Artemisia afra and Modern Diseases
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Abstract
Herb Artemisia afra has recently attracted worldwide attention of researchers for its possible use in the modern diseases like diabetes, cardiovascular diseases, cancer, respiratory diseases etc. This review is exhaustive and systematic organization of the available literature on Artemisia afra (A. afra) from January 1922 to July 2011. The literature survey presents the number of publications with respect to time. Patents are briefly described; the traditional uses are classified and summarized. Some emphasis is given to the data and projections of modern diseases and the ongoing research in this area in the context of title of this review. The pharmacognostic aspects, chemical constituents and factors affecting it, the activity, analysis & quality control, pharmaceutical dosage form etc. is dealt in this review.

Keywords: Artemisia afra; Patents; Traditional uses; Chemical constituents; Activity; Toxicity; Dosage form

Introduction
Man has been able to appreciate through his superior observing and learning capabilities to use and exploit the natural resources, the flora and fauna for his survival and comfort, to alleviate pain and to cure diseases; to constantly improve upon his health and build longevity. WHO [1] reports that 80% population of Asian and African countries depend on traditional medicine to treat various infectious and chronic disease conditions. The popularity of this system of medicine is due to people’s faith in traditional age old methods, its accessibility and affordability [2-4].

South Africa is considered the “hotspot” for its unique and diverse botanical heritage [5,6]. Recent statistics show that about 25% of the total number of higher plants in the world are found in South Africa [7] although its land surface make up less than 1% of the earth [5]. According to the “African Plant Checklist and Database Project” [8], a total of 50,136 angiosperm taxa occur in tropical and southern Africa. It is estimated [5,9] that about 3000 medicinal plants are used in South Africa by traditional healers with an estimated 27 million consumers a year. Of these, only 350 species are most commonly used and about 38 indigenous species have been commercialized to some extent (i.e. they are available as processed materials in modern packaging and in various dosage forms as teas, tinctures, tablets, capsules or ointments). Very few medicinal plants are studied for their potential therapeutic properties [11]. Several others are also produced for multi-million Rand informal markets [12-14]. Basic information about most widely used species can be found in van Wyk et al. [6,9] and Diederichs [15]. It is generally accepted [16] that natural resources will play a major role in the socioeconomic development of the African continent. It is found that herbal treatments are highly lucrative in the international market. The annual revenues in Western Europe reached US $5 billion in 2003-04, in China sales of products totaled US $14 billion in 2005 and herbal medicine revenue in Brazil was US $160 million in 2007 [17] and involves qualified traditional healers, as well as thousands of commercial gatherers who supply both the formal and informal entrepreneurial sectors of the South African economy [17-22].

A. afra is one of the important and most widely used herbs in the traditional medicine. In recent years, it has gained significant attention from the scientific community. Studies have been conducted either to verify or substantiate the traditional use of this herb. Further, its use is also being investigated in the modern diseases like diabetes, cardiovascular diseases, cancer, respiratory diseases etc. With the quantum of work going around and the various properties that are being studied, it was felt to undertake an exhaustive literature survey of this herb A. afra from South Africa, and scientifically compile the information in a comprehensive review.

Literature Search
The number of hits on the internet based science-specific search engine “Scirus” [23] up to mid July 2011 for the key words and the details thereof are given in Table 1. The significance of genus Artemisia is seen in its number of hits, which is 89,080.

The total number of hits appeared for “Artemisia afra” (A. afra) were 885 of which, 5 had no dates. Figure 1 is the graph of 162 publications that appeared in Journal Sources classified and plotted on yearly basis from Jan. 1922 to Nov. 2011 for “A. afra”.

Only two scientific publications based on laboratory work were found in the literature over a span of half a century, first by Goodson in Jan. 1922 [24] and then second by Bohlin and Zdero in 1972 [25]. Both the papers report the constituent’s of A. afra. Goodson investigated if A. afra contained anything that could be regarded as a precursor or a derivative of santonin in consequence of the difficulty of obtaining santonin that was then used as the sole source of anthelmintic. He showed that A. afra contains camphor, a wax–ester probably ceryl cerotate, triacotante, scopoletin and quebrachitol and none which

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Received December 18, 2010; Accepted November 24, 2011; Published November 28, 2011


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could be connected to santonin. While, Bohlman and Zdero [25] investigated to compare other constituents in *A. afra* with those of the old world *Artemisia* species and reported that the roots contained besides isomeric coumarins (mainly (VI)) the known acetylenes (I to V) while the aerial parts contained thujone and umbelliferone-derivatives and no acetylenes (Figure 2). However, Jakupovic et al team [26] of researchers reported additionally 10 new guaianolides and 5 glucolides and also 12-hydroxy-α-cyperone elucidated by high field NMR techniques and some chemical transformations. It can be said that up to 1988, scientific curiosity was generally confined in determining the constituents of *A. afra* essential oil and assigning chemical structure to it.

From Figure 1, it can be said that up to year 2000, *A. afra* did not attract the researchers but only later, especially from 2005 onwards with an average of 18 publications per year. The University of Western Cape and Rhodes University, South Africa is doing lot of research on this plant. The scientific studies made on the plant extracts/essential oil from 1993 onwards were in the direction of finding out the activity namely antifungal [27], antibacterial [28], antioxidant [29], toxicity [30], anti-cancer [31], antitubercular [32], antimalarial [33] antitrypanosomal [34], protective myocardial [35], protective intestinal epithelial Caco-2 cells [36], anti-ulcerative [37] effect on Central Nervous System [38] etc. Pharmaceutical efforts were also made to prepare tea bags from the leaves of *A. afra* [39] to liposomal encapsulation of the essential oil [40] for clinical trials. The traditional claims were also scientifically investigated especially for gynecological complaints [4] and in respiratory disorders [41]. The veterinary anti-oxidant use in attenuating coccidosis in broiler chicken was also explored by Naidoo [42].

The quantitative estimations of plant extracts by using modern equipments like GCMS and GC; HPLC and UV absorption and Mass Spectroscopy was taken up by Oyedeji et al. [43] and Avula et al. [44] respectively in 2009. In 1997, the first European patent was granted to Whittle and Skett [45] that relates to administration of compounds for use in the treatment of diabetes and in 2008, two patents viz. Omer [46] and Bobotas et al. [47] were granted. Details are given under the headings "Omer patent to counteract weight loss & treat other diseases in cancer patients" and "Bobotas et al patent for diabetes and cardio-vascular diseases" of this review. Jager et al’s [48] patent came in 2009. The literature search [23] for *A. afra* along with the additional key words of pharmacological importance and the number of hits are compiled in Table 1.
A pubmed data base [49] search till 13th July 2010 with the search key word “Artemisia” contained 1851 hits of which 91 were reviews, and for “A. afra” only 24 articles of which 1 was a review entitled “A broad review of commercially important southern African medicinal plants” by van Wyk in Oct. 2008 issue of Journal of Ethnopharmacology [7]. With this background of A. afra gaining importance and an objective to compile a comprehensive review with the available scientific information in one paper, this review is being written.

Patents

There are four utility patents given for A. afra from Oct. 1997 till July 2011. Two patents each were granted in US and in Europe. Two patents mainly are in diabetes, one in cancer and; one in diabetes and cardiovascular disease. The gist of all the four patents is given below in reverse chronological order. It is expected to give readers some clues for further research and application.

**Jager et al patent to prevent/ treat diabetes and associated secondary diseases**

The Jager et al. [48] patent relates to a physiologically active composition in pure or mixture form containing Artemisia extract of at least one of A. dracunculus, A. herba-alba, A. judaica, A. vulgaris, A. absinica, A. absinthium, A. afra, A. cannamensis, A. pallens, A. annua, A. abrotanum, A. ludoviciana, A. capillaris or A. scoparia to prevent or treat (pre)diabetes and associated accompanying diseases or secondary diseases. The patent claims that at least one of following could happen: (a) the blood sugar level in a mammal would be lowered, (b) the insulin resistance would be lowered, (c) hepatic glucose release would be lowered, (d) the postprandial glucose level would be lowered, (e) the activity of GLP-1 (“glucagon-like-peptide 1”) would be raised, (f) the binding capacity between GLP-1 and the associated receptor would be raised, (g) the conversion of glucose to glycogen would be raised, (h) the expression of the IRS-2 (“insulin receptor substrate 2”) polypeptide would be raised, and (i) the insulin-controlled glucose uptake would be raised. The composition can be given as a food supplement, a drink, a food, a dietetic food, a functional food or a sport food wherein the effective daily amount of the composition would be between 0.1 and 500 mg/kg/daily with respect to bodyweight.

**Omer patent to counteract weight loss & treat other diseases in cancer patients**

The patent assigned solely to Omer [46] based on clinical trial claims to counteract the weight loss and nutritional deficiency of cancer patients, and to treat Hodgkin and Non-Hodgkin lymphomas, autoimmune diseases, IgA-Nephropathy (glomerulonephritis) and human cancers with a herbal preparation containing Artemisia. The object of the patent is to (a) circumvent resistance to conventional chemotherapy of these diseases, (b) increase the effectiveness of chemotherapy when added to standard chemotherapy treatment, (c) provide treatment to those cancer patients and IgA Nephropathy where no effective treatment is available so far, (d) improve nutrition of patients suffering from progressing cancer, as all cancer patients start losing weight at some stage of their disease, (e) provide a composition aforesaid that acts without exerting toxic side effects and (f) provide a disease-specific synergistic composition in convenient dosage form. The preparation could be of any species from Artemisia viz., A. absinthium, A. annua, A. vulgaris and A. capillaris or any bitter or aromatic herb or shrub of the genus Artemisia of the family Asteraceae, distributed throughout many parts of the world; which shall also contain 10-80% by weight of ginger root (Zingiber officinale rhizomes) and 10-80% by weight of large cardamom (Amomum subulatum). The amount of herbs in the dose could be sufficient to suppress the progress of the disease. The preparation could be prepared either by grinding (filling the powder in hard gelatin capsules or pressing them in tablets), solvent extraction or distillation (tincture), which may also contain an inert pharmaceutical carrier. This preparation could be used in combination with conventional standard therapy to modulate the immune system of the human body. The dose for various forms could be: (a) Dried Herbal Powder: 3-6 tablets per day as 750 mg pressed tablets, (b) Liquid Extract: 2 ml three times a day (equivalent to 6 gm of herb), (c) Distilled Preparations: 2 ml three times a day (equivalent to 6 gm of herb) and (d) Tincture (powdered herbal extracts): 6-9 capsules per day as 450 mg capsules of mixtures.

**Bobotas et al patent for diabetes and cardio-vascular diseases**

The patent assigned to Bobotas et al. [47] relates to methods of using different compositions comprising a (i) cannabinoid 1 (CB1) antagonist, (ii) a dyslipidemic agent, and/or (iii) a metabolic regulator...
useful in treating hypertriglyceridemia, hypercholesteremia, mixed dyslipidemia, vascular disease, atherosclerotic disease, and/or obesity; preventing and/or reducing cardiovascular and/or vascular events; reducing insulin resistance, fasting glucose levels, and/or postprandial glucose levels; and preventing and/or reducing the incidence of and/or delaying the onset of metabolic syndrome. The preferred dyslipidemic agents could be omega-3 fatty acids, peroxisome proliferator-activated receptor (PPAR) agonists/antagonists, microsomal triglyceride transfer protein (MTP) inhibitors, and/or dipeptidyl peptidase-4 (DPP4) inhibitors; and the preferred metabolic regulators could be sarsasapogenin, smilagenin, steroild glycosides and extracts thereof, and extracts of Artemisia spp.; either alone or in combinations with CB1. The dosage form could be a tablet, hard/soft gelatin capsule, powder that could be dispersed in a beverage, liquid or infusion for oral use, and injectables. The dosage can vary from 1-10 units depending on the combination and requirement.

Whittle and skett pharmaceutical patent in diabetes and hyperglycemia

The Whittle and Skett patent [45] relates to administration of pharmaceutical compounds and compositions for use in the treatment of diabetes or other hyperglycaemic defects of carbohydrate metabolism which includes extracts from plant Artemisia spp. (A. herba-alba, A. pallens or A. afra, A. judaica), so prepared that it contains effective ingredients viz., insulinomimetic and substance having glucagon antagonist properties with acceptable excipient which can be given orally or by parental route. The patent also relates how the manufacture method of successive fractionation of the plant extract improves its utility by reducing its toxicity and yielding insulin-like and glucagon antagonist activities thereby increasing therapeutic efficacy. To achieve this, the alcoholic extract obtained by (i) extracting the plant with water, (ii) concentrating the extract to dryness, and (iii) treating the dry residue with alcohol with successive chromatographic procedures around baby's neck [57]. The use of Artemisia spp. in combination with other medicinal plants has been widely documented in the ethnobotanical literature is given [58] in Table 2.

Traditional Uses

A. afra belonging to genus Artemisia is exceptionally and widely used in many parts of the world either alone or in combination with other plants as herbal remedies for a variety of ailments like simple headache to neurological disorder like epilepsy. There are more than 1 lakh traditional healers practicing in South Africa [13]. In this section, the various conditions in which A. afra is being traditionally used, as cited in the literature is given.

Respiratory tract related problems

It is primarily used in common cold, cough, sore throat, influenza, asthma as it is said to clear the respiratory and bronchial passages [50-53]. The leaves are heated and the vapors inhaled to alleviate symptoms of colds and flu [52,54]. It is also used to clear the blocked nasal passage by inserting fresh leaves in the nostrils or by using as snuff; to relieve pain in the throat in scarlet fever, either the hot infusion is used as gargle or the throat is exposed to vapors [52,55]. The leaves are commonly smoked by some tribes to help release phlegm, to ease and soothe a sore throat, coughing at night [56]. For cold and chest problems in infants, fresh leaves are placed in flannel bag and hung around baby’s neck [57]. The use of A. afra in combination with other medicinal plants has been widely documented in the ethnobotanical literature is given [58] in Table 2.

Gastro intestinal disorders

It is used in the digestive complaints like indigestion, colic, constipation, flatulence, gastritis, dry dyspepsia and to get rid of intestinal worms [51,59-61]. It is consumed to overcome general debility and as an appetite [62-64]. The leaves are prepared as an infusion or decoction and taken orally.

Topical use for skin afflictions

Watt and Breyer-Brandwijk [52] report that the (i) extract is applied

<table>
<thead>
<tr>
<th>Plant in combinations</th>
<th>Uses</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. afra and E. globulus</td>
<td>Respiratory complaints</td>
<td>Crushed leaves or steam from infusions are inhaled or decoctions are taken</td>
</tr>
<tr>
<td>A. afra and A. betulina</td>
<td>Respiratory complaints</td>
<td>Herbal wine</td>
</tr>
<tr>
<td>A. afra and Zanthoxylum capense</td>
<td>The Europeans and Africans use it in febrile conditions, and it is used as a treatment for colds</td>
<td>A decoction and an infusion of the leaf is used</td>
</tr>
<tr>
<td>A. afra and O. asteriscoides</td>
<td>Respiratory complaints</td>
<td>Tincture</td>
</tr>
<tr>
<td>A. afra, E. globulus and Leonotis microphylla</td>
<td>Fever, chest infections and digestive disturbances</td>
<td>Infusion</td>
</tr>
<tr>
<td>A. afra, Z. capense and Allium sativum</td>
<td>Respiratory complaints</td>
<td>Decoction</td>
</tr>
<tr>
<td>A. afra and Lippia javanica</td>
<td>Fevers, respiratory complaints, measles and as a prophylactic against lung inflammations</td>
<td>Infusion, taken with milk</td>
</tr>
<tr>
<td>A. afra, O. asteriscoides and E. globulus</td>
<td>Respiratory complaints</td>
<td>Infusion, tincture</td>
</tr>
<tr>
<td>A. afra and Tetradenia riparia and salt</td>
<td>Coughs</td>
<td>Decoctions</td>
</tr>
<tr>
<td>A. afra and Alepidea amalambica</td>
<td>Colds and flu</td>
<td>Leaves and root/rhizome</td>
</tr>
<tr>
<td>A. afra and Warburgia salutaris</td>
<td>Acute bronchitis, coughs from colds or flu, fever</td>
<td>Leaves and bark</td>
</tr>
<tr>
<td>A. afra, A. amalambica and Leonotis leonurus.</td>
<td>Asthma</td>
<td>Leaves and root</td>
</tr>
<tr>
<td>A. afra, W. salutaris and Acorus calamus</td>
<td>Chronic bronchitis and emphysema</td>
<td>Leaves, bark and rhizome</td>
</tr>
</tbody>
</table>

Reprinted from South African Journal of Botany, 76(4), S. Suliman, S. F. van Vuuren, A. M. Viljoen, Validating the in vitro antimicrobial activity of Artemisia afra in polyherbal combinations to treat respiratory infections, 655-661, Copyright 2010, with permission from Elsevier [58].

Table 2: Traditional use of A. afra in combination with other plant species for the treatment of respiratory complaints.
topically to ease the pain and hasten bursting of boils, carbuncles, large acne pimples; (ii) hot bath in the decoction is used to bring out the rash in measles, mumps, chicken pox; (iii) infusion or decoction is used to bathe hemorrhoids, herpes, venereal sores; (iv) poultice (of the leaf) is applied as a dressing to relieve neuralgia, to the swelling of mumps and other glandular or skin inflammations and (v) lotion is used to wash the body to rejuvenate the skin.

**Gynecological problems**

It is used for dysmenorrhea [9], amenorrhea and menstrual cramps [4]. The genitalia are steamed with vapors for menstrual chills and also after childbirth, while decoctions of leaves have been administered for extended labor [65].

**Fever**

The decoction of garlic leaves and bulbs is mixed with *A. afra* and *Xanthoxylum capensis* and used as febrifuge [52], a decoction of the plant is drunk as a remedy for fever [66]. An infusion of *A. afra* is widely used in Malaria [66] along with *Lippia javanica* [52]. Bally [67] reports that a poultice is applied on inflamed throat and for fever in children.

**Miscellaneous uses**

An infusion of a double handful of leaves with a quart of hot water is administered either as enema or emetic for febrile complaints [52]. It is also used in the inflammatory disease like rheumatism [29], gout [51]; neurological disorder like epilepsy [68], in haematuria and to alleviate stabbing pain [69] and as anti-fertility agent [70]. According to Watt and Beyer-Brandwijk [52], *A. afra* has been used to keep urine free from sugar in the case of diabetes mellitus, reports Deutschländer et al. [71], while it is used in tinea capitis reports Abebe and Ayehu [69].

**Scope of *A. afra* in Modern Diseases**

In the present mechanized life of less physical activity and more mental work, it is pertinent to discuss the afflictions of modern mankind that would also be carried over to new generations, in the context of ongoing global research on the herb *A. afra*.

WHO [72] states that aging of populations in low- and middle-income countries will result in significant increase in the total deaths mostly from non-communicable diseases (NCDs) over the next 25 years, which would be mainly from cardiovascular diseases (CVD), cancers, diabetes and chronic respiratory diseases, causing an estimated 35 million deaths each year. It reports that in year 2004, ~58.8 million deaths occurred globally, of which ~27.7 million were of females and ~31.1 millions of males. More than half of all deaths involved people 60 years and older, of whom 22 million were people aged 70 years and older and 10.7 million were people aged 80 years and older; that almost one in five deaths in the world was of a child under the age of five year. Figure 3 shows the distribution of deaths at all ages for 12 major causes, illustrating the relative importance of the respective causes of death and of male-female differences, in year 2004. WHO projections of Global Burden of Disease (GBD) by cause for 2008, 2015 and 2030 are given in Table 3, based on 2004 GBD estimates as a starting-point [72].

**Diabetes**

Diabetes is a life threatening condition. The number of people getting affected by diabetes is increasing due to population growth, aging, urbanization, increasing prevalence of obesity and mechanized lifestyle. The studies undertaken by Roglic et al. [73] reveals that diabetes is the fifth leading cause of death, killing ~2.9 million people in the year 2000, which is equivalent to 5.2% of all deaths. The prevalence of diabetes and the number of people of all ages with diabetes in the year 2000 and projections for 2030 was estimated by Wild et al. [74]. The paper reports that the prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. The prevalence of diabetes is higher in men than in women, but there are more women with diabetes than men.
Year | 2008 | 2015 | 2030
--- | --- | --- | ---
Population (in billion) | 670628 | 718688 | 811059

<table>
<thead>
<tr>
<th>Disease</th>
<th>(in 000s)</th>
<th>% Total</th>
<th>(in 000s)</th>
<th>% Total</th>
<th>(in 000s)</th>
<th>% Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Deaths</td>
<td>58766</td>
<td>100.0</td>
<td>60856</td>
<td>100.0</td>
<td>67790</td>
<td>100.0</td>
</tr>
<tr>
<td>I. Communicable diseases, maternal and perinatal conditions and nutritional deficiencies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious and parasitic diseases (like Tuberculosis, STDs, HIV/AIDS, diarrhea, Meningitis, Hepatitis, Malaria, Trypanosomiasis etc.)</td>
<td>8427</td>
<td>14.3</td>
<td>7044</td>
<td>11.6</td>
<td>4216</td>
<td>6.2</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>3816</td>
<td>6.5</td>
<td>3427</td>
<td>5.6</td>
<td>2871</td>
<td>4.2</td>
</tr>
<tr>
<td>Maternal conditions</td>
<td>424</td>
<td>0.7</td>
<td>316</td>
<td>0.5</td>
<td>180</td>
<td>0.3</td>
</tr>
<tr>
<td>Perinatal conditions (e)</td>
<td>2913</td>
<td>5.0</td>
<td>2606</td>
<td>4.3</td>
<td>1898</td>
<td>2.8</td>
</tr>
<tr>
<td>Nutritional deficiencies</td>
<td>401</td>
<td>0.7</td>
<td>313</td>
<td>0.5</td>
<td>205</td>
<td>0.3</td>
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<tr>
<td>II. Noncommunicable conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant neoplasms (like cancer of mouth &amp; oropharynx, oesophagus, stomach, colon/rectum, liver, pancreas, trachea/bronchus/lung, melanoma &amp; skin, breast, cervix cancer uteri, corpus uteri, prostate, bladder, lymphomas, multiple myeloma, leukaemia etc.)</td>
<td>8097</td>
<td>13.8</td>
<td>9259</td>
<td>15.2</td>
<td>11928</td>
<td>17.6</td>
</tr>
<tr>
<td>Other neoplasms</td>
<td>178</td>
<td>0.3</td>
<td>201</td>
<td>0.3</td>
<td>253</td>
<td>0.4</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1294</td>
<td>2.2</td>
<td>1656</td>
<td>2.7</td>
<td>2229</td>
<td>3.3</td>
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<tr>
<td>Nutritional/endocrine disorders</td>
<td>310</td>
<td>0.5</td>
<td>331</td>
<td>0.5</td>
<td>395</td>
<td>0.6</td>
</tr>
<tr>
<td>Neuropsychiatric disorders (like schizophrenia, epilepsy, alcohol use disorders, Alzheimer and other dementias, Parkinson disease, drug use disorder etc.)</td>
<td>1320</td>
<td>2.2</td>
<td>1429</td>
<td>2.3</td>
<td>1757</td>
<td>2.6</td>
</tr>
<tr>
<td>Sense organ disorders</td>
<td>5</td>
<td>0.0</td>
<td>5</td>
<td>0.0</td>
<td>6</td>
<td>0.0</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>17690</td>
<td>30.4</td>
<td>19388</td>
<td>31.9</td>
<td>23578</td>
<td>34.8</td>
</tr>
<tr>
<td>Respiratory diseases (like chronic obstructive pulmonary disease, asthma)</td>
<td>4426</td>
<td>7.5</td>
<td>5220</td>
<td>8.6</td>
<td>7373</td>
<td>10.9</td>
</tr>
<tr>
<td>Digestive diseases (like peptic ulcer disease, cirrhosis of the liver etc.)</td>
<td>2010</td>
<td>3.4</td>
<td>2015</td>
<td>3.3</td>
<td>2164</td>
<td>3.2</td>
</tr>
<tr>
<td>Diseases of the genitourinary system (like Nephritis/nephrosis, benign prostrate hypertrophy)</td>
<td>980</td>
<td>1.7</td>
<td>1089</td>
<td>1.8</td>
<td>1376</td>
<td>2.0</td>
</tr>
<tr>
<td>Skin diseases</td>
<td>71</td>
<td>0.1</td>
<td>80</td>
<td>0.1</td>
<td>103</td>
<td>0.2</td>
</tr>
<tr>
<td>Musculoskeletal diseases</td>
<td>131</td>
<td>0.2</td>
<td>142</td>
<td>0.2</td>
<td>175</td>
<td>0.3</td>
</tr>
<tr>
<td>Congenital abnormalities</td>
<td>408</td>
<td>0.7</td>
<td>373</td>
<td>0.6</td>
<td>294</td>
<td>0.4</td>
</tr>
<tr>
<td>Oral diseases</td>
<td>3</td>
<td>0.0</td>
<td>4</td>
<td>0.0</td>
<td>5</td>
<td>0.0</td>
</tr>
<tr>
<td>III. Injuries</td>
<td>5663</td>
<td>9.6</td>
<td>5957</td>
<td>9.8</td>
<td>6801</td>
<td>10.0</td>
</tr>
<tr>
<td>Unintentional injuries</td>
<td>3977</td>
<td>6.8</td>
<td>4181</td>
<td>6.9</td>
<td>4786</td>
<td>7.1</td>
</tr>
<tr>
<td>Intentional injuries</td>
<td>1685</td>
<td>2.9</td>
<td>1777</td>
<td>2.9</td>
<td>2015</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Table 3: Projected deaths by cause, globally [72].

The urban population in developing countries is projected to double between 2000 and 2030. The most important demographic change to diabetes prevalence across the world appears to be the increase in the proportions of people >65 years of age. The three nations which top the list in prevalence of diabetes are India, China and U.S. with estimated 31.7, 20.8 and 17.7 million people affected by diabetes in the year 2000; is projected to reach 79.4, 42.3 and 30.3 million people in the year 2030, respectively.

Cardio-vascular diseases

As the average human life expectancy has increased, so has the impact of ageing and age-related diseases like CVDs. CVDs are a group of disorders [75] of the heart and blood vessels and include (a) coronary heart disease – disease of the blood vessels supplying the heart muscle, (b) cerebrovascular disease - disease of the blood vessels supplying the brain, (c) peripheral arterial disease – disease of blood vessels supplying the arms and legs, (d) rheumatic heart disease – damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria, (e) congenital heart disease - malformations of heart structure existing at birth and (f) deep vein thrombosis and pulmonary embolism – blood clots in the leg veins, which can dislodge and move to the heart and lungs.

One of the major causes of CVDs [76] is essential hypertension, known as the silent killer, which does not cause symptoms for many years until a vital organ is damaged [77]. Essential hypertension is multi-factorial in origin [78], cannot be cured but can be controlled [79-80] effectively by use of medicine [81]. The other non-pharmacological approach [82] could be through (a) weight control [83-85], (b) sodium restriction [86-90], (c) fat content [90], (d) alcohol restriction [91-92], (e) physical exercise [93-94], (f) relaxation therapies for stress reduction [95-97] and (g) potassium therapy [98-99].

CVDs are the number one cause of death globally [100]. An estimated 17.1 million people died from CVDs (29% of all global deaths) in 2004. Of these deaths, ~7.2 million and ~5.7 million deaths were due to coronary heart disease and stroke, respectively. 82% of CVD deaths take place in low- and middle-income countries and occur almost equally in men and women. It is projected that by 2030, almost 23.6 million people will die from CVDs, mainly from heart disease and stroke, with largest increase in number of deaths would be in the South-East Asia Region, WHO [101]. There are currently about 800...
million people with high BP worldwide. The current prevalence in many developing countries, particularly in urban societies, is already as high as those seen in developed countries [102-103]. Studies indicate that (i) by lowering of each 10 mmHg of systolic BP, there is 1/3rd decrease in risk of stroke in people of age between 60-79 years; (ii) by lowering diastolic blood pressure (DBP) by 2-7% below 95 mmHg, million deaths per year from coronary heart disease and stroke can averted by 2020.

**Cancer**

Cancer [104] is a generic term for a large group of diseases that can affect any part of the body. Other terms used are malignant tumours and neoplasms. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs. It arises from one single cell. The transformation from a normal cell into a tumour cell is a multistage process, typically a progression from a pre-cancerous lesion to malignant tumours. These changes are the result of the interaction between a person’s genetic factors and three categories of external agents, including (i) physical carcinogens, such as ultraviolet and ionizing radiation, (ii) chemical carcinogens, such as asbestos, components of tobacco smoke, aflatoxin (a food contaminant) and arsenic (a drinking water contaminant) and (iii) biological carcinogens, such as infections from certain viruses, bacteria or parasites. The relative importance of the most common cancers [72] in terms of number of deaths at all ages is summarized in Table 4.

Globally lung cancer (including trachea and bronchus cancers) are the most common cause of death from cancer among men, and stomach cancer mortality is second. Colon and rectum cancers are the 4th leading cause & oesophagus cancer the 5th leading cause globally. Prostate cancer is the 6th globally. For woman, 15 cancers are ranked, of which the most common is the breast cancer, followed by cancers of trachea, bronchus, lung and stomach cancer. Other cancers of female reproductive system are Cervix uteri (5th), ovary (8th) and Corpus uteri (13th) the leading cause of death in woman.

In 2005, 7.6 million people died of cancer [105]. WHO [106] projects that with steadily increasing proportion of elderly people in the world will result in approximately 50% increase in new cancer cases over next 20 years. From the studies based on 5-year prevalence between 1998-2002, WHO projects that the number of people affecting from cancer would rise from ~10.9 million in 2002 to ~16 million in 2020, almost nearly a 50% increase; 2/3rd of them would be from newly industrialized and developing countries. It is estimated that almost 7 million people would die each year of cancer and 10.3 million by 2020 unless proper measures are not taken. Dr. John R. Seffrin, President, UICC states, “Cancer is potentially the most preventable and most curable of the major life-threatening disease facing human kind. We can save 2 million lives by 2020 and 6.5 million by 2040.”

### Chronic respiratory disease

As per WHO [107] “chronic respiratory diseases” are chronic diseases of the airways and other structures of the lung. Some of the most common are asthma, chronic obstructive pulmonary disease (COPD), respiratory allergies, occupational lung diseases and pulmonary hypertension.

Asthma [108] is a chronic disease characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person. Symptoms may occur several times in a day or week in affected individuals, and for some people become worse during physical activity or at night. Asthma is the most common chronic disease amongst children. According to WHO estimates, 300 million people suffer from asthma and 0.25 million people died of asthma in 2005. COPD [109] is a lung ailment that is characterized by a persistent blockage of airflow from the lungs. It is an under-diagnosed, life-threatening lung disease that interferes with normal breathing and is not fully reversible. An estimated 210 million people have COPD worldwide. More than 3 million people died of COPD in 2005, which is equal to 5% of all deaths globally that year. The primary cause of COPD is tobacco smoke (through tobacco use or second-hand smoke). Total deaths from COPD are projected to increase by more than 30% in the next 10 years without interventions to cut risks, particularly exposure to tobacco smoke. Allergic rhinitis or hay fever [110] happens when one breathes in something to which he/she is allergic, and the inside of the nose becomes inflamed and swollen. Sinusitis [110] is an inflammation of the lining inside the sinuses which can be acute or chronic. When the sinuses become blocked and fill with fluid, germs can grow and cause symptoms such as headache and nasal yellowish secretions. Blocked sinuses can be caused by the common cold, hay fever or nasal polyps (small lumps inside the nose). Allergic rhinitis and sinusitis are linked to each other. Acute sinusitis usually subsides without any need for specific treatment. Chronic sinusitis may require antibiotics, decongestants or steroid nasal sprays. Pulmonary hypertension [111] is a condition in which there is high blood pressure in the lung arteries as the arteries become narrow affecting the blood flow. Over time, some of the arteries may stiffen and become completely blocked, causing the right side of heart to work harder to pump blood through the lungs. Over time, the heart muscle weakens and loses its ability to pump enough blood for the body’s needs. The extra stress causes the heart to enlarge and become less flexible. Heart failure is one of the most common causes of death in people who have pulmonary hypertension. In some cases, pulmonary hypertension is caused by schistosomiasis, a worm infection common in Africa and Latin America; and sickle cell disease, a genetic abnormality of blood which is common in persons of African origin. Difficulty in breathing or shortness of breath is the main symptom of pulmonary hypertension. Other symptoms are fatigue, dizziness, swelling in the ankles or legs (edema), bluish lips and

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Type of Cancer</th>
<th>Ranking in Men</th>
<th>Ranking in Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Trachea, bronchus, lung cancers</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2.</td>
<td>Stomach cancer</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3.</td>
<td>Liver cancer</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>4.</td>
<td>Colon and rectum cancers</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>5.</td>
<td>Oesophagus cancer</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>6.</td>
<td>Prostate cancer</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>7.</td>
<td>Mouth and oropharynx cancers</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>8.</td>
<td>Lymphomas &amp; multiple myeloma</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>9.</td>
<td>Leukaemia</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>10.</td>
<td>Bladder cancer</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>11.</td>
<td>Pancreas cancer</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>12.</td>
<td>Melanoma &amp; other skin cancers</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>13.</td>
<td>Breast cancer</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>15.</td>
<td>Ovary cancer</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>16.</td>
<td>Corpus uteri cancer</td>
<td>-</td>
<td>13</td>
</tr>
</tbody>
</table>

**Table 4:** Ranking of most common cancer among men and women according to number of deaths, by cancer site, WHO worldwide data, 2004 [72].
skin (cyanosis), chest pain, racing pulse and palpitations. There are no mortality details on the allergic rhinitis or hay fever and pulmonary hypertension on WHO website.

**Pharmacognostic Aspects**

**Common name**


The genus name *Artemisia* is derived in honor of the Greek goddess of hunting Artemis [115]. Another story [116] goes that the name is kept after Artemisia, the famous botanical and medical researcher and the wife of the Greek/Persian King Mausolus, who built a magnificent Mausoleum tomb known as seven Wonders of the Ancient World, after his death in 353 BC.

**Taxonomy**

*Artemisia afra* belongs to Domain: Eukaryota, Kingdom: Plantae, Subkingdom: Viridaeplantae, Phylum: Tracheophyta, Subphylum: Euphyllphytina, Infra phylum: Radiatopses, Class: Magnoliopsida, Subclass: Asteridae, Superorder: Asteranae, Order: Asterales, Family: Asteraceae, Subfamily: Asteroideae, Tribe: Anthemideae, Genus: Artemisia, Specific epithet: afra- Jacq., Botanical name: *Artemisia afra* [117]. The *Asteraceae* is one of the most important family of plants in the world. More than 23000 species from about 1300 genera have been identified [118]. Many species have been used as sources of rubber, medicines, edible oils, vegetables, pesticides and so on. Some are popular ornamental plants. The genus *Artemisia* contains more than 400 species [119,120].

**Phylogeny**

The review paper by Hayat et al. [121] discusses the development in the classification and phylogeny of genus *Artemisia* L. They report that this plant group could have been originated in temperate Asia (mesothermic subarctic or semihumid environments prevailing near Ural Mountains); in the mid-tertiary period of Cenozoic era, and the centers of diversity of this genus could be in the temperate and cold temperate regions of Eurasia, North America and Asia. The paper discusses the basis of disagreements amongst the Scientists with respect to taxonomic treatment of *Artemisia* in the last half decade for maintaining a single large genus of over 500 species to the recognition of six to eight genera within its taxonomic boundaries. The conclusion of (i) palynological, (ii) karyological, (iii) floral & capitular morphological and (iv) molecular phylogenetic studies for pollen evaluation, chromosomal counts & polyploidy, evolution of floral characters and molecular phylogeny respectively undertaken by various researchers are reported.

**Geographical distribution**

*A. afra* is a herb growing in the high land areas of Eastern and Southern Africa altitudes ranging between 1500 and 3000m where the soils range from volcanic ash, loamy sands, to sandy or calcareous clay loams of volcanic or granitic origin [114,122]. The plant grows in the South and Eastern regions of the continent and has been located in Ethiopia, Kenya, Tanzania, Zaire, Zambia, Zimbabwe, Angola and the Republic of South Africa [52,122]. In South Africa, it usually grows in rocky mountainous areas along forest margins and stream sides and its natural distribution extends from the Northern and Eastern Transvaal to the Western Cape, except the Northern Cape [123]. It is also predominantly found in Asia, Europe and North America [119,120]. The geographical distribution of *A. afra* in South Africa [124] with the copyright permission from Scott & Springfield [125] is given in Figure 4. It’s one of the domesticated plant in these regions [126].

**Plant description**

*Artemisia afra* is a medium sized multi-stemmed, clump-forming woody perennial shrub, which grows up to 2 meters in height with a leafy, hairy ridged stem [6,112].

Its soft leaves are finely-divided (like a fern), are silver-grey due to the presence of fine hairs reaching in length up to 80 mm and
An image from BBC Magazines Ltd. [128] is given in Figure 5a. The adaxial surface of the leaf is darker compared to its abaxial surface [6]. Figure 5b is the picture of fully grown plant from the South African Biodiversity Institute’s Plant Information [112]. The plant has an easily identifiable aromatic odour and smells pungent and sweet after bruising [129]. It produces pale yellow tubular florets, with few outer female and inner bisexual florets occurring in an elongated racemose panicle, an image from the book, Wild flowers of Northern South Africa [130] is given, Figure 6.

The capitula are small, receptacle flat and naked. The African wormwood produces small, inconspicuous wild fertilized flowers between March and July, and the seeds are produced from August to November. The fruits are about 1 mm long, somewhat 3-angled and slightly curved with a silvery-white coating [11,53,131].

**Histology**

The salient microscopic properties presented here are obtained from the Monograph of “Artemisia afra Herba” given by South African Medical Council Research, South Africa Health Information [124] and copyright permission [125], Figure 7 (i – ix). (i) Fibrous layer of anther; (ii) corolla showing papillate inner epidermis; (iii) tricolporate yellow-brown pollen grains, ± 20 µ in diameter; (iv) polygonal epidermal cells of upper leaf lamina; (v) small block-like cells of stamen filament; (vi) epidermal cells of lower leaf lamina with sinuous slightly thickened walls; (vii) fragment of corolla (tubular floret) with microcrystals of calcium oxalate; (viii) vessels of stamen filament and (ix) fragments of corolla with striated outer epidermis.

**Cultivation and collection**

The intensive harvesting of medicinal plants for use and commercial trade in South Africa poses a threat to many species. Hence, cultivation has been considered as an alternative to collection in the wild. Keirungi and Fabricius [118] assessed the feasibility of cultivating 17 selected medicinal plants based on its medicinal importance in Nqabara Administrative Area on South Africa’s Wild Coast and reported that *A. afra* holds 8th rank in the list of important medicinal plant with a market value.
Factors affecting cultivation of medicinal plants: The main factors which generally affect the cultivation of medicinal plants can be stated as (i) proximity to plant source, (ii) time spent in collecting the plant, (iii) number of ailments perceived to be healed i.e., frequency of usage, (iv) retention of activity, (v) ease to cultivate - availability of seeds or grafts, soil quality, vulnerability to pests, modest water requirements, maintenance etc., (vi) impact on other plants, (vii) market value and economic potential and (ix) awareness amongst people that they have been causing adverse effect on large trees due to plucking shrubs around its vicinity and willingness to conserve indigenous forests.

Habitat: *A. afra* is very drought resistant and hardy [53], common to arid soils [131], open to sunny situation with light, well drained soil [131]. The optimal temperature and annual rain fall as described in FAO *Artemisia afra* Data Sheet are 22-33°C and 550-750 mm respectively [114].

Cultivation: The Plant Biology Guide to Growing Artemisia Wormwood [132] mentions that the seeds can be sown either in spring or autumn, in well drained soil at a pH of 5.5 to 7. The seedlings should be put out after the last frost and planted from 30 cm (small species) to 60 cm (larger species). Fertilizer should be applied in the early spring, and mulch applied in the late autumn. The leaves can be harvested any time. A very quick and easy way to propagate is from cuttings [53] in summer and by division in spring, prune in spring to stimulate growth. These would grow in any soil and needs just occasional watering and cutting back.

The South Africa Department of Agriculture, Directorate of Plant Production, Division of Industrial Crops [133] has compiled in collaboration with members of South African Essential Oils Producer Association (SAEOPA) and KARWIL consultancy all the vital aspects involved in the production of *Artemisia afra*. It is made freely available on the official website of Directorate of Agriculture Information Services viz., http://www.nda.agric.za/publications. It is a 26 page document comprising 5 parts along with references for further reading. It details general aspects (like classification, origin & distribution, production levels, major production areas in South Africa, plant description, climatic & soil requirements); cultivation practices (like propagation, soil preparation & planting, fertilization & irrigation; pest, disease & weed control, mulching & harvesting); post-harvest handling (like sorting & distillation, grading; packaging, storage & marketing); production schedule and finally its utilization.

Choice of genotypes: Graven et al. [134] demonstrated that by selecting superior genotypes from the wild and cultivating it, provides major opportunities for the economic advancement of the new crop as the chemical composition in a plant is genetically determined and should not affect when cultivated. The thujone content in wild *A. afra* plants varies from 10% to 93% between individual plants. When the mother plant containing 91% thujone was selected and propagated by root cuttings, the results showed that the thujone content of the vegetatively propagated cuttings did not vary by more than 2% over 5 generations of vegetative propagation. The author suggests that the identification of mother plants having the desired chemical composition, coupled with vegetative propagation will retain the desired genetic characteristics, and facilitate the development of superior clones for cultivation. In this manner, clones can be developed which exceed the minimum standards for the active ingredients as required by the phyto-medicinal and essential oil industries.

Socio-economic impact: A study by team of Wiersum et al. [135] was carried out in the Amatola region of Eastern Cape, South Africa,
to assess whether cultivation of medicinal plants can serve as a tool for combined biodiversity conservation and poverty alleviation. The natives were found to use more than 100 plants, of which over 50 species were found to be cultivated in the home gardens. A. afra topped in the cultivation frequency list standing at 40%. The authors conclude that cultivation of medicinal plants play a significant role in the maintenance of cultural identity, increased human capital and dignity by alleviating poverty. However, one should not be too optimistic about the scope of medicinal plant cultivation by poor people as a practical strategy for in situ conservation of threatened species as (i) the preferred species for cultivation may not necessarily be the most threatened species and (ii) it was still not clear whether such cultivation substitutes the collection of wild species or supplements it.

### Chemical Constituents

There are extensive data showing that the flavonoid synthesis is influenced by different abiotic (geographical variation, UV light radiation, drought, ozone), biotic (phytopathogens, insect deterents) factors [136]. Also, there are human factors like method of cultivation, processing parameters (collection, drying etc.) and extraction techniques that influence the plant constituents both qualitatively and quantitatively. These are discussed in this section.

#### Method of extraction on yield and chemical composition

Asfaw et al. [137] studied the four different methods of extraction viz., (i) hydrodistillation (HD), (ii) microwave assisted extraction (MAE), (iii) ultrasound assisted extraction (UAE), and (iv) liquid/supercritical CO2 extraction (I-CO2 and sc-CO2) to determine its extractive property both in terms of yield and chemical composition from A. afra plant. In general, the essential oil obtained from each method of extraction were similar in appearance - pale colored and fragranced. The details of the components with Kováts indices determined by Gas Chromatography – Flame Ionization Detector (GC-FID) from 900 to 1350 are given in Table 5. The yields were highest with I-CO2 and sc-CO2 (3.2% v/w), followed by traditional HD (1.5% v/w). The lowest yield was obtained with UAE (0.7% v/w). When a comparison of different fractions obtained was made for yogomi alcohol content in the extracts obtained from I-CO2 and sc-CO2, UAE, MAE and HD, it was found to be 0.4%, 0.1%, 3.6% and 8.1% respectively. Eight sesquiterpenes could only be detected in the sc-CO2, I-CO2, and UAE, with relative percentage peak areas of 13%, 16% and 29%, respectively. The differences could be ascribed to the solubility differences or instability of compounds during the different methods of extraction.

#### Method of analysis

To identify 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 [137]. Liu et al. [129] classified and compiled 131 volatile secondary metabolites and 44 non-volatile secondary metabolites from A. afra oil in 4 and 10 categories from 16 and 8 published papers respectively to date and is summarized in the Table 6.

#### Geographical variation

The main components of the volatile secondary metabolites in A. afra varied enormously in plants from different geographical regions. The major constituent in Ethiopian oil [138] was artemisyl acetate (24.4–32.1%) while it was 1,8-cineole (67.4%) in Kenyan oil [139]. In Zimbabwean oil, α- and β-thujone (52%) was the major constituent [140] while α-thujone (54.2%) was in South African oil [141].

Viljoen et al. [142] analyzed the hydro-distilled essential oil by GC-MS obtained from aerial parts of 16 individual A. afra plants collected from four natural population [viz., 3 plants each from Setibeng (Lesotho), Giant’s Castle (KwaZulu-Natal), Qwa-qwa (Free State) and 7 plants from Klipriverberg (Gauteng)] and found that quantitative and qualitative variation within and between natural populations with no correlation to the geographical distribution.

Oyedeji et al. [43] studied the α-thujone content isolated from

<table>
<thead>
<tr>
<th>l&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Compound</th>
<th>Relative peak areas (%)</th>
<th>I-CO&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Sonic&lt;sup&gt;c&lt;/sup&gt;</th>
<th>µ-wave&lt;sup&gt;d&lt;/sup&gt;</th>
<th>HD&lt;sup&gt;e&lt;/sup&gt;</th>
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<tr>
<td>903</td>
<td>Santonolina triene</td>
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<tr>
<td>917</td>
<td>A-Pinene</td>
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<td>-</td>
<td>-</td>
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<tr>
<td>956</td>
<td>Camphene</td>
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</tr>
<tr>
<td>999</td>
<td>Yogomi alcohol</td>
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<td>0.4</td>
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<tr>
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<td>Limonene</td>
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<tr>
<td>1305</td>
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<tr>
<td>13</td>
<td>Sesquiterpenes</td>
<td>13</td>
<td>16</td>
<td>29</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Exponentially determined Kováts indices on the DB-5 column.

<sup>b</sup>scCO<sub>2</sub>: Extraction carried out for 20 min. at 50 °C, 100 bar, liquid CO<sub>2</sub> (at -10 °C) was delivered to the extractor vessel at a constant flow rate of 5 mL min<sup>-1</sup>.

<sup>c</sup>I-CO<sub>2</sub>: Extraction carried out for 20 min. at 30 °C, 100 bar, liquid CO<sub>2</sub> (at -10 °C) was delivered to the extractor vessel at a constant flow rate of 5 mL min<sup>-1</sup>.

<sup>d</sup>Ultrasonic irradiation for 30 min., in diethyl ether at ambient temperature and pressure.

<sup>e</sup>Microwave irradiation for 10 min, at ambient pressure.

<sup>f</sup>Hydrodistillation for 180 min.


Table 5: A. afra components determined by GC-FID analysis.
essential oil obtained by hydrodistillation of twigs of *A. afra* plants obtained from different locations in the Eastern Cape, Free State and KwaZulu-Natal by GC and GCMS. Their analysis revealed compositional variations in the levels of α- and β-thujone, 1,8-cineole and camphor. α-thujone was the major component of the essential oils of *A. afra* from Philippolis (Free State) and Keiskammahoek (Eastern Cape) (62-74%), while the camphor content was very low (≤0.1-0.6%). The samples from Gqumahshe, Hogsback (Eastern Cape) and Empangeni (KwaZulu Natal) had low α-thujone contents (3.7-20.0%) while 1,8-cineole (13.0-49.5%) and camphor (13.9-21.2%) were the main components of the essential oils.

Avula et al. [44] estimated five flavonoids viz., (i) apigenin, (ii) chrysoeriol, (iii) tamarixetin, (iv) acacetin and (v) and genkwanin (Figure 8) by HPLC-UV and HPLC-MS technique to determine flavonoids in the aerial parts of the 11 samples of *Artemisia afra* Jacq. ex Willd plant obtained from widely separated populations in the provinces of Kwa-Zulu Natal and the Western Cape in South Africa. Figure 9 was plotted from the data published by them, which shows that the geographical variation does effect the total % content of flavonoids and the proportions of which varies in almost all samples accordingly for each ingredient, seen by uncrossed curves in the graph. Other details are given in under the heading "Analysis and Quality Control".

**Effect of cultivation**

Chagonda et al. [143] reports the difference in volatile oils obtained from wild and organically cultivated plants of *Artemisia afra* (Jacq.) (Compositae) from two pilot sites in Zimbabwe. The oil yield from the cultivated plant was between 0.33 and 0.60% (v/w), greenish- to brownish-yellow in color. Oils from the two cultivated sites had pleasant but different and distinct odours. The constituents of volatile secondary metabolites obtained by steam distillation were analyzed by GC-MS and are given in Table 7. Analysis of oils from fresh cultivated *A. afra* showed the presence of two chemotypes: one dominated by artemisia ketones (32.1-34.8%), α-copaene/camphor (21.8-24.4%) and 1,8-cineole (10.9-16.9%) and cultivated in Harare, and the other by 1,8 cineole (23.5-28.7%), α-copaene/camphor (20.2-21.3%) and borneol (14.2-17.0%) cultivated in Murehwa. The cineole chemotype had, as other notable minor components, bornyl acetate (1.6-3.3%), β-caryophylene (2.0-5.0%), sabine (0.6-7.9%) and camphene (3.0-

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Component Type</th>
<th>No. of Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Monoterpenoids</td>
<td>83</td>
</tr>
<tr>
<td>2.</td>
<td>Sesquiterpenes</td>
<td>30</td>
</tr>
<tr>
<td>3.</td>
<td>Guianolides</td>
<td>6</td>
</tr>
<tr>
<td>4.</td>
<td>Others</td>
<td>15</td>
</tr>
<tr>
<td>5.</td>
<td>Probably contained compounds</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>131</strong></td>
</tr>
</tbody>
</table>

| 5. | Sesquiterpenes | 1 |
| 6. | Glaucoles      | 7 |
| 7. | Guianolides    | 6 |
| 8. | Others         | 1 |
| 9. | Triterpenes    | 4 |
| 10.| Long chain alkanes | 6 |
| 11.| Coumarins      | 5 |
| 12.| Organic acids  | 1 |
| 13.| Glycosides     | 1 |
| 14.| Flavonoids     | 11 |
| **Total** |               | **43**            |

Table 6: Volatile and non-volatile secondary metabolites in *A. afra*.

Figure 8: Structure of flavonoids from [44].
5.6%). The oil from the semi-dried plant material with the cineole chemotype had a similar pattern in its oil composition to that from the fresh plant and contained 1,8-cineole (22.5-29.3%), borneol (17.9-19.1%) and α-copaene/camphor (6.2-19.9%) as the major components. Bornyl acetate (2.7-4.2%), β-caryophyllene (2.0-2.8%) and camphene (3.4-3.5%) were notable minor constituents. Differences in oil composition were observed between fresh and semi-dried plant material and dry plant material (winter post-harvested collected dry plant B, with the later yielding α-copaene/camphor (50.6%) as the major component.

**Method of drying**

The impact of drying methods on the quantity and quality of the essential oil of *A. afra* was studied by Asekun et al. [144]. The yields of oil from the plant differed according to the drying methods; viz: 0.18 %, 0.88 %, 1.54 % and 1.88 % for fresh, oven-dried, air-dried and sun-dried oils, respectively. They also found that the oil extracted from fresh plants contained artemisia ketone (6.9%) which was absent in the oil extracts obtained from air- and sun dried plants. Extracts from sun-dried plants had 14 components and the lowest number. Oyedeji et al [43], studied the α-thujone content isolated from essential oil obtained by hydrodistillation of fresh and dried twigs of *A. afra* plants by GC and GC-MS and found that the concentration of α-thujone increased significantly in the dry leaves when compared with the fresh leaves.

**Variation between plants**

It is already dealt under the heading “Geographical variation”, that

**Figure 9:** % Content of flavonoids of Apigenin (□), Chrysoeriol (O), Tamarixetin (Δ) Acacetin (▲) and Genkwanin (◊) by HPLC–UV method and Apigenin (■), Chrysoeriol (●), Tamarixetin (▲) Acacetin (▼) and Genkwanin () by HPLC-MS method.

<table>
<thead>
<tr>
<th>No.</th>
<th>Component†</th>
<th>A = wild (A (%) 1996 n = (3))</th>
<th>B = cultivated UZ Farm (B (%) 9/1996 (1))</th>
<th>C = cultivated Murehwa (B (%) 5/97 (3))</th>
<th>C1 (%) 5/97 (1)</th>
<th>C2 (%) 4/98 (2)</th>
<th>C3 (%) 4/98 (1)</th>
<th>C4 (%) (2)</th>
<th>% dry herb C1 (%) (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tricylene</td>
<td>0.1-0.2</td>
<td>tr</td>
<td>0.1-0.2</td>
<td>0.1</td>
<td>0.3</td>
<td>---</td>
<td>tr-0.2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>α-Pinene + α-thujone</td>
<td>0.4-1.1</td>
<td>0.3</td>
<td>0.8</td>
<td>0.5-1.1</td>
<td>0.7</td>
<td>1.3</td>
<td>1.75</td>
<td>0.9-1.1</td>
</tr>
<tr>
<td>4</td>
<td>α-Fenchene</td>
<td>0.2-1.0</td>
<td>1.4</td>
<td>0.6-1.1</td>
<td>0.7</td>
<td>0.4-0.9</td>
<td>---</td>
<td>0.6</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td>Camphene</td>
<td>0.3-3.9</td>
<td>8.0</td>
<td>3.9-4.0</td>
<td>0.6</td>
<td>3.0-3.8</td>
<td>3.0</td>
<td>5.2</td>
<td>5.6</td>
</tr>
<tr>
<td>6</td>
<td>β-Pinene</td>
<td>0.1-0.7</td>
<td>0.4</td>
<td>0.3-0.4</td>
<td>3.7</td>
<td>0.2-0.3</td>
<td>0.3</td>
<td>1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>7</td>
<td>Sabinene</td>
<td>0.1-2.6</td>
<td>0.2</td>
<td>0.3-0.4</td>
<td>0.3</td>
<td>0.2-0.5</td>
<td>7.9</td>
<td>0.6</td>
<td>7.3</td>
</tr>
<tr>
<td>8</td>
<td>Myrcene</td>
<td>0.1-1.0</td>
<td>1.6</td>
<td>0.5</td>
<td>0.3</td>
<td>0.6</td>
<td>1.0</td>
<td>1.1</td>
<td>tr-0.6</td>
</tr>
<tr>
<td>9</td>
<td>α-Terpine</td>
<td>0.1-1.1</td>
<td>0.3</td>
<td>0.3</td>
<td>---</td>
<td>0.2-1.8</td>
<td>0.5</td>
<td>0.3</td>
<td>1.1</td>
</tr>
<tr>
<td>10</td>
<td>Dihydro-1,8-cineole</td>
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<td>0.1</td>
<td>0.7</td>
<td>tr-0.3</td>
<td>0.2</td>
<td>0.7</td>
<td>0.2</td>
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<tr>
<td>11</td>
<td>Limonene</td>
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<td>0.1</td>
<td>0.5</td>
<td>---</td>
<td>0.5</td>
<td>tr-0.6</td>
</tr>
<tr>
<td>12</td>
<td>1,8-Cineole</td>
<td>0.27-9.9</td>
<td>10.7</td>
<td>16.5-16.9</td>
<td>15.7</td>
<td>10.9-15.3</td>
<td>23.5</td>
<td>25.1</td>
<td>28.7</td>
</tr>
<tr>
<td>13</td>
<td>(E)-β-Ocimene</td>
<td>0.1-0.3</td>
<td>tr</td>
<td>0.2</td>
<td>---</td>
<td>tr-1.0</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>14</td>
<td>γ-Terpinolene</td>
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<td>0.7</td>
<td>0.6</td>
<td>---</td>
<td>tr-0.2</td>
<td>1.3</td>
<td>0.2</td>
<td>2.6</td>
</tr>
<tr>
<td>15</td>
<td>p-Cymene</td>
<td>0.3-2.0</td>
<td>0.8</td>
<td>1.0-1.1</td>
<td>1.6</td>
<td>0.6-1.5</td>
<td>1.2</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>16</td>
<td>Terpinolene</td>
<td>0.1-0.5</td>
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<td>0.2</td>
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<td>0.3</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>17</td>
<td>Artemisia ketone</td>
<td>6.3-41.9</td>
<td>0.1</td>
<td>32.1-32.5</td>
<td>34.8</td>
<td>32.1-33.1</td>
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<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>18</td>
<td>Santolina alcohol</td>
<td>3.1-10.1</td>
<td>---</td>
<td>2.5-4.5</td>
<td>8.0</td>
<td>2.7-4.3</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>19</td>
<td>α-Thujone</td>
<td>1.0-2.9</td>
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<td>0.5</td>
<td>0.5</td>
<td>0.2-4.9</td>
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<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>20</td>
<td>Artemisyl acetate</td>
<td>tr-0.1</td>
<td>---</td>
<td>0.5</td>
<td>1.0-0.9</td>
<td>0.1</td>
<td>---</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>21</td>
<td>β-Thujone</td>
<td>tr</td>
<td>---</td>
<td>0.2</td>
<td>---</td>
<td>0.3</td>
<td>0.5</td>
<td>0.5</td>
<td>tr-0.6</td>
</tr>
<tr>
<td>22</td>
<td>cis-Sabinene hydrate</td>
<td>0.2-0.5</td>
<td>0.4</td>
<td>0.1</td>
<td>---</td>
<td>tr-0.2</td>
<td>1.3</td>
<td>0.8</td>
<td>1.3</td>
</tr>
<tr>
<td>23</td>
<td>Artemisia alcohol</td>
<td>tr-0.3</td>
<td>0.1</td>
<td>---</td>
<td>0.1</td>
<td>---</td>
<td>---</td>
<td>0.1</td>
<td>---</td>
</tr>
<tr>
<td>24/25</td>
<td>α-Copaene/Camphor</td>
<td>8.5-27.1</td>
<td>50.3</td>
<td>23.0-23.1</td>
<td>21.8</td>
<td>24.3-24.4</td>
<td>20.6</td>
<td>21.3</td>
<td>20.2</td>
</tr>
<tr>
<td>26</td>
<td>trans-Sabinebre hydrate</td>
<td>1.8-4.4</td>
<td>3.5</td>
<td>0.1-3.5</td>
<td>3.5</td>
<td>3.0-3.7</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>27</td>
<td>cis-p-Menth-2-en-1-ol</td>
<td>0.2-0.4</td>
<td>0.8</td>
<td>0.1-0.2</td>
<td>---</td>
<td>0.1-0.5</td>
<td>1.0</td>
<td>0.9</td>
<td>1.5</td>
</tr>
<tr>
<td>28</td>
<td>Bornyl acetate</td>
<td>0.3-1.5</td>
<td>0.5</td>
<td>0.2-0.3</td>
<td>0.7</td>
<td>0.6-0.7</td>
<td>3.3</td>
<td>1.6</td>
<td>1.8</td>
</tr>
<tr>
<td>29</td>
<td>β-Caryophyllene</td>
<td>0.5-2.3</td>
<td>1.2</td>
<td>0.7</td>
<td>0.4-0.8</td>
<td>5.0</td>
<td>2.0</td>
<td>2.4</td>
<td>2.0-2.8</td>
</tr>
<tr>
<td>30</td>
<td>Terpinene-4-ol</td>
<td>tr-0.1</td>
<td>---</td>
<td>0.1</td>
<td>---</td>
<td>tr-0.1</td>
<td>0.5</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>31</td>
<td>Myrtenal</td>
<td>---</td>
<td>0.1</td>
<td>---</td>
<td>0.6</td>
<td>0.4</td>
<td>0.3</td>
<td>0.3</td>
<td>tr-0.6</td>
</tr>
<tr>
<td>32</td>
<td>trans-p-Meth-2-en-1-ol</td>
<td>0.2-0.3</td>
<td>0.1</td>
<td>---</td>
<td>0.1-0.2</td>
<td>0.4</td>
<td>0.3</td>
<td>0.2</td>
<td>tr-0.3</td>
</tr>
<tr>
<td>33</td>
<td>Not identified</td>
<td>tr-0.1</td>
<td>---</td>
<td>0.1</td>
<td>---</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>
the constituent do vary between two plants.

Variation within plants

The oil obtained from different parts of the same plant showed variation in the constituents [142]. Goodson [24] found camphor, a wax ester, triacontane, scopoletin and quebrachitol in the flowering tops of A. afra. Bohlmann and Zdero [25] revealed that the roots of A. afra contained isomeric coumarins and five acetylenes, while the aerial parts contained thujone and umbelliferone-derivatives and no acetylenes. Similar variations were reported in the volatile secondary metabolite composition between the leaves [139] and the whole plant [140]. The results showed that the oil obtained from the leaves mainly consisted 1,8-cineole (67.4%); while yogomoi alcohol (21.6-26.8%) predominated in the oil extracted from the whole plant.

Activity Reported in the Literature

The scientific research in determining the activity of A. afra for its medicinal properties and the publications thereof are given in this section.

Anti-fungal and anti-bacterial

Recent studies have demonstrated that steam distilled A. afra oil possess antimicrobial [140] properties. The author report that out of 25 bacterial species and three filamentous fungi used to assess the anti-microbial properties, 15 test bacteria and one fungus showed high degree of inhibition of growth caused by volatile oil. The most susceptible organisms were Acinetobacter calcoaceticus, Beneckea natrienges, Brevibacterium linens, Brochothrix thermosphaeta, Citrobacter freundii, Klebsiella pneumonia and Serratia marcescens.

Trypanocidal and cytotoxic

Nibert and Wink [34] studied in vitro effects on antitrypanosomal and cytotoxic activities using T. b. brucei and human leukaemia cell, HL-60 against standard drug diminazene aceturate. The IC50 (concentration at which 50% of the growth of cells is inhibited) and SI (Selectivity Index, which is the ratio of cytotoxicity of drug against HL-60 to its activity against T. b. brucei) for A. afra are given in Table 8.

The biological activity was attributed to the major compounds of the extract viz., epolylinalol (29.10%) and dihydrocostunolide (22.14%) and Artemisia afra for its medicinal properties and the publications thereof are given in this section.

Table 7: Percentage of major constituents in wild and cultivated A. afra.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ-Terpinol</td>
<td>0.1-2.5</td>
</tr>
<tr>
<td>α-Terpinol</td>
<td>0.1-0.7</td>
</tr>
<tr>
<td>1,8-Cineole</td>
<td>67.4%</td>
</tr>
<tr>
<td>Aldehydes</td>
<td>tr-0.5</td>
</tr>
<tr>
<td>Myrtenol</td>
<td>tr-0.1</td>
</tr>
<tr>
<td>Calamene</td>
<td>0.1-0.9</td>
</tr>
<tr>
<td>cis-Carveol</td>
<td>---</td>
</tr>
<tr>
<td>Not identified</td>
<td>---</td>
</tr>
<tr>
<td>trans-Caryophyllene oxide</td>
<td>tr-0.1</td>
</tr>
<tr>
<td>Methyl linolenate</td>
<td>tr-0.1</td>
</tr>
<tr>
<td>Germacrene-D-4-ol</td>
<td>---</td>
</tr>
<tr>
<td>Methyl linolenate**</td>
<td>---</td>
</tr>
<tr>
<td>ρ-Cymen-8-ol</td>
<td>---</td>
</tr>
<tr>
<td>Spathulenol</td>
<td>---</td>
</tr>
<tr>
<td>T-muurolol</td>
<td>tr-0.5</td>
</tr>
<tr>
<td>Intermedeol</td>
<td>tr-0.4</td>
</tr>
<tr>
<td>Not identified</td>
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</tr>
</tbody>
</table>

Table 8: Trypanocidal and cytotoxic activities of artemisinin and crude extract from A. afra.

<table>
<thead>
<tr>
<th>Substance</th>
<th>IC50 (µg/ml)</th>
<th>Selectivity Index (SI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. b. brucei</td>
<td>HL-60</td>
<td></td>
</tr>
<tr>
<td>MeOH Extract</td>
<td>77.54</td>
<td>132.97</td>
</tr>
<tr>
<td>CH2Cl2 Extract</td>
<td>25.27</td>
<td>123.21</td>
</tr>
<tr>
<td>Diminazene aceturate drug</td>
<td>0.088</td>
<td>&gt;128.88</td>
</tr>
</tbody>
</table>

J Pharmacogenomics Pharmacoproteomics, an open access journal
ISSN: 2153-0645
Volume 2 • Issue 3 • 1000105
ethno-medical information in the various locations in the Eastern Cape Province in South Africa consisting of many villages classified as rural and poor in the treatment of diabetes. Their studies revealed that 14 species belonging to six families were frequently used. Plants from the family Asteraceae were most commonly used in the treatment of diabetes constituting 50% of the plant. Infusion of leaves or roots of A. afra was mixed with sugar to mask the bitterness and consumed for a long period on daily basis.

Anti-cancer

The potential of using natural products as anti-cancer agents was recognized by the U.S. National Cancer Institute (NCI) in 1950s and since then been contributing to the discovery of naturally occurring anti-cancer agents [146]. With the discovery of vinca alkaloids, vinblastine and vincristine and isolation of the cytotoxic podophyllotoxins from plant sources in 1950s, more plants were screened for anti-cancer agents. As a result, the US NCI initiated an extensive plant collection program to potentially lead them to the discovery of novel chemotypes showing a range of cytotoxic activities [147] in 1960s. Over 60% of currently used anti-cancer agents are derived in one way or another from natural sources, including plants, marine organisms and micro-organisms [148,149]. However, Cragg & Newman [148] report that there is no plant derived clinical anti-cancer agents as yet reached the stage of approved therapy. A collaborative research programme between US NCI and South Africa Council for Scientific & Industrial Research (CSIR) initially screened 7500 randomly selected plant extracts representing 700 taxa for anti-cancer agents. Several articles have been published on the evaluation of plants for this program [147,150-153]. Several reports indicated the anti-cancer activity against three human cell lines namely breast MCF7, renal TK-10 and melanoma UACC62 and A. afra was one of the 32nd plant extracts to have exhibited potent anti-cancer activity [150]. Further, it was screened against 60 human cancer cell lines organized into sub-panels representing leukemia, melanoma and cancer of the lung, colon, kidney, ovary and central nervous system [31]. The anti-cancer activity for plant extract was labeled moderate when the Total Growth Inhibition (TGI – drug concentration that is indicative of the cytostatic effect of the test agent) was observed in the range of 6.25-15 μgm/mL for at least two cell lines. The DCMI-MeOH (1:1 ratio) A. afra leaf extract had 26.62 μgm/mL, 15.00 μgm/mL and 9.73 μgm/mL for Renal TK10, Breast MCF7 and Melanoma UACC62 cancer cell lines against standard Etoposide as a positive control (Renal TK10: 27.00 μgm/mL, breast MCF7: >100 μgm/mL and melanoma UACC62: 36.20 μgm/mL). A. afra leaf extract was further tested for selective cytoxicity over a defined range of concentrations to determine the relative degree of Growth Inhibition (GI50) against each cell lines namely leukemia (L) lines (CCFR-CEM, HL-60(TB), K-562, MOLT-4, RPMI-8226), non-small cell lung cancer(NSCLC) lines [A549/ATCC, EKVX, HOP-62, NCI-H226, NCI-H23, NCI-H322M, NCI-H460, NCI-H522], colon cancer (CL) lines [COLO205, HCT-116, HT-15, HT-29, KM12, SW-620], central nervous system cancer (CNSC) lines [SF-268, SF-295, SF-539, SNB-19, U251], melanoma (M) lines [LOX IMVI, M14, SK-MEL-2, SK-MEL-28, SKMEL-5, UACC-257, UACC-62], ovarian cancer (OC) lines [IGROV1,OVCA-3, OVCA-5, OVCA-8, SK-OV-3], renal cancer (RC) lines [786-0, A498, ACHN, CAKI-1, SN12C, TK-10, UO-31], prostate cancer (PC) lines [PC-3, DU-145] and breast cancer (BC) lines [MCF7,NCI-ADR-RES, MDA-MB-231/ATCC, HS 578T, MDA-MB-435, MDAN, BT-549]. The log GI50 value for A. afra extract was 1.02 M and the TGI (μgm/mL) for three most active cell lines were 13.49 (NSCLC NCI-H522); 13.49 (melanoma SK-MEL-5); 14.13 (colon HT29). Fouche et al. [31] research group conclude from their study that the leaf extract of A. afra plant to exhibit moderate anti-cancer activity. However, it can provide leads for the development of novel anti-cancer agents.

It is reported that the flavonoids present in the A. afra to have chemo-protective activity against skin cancer (e.g. apigenin); inhibitory effects on chemically induced mammary gland, urinary bladder and colon carcinogenesis in laboratory animals (e.g. hesperetin); and anti-carcinogenic and platelets anti-aggregatory effects (e.g. quercetin) [151,152]. Furthermore, the flavonoid luteolin has been shown to exhibit anti-mutagenic and anti-tumorigenic activities [153].

Cardiovascular

The effect of A. afra Jacq. ex. Wild herb on isoproterenol (ISO)-induced myocardial injury in male albino rats of Wister strain was investigated by Sunmonu and Afolayan [35]. Pretreatment with the aqueous leaf extract of the plant at 100 and 200 mg/kg body weight for 30 days prevented the elevation of serum marker enzymes namely lactate dehydrogenase (LDH), aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) in myocardial injured rats. ISO-induced animals exhibited decreased levels of glutathione reductase (GR), glutathione peroxides (GPx), superoxide dismutase (SOD) and glutathione (GSH) in the heart, which were restored near normal levels following treatment with the herb. The extract also attenuated lipid peroxidation (LPO) in the heart and restored the lipid profile to near normalcy, an improved the atherogenic index. The effect was more prominent at 200 mg/kg body weight. Authors suggest that the aqueous extract of A. afra exerts cardio protective antihyperlipidemic and antioxidant activities by synthesizing endogenous antioxidants in ISO-induced myocardial injury.

Guantai & Addae-Mensah [154] investigated the cardiovascular effects of a mixture of long chain fatty esters (C44H 88O2) and scopoletin isolated from A. afra and an aqueous extract of the plant in rabbits. They found that the long chain fatty esters induced hypotensive effects at doses of 0.5, 1.0, 1.5 and 3 mg/kg. The diastolic pressure was affected more than the systolic. Aqueous A. afra extract (10-45 mg/kg) had a hypotensive effect in vivo and a dose-dependent biphasic effect on the heart in vitro. Lower doses induced an initial cardio-stimulation followed by cardio-depression, whereas higher doses were mainly cardio-depressant. Scopoletin, a coumarin derivative, at a dose of 1.0-2.5 mg/kg, induced a dose-dependent decrease in inotropic activity plus an appreciable decrease in chronotropic effects, especially at higher dose levels. These results suggest that A. afra and its constituents are potentially useful for the management of hypertensive conditions.

Respiratory infections

The synergistic antimicrobial effects of A. afra essential oil when combined with other essential oils obtained from Agathosma betulina, Eucalyptus globulus, and Osmotopsis asteriscoides were investigated by Sulkiman et al. [58] against M. catarrhalis ATCC 23246, K. pneumoniae NCTC 9633, E. faecalis ATCC 29212, C. neoformans ATCC 90112 test organisms by estimating Fractional Inhibitory Concentration using MIC data [155]. The modified version of FIC Index (FIC\_mod)
was adopted from Odds [156] that included an additive interpretation [157,158] were determined using following equations:

$$FIC_{\text{index}} = FIC_I + FIC_{II}$$

where $FIC_I$ and $FIC_{II}$ are calculated as follows

$$FIC_I = \frac{MIC(A + B)}{MIC(A)} = X$$
$$FIC_{II} = \frac{MIC(A + B)}{MIC(B)} = Y$$

where “A” represented $A.~afra$ and “B” represented either $A.~betulina$, $E.~globulus$ or $O.~asteriscoides$.

The data were further evaluated by plotting isobolograms that considered different ratios at which the two plant samples were combined [155] by taking $FIC_I$ and $FIC_{II}$ values as $X$ and $Y$- axes values respectively. The effect of combination of essential oils were considered synergistic ($<0.5$), additive ($0.5-1.0$), non-interactive ($1.0-4.0$) or antagonistic ($>4.0$). The authors report that the individual oils exhibited moderate antimicrobial activity. The MIC values for $A.~afra$, $A.~betulina$, $E.~globulus$, and $O.~asteriscoides$ ranged (2.6–9.3), (6.0–16.0), (1.3–8.0) and (0.6–8.0) mg/mL respectively against the selective pathogens used in the study. The combination proportions of essential oils between $A.~afra$ and other oil was varied from 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 1:9. They also report that their studies did not show any antagonistic interactions but predominantly found additive ($0.5-1.0$) activity. However, combination of $A.~afra$ oil with $O.~asteriscoides$ in 8:2 ratio yielded synergistic interaction with $MIC$ value of 0.5. The authors suggest that additive/synergistic effect of combination of essential oils needs to be substantiated to establish efficacy through clinical studies.

Viljoen et al. [142] studied the effects of geographical variation on $A.~afra$ essential oil content (details discussed under the heading “Geographical variation” of this review) and antimicrobial activity. The antimicrobial activity studies by time-kill methodology using the respiratory pathogens $C.~neoforans$ and $K.~pneumoniae$ showed prominent antimicrobial effect within 10 min at 0.75% concentration for $K.~pneumoniae$ and within 60 min at 1% concentration for $C.~neoforans$. Investigations of the four major compounds most abundant in the $A.~afra$ oil (Artemisia ketone, 1,8-cineole, α- and β-thujone) indicated minimal antimicrobial activity when investigated independently and in various combinations against $K.~pneumoniae$.

To elucidate the rationale behind burning and then inhaling the liberated smoke for its antimicrobial activity, Braithwaite et al. [41] designed an apparatus to simulate the burning process that occurs in a traditional setting and captured the smoke fractions for analysis and bioassay. Parallelly, extracts of MeOH and aceton as well as the essential oil (for the aromatic species) were also prepared and assayed. The anti-microbial studies revealed that the ‘smoke-extract’ obtained after burning had lower minimum inhibitory concentration (MIC) values than the corresponding solvent extracts and essential oils. The combustion, aceton and MeOH extracts produced different chromatographic profiles, wherein several compounds noted in the smoke fraction were not present in the extracts, suggesting that the combustion process produced an ‘extract’ with superior antimicrobial activity and provided in vitro evidence for inhalation of medicinal smoke as an efficient mode of administration in traditional healing.

**Anti-tuberculotic**

To verify the traditional phytotherapeutic usefulness of $A.~afra$ extracts in tuberculosis, Ntutela et al. [159] investigated if $M.~aurum$ and $M.~tuberculosis$ replication could be controlled. The authors used aqueous-, MeOH- and DCM extracts of $A.~afra$ and found that the bacterial replication was inhibited in the $M.~aurum$ cultures by DCM extract only. Activity of the DCM extract was confirmed in dose-dependent studies against both $M.~aurum$ and $M.~tuberculosis$ with an IC$_{50} = 270~\mu g/mL$ and IC$_{50} = 290~\mu g/mL$, respectively. Fractionation of the DCM extract and evaluation of its in vitro antymycobacterial activity was found to be mostly associated with isolate fraction C8 that contained several sesquiterpene lactones, the most prominent of which were Artemin and Arsubin. Evaluation of the bactericidal efficacy in vitro showed that isolate fraction C8 reduced replication of $M.~aurum$ and $M.~tuberculosis$ in a dose-dependent manner with IC$_{50} = 1.9~\mu g/mL$ and IC$_{50} = 2.0~\mu g/mL$, respectively, and an MIC = 10 mg/mL. Further, isolate fraction C8 and the DCM extract were administered to $M.~tuberculosis$-infected mice at a tolerated dose of 1000 mg/kg for up to 26 weeks and mycobacterial burdens compared to untreated-, INH/RIF treated- and aqueous-extract-treated animals to assess its in vivo bactericidal activity. Bacterial replication remained unaffected during treatment with either isolate fraction C8 or the DCM extract resulting in pulmonary and splenic bacilli burdens comparable to that of untreated mice. In contrast, INH/RIF (Isonicotinicot Hydradize / Rifampin) treatment cleared $M.~tuberculosis$ infection after only 8 weeks to undetectable levels. Interestingly, treatment of $M.~tuberculosis$-infected mice with aqueous extract of $A.~afra$ regulated pulmonary inflammation during early infection notwithstanding its inability to inhibit mycobacterial growth. Their study clearly demonstrated that $A.~afra$ contains in vitro anti-mycobacterial activity, modulated pulmonary inflammation in early mycobacterial infection, and that the mouse experimental tuberculosis model could serve as a useful assay for evaluating the utility of phytotherapy. Studies carried out by Mativandelela et al. [32] also supported the traditional use of $A.~afra$ in TB-related symptoms. The MIC against $M.~smegmatis$ were in the range of 0.781 to 6.25 mg/mL.

**Anti-malarial**

$A.~afra$ has been used as an infusion to treat malaria in the southern parts of Africa. Clarkson et al. [160] studied 134 species of plants native to South Africa representing 54 families for in vitro anti-plasmodial activity against $P.~falciparum$ strain D10 using the parasite lactate dehydrogenase (pLDH) assay to identify the potential sources of new antimicrobial. Of the species assayed, 49% showed promising anti-plasmodial activity (IC$_{50} \leq 10~\mu g/mL$) while 17% were found to be highly active (IC$_{50} \leq 5~\mu g/mL$). The IC$_{50}$ value for $A.~afra$ leaf extract in (i) DCM, (ii) DCM/MeOH (1:1), (iii) MeOH and (iv) Water were 5, 7.3, 8 and >100 indicating non-polar solvent DCM extract to have highest activity against the $P.~falciparum$, substantiating the activity reported earlier by Kraft et al. [161]. Liu et al. [162] investigated the antiplasmodial activity of various extracts of $A.~afra$ and $A.~annua$ including an ethnopharmacological prepared sample by using multivariate data analysis. The extracts were tested for activity against $P.~falciparum$ 3D7 (chloroquine-sensitive strain) with chloroquine, quinine and artemisinin as positive controls. The apolar fractions of both $A.~afra$ and $A.~annua$ showed activity against $P.~falciparum$.
while activity were only found in the tea infusion of A. annua. The authors concluded that there aren’t any in vitro activity in the tea infusion (polar extract) of A. afra. Similar conclusions were found by Kraft et al. [160] with lipophilic extracts (apolar) of the aerial parts of A. afra in the in vitro studies. The A. afra extract were found to be most active against the chloroquin-sensitive strain PoW and against the chloroquine-resistant clone Dd2 of P. falciparum when evaluated with Cussonia spicata (Araliaceae), Vernononia colorata, V. natans (Asteraceae), Parinarium curatellifolia (Chrysobalanaceae), Cluitia hirsuta, Flueggea virosa, (Euphorbiaceae), Adenia gummifera (Passifloraceae) and Hymenodictyon floribundum, (Rubiaceae). Bioassay-guided fractionation of the extract of A. afra yielded seven flavonoids, of which acacetin, genkwanin and 7-methoxyacacetin showed in vitro activity; the IC50 values ranged from 4.3-12.6 µgm/mL. In addition, several sesquiterpene lactones could be obtained from the most active fractions. Whereas eudesmaafraglaucolide proved to be inactive, the guaianolides 1-desoxy-1α-peroxy-rupicolin A-8-O-acetate, 1αlpha, 4αlpha-dihydroxybishopsolicepolide and rupicolin A-8-O-acetate revealed in vitro anti-plasmodial activity.

Anti-spasmodylic

Mulatu and Mekonnen [163] tested the ethanol and aqueous extracts of A. afra and leaf of A. rehan (from powdered dried leaf and root) isolated mouse duodenum (MD) and guinea pig ileum (GPI). They tested different concentrations of each extract of the plants ranging from 20-200 µgm/ml in the presence of agonist control, acetylcholine (in MD) and histamine (in GPI) as contraction stimulants. They conclude that A. afra leaf ethanol (ALE) and A. rehan leaf ethanol (RLE) significantly reduced both spontaneous rhythmic and agonist-induced contractions of MD and GPI. ALE and RLE caused mean contractile response of 44.3 (±0.9% at a dose of 160 µgm/ml) and 35 (±2.7%) respectively at maximal doses of 200 µgm/ml in isolated GPI; thus justifying the traditional use of these plants in stomach pains and intestinal cramps.

Anti-histaminic and narcotic analgesic

A. afra has been reported to contain anti-histaminic and narcotic analgesic effects [53,124].

Anti-oxidant

The volatile oil from A. afra is shown to have exerted considerable anti-oxidative effect [140]. The anti-oxidant activity of the oil in preventing the discoloration of β-carotene and linoleic acid is given in the Monograph [124]. The free radical ‘OH scavenging of the environmental isolates identified as C. albicans ATCC 27853; C. albicans ATCC 10231; A. niger ATCC 16404 and two environmental isolates identified as P. aeruginosa and R. pickettii by Challenge Test. The concentration of essential oils in aqueous cream was 0.5, 1.0 and 1.5% v/w of individual oil as sole preservative and the control cream contained commercial preservative. Their studies show that the antimicrobial property of essential oils in the test creams in all the three concentrations were better than the control cream except P. incana which were almost similar to that of control cream. The Challenge Test in almost all test creams showed log10 reductions within 24 hrs, two to three log10 reductions in 2 days and four log10 within 2-7 days, suggesting their use as natural cosmetic preservatives.

Preservative

Preservation of any product is an important integral part of product development. Generally, a combination of preservatives is used for wide spectrum antimicrobial activity. Use of natural plant products is generally considered to be safe in comparison to synthetic preservatives. The preservative use of aromatic essential oils in part or full in cosmetic preparations not only prevents the product from microbial spoilage but also enhances dermato-cosmetic properties [164]. Muyima et al. [165] evaluated the preservative capabilities of the essential oils obtained from A. afra and others viz., P. incana, L. officinalis and R. officinalis in aqueous cream by Challenge Test against seven micro-organisms namely E. coli ATCC 35218; S. aureus ATCC 2592; P. aeruginosa ATCC 27853; C. albicans ATCC 10231; A. niger ATCC 16404 and two environmental isolates identified as P. aeruginosa and R. pickettii by Challenge Test. The concentration of essential oils in aqueous cream was 0.5, 1.0 and 1.5% v/w of individual oil as sole preservative and the control cream contained commercial preservative. Their studies show that the antimicrobial property of essential oils in the test creams in all the three concentrations were better than the control cream except P. incana which were almost similar to that of control cream. The Challenge Test in almost all test creams showed log10 reductions within 24 hrs, two to three log10 reductions in 2 days and four log10 within 2-7 days, suggesting their use as natural cosmetic preservatives.

Ashebir and Ashenafi [166] assessed the in vitro antibacterial activity of A. afra leaves traditionally used in the food borne diseases. The growth or inhibition of micro-organisms like B. cereus, S. aureus, S. boydii, S. flexineri, S. typhimurium and E. coli were determined in culture media using 5% weight by volume crude extract of A. afra leaves in distilled water. Their results showed that B. cereus and S. aureus had markedly lower final counts in the media containing crude preparation when compared to Control (without the crude extract). Retarding effect were noted on S. Flexineri and S. Boydii in the initial stages. The counts of S. typhimurium were as low as one log unit against the Control until eight hours while it had no effect on E. coli. Hence, the authors suggested of taking extract at four hours intervals to enhance the anti-microbial effect.

Insecticide

The volatile oil obtained from the ground parts of the crop showed antimicrobial activity against various bacteria and fungi of public health or agricultural significance [124]. A. afra is also known to have good insecticidal properties and can be used as a companion plant to reduce pest pressure on crops. It is planted as a border plant surrounding other medicinal or vegetable plants. It is used in formulations for animal shampoos and insect repellents [124].

Analysis and Quality Control

Avula et al. [44] developed a simple and specific High Performance Liquid Chromatography (HPLC) technique to determine flavonoids viz., (i) apigenin, (ii) chrysoeriol, (iii) tamarixetin, (iv) acacetin and (v) genkwanin (Figure 8) in the aerial parts of the 11 samples of Artemisia frigida Jacq. ex Willd plant obtained from widely separated populations in the provinces of Kwa-Zulu Natal and the Western Cape in South Africa. They also validated the technique for accuracy and precision before undertaking quantitative analysis. The limits of detection (LOD) by HPLC-MS were found to be 7.5, 7.5, 10, 2.0, and
the dose preparation and administration methods are made.

Profiles to that of loose leaves, but could be still used if adjustment in the (i) tea bag were a suitable dosage form for evaluated the dosage form criteria. He concluded from his studies that from the freeze-dried aqueous extract to minimize dose variation and could be manufactured from the dried extract of very hygroscopic. However, tablets of suitable pharmaceutical quality that the dried aqueous extract of tablets from South Africa in an attempt to develop a pharmaceutically acceptable progress that would be made public with filing of the patent for product possibility to hope that some parallel ongoing synthetic work is in full

Table: A. afra leaves were problematically standardized dried leaves and A. afra leaves and A. afra " herbal preparation for asthma. The protocol was designed to test the bronchodilatory effect of the herbal plant Artemisia afra was prepared to undertake clinical study to evaluate the efficacy and safety of A. afra" herbal preparation for asthma. The protocol was designed after incorporating various aspects given in the Guidelines of different Countries including WHO by thoroughly going through the Guidelines available on the web between Feb. to Aug. 2003. They submitted the Protocol to the Medical Control Council and Ethics Committees which was rejected on account of lack of safety data, toxicological studies and pharmacokinetics of the drug. The researchers however feel that permission to undertake clinical study should be considered on the basis of historical use of herb to circumvent the issue of lack of safety data. In this context, it is pertinent to mention the recent efforts made at global level in the direction of conduct of Clinical Trials so as to prevent the patients from self-medication with unregulated products raising number of safety concerns that exists for lack of specific Guidelines to conduct Clinical Trials in herbal/traditional medicines. As per the Innovations Report [172], world’s first clinical study on
African traditional medicine will be undertaken by The International Center for Indigenous Phytherapy Studies (TICIPS) in collaboration with the University of Missouri-Columbia and the University of the Western Cape, South Africa. The center will be funded by a $4.4 million, 4-year grant from the National Center for Complementary and Alternative Medicines (NCCAM), a division of the National Institutes of Health. On the 7th International Clinical Trials Day 2011, a Multi-disciplinary University Traditional Health Initiative (MUTHI) which is new international consortium with the aim of increasing the capacity of African clinical and public health researchers to conduct trials of traditional medicines was launched by Prof. Quinton Johnson, Director of the South African Herbal Science and Medicine Institute at the University of the Western Cape outlining its plans to facilitate the assessment of the medicinal properties of plants [173]. With an intensity of “one-world medicine” for the sake of all patients in industrialized and developing countries, Effther [174] discussed strategies for (i) preservation of traditional knowledge on natural medicines, (ii) sustainability of medicinal herbs and natural products, and (iii) standardization and quality control.

**Conclusion**

From the available literature, it can be stated that *A. afrains* is a potential herb showing activity for many ailments. The capabilities that Mother Nature has imbibed in this plant has been only attempted and explored in past few years, needs to be accelerated in all the areas so that successful products are available for mass consumption to alleviate diseases afflicting mankind. This review is a humble effort to compile the existing literature in one paper, covering maximum aspects of *A. afrains* with a hope to benefit the researchers.

**Acknowledgements**

Gayathri V. Patil acknowledges Prof. J. K. Lalla for the constant motivation, moral support and guidance. Authors express their thanks to Dr. S. C. Jindal, Librarian, Central Science Library, University of Delhi, Delhi 110007 for the cooperation.

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