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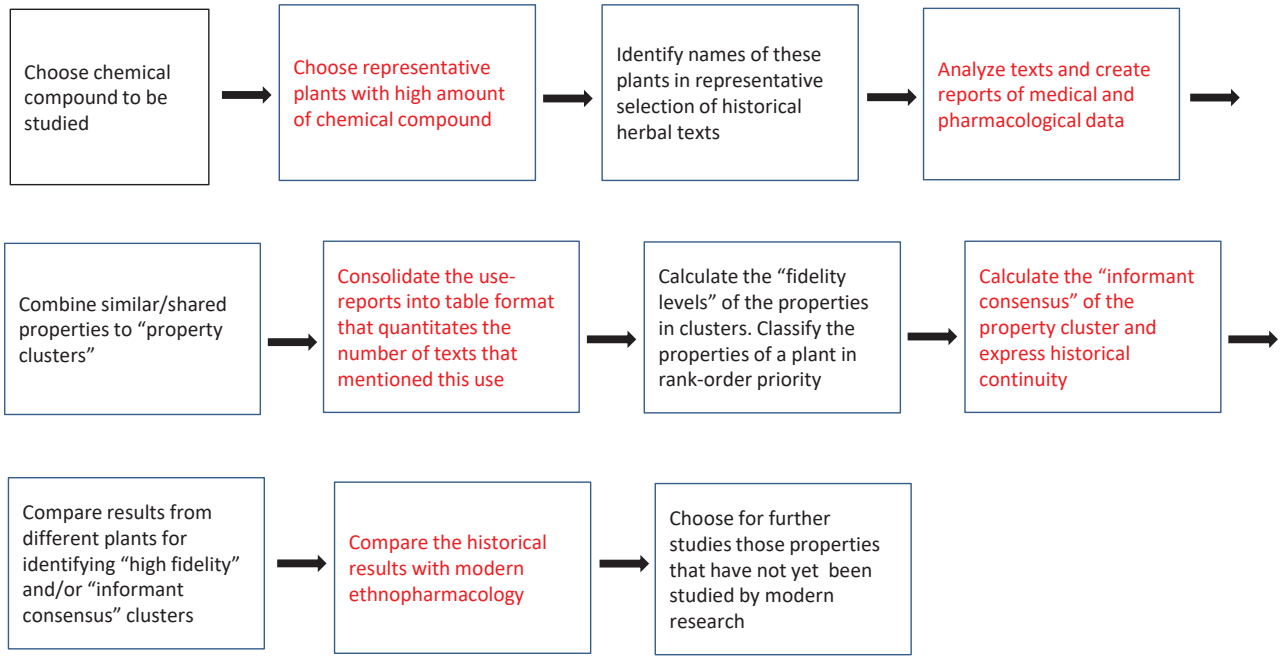
Review article *מאמר סקירה*

Uses of citral-containing plants in ancient and medieval herbology

h. M. Paavilainen[1, 2], A. Heilig[1], R. Ofir[1, 2*]

[1] Dead Sea & Arava Science Center, Central Arava Branch, Sapir m. p. Arava 86825, Israel (until 2008)
[2] History of Medicine, Hebrew University of Jerusalem, Hadassah Medical School, Israel
[3] Regenerative Medicine & Stem Cell Research Center, Ben Gurion University of the Negev, Beer Sheva 84105, Israel
* Corresponding author: rivir@bgu.ac.il

GRAPHICAL ABSTRACT



ABSTRACT

Keywords:
Ancient medicine
Cancer chemoprevention
Ethnopharmacology
Therapeutic use
Citral
Cymbopogon
Melissa
Verbena

Ancient/medieval herbal and medical literature was reviewed to (a) examine historical records regarding the use of citral-containing plants in the treatment of cancer; (b) determine which kinds of cancer were addressed; and (c) identify other common uses of citral-containing plants, and potential novel pharmacotherapeutic applications for citral. An adapted version of the Informant Consensus Model was used to gather data, and for each of the property complexes a "fidelity level" was calculated to rank the properties by priority based on their claimed relative probability. *Cymbopogon* was described by 19 authors, with 543 use-reports, *Melissa* was described by 18 authors with 541 use-reports, while *Verbena* had 19 authors and 739 use-reports. Among the numerous references to the three plants as anti-tumor drugs, tumors or swellings in uterus, liver or spleen, and hard or inflamed tumors in general were specifically indicated. Most of the medical uses attributed to all three plants had a strong ethnopharmacological backing, and all were supported with modern biomedical data on citral-containing plants. The effects claimed by the ancient authors, but not yet correlated with the results of modern research on citral, could become potential sources for new and unique uses of the plants.

1. Introduction

Our interest in citral arose from a study in which Dudai et al. (2005) demonstrated that from a 44.5 µM concentration of the compound was sufficient to induce apoptosis in several hematopoietic cancer cell lines through activation of the protein procaspase-3. This concentration is equivalent to the concentration of citral in a cup of tea prepared from 1 g of lemon grass. The anti-cancer effect of the compound depends on the unique structure of a double bond in conjunction with an aldehyde group, which the authors suggest might be a core structure for the design of a new family of pro-apoptotic drugs. One of the characteristics of pro-caspase activation is the dimerization of two procaspase-3 molecules. This action triggers a process of proteolytic cleavage of more procaspase-3 molecules. Preliminary results allow us to assume that the unique structure of a double bond in conjunction with an aldehyde group, such as in citral, leads to the dimerization. Assuming so, modifications of citral that preserve this unique structure may create active molecules that are highly effective in inducing apoptosis in cancer cells.

Ethnopharmacology can drastically shorten discovery time in pharmacological research, utilizing the collective experience of traditional healers throughout generations. The strength of medieval medical literature as a source of herbal information lies in the fact that the effects of a treatment have been tested in humans and results have been observed over a period of several generations. Earlier research shows medieval drug therapies are, in general, solidly based on experience, developing in the interplay between tradition and innovation (Buenz et al., 2004; Buenz et al., 2006; Riddle, 1985a; Sehgal et al., 1994). These therapies did, in fact, offer relief if not healing to patients, and form a collection of material suitable for ethnopharmacological research.

Citral is a chief constituent of the essential oils of many lemon-scented aromatic plants such as West Indian lemongrass (*Cymbopogon citratus* [DC. ex Nees] Stapf. [Poaceae] (Lewinsohn et al., 1998), lemon balm (*Melissa officinalis L.*; Lamiaceae; Araujo et al., 2003), and vervain (*Verbena officinalis L.*; Verbenaceae; List and Hörhammer, 1979, p. 423). It is widespread in the plant kingdom, giving its typical lemon scent to one or a few subspecies of several genera, including lemon eucalyptus (*Eucalyptus citriodora Hook.*; Myrtaceae) and lemon mint (*Monarda citriodora Cerv.*; Labiatae; Duke, 2006). In addition, citral-containing plants are widespread globally; many of them are part of local medical traditions (Plants for a Future, 2004; NewCrop, 2006).

Citral (3,7-dimethyl-2,6-octadienal) is a natural mixture of the isomeric acyclic monoterpene aldehydes geranial (trans-citral, citral A) and neral (cis-citral, citral B). Because it can elicit powerful and relevant reactions (Dudai et al., 2005) and produce pharmacological effects that have been little studied, we became motivated to seek other possible uses for this interesting chemical compound.

The aim of our research was threefold: First, to examine historical records for the use of citral-containing plants in cancer treatment. Second, to identify other common uses of citral-containing plants in the Middle Eastern-European medical tradition and novel pharmacotherapeutic applications for citral. Third, to determine which kinds of cancer should be addressed provided the data supports recommendations for cancer therapy.

The varying amount of citral in different plants of the same species causes methodological problems. For example, the genetic variation within the same species or subspecies and the existence of chemotypes with differing primary components of the essential oil can dramatically influence the medicinal properties of a plant (Freire et al., 2006; Viljoen et al., 2005). The amount of the various chemicals depends also on many external factors, including the locale: climate, soil, altitude; harvesting and storing methods; and even the time of the day (Scarborough, 1987, p. 3; Riddle, 1985b, pp. xxiv-xxv; Gu et al., 2004; Gil et al., 2002; Kothari et al., 2004; Orav et al., 2004; Agnihotri et al., 2005; Shunying et al., 2005). Extraction methods and oil processing methods also influence its chemical composition (Sorensen and Katsiotis, 2000; Tam et al., 2006). Since most plant subspecies, chemotypes and ecotypes have similar but non-identical phytochemistries (Riddle, 1992, p. 33), it is useful to assume that if one variety of the plant has a certain chemical compound causing a pharmacological effect, another variety of the plant (to which the same effect is attributed) would also possess the chemical compound. While this constitutes an assumption, several assumptions pointing in the same direction that are confirmed by other results of the research can become cumulative evidence (Riddle, 1992, pp. 79–80). This applies also to the changes that the plants might have undergone during thousands of years. Although their chemistry might not be identical, a rough chemical proximity exists (Riddle, 1985b, p. 41; see, however, also Buenz and Schnepple, 2007). Therefore, we decided to study all plants of the same genus together, without concentrating on the recommended plant species. The reasons were threefold: (a) accurate plant identifications on the species level are, in most cases, not possible; (b) for evaluation purposes, in many cases only one or two species of a plant genus have been studied in depth while the remainder have only a few sparse remarks; and (c) most species of a plant genus have a similar but non-identical phytochemistry (Riddle, 1992, p. 33). Our study will not specify the parts of the plant used. Our

sources recommend that in addition to leaves, the seeds, roots and stalk of the plants are beneficial for healing purposes, and many accounts completely omit mentioning what part was used. Although citral is particularly abundant in the aerial parts of lemongrass, lemon balm and vervain, it exists also in the other parts, and therefore, we deemed it to be clearer for the general purpose of the study to ignore this question.

2. Materials and methods

The general methodological process is shown in Figure 1.

2.1. Selection of Source Material

We used an adapted version of the Informant Consensus Model, developed by Trotter and Logan (1986) and modified by Heinrich (2000), and the method for bioprospecting historical texts developed by Buenz et al. (2004, 2005).

We selected 23 herbals (or parts of medical encyclopedias dealing with herbs) starting from Dioscorides' (c. 40–90) *De Materia Medica* to the time of the 17th-century herbalists Nicholas Culpeper and Blas de la Madre de Dios, using the Stannard (1974) definition of the term "herbal".

Most of the material selected originated in an area ranging from Persia to Spain, and from North Africa to England and Germany. In addition, we included some herbals describing non-European plant uses. The final selection is shown in Table 1.

2.2. Species studied

From the 23 herbals, information on three species was collected: West Indian lemongrass (*Cymbopogon citratus* [DC. ex Nees] Stapf), lemon balm (*Melissa officinalis* L.), and vervain (*Verbena officinalis* L.). These plants were chosen because they (a) contain relevant amounts of citral; (b) belong to plant genera in which citral is present in other subspecies of the genus, thereby obviating the difficulty of plant identification on the subspecies level (Hegnauer, 1962–1986); (c) belong to different plant families, lessening the risk that a common pharmacological effect be based on another chemical; and (d) grew in the Old World and therefore, enough written material is available to make the research meaningful.

We based our plant identifications on the results of earlier, well-based scholarship as seen in the appropriate literature.

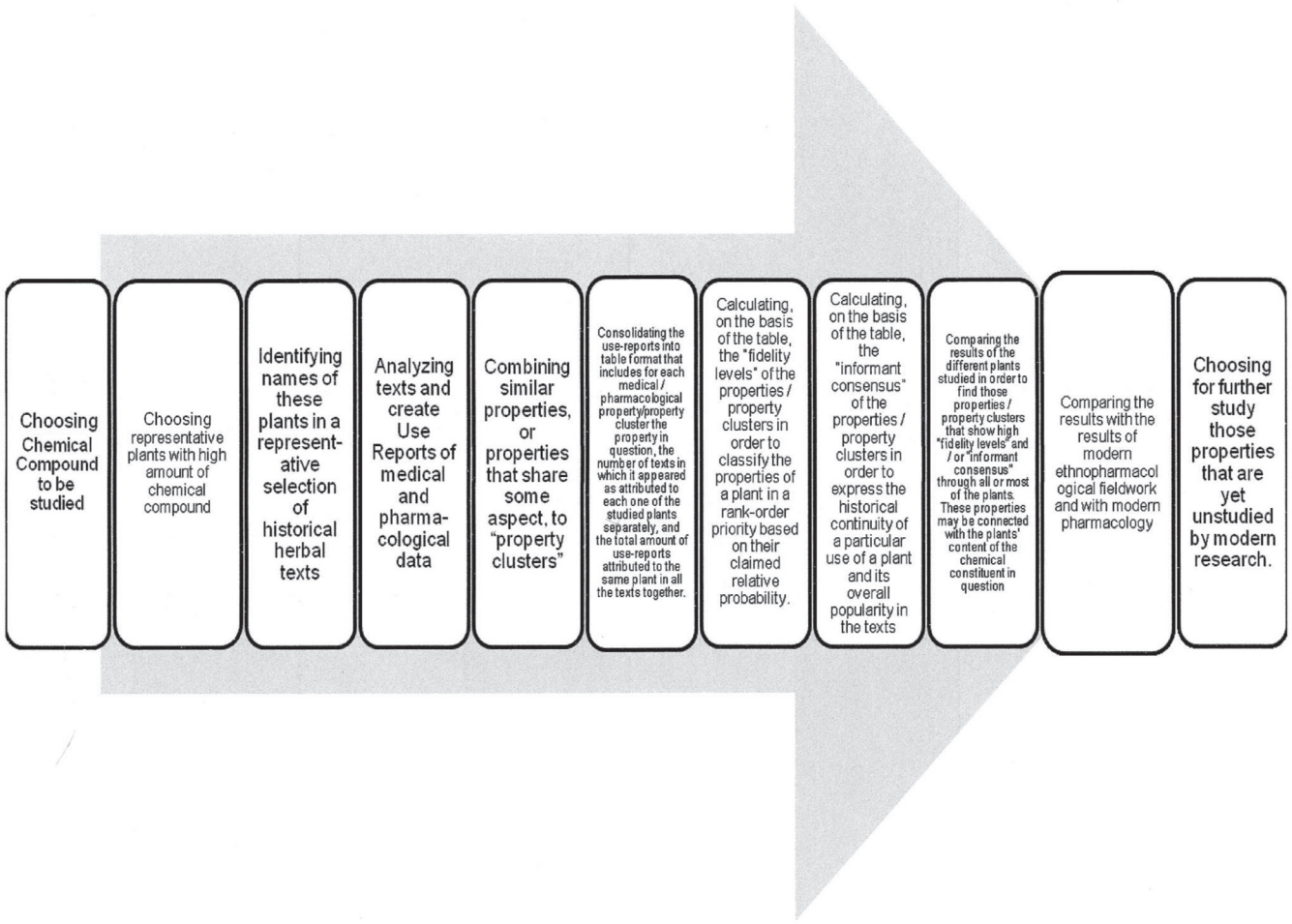


Figure 1: Sequence of events demonstrating the general methodological approach used in the research

Table 1: The herbals and medical encyclopedias used in the study

Author/Title	Date	Author's location	Text used
Dioscorides	1st cent. CE	Anazarbos (Turkey)	Dioscorides, P., 1902. Des Pedanios Dioscurides aus Anazarbos Arzneimittellehre in fünf Büchern. Trans. and comm. J. Berendes. Ferdinand Enke, Stuttgart.
Galen	2nd cent. CE	Pergamum / Rome	Galenus, C. G, 1964-65. Opera omnia. Ed. C. G. Kühn. [Facsimile reprint of C. Cnobloch Leipzig, 1821-33 edition.] Olms, Hildesheim.
Asaf ha-Rofe	6th cent.	Mesopotamia	Asaf ha-Rofe', 1916. Sefer Refu'ot, trans. L. Venetianer, in L. Venetianer, Asaf Judaeus: der aelteste medizinische Schriftsteller in hebraeischer Sprache. Strassburg, K. J. Trubner.
"Old English Herbarium"	6th cent.	England	van Arsdall, A.. 2001. The Old English Herbarium in a new context. PhD Thesis, Albuquerque, University of New Mexico, 2001
al-Tabari	9th cent.	Persia	al-Tabari, A. b. R., 1928. Firdaws al-hikmah fi al-tibb. Ed. M. Z. al-Siddiqi. Aftab, Berlin.
Ishaq Israeli	9th – 10th cent.	Kairouan	Israeli, I. [1515]. Omnia opera Ysaac in hoc volumine contenta: cum quibusdam alijs opusculis. [Jean de La Plate for Barthelemy Trot, Lyons]. Electronic edition 1995 by Bibliothèque nationale de France (BnF).
al-Razi	9th – 10th cent.	Persia	Al-Razi, M. b. Z., 1955-1970. Kitab al-Hawi fi al-Tibb. Vols. XXI-XXII. Osmania Oriental Publications, Hyderabad.
Ibn Sina	10th – 11th cent,	Persia	Ibn Sina, H. a. A. 1877. Kitab al-Qanun fi-l-Tibb. Dar Sadir, Beirut.
"Macer floridus"	11th cent.	France	Macer Floridus, [2001]. Höhepunkte der Klostermedizin: der "Macer floridus" und das Herbarium des Vitus Auslasser. Ed. and trans. J. G. Mayer and K. Goehl. Holzminden, Reprint-Verlag Leipzig.
"Flos medicinae scholae Salerni"	11th cent.	Italy	Flos medicinae scholae Salerni, 1852-59. In: Collectio Salernitana: ossia documenti inediti, e trattati di medicina appartenenti alla scuola medica Salernitana. Vol. 5. Eds. G. E. T. Henschel, C. Daremberg, and S. de Renzi. Filiatre-Sebezio, Napoli.
Hildegard von Bingen	12th cent.	Germany	H. v. Bingen, 1998. Hildegard von Bingen's Physica : the complete English translation of her classic work on health and healing. Trans. Priscilla Throop. Rochester, Vt., Healing Arts Press.
Albertus Magnus	13th cent.	Germany	Albertus Magnus, 1867. De vegetabilibus libri VII: historiae naturalis pars XVIII. Eds. E. H. F. Meyer and K. Jessen. G. Reimeri, Berlin.
Ibn al-Baytar	13th cent	Spain / Egypt / Syria	Ibn al-Baytar, a. M., 1992/1412. Kitab al-gami' li-mufradat al-adwiyah w-al-aghdhiyah. Dar al-kutub al-'ilmiyah, Beirut.
Rufinus de Rizardo	13th cent.	Italy	Rufinus, 1946. Herbal of Rufinus. Ed. L. Thorndike. The University of Chicago Press, Chicago.
Ibn Qayyim al-Jawziyya	14th cent.	Syria	Ibn Qayyim Al-Jawziyya, M. b. A. B., 1998. Medicine of the prophet. Trans. Penelope Johnstone. Cambridge, Islamic Texts Society.
Otto Brunfels	16th cent.	Germany	Brunfels, O., 1530. Herbarvm vivae eicones ad naturae imitationem... Argentorati, apud Ioannem Schottum. http://fondosdigitales.us.es/ books/digitalbook
Hieronymus Bock	16th cent.	Germany	Bock, H., 1964. Kreütterbuch darin underscheidt Nammen und Würckung der Kreütter, standen. Josiam Rihel, Strassburg, 1577. Reprint Konrad Kölbl, München.
Leonhart Fuchs	16th cent.	Germany	Fuchs, L. 1549. De historia stirpium commentarii insignes. B. Arnolletum, Lyon. Electronic edition 1995 by Bibliothèque nationale de France.
Nicolas Monardes	16th cent.	Spain	Monardes, N., 1580. La historia medicinal de las cosas que se traen de nuestras Indias Occidentales (1565-1574). Sevilla, Fernando Diaz.
Francisco Hernandez	16th cent.	Spain / Mexico / Philippines	Hernández, F., 1942-1946. Historia de las plantas de Nueva España. Trans. José Rojo. México, Imprenta Universitaria.

Author/Title	Date	Author's location	Text used
Jacob Theodor Tabernaemontanus	16th cent.	Germany	Tabernaemontanus, I. T., 1970. Neu vollkommen Kräuter-Buch [...] 4th Ed., K. Kölbl, Grünwald bei München, 1970. Reprint of: J.L. König, Basel, 1731.
Gregorio Lopez	16th cent.	Mexico	López, G. 1982. El tesoro de medicinas de Gregorio López 1542-1596. Ed. and comm. F. Guerra. Instituto de cooperación iberoamericana, Ediciones cultura hispánica, Madrid.
al-Antaki	16th cent.	Syria / Cairo	al-Antaki, D. b. A., 1356 (A. H.) Tadhkirah ula li-lbab wa-l-gamic li-l-cagab al-cugab. Al-Matba'ah al-'Utmaniyyah, Misr.
John Gerard	16th – 17th cent.	England	Gerard, J., 1633. The herball or generall historie of plantes. Adam Islip Ioice Norton and Richard Whitakers, London.
John Parkinson	16th – 17th cent.	England	Parkinson, J. 1640. The theater of plants, Or, An herball of a large extent. T. Cotes, London. Retrieved from Early English Books Online, http://eebo.chadwyck.com.
Nicholas Culpeper	17th cent.	England	Culpeper, N., 1652. The English physitian: or an astrologo-physical discourse of the vulgar herbs of this nation. London, Peter Cole. In http://www.med.yale.edu/ library/historical/ culpeper/ culpeper.htm
Blas de la Madrede Dios	17th cent.	Philippines	Blas, Fr., 1984. El libro de medicinas caseras de Fr. Blas de la Madre de Dios : Manila, 1611. Ed. and comm. F. Guerra. Madrid, Ediciones cultura hispánica.

For example, in the case of *Cymbopogon*, the names used to collect data from the texts included the following words in various languages: Greek—*schoinos, schoinanthos*; Arabic—*idhkhir*; Latin—*squinantum, squinantum arabicum, juncus odoratus*; German—*Cameelenheu*; Spanish—*paja de Meca, junco oloroso*; and Aztec—*zacatlatlauhqui*.

2.3. Lemongrass in Jewish sources

Lemongrass and its relatives appear in Jewish sources through the centuries, starting from the Bible. The preparation of holy anointing oil for the Tabernacle included *qene-bosem*, translated here as "sweet-smelling cane": "Also take for yourself quality spices—five hundred shekels of liquid myrrh, half as much sweet-smelling cinnamon (two hundred and fifty shekels), two hundred and fifty shekels of sweet-smelling cane..." (Ex. 30: 23, NKJV). Also, the words of the prophet Jeremiah refer to sacred use of the sweet grasses, here called *qane ha-tov*, "sweet cane": "For what purpose to Me comes frankincense from Sheba, and sweet cane from a far country?" (Jer. 6: 20). The sweet grasses were thus a trading item, as can also be seen from the description of the city of Tyre by the prophet Ezekiel: "Dan and Javan paid for your wares, traversing back and forth. Wrought iron, cassia, and cane were among your merchandise." (*qane* = "cane"; Ez. 27: 19). According to Zohary (1983; 196), these grasses may have included *Cymbopogon martinii, C. schoenanthus* Spreng. and *C. citratus* (DC.) Stapf.

Jewish medical tradition has always been heavily influenced by the traditions of the surrounding nations in the Middle East, especially by the Mesopotamians and the Greeks (Dioscorides, Galen), to which the personal experiences of the physicians and the local folklore were added. As a result of the lasting influence of the Greek authors on Arabic and, later on, Latin medical curriculums, their uses of *materia medica* continue to be seen throughout the writings of the Jewish scholars up to the 17th and 18th centuries. Dioscorides (c. 40–90) in his *De Materia Medica* describes the pharmacological effects of *schoinos* (lemongrass and its relatives) as follows:

... Choose that which is new, red, and full of flowers; which when cut or cleft inclines to a purple colour, is thin, smells sweet like a rose when it is rubbed between the hands, and bites the tongue with considerable burning. Use the flower, the reeds and the root. It is diuretic, bringing down the menstrual flow, and dissolving gaseousness. It causes catarrh in the head. It is mildly astringent. It has a breaking, digesting and opening strength. The flowers of it used in drink are good for bloody vomiting and a painful stomach, as well as the lungs, liver and kidneys. It is mixed with antidotes, but the root is more astringent and therefore is given for a squeamish stomach. One teaspoonful is good for dropsy and convulsions, and is given for some days with the same amount of pepper. A decoction of it as a hip bath is most convenient for inflammation around the vulva. It is also called Babylonian [juncus] or *teuchitis*. (Dioscorides, 2000, 1: 16)

In one of the earliest preserved Hebrew medical documents, *Sefer ha-Refu'ot* by Asaf ha-Rofe (6th cent., Babylonia?), the author attributes the following effects to lemongrass: (1) moderate warming power; (2) diuretic; (3) emmenagogue; (4) removes the winds [= intestinal gases]; (5) causes headaches; (6) helps those who vomit or cough up blood from the liver or the lungs; (7) helps those who suffer from a liver, lung, spleen and especially kidney problem; 8) breaks kidney stones; (9) helps against dropsy and fierce palpitations; (10) heals bad ulcers; (11) makes hair grow.

"For hydropsy and fierce palpitations of heart, the patient should take a drachma of lemongrass and a drachma of pepper and boil them in water or wine. For bad ulcers, lemongrass should be ground to powder and spread on the ulcerating area. Lemongrass cooked in vinegar and applied on the head enhances hair growth" (Asaf ha-Rofe, 1916, p. 133). Most of Asaf's recommendations originated from Dioscorides' text, but some are modified and some are novel.

Westwards, in the Mediterranean surroundings, lived Isaac Israeli (9th–10th cent.), an Arabic-writing Jewish physician who was born in Egypt and studied there. He wrote most of his books in Kairouan (modern Tunis); in his writings he restated several of the uses for lemongrass mentioned by Asaf ha-Rofe: "(1) it is hot and dry in 1st degree burn; (2) diuretic; (3) emmenagogue; and (4) breaks stones (drunk as a decoction). Some of the uses are slightly modified: its flowers stop bleeding caused by liver and stomach abscesses, and its smell makes ones head heavy and induces sleep. The plant has a tart and sharp taste" (Israeli, [1515], fol. lxix).

Moses ben Maimon (Maimonides, ha-Rambam; 1135/1138–1204; Andalusia – Morocco – Egypt), the greatest Jewish medical writer of the Middle Ages, elaborates in his commentary on Galen's On the compound remedies arranged according to the location of the ailment on the issue already touched on by Isaac Israeli - internal abscesses. According to Galen's abstract advice: "An appropriate therapy in general for abscesses occurring deep inside the body is to treat them with refining and drying drugs" (Maimonides, 2007, 9: 87).

Maimonides adds the practical interpretation: "… since most internal abscesses are followed by fever, it is necessary for a physician to remember those remedies that Galen has specified as attenuating and drying, next to their degrees of heat and dryness. Of the medications that dry and attenuate and are hot and dry in the first degree, there are four that are commonly used: agrimony, lemongrass, tamarisk, and pistachio. Of the medications that are hot and dry in the second degree, there are eight: Roman nettle, balsam..." (Maimonides, 2007, 9: 88)

2.4. Data collection and tabulation

Comments associated with the plants' medicinal and/or pharmacological properties were extracted, including the symptoms and diseases for which they were recommended, as understood in the contemporaneous context of the texts. These comments correspond to "use-reports" (Heinrich, 2000), defined as single records of a medicinal/pharmacological property from the selected texts (Treyvaud Amiguet et al., 2004). Identical records of properties attributed to a plant under the same plant name were counted as separate use-reports. Comparisons to other plants (e.g., "...has the same effect as orange leaves...") were disregarded, unless the property in question was specifically mentioned. The use-reports were consolidated into a table that includes the property in question, the number of texts in which it appeared as attributed to each one of the three plants separately, and the total amount of use-reports attributed to the same plant in all the texts together. As the total number of use-reports differed for each plant because not all plants were described by all authors and the data on each of the plants differed, the results for all three plants were not calculated together. This table (not shown, but available from the authors) allowed us to estimate the relative importance of each of the medicinal plant qualities in the framework of continuous medical tradition.

2.5. Fidelity level

Using the method developed by Friedman et al. (1986), we calculated a "fidelity level" (FL) to rank each property or property complex based on its claimed relative probability. The properties were arranged in accordance with the percentage of texts suggesting the same medicinal property for a given species, compared with the total number of texts reporting any sort of use for that plant. The fidelity level of each property or property cluster was determined as follows: $FL = (Ip/Iu) \times 100$, where Ip is the number of herbal texts that mentioned the use of a species for a particular purpose, and Iu is total number of texts that mentioned the plant for any use. The fidelity level expresses the ongoing popularity of a drug, which has been recognized to have a potential effect elsewhere (Scarborough, 1987).

2.6. Property clusters

In classifying the uses and properties of the plants into property clusters, we decided against their division using the more standard methods, such as those devised by Cook (1995), because ancient and medieval diseases, symptoms, and medicinal property categories differ so strongly from modern ones. Instead, we used both the categories of the medical system itself to discern meaningful connections, as well as modern

categories, that seemed to open up more heuristically important pathways.

The total number of use-reports for a particular medicinal property/property cluster in a particular plant is termed: **Nuse-report 1**. (Nuse-report = N use-report = Number of total use-reports, namely, how many times the plant is mentioned in the sources as being used in a particular way, for example as a purgative) .

Nuse-reports for all the use-reports for that particular plant was termed: Nuse-report all, namely, all the reports on all the uses are counted. The Nuse-reports were converted to a function of Fic (Fic = Informant Consensus Function) as follow:

Fic = (Nuse-report 1/Nuse-report all) x 100.

This value expresses not only the historical continuity of the use, but also its overall popularity in the texts, as multiple recommendations of the plant for a particular use by the same author increase this value. The higher the value of Fic, the higher the cultural importance of a particular plant use, and the more it might point to new, scientifically interesting roads of research (Treyvaud Amiguet et al., 2004).

2.7. Analysis of data comparing citral-containing species

In comparing taxa, it is important to remember the limitations of working with historical data, especially the researcher's inability to clarify problematic issues with the informants. If a particular property has not been attributed to a particular plant, it does not warrant the assumption that the plant does not have that quality; it only means the issue has not been studied yet (Browner et al., 1988). Therefore, we searched for general tendencies, strong existence of the property in two plants, and weaker findings in all three.

We based the choice of plant medicinal properties for further evaluation on two parameters: (1) Fidelity level is the historical continuity of the use of a particular plant for a particular purpose. We considered FLs ≥ 50 as strongly relevant, with weakly relevant FLs in the range of 40–49. (2) The Informant Consensus Function (Fic) is the overall popularity of the attribution of a certain property to a certain plant. Strong relevancy was determined at ≥ 5.00. This means that at least 5% of the use-reports on a given plant are connected with a particular property. Weakly relevant Fic values were determined to have a range of 2.00–4.99. To find properties that could be due to the citral content in the three plants, we then rated the properties and property clusters according to their assumed relevance. Properties that had a strongly relevant FL and/or a strongly relevant Fic for all three plants were rated at the highest probability level (PLI). Those having two strongly relevant and one weakly relevant FL and/or two strongly relevant and one weakly relevant Fic were rated at the second probability level (PLII). The third level (PLIII) consisted of property attributions having only two strongly relevant FLs and/or two strongly relevant Fics. The fourth level (PLIV) included properties having one strongly relevant and two weakly relevant FLs and/or one strongly relevant and two weakly relevant Fics, or three weakly relevant FLs and/or three weakly relevant Fics.

Property clusters include problems of various etiologies possibly needing different treatments and were further classified into subcategories to determine the relevant features.

The most prominent symptoms and diseases [with Fic ≥ 0.5 for a single plant, or two or three plants exhibiting the property] were then diagnosed to determine the potential pharmacological functions of the three plants studied. Because the main chemical compounds of these plants differ, any common pharmacological effect might be due to their citral content. These results were evaluated through a survey of the current literature on *Cymbopogon, Melissa,* and *Verbena* and citral by querying for relevant bioactivity based on the elucidated pharmacological function from the ancient and medieval herbals, using the medical databases PubMed and NAPRALERT. This was correlated with the pharmacological function that could be expected to validate at least part of the properties ascribed to the plants (Buenz et al., 2004, 2005).

3. Results and discussion

3.1. Main results

Cymbopogon was described by 19 authors, with 543 use-reports; *Melissa* described by 18 authors with 541 use-reports, while *Verbena* had 19 authors and 739 use-reports.

Eighteen different clusters of medicinal properties showing the most prominent recommendations for the use of citral-containing plants taken together, may indicate the best uses of citral (Table 2). Two of the clusters, warming/against cold, and cold diseases and drying/against moistness, represent culture-bound syndromes, and were thus excluded (Heinrich, 2000). The main issues at PLI were clusters connected with stomach problems, pain therapy, respiratory problems, and gynecological problems, while PLII added clusters connected with swellings/tumors, teeth and mouth problems, cleaning and strengthening. In PLIII, the most important issues concern the antidote effect, the healing effect on wounds and ulcers, liver problems and jaundice, and animal bites and stings (mostly poisonous, but not necessarily). The diuretic effect was combined on the one hand to urinary tract therapy, and on the other to heart problems and hydropsy. PLIV added anti-inflammatory and astringent properties.

Table 2: Medical/pharmacological properties of citral-containing plants with the highest potential for further studies. All = total number of use-reports for a given plant/property; Bks = number of texts in which a given plant is attributed a given property; FL = fidelity level; Fic = informant consensus function; PL = probability level; Ag= against; s/t/h/i = swellings/tumors/hardenings/inflammation; Agc= against cold; Agcd= against cold disease; H/w = hot/warming; Cp/lp= chest and lung problems; H/hp/d= heart and hydropsy and diuretic; Gp= gynecological problems; Sp= stomach problems

Quality/Action		**Cymbopogon**				**Melissa**				**Verbena**			
	PL	All (543)	Bks (19)	FL	Fic	All (541)	Bks (18)	FL	Fic	All (739)	Bks (19)	FL	Fic
H/w + Agc + Agcd	I	34	14	73.7	6.3	42	11	61.1	7.8	21	12	63.2	2.8
Sp		70	16	84.2	12.9	45	13	72.2	8.3	36	12	63.2	4.9
Ag pain (explicit)		60	12	63.2	11.0	39	8	44.4	7.2	72	16	84.2	9.7
Gp		49	15	78.9	9.0	34	10	55.6	6.3	28	12	63.2	3.8
Cp/lp		28	13	68.4	5.2	19	11	61.1	3.5	40	9	47.4	5.4
Ag s/t/h	II	48	12	63.2	8.8	13	7	38.9	2.4	30	13	68.4	4.1
Dry + drying + Ag moisture		13	9	47.4	2.4	11	9	50.0	2.0	32	12	63.2	4.3
Cleaning		12	7	36.8	2.2	20	9	50.0	3.7	14	10	52.6	1.9
Strengthening + beneficial		27	8	42.1	5.0	50	12	66.7	9.2	28	8	42.1	3.8
Teeth/mouth		12	8	42.1	2.2	16	10	55.6	3.0	26	11	57.9	3.5
Ulcers/cleans ulcers	III	5	3	15.8	0.9	15	10	55.6	2.8	44	11	57.9	6.0
Wounds/ulcers/burns + cleaning them		5	3	15.8	0.9	17	11	61.1	3.1	96	16	84.2	13.0
Hp/h/d		28	15	78.9	5.2	39	10	55.6	7.2	10	6	31.6	1.4
Liver/jaundice		34	13	68.4	6.3	4	4	22.2	0.7	32	10	52.6	4.3
Ag poisons		6	5	26.3	1.1	34	11	61.1	6.3	30	12	63.2	4.1
Ag stings/bites		2	2	10.5	0.4	25	10	55.6	4.6	23	10	52.6	3.1
Ag bleeding + astringent + flows	IV	56	14	73.7	10.3	11	7	38.9	2.0	21	7	36.8	2.8
Ag hot s/t/i		17	8	42.1	3.1	11	4	22.2	2.0	30	11	57.9	4.1

Property clusters include problems of various etiologies possibly needing different treatments and were further classified into subcategories to determine the relevant features. Tables 3-9 show the subcategories determined from the data in Table 2 that were PLI or included substantial reference to cancer. Table 10 shows some of the culturally relevant categories divided into subcategories.

Duke (2006) attributes each of the above-mentioned property clusters of high relevance to each of the three plants, or other plants of the same genera. However, the chemical compound causing the effect was not mentioned. On the chemical level, the PubMed and NAPRALERT databases ascribe a strong connection to citral in seven property clusters, a moderate connection in two, a weak one in three, and no connection in one.

The validity of our method is affirmed by the results. Most of the seven property clusters included in the final analysis had a strong ethnopharmacological backing. All were supported by comparison with modern biomedical data on citral-containing plants. In addition, the majority of the clusters showed strong modern evidence for their effect being at least partly attributable to their citral content. This all seems to corroborate the utility of the method, not as an exact predictor, but as a useful heuristic tool.

As our research shows, the potential value of citral, although a well-known and much-studied chemical compound, may not yet be fully realized. The effects ancient authors claimed citral has (including analgesic, anti-asthmatic, tonic, and antidepressive effects, and effect on uterine tumors) have not yet been confirmed by modern research and may become potential sources for novel uses of citral.

However, the wider methodological implications of the work may be still more important than those particularly connected with citral. The comparisons between our results and modern ethnopharmacological work on the one hand, and modern phytopharmacology on the other, show that both support our results, corroborating the validity of the method. At the same time, they show the wide areas that modern pharmacological research has not yet investigated. It seems that the method presented here could be successfully applied to other known chemical compounds in order to expand their range of possible uses. Additional methods using historical materials to assess beneficial substances may validate the use of traditional knowledge in the search for new drugs.

Table 3: Alleviate stomach problems. Comparison between the culturally relevant uses of citral-containing plants in ancient and medieval herbal literature to modern biomedicine. C= lemongrass (*Cymbopogon*); M= lemon balm (*Melissa*); V= vervain (*Verbena*); Cit = citral

Properties	Biomed Data (Cit)	Biomed (C, M, V)	EP Data
General effect	No gastrointestinal effect (except Intraperitoneally; cit or C)		
Flatulence		Carminative (M)	Carminative (C, M)
Swellings/tumors in intestines		Anticarcinomic (colon; C); anticancer (forestomach [M]; colon) [M,V]); antiangiogenic (C,V); antitumor (M,V); antitumor (colon [C, M, V]; forestomach [C, M]; stomach [C, M, V]; antitumor-promoter (C, M, V)	
Intestinal pain			For stomach-ache (C,V)
Colic	Antispasmodic (intestinal); muscle relaxant (in high doses); relaxant effect on ileum contractions.	Anticolitic (C); antinociceptive (C, M); analgesic (C, M, V); anesthetic (C, M); antispasmodic (C, M, V); enterorelaxant (M)	For stomach cramps (V); antispasmodic (C, M, V)

Table 4: Against pain (explicit). C= lemongrass (*Cymbopogon*); M= lemon balm (*Melissa*); V= vervain (*Verbena*); Cit = citral

Properties	Biomed (C, M, V)	EP Data
Analgesic effect	Analgesic (C, M, V); anesthetic (C, M); antinociceptive (C, M); narcotic (M); counter-irritant (C, M)	For afterpains (V); anodyne (C, M)
Headache	Counter-irritant (C, M)	For headache (C, M)
Intestinal pain		For stomachache (C, V)
Joint pain	Antiarthritic C,M,V); antirheumatic (C, M, V); counterirritant (C, M)	For rheumatism (C, V); for arthritis (V)
Liver pain	Hepatoprotective (C, M, V); hepatotonic (C)	
Toothache	Anticariogenic (C, M, V)	For toothache (C, M)
Urinary tract pain Uterine pain	Urinary antiseptic (M) (See Table 9.)	

Table 5: For chest and lung problems. C= lemon grass (*Cymbopogon*); M= lemon balm (*Melissa*); V= Vervain (*Verbena*); Cit = citral

Properties	Biomed Data (Cit)	Biomed (C, M, V)	EP Data
General effect			Pectoral (C)
Shortness of breath	Antifungal (e.g., vs. Aspergillus niger, A flavus, Penicillium digitatum, Penicillium italicum, Geotrichum candidum); anti-aflatoxigenic; anti-convulsant; muscle relaxant	Anti-allergic (C, M, V); anti-asthmatic (C, M); anti-histaminic (C, M, V); histamine-inhibitor (M, V); bronchoprotectant (C, M); bronchorelaxant (C, V); tracheorelaxant (M); fungicide (C, M, V); respirastimulant (V); ACE-inhibitor (C, M)	
Cough	Antifungal; anti-aflatoxigenic; antimicrobial vs. Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans, methicillin-resistant S. aureus (MRSA), Aspergillus niger, Klebsiella pneumoniae, Propionibacterium acnes; antibacterial	Antitussive (C, M); tracheorelaxant (M); anti-allergic (C, M, V); antibacterial (C, M, V); antibronchitic (C, M); bronchoprotectant (C, M); bronchorelaxant (C, V); fungicide (C, M, V); Gram (-) icide (C, M); Gram (+) icide (C, M)	Antiseptic (C, M); for cough (C); for bronchitis (V); for pertussis (V)
Consumption/ tuberculosis	Antimicrobial; antibacterial	Antitubercular (C, M); antibacterial (C, M, V); Gram (-) icide (C, M); Gram (+) icide (C, M)	For tuberculosis (C); for scrofula (V)
Coughing up blood		Coagulant (V); hemostat (C, V)	

Table 6: For swellings/tumors and hardenings. C= lemon grass (*Cymbopogon*); M= lemon balm (*Melissa*); V= Vervain (*Verbena*); Cit = citral

Properties	Biomed Data (Cit)	Biomed (C, M, V)	EP Data
Swellings/tumors, general effect	Induces apoptosis in human leucemic (HL-60) cells; inducer of caspase-3 in tumor cell lines; anti-cancer potential	VEGF-Inhibitor (C); anti-angiogenic (C, V); anticancer (C, M, V); anticarcinogenic (C, M, V); anticarcinomic (C, M, V); antimetastatic (C, M, V); antitumor (C, M, V); antitumor promoter (C, M, V); cancer preventive (C, M, V); chemopreventive (C, M, V)	Against cancer (V); against tumors (M, V)
Hard swellings/ tumors		Tyrosine kinase inhibitor (C, M)	
Hot swellings/ tumors/ inflammations	Weak anti-inflammatory activity vs. TPA-induced edema	TNF-alpha inhibitor (C); prostaglandin synthesis inhibitor (C, M); anti-inflammatory (C, M, V); anti-prostaglandin (M, V); counterirritant (C, M)	
Cold swellings/tumors/ edemas	Antitumor activity vs. Yoshida ascites; cytotoxic activity vs. Ehrlich ascites	Anti-edemic (C, M, V)	For edema (V)
Swellings/tumors of the liver	Very toxic effect against human cell lines: HepG2 (a hepatocarcinoma-derived cell line)	Anticancer (liver; M); anti-angiogenic (C, V); antitumor (liver; M); hepatoprotective (C, M, V)	
Swellings/tumors of the skin	Antioxidant role of GST induction in skin; skin cancer preventive	Anticancer (Skin; M); anti-acne (C, M); antidermatic (C, M); antimelanogenic (M, V); antimelanomic (C, M); antitumor (skin; C, M, V)	
Swellings/tumors of the testicles	Causes benign prostatic hyperplasia (BPH)	Antitumor (prostate; C, M)	
Swellings/tumors in the throat			For tumors of throat (V)
Hardness of the liver		Hepatotonic (C)	For liver sclerosis (M); for cirrhosis (V)
Hardness of spleen		Antimalarial (C, M, V)	
Swellings/tumors in the intestines		(See Table 3.)	
Uterine swellings/tumors		(See Table 9.)	

Table 7: For liver problems. C= lemon grass (*Cymbopogon*); M= lemon balm (*Melissa*); V= Vervain (*Verbena*); Cit = citral

Properties	Biomed Data (Cit)	Biomed (C, M, V)	EP Data
General			For kidney and liver trouble (V)
Swellings/tumors of the liver	Induces apoptosis in human leucemic (HL-60) cells		
Obstructions of the liver	Effect on lipid metabolism; very toxic effect against human cell lines: HepG2 (a hepatocarcinoma-derived cell line)	Hepatotonic (C)	
Liver pain		Analgesic effect; hepatoprotective (C, M, V);	
Hardness of liver	See Table 6	hepatotonic (C)	

Table 8: For hot swellings and/or tumors with inflammations. C= lemon grass (*Cymbopogon*); M= lemon balm (*Melissa*); V= Vervain (*Verbena*); Cit = citral

Properties	Biomed Data (Cit)	Biomed (C, M, V)	EP Data
Hot swellings/tumors/ inflammations, general effect	Swellings/tumors, general effect; hot swellings/tumors/ inflammations	Swellings/tumors, general effect; hot swellings/tumors/ inflammations	Swellings/tumors, general effect
Hot swelling/tumor/inflammation in the eye		Anticataract (C)	
Hot swellings/tumors /inflammation of the skin	Antioxidant role of GST induction in skin; skin cancer preventive	Anti-cancer (skin; M); Anti-acne (C, M); antidermatic (C, M); anti-erythemic (C); antimelanogenic (M, V); antimelanomic (C, M); antitumor (skin; C, M, V)	
Hot swellings/tumors /inflammations in the uterus	Against inflammatory diseases of female organs	Anticancer (cervix; M); antitumor (cervix; M, V)	

Table 9: Gynecological problems. C= lemon grass (*Cymbopogon*); M= lemon balm (*Melissa*); V= Vervain (*Verbena*); Cit = citral

Properties	Biomed Data (Cit)	Biomed (C, M, V)	EP Data
Uterine pain	Antiyeast vs. *Candida albicans*; against inflammatory diseases of female organs; antimicrobial; inhibits mycelia growth of *Candida albicans*, which gives the fungus the capacity to invade mucosal tissues; potential value for the treatment of vaginal candidiasis; estrogenic activity (in high concentrations); antifungal; antibacterial	Analgesic effect; anti-PMS (C); antibacterial (C, M, V); candidicide (C, M, V); estrogenic (C); Gram (-) icide (C, M); Gram (+) icide (C, M)	
Uterine tumors/swellings	Against inflammatory diseases of female organs	Anti-cancer (cervix; M); antitumor (cervix; M, V); anti-angiogenic (C, V)	
Cleans the uterus	Estrogenic effect	Estrogenic (C)	
Emmenagogue	Estrogenic effect	Estrogenic (C)	Emmenagogue (C, M, V)
Missing menstrual period	Estrogenic effect	Estrogenic (C)	Against amenorrhea (V)
Syphilis	Against inflammatory diseases of female organs; antibacterial	Antibacterial (C, M, V)	

Table 10: Some of the culturally relevant categories divided into subcategories. Ag=Against, Fic = Informant Consensus Function; number without brackets = the Fic value; number in brackets = amount of use-reports

Properties	Fic values		
	Cymbopogon	Melissa	Verbena
Stomach problems			
Flatulence	2.8 (15)	0.4 (2)	0.3 (2)
Inflammation/hot swelling/ tumor in intestines	0.9 (5)	—	—
Cold swellings/tumors	0.2 (1)	—	—
Hard swellings/tumors	0.4 (2)	—	—
Swellings/tumors in intestines (undefined)	2.0 (11)	—	—
Swellings/tumors in intestines (total)	2.9 (16)	—	—
Intestinal pain	2.0 (11)	2.2 (12)	1.5 (11)
Colic	—	1.8 (10)	0.3 (2)
Diarrhea	0.4 (2)	—	0.1 (1)
Diarrhea, bloody	—	1.7 (9)	0.3 (2)
Peptic ulcer	0.2 (1)	0.4 (2)	—
Nausea/vomiting	1.1 (6)	—	0.3 (2)
Intestinal parasites	—	—	1.5 (11)
Ag pain (explicit)			
Analgesic effect (general)	1.1 (6)	—	0.5 (4)
Chest pain	0.2 (1)	—	0.1 (1)
Earache	—	—	0.3 (2)
Eye pain	—	0.2 (1)	0.3 (2)
Gout, pain of	—	0.6 (3)	—
Headache	—	0.4 (2)	2.3 (17)
Heart, pain of	—	—	0.1 (1)
Intestinal pain	2.0 (11)	2.2 (12)	1.5 (11)
Joints, pain of	0.2 (1)	0.9 (5)	0.5 (4)
Kidney pain	1.7 (9)	—	—
Liver pain	2.0 (11)	—	0.4 (3)
Lung pain	0.9 (5)	—	0.1 (1)
Spleen pain	0.2 (1)	—	—
Testicular pain	—	—	0.3 (2)
Toothache	0.4 (2)	1.7 (9)	0.8 (6)
Pain of urinary tract	0.7 (4)	—	—
Uterine pain	1.3 (7)	0.4 (2)	0.7 (5)
Pain of bee sting	—	0.2 (1)	—
Hemorrhoidal pain	—	0.2 (1)	0.1 (1)
Pains of stones	—	—	0.3 (2)
Ag chest + lung problems			
Lung pain	0.9 (5)	—	—
Asthma	—	0.6 (3)	—
Shortness of breath	0.2 (1)	0.2 (1)	0.3 (2)
Difficulty of breathing	—	1.8 (10)	0.8 (6)
Cough	0.6 (3)	0.2 (1)	0.4 (3)
Expectorant	0.2 (1)	—	—
Consumption / tuberculosis	2.4 (13)	0.2 (1)	1.1 (8)
Coughing up blood	2.4 (13)	—	0.1 (1)
Ag swellings/tumors + hardenings			
Swellings/tumors (undefined)	5.0 (27)	0.9 (5)	1.6 (12)
Hard swellings/tumors	1.7 (9)	1.5 (8)	0.3 (2)
Hot swellings/tumors/ inflammations	3.1 (17)	0.9 (5)	1.1 (8)
Cold swellings/tumors/ edemas	0.2 (1)	—	0.7 (5)
Swellings/tumors behind the ears	—	—	0.3 (2)
Swellings/tumors in the eye	—	—	0.1 (1)
Swellings/tumors in the intestines	2.9 (16)	—	—
Swellings/tumors of the kidneys	0.2 (1)	—	—
Swellings/tumors of the liver	2.4 (13)	0.2 (1)	—
Swellings/tumors of the skin	—	0.9 (5)	0.7 (5)
Swellings/tumors of the testicles	—	—	0.4 (3)
Swellings/tumors in the throat	—	0.7 (4)	0.1 (1)
Swellings/tumors in the uterus	1.3 (7)	—	0.4 (3)
Swellings/tumors of the uvula	0.2 (1)	—	—
Hard swellings/tumors in the muscle	—	0.4 (2)	—
Hardness/swellings/tumors of the liver	0.4 (2)	0.2 (1)	—
Hardness/swellings/tumors of the spleen	0.6 (3)	0.2 (1)	0.1 (1)
Ag ulcers			
Corroding, festering ulcers	—	0.2 (1)	0.9 (7)
Dirty ulcers	—	0.4 (2)	0.5 (4)
Malignant ulcers	0.2 (1)	—	0.9 (7)

Properties	Fic values		
	Cymbopogon	Melissa	Verbena
Spreading ulcers	0.2 (1)	—	0.7 (5)
Ulcers in the legs	—	—	0.3 (2)
Ulcers of the male genitals	—	—	0.1 (1)
Ulcers/sores in the mouth	0.4 (2)	—	0.9 (7)
Peptic ulcers	0.2 (1)	0.4 (2)	—
Ulcers in the throat	—	0.2 (1)	0.5 (4)
Ag heart problems/hydropsy/ diuretic			
Heart disease	0.2 (1)	0.7 (4)	—
Pains of the heart	—	—	0.1 (1)
Palpitations	0.2 (1)	1.1 (6)	—
Weakness of heart	—	2.4 (13)	—
Loss of consciousness due to weakness of heart	—	0.6 (3)	—
Melancholic vapors in the heart	—	0.6 (3)	—
Dropsy/edema	1.5 (8)	—	0.5 (4)
Diuretic	3.7 (20)	—	0.7 (5)
Ag jaundice/liver problems			
Swellings/tumors of the liver	2.4 (13)	0.2 (1)	—
Hot swellings/tumors/ inflammations of the liver	0.7 (4)	—	—
Obstructions of the liver	0.2 (1)	—	0.5 (4)
Liver pain	2.0 (11)	—	0.4 (3)
Hardness/hard swellings/ tumors of liver	0.4 (2)	0.2 (1)	—
Jaundice	—	—	2.4 (18)
Ag poisonous stings/bites			
Snake poison	0.4 (2)	0.2 (1)	1.1 (8)
Spider poison	—	1.1 (6)	0.3 (2)
Scorpion sting	—	1.5 (8)	0.4 (3)
Bee/wasp sting	—	0.9 (5)	—
Ag bleeding/astringent/ flows			
Bleeding (in general)	0.6 (3)	—	0.4 (3)
Bleeding from kidneys	0.2 (1)	—	—
Blood in excrement	—	0.2 (1)	0.1 (1)
Blood in urine	0.2 (1)	—	0.1 (1)
Diarrhea with blood	—	1.7 (9)	0.3 (2)
Checks menstrual flow	1.1 (6)	—	—
Coughing blood	2.4 (13)	—	0.1 (1)
Astringent	3.5 (19)	0.2 (1)	0.7 (5)
Secretions in the eyes	—	—	1.4 (10)

Properties	Fic values		
	Cymbopogon	Melissa	Verbena
*Ag hot swellings/tumors/ inflamma*tions			
Hot swellings/tumors/ inflammations (in general)	0.4 (2)	0.4 (2)	0.7 (5)
Hot swelling/tumor/ inflammation in the eye	—	—	0.4 (3)
Hot swellings/tumors/ inflammations in the intestines	0.9 (5)	—	—
Hard inflammations/hot tumors/swellings of the kidneys	0.2 (1)	—	—
Hot swellings/tumors/ inflammations of the liver	0.7 (4)	—	—
Hot swellings/tumors/ inflammation of the skin	—	0.7 (4)	2.4 (18)
Hot swellings/tumors/ inflammations in the uterus	0.9 (5)	—	—
Ag gynecological problems			
Uterine pain	1.3 (7)	0.4 (2)	0.7 (5)
Tumors/swellings in the uterus	1.3 (7)	—	0.4 (3)
Difficulty in conceiving	—	0.2 (1)	—
Cleans the uterus	0.2 (1)	0.7 (4)	—
Emmenagogue	4.2 (23)	2.4 (13)	0.5 (4)
Missing menstrual period	1.1 (6)	0.2 (1)	0.1 (1)
Wounds of female genitals	—	—	0.1 (1)
Checks uterine bleeding	0.9 (5)	—	—
Syphilis	0.6 (3)	—	0.3 (2)

3.2. Probability level I findings

At PLI, in the category of "stomach problems", the strongest attested feature for all three plants is intestinal pain with Fic rates ranging from 1.5 to 2.2. This feature could be connected either with the possible analgesic property of citral, or with a particular effect on the stomach. The effect of the three plants against intestinal pain was confirmed by the PubMed results, but could not be attributed to citral by either database. However, citral is an antispasmodic, and this effect could lessen several types of intestinal pains. The other property mutual to all three plants is carminative. The effect of lemongrass is clearly the strongest, and ethnopharmacological data for lemongrass and lemon balm validate this quality, as does Duke (2006) for lemon balm.

The rest of the subcategories are either mentioned only a few times, or they are strongly represented only for one plant. Intestinal swellings/tumors are mentioned only in connection with lemongrass, but with an Fic = 2.9. Ethnopharmacological data is sparse, but biomedical databases confirm the property in all three plants and in citral. With an Fic of 1.5, vervain should be the drug *par excellence* against intestinal parasites, and this point is confirmed by ethnopharmacological data, although biomedical data mentions only lemongrass and lemon balm.

The historical sources specify pain management by all three plants including intestinal pain, uterine pain (the term is quite general and might include any inner female organs), joint pain, and toothache. Lemongrass was commonly used to reduce intestinal and uterine pain, whereas lemon balm was most often recommended for toothache. On the pain-alleviating effects of a single plant, lemongrass is recommended for kidney and liver pain, and vervain for headache. Both ethnopharmacological data and biomedical data strongly confirm the analgesic effect of all three plants in this regard. A possible effect of citral against different kinds of pain could be connected with its antispasmodic and muscle-relaxant qualities. All three plants have other chemical constituents that could explain their pain-alleviating effects (lemongrass: caryophyllene, myrcene, quercetin; lemon balm: caffeic acid, chlorogenic acid, myrcene, thymol, ursolic acid; and vervain: adenosine, caffeic acid, hastatoside, ursolic acid; Duke, 2006). However, the possibility of citral as the common denominator of these plants might also be worth assessing.

For gynecological problems, the most important uses of the plants are against uterine pain and as emmenagogues. Uterine pain is difficult to evaluate because it can have several underlying causes. Duke (2006) mentions lemon grass as an anti-premenstrual syndrome medication, all three plants as pain-alleviating, and as having hormonal effects. Citral is an antibacterial and effective against Candida and other yeasts and fungi, thus possibly eliminating the cause of the pain. Citral electrophoresis has also been found effective against inflammatory diseases of female organs.

Ethnopharmacological sources confirm the use of these three plants as emmenagogues, although the estrogenic effect has been reported only for lemon grass, at least partly based on its citral content.

The last of the PLI categories, having the highest potential for validity, consists of various chest and lung problems. The historical indications common to all three plants are that of breathing complaints (shortness of breath, difficulty of breathing, and asthma), coughing and tuberculosis. Ethnopharmacological data supports the plants' anti-asthmatic activity, and biomedical databases confirm the antiallergic, bronchorelaxant, tracheorelaxant, and anti-asthmatic effects. Citral itself is an antispasmodic, muscle relaxant, and antifungal, all of which could explain the effects mentioned in the ancient herbal literature. The claim for antituberculotic effects of lemongrass and vervain is also strengthened by ethnopharmacological evidence and biomedical research. Lemongrass and lemon balm (with geraniol as the active compound in both) are also both antituberculotic, and all three plants are defined in general terms as antibacterial. Modern research also confirms the antibacterial effects of citral but does not mention Mycobacterium tuberculosis.

3.3. Cluster properties and cancer

Another important questions we wished to answer related to whether the data supported recommendations for the use of citral-containing plants in the treatment of cancer. The most relevant category – "Various swellings/tumors and hardenings" – is found within PLII. The subcategories with the highest potential for validity are hard swellings/tumors and hot swellings/tumors (or inflammations). Neither is mentioned in ethnopharmacological sources as indications for use of the plants, although biomedical databases support their anti-inflammatory effects. Hard swellings/tumors and hardenings can include several modern categories, from calluses to cirrhosis and malignant neoplasms. The cultural importance given to this category by the ancient and medieval texts clearly points out that further research is necessary, in spite of the lack of ethnopharmacological corroboration. Lemongrass is linked to an effect on intestinal, hepatic, and uterine tumors/swellings. Although none of these usages is corroborated by the ethnopharmacological data, biomedical databases validate

them (except for lemongrass with uterine tumors). Biomedical databases show quercetin in lemongrass and catechins in lemon balm as tyrosine kinase inhibitors, which hints to their potential effect against solid tumors. However, the insufficient information on citral-containing plants in connection with hard tumors makes this an interesting subject for future research, as this feature is prominent in older medical literature.

The category on liver problems shows an uneven picture. Lemon balm's effect on liver is scarcely mentioned. Lemongrass shows an alleged strong effect on swellings/tumors of the liver, but in the ethnopharmacological data lemongrass is not discussed in this connection. Vervain is used for hot swellings/tumors (or inflammations) of the liver. Biomedical data shows lemon balm as effective against liver tumors and cancer, lemongrass as hepatotonic, and all three plants as hepatoprotective. While citral is toxic against HepG2, a hepatocarcinoma-derived human cell line, the variety of potential causes prevents a detailed evaluation.

The issue of hot swellings/tumors or skin inflammations is a wide category with the common denominator of localized inflammation. The effects of the three citral-containing plants, as described in modern literature, range from antiacne and antidermatic effects (lemongrass, lemon balm) to antitumor effects on skin, and antimelanomic/antimelanogenic effects (all three plants). Citral itself has an antioxidant role in glutathione S-transferase induction in skin, providing a new insight into skin-cancer prevention.

3.4. Novel uses of citral

The most interesting part of our present work is the medicinal properties claimed by the ancient authors that cannot be correlated with the results of modern research. Considering the high level of validation we found in comparing the other properties with modern biomedicine, it seems justified to consider the lack of modern correlates for medicinal properties and property clusters as unfinished modern research, rather than a sign of false claims in the herbals. As a result, these properties are potential sources for novel uses of citral.

The next step in research may be studying the listed main uses of citral-containing plants, as well as other additional citral-containing plants, such as citrus plants, to better define which of the properties have the highest potential of being connected to the citral content of the plants. After identification, these properties will require further research. Another direction is to make the method more flexible and less time-consuming.

4. Conclusions

Lemongrass, lemon balm, and vervain are recommended in ancient and medieval sources for swellings/tumors and hardenings. While there is no doubt that ancient and medieval authors included items under terms that we do not define as "cancer", and that we have cancers that were not yet recognized, we are certain that cancer was treated (Riddle, 1985a). The variety of different, possibly cancer-related issues treated with citral-containing plants is impressive, and leads to hope for a wide effect of the compound as an anticancer drug.

Other common properties of citral-containing plants were indeed found. We showed a close connection between the claims of the ancient and medieval herbals for the use of citral-containing plants and the results of the modern research concerning these plants or their chemical constituents. These results are mostly corroborated by modern ethnopharmacological data. However, citral as a chemical has not been extensively studied; thus, on the basis of the cumulative claims on the medicinal effects of the plants containing it, we recommend further research on the most prominently recommended pharmacological properties in the old herbal texts.

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