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Review

Artemisia afra: A potential flagship for African medicinal plants?

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Abstract

The genus *Artemisia* consists of about 500 species, occurring throughout the world. Some very important drug leads have been discovered from this genus, notably artemisinin, the well known anti-malarial drug isolated from the Chinese herb *Artemisia annua*. The genus is also known for its aromatic nature and hence research has been focussed on the chemical compositions of the volatile secondary metabolites obtained from various *Artemisia* species. In the southern African region, *A. afra* is one of the most popular and commonly used herbal medicines. It is used to treat various ailments ranging from coughs and colds to malaria and diabetes. Although it is one of the most popular local herbal medicines, only limited scientific research, mainly focussing on the volatile secondary metabolites content, has been conducted on this species. The aim of this review was therefore to collect all available scientific literature published on *A. afra* and combine it into this paper. In this review, a general overview will be given on the morphology, taxonomy and geographical distribution of *A. afra*. The major focus will however be on the secondary metabolites, mainly the volatile secondary metabolites, which have been identified from this species. In addition all of the reported biological activities of the extracts derived from this species have been included as well as the literature on the pharmacology and toxicology. We aim at bringing together most of the available scientific research conducted on this species, which is currently scattered across various publications, into this review paper.

Keywords: *Artemisia afra*; Traditional African Medicine; Volatile secondary metabolites

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1. Introduction

Traditional Chinese Medicine (TCM) is a well-known and well-studied research field. Many academic and pharmaceutical institutions around the World fund research into TCM with the aim of finding new pharmaceutical entities, establishing quality control protocols and to prove the efficacy of these traditional medicines. Compared to TCM, the traditional African medicine research is lagging behind. One of the main reasons for this is that the available information on medicinal plants is not always well documented. Furthermore, Africa encompasses a huge area with diverse cultures and languages, which makes sharing of information difficult. The lack of well-funded research institutions or pharmaceutical companies on the continent is also adding to the problem. African researchers should therefore aim at establishing their own "Traditional African Medicine" (TAM), which on the long run should bring to Africa the same economical and social benefits that TCM has brought to China. In order to achieve this goal, it would be extremely beneficial to the cause if one can identify a flagship species which will epitomize the end goal of establishing a TAM. For this reason, we have decided to review most of the scientific literature available on the endemic *Artemisia afra* Jacq. (Asteraceae) species to establish if it might have the same medicinal potential as the Chinese *A. annua* species.

Artemisia afra is one of the most popular and commonly used herbal medicines in southern Africa. However, only limited research has been conducted on this species. According to a recent publication by Van Wyk (2008), only 42 scientific publications and 2 patents related to *A. afra* are available of which 27 publications and 1 patent were published between 2001 to 2008. This indicates that interest in *A. afra* has increased significantly during recent years, prompting us to gather all available research on *A. afra* and combine it into this review paper. We could not find any previous reviews written on this species and therefore we thought it important to take stock of what has been done in the past, in order to provide a solid foundation and direction to any future research that may be conducted on this species.

2. Botanical aspects

2.1. Morphology

Artemisia afra is a perennial woody shrub, which grows up to 2 m tall with a leafy, hairy and ridged stem (Van Wyk et al., 1997). Its leaves are of soft texture, dark green on the adaxial surface and a lighter green on the abaxial surface, reaching a length of 8 cm and a width of 4 cm. *Artemisia afra* blossoms from January to June, producing yellow, butter-coloured flowers with abundant bracts (Hilliard, 1977). The plant has an easily identifiable aromatic odour and smells pungent and sweet after bruising. The fruit is approximately 1 mm in length, covered with a silvery-white coating and the shape is slightly 3-angled and curved. In winter, the branches rapidly regenerate from the base directly after dying back (Hilliard, 1977; Van Wyk et al., 1997).

2.2. Taxonomy

Artemisia afra is classified into Kingdom: Plantae, Division: Mannoliphyta, Class: Magnoliopsida, Sub-class: Asteridae, Order: Asterales, Family: Asteraceae, Genus: *Artemisia* and Species: *Artemisia afra.* The genus name *Artemisia* was derived from the name of the Greek goddess of hunting, Artemis (Jackson, 1990).

2.3. Distribution

Artemisia afra occurs in the mountain regions of Kenya, Tanzania, Uganda and as far north as Ethiopia. It is also widely distributed in southern Africa, such as South Africa, Namibia, and Zimbabwe. In South Africa, it grows in the northern provinces of Gauteng and Limpopo along the eastern parts of South Africa, including Swaziland and Lesotho, to the Western Cape in the south. It is also abundantly found in KwaZulu-Natal province from the coast to the Drakensberg (Van Wyk et al., 1997; Hilliard, 1977) at altitudes of 20 to 2440 m on damp slopes, along streamsides and forest margins.

3. Ethnopharmacology and utilization

The many different common or local names describing this plant may be ascribed to the widespread use by different ethnic groups (Watt and Breyer-Brandwijk, 1932). In the Xhosa language it is known as "Umhlonyane", the Zulu language "Mhlonyane", in Sotho "Lanyana", Tswana "Lengana", English "African wormwood" and in Afrikaans "Wilde als". It is usually employed for treating a variety of ailments such as coughs, colds, headaches, chills, dyspepsia, loss of appetite, gastric derangements, colic, croup, whooping-cough, gout, asthma, malaria, diabetes, bladder and kidney disorders, influenza, convulsions, fever, heart inflammation, rheumatism and is also used as a purgative (Watt and Breyer-Brandwijk, 1932; Thring and Weitz, 2006). These uses indicate that *A. afra* possesses antiviral, antibacterial and anti-inflammatory activities.

Many different preparations of this plant are employed to treat the various symptoms and ailments. A syrup prepared from

A. afra is used for bronchial troubles, while infusions or decoctions can be applied as a lotion to bathe hemorrhoids and for earache. An infusion of leaves or roots of this species is also used for the treatment of diabetes in the Eastern Cape Province of South Africa (Erasto et al., 2005; Mahop and Mayet, 2007). Respiratory infections are treated through inhaling the vapour from boiling leaves and this vapour is also used to treat menstrual chill. Fresh tips are inserted into the nose for colds and headaches and into hollow teeth to treat toothache. The poultice of the leaves can be applied to relieve neuralgia, to treat the swellings in mumps and is placed on the abdomen to treat infantile colic. It is also helpful to reduce colic by administering a tincture made of the leaves wetted by brandy (Watt and Breyer-Brandwijk, 1932).

Artemisia afra is also used as an infusion. Usually, a quarter cup of fresh leaves is added to a cup of boiling water and the infusion is allowed to draw for 10 min. The mixture is then strained and the resulting infusion is sweetened with honey. This preparation is taken orally for relief of most of the above-mentioned ailments (Roberts, 1990).

The use of other medicinal plants or substances in combination with *A. afra* is also documented in African ethnopharmacology. In South Africa, preparations of *A. afra* are often made in combination with brandy, sugar, ginger, thyme, rosemary, mint, chamomile, *Osmitopsis asteriscoides* or *Eucalyptus globulus*. A combination of *A. afra* and *E. globulus* is employed to treat influenza, and the infusion of the leaves and stems of *Lippia asperifolia* and *A. afra* is used as a formula for fevers, influenza, measles, and as a prophylactic against lung inflammations (Watt and Breyer-Brandwijk, 1932). Decoctions of the leaves of *A. afra* and *Agrimonia bracteata* are used for colds in southern Africa while decoctions of *Tetradenia riparia* and *umhlonyane* (Xhosa name for *A. afra*) with salt are used to treat coughs in the Transkei region of the Eastern Cape Province of South Africa (Hutchings et al., 1996).

4. Chemistry

A major problem for using this plant by traditional means is claimed to be variations in the phytochemical composition (Dube, 2006). The volatile components are easily lost during the production of traditional preparations as was shown by Asfaw et al. (2005). Eight sesquiterpenes were lost during hydrodistillation, which aimed at simulating the traditional preparation method. Most work focussed on the volatile secondary metabolites obtained from *A. afra*, while only relatively few publications reported on other types of secondary metabolites identified in this plant. In the following sub-sections, secondary metabolites identified from *A. afra* will be discussed with their corresponding references.

4.1. Volatile secondary metabolites

Many different extraction methods have been employed to isolate volatile secondary metabolites from *A. afra*. This includes hydrodistillation (HD), microwave assisted extraction (MAE), ultrasound assisted extraction (UAE) and liquid/

Table 1
Volatile secondary metabolites identified in *Artemisia afra*.

Component	Author
Monoterpenoids	
artemisia alcohol	Gavarry (1977); Chagonda et al. (1999); Viljoen et al. (2006)
artemisia ketone	Gavarry (1977); Moody et al. (1994); Chagonda et al. (1999); Viljoen et al. (2006); Asekun et al. (2007); Vagionas et al. (2007)
artemisyl acetate	Worku and Rubiolo (1996); Chagonda et al. (1999); Viljoen et al. (2006)
ascaridole	Viljoen et al. (2006)
azulene	Do Vale (1963)
borneol	Do Vale (1963); Mwangi et al. (1995); Chagonda et al. (1999); Muyima et al. (2002); Viljoen et al. (2006); Asekun et al. (2007)
bornyl acetate	Do Vale (1963); Chagonda et al. (1999); Viljoen et al. (2006)
camphene	Do Vale (1963); Chagonda et al. (1999); Muyima et al. (2002); Viljoen et al. (2006)
camphor	Do Vale (1963); Libbey and Sturtz (1989); Graven et al. (1992); Chagonda et al. (1999); Burits et al. (2001); Muyima et al. (2002); Viljoen et al. (2006); Asekun et al. (2007); Vagionas et al. (2007)
cis-carveol	Chagonda et al. (1999)
caryophylla-2(12),6(13)-dien-5-one	Viljoen et al. (2006)
cis-chrysanthenol	Viljoen et al. (2006)
chrysanthenone	Viljoen et al. (2006)
cis-chrysanthenyl acetate	Viljoen et al. (2006)
1,8-cineole	Do Vale (1963); Gavarry (1977); Libbey and Sturtz (1989); Graven et al. (1992); Moody et al. (1994); Mwangi et al. (1995); Chagonda et al. (1999); Muyima et al. (2002); Viljoen et al. (2006); Asekun et al. (2007); Vagionas et al. (2007)
cumin alcohol	Viljoen et al. (2006)
dehydro carvyl acetate	Viljoen et al. (2006)
dehydro-1,8-cineole	Chagonda et al. (1999); Viljoen et al. (2006)
dehydrosabinaketone	Viljoen et al. (2006)
cis-2,7-dimethyl-4-octene-2,4-diol	Moody et al. (1994)
cis-1,2-epoxy-terpinen-4-ol	Viljoen et al. (2006)
α-fenchene	Chagonda et al. (1999)
geraniol	Asfaw et al. (2005)
4α-hydroxy achipendol	Viljoen et al. (2006)
4β-hydroxy achipendol	Viljoen et al. (2006)
isoamyl isovalerate	Viljoen et al. (2006)
isopiperitone	Viljoen et al. (2006)
lavandulol	Viljoen et al. (2006)
lavanduyl acetate	Viljoen et al. (2006)
limonene	Do Vale (1963); Chagonda et al. (1999); Viljoen et al. (2006)
linalool	Asfaw et al. (2005); Viljoen et al. (2006)
linalool acetate	Muyima et al. (2002)
trans-linalool oxide furanoid form	Viljoen et al. (2006)
trans-p-menth-2,8-dien-1-ol	Viljoen et al. (2006)
trans-p-menth-1(7),8-dien-2-ol	Viljoen et al. (2006)
cis-p-menth-2-en-1-ol	Chagonda et al. (1999); Viljoen et al. (2006)
trans-p-menth-2-en-1-ol	Viljoen et al. (2006)
p-mentha-1,4-dien-7-ol	Viljoen et al. (2006)

(continued on next page)

Table 1 (*continued*)

Component	Author
p-mentha-1,8-dien-10-ol	Viljoen et al. (2006)
cis-p-mentha-1-(7), 8-dien-2-ol	Viljoen et al. (2006)
trans-p-meth-2-en-1-ol	Chagonda et al. (1999)
p-menthatriene	Asfaw et al. (2005)
2-methyl butyl isovalerate	Viljoen et al. (2006)
myrcene	Chagonda et al. (1999); Viljoen et al. (2006)
myrtenal	Chagonda et al. (1999); Viljoen et al. (2006)
myrtenol	Chagonda et al. (1999); Viljoen et al. (2006)
(E)-β-ocimene	Chagonda et al. (1999); Viljoen et al. (2006)
(Z)-β-ocimene	Viljoen et al. (2006)
β-phellandrene	Muyima et al. (2002)
α-pinene	Do Vale (1963); Graven et al. (1992); Chagonda et al. (1999); Muyima et al. (2002); Viljoen et al. (2006)
β-pinene	Chagonda et al. (1999); Muyima et al. (2002); Viljoen et al. (2006)
pinocarvone	Viljoen et al. (2006)
trans- pinocarveol	Viljoen et al. (2006)
piperitol	Chagonda et al. (1999)
cis-piperitol	Viljoen et al. (2006)
trans-piperitol	Viljoen et al. (2006)
piperitone	Viljoen et al. (2006)
trans-piperitone oxide	Viljoen et al. (2006)
sabinaketone	Viljoen et al. (2006)
sabinene	Chagonda et al. (1999); Viljoen et al. (2006)
trans-sabinol	Viljoen et al. (2006)
cis-sabinene hydrate	Chagonda et al. (1999); Viljoen et al. (2006)
trans-sabinene hydrate	Chagonda et al. (1999); Viljoen et al. (2006)
sabinyl acetate	Viljoen et al. (2006)
santolina alcohol	Chagonda et al. (1999); Viljoen et al. (2006)
santolina triene	Asfaw et al. (2005); Viljoen et al. (2006)
santolinyl acetate	Viljoen et al. (2006)
terpinen-4-ol	Mwangi et al. (1995); Chagonda et al. (1999); Viljoen et al. (2006)
α-terpinene	Chagonda et al. (1999); Muyima et al. (2002); Viljoen et al. (2006)
γ-terpinene	Chagonda et al. (1999); Viljoen et al. (2006)
4-terpineol	Burits et al. (2001)
α-terpineol	Chagonda et al. (1999); Viljoen et al. (2006)
δ-terpineol	Chagonda et al. (1999); Viljoen et al. (2006)
terpinolene	Chagonda et al. (1999); Viljoen et al. (2006)
3-thujanone	Muyima et al. (2002)
α-thujene	Viljoen et al. (2006)
β-thujene	Muyima et al. (2002)
α-thujone	Libbey and Sturtz (1989); Graven et al. (1992); Chagonda et al. (1999); Viljoen et al. (2006); Asekun et al. (2007); Vagionas et al. (2007)
β-thujone	Libbey and Sturtz (1989); Graven et al. (1992); Chagonda et al. (1999); Viljoen et al. (2006); Asekun et al. (2007)
tricyclene	Viljoen et al. (2006)
tricylene	Chagonda et al. (1999)
cis-verbenol	Viljoen et al. (2006)
yomogi alcohol	Worku and Rubiolo (1996); Viljoen et al. (2006)
Sesquiterpenes	
trans-α-bergamotol	Viljoen et al. (2006)
bicycloelemene	Viljoen et al. (2006)
bicyclogermacrene	Chagonda et al. (1999); Viljoen et al. (2006)
α-bisabolol	Viljoen et al. (2006)
δ-cadinene	Chagonda et al. (1999); Viljoen et al. (2006)
caryophylladienol-II	Viljoen et al. (2006)
chamazulene	Burits et al. (2001)
davanone	Burits et al. (2001)

Table 1 (*continued*)

Component	Author
Sesquiterpenes	
calamenene	Chagonda et al. (1999)
caryophyllene oxide	Viljoen et al. (2006)
trans-caryophyllene oxide	Chagonda et al. (1999)
β-caryophyllene	Chagonda et al. (1999); Viljoen et al. (2006)
α-copaene	Chagonda et al. (1999); Viljoen et al. (2006)
β-costol	Viljoen et al. (2006)
cubebol	Viljoen et al. (2006)
epi-cubebol	Viljoen et al. (2006)
1-epi-cubenol	Viljoen et al. (2006)
(Z)-β-farnesene	Viljoen et al. (2006)
germacrene	Burits et al. (2001)
germacrene D	Viljoen et al. (2006)
germacrene D-4-ol	Chagonda et al. (1999); Viljoen et al. (2006)
globulol	Viljoen et al. (2006)
α-humulene	Viljoen et al. (2006)
intermedeol	Chagonda et al. (1999)
intermediol	Viljoen et al. (2006)
α-muurolol	Viljoen et al. (2006)
t-muurolol	Chagonda et al. (1999); Viljoen et al. (2006)
(E)-nerolidol	Viljoen et al. (2006)
β-selinene	Viljoen et al. (2006)
spathulenol	Chagonda et al. (1999); Viljoen et al. (2006)
Others	
artemisal	Do Vale (1963)
berbenome	Muyima et al. (2002)
cuminaldehyde	Chagonda et al. (1999); Viljoen et al. (2006)
ar-curcumene	Viljoen et al. (2006)
p-cymen-8-ol	Chagonda et al. (1999); Viljoen et al. (2006)
p-cymene	Chagonda et al. (1999); Viljoen et al. (2006)
4-hydroxy-4-methylcyclohex-2-enone	Viljoen et al. (2006)
isopropyl-3-methylbenzene	Muyima et al. (2002)
p-isopropyl phenol	Viljoen et al. (2006)
(Z)-jasmone	Viljoen et al. (2006)
methyl linolenate	Chagonda et al. (1999)
octadecanol	Viljoen et al. (2006)
1-octen-3-ol	Muyima et al. (2002); Viljoen et al. (2006)
tricosane	Moody et al. (1994)
pentylbenzene	Muyima et al. (2002)
Probably contained compounds	
d-myrthenal	Do Vale (1963)
umbellulone	Do Vale (1963)
vetivazulene	Do Vale (1963)

supercritical CO_2 extraction (l-CO_2 and sc-CO_2) (Asfaw et al., 2005). In this paper, the four extraction methods were tested according to the yields and chemical composition of the oil. The results demonstrated that l-CO_2 and sc-CO_2 gave the highest yields (3.2%, v/w), followed by traditional HD (1.5%, v/w) and MAE (1.3%, v/w). The lowest yield was achieved with UAE (0.7% v/w). A comparison of the different fractions obtained revealed that the yogomi alcohol content in the extracts obtained from l-CO_2 and sc-CO_2, UAE, MAE and HD was 0.4%, 0.4%, 0.1%, 3.6% and 8.1%, respectively. In addition, eight sesquiterpenes could only be detected in the sc-CO2, l-CO2 and UAE, with relative percentage peak areas of 13%, 16% and 29%, respectively. These differences might

also be due to the solubility differences or instability of compounds during the different methods of extraction.

For the identification of the major components in the oil, the only reported analytical equipment used was gas chromatography coupled with either a flame ionization detector or mass spectroscopy detector (Asfaw et al., 2005). Until now, 131 compounds have been identified from the oil of *A. afra*. Most of these compounds can be classified as monoterpenes and sesquiterpenes. Several other components have also been found during various other studies and are listed in Table 1 with the corresponding references.

4.2. Non-volatile secondary metabolites

Early in the 1920s, Goodson (1922) found that *A. afra* contained a wax-ester (probably ceryl cerotate), triacontane, scopoletin and quebrachitol. During the following decades, a few other publications reported on new secondary metabolites identified from this species. Table 2 lists the non-volatile secondary metabolites identified in *A. afra* and the corresponding references.

5. Chemical variation in *A. afra*

The volatile secondary metabolite content in *A. afra* vary frequently and is mainly due to the following factors:

(a) Geographical variation: The main components of the volatile secondary metabolites identified in *A. afra* fluctuate enormously in plants collected from different geographical regions. It is reported that artemisyl acetate (24.4–32.1% of the total oil) was found to be the major constituent in Ethiopian oil (Worku and Rubiolo, 1996) while 1,8-cineole (67.4%) was found to be the major constituent in Kenyan oil (Mwangi et al., 1995). In Zimbabwean oil, α- and β-thujone (52%) was the major constituent (Graven et al., 1992) while only α-thujone (54.2%) was found to be the major constituent of South African oil (Libbey and Sturtz, 1989).
Chagonda et al. (1999) found that the major constituents of the volatile secondary metabolites from *A. afra* grown in Zimbabwe, showed a large variation between cultivated and wild populations. The oil of wild populations contained artemisia ketone (6.3–41.9%), 1,8-cineole (0.1–27.9%), α-copaene/camphor (8.5–27.1%) and santolina alcohol (3.1–10.1%) while the oil of the cultivated populations mainly contained artemisia ketone (32.1–34.8%), α-copaene/camphor (21.8–24.4%), 1,8-cineole (10.9–15.7%) and santolina alcohol (2.7–8.0%). However, the oil from plants cultivated at a different site, contained mainly 1,8-cineole (22.5–29.3%), α-copaene/camphor (6.2–21.3%), borneol (14.2–19.1%) and camphene (3.0–5.6%). Fig. 1 represents the chemical structures of the most commonly occurring major compounds in the volatile secondary metabolites of *A. afra*.

(b) Different plant parts used: Most *A. afra* oils analysed were obtained from the aerial plant parts (Chagonda et al.,

Table 2
Non-volatile secondary metabolites identified from *Artemisia afra*.

Component	Author
Sesquiterpenes	
β-farnesene	Jakupovic et al. (1988)
Sesquiterpene lactones	
Glaucolides	
artemisia glaucolide	Jakupovic et al. (1988)
eudesmaafraglaucolide	Jakupovic et al. (1988); Kraft et al. (2003)
glaucolide 7	Jakupovic et al. (1988)
1α-hydroxyafraglaucolide	Jakupovic et al. (1988)
1β-hydroxyafraglaucolide	Jakupovic et al. (1988)
1α-hydroxyisoafraglaucolide	Jakupovic et al. (1988)
12-hydroxy-α-cyperone	Jakupovic et al. (1988)
Guaianolides	
11,13-dehydromatricarin	Kraft et al. (2003)
guaianolides 1 (2 derivatives)	Jakupovic et al. (1988)
guaianolides 2 (6 derivatives)	Jakupovic et al. (1988); Kraft et al. (2003)
guaianolides 3 (11 derivatives)	Jakupovic et al. (1988); Kraft et al. (2003)
guaianolides 4 (2 derivatives)	Jakupovic et al. (1988)
guaianolides 5 (3 derivatives)	Jakupovic et al. (1988)
Others	
Taurin	Nkunya et al. (1992)
Triterpenes	
α-amyrin	Silbernagel et al. (1990)
β-amyrin	Silbernagel et al. (1990)
friedelin	Silbernagel et al. (1990)
squalene	Jakupovic et al. (1988)
Long chain alkanes	
cerylcerotinate	Silbernagel et al. (1990)
nonacosane	Silbernagel et al. (1990)
triacontane	Goodson (1922)
6-triacontanone	Nkunya et al. (1992)
wax ester	Silbernagel et al. (1990)
wax ester (probably ceryl cerotate)	Goodson (1922)
Coumarins	
12-hydroxy-α-cyperone	Jakupovic et al. (1988)
isofraxidin	Jakupovic et al. (1988)
scopoletin	Goodson (1922)
umbelliferone derivatives	Bohlmann and Zdero (1972)
ouebrachitol	Goodson (1922)
Organic acids	
4-methylbenzoic acid	Nkunya et al. (1992)
Glycosides	
β-D-glucopyranoside	Jakupovic et al. (1988)
Flavonoids	
acacetin	Kraft et al. (2003)
aglycon	Wollenweber and Mann (1989)
apigenin	Kraft et al. (2003)
chrysoeriol	Kraft et al. (2003)
diosmetin	Kraft et al. (2003)
genkwanin	Kraft et al. (2003)
7-methoxyacacetin	Kraft et al. (2003)
ouercetin	Dube (2006)
kaempferol	Dube (2006)
tamarixetin	Kraft et al. (2003)
luteolin	Dube (2006)

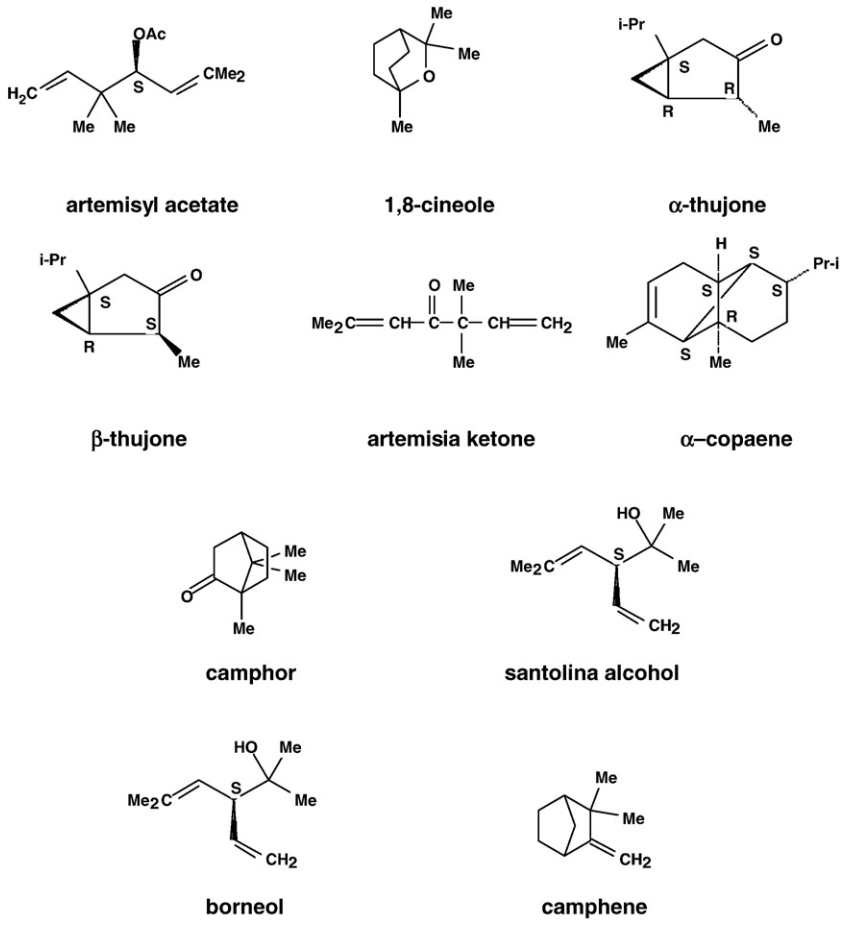

Fig. 1. Chemical structures of the most commonly occurring major volatile secondary metabolites from *Artemisia afra*.

1999; Burits et al., 2001; Viljoen et al., 2006; Vagionas et al., 2007). Analysis of oils obtained from different plant parts showed that the chemical components varied depending on the plant part used e.g. Goodson (1922) found camphor, a wax ester, triacontane, scopoletin and quebrachitol in the flowering tops of *A. afra*. Bohlmann and Zdero (1972) revealed that the roots contained isomeric coumarins and five acetylenes, while the aerial parts contained thujone and umbelliferone-derivatives, but no acetylenes. The same variation occurred in the volatile secondary metabolite composition between the leaves of *A. afra* (Mwangi et al., 1995) and the whole plant (Worku and Rubiolo, 1996). The results showed that the oil obtained from the leaves consisted mainly of 1,8-cineole (67.4%), while yomogi alcohol (21.6–26.8%) and artemisyl acetate (24.4–32.1%) predominated in the oil extracted from the whole plant.

(c) Drying methods: Asekun et al. (2007) reported that the yields and compositions of oil from *A. afra* varied according to the drying method used. Yields obtained were 0.18%, 0.88%, 1.54% and 1.88% for fresh, oven-dried, air-dried and sun-dried material respectively. They also found that artemisia ketone was present in the oil extracted from the fresh material but was absent in the oil extracted from the air-dried and sun-dried material.

(d) Variation within the natural population: Viljoen et al. (2006) collected 16 individual *A. afra* samples from four natural populations, Setibeng (Lesotho), Giant's Castle (KwaZulu-Natal), Qwa-qwa (Free State) and Kliprivers-berg (Gauteng) and found qualitative and quantitative differences within and between populations.

6. Biological effect of *A. afra* extracts

Considering the many traditional uses, the plant has been studied for various biological activities. These activities will be discussed in the following paragraphs with their corresponding references.

6.1. Biological activities

A. afra is rich in terpenes and is therefore likely to have valuable biological activities. From the available literature the results of conducted tests indicated that this plant has a broad spectrum of inhibitory activity against the organisms listed in Table 3. Most of the activities were expressed in zone of inhibition, while relatively few studies determined the minimum

Table 3
Reported activities of extracts obtained from *Artemisia afra* against selected microorganisms.

Microorganism	Minimum inhibitory concentration (mg/ml)	Minimum inhibitory percentage (%)	Diameter of zone of inhibition (mm) [a]	IC50 (μg/ml)	Author
Gram-positive bacteria					
Bacillus cereus	–	–	9.5±1.0	–	Mangena and Muyima, 1999
B. subtilis	4.0	–	14.5±2.4	–	Rabe and Van Staden, 1997; Mangena and Muyima, 1999
Listeria monocytogenes	–	–	25.0±1.4	–	Mangena and Muyima, 1999
Micrococcus luteus	–	–	12.0±0.0	–	Mangena and Muyima, 1999
Mycobacterium smegmatis	1.6	–	–	–	Mativandlela et al., 2008
M. tuberculosis	na [b]	–	–	–	Mativandlela et al., 2008
Staphylococcus aureus	2.0	–	14.0±0.0 [c] 21.3±2.0 [d]	–	Rabe and Van Staden, 1997; Mangena and Muyima, 1999; Muyima et al., 2002; Van Vuuren and Viljoen, 2006
S. aureus	–	>1	–	–	Huffman et al., 2002
S. aureus 1639 (Methicillin resistant)	–	0.25	–	–	Huffman et al., 2002
S. epidermis	4.0	–	10.0±0.0	–	Mangena and Muyima, 1999; Rabe and Van Staden, 1997
Streptococcus pyogenes	–	–	28.0±0.0	–	Mangena and Muyima, 1999
Gram-negative bacteria					
Acinetobacter calcoaceticus	–	–	10.0±0.0	–	Mangena and Muyima, 1999
A. lwoffii	–	–	11.0±1.4	–	Mangena and Muyima, 1999
A. johnsonii	–	–	23.0±1.4	–	Mangena and Muyima, 1999
Enterobacter aerogene	–	–	10.5±1.0	–	Mangena and Muyima, 1999
E. cloacae	–	–	10.5±1.9	–	Mangena and Muyima, 1999
Erwinia chrysanthemi	–	–	11.0±1.4	–	Mangena and Muyima, 1999
E. carotovora	–	–	18.5±1.2	–	Mangena and Muyima, 1999
Escherichia coli K12	–	–	17.5±2.0	–	Mangena and Muyima, 1999
E. coli (SR) [e]	–	–	9.5±1.2	–	Mangena and Muyima, 1999
Proteus mirabilis	–	–	12.0±2.0	–	Mangena and Muyima, 1999
Pseudomonas aeruginosa [f]	–	–	6.0±0.0	–	Muyima et al., 2002
P. aeruginosa	–	>9.0	–	–	Huffman et al., 2002
P. aeruginosa	–	–	6.0±0.0	–	Muyima et al., 2002
P. fluorescens	–	–	6.0±0.0	–	Mangena and Muyima, 1999
Ralstonia picketti	–	–	21.7±2.9	–	Muyima et al., 2002
Salmonella enteritidus	–	–	14.0±2.8	–	Mangena and Muyima, 1999
S. newport	–	–	14.5±1.2	–	Mangena and Muyima, 1999
S. poona	–	–	12.0±2.3	–	Mangena and Muyima, 1999
S. thompson	–	–	13.5±1.4	–	Mangena and Muyima, 1999
S. typhi	–	–	10.0±0.0	–	Mangena and Muyima, 1999
S. typhimurium (SR) [e]	–	–	11.0±1.8	–	Mangena and Muyima, 1999
S. typhimurium (WT) [g]	–	–	11.6±4.9	–	Mangena and Muyima, 1999
Shigella flexneri	–	–	13.0±3.4	–	Mangena and Muyima, 1999
S. sonnei	–	–	9.5±1.0	–	Mangena and Muyima, 1999
Yersinia enterocolitica	–	–	15.5±2.5	–	Mangena and Muyima, 1999
Fungi					
Candida albicans	–	–	22.3±1.6	–	Muyima et al., 2002
C. albicans	–	0.25	–	–	Huffman et al., 2002
Crytococcus neoformans	–	0.5	–	–	Huffman et al., 2002
Dekkera bruxellensis	–	–	12.7±0.7	–	Mangena and Muyima, 1999
Hanseniaspora vinae	–	–	21.0±1.4	–	Mangena and Muyima, 1999
Hyphopichia burtonii	–	–	19.5±1.9	–	Mangena and Muyima, 1999
Pichia anomala	–	–	14.5±0.7	–	Mangena and Muyima, 1999
P. fabianii	–	–	12.3±3.2	–	Mangena and Muyima, 1999
P. jadinii	–	–	13.8±2.7	–	Mangena and Muyima, 1999
Saccharomyces cerevisiae UOFS Y0149	–	–	18.5±2.5	–	Mangena and Muyima, 1999
S. cerevisiae UOFS Y150	–	–	20.0±1.5	–	Mangena and Muyima, 1999
S. cerevisiae UOFS Y0154	–	–	22.3±2.8	–	Mangena and Muyima, 1999
Torulaspora delbruckii UOFS Y0159	–	–	12.0±0.0	–	Mangena and Muyima, 1999
T. delbruckii UOFS Y160	–	–	10.0±0.0	–	Mangena and Muyima, 1999
Zygosaccharomyces bailii	–	–	11.5±0.6	–	Mangena and Muyima, 1999

(continued on next page)

Table 3 (*continued*)

Microorganism	Minimum inhibitory concentration (mg/ml)	Minimum inhibitory percentage (%)	Diameter of zone of inhibition (mm)[a]	IC50 (μg/ml)	Author
Protozoa					
P. falciparum D6[h]	–	–	–	9.0±0.5[i, j]	Gathirwa et al., 2007
P. falciparum D10	–	–	–	5.0[k]	Clarkson et al., 2004
P. falciparum Dd2	–	–	–	15.3	Kraft et al., 2003
P. falciparum PoW	–	–	–	8.9	Kraft et al., 2003
P. falciparum W2[l]		–		4.0±1.0[i, j]	Gathirwa et al., 2007

Results are expressed with standard deviations only if included in the original publication.

[a] Antimicrobial activity of undiluted essential oil of *A. afra* was evaluated by diameter of zone of inhibition in millimeters (including disc diameter of 6 mm) against selected microorganism;

[b] No activity at highest concentration tested;

[c] Data from Mangena and Muyima, 1999;

[d] Data from Muyima et al., 2002;

[e] Streptomycin resistant strain;

[f] *Pseudomonas aeruginosa* isolated from environment and identified by API identification system;

[g] Wild type;

[h] Chloroquine sensitive;

[i] The highest activity appeared in methanolic extract;

[j] High activity: IC_{50}(10 μg/ml;

[k] High activity: $IC_{50} \leq 5$ μg/ml;

[l] Chloroquine resistant.

inhibitory concentration (MIC), minimum inhibitory percentage (MIP), or IC_{50} values. Not all of the publications provided statistical data such as the standard deviations obtained.

Poswal and Witbooi (1997) found that, of the five plant species evaluated, the oils of *A. afra* and *Lavandula angustifolia* were the most effective against *Pseudomonas syringae* pv. *Syringae*, while the *A. afra* extract was least active against *P. solanacearum.* Different strains of the same species also showed different susceptibilities to *A. afra* extracts. *P. solanacearum* Ps46 proved more susceptible than *P. solanacearum* Ps62 to the plant oil. The activity of *A. afra* oil was determined against different strains of yeasts. Eventually, *Hanseniaspora vinae* and *Saccharomyces cerevisiae* were the most susceptible to the oil, while *Zygosaccharomyces bailii* and *Dekkera bruxellensis* were proved to be the least sensitive (Mangena and Muyima, 1999).

Rabe and Van Staden (1997) tested the antimicrobial activities of the extracts of *A. afra* against *Staphylococcus aureus*, *S. epidermis* and *Bacillus subtilis*, the results showed that the lowest MIC was achieved against *S. aureus*. They also reported that the majority of the antibacterial activity of *A. afra* extracts was present in the methanol extracts instead of water extracts. Mangena and Muyima (1999) also found that of 29 species of bacteria and 12 strains of yeast tested, only three species of bacteria (*Escherichia coli*, *P. aeruginosa* and *P. fluorescens*) and one strain of yeast (*Torulaspora delbruckii*) did not show obvious dose–effect relationship when three different concentrations of *A. afra* oil were used (undiluted, 1:1 and 1:2 dilutions). Muyima et al. (2002) did a similar experiment and the results showed that in most cases only the highest concentrations of *A. afra* oil inhibited the tested bacteria, except against *P. aeruginosa* ATCC 27853 and strains of *P. aeruginosa* isolated from the environment. Asres et al. (2001) indicated that the crude methanolic extract of *A. afra* did not inhibit *Mycobacterium tuberculosis*.

Kraft et al. (2003) found that the lipophilic extracts of the aerial parts of *A. afra* showed the highest activity against the chloroquine-sensitive *Plasmodium falciparum* strain PoW and against the chloroquine-resistant clone Dd2 of *P. falciparum*, compared to the lipophilic extracts of *Cussonia spicata*, *Clutia hirsute*, *Vernonia natalensis*, *Parinari curatellifolia*, *Flueggea virosa*, *Adenia gummifera*, *Hymenodictycon floribundum* and the hydrophilic extracts of all above species including *A. afra* itself and *V. colorata.* They also indicated that the antiplasmodial effect of *A. afra* was probably due to the additive or even synergistic activity of the complex mixture of substances found in the extract. Clarkson et al. (2004) reported that the dichloromethane extract exhibited the strongest antiplasmodial activity against *P. falciparum* D10 (IC_{50} value of 5 μg/ml) compared to the dichloromethane/methanol (1:1), methanol and water extracts (IC_{50} value of 7.3, 8.0 and >100.0 μg/ml, respectively). Gathirwa et al. (2007) proved that the methanolic extract of *A. afra* showed more activity against *P. falciparum* D6 and *P. falciparum* W2 (IC_{50} values of 9.04±0.54 and 3.98±0.98, respectively), compared to the water extract (IC_{50} values of 11.23±1.98 and 4.65±0.64, respectively). In addition, the *P. berghei* infected mice treated with the methanolic extract had a longer survival time (19.21±3.57 days) than those treated with the water extract (17.85±2.81). Both studies indicated that the antiplasmodial compounds in this plant are more soluble in lipophilic solvents than hydrophilic solvents. Jenett-Siems et al. (2002) indicated that *A. afra* was not very suitable for antiplasmodial treatment because the activity of the isolated compound (e.g. a sesquiterpene lactone) was lower than the toxicity against ECV-304 cells. However, Kraft et al. (2003) discovered that two types of compounds were responsible for the antiplasmodial effect of this plant, including flavonoids (7-methoxyacacetin, acacetin, genkwanin and apigenin) and sesquiterpene lactones (1-desoxy-1α-peroxy-rupicolin A-8-O-acetate, rupicolin A-8-O-acetate and 1α,4α-dihydroxybishopsolicepolide).

The University of Zululand started to combine *A. afra* with standard forms of treatment for HIV positive patients (Mulholland and Drewes, 2004). Positive results obtained suggest that *A. afra* exhibits some antiviral activity or immune boosting properties.

6.2. Spasmolytic properties

Mulatu and Mekonnen (2007) tested the traditional folk use of *A. afra* for stomach pains and intestinal cramps. The results showed that the ethanolic extract of *A. afra* leaves, significantly reduced spontaneous rhythmic and agonist-induced contractions of isolated mouse duodenum and guinea pig ileum.

6.3. Cardiovascular effect

The aqueous *A. afra* extracts displayed a hypotensive effect *in vivo* and a concentration-dependent biphasic effect on the heart *in vitro*. Low concentrations induced an initial cardio stimulation followed by cardio depression, while higher concentrations mainly showed cardio depression. In addition, a compound isolated from *A. afra,* scopoletin, induced a dose-dependent decrease in inotropic activity and a decrease in heart rate, especially at higher doses (Guantai and Addae-Mensah, 1999).

6.4. Antioxidant activity

Artemisia afra has been used to treat various inflammatory diseases such as rheumatism, fever and diabetes (Halliwell and Gutteridge, 1989). It was shown that the anticoccidial potential of this plant is also due to its antioxidant activity (Naidoo et al., 2008). Burits et al. (2001) used a rapid TLC screening method for the evaluation of the antioxidant activity of *A. afra.* It was claimed that the volatile oils of *A. afra* could play a role as a nonspecific donor for hydrogen atoms or electrons in the diphenylpicrylhydrazyl assay and it was further shown to be an effective hydroxyl radical scavenging agent in the deoxyribose degradation assay. The oil of *A. afra* also showed antioxidant potential in the bioassay for non-enzymatic lipid peroxidation in liposomes. According to the results of various activity tests and GC-MS analysis, the sesquiterpene, chamazulene, was suggested to be responsible for the radical scavenging effect of the oil.

6.5. Sedative and CNS-acting activities

Artemisia species have been proven to have anti-convulsive and $GABA_A$-benzodiazepine receptor-binding activity (Sayyah et al., 2004; Salah and Jäger, 2005). Stafford et al. (2005) discovered sedative and CNS-acting activities of *A. afra* according to the $GABA_A$-benzodiazepine receptor-binding assay. The results showed that the ethanolic extract of the plant had a good dose-dependent activity (binding % of 5.0 ± 0.9, 45.3 ± 3.5 and 81.8 ± 4.2 at concentrations of 0.455 mg/ml, 0.046 mg/ml and 0.005 mg/ml respectively). It was also claimed that flavonoids were the active compounds related to the sedative and CNS-acting activities.

6.6. Antidepressant activity

According to the monoamine hypothesis, some transmitters, such as serotonin, noradrenalin, dopamine, GABA and L-glutamate, are related to depression (Rang et al., 1999). Therefore, several antidepressants available on the market today are based on selective inhibition of serotonin reuptake. Nielsen et al. (2004) reported that the ethanolic extract of *A. afra* showed a low affinity to the serotonin transporter protein (Less than 50% [^{3}H] citalopram binding at the highest concentration of 5 mg/ml). The affinity of this extract exhibited a concentration-dependent relationship, which indicated that *A. afra* possesses a certain potential to treat depression.

6.7. Toxicity

Jenett-Siems et al. (2002) found that a sesquiterpene lactone isolated from *A. afra* was responsible for the observed cytotoxicity. The crude ethanolic extract of *A. afra* also showed cytotoxicity in Vero cells with an IC_{50} value of 113.0 ± 2.05 μg/ml (Mativandlela et al., 2008). Acute and chronic toxicity of this plant was also exhibited through *in vivo* tests in rodents. In the acute toxicity assay, single intraperitoneal injections (1.5–5.5 g/kg) and single oral doses (2–24 g/kg) of an aqueous extract of *A. afra* were administered to observe the toxicity of this plant in rodents. The intraperitoneal route of administration induced a regular dose-dependent increase in the mortality and incidence of general behaviour adverse effects, while the oral route showed a dose-independent result. Meanwhile, the LD_{50} of these two routes of administration were found to be 2.45 and 8.96 g/kg, respectively. A chronic toxicity assay was also performed in rodents by administering oral doses of an *A. afra* extract (0.1 or 1 g/kg/day) for 3 months. The result showed that no significant changes occurred in general behaviour, body weight, haematological and biochemical parameters, organ weights and morphology of organs (Mukinda and Syce, 2007).

7. Quality control

Artemisia afra has been traditionally used to treat symptoms which can be related to malaria. Although there are only few scientific publications available to support this, a commercial company is currently selling an *A. afra* product which they claim to be effective in the treatment of malaria. The claim is further supported by the fact that the activity of their product can be ascribed to the well known antiplasmodial compound, artemisinin. Due to these claims a study was performed to establish a quality control protocol and metabolomic differentiation between *A. afra* and the well known *A. annua* (which contains artemisinin). This study was conducted in order to establish a rapid metabolomics approach and to carry out quality control on these herbal formulations (Van der Kooy et al., 2008). The claim that artemisinin (so far only found in *A. annua*) is responsible for the antiplasmodial effects of *A. afra* was investigated and disproved. The results indicated that these two plant species (*A. afra* and *A. annua*) could easily be identified based on their metabolomic profiles. The separation between the two

species was mainly due to the three methyl signals of artemisinin in the NMR spectrum. Additional LC-MS analysis also demonstrated that artemisinin could not be detected in the *A. afra* samples.

8. Discussion and conclusions

Artemisia afra is widely distributed in the southern parts of Africa. It is therefore one of the most utilized plants in the African ethnopharmacology. This review aimed at describing the different uses of *A. afra*, either alone or in combination with different substances or species, in treating various ailments. The main focus of this review was however to bring together all available scientific research that has been conducted on this species. The identification of the volatile secondary metabolites obtained from this species received a lot of attention as is reflected by the number of papers that has been published on this matter.

The differences in the chemical profiles of the volatile constituents of *A. afra* can be ascribed to geographical variations, different plant parts used, different sample preparation and extraction methods and genetic differences within populations. The obtained variation makes quality control of this species extremely difficult. Although three of the above-mentioned causes for variation can be controlled, the natural variation between individuals cannot be controlled in the wild. Future research should therefore focus on establishing reproducible quality control methods in order to minimize the variation found in the volatile secondary metabolites, but also the non-volatile secondary metabolites, between individuals. In addition, all the secondary metabolites reported in literature are listed in this review in order to be able to conduct future dereplication studies.

Artemisia afra has also been tested against a multitude of microorganisms as can be seen from Table 3. Future research should however first focus on establishing quality control protocols, followed by testing the extracts against the microorganisms which showed the highest sensitivities. Although *A. afra* has been tested for its antiplasmodial activity (Jenett-Siems et al., 2002; Kraft et al., 2003; Clarkson et al., 2004; Gathirwa et al., 2007), this has not yet been fully demonstrated. It has also been proven that this species does not contain the antiplasmodial component, artemisinin (in detectable levels), which occurs in *A. annua* (Van der Kooy et al., 2008). Due to the traditional use and commercial claims that *A. afra* is effective as a prophylactic as well as treating uncomplicated malaria, this aspect should be researched further. Research in this area should focus on determining the antiplasmodial activity of *A. afra* samples from various regions as well as at different growth stages. If compared to the well known antiplasmodial plant, *A. annua*, it was shown that the active component, artemisinin, is present at its highest concentration just before flowering. The concentration of this compound can fluctuate between 0.01%–1.00% (Liu et al., 2006). If a similar antiplasmodial compound is present in *A. afra,* the growth stage at which to produce an extract to perform the bioassays, becomes extremely important.

Based on the data presented in this review it can be concluded that *A. afra* might become a future flagship species for TAM, if the problems associated with quality control could be solved and more importantly, if we can identify the active component(s), especially the antiplasmodial secondary metabolites, in this species.

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