The Potential Medicinal Benefits of the *Artemisia* Genus

Word Count: 5460
Table of Contents

Abstract____________________________________________________pg. 3

Introduction____________________________________________________pg. 4-6
  Traditional Medicine__________________________________________pg. 4
  The Genus Artemisia__________________________________________pg. 5-6

Artemisia annua L.________________________________________________pg. 7-15
  General Facts and Traditional Uses______________________________pg. 7
  Biological Activity____________________________________________pg. 7-12
  Clinical Trials________________________________________________pg. 12-13
  Toxicity_______________________________________________________pg. 13-14
  Prospects____________________________________________________pg. 14-13

Artemisia herba-alba Asso.________________________________________pg. 16-20
  General Facts and Traditional Uses______________________________pg. 16
  Biological Activity____________________________________________pg. 16-19
  Clinical Trials________________________________________________pg. 19
  Toxicity_______________________________________________________pg. 19
  Prospects____________________________________________________pg. 20

Artemisia afra Jacq.______________________________________________pg. 21-24
  General Facts and Traditional Uses______________________________pg. 21
  Biological Activity____________________________________________pg. 21-23
  Clinical Trials________________________________________________pg. 23
  Toxicity_______________________________________________________pg. 24
  Prospects____________________________________________________pg. 24

Conclusion____________________________________________________pg. 25-26

Acknowledgements______________________________________________pg. 27

References______________________________________________________pg. 28-35
Abstract:

This report looked at the most medicinally important species in the *Artemisia* (Asteraceae) genus, to determine the potential medicinal benefits of the genus as a whole. The aim of the report was to provide a solid foundation of knowledge, to facilitate and encourage research into this promising group of organisms. The traditional uses, biological activities, as well as any clinical trials and future prospects, of *Artemisia annua*, *A. herba-alba* and *A. afra* were outlined by compiling the known information on these three. The focus was on the anti-malarial and anti-cancer properties of *A. annua*, as they have been researched and understood the best, allowing insight into mechanisms common to the genus. In the end it was determined that the potential of the genus for future plant-based medication is significant. Potential research into other members of the genus could include areas such as parasiticidal, fungicidal and bactericidal activity, immune-modulatory effects, and anti-cancer properties. The promising anti-diabetic effects of *A. herba-alba* are of interest too, and testing for similar activity in other species of the genus may be fruitful. The current interest in *A. afra* and the new research effort, The International Center for Indigenous Phytotherapy Studies, will result in more data on these traditional herbs in the near future, promising interesting things to come.
Introduction

Traditional Medicine

‘Traditional Medicine’ as defined by WHO as ‘The sum knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures that are used to maintain health, as well as to prevent, diagnose, improve, or treat physical and mental illnesses’ (Anon a, 2008) includes the use of plants to cure a variety of afflictions and is common practice throughout a variety of cultures which don’t have easy access to western medicine such as in Africa and South America (Ernst, 2000). Before the advent of contemporary orthodox medicine, the western world was also reliant on herbal treatment (Ernst, 2000). Archaeologists have found evidence in 65000 year old Neanderthal burials of medicinal plant pollen in the wounds (Galanti, 2008). Even chimpanzees have been shown to ingest a variety of medicinal herbs to fight parasites (Wrangham, 1996). Many contemporary drugs are based on simple extracts from plants such as atropine from the deadly nightshade, Atropa belladonna (Turkington & Mitchell, 2010). According to WHO, 80% of the world’s population uses herbal or plant-based medicine as their primary form of healthcare treatment (Anon a, 2008). Herbal treatment even forms an integral part of the healthcare system in China (Barnes et al., 2007). Despite these worldwide acknowledged medicinal benefits, herbal treatment is confined to the realm of alternate and complementary medicine in the western world (Cumming et al., 2007). The Artemisia genus in particular is used frequently in traditional medicine, even though it has much promise for proven medicinal benefits.
Artemisia Genus

Many plants from the *Artemisia* genus are used throughout different cultures as traditional medicine (Willcox, 2009). The genus’ name is derived from the Greek goddess Artemis who gave artemisian plants to Chiron the Centaur (Wright, 2002). *Artemisia* is one of the largest genera in the family of the Asteraceae and also one of the most widely distributed (El-Sahhar, 2010). There are a total of over 300 species, with the majority located in China (150 species), ex-USSR (174 species), and Japan (50 species) (Wright, 2002). The number of species in Europe totals 57 species (Stach et al., 2007). *Artemisia ssp.* are often aromatic herbs or low shrubs (Wright, 2002). The *Oxford Dictionary of Plant Sciences* states the following common morphological characteristics of the genus: “Leaves that are alternate, and much divided pinnately into narrow segments. The flower heads are tiny, usually numerous, often woolly, and gathered into racemes or panicles. The receptacle is flat and naked, and all the florets are tubular and surrounded by overlapping, scarious-edged bracts. There is no pappus.” (Allaby, 2006), see Figure 2.

Taxonomically, *Artemisia* species have been divided into sub-genera and sub-species according to morphological cues, however molecular studies have revealed inconsistencies which may lead to a revision of the classification in the future (Wright, 2002). *Artemisia* species serve a variety of uses such as as ornamental decoration, flavoring, perfume, and of course as medicinal plants (Wright 2002). The most well-known artemisian species is *Artemisia annua*, having made headlines a few years ago as a completely novel treatment for malaria (Anon b, 1998), see Figure 1. The battle against malaria was getting harder as resistance to new drugs developed at accelerating speeds, but...
then *Artemisia annua* was discovered has been used until now, with resistance reports having been minimal due to it being administered in combination with a different drug (Ringwald, undated). The main aim of this report is to outline different *Artemisia* species in order to concentrate all available medicinal information to facilitate research into this genus which may hold a variety of other herbs which may prove to be as useful as *A. annua*. This report will cover the medicinal properties of some of the more important species in the genus and discuss the implications of these on the potential medicinal properties of the genus as a whole.
**Artemisia annua L.**

**General Facts and Traditional Uses**

The first species that will be covered in this report is *Artemisia annua*, this being due to its current status of a medically very important *Artemisia* species. It is a species indigenous to Asia, specifically from China (Anderson, 1984), see Figure 3. Traditionally having been used in Traditional Chinese Medicine (TCM), the conditions that it supposedly cures are ‘heat syndromes’ such as chills or fevers, with malaria falling into the latter category (Wright, 2002). Other medicinal uses for *A. annua* include treatment for hemorrhoids (Ferreira & Janick, 2009), leukemia, melanoma, neonatal jaundice, for immunosuppression, and as an anti-bacterial, anti-parasitic, antioxidant and as an antiviral (Anon c, undated).

**Biological Activity**

The best researched biological activity of *A. annua* is its malaria action, which is due to *A. annua*‘s main biological compound ‘artemisinin’(Lackie, 2010). Artemisinin and its various derivatives such as artemether, dihydroartemisinin, and artesunate, see Figure 5, are all sesquiterpene lactones (Cui & Su, 2010). They all act in radically different ways to pre-existing malarial drugs, resulting in their importance in treating *Plasmodium* strains which are resistant to other drugs, such as quinine (Meshnick, 2002). It is very fast acting, with clinical responses being visible after minutes, and is
effective against virtually all malaria stages (Cui & Su, 2010) except for the primary and dormant liver stages (Seth & Seth, 2009), see figure 4 for the lifecycle of the malaria parasite.

The main drawback of artemisinin is its short half-life which excludes it from being used for prophylaxis (Cui & Su, 2010).

Even though a lot of research has gone into elucidating the mode of action of artemisinin, it is still not clear, and many controversies about its action have surfaced (Neill, 2011). The mode of action which is most widely accepted is centered on the reactive peroxide bridge (Meshnick, 2002), the latter, after having been removed experimentally, strips artemisinin of its anti-malarial properties (Krishna et al., 2004). See Figure 5 for the peroxide bridge being present in all derivatives. It is thought that artemisinins after becoming activated, exhibit an opening of their ring structure, exposing the peroxide bridge which generates carbon-centered free radicals or reactive oxygen species (ROS).

Figure 4. Showing the lifecycle of the *Plasmodium* parasite. All stages in the human host are susceptible to artemisinin, except for hypnozoites (dormant liver stages) and the primary liver stages which are seen in the hepatic cell above.

[sciedirect.com/science/article/pii/S0378111910002933]

Figure 5. Showing the structure of artemisinin and some derivatives. Notice the peroxide bridge present in all of them. [www.scielo.br]
(Zhang et al., 1992). These modulate oxidative stress in the parasite and lower antioxidant and glutathione levels (Cui & Su, 2010). Two mechanisms for the activation of artemisinin have been proposed, the first being dependent on haem and the second on carbon centered free radicals (Krishna et al., 2004). See Figure 6 for a diagram of both mechanisms and their pathways of causing the ring opening.

The free radicals formed then proceed to alkylate close-by cells, such as the parasitized red blood cells (Krishna et al., 2004). This alkylation when done in vitro with synthetic alkyl agents was shown to need higher concentrations compared to those generated in normal medication with artemisinin (Cui & Su, 2010). This indicates that the free radicals released during in vivo administration must act in a selective way, but where this selectivity stems from is as yet poorly understood (Wu & Liu, 2003). Currently there have been no major reports of resistance to artemisinin, but individual cases of ineffective treatment are surfacing in India (Anon d, 2011) and Cambodia (Denis et al., 2006), having

**Figure 6.** Showing two proposed pathways of how artemisinin becomes activated: a) through ferrous haem, b) through the heam losing the second C-4 radical 16 (Krishna et al., 2004). [http://archives.who.int/eml/expcom/children/Applications/REF8.pdf]
prompted research into possible mechanisms of resistance in mosquitoes (Cui & Su, 2010).

Artemisinin is only administered as ACT (Artemisinin Combination Therapy) which is artemisinin in combination with a different anti-malarial which has a longer half-life and is sometimes, in P. vivax infections, complemented with primaquine which is effective against hypnozoites, the dormant liver stages (Bassat, 2011); overall greatly reducing the risk of resistance developing.

Beside the anti-malarial properties described above, A. annua also exhibits a variety of other medicinal benefits which have been discovered and elucidated in part thanks to its use as an anti-malarial. The most important and promising is its induction of apoptosis in human cancer cells (Singh & Lai, 2004). Artesunate, a derivative of artemisinin, was tested against 55 cancer cell lines of the Developmental Therapeutics Program of the National Cancer Institute, US, which showed that artesunate was effective at comparable concentrations to commercially available cancer drugs (Efferth et al., 2001). The anti-tumor action stems from the endoperoxide bridge, similar to the parasiticidal action, with experiments having shown that the anti-tumor action is one-fiftieth or less of its natural action after the endoperoxide bridge had been removed (Mercer et al., 2007). The remaining action must be due to an alternative mechanism (Beekman, 1998), but it is as of yet poorly understood. The anti-tumor action is dependent on iron, apparent in iron-preloaded cells experiencing a 100-fold increase in artemisinin cytotoxicity (Lai et al., 2005). This also explains the high specificity for tumor cells: these express significantly higher amounts of transferrin receptors compared to non-cancerous cells to sustain the increased metabolic activities, resulting in high iron concentrations and hence high susceptibility to artemisinin and its derivatives (Crespo-Ortiz & Wei, 2012). The specific mechanism by which it actually damages the tumor cells is still being debated on, a variety of mechanisms having been proposed, see Figure 7. Oxidative stress induced in cancer cells through ROS is a common anti-cancer mechanism due to cancer cells’ low concentrations of antioxidants, causing artemisinin-generated ROSs to generally be seen as the main anti-cancer agents (Crespo-Ortiz & Wei, 2012). It is possible that it is not just one of the mechanisms in Figure 6 but rather a combination of them which is responsible for the anti-cancer properties of the artemisinin
family. This in turn enhances their prospects for treating drug-resistant tumors and lowers the chance of the tumors developing resistance to them through mutations (Efferth, 2005).

![Figure 7](http://www.hindawi.com/journals/jbb/2012/247597/fig2/)

**Figure 7.** Showing possible anti-cancer mechanisms postulated for artemisinin derivatives:
(a) Activation of artemisinin in endosome through transferrin-released-iron causes lysosomal disruption and ROS release resulting in cell death (Crespo-Ortiz & Wei, 2012).
(b) Specific binding of heme to artemisinin inside the mitochondrion may generate carbon-centered radicals which interfere with the electron transport chain causing apoptosis.
(c) The ROS may cause endoplasmic reticulum stress leading to calcium deficiency and following that to apoptosis (Li et al., 2009).
(d) Alternatively, the ROSs may cause DNA damage leading to cell death.

Beside its anti-cancer and antimalarial activity, *A. annua* has also been demonstrated to have a variety of other medicinal benefits, such as to treat a *Schistosoma* infection (Utzinger et al., 2010). Oral ingestion of artemisinin has also been found to act as a potent anti-inflammatory in severe inflammatory conditions (Shakir et al., 2011). Artemisinin and its derivatives have also demonstrated antibacterial activity against gonococci and anaerobic bacteria (Shoeb et al., 1990). A study which induced sepsis in mice found artemisinin to provide protection by reducing serum concentration
levels of tumor necrosis factor alpha and when given in conjunction with unasyn, an antibacterial consisting of ampicillin sodium and sulbactam sodium (Chen et al., 1992), reduced mortality rates from a lethal *Escherichia coli* infection from 100% to 33.3% (Wang et al., 2006). Further investigations into these antimicrobial effects found artesunate to be synergistic with β-lactam antibiotics against *E. coli* by inhibiting a multidrug efflux pump system AcrAB-TolC (Li et al., 2011). In addition to these, artemisinin has been proven to exert potent antiviral activity against a variety of different viruses, inhibiting hepatitis B and C, bovine viral diarrhea virus, and *Herpesviridae* viruses including human cytomegalovirus (Efferth et al., 2008). Recent findings indicate artesunate is 10-times as effective in treating human cytomegalovirus compared to artemisinin (Chou et al., 2011). It is especially effective in treating therapy-resistant mutants, and it displayed a synergistic effect with the current anti-viral of choice, maribavir (Chou et al., 2011).

**Clinical Trials**

Many clinical trials have been done to examine the antimalarial properties of artemisinin such as one including 2352 patients infected with *Plasmodium falciparum* or *P. vivax* which all recovered rapidly after being administered artesunate, intramuscular artemether, dihydroartemisinin tablets or artemisinin suppositories (Li et al., 2004). Early clinical trials date back to 1991 where artemisinin was tested against multi-drug resistant *Plasmodium* strains in Thailand and proved to be 90-100% effective (Bunnag et al., 1991). Erah et al. have recently reviewed all clinical trials for antimalarials published between 2005 and 2009, a total of sixty-two, and have found that even with some resistance to artemisinin arising in remote areas, it remains the best choice of treatment for uncomplicated malaria (2010).

Different analogs of artemisinin have been used in some human clinical cases to treat for cancer, such as artemether having successfully treated pituitary macroadenoma (Singh & Panwar, 2006). Artesunate not only reduced a laryngeal squamous cell carcinoma by over 70% in two months (Singh
& Verma, 2002), but also stabilized a progressing stage IV uveal melanoma (Berger et al., 2005). A large scale clinical trial involving 120 patients suffering from advanced non-small cell lung cancer showed a 13% increase in 1-year survival rates in patients treated with chemotherapy of vinorelbine and cisplatin in conjunction with artesunate compared to patients treated with only the chemotherapy and a placebo(Zhang et al., 2008). The patients on artesunate also showed a significant improvement in disease progression and control (Zhang et al., 2008). Two other notable clinical trials assessing the anti-cancer properties of artemisinin derivatives include a UK trial which was completed in 2011 about colorectal adenocarcinoma being treated with artesunate for which no results were published (Crespo-Ortiz & Wei, 2012) and an ongoing German trial into the use of artesunate to treat advanced breast cancer (Crespo-Ortiz & Wei, 2012).

A variety of small scale clinical trials have been performed to test the effect of artemisinin and its analogs’ effects on Schistosoma infections, finding a 25% reduction of adult Schistosoma haematobium helminthes following a treatment of artesunate and a 61% reduction with an ACT treatment of artesunate-mefloquine which also reduced eggs by 96% in a study of 83 patients (Keiser et al., 2010). Another small scale clinical trial found an astonishing 92.6% cure rate and 95% reduction in excreted eggs in 27 children infected with S. haematobium who were treated with either sulfadoxine/pyrimethamine and artesunate or with amodiaquine and artesunate (Boulanger et al., 2007). Two large scale clinical trials involving 392 and 106 patients however found much lower cure rates of 44% and 14% respectively (Utzinger et al., 2010)(Obonyo et al., 2010).

Toxicity

Tests of the toxicity of artemisinin in pregnant rats has been tested for at different doses for both early pregnancies (7-13 days) and late pregnancies (14-20 days), results showing significant decreases in maternal testosterone and progestagens which caused high percentages of post-implantation losses (Boareto et al., 2008). Significant toxicity has been found in various animal trials including the
previously mentioned embryotoxicity, but also neuro-, geno-, hemato-, immuno-, cardio-, and nephrotoxicity (Efferth & Kaina, 2010). Long-term low-concentration exposure to artemisinin due to intra-muscular injections was significantly more toxic than short-term high-concentrations which had no side-effects (Efferth & Kaina, 2010).

**Prospects**

ACTs have already become the first line of defence for malaria in most parts of the world, but research into artemisinin is ongoing and accelerating. Recently a new continuous-flow synthetic procedure for artemisinin has been developed in Germany which will allow the synthesis of artemisinin to be both cheaper and easier (Halford, 2012), being able to produce 2000 grams a day with the reactor which may cost as little as $10000 (Kupferschmidt, 2012). The shortcomings of artemisinin, high recrudescence and relapse rates due to not killing primary liver stages and hypnozoites of *Plasmodium,* seem to be dealt with soon as a new combination-therapy including curcumin has been found to protect from relapses and recrudescence by activating a TLR2-mediated immune response resulting in anti-parasite antibodies being produced (Vathsala et al., 2012).

Artemisinin and its derivatives show a lot of promise as anti-cancer drugs, with artemether, artesunate and dihydroartemisinin all being licensed for therapeutic use in cancer therapy (Crespo-Ortiz & Wei, 2012). Due to their specific anti-cancer mechanisms and molecular targets not yet having been fully elucidated, artemisinins hold much potential for discovery and improvement in their already significant anti-cancer properties. Research is ongoing and the near future will hold much advancement in this area.

The efficacy of artemisinin and its derivatives to treat schistosomiasis as combination therapies is low compared to that of praziquantel (Utzinger et al., 2010), but it does seem promising for countries which have both a high malaria and a high schistosomiasis burden, as its use may have a double benefit in that scenario (Obonyo et al., 2010). The ambiguous clinical trial results are also open for
further investigations: the high cure rates of the small scale clinical trials are unlikely to be attributed solely to chance. There is a need for further clinical trials testing a variety of other ACT combinations, as the large scale trials were limited to sulfalene and pyrimethamine (Utzinger et al., 2010).

The potential uses of artemisinin in supporting treatments of sepsis are inspiring, however research in this area is small and much is still to understand and elucidate. On the other hand, the possibility of an ACT-style antibiotic of artesunate combined with β-lactam antibiotics may fuel research in this area, especially due to the recent surges of drug-resistance in *E. coli* (Yu, 2011).
**Artemisia herba-alba** Asso.

**General Facts and Traditional Uses**

*Artemisia herba-alba*, commonly known as white wormwood or desert wormwood, is an artemisian species found in the steppes of the Middle East (Mohamed et al., 2010), with a characteristically whitish appearance, see Figure 8, hence the common name. As is common with artemisian species, *A. herba-alba* has been used extensively as a traditional medicine to cure a variety of conditions, including toothache, intestinal and respiratory diseases, enteritis, and diabetes mellitus (Wright, 2002). Other traditional medicinal uses described include administration as an antibacterial, analgesic, and antispasmodic herbal tea (Laid et al., 2008), to treat for arterial hypertension (Ziyyat et al., 1997) and to kill ascaris worms (Mohamed et al., 2010).

**Biological Activity**

Research into *A. herba-alba* has elucidated and discovered a variety of statistically significant medicinal benefits, such as moderate anti-oxidant levels which, in rats, prevented weight gain, and resulted in an increase in iron status, conjugated dienes, plasma glucose and lipids, which suggests a potential use of *A. herba-alba* in combating obesity, oxidative stress, and free-radical related disorders (Abid et al., 2007).
The flavonoids extracted from *A. herba-alba* have also been shown to have immune-modulatory activity, see Figure 9. They down-regulate a Th1 cytokine response and up-regulate a Th2 response, while protecting against nitric oxide induced damage by inhibiting NO production, suggesting potential uses in treating inflammatory diseases such as Adamantiades-Behcet’s disease (Messaoudene et al., 2011).

*A. herba-alba* is frequently used as an antidote in Jordan to treat for snake-bites and scorpion stings (Wright, 2002), it was shown to inhibit 100% of the hemolytic effect of the venoms (Sallal & Alkofahi, 1996).

*A. herba-alba* also exhibits potent parasiticidal activity: the nematicidal activity of *A. herba-alba* was tested against 19 other herbs to treat for two root-knot nematodes: *A. herba-alba* was the most effective causing up to 54% mortality after three days of administration (Al-Banna et al., 2003).

Helminths were also found to be treatable with *A. herba-alba*, with *Enterobius vermiculus* infections...
being 100% curable with three days of ingesting an aqueous *A. herba-alba* solution (Al-Waili, 1988). French researchers have also tested the potential anti-leishmanial activity of *A. herba-alba* in vitro, finding strong activity from essential oils at concentrations as low as 2μg/ml, with aqueous extracts showing similar effectiveness at twice the concentration, 4μg/ml (Hatimi et al., 2001). Aqueous extracts also showed similar parasiticidal activity as albendazole in treating ascaridosis in *Heterakis gallinarum* infected turkey poults (Seddiek et al., 2011).

Anti-fungal activity has also been recorded for some essential oils in *A. herba-alba*, Carvone and Piperitone, though the effect is very weak. Amphotericin B, for example, has a 5617-fold higher efficacy against *Candida albicans* than *A. herba-alba* (Roger et al., 2008). On the other hand, in-vitro trials of the oils showed very strong efficacy against *Candida* and *Microsporum* (Charchari et al., 1996), suggesting that further research in this area is needed.

One traditional use of *A. herba-alba* that has been researched comparatively well is that of its use to treat for diabetes mellitus and hypertension, as it is used in Iraq to treat for diabetes (Al-Shamaony et al., 1994). *A. herba-alba* was given as an aqueous solution, as is prescribed in the traditional folk medicine, to diabetic mice, which consequently showed a 22% reduction of plasma glucose after six hours, and were protected from weight loss compared to untreated mice (Al-Shamaony et al., 1994). The solution also caused a decrease in serum lipids which can cause coronary heart diseases at high levels (Davidson, 1981), and are a consequence of diabetes, thus further supporting its use as a potential treatment for diabetes mellitus (Wright, 2002).

The traditional uses of the herb as an antibacterial have also been tested, and have been found to be present in the form of essential oils (Yashphe et al., 2006). The efficacy of *A. herba-alba* against different bacteria was tested and has been found to vary depending on the population tested (Mohamed et al., 2010). Anti-bacterial action was found against both gram-positive and gram-negative bacteria but was usually low, with the strongest activity overall being against *Streptococcus, Pseudomonas* and *Serratia*, with *Escherichia coli* being least affected (Mohamed et al., 2010). In
addition to these anti-bacterial effects, anti-spasmodic activity was also investigated and found to be 100-1000 times higher than the anti-bacterial activity (Yashphe et al., 1987), which is thought to be the reason for A. herba-alba’s traditional use against intestinal disturbances. This variation in population efficacy opens up the possibility of culturing A. herba-alba to increase overall concentrations of the essential oils responsible for the anti-bacterial and anti-spasmodic activity.

*A. herba-alba* also shows promising use as an anti-depressant, by having high affinity to the GABA-benzodiazepine receptor site (Stafford et al., 2005).

Lastly, *A. herba-alba* also acts in inhibiting anti-biotic resistance from developing in certain bacteria, if it is given in conjunction with an antibiotic (Aburjai et al., 2001) and it can also act as a protective agent against ethanol induced damage to the stomach, suggesting that it can strengthen the gastric mucosal barrier (Gharzouli et al., 1999).

**Clinical Trials**

There is currently some interest in researching the positive effects of *A. herba-alba* extracts on diabetes. Small scale preliminary trials have been conducted to confirm the blood-sugar-lowering effects of the extract, in addition to stating that no side-effects were observed and that the patients had good remission from the diabetic symptoms (Al-Waili, 2007).

**Toxicity**

No toxicity tests have been done on *A. herba-alba*, but it can be supposed through the wide use as a traditional medicine, that no significant toxicity is present, however further research into this area is necessary.
Prospects

No clinical trials are currently being performed on *A. herba-alba*, and there seems to be little interest in it compared to some other species in the genus such as *A. annua*. It does hold a lot of potential though, especially in its use as an anti-diabetic drug. It is possible that with major discoveries in related species, *A. herba-alba* may receive more attention and get its own time to shine.
**Artemisia afra Jacq.**

General Facts and Traditional Uses

*Artemisia afra*, another important artemisian species with medicinal properties, is the only indigenous species from the *Artemisia* genus in the African continent, being prevalent from South Africa up to Ethiopia (van der Walt, 2004), see Figure 10. Due to its status as a medicinal herb in Africa, being used by many native groups, and due to the discovery of the medicinal benefits of *A. annua*, interest and research into this promising herb has increased significantly since 2001 (Liu *et al.*, 2008), see Figure 11. The traditional African medicinal uses of *A. afra* include the treatment of colds, coughs, influenza, sore throat, asthma, pneumonia, blocked nose, stomach ailments, headache, earache, poor appetite, heartburn, parasites, measles, gout, diabetes, colic, flatulence, constipation, malaria, and wounds (Van Wyk, 2008), showing the vast range of diseases and conditions it is applied for and thus its large medicinal potential.

![Figure 10. Artemisia afra. Notice the typical artemisian leaves. (www.plantzafrica.com)](image)

![Figure 11. Showing the increase in number of results on Scirus, a search engine for scientific articles, for Artemisia afra. (omicsonline.org/2153-0645/2153-0645-2-105.php)](image)
Biological Activity

A variety of these traditional uses have been tested for statistically significant benefits resulting from the use of *A. afra*, such as for the stomach ailments for which ethanolic extracts of *A. afra* leaves resulted in reductions in spontaneous rhythmic and agonist-induced contractions of isolated mouse duodenum and guinea pig ileum (Mulatu & Mekonnen, 2007), thus confirming traditional practices.

Strong anti-oxidant activity has also been found in *A. afra* (Graven *et al.*, 1992), resulting in efficient anticoccidial action in poultry (Naidoo *et al.*, 2008) and use in treating fever, rheumatism, and diabetes (Halliwell & Gutteridge, 1989). The anti-oxidant activity is thought to be due to it acting as a non-specific donor for hydrogen atoms (Liu *et al.*, 2008) and by being an effective hydroxy radical scavenging agent (Burits *et al.*, 2001).

Neurological effects have been found for aqueous *A. afra* extracts, notably a dose-dependent sedative effect on the CNS through binding to the GABA$_A$-benzodiazepine receptor site (Stafford *et al.*, 2005), and ethanol extracts of *A. afra* show low affinity to serotonin transmitter proteins, indicating potential uses as an anti-depressant for *A. afra* (Nielsen *et al.*, 2004).

Cardiovascular activity has been evident in *A. afra* as well, having a concentration-dependent hypotensive and biphasic effect on the heart (Liu *et al.*, 2008). An extracted compound from *A. afra* named scopoletin also caused decreases in inotropic activity and heart rate (Guantai & Addae-Mensah, 1999), suggesting uses for *A. afra* in managing hypertensive conditions (Patil *et al.*, 2011). *A. afra* displayed cardioprotective effects in a study where isoproterenol-induced myocardial injury in rats were treated for with aqueous extracts of *A. afra*, improving the lipid imbalance caused by ISO and the atherogenic index (Sunmonu & Afolayan, 2010).

Antibacterial and antifungal activity has also been tested for in *A. afra*, showing high degrees of growth inhibition of 15 species of bacteria and one species of fungi (Graven *et al.*, 1992). In another...
study, researchers found potent *in vitro* anti-mycobacterial activity and pulmonary inflammation modulation in *Mycobacterium tuberculosis*-infected mice (Ntutela *et al.*, 2009).

While screening 7500 different plant extracts for anti-cancer properties, *A. afra* was one of 32 plant extracts to have showed significant anti-cancer activity, specifically against melanoma, renal, and breast cancer (Fouche *et al.*, 2008). Following from this, its anti-cancer properties have also been labeled as ‘moderate’ when it was tested against 60 cancer cell lines, with its most significant activity being logged for colon, melanoma, and non-small cell lung cancer (Patil *et al.*, 2011). Flavonoids found in *A. afra* have exhibited anti-carcinogenic, anti-mutagenic, and anti-tumorigenic properties (Patil *et al.*, 2011).

Lastly, *A. afra* has also been screened for anti-malarial properties, which showed promising *in vitro* anti-plasmodial activity when seven flavonoids and sesquiterpene lactones were extracted through guided bio-essay fractionation and tested (Kraft *et al.*, 2003). Highly potent anti-plasmodial activity of *A. afra* has also been found by a different research team, showing the highest activity is achieved when the extract is extracted in dichloromethane (Clarkson *et al.*, 2004). The anti-plasmodial activity is only present in apolar solutions, resulting in the traditional herbal teas not having any antimalarial uses (Liu *et al.*, 2010).

**Clinical Trials**

Up until now there have been no clinical trials performed on *A. afra*, however there has been a request to perform a clinical trial on the use of *A. afra* in treating mild and moderate asthmatic subjects, however the permission was not granted due to a lack of safety data (Patil *et al.*, 2011). Also, The International Center for Indigenous Phytotherapy Studies is a new research effort based in South Africa which with a fund of $4.4million will perform clinical trials on the most frequently used plants in traditional medicine in Africa (Basi, 2007).
Toxicity

Toxicity tests done on *A. afr* extracts in rodents have found them to be non-toxic with high LD_{50}S of 2.45 and 8.96 g/kg for intraperitoneal and oral doses, and even demonstrated to be hepatoprotective at high doses (Mukinda & Syce, 2007). Also, no significant changes in morphology, physiology and behavior were observed after three months of administration (Mukinda & Syce, 2007).

Prospects

Due to the recent findings on *A. afr*’s biological activities, research into the biological effects of *A. afr* is speeding up, with over half of all publications on *A. afr*, 27 out of 42, having been published between 2001 and 2008 (Van Wyk, 2008). A comprehensive review (Patil et al., 2011) has been published in November 2011 on *A. afr*, compiling all known scientific data on the species and will most probably act as a primer for many new research endeavors into exploring this plant which may hold as much or more medicinal importance than *A. annua*. 
Conclusion

This report set out to provide a comprehensive outline of the medically most important *Artemisia* species and to extrapolate that medical knowledge to the genus as a whole. *Artemisia annua* is the plant which has brought plant-based medication back into the spotlight. Its biological activities are well-researched and broad, and this set it out as being an ideal species to introduce the genus. *Artemisia herba-alba* followed, being a species which is widely known as a medicinal plant with a wide range of *in vitro* and animal-based experiments having been performed to outline its biological activities, but it lacks clinical trials, a situation many medicinal plants find themselves in. The last species, *Artemisia afra*, is a species which is currently receiving much attention and is likely to have extensive research performed on it in the near future; however it currently has fewer proven medicinal benefits than the others. These three different situations complement each other to provide a general view of the genus itself.

At this point it is possible to extrapolate from these findings to detail similarities among these three species and to suggest new routes to take in researching this genus in the future. All three species have exhibited some degree of parasiticidal activity, and it is certain that this activity was only discovered in *A. herba-alba* and *A. afra* due to the potent anti-malarial activity of *A. annua*. Nonetheless, parasiticidal activity seems common in the *Artemisia* genus, and further research into this area to discover more members with potent anti-parasite activity is recommended. *A. annua* and *A. afra* have both exhibited anti-cancer activity, and it might be an idea to screen other members of the genus for these effects, including *A. herba-alba*. *Artemisia ssp.* seem to have anti-oxidant, anti-fungal, anti-bacterial, and immuno-modulatory activities which are all potential areas for future research. Overall, the majority of traditional uses for the different herbs have been proven to have a scientific foundation. This opens up the possibility for increased testing of traditional uses of other herbal medicine, such as the new research effort based in South Africa. The future of plant-based medication is bright.
Due to this report handling traditional medicine of indigenous people, a lot of information is unavailable. Artemisinin had been used for extended periods of time in China before the first reports were translated into English. The length of this report also limited the amount of information that was able to be put forth: there are a variety of other species of interest in the *Artemisia* genus which were not able to be described here, such as *Artemisia absinthium*, *A. vulgaris*, and *A. montana*. *A. absinthium* has for example strong potential as medication for Crohn’s disease (Omer et al., 2007), as well as antibacterial, antifungal (Juteau et al., 2003), anthelmintic (Tariq et al., 2009) and a variety of other biological activities. *A. vulgaris* on the other hand showed potency in treating trichinellosis (Caner et al., 2008) whereas research in *A. montana* has resulted in the extraction of three aldose reductase inhibitors: important potential candidates to treat or prevent diabetic conditions (Jung et al., 2011). In the end, this report is in no way exhaustive: research on plant-based medicine is rapid, with over half-a-dozen of the journals referenced to in this report having been published within a month of writing it.

On the other hand, this report succeeds in what it set out to achieve: to give an overview of the *Artemisia* genus in general, while focusing on the medicinal benefits. These are now clearly outlined for three species and the medicinal benefits have been extrapolated to the entire genus. The report has demonstrated the importance of this genus and the untapped potential it still holds. Research is ongoing, and hopefully in the future *A. annua* will not be the main focus of a report on this genus, but rather be accompanied on equal footing with other species which have helped mankind as much as it did.
Acknowledgements

I would like to thank my dissertation supervisor, Dr. Tony Polwart, for helping me throughout the writing of this report.

I also want to thank Keele University for providing me with library books and the online journals I would not have had access to without them.

Finally, I want to say thank you to my parents for financially enabling me to be at University and writing this report.
References:


Figure 2. (undated) *Artemisia vulgaris* L.. Accessed through: www.plant-pictures.de [Seen: 05.11.2011]


Figure 8. (undated) *Artemisia herba-alba*. Accessed through: http://eol.org/pages/6180100/overview [Seen: 15.02.2012]

Figure 9. (2011) Effect of Artemisia herba-alba extracted flavonoids on IL-12 in PBMC from patients with ABD. Accessed through: journal-inflammation.com/content/8/1/35/figure/F3 [Seen: 22.03.2012]


Li, B. et al. (2011) Artesunate enhances the antibacterial effect of β-lactam antibiotics against Escherichia coli by increasing antibiotic accumulation via inhibition of the multidrug efflux pump system AcrAB-TolC. Journal of Antimicrobial Chemotherapy, 66, 769-777.


