity (Galeotti et al. 2002) Probable TRPM8 involvement* (Behrendt et al. 2004)
(-)-Menthol	Monocyclic	Secondary	TRPM8 (Abe et al. 2006, Farco & Grundmann, 2013) Opioid (Galeotti et al. 2002) Ca++channel (Swandulla et al. 1987)
Menthol	Monocyclic	Secondary	Na+ channel (Haeseler et al. 2002)
Nerol	Linear	Primary	Mechanism not yet understood (González et al. 2016)
α-Terpineol	Monocyclic	Tertiary	Mechanism not yet understood (Quintans-Júnior et al. 2011) Anti-inflammatory pathways# (De Oliveira et al. 2012)

Table 7. Monoterpene alcohols, -OH position, TRP channel modulation, and analgesic activity.
* No direct relationship between TRP involvement and analgesic activity was found, but the research suggests this is possible and perhaps likely.
# "Anti-inflammatory pathways" include NO, TNF-α release and synthesis, COX expression, etc.

2. Secondary alcohols have the hydroxyl group on a carbon atom that is bound on either side by two more carbon atoms. They can oxidize to ketones. Menthol, isopulegol, borneol, and verbenol are examples from figures 11 and 12.

3. Tertiary alcohols have the hydroxyl group on a carbon atom that is bound on all three remaining bonds by other carbon atoms. Tertiary alcohols cannot be oxidized, and thus will not form aldehydes or ketones. Linalool, terpinen-4-ol, and α-terpineol are examples from figures 10 and 11.

4.3.2 Transient receptor potential channel binding

Looking specifically at TRP binding, different molecules interact with different types of TRP receptors. The mode of interaction (agonism/antagonism) can also be different. Although potencies are very different between compounds, the final effect is dose-dependent and can be the same for different molecules. Even when looking at specific targets, TRP binding is not limited to MAs (Kumamoto and Fujita, 2016; Macpherson *et al.,* 2006; Matsushita *et al.,* 2013).

TRPM8, for example, is a common target of compounds belonging to different functional groups (menthol, 1,8-cineole, thymol, hydroxycitronellal, citral) often sharing the same mode of activity (agonism) (Behrendt *et al.,* 2004; Bharate and Bharate, 2012; Kumamoto and Fujita, 2016; Stotz *et al.,* 2008). At the same time, not all MAs bind to TRP receptors.Therefore TRP binding, like analgesic activity, is neither unique to MAs, nor is it universal in MAs. We included a consideration of -OH position in table 7 to see if it affected TRP receptor response to MAs.

The addition of the -OH position as a descriptor does not appear to contribute much to the predictive value of FGT either as not all molecules with the same linearity and -OH position share the same effects on the same mechanisms.

4.4 Summary of monoterpene alcohol characteristics

FGT is only useful if it can isolate a functional group which has specific activities that are common to its members and that are more potent than the same activities in most other functional groups. Our review showed that only one property was found in more than 50% of MAs: 65% (11 of 17) were anti-inflammatory. Even this property is not special to MAs since it is also seen in most other functional groups (figure 9).

Our review of MAs revealed four notable properties – analgesic, sedative, anticonvulsant, and anti-inflammatory – that are also found in many other functional groups. Many MAs do not show the activity shared by others and some are only partially active; others share patterns of activity that reveal clusters centered around MA subgroups, which are defined only partially by chemical structure (linear, monocyclic, or bicyclic).

Even when we added 3-D structure and -OH position descriptors, it did not add more predictive power to the FGT model. Moreover, when we focused on specific activities, we found that each molecule possessed an intrinsic pattern of activity not shared by other similar molecules. This is shown with linalool and geraniol, (+)-menthol and (-)-menthol, and dihydrocarveol and terpinen-4-ol. We found that the molecular similarity of isomers does not necessarily imply functional similarity. Exceeding standard perspectives on functional group theory by including several other descriptors also does not reveal clear structure–activity relationships for the most well-researched functional group.

5 Extrapolation from constituents to whole essential oils

FGT is firmly based on the idea that the properties of a constituent carry over to an essential oil that contains it. This makes sense, but with certain provisos and limitations. Simple logic dictates that the higher the percentage of a constituent, in either a single oil or blend, the more its properties will carry over. For any pharmacological property there is a threshold dose. Below

this dose there will be no effect. This suggests, for example, that the more essential oils there are in a blend, the less effective any single constituent will be. However, this does not take into account possible synergy or antagonism of the constituents.

The net effect of any mixture will likely include some synergistic effects, some antagonistic effects, and some additive effects. For example, the antioxidant activity of 10 essential oils was shown statistically to be mostly additive, i.e., what would be expected from the activity of their individual constituents (Bentayeb et al., 2014). When measuring the anticholinesterase action of *Salvia lavandulaefolia* essential oil, a combination of camphor and 1,8-cineole was found to be antagonistic, i.e., less than expected (Savelev *et al.,* 2003). The opposite, a greater than expected effect known as synergy, is also possible. This was seen in Citrus bergamia oil when testing for cytotoxicity against a type of brain cancer cell. None of the individual constituents were effective, but two of them – limonene and linalyl acetate – were highly effective when combined (Russo *et al.,* 2013).

For many – perhaps even most – essential oils, these complexities mean that predicting pharmacological properties from those of their major constituents can be problematic since unexpected effects can take place when just the major constituents are combined. This does not consider the possible influence of minor constituents, and sometimes these have major effects. An obvious example is that of phototoxicity. Phototoxic constituents often constitute only 1% of an essential oil, yet they can have dramatic effects in the presence of UV radiation. This does not show synergy but rather the potential importance of minor constituents. In *Ocimum gratissimum* oil none of the individual constituents (eugenol, 1,8-cineole, and β-caryophyllene) demonstrated the sedative effect of the whole essential oil, but it was not tested whether this was due to major or minor constituent synergy (Galindo *et al.,* 2010).

It is common to find summaries of essential oils listing percentages of phenols, ketones, esters, etc. However, this tells us very little about the properties of the essential oil and can be misleading if unfounded assumptions are made about specific functional groups. For example, *Artemisia annua* oil containing up to 34% artemisia ketone is flagged as neurotoxic by Franchomme and Pénöel (1990) because of their premise that ketones are all neurotoxic. However, an *A. annua* oil with 35% artemisia ketone was only neurotoxic in mice at doses of 1,500 mg/kg i.p., and not at lower doses (Radulovic *et al.,* 2013). This is equivalent to a human injection of about 100 g, and therefore *A. annua* oil is likely not neurotoxic, unless used in a massive overdose.

6 Functional group theory as a learning tool

Any in-depth education about essential oils should include information about constituent chemistry and pharmacology/toxicology. Students need to know, for example, that thujone is neurotoxic to rodents, that common Sage *(Salvia officinalis)* oil contains lots of thujone, and that this essential oil can cause convulsions in humans when ingested (Burkhard *et al.,* 1999).

We propose that this is an easier and more logical method than learning that "all ketones are neurotoxic, *ar*-turmerone is a ketone, and Turmeric *(Curcuma longa)* oil contains lots of ar-turmerone and should be neurotoxic but actually is not because this is an exception to the rule." None of that thought process needs to happen if we simply identify which ketones are neurotoxic and focus on them in terms of safety. Students should do the work of learning about individual essential oils and individual constituents. Not receiving instruction in FGT makes this process easier.

> ***But if one is serious about the pharmacology of essential oils or other preparations, it's time to move beyond simplistic generalisations, towards individual constituents and their interactions.*** **-Petra Ratajc (2018)**

When studying the action of essential oil constituents in the body, students will find some commonalities within functional groups. Some of these occur because the molecules are similar. Students will also learn about functional groups since they are a basic part of learning essential oil chemistry. But learning functional group theory as a shortcut to understanding the complexity of these natural substances is not sensible nor logical, and it cannot be justified.

7 Conclusions

Our analysis found that FGT is a limited SAR model accompanied by unscientific references to a supposed role of electrical resistivity and polarity in determining therapeutic activity. Our review of FGT literature revealed no attempt at systematic and statistical treatment of data, hence no attempt to build a predictive or descriptive model. None of the FGT literature explains the methodology used to gather supporting data, and claims are not supported by evidence in many circumstances. Many of the activities assigned to chemical classes are based on practitioners' opinions of a very limited set of essential oils, and authors sometimes differ in the properties they ascribe to the same functional group.

FGT is only useful if it can isolate a functional group which has specific activities that are common to its members and are more potent than the same activities in most other functional groups. Its explanatory and predictive powers are otherwise highly limited. Our review of monoterpene alcohols, the most well-researched functional group, revealed that their most notable properties also cross over into other functional groups. Many MAs do not show the activity shared by others and are partially active. Others do share patterns of activity, but these are defined only partially by chemical structure (linear, monocyclic, or bicyclic). We found that each MA possessed an intrinsic pattern of activity not shared by other similar molecules and that the molecular similarity even of isomers does not necessarily imply functional similarity.

A major assertion of FGT is that MAs are CNS stimulants. However, our review found that many MAs are sedative/CNS depressant, and we found none with evidence of CNS stimulant activity.

FGT does possess some descriptive power when analysis remains at a general, unspecific level. This is especially the case when mechanistic activity is not considered. However, even at this level functional groups are just one of many useful descriptors, and most ascribed properties are too generic to be useful. Going beyond the functional group to include greater levels of complexity does not reveal clear structure–activity relationships for the most well-researched functional group.

FGT is not currently able to perform its purported descriptive and predictive functions, its conclusions are too absolute, and many of its claims do not stand up to scrutiny. FGT is therefore not a useful tool for research because it fails to identify the most relevant molecular features linked to activity, and it is not useful for teaching because it suggests solid and fixed relationships that do not exist.

The action of a single major constituent is of great relevance to the action of an essential oil containing it. However, the assumption that constituent activity can be readily extrapolated to essential oil activity can be problematic, because it does not consider possible antagonistic or synergistic interactions between constituents.

If we are looking for ways to understand the properties of essential oils and constituents, we should simply look at the research on those essential oils and constituents and look for QSAR data if there is any. There is no need to create an elaborate framework based on simplistic generalizations.

> ***"FGT is only useful if it can isolate a functional group which has specific activities that are common to its members and are more potent than the same activities in most other functional groups. Its explanatory and predictive powers are otherwise highly limited."***

8 Limitations

This is not a systematic analysis and does not claim to identify the real factors that determine SAR for terpenoids. This would be a complex and time-consuming task that would need to be carried out with powerful statistical and computing techniques by SAR experts. We examined MAs in detail because there is more published research for MAs than for any other functional groups. δ

9 Abbreviations

BMA	Bicyclic monoterpene alcohol
CAP	Compound action potential
CAT	Catalase
CNS	Central nervous system
COX-2	Cyclooxygenase-2
CYP	Cytochrome P450
EC	Effective concentration
FGT	Functional group theory
GABA	Gamma-aminobutyric acid
GST	Glutathione S-transferase
HMGCoA	3-Hydroxy-3-methyl-glutaryl-coenzyme A
HOMO	Highest occupied molecular orbital
IL	Interleukin
LMA	Linear monoterpene alcohol
LogKo/w	This is the logarithm of the partition coefficient between n-octanol and water (Ko/w). It is a measure of the lipophilicity or hydrophobicity of a molecule and is sometimes written LogP.
LogKp	This is the logarithm of the skin permeability coefficient (Kp), and it is used to relate the skin permeability of compounds to their physicochemical parameters or structure descriptors in quantitative structure–property relationship (QSPR) models.
LUMO	Lowest unoccupied molecular orbital
MA	Monoterpene alcohol
MMA	Monocyclic monoterpene alcohol
NFkB	Nuclear factor kappa B
nAChR	Nicotinic acetylcholine receptor
NO	Nitric oxide
pH	Acidity/alkalinity scale
PPAR	Peroxisome proliferator-activated receptor
QSAR	Quantitative structure–activity relationship
QSPR	Quantitative structure–property relationship
SAR	Structure–activity relationship
SOD	Superoxide dismutase
TNF	Tumor necrosis factor
TRP	Transient receptor potential 10 10

This list does not include many abbreviations used in Table 8.

Molecular type	Molecule	Activity	Test/Model	Dose, methods of administration	Mechanism and targets. Isomer stated where known	References
Monoterpene alcohol; bicyclic; camphane type	Borneol	Analgesic, anti-inflammatory	Swiss albino mice WAA, FT, HP, Rotarod Test, Grip Strength Test. Leukocyte migration in peritoneal cavity.	5, 25-50 mg/kg i.p.	Peripheral and central (weaker) analgesic activity without motor deficit. Decreases leukocyte migration. No mechanism elucidated.	de Silva Almeida *et al.,* 2013
Monoterpene alcohol; bicyclic; camphane type	Borneol	Anticonvulsant	Swiss mice PTZ and MES seizures induced model.	50, 100, 200 mg/ kg i.p.	(-)-Borneol Prolongs seizure latency. Probable involvement of GABAergic system.	Quintans-Júnior *et al.,* 2010
Monoterpene alcohol; bicyclic; camphane type	Borneol	Anti-epileptogenic, antioxidant	Swiss albino mice PTZ-induced kindling model.	5, 10-25 mg/kg i.p.	Suppression of epileptogenesis. Decreases LPO and GFAP. Increases levels of GSH, CAT and SOD.	Tambe et al., 2016
Monoterpene alcohol; bicyclic; camphane type	Borneol	Antihyperalgesic	ICR mice SNL and CFA i.pl. neuropathic and inflammatory hypersensitivity models.	125, 250-500 mg/ kg p.o. 15, 30, 60 µg i.t.	(+)-Borneol Ameliorates mechanical hyperalgesia probably via GABAergic system.	Jiang et al., 2015
Monoterpene alcohol; bicyclic; camphane type	Borneol	Antioxidant	SD rats Oxidative stress liver model with MB/VL or DMNQ.	17-34 mg/kg p.o.	(-)-Borneol Increases resistance of DNA to oxidative damage. Significantly increases intracellular GSH. No enzymatic activity (GPx, SOD) involved.	Horváthová *et al.,* 2012
Monoterpene alcohol; bicyclic; camphane type	Borneol	Antioxidant, neuroprotective	Wistar rats OGD/R model.	0.003-0.3 µM	Inhibits NO overproduction, and iNOS activity and up-regulation. Attenuates the up-regulation of TNF-α and ICAM-1. Reduces activity of caspase-3 and 9, inhibits NF-kB nuclear translocation, inhibits IκBα degradation but does not affect the activation of p-IKKα and p-SAPK/JNK.	Liu et al., 2011
Monoterpene alcohol; bicyclic; camphane type	Borneol	CNS depressant	Xenopus oocytes expressing α1β2γ2L GABAA receptors.	(+)-Borneol EC50 248 µM (−)-Borneol EC50 237 µM	Enhancement of GABA through modulation and direct binding at GABAA α1β2γ2L receptor but not at the BZD site. Different patterns of the two enantiomers, depending on GABA concentration. (-)-Borneol acts as a partial agonist at high EC and as a modulator like (+)-borneol at lower EC.	Granger et al., 2005

Table 8. Monoterpene alcohols, their structure, activity, type of test, dose, and known mechanism(s) of action.

Molecular type	Molecule	Activity	Test/Model	Dose, methods of administration	Mechanism and targets. Isomer stated where known	References
Monoterpene alcohol; bicyclic; camphane type	Borneol	CYP modulation	Rats	33, 100, 300 mg/ kg p.o.	Increases hepatic CYP2B1/2 activity, mRNA expression, and protein expression. No CAR activation.	Chen et al., 2017
Monoterpene alcohol; bicyclic; camphane type	Borneol	CYP modulation	Rats	33, 100, 300 mg/ kg p.o.	CYP2D induction.	Chen et al., 2015
Monoterpene alcohol; bicyclic; camphane type	Borneol	nAChRs binding	Bovine adrenal chromaffin cells	300 µM	Non-competitive inhibition at a different site of ACh and nicotine. No Ca and Na kinetic involvement.	Park *et al.,* 2003
Monoterpene alcohol; bicyclic; camphane type	Borneol	Nerve conduction	Frog (Rana nigromaculata) sciatic nerve Air gap method.	3 Mm/L	(+)-Borneol Reduces CAP amplitudes in a reversible and dose-dependent manner. (-)-Borneol reduces CAP amplitudes in a weaker and non-reversible manner.	Ohtsubo *et al.,* 2015
Monoterpene alcohol; bicyclic; camphane type	Borneol	Neuroprotective	SH-SY5Y cells Aβ-induced oxidative stress model.	100 µM	(-)-Borneol and (+)-borneol inhibit Aβ-induced cell cytotoxicity. Antioxidant and antiapoptotic mechanism via up-regulation of Nrf2 and Bcl-2. Decreases expression of Bax. (+)-Borneol more active.	Hur *et al.,* 2013
Monoterpene alcohol; bicyclic; camphane type	Borneol	TRP modulation	Guinea pigs Human corneal epithelial cells HEK293 cells expressing TRPM8 receptors	100 µM - 2 mM	(+)-Borneol Demonstrates TRPM8 receptor agonism (markedly weaker than menthol). TRPM8 activation induces a Ca^{++} influx. Increases tear production in a temperature- and dose-dependent manner (stronger at 25°C than at 35°C).	Chen *et al.,* 2016
Monoterpene alcohol; bicyclic; camphane type	Borneol	TRP modulation	HEK293T cells expressing hTRPA1	1 mM	Inhibits hTRPA1 in a dose-dependent manner. S873, T874, and Y812 residues are critically involved in the interaction with the -OH group.	Takaishi *et al.,* 2014
Monoterpene alcohol; bicyclic; camphane type	Borneol	TRP modulation	HEK293 cells expressing TRPV3 and TRPM8	2 mM	(+)-Borneol Demonstrates TRPV3 agonism (stronger than camphor). No TRPM8 agonism.	Vogt-Eisele *et al.,* 2007

Table 8. Monoterpene alcohols, their structure, activity, type of test, dose, and known mechanism(s) of action.

Molecular type	Molecule	Activity	Test/Model	Dose, methods of administration	Mechanism and targets. Isomer stated where known	References
Monoterpene alcohol; bicyclic; camphane type	Borneol	TRP modulation	*Xenopus* oocytes and neurons cultured from trigeminal ganglia expressing TRPA1 receptors	IC 0.3 mM	(-)-Borneol Demonstrates TRPA1 inhibition.	Sherkheli *et al.*, 2015
Monoterpene alcohol; bicyclic; camphane type	Borneol	UGT modulation	SD rats Morphine metabolism.	100-500 µM	UGT2B7 inhibition stronger for the racemic form than (-)-borneol.	Ishii *et al.*, 2012
Monoterpene alcohol; bicyclic; camphane type	Borneol	UGT modulation	CD-1 mice SD rats *In vitro* assay. Propofol metabolism.	100-200 mg/kg i.p	Racemic form prolongs propofol anesthesia. (-)-Borneol inhibits propofol glucoronidation.	Lin *et al.*, 2006
Monoterpene alcohol; bicyclic; camphane type	Borneol	Vasorelaxant	Wistar rats, isolated rat thoracic aorta artery rings	200 µM	(-)-Borneol Decreases Ca^{++} influx by blocking the L-type Ca channels. Promotes calcium mobilization from the intra-cellular stores. K^{+} channel activation.	Silva-Filho *et al.*, 2011
Monoterpene alcohol; monocyclic	Carveol	TRP modulation	HEK293 cells expressing TRPV3 and TRPM8	10-9 - 10-3 M	(-)-Carveol Demonstrates TRPV3 agonism (stronger than camphor).	Vogt-Eisele *et al.*, 2007
Monoterpene alcohol; monocyclic	Carveol	TRP modulation	Flp-In 293 cells and HEK293T cells expressing hTRPA1 and hTRPV1 respectively	2 mM	(-)-Carveol Demonstrates weak, almost full agonism on hTRPA1.	Moon *et al.*, 2015
Monoterpene alcohol; monocyclic	Carveol	nAChRs binding	*Xenopus oocytes* expressing human α7 nicotinic acetylcholine receptors	EC 189.1±26.8	Inhibition of human nicotinic acetylcholine receptors in a non--competitive and concentration-dependent manner.	Lozon *et al.*, 2016
Monoterpene alcohol; monocyclic	Carveol	CYP modulation, UGT modulation	CD-1 mice SD rats *In vitro* assay. Propofol metabolism.	100-200 mg/kg i.p. 200 µM	(-)-Carveol Prolongs anesthesia time by inhibiting CYP450 catalyzed propofol metabolism.	Lin *et al.*, 2006

Table 8. Monoterpene alcohols, their structure, activity, type of test, dose, and known mechanism(s) of action.

Molecular type	Molecule	Activity	Test/Model	Dose, methods of administration	Mechanism and targets. Isomer stated where known	References
Monoterpene alcohol; monocyclic	Carveol	CNS depressant	*Xenopus* oocytes expressing rat GABA α1β2 and human GABA α1β2γ2 HEK293 cells expressing human GABA α1β2γ2	30-100, 600 μM	(-)-Carveol Enhances $GABA_AR$ evoked current binding γ2 subunit independent via allosteric modulation (phasic inhibition).	Kessler *et al.*, 2014
Monoterpene alcohol; linear	Citronellol	Analgesic	Albino Swiss mice FON, CTO, GTO.	25, 50, 100 mg/kg i.p.	S-(-)-β-Citronellol Inhibits orofacial pain. Probable involvement of retrosplenial cortex and periaqueductal grey.	Brito *et al.*, 2013
Monoterpene alcohol; linear	Citronellol	Analgesic	Albino Swiss mice CG-induced edema, MHC MHP, MHTNF-α, MHD.	25, 50, 100 mg/kg i.p.	S-(-)-β-Citronellol Reduces mechanical hyperalgesia through the spinal cord; lamina I inhibition.	Brito *et al.*, 2015
Monoterpene alcohol; linear	Citronellol	Analgesic, anti-inflammatory	Albino Swiss mice WAA, FT, HP, Rota rod test, CG-induced pleurisy. LPS stimulated macrophages.	25, 50, 100 mg/kg i.p.	S-(-)-β-Citronellol Inhibits pain phases I (central, opioid system) and II (peripheral inflammation). Inhibits both neutrophil infiltration and increase in TNF-α levels. Decreases NO.	Brito *et al.*, 2012
Monoterpene alcohol; linear	Citronellol	Anticonvulsant, nerve conduction	Albino Swiss mice Rat isolated nerve PTZ- and PIC-induced seizure model. MES-induced seizure model.	100, 200, 400 mg/kg i.p.	(+)-Citronellol Increases seizure latency and eliminates extensor reflex. CAP is markedly inhibited.	de Sousa *et al.*, 2006
Monoterpene alcohol; linear	Citronellol	Anti-inflammatory	BAEC cells	100, 200-400 μM	PPARα (stronger) and PPARγ activation. COX-2 suppression in a PPARγ-dependent manner.	Katsukawa *et al.*, 2011
Monoterpene alcohol; linear	Citronellol	Anti-inflammatory	Murine macrophage RAW 264.7 cells LPS-induced model.	50-500 μM	(±)-β-Citronellol Lessens both PGE2 and NO levels. Decreases iNOS enzymatic activity but not expression. Attenuates protein and mRNA expression of COX-2. Decreases NF-κB p65l and restores IκBα levels.	Su *et al.*, 2010

Table 8. Monoterpene alcohols, their structure, activity, type of test, dose, and known mechanism(s) of action.

Molecular type	Molecule	Activity	Test/Model	Dose, methods of administration	Mechanism and targets. Isomer stated where known	References
Monoterpene alcohol; linear	Citronellol	Anti-inflammatory	ICR mice CMC IgE-induced degranulation *in vitro* model.	0.125-1 mM	Citronellol inhibits the induction of TNF-α, and suppresses the phosphorylation of MAPK ERK, but not p38 and the production of inflammatory cytokines in mast cells. (-)-Citronellol, more effectively than (+)-citronellol, suppresses CMC degranulation.	Kobayashi *et al.*, 2016
Monoterpene alcohol; linear	Citronellol	Effects on contractility	Wistar rats Rat trachea *in vitro* model.	10-1000 μM	(±)-β-Citronellol Preferentially inhibits contractions that more involve voltage--operated than receptor-operated pathways. No TRPV1 or TRPA1 involvement.	Vasconcelos *et al.*, 2016
Monoterpene alcohol; linear	Citronellol	Nerve conduction	Frog *(Rana nigromaculata)* sciatic nerve Air gap method.	3 Mm/l	S-(-)-β-Citronellol Inhibits CAP amplitude in a partially reversible manner. No TRP involvement. The -OH group gives stronger activity at the end of the carbon chain.	Ohtsubo *et al.*, 2015
Monoterpene alcohol; monocyclic	Dihydrocarveol	CNS depressant	Swiss mice PTB-induced sleeping time.	150 mg/kg i.p.	(+)-Dihydrocarveol is ineffective.	de Sousa *et al.*, 2007c
Monoterpene alcohol; monocyclic	Dihydrocarveol	TRP modulation	HEK293 cells expressing TRPV3 and TRPM8	2 mM	TRPV3 agonism (markedly stronger than camphor).	Vogt-Eisele *et al.*, 2007
Monoterpene alcohol; monocyclic	Dihydrocarveol	TRP modulation	*Xenopus* oocyte expressing TRPV3	3-10 mM	TRPV3 agonism induces tachyphylaxis more than acute desensitization.	Sherkheli *et al.*, 2009
Monoterpene alcohol; bicyclic; camphane type	Fenchyl alcohol	TRP modulation	HEK293T cells expressing hTRPA1	1 mM	Inhibits hTRPA1 in a dose-dependent manner. S873, T874, and Y812 residues are critically involved in the interaction with the -OH group.	Takaishi *et al.*, 2014
Monoterpene alcohol; linear	Geraniol	Ache modulation	Ellman *et al.* colorimetric method.	1-100 mM	Reversible, weak inhibition of AChE.	López & Pascual-Villalobos, 2010
Monoterpene alcohol; linear	Geraniol	Analgesic, nerve conduction	Swiss mice WAA, FT, GT. CAP measurement on sciatic nerve.	12.5, 25 or 50 mg/kg i.p, 50 or 200 mg/kg p.o.	Analgesic effect without opioid system involvement. Reduces peripheral nerve excitability (CAP inhibition). More effective on pain related to inflammation.	La Rocca *et al.*, 2016

Table 8. Monoterpene alcohols, their structure, activity, type of test, dose, and known mechanism(s) of action.

Molecular type	Molecule	Activity	Test/Model	Dose, methods of administration	Mechanism and targets. Isomer stated where known	References
Monoterpene alcohol; linear	Geraniol	Anti-inflammatory Ameliorates fructose-induced obesity, dyslipide-mia, hyper-tensi-on, hyperuricemia, and hyperglycemia	Wistar rats MS-induced model.	250 mg/kg p.o.	Suppresses fructose-mediated increase in HbA1c and RAGE. Up-regulates the transcription and activation of PPAR-γ. Partial activity on PPAR-α. Decreases both AST and ALT activities. Decreases TNF-α and IL-1β serum levels. Suppresses hepatic NO and lipid peroxides and enriched NPSH via the activation of both GPx and GR.	Ibrahim *et al.,* 2015
Monoterpene alcohol; linear	Geraniol	Anti-inflammatory, antiasthmatic	BALB/c mice Ovalbumin-induced allergic asthma model.	100-200 mg/kg by gavage	Reduces eotaxin levels. Attenuates infiltration of eosinophils. Reduces TH2 cytokines (including IL- 4, 5, and 13), increases TH1 cytokine IF-γ in bronchoalveolar lavage fluid, and reduces ovalbumin-specific IgE. In serum. Enhances T-bet (TH1 response) mRNA and reduces GATA-3 (TH2 response) mRNA expression. Enhances Nrf2 protein expression and activated Nrf2-directed antioxidant pathways, such as glutamate-cysteine ligase, SOD, and GST; enhances formation of reduced GTH and reduces formation of MDA.	Xue *et al.,* 2016
Monoterpene alcohol; linear	Geraniol	Antiarrhythmic	Guinea pig left atria cells	300 μM	Decreases Ca^{2+} influx, directly blocking L-type calcium channels. Prolongs AP duration by inhibition of K+ channels. Negative inotrope and chronotrope effect.	de Menezes-Filho *et al.,* 2014
Monoterpene alcohol; linear	Geraniol	Antidyslipidemic	Syrian hamsters Atherogenic diet model.	50, 100, 200 mg/ kg p.o.	Inhibits HMGCoA reductase. Normalizes LCAT activity. Suppresses lipogenesis.	Jayachandran *et al.,* 2015
Monoterpene alcohol; linear	Geraniol	Antidyslipidemic	Baby hamster kidney cell lines, C100 and SV28	0.4 mmol/L	Suppresses HMG-CoA reductase synthesis by 98% and lowers its mRNA levels.	Peffley and Gayen, 2003
Monoterpene alcohol; linear	Geraniol	Anti-inflammatory	Wistar rats TNBS-induced colitis model.	250 mg/kg p.o.	Lessens LPO and NO levels. Decreases PGE2, IL1β, ICAM-1 and MPO levels. Decreases content and expression of GSK-3β, β-catenin, p38-MAPK, and NF-Kβ Increases PPARγ levels.	Soubh *et al.,* 2015

Table 8. Monoterpene alcohols, their structure, activity, type of test, dose, and known mechanism(s) of action.

Molecular type	Molecule	Activity	Test/Model	Dose, methods of administration	Mechanism and targets. Isomer stated where known	References
Monoterpene alcohol; linear	Geraniol	Anti-inflammatory	Murine macrophage RAW 264.7 cells LPS-induced model.	50-500 μM	Lessens both PGE2 and NO levels. Decreases protein and mRNA expression of iNOS. Attenuates protein and mRNA expression of COX-2. Decreases NF-κB p65l and restores IκBα levels.	Su et al., 2010
Monoterpene alcohol; linear	Geraniol	Anti-inflammatory	BAEC cells	100, 200-400 μM	PPARα and PPARγ (stronger) activation. COX-2 suppression in a PPARγ-independent manner.	Katsukawa *et al.,* 2011
Monoterpene alcohol; linear	Geraniol	Anti-inflammatory	Mice TPA-induced inflamma-tory and oxi-dative response on skin.	250 μg topically	Decreases p38MAPK, NF-κB (p65), and COX-2.	Khan *et al.,* 2013
Monoterpene alcohol; linear	Geraniol	Anti-inflammatory, antidepressant	ICR mice CUMS model. FST, TST.	20-40 mg/kg p.o.	Alleviates depression-related behaviors. Reverses CORT elevation. Decreases IL-1β, NF-kB, and NLRP3 inflammasome expression and activation.	Deng *et al.,* 2015
Monoterpene alcohol; linear	Geraniol	Anti-inflammatory, antioxidant	Wistar rats 2-AAF-induced liver tissue damage.	100-200 mg/kg p.o.	Lessens LPO levels. Increases SOD, CAT, GR, and GPx activities and GTH level. Decreases level of serum toxicity markers (AST, ALT, LDH). Down-regulates the expression of caspase-3, 9, COX-2, NFkB, PCNA, iNOS, and VEGF. Significantly decreases disintegration of DNA.	Hasan and Sultana, 2015
Monoterpene alcohol; linear	Geraniol	Anti-inflammatory, vasoprotective	Wistar rats MS and STZ-induced diabetes. Aorta isolates and MG aorta isolates.	10-300 μM	Alleviates exaggerated vasoconstriction, improves vasodilatation. Inhibits voltage-dependent and receptor-mediated Ca^{2+} channels.	El-Bassossy *et al.,* 2016
Monoterpene alcohol; linear	Geraniol	Gastro and duo-deno protection	Swiss mice/Wistar rats EIGU model. I/R-induced gastric ulcer model. Cysteamin-induced duodenal ulcer.	7.5-100, 200 mg/ kg p.o.	Markedly reduces the area of ulcers in all models. Decreases MPO levels. Increases GSH and NO levels and mucus production. Probable TRP and PG involvement.	de Carvalho *et al.,* 2014

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Monoterpene alcohol; linear	Geraniol	Nerve conduction	Frog *(Rana nigromaculata)* sciatic nerve Air gap method.	3 Mm/l	Reversible CAP amplitude inhibition. No TRP involvement. The -OH group gives stronger activity at the end of the carbon chain.	Ohtsubo *et al.*, 2015
Monoterpene alcohol; linear	Geraniol	TRP modulation	HEK293 cells expressing TRPM8 receptors	Different concentrations	Weak TRPM8 agonist (no TRPV1 activity).	Behrendt *et al.*, 2004
Monoterpene alcohol; bicyclic; camphane type	Isobor-neol	CNS depressant	Swiss mice PTB-induced sleeping time.	150 mg/kg i.p.	(±)-Isoborneol Ineffective. No mechanism elucidated.	de Sousa *et al.*, 2007c
Monoterpene alcohol; bicyclic; camphane type	Isobor-neol	CNS depressant	*Xenopus* oocytes expressing α1β2γ2L $GABA_A$ receptors	Different doses	Enhancement of GABA through modulation and direct binding at $GABA_A$ α1β2γ2L receptor. At high EC, acts as partial agonist; weaker than (-)-borneol and at lower EC as a modulator.	Granger *et al.*, 2005
Monoterpene alcohol; bicyclic; camphane type	Isobor-neol	TRP modulation	HEK293 cells expressing TRPV3 and TRPM8	2 mM	TRPV3 agonist (weaker than camphor). No TRPM8 agonism.	Vogt-Eisele *et al.*, 2007
Monoterpene alcohol; monocyclic	Isomen-thol	UGT modulation	SD rats Morphine metabolism.	100-300 μM	(+)-Isomenthol Demonstrates UGT2B7 inhibition. Strongest compound analyzed.	Ishii *et al.*, 2012
Monoterpene alcohol; monocyclic	Isopulegol	Anticonvulsant	Swiss mice PTZ-induced seizures model.	100-200 mg/kg i.p.	Possible positive allosteric modulation of $GABA_AR$. Prevents increase in TBARS levels. Maintains catalase and GSH levels.	Silva *et al.*, 2009a
Monoterpene alcohol; monocyclic	Isopulegol	CNS depressant	Swiss mice PTB-induced sleeping time.	150 mg/kg i.p.	Prolongs PTB-induced sleeping time. No mechanism elucidated.	de Sousa *et al.*, 2007c
Monoterpene alcohol; monocyclic	Isopulegol	CNS depressant	Swiss mice Open field, elevated plus maze (EPM), rota rod, hole board, PTB--induced sleeping time, tail suspension, forced swimming tests.	25-50 mg/kg i.p.	Prolongs PTB-induced sleeping time, without effect on motor coordination. Shows depressant and anxiolytic-like effects. No mechanism elucidated.	Silva *et al.*, 2007
Monoterpene alcohol; monocyclic	Isopulegol	CNS depressant	*Xenopus* oocytes expressing rat GABA α1β2 and human GABA α1β2γ2 HEK293 cells expressing human GABA α1β2γ2	30-300, 600 μm	Enhances $GABA_AR$ evoked current γ2 subunit independently via allosteric modulation (phasic inhibition).	Kessler *et al.*, 2014

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Molecular type	Molecule	Activity	Test/Model	Dose, methods of administration	Mechanism and targets. Isomer stated where known	References
Monoterpene alcohol; monocyclic	Isopulegol	Gastroprotective	Swiss mice Ethanol-induced gastric ulcer (EIGU) model.	100-200 mg/kg p.o.	Attenuates gastric damage increasing GSH levels. Possible participation of K_{ATP} channels and PG.	Silva *et al.*, 2009a
Monoterpene alcohol; monocyclic	Isopulegol	TRP modulation	HEK293 cells expressing TRPV3 and TRPM8	2 mM	(-)-Isopulegol Demonstrates TRPV3 agonism (weaker than camphor).	Vogt-Eisele *et al.*, 2007
Monoterpene alcohol; linear	Linalool	Analgesic	CD-1 mice WAA, HP.	25-100 mg/kg s.c.	(-)-Linalool Involves opioidergic and cholinergic system.	Peana *et al.*, 2003
Monoterpene alcohol; linear	Linalool	Analgesic	CD-1 mice/Wistar rats HPT, FT.	50-150 mg/kg s.c.	(-)-Linalool Involves muscarinic (M_2) opioid and dopamine (D_2) systems. Key role of K_{ATP} channel.	Peana *et al.*, 2004
Monoterpene alcohol; linear	Linalool	Analgesic	CD-1 mice HPT.	25-100 mg/kg s.c.	(-)-Linalool Involves adenosinergic system. Modulation of A_1 and A_2A receptors.	Peana *et al.*, 2006a
Monoterpene alcohol; linear	Linalool	Analgesic	ddY (SD) mice NC.	1.25-10 µg/paw i.pl.	(±)-Linalool Involves peripheral opioid receptor.	Sakurada *et al.*, 2011
Monoterpene alcohol; linear	Linalool	Analgesic, antinociceptive	Macrophage cell line J774.A1 LPS-induced inflammation model.	0.0001-0.01-1 mM	(-)-Linalool Inhibited iNOS enzymatic activity. It did not inhibit the expression of iNOS or COX-2, nor did it inhibit PGE2 release.	Peana *et al.*, 2006b
Monoterpene alcohol; linear	Linalool	Analgesic, antinociceptive	Swiss mice NG, BG, BAMPA, BNMDA, BKBAPD, and BSP.	10-200 mg/kg i.p. 5-100 mg/kg p.o. 10-300 ng/paw i.pl. 0.1-3 µg/site i.t.	(-)-Linalool Involves glutamatergic system. Modulates AMPA, NMDA, kainate glutamatergic receptor (iGluR).	Batista *et al.*, 2008
Monoterpene alcohol; linear	Linalool	Analgesic, anti-inflammatory	Swiss mice PSNL, CFA model. Biting induced by IL-1β, TNF-α model.	50-200 mg/kg, i.p. 1 pg/site i.t.	(-)-Linalool Demonstrates NMDA receptor modulation.	Batista *et al.*, 2010
Monoterpene alcohol; linear	Linalool	Analgesic, anti-inflammatory	Mice MHCA, THCA, NC, NG.	No data	(-)-Linalool Inhibits both TRPA1 and NMDA iGluR signaling.	Batista *et al.*, 2011
Monoterpene alcohol; linear	Linalool	Anticonvulsant	Mice	100-300 mg/kg	Comparison between (+)-, (-)-, and (±)-linalool. Demonstrates that the two enantiomers have similar qualitative anticonvulsant activity but show different potencies.	de Sousa *et al.*, 2010

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Molecular type	Molecule	Activity	Test/Model	Dose, methods of administration	Mechanism and targets. Isomer stated where known	References
Monoterpene alcohol; linear	Linalool	Anticonvulsant	Wistar rats and Albino mice Rat cerebral cortex *in vitro* model. NMDA-induced convulsion. QUIN-induced convulsion. PTZ-induced kindling.	0.1-5 mM *in vitro* model 350 mg/kg i.p. in NMDA model 15, 30-45 mM i.c.v. in QUIN model 2.2-2.5 g/kg p.o. in PTZ model	(±)-Linalool Modulates glutamate activation expression in vitro (competitive antagonism of L-[3H] glutamate binding) and *in vivo* (delayed NMDA convulsions and blockage of QUIN convulsions). Partially inhibits and significantly delays the behavioral expression of PTZ-kindling but does not modify PTZ-kindling-induced increase in L-[3H] glutamate binding.	Elisabetsky *et al.,* 1999
Monoterpene alcohol; linear	Linalool	Antidyslipidemic	C57BL/6J mice HepG2 cells	0.57-120 mg/mouse p.o. 0.1-0.5 mM	Decreases TC, LDL, and TG levels. Increases HDL levels. Suppresses HMGCoA reductase protein expression by reducing the binding of SREBP-2 to its promoter and inducing its ubiquitin-dependent proteolysis.	Cho *et al.,* 2011
Monoterpene alcohol; linear	Linalool	Anti-inflammatory	LPS-stimulated BV2 microglia cells	25, 50, 100 µg/ml	Inhibits LPS-induced TNF-α, IL-1β, NO, and PGE2 production in a dose-dependent manner. Inhibits LPS-induced NF-κB activation and induced nuclear translocation of Nrf2 and expression of HO-1.	Li *et al.,* 2015
Monoterpene alcohol; linear	Linalool	Anti-inflammatory	C57BL/6 mice cigarette smoke (CS)--induced acute lung inflammation	10, 20, 40 mg/kg i.p.	Significantly attenuates lung inflammation. Inhibits infiltration of inflammatory cells and TNF-α, IL-6, IL- 1β, IL-8, and MCP-1 production. Inhibits induced lung MPO activity and pathological changes. Suppresses induced NF-κB activation in a dose-dependent manner.	Ma *et al.,* 2015
Monoterpene alcohol; linear	Linalool	Anti-inflammatory	Human lung adenocarcinoma epithelial cell line A549 *P. multocida*-induced inflammation in C57BL/6J mice.	200 µl s.c.	Elevates nuclear Nrf-2 protein translocation and consequently improves antioxidant enzyme expression. Decreases lung neutrophil accumulation and levels of TNF-α and IL-6.	Wu *et al.,* 2014
Monoterpene alcohol; linear	Linalool	Anti-inflammatory	BALB/c mice LPS-induced injury model. RAW 264.7 mouse macrophage cell line LPS stimulated.	40, 80, 120 µg/mL *in vitro* 25 mg/kg i.p.	Attenuates the production of LPS-induced TNF-α, IL-6 both *in vitro* and *in vivo.* Blocks phosphorylation of IkBa protein, p38, c-Jun terminal kinase, and extracellular signal-regulated kinase.	Huo *et al.,* 2013

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Monoterpene alcohol; linear	Linalool	Anti-inflammatory	Wistar rats STZ-induced diabetes and renal injury.	25 mg/kg p.o.	(-)-Linalool (≥ 80% purity) Restores glucose-metabolizing enzymes, collagen content, and GLUT-1 expression, and prevents nephrin loss. Rescues kidney from oxidative stress and inflammation by decreasing the expression of TGF-β1 and NF-Kβ. Mitigates ultrastructural changes.	Deepa and Venkatraman Anuradha, 2013
Monoterpene alcohol; linear	Linalool	Anxiolytic	ICR mice OFT, EPT, LDT.	500 mg/kg p.o.	Equal anxiolytic effect in all three models for both enantiomers. S-(+)-linalool reduced the amount of 5-HT, DA, and NE released from mouse brain frontal cortex and hippocampus.	Cheng *et al.*, 2015
Monoterpene alcohol; linear	Linalool	Anxiolytic	Human clinical trial	Inhalation	Both enantiomers have a relaxing effect. S-(+)-Linalool has an activating effect on HR, BP, and CRT (in the preparation period, but not in the testing or recreation periods). R-(-)-Linalool exerts a sedating effect on HR.	Höferl *et al.*, 2006
Monoterpene alcohol; linear	Linalool	CNS depressant	*Xenopus* oocytes expressing rat GABA α1β2 and human GABA α1β2γ2 HEK293 cells expressing human GABA α1β2γ2	300-1000 μm	Independently enhances GABAAR evoked current γ2 subunit via allosteric modulation (phasic inhibition). EC_{50} higher than the mono and bicyclic alcohols tested.	Kessler *et al.*, 2014
Monoterpene alcohol; linear	Linalool	Sedative, anxiolytic	ICR mice OF test. EPM test and LDB test.	Inhalation 0.55-1.10 -2.2 % v/v for 10 minutes	Shows significant anxiolytic effect in EPM test.	Zhang *et al.*, 2016
Monoterpene alcohol; linear	Linalool	CNS depressant	Albino mice PTB-induced sleeping time. Rotarod test.	Inhalation in chamber 1% or 3% saturated for 60 minutes	(±)-Linalool Increases PTB-induced sleeping time and body temperature without motor coordination impairment. 3% (±)-linalool decreases locomotion.	Linck *et al.*, 2009
Monoterpene alcohol; linear	Linalool	Sedative, anxiolytic	Albino mice. LDT, Step-down inhibitory avoidance test and another behavioral test.	Inhalation in chamber 1% or 3% saturated	3% in LDT increases time spent in light area. Is amnesic in step-down inhibitory avoidance test. Shows anxiolytic profile in behavior tests.	Linck *et al.*, 2010
Monoterpene alcohol; linear	Linalool	Sedative, anxiolytic	Day old chicks OF test.	0.86, 8.6, 86 mg/ chick i.c.v.	Doses of 8.6 and 86 mg of linalool decrease number of crossed squares, attempted escapes, defecations, and distress calls, and increase sleeping posture.	Gastón *et al.*, 2016

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Monoterpene alcohol; linear	Linalool	Sedative	Human clinical trial IBVA-EEG measurement and sensory evaluation.	Inhalation	Racemic linalool decreased beta wave activity after hearing environmental sound after, rather than before work. This effect was identical to that observed for (R)-(-)-linalool. (S)-(+)-Linalool demonstrated the opposite activity.	Kobayashi *et al.,* 2016
Monoterpene alcohol; linear	Linalool	Sedative	Swiss mice. Sedation effect in normal and over-agitated condition (caffeine).	I hour inhalation period 20-50 mg per compound	Decreases motility in normal conditions and also in over-agitation condition.	Vasconcelos *et al.,* 2016
Monoterpene alcohol; linear	Linalool	Antidepressant-like	ICR mice FST using specific antagonist to assure the monoaminergic system involvement.	100 mg/kg i.p.	Exerts antidepressant-like activity through interaction with the serotonergic pathway through interaction with postsynaptic 5-HT_{1A} receptors. Interacts with the adrenergic system through α2 receptors.	Ohtsubo *et al.,* 2015
Monoterpene alcohol; linear	Linalool	CYP modulation	Microsome isolations from Wistar rats	40, 120, 360 mg/kg i.g.	(-)-Linalool Increases metabolic activity of CYP2A *in vivo.* Shows weak competitive inhibition of CYP2C6 *in vitro.*	de Sousa *et al.,* 2007c
Monoterpene alcohol; linear	Linalool	Nerve conduction	Frog *(Rana nigromaculata)* sciatic nerve Air gap method.	3 Mm/l	(±)-Linalool and (-)-linalool Exert similar poor CAP amplitude inhibition (they differ in reversibility). The -OH group gives weaker activity in the middle of the carbon chain.	Vogt-Eisele *et al.,* 2007
Monoterpene alcohol; linear	Linalool	Nerve conduction	Wistar rats ORCs Rat cerebellar Purkinje cells *in vitro* model.	3-10 mM	Non-selective inhibition voltage gated channels.	Sherkheli *et al.,* 2009
Monoterpene alcohol; linear	Linalool	Nerve conduction, local anesthetic	Wistar rats sciatic nerve and preparations of intact and dissociated neurons of dorsal root ganglion	0.3-2 mM 0.1-6 mM	Reversibly blocks sciatic nerve excitability. Inhibits CAP amplitude. Acts on the somatic sensory system with local anesthetic properties, since it blocked the action potential by acting on voltage- dependent Na+ channels.	Takaishi *et al.,* 2014
Monoterpene alcohol; linear	Linalool	Neuroprotective	Homozygous triple transgenic AD model (3xTg-AD) and non-transgenic (Non-Tg) mice	25 mg/kg p.o.	(±)-Linalool Demonstrates a significant reduction in extracellular β-amyloidosis, tauopathy, astrogliosis, and microgliosis as well as a significant reduction in the levels of the pro-inflammatory markers p38 MAPK, NOS2, COX2, and IL-1β.	Sabogal-Guáqueta *et al.,* 2016

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Monoterpene alcohol; linear	Linalool	Neuroprotective, antioxidant	SD rat cortical cells OGD/R-induced neuronal injury model.	10 μM	(-)-Linalool Restores CAT and SOD activities and inhibits microglial migration induced by MCP-1.	Park *et al.*, 2016
Monoterpene alcohol; linear	Linalool	TRP modulation	HEK293 cells expressing TRPM8 receptors	Different concentrations	Weak TRPM8 agonist (no TRPV1 activity).	Behrendt *et al.*, 2004
Monoterpene alcohol; linear	Linalool	TRP modulation	HEK293 cells expressing TRPV3 and TRPM8	2mM	(+)-Linalool Demonstrates TRPV3 agonism (weaker than camphor).	Vogt-Eisele *et al.*, 2007
Monoterpene alcohol; monocyclic	Menthol	5-HT receptor modulation	HEK293 cells heterologously expressing human 5-HT_{3A} and 5-HT_{3AB} receptors	IC 20 μM circa	(+)-Menthol and (-)-menthol Non-competitively inhibit activation of human 5-HT3 receptors in the low and middle micromolar range. No stereoselectivity, but (-) isomer more potent antagonist at 5-HT_{3A}- vs 5-HT_{3AB}. Blocks 5-HT mediated calcium influx.	Walstab *et al.*, 2014
Monoterpene alcohol; monocyclic	Menthol	5-HT receptor modulation	Xenopus oocytes expressing 5-HT_3 receptor Acutely dissociated nodose ganglion neurons	0.1-1 mM	Acts as a non-competitive antagonist of the 5-HT3 receptor without GTPγS involvement. No stereoselectivity between (-)-, (+)-, and (±)-menthol.	Ashoor *et al.*, 2013
Monoterpene alcohol; monocyclic	Menthol	Analgesic-like	Swiss mice HP, WAA.	1-10 mg/kg p.o. 5-10 μg/site i.c.v. 10-50 mg/kg p.o. 10-50 μg/site i.c.v.	The (+) isomer shows no antinociceptive activity. The (-) isomer selectively activates κ-opioid receptors. Elevates pain threshold and down-regulates cytokine and inflammation mediators.	Galeotti *et al.*, 2002
Monoterpene alcohol; monocyclic	Menthol	Analgesic-like	Cultured dorsal root ganglion cells from chick and rat embryos	0.1-1 mM	(-)-Menthol Blocks currents through the low voltage-activated Ca channel and facilitates inactivation gating of the classical high voltage-activated Ca channel.	Swandulla *et al*, 1987
Monoterpene alcohol; monocyclic	Menthol	Analgesic-like, local anesthesia	(HEK293 cells) expressed rat neuronal (rat type IIA) and human skeletal muscle (hSkM1) sodium channels	IC 376 (skeletal) and 571 (neuronal) μmol K_d 97 (skeletal) and 106 (neuronal) μmol	Antinociceptive and local anesthetic effects might be mediated via blockade of voltage-operated sodium channels.	Haeseler *et al.*, 2002

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Monoterpene alcohol; monocyclic	Menthol	Analgesic-like, anti-inflammatory	LPS-stimulated human monocytes	10 superset-7 g/ml	(-)-Menthol Significantly suppressed LTB-4, PGE2, and IL-1β.	Juergens *et al.,* 1998
Monoterpene alcohol; monocyclic	Menthol	Analgesic-like, cooling	SD rats HT, VFPW, CPT.	0.01-40% topical	(-)-Menthol Dose-dependently increases the latency for noxious heat-evoked withdrawal. The highest concentration (40%) reduced mechanical withdrawal thresholds, with no effect at lower concentrations. Has a biphasic effect on cold sensitivity in rats. Findings support TRPM8 as a peripheral target of pain modulation.	Klein *et al.,* 2010
Monoterpene alcohol; monocyclic	Menthol	Analgesic, cooling, TRP modulation	Various (review paper)	Different doses/ concentrations	(-)-Menthol Demonstrates TRPM8 agonism and related analgesic activity and cooling sensation. Specific site of interaction with some AA residues. TRPA1 agonism at lower dose and antagonism at higher doses and relative activities on analgesic activity and cooling sensation. Hydrophobic and not covalent interaction in transmembrane domain 5.	Farco and Grundmann, 2013
Monoterpene alcohol; monocyclic	Menthol	Antihypertensive, vasorelaxant, TRP modulation	Spontaneously hypertensive rats (SHR) and Wistar- Kyoto rats WKY TRPM8−/− and Wild Type mice Vascular smooth muscle cells (VSMCs)	0.5% capsule orally 30 or 100 μmol/L	TRPM8 activation attenuates vasoconstriction via RhoA/Rho kinase pathway inhibition in wild-type mice, but the effect was absent in TRPM8−/−mice. TRPM8 effect was associated with inhibition of intracellular calcium release from the sarcoplasmic reticulum, RhoA/Rho kinase activity, and sustained arterial contraction in the *in vitro* study.	Sun *et al.,* 2014
Monoterpene alcohol; monocyclic	Menthol	Anti-inflammatory	ICR mice DMBA/TPA-induced inflammation oxidative stress and skin carcinogenesis.	20-80 mg/kg topical	Suppresses the expression of COX-2. Down-regulates the expression of NF-κB, ERK, and p38. Normalizes levels and activities of CAT, GSH, GPx, and GST. Decreases MDA and ROS levels.	Liu *et al.,* 2015
Monoterpene alcohol; monocyclic	Menthol	CNS depressant	Swiss mice PTB-induced sleeping time.	150 mg/kg i.p.	(±)-Neomenthol Prolongs sleeping time; (-)-menthol is ineffective.	de Sousa *et al.,* 2007c

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Monoterpene alcohol; monocyclic	Menthol	CNS depressant, GABAR modulation	SD rats for kindling and anticonvulsant model. ICR mice Z seizure model hippocampal CA1 pyramidal neurons *in vitro*.	200 mg/kg i.p. 780 µg in5 ml DMSO solution i.c.v. 300 µM	Menthol Not only enhances the currents induced by low concentrations of GABA, but also directly activates GABAA receptor in the CA1 region of rat hippocampal slices. Enhances tonic GABAergic inhibition, although phasic GABAergic inhibition was unaffected, (+)-, (-)-, and (±)- Menthol and (-)-neomenthol all significantly enhance I GABA induced by 1 µM GABA.	Zhang *et al.,* 2008
Monoterpene alcohol; monocyclic	Menthol	CNS depressant $GABA_A$ receptor modulation	*Xenopus* oocytes expressing GABAA receptors *In vivo* tadpole anesthetic assay.	1-1000 µM	(+)-Menthol May exert its actions on GABAA receptors via sites distinct from benzodiazepines, steroids, and barbiturates, and via sites important for modulation by Propofol. Involvement of TM-4 and TM-3 on β2 subunit. (+)-Menthol and (+)-isomenthol are more potent anesthetics than (-)-menthol.	Watt *et al.,* 2008
Monoterpene alcohol; monocyclic	Menthol	Cough inhibitor, TRP modulation	Human clinical trial TRPA1 and TRPM8 agonist (menthols) in capsaicin aerosol-induced cough model.	10^{-3} M Nasal application	TRPA1 relevant agonists significantly enhance urge to cough ($p<0.05$) but no statistically significant modulation of the cough threshold and cumulative cough response. In contrast, (+)- and (-)-menthol significantly modulate all parameters including cough threshold ($p<0.05$), urge to cough ($p<0.01$), and cumulative cough response ($p <0.01$), showing strong anti-irritant potential.	Buday *et al.,* 2012
Monoterpene alcohol; monocyclic	Menthol	Counterirritant	C57Bl/6J mouse Plethysmograph model subjected to primary smoke irritants acrolein and cyclohexanone and smoke of Kentucky reference 2R4 cigarettes.	Vapor inhalation 8-60 ppm	(-)-Menthol Strongly suppresses respiratory irritation responses (through TRPM8) and increases blood cotinine (nicotine metabolite) levels.	Ha *et al.,* 2015
Monoterpene alcohol; monocyclic	Menthol	Chronic cough inhibitor	Human clinical trial patients with chronic cough Capsaicin-induced cough model.	Inhalation of nebulized 0.5% or 1% solution	In the 1% group, cough threshold was significantly higher ($p< 0.02$) compared to after placebo inhalation and to the 0.5% group. Peak inspiratory flows were not reduced. Force inspiratory flow was not lowered by the 1% solution.	Millqvist *et al.,* 2013

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Molecular type	Molecule	Activity	Test/Model	Dose, methods of administration	Mechanism and targets. Isomer stated where known	References
Monoterpene alcohol; monocyclic	Menthol	Effect on cardio-vascular system, antihypertensive	Right ventricular myocytes from New Zealand White rabbit isolated at near–physio-logic temperature	1 mM	(-)-Menthol Blocks cardiac $I_{Ca,L}$ at concentrations similar to those reportedly effective in TRPM8 agonism. Blocks late $I_{Ca,L}$ w/greater efficacy than peak one. No voltage dependence. Possible allosteric modulation of the L-type Ca^{2+} channel.	Baylie *et al.*, 2010
Monoterpene alcohol; monocyclic	Menthol	Gastroprotective	Wistar rats EIGU model.	50 mg/kg p.o.	(-)-Menthol Decreases the activity of MPO and SOD. Decreases Bax protein level and increases HSP-70. Increases protein levels of GSH, GSH-Px, and GR. Decreases levels of TNF--a and IL-6 and increases IL-10 levels.	Rozza *et al.*, 2014
Monoterpene alcohol; monocyclic	Menthol	Gastroprotective, anti-diarrheal, antiperistaltic activity	Wistar rats EIGU and IIGU models.	50 mg/kg p.o.	(-)-Menthol Increases amount of mucus and PGE2 production. Involves NP-SH compounds and stimulation of K^{+}_{ATP} channels. No activation of calcium ion channels or production of NO. Decreases H^{+} concentration in gastric juice. No mechanism for the other two activities.	Rozza *et al.*, 2013
Monoterpene alcohol; monocyclic	Menthol	Subjectively improves nasal airflow without decreasing nasal resistance	Human clinical trial VAS scale for the evalu-ation of nasal patency.	5 g per 2 minutes Vapor inhalation	(-)-Menthol: No statistically significant differences in rhinomanometric values. 16/18 volunteers report an improvement in nasal breathing based on VAS. TRPM8 activation and subsequent cool sensation evokes the subjective feeling of a clear and wide nose.	Lindemann *et al.*, 2015
Monoterpene alcohol; monocyclic	Menthol	nAChRs modulation	Wistar rat trigeminal ganglia isolated human α4β2 nAChR expressed in HEK tsA201 cells	100 μM	(-)-Menthol Reversibly reduces nicotine-activated whole-cell currents throu-gh nAChRs in isolated trigeminal ganglia. Observations include shortening of channel open time, prolon-gation of channel closed time, and an increase in single channel amplitude, all leading to a reduction in single channel current. Negative allosteric modulation of nAChRs.	Hans *et al.*, 2012
Monoterpene alcohol; monocyclic	Menthol	TRP modulation	CHO-K1/FRT cells expressing murine TRPM8	0.1-10 mM	Rapidly activates currents in TRPM8-expressing cells, but not in non-transfected CHO cells, at temperatures above the threshold for cold activation. Calcium current involved. TRPM8 agonism.	Peier *et al.*, 2002

Table 8. Monoterpene alcohols, their structure, activity, type of test, dose, and known mechanism(s) of action.

Molecular type	Molecule	Activity	Test/Model	Dose, methods of administration	Mechanism and targets. Isomer stated where known	References
Monoterpene alcohol; monocyclic	Menthol	TRP modulation	SD rats HT, VFPW, CPT.	0.01-40% topical	(-)-Menthol Dose-dependently increased the latency for noxious heat-evoked withdrawal. Highest concentration (40%) reduced mechanical withdrawal thresholds, with no effect at lower concentrations. Had a biphasic effect on cold sensitivity in rats, supporting TRPM8 as a potential peripheral target of pain modulation.	Klein *et al.,* 2010
Monoterpene alcohol; monocyclic	Menthol	TRP modulation	CHO cell culture expressing TRPA1	1 μM to 1 mM	(-)-Menthol Has stronger activity than other menthol isomers on TRPA1 activation. Sub-micromolar to low-micromolar concentrations cause channel activation, whereas higher concentrations lead to a reversible channel block.	Karashima *et al.,* 2007
Monoterpene alcohol; monocyclic	Menthol	TRP modulation	CHO and HEK293T cells expressing human hTRPA1 and murine mTRPA1 models.	Different doses 0-3000 μM	(-)-Menthol hTRPA1 agonist and has a bimodal action in mTRPA1. Acts like an activator at lower doses and an inhibitor at higher doses, The aa residues in TM5 play a pivotal role.	Xiao *et al.,* 2008
Monoterpene alcohol; monocyclic	Menthol	TRP modulation	HEK293 cells expressing TRPV3 and TRPM8	2 mM	(-)-Menthol Demonstrates TRPV3 agonism (weaker than camphor) and strong TRPM8 agonism.	Vogt-Eisele *et al.,* 2007
Monoterpene alcohol; monocyclic	Menthol	TRP modulation	*Xenopus* oocytes expressing TRPV3	3-10 mM	(-)-Menthol Demonstrates TRPV3 agonism. Preferentially induces tachyphylaxis than acute desensitization.	Sherkheli *et al.,* 2009
Monoterpene alcohol; monocyclic	Menthol	TRP modulation	Flp-In TREx293 cells expressing TRPM8	20 μM	(-)-Menthol Shows that α and/or βI subtype in conventional Ca^{2+}-dependent PKC, mediates menthol-induced TRPM8 desensitization.	Abe *et al.,* 2006
Monoterpene alcohol; bicyclic; pinane type	Myrtenol	Analgesic	Swiss mice WAA, FT, HP, NC, GT, RT.	75 mg/kg i.p	(-)-Myrtenol Inhibits only II phase pain, i.e., the inflammatory phase.	Silva *et al.,* 2014

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Molecular type	Molecule	Activity	Test/Model	Dose, methods of administration	Mechanism and targets. Isomer stated where known	References
Monoterpene alcohol; bicyclic; pinane type	Myrtenol	Anti-inflammatory	Swiss mice Paw edema induced by CG, 5-HT, HIST, PGE2, 48/80 compound Neutrophil migration CG induced in peritoneal cavity.	25, 50, 75 mg/kg i.p. 75 mg/kg i.p.	(-)-Myrtenol Edema reduction. Decreases neutrophil and leukocyte migration. It decreases MPO and IL-1β.	Silva *et al.,* 2014
Monoterpene alcohol; bicyclic; pinane type	Myrtenol	Anxiolytic	Wistar rats EPMT, LDT, OFT, RT.	25, 50, 75 mg/kg i.p.	(-)-Myrtenol Demonstrates anxiolytic effect without locomotor activity impairment. GABA involvement.	Moreira *et al.,* 2014
Monoterpene alcohol; bicyclic; pinane type	Myrtenol	CNS depressant	Swiss mice PTB-induced sleeping time.	150 mg/kg i.p.	(-)-Myrtenol Prolongs PTB-induced sleeping time. No mechanism elucidated.	de Sousa *et al,* 2007c
Monoterpene alcohol; bicyclic; pinane type	Myrtenol	CNS depressant	*Xenopus* oocytes expressing rat GABA α1β2 and human GABA α1β2γ2 HEK293 cells expressing human GABA α1β2γ2	10-100, 300 μM	Independently enhances $GABA_AR$ evoked current γ2 subunit, via allosteric modulation (phasic inhibition).	Kessler *et al.,* 2014
Monoterpene alcohol; bicyclic; pinane type	Myrtenol	CNS depressant	HEK293 cells expressing GABA α1β2δ murine DGGC	100 μM	Enhances $GABA_AR$ evoked current in α1β2δ extra-sinaptic subtype via allosteric modulation (tonic inhibition).	van Brederode *et al.,* 2016
Monoterpene alcohol; bicyclic; pinane type	Myrtenol	Gastroprotective	Swiss mice Absolute ethanol-induced gastric lesions.	25, 50, 100 mg/kg p.o.	(-)-Myrtenol Attenuates gastric damage through NO, PG, and GABAAR involvement. Decreases MDA, MPO, and ROS levels. Increases levels of GSH, SOD, GPx, and CAT.	Viana *et al.,* 2016
Monoterpene alcohol; monocyclic	Neoisopulegol	CNS depressant	Swiss mice PTB-induced sleeping time.	150 mg/kg i.p.	Prolongs PTB-induced sleeping time. No mechanism elucidated.	de Sousa *et al.,* 2007c
Monoterpene alcohol; linear	Nerol	Analgesic, anti-inflammatory, gastroprotective	BALB/c mice Oxazolone-induced colitis model. EIGU model.	10, 30-300 mg/kg p.o.	Histologic damage reduction in colonic and gastric surface. Reduction of TNF-α and IL-13 levels. Reduction of hyperalgesia.	González-Ramírez *et al.,* 2016
Monoterpene alcohol; linear	Nerol	Sedative, anxiolytic	Albino Swiss mice OFT, EPM, LDT, Rota Rod test.	30, 60, 90 mg/kg i.p.	Possible anxiolytic effect.	Henrique *et al.,* 2013

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Molecular type	Molecule	Activity	Test/Model	Dose, methods of administration	Mechanism and targets. Isomer stated where known	References
Monoterpene alcohol; monocyclic	Perillyl alcohol	Anti-inflammatory, antioxidant	Wistar rats MCAO/reperfusion injury model.	25, 50, 100 mg/kg p.o.	Neuroprotective effect. Decreases lipid peroxidation. Restores levels of GSH, GPx, GR, and CAT l. Inhibition of IL-1β, IL-6, and TNF-α level and down regulation of COX-2, NOS-2, and NF-κB.	Islam *et al.*, 2015
Monoterpene alcohol; monocyclic	Perillyl alcohol	Anti-inflammatory, antioxidant	Wistar rats Ethanol-induced acute liver injury model.	50-100 mg/kg	Protective hepatic effect. Decreases LPO. Free radical scavenger. Improves levels of GSH, GR, GPx, G6PD, and CAT. Down-regulation of NF-κB and TNF-α.	Khan *et al.*, 2011
Monoterpene alcohol; bicyclic; pinane type	Pinocarveol	CNS depressant	*Xenopus* oocytes expressing rat GABA α1β2 and human GABA α1β2γ2 HEK293 cells expressing human GABA α1β2γ2	10-100, 600 μM	*trans*-Pinocarveol Enhances GABAAR evoked current γ2 subunit independently via allosteric modulation (phasic inhibition).	Kessler *et al.*, 2014
Monoterpene alcohol; bicyclic; pinane type	Pinocarveol	TRP modulation	HEK293 cells expressing TRPV3 and TRPM8	2 mM	*(-)-trans*-Pinocarveol Demonstrates TRPV3 agonism (weaker than camphor).	Vogt-Eisele *et al.*, 2007
Monoterpene alcohol; monocyclic	Terpinen-4-ol	Anticonvulsant	Swiss mice/Wistar rats PTZ, 3-MP, PTZ/EEG recording DRG Patch Clamp Test.	25-200 mg/kg i.p. 50-200 mg/kg i.p. 10, 20, 40 ng/2μl i.c.v. 0.1-1.0 mM	Increases convulsion latency without GABA receptor involvement. Decreases Na current through voltage-dependent sodium channel.	Nóbrega *et al.*, 2014
Monoterpene alcohol; monocyclic	Terpinen-4-ol	Anticonvulsant, CNS depressant	Swiss mice Locomotor activity, PTB-induced sleeping time, PTZ, PIC, MES induced seizures model.	100 mg/kg i.p. 100-200 mg/kg i.p. 100-300 mg/kg i.p. 200-300 mg/kg i.p. 300 mg/kg i.p.	(-)-Terpinen-4-ol Increases convulsion latency and prolongs PTB-induced sleeping time. Possible GABA receptor involvement.	de Sousa *et al.*, 2009
Monoterpene alcohol; monocyclic	Terpinen-4-ol	Antifungal, anti-inflammatory	100 clinical strains of *C. albicans* CLSI M-27A broth micro-dilution method. XTT reduction assay. OKF6- TERT2 epithelial cells.	MIC50 0.25% (v/v) MIC90 0.5% (v/v)	Compromises cell integrity, causing leakage of contents. Strong activity on fungal biofilm. Decreases IL-8 expression.	Ramage *et al.*, 2012
Monoterpene alcohol; monocyclic	Terpinen-4-ol	Anti-inflammatory	Murine macrophages HKCA /LPS in vitro	200, 400, 800 μg/ml in vitro	Decreases MPO activity and MIP-2 (IL-8 murin homologue) *in vivo*. Decreases TNF-α and MIP-2 *in vitro*.	Ninomiya *et al.*, 2013

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Molecular type	Molecule	Activity	Test/Model	Dose, methods of administration	Mechanism and targets. Isomer stated where known	References
Monoterpene alcohol; monocyclic	Terpinen-4-ol	Anti-inflammatory	LPS activated monocytes	0.052% (v/v)	Decreases TNF-α, IL-1β, IL-8, IL-10, and PGE_2.	Hart *et al.*, 2000
Monoterpene alcohol; monocyclic	Terpinen-4-ol	Nerve conduction	Wistar rats	6.0 mM	(-)-Terpinen-4-ol Inhibits both transient and sustained total K current.	dos Santos-Nascimento *et al.*, 2015
Monoterpene alcohol; monocyclic	α-Terpineol	Antihyperalgesic	Mice MHC, MHTNF-α, MHD, $MHPGE_2$.	25, 50, 100 mg/kg i.p.	Inhibition of TNF-α production and release.	de Oliveira *et al.*, 2012
Monoterpene alcohol; monocyclic	α-Terpineol	Analgesic	Mice WAA(NAL), FT, HP, NG, NC.	25, 50, 100 mg/kg i.p.	Peripheral and central action.	Quintans-Júnior *et al.*, 2011
Monoterpene alcohol; monocyclic	α-Terpineol	Anticonvulsant	Mice PTZ and MES.	100-200 mg/kg i.p. 200-400 mg/kg i.p	(±)-α-Terpineol Increases convulsion latency. Decreases incidence of hindlimb extension.	de Sousa *et al.*, 2007b
Monoterpene alcohol; monocyclic	α-Terpineol	Anti-inflammatory	Mice CG-induced pleurisy. NO induces production in murine macrophages.	1, 10, 100 μg/mL	Reduction of neutrophil influx. NO production inhibited.	de Oliveira *et al.*, 2012
Monoterpene alcohol; monocyclic	α-Terpineol	Neuroprotective,	Rats. Induced cerebral ischemia/reperfusion injury.	100 mg/kg i.p.	Facilitates LTP induction. Decreases MDA.	Moghimi *et al.*, 2016
Monoterpene alcohol; bicyclic; pinane type	Verbenol	antioxidant	SD rats MCAO/reperfusion model. OGD/reoxygenation model. ORAC and DPPH assay.	100 mg/kg i.p.	(S)-*cis*-Verbenol Scavenges peroxyl radicals. Decreases TNF-α and IL-1β levels and maintains TGF-β levels.	Choi *et al.*, 2010
Monoterpene alcohol; bicyclic; pinane type	Verbenol	CNS depressant	Xenopus oocytes expressing rat GABA α1β2 and human GABA α1β2γ2 HEK293 cells expressing human GABA α1β2γ2	30-100, 300 μM	(S)-*cis*-Verbenol Enhances $GABA_AR$ evoked current γ2 subunit independently via allosteric modulation (phasic inhibition).	Kessler *et al.*, 2014
Monoterpene alcohol; bicyclic; pinane type	Verbenol	CNS depressant	HEK293 cells expressing GABA α1β2δ murine DGGC	100-600 μM	(S)-*cis*-verbenol Enhances $GABA_AR$ evoked current in α1β2δ extrasinaptic subtype via allosteric modulation (tonic inhibition).	van Brederode *et al.*, 2016

Table 8. Monoterpene alcohols, their structure, activity, type of test, dose, and known mechanism(s) of action.

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