CHAPTER 1

GENERAL INTRODUCTION

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1.1 Background on constipation

Constipation is generally defined as the irregular and infrequent evacuation of the bowels with straining to defeacate as the main symptom (Camilleri, 2005; Wintola et al., 2010). It is one of the commonest and most reported gastrointestinal problems in which a person or an animal passes out small amounts of hard and dry stool, usually fewer than three times a week (Saito et al., 2002; Liu et al., 2005; Sinclair, 2010). It is a common clinical problem with various symptoms such as abdominal pain, hard stool, recurrent urinary tract infections, incomplete evacuation, infrequent defeacation and inconsistent soiling (Saito et al., 2002; Sinclair, 2010). Constipation is the most troublesome side effect of pain management affecting 3-15% of the general population and causing varieties of physical symptoms and in terminal illness may be a cause of restlessness (Jones and Lydeard, 1992; Mostafa et al., 2003; Goodman and Wilkinson, 2005; Chappell et al., 2008). It increases the internal pressure of the intestine and blood vessels around the anus thereby causing hemorrhoids, proctitis fissures, diverticulitis and probably tumors (Alam and Rees, 1997; Farr et al., 2002). Constipation depletes and increases the workload of the excretory organs, thereby slowing down metabolism, delaying both the elimination of waste materials as well as growth and repairs of cells and in some cases, may cause the inactivity or death of cells.

1.1.1 Prevalence of constipation

Constipation is most prevalent in women than men, non white than whites, in children than in adults and in older than in younger adults (Camilleri, 2005). The risk factor of constipation is exclusively in women with physical inactivity, history of sexual abuse, symptom of depression, low income and limited education (Johanson et al., 1989). Worldwide, population-
based studies have suggested that about 9% of children and 10-20% of adults have one or more symptoms of constipation (Cheng et al., 2003; Croffie, 2006).

Constipation is also common in the older people in the community, most of who are living in care centres (Wald, 2000). The aging process is accompanied by loss of sensitivity of the sensory reflexes responsible for normal bowel functions. These reduce the muscle tone in the small and large intestine, decreased bowel motions and possibly faecal stasis (Luscombe, 1999). Aging-related changes include loss of enteric neurons and increase susceptibility to the adverse effects of medication (Sinclair, 2010). Symptoms of constipation in the elderly however contribute to the aged people’s transfer from their homes to care institute (Wald, 2000). An international survey reported that about 20-50% of the older people living in community had symptoms of constipation (Chiarelli et al., 2000; Annels and Koch, 2002). Constipation in the elderly seems to be a much greater problem in South Africa which can result into lowering the quality of life of the aged (Meiring and Joubert, 1998).

Its prevalence among the elderly is 28%, which is particularly higher in stroke patients accounting for 30-60% (Su et al., 2009). Constipation prevalence of 34% in children has been reported in Great Britain, 10% of the general population, 20% of elderly living at home, 49% of those in long-term care, and 70% of persons with learning disabilities have been reported to have chronic constipation (Loening-Baucke et al., 2004; Sinclair, 2010). Studies have shown that 29% of South Africa’s population, consisting of both black and white suffers from constipation; especially the elderly people (Meiring and Joubert, 1998; Mugie et al., 2011). However, the prevalence of constipation in the Eastern Cape Province of South Africa in particular has not been documented.
1.1.2 Causes of constipation

Disruption of the normal physiology of defecation leads to constipation, which impaired propulsion, defective sensation and outlet obstruction (Croffie, 2006). Normal bowel function requires coordination of motility, mucosal transport and defecation reflexes. This depends on the central nervous system mechanism with the activity of the peripheral or autonomic nervous system and varieties of gastrointestinal hormones (Mancini and Bruera, 1998). Unfavorable conditions of the digestive and eliminative organs can result into emotional stress, mental strain and tension causing the organs to become tense and under-active (Petticrew et al., 2001). This could cause chemical imbalances and abnormal secretions in the body. According to Cullen and O’Donoghue (2007), hormonal changes in the body, due to pregnancy, could also contribute to constipation as a result of pressure added to the intestine from the uterus which may possibly affect the bowel.

Most cases of constipation arise from inadequate intake of dietary fibre and dehydration associated with low fluid intake. This dietary fibre comprises of carbohydrates found in bran of whole grains, leaves and stem of plants, nuts, seeds, fruits and vegetables (Gallagher and O’Mahony, 2009). They make the stool bulkier, softer and easy to pass out thereby producing a sensation of fullness which eventually lowers blood sugar, cholesterol and improve health (Muller-Lissner, 1988). Health-related literatures has established the relationship between dietary fibre and bowel function, which has led to the dominant belief that reduction in consumption of dietary fibre, is a risk factor of constipation (Richmond and Wright, 2004). Dehydration associated with low fluid intake or excessive sweating is also a major cause of constipation as the body tends to conserve water by absorbing maximum amount of fluid leading to dry, hard stool (Luscombe, 1999).
Constipation may also be caused by the side effect of medications. Supplements, opioid analgesic are the most notable offenders and diuretics (Mancini and Bruera, 1998; Selby and Warwick, 2010). Diuretics make water to be expelled faster in the body, causing loss of water in the faeces. The abuse of over-the-counter laxatives also causes the body to rely on this medication, causing constipation instead of relieving it. Pain reliever and other anti-depressant cause paralysis or slow peristaltic movement as well as difficulty in defeacation. According to Annels and Koch (2002), the nursing practices tend to be silent about the need for considering medication as a source of constipation.

Constipation is also caused by the tendencies to withhold urges to defecate, where there is lack of accessible toilets facilities, privacy and anal pains from streptococcal anusitis or sexual abuse (Croffie, 2006). Inappropriate toilet training in toddlers may also lead to withholding and eventual inevitable passage of dry hard stool with discomfort. Lack of physical activity can lead to constipation, for instance after accident or during illness and in older people who cannot move around (Lusconbe, 1999). Regular exercise is necessary to strengthen the lower colon muscle and promote normal muscle contraction in the bowel. This exercise increases the speed of transporting waste material through the intestinal tract and help in preventing colon cancer. Most elderly people and patients who are bed ridden or hospitalized are susceptible because of their incapacitation (Luscombe, 1999). Those with regularly ignoring the urge to defeacate may slow down gastrointestinal transit time, thereby causing constipation (Sinclair, 2010).

1.1.3 Types of constipation

There are two types of constipation; functional constipation and chronic constipation; these two types with their symptoms are shown in Figure 1.
Figure 1: Types of constipation (Horn, 2008)
Apart from the two major types of constipation discussed in Figure 1, there are other related gastrointestinal problems viz:

*Functional bowel disorder (FBD):* This is a disorder which affect the mid or lower gastrointestinal tract, and comprise both functional constipation and functional diarrhoea. Though the precise etiologic basis of FBD is not known, it symptoms is characterized by the absence of a structural or biochemical explanation (Saito et al., 2002).

*Irritable bowel syndrome (IBS):* Irritable bowel syndrome is a highly prevalent functional gastrointestinal disorder affecting 15 to 20% of the general population, with a substantial impact on morbidity and quality of life (Fass et al., 2001; Saito et al., 2002). It is characterized by unexplained abdominal pain, discomfort, and bloating in association with altered bowel habits. IBS can be classified as either diarrhea-predominant (IBS-D), constipation predominant (IBS-C) or IBS with alternating stool pattern (IBS-A). The pathophysiology of IBS is not well understood, but evidence of abnormal gastrointestinal motor function, visceral hypersensitivity, autonomic dysfunction, and psychological factors indicate disturbances within the enteric nervous system and the brain-gut axis (Holten et al., 2003; Longstreth et al., 2006; Stark et al., 2007).

### 1.1.4 Effects of constipation

Constipation compromises wound healing or open wound in case of lesion or surgery, which can result into nasty odour from the skin (Hasler and Owyang, 1995). Hemorrhoids are risk factors of constipation resulting from prolong straining of the anal spincher while trying to force bowel movement. These cause tear on the skin around the anus as a result of over stretched, which could lead to rectal bleeding. The spincher muscle and nerves around the
muscle is damaged leading to the loss of tone from the surrounding muscle (Luscombe, 1999). Complications such as in bowel perforation can also arise because of hardened faecal matter. This hardening of faecal matter punctures through the intestinal wall and spill into the abdominal area, thereby, causing severe infections to the organs housed in the abdominal cavity. This may be fatal, if not treated immediately. Other anatomical consequences are formation of faecal stones in the rectum, which burdens the body with foreign bodies, causes self-intoxication and perhaps liver damage (Lennard-Jones, 1993; Farr et al, 2002).

Pregnant females are often inconvenienced by constipation. The various reasons for this include exertion of pressure on the colon by the growing uterus, possible reduction in dietary roughages and fluid intake, reduction in physical activities and increase in the level of progesterone which inhibits gastrointestinal smooth muscle activity (Luscombe, 1999). According to Anderson (1984), about 38% and 20% of women experience constipation in their second and third trimesters respectively. In addition, patients with no history of bowel problems may develop constipation for the first time during pregnancy (Cullen and O’Donoghue, 2007).

1.2 Treatment options for constipation

Treatment of constipation includes changes in dietary fibre, increasing fluid intake, taking regular exercise and habitual use of laxatives (Luscombe, 1999; Annels and Koch, 2003). The use of laxatives, both prescribed and non-prescribed is very common as a means of treating constipation. Statistics have shown that 43% of white and 76.6% of black South Africans indulge in the use of laxatives, out of which 14.3% and 21.5% respectively, use more than one laxative at a time to curb the menace of constipation (Meiring and Joubert, 1998). Some of the most commonly used OTC laxative in Eastern Cape of South Africa is shown in Figure 2.
Figure 2: Commonly used over-the-counter (OTC) laxatives available in the Eastern Cape Province, South Africa.
The treatment with orthodox drugs such as puritone, gaviscon, senokot and soflox is however common but relatively slow acting and beyond the reach of common rural dwellers (Meite et al., 2010; Wintola et al., 2010). The inability of these drugs to effectively relieve the symptoms and to treat constipation have however, led to the misuse of laxatives (Meiring and Joubert, 1998). This therefore, resulted into potential harm to the bowel and to some side effects like bloating, abdominal pains as well as the desired to be free of the laxatives (Annells and Koch, 2002; Meite et al., 2010).

Till today, the majority of the affected persons in South Africa rely mostly on herbal remedy for the treatment of constipation (Wintola and Afolayan, 2010). This approach is individualized depending on the intensity of the symptom and the degree of other related conditions (Drossman and Thompson, 1992). There is the need therefore, for the development of a safe, easily accessible and cost effective drug from herbal preparations.

1.3 The use of medicinal plants for the treatment of constipation

Medicinal plants are still being used traditionally in developing countries for the treatment of numerous human diseases including constipation. They form an important foundation of various medicines especially in remote villages where it is difficult to obtain modern drugs (Van Wyk et al., 1997; Kong et al., 2003). Medicinal plants contribute about 50% of the total drugs used in the world today (Van Wyk et al., 1997; Kong et al., 2003). In South Africa, about 38 out of the 3000 indigenous medicinal plant species have been commercialized as phytomedicines (Van Wyk, 2008). Some of these plants are used by traditional healers and herbalists for the treatment of constipation. Apart from their being fast acting, cheap and ready availability, the users of medicinal plants for the treatment of constipation also get the feeling of

The use of medicinal plant is partly due to the fact that synthetic drugs always show adverse reactions in the body and other undesirable side effects which may have substantial impact on morbidity and quality of life (Drossman et al., 1993; De Lillo and Rose, 2000; Erasto et al., 2005). The use of herbal medicine in the treatment of constipation is therefore, vital to the provision of primary health care of the rural population of the Eastern Cape. This view has been supported through numerous studies of the biological activity of plant extracts such as antispasmodic, intestinal transit delay agents, gut motility suppressor, electrolyte secretion reduction and water stimulation adsorption agents (Palombo, 2006). In these studies, the activity of the extracts, in most cases was attributed to the presence of phytochemicals with the laxative properties. These phytocomponents include terpenoids, sterol, flavonoids, phenolic, tannins and alkaloids. These compounds are converted in the colon to their active forms (Longanga-Otsudi et al., 2000; Havagiray et al., 2004; Jagan Mohan Rao et al., 2007). The phytochemicals are
believed to stimulate peristalsis and reduce water reabsorption, leading to the softening of stools (Meite et al., 2010; Wintola et al., 2010).

1.4 The choice of *Aloe ferox* for this study

At the beginning of this study, an ethnobotanical survey was carried out on the plants used by the traditional healers, rural dwellers and herbalists for the treatment of constipation in the Eastern Cape Province of South Africa. The results of the survey showed a total of 10 plants from 8 families that are used traditionally in the study area for laxative purposes. Out of these plants, *A. ferox* (Figure 3) was frequently mentioned by the herbalist and rural elderly people as the commonest plant species used for the treatment and management of constipation (Wintola and Afolayan, 2010). The species had the highest frequency of citation (60%) and is readily available throughout the year. Hence, *A. ferox* was chosen for this present study.
Figure 3: *Aloe ferox* Mill. in its natural habitat.
Aloe ferox Mill (Aspodelaceae) is known as Cape aloe (English) and ikhala (Xhosa). It is widely distributed in Lesotho, Free State, Western and Eastern Cape of South Africa (Shackleton and Gambiza, 2007). It is an arborescent perennial shrub reaching 2-3 m in height (Fig. 3). The plant has large thick succulent leaves bearing brown spines on the margin with attractive flowers, usually bright orange, which are glaucous and oval-lanceolate and are compactly arranged on 5-12 racemes (Van Wyk and Smith, 1996). It grows in all weather in bush veld, road sides, gardens and undisturbed places.

1.4.1 Traditional uses

For centuries, the plant is used therapeutically for the treatment of constipation (Watt and Breyer-Brandwijk, 1962; Jia, et al., 2008). Today the plant has been accepted widely for its antiseptic, laxative, moisturising, cleansing and anti-inflammatory properties (Van Wyk et al., 2002; Loots et al., 2007). Currently, the fresh and dried leaf juice of A. ferox is used directly as infusion and decoction traditionally for the treatment of various diseases such as skin cancer, gastrointestinal disorder, inflammation, burns, psoriasis (Grierson and Afolayan, 1999; Loots et al., 2007; Jia et al., 2008; Wintola and Afolayan, 2010).

1.4.2 Phytochemicals

Several phytochemicals have been isolated from A. ferox; some of which are 1,8-dihydroxy-3-hydroxymethyl-9,10-anthracenedione (aloe-emodin), 1, 8-dihydroxy-3-methyl-9,10-anthracenedione (chrysophanol) and 10-C-β-D-glucopyranosyl-1,8-dihydromethyl-9-anthracenone(aloin A) which have been found to be bioactive, against microbial infections (Kambizi et al., 2004). Viljoen, (2008) confirmed the presence of several antioxidant polyphenol
in the leaf gel extract of *A. ferox*. In a similarly view, lyophilized leaf gel extracts of *A. ferox* was reported to show antioxidant activity as confirmed by ORAC and FRAP analysis as well as showing that the non-flavanoid polyphenols contribute to the total phenolic content (Loot et al., 2007).

### 1.4.3 Bioactivity

The crude extract of *A. ferox* possesses significant activity against some bacteria and fungi (Afolayan et al., 2002; Kambizi et al., 2004). An anti-inflammatory and analgesic activity of the whole leaf extract of *A. ferox* on Wistar rats was reported in a recent study (Mwale and Masika, 2010). Other pharmacological activities of the leaf gel and pulp has also been reported (Van Wyk et al., 2002; Yagi et al., 2003; Langmead et al., 2004; Mwale and Masika, 2010). Yagi et al. (2003) reported a strong superoxide and DPPH radical scavenging potential of *A. ferox* leaf gel while working on the Aloesin derivatives of the plant. Loot et al. (2007) justified and characterised *A. ferox* lyophilized leaf gel (LGE). The authors concluded based on the activity shown in the study that the extract could help in alleviating symptom resulting from oxidative stress. Despite the numerous folkloric uses of *A. ferox* as a laxative agent in the Eastern Cape, there is dearth of scientific evidence to substantiate such claim. The aim of this study therefore, was to evaluate the laxative efficacy and toxicological effects of *A. ferox* with a view to validating its acclaimed use by the traditional medicine practitioners in the Province.

### 1.5 Rationale for this study

Constipation has been a very common complaint in clinical medicine. It is a rising problem in modern society with approximately one-fifth of all adults suffering from the ailment
(Rantis et al., 1997). It has been in existence for more than 7000 years. According to Boschung (1997), constipation has been a problem since man stopped feeding solely on roots, grains and berries but on meat products. The nutritional intake of poor dietary fibre resulted into inadequate filling of the intestine, which eventually reduced the water-binding capacity of the readily absorbed foods (Boschung, 1997, Rantis et al., 1997). The use of laxatives for the treatment of constipation is deeply rooted in medical and social tradition (Farr et al., 2002). Unfortunately, laxatives are used too frequently without justification and in some cases one or more are combined hoping for better efficacy. Laxatives when used regularly over a period of time may cause an atonic colon (loss of muscle tone in the colon), thus increasing constipation and exacerbating the underlying problems. Therefore, to stop the abuse of laxative, effective and natural medicinal plants should be advised, since patients often increase the dose of the orthodox laxatives to achieve better results. The rationales for this study are detailed under the following sub-headings:

1.5.1 Ethnobotanical study of plants used for the treatment of constipation

Herbal remedies are commonly employed in developing countries for the treatment of various diseases, including constipation. The Eastern Cape Province of South Africa is not left out in the use of herbal medicine for the treatment of constipation which has been in existence for years. However, most of the experiences and knowledge of the traditional health workers lack accurate documentation, since information is passed verbally from one generation to another. Unfortunately, this information is lost as a result of lack of proper documentation. There is therefore the need for proper documentation before this vital information are lost forever (Reddy et al., 2010). There is also limited scientific evidence regarding the safety and efficacy to
back up the continued therapeutic application of these remedies. Hence, thorough scientific investigations of medicinal plants are imperative in order to validate their folkloric usage (Zhu et al., 2002). One of the objectives therefore, was to gather and document information from traditional healers, elderly rural dwellers, and herbalist (Sangomas) on the plants used in the province for the treatment of constipation. Collections of these plants were deposited in the Griffen’s herbarium of University of Fort Hare.

1.5.2 The laxative activity of Aloe ferox in the treatment of loperamide-induced constipated rats

Today, in-vivo animal-based studies are being employed to evaluate the biological activity of medicinal plants. To determine the laxative activity of the aqueous whole leaf extract of A. ferox therefore, constipation was induced with loperamide in Wistar rats. Loperamide was used because it increases the amount of time substances stay in the intestine, allowing for more water to be absorbed out of the faecal matter. This decreases the colonic mass movements and suppresses the gastrocolic reflux (Katzung, 2004). This was the first time that the whole leaf extract of A. ferox was evaluated for its laxative property. Other workers have focused on aloe gel, exudate and pulp extracts (Loots et al., 2007; Botes et al., 2008; Viljoen, 2008).

1.5.3 Effect of A. ferox aqueous leaf extract on the biochemical parameters in loperamide-induced constipated rats

The therapeutic activity of medicinal plants is attributed to the presence of biologically active compounds in the crude extracts (Dosumu et al., 2010). However, along with these therapeutic contents are potentially toxic compounds which may have adverse side effects on humans and animals. As a result, continuous evaluation of medicinal plants is required not only
to establish the scientific basis for their activity but to make clarifications on their safety or toxicity risk. A few clinical trials have evaluated the safety and possible level of the traditional herbal preparations all over the world (Palombo, 2006). One of the objectives of this research therefore, was to evaluate the toxicity of the aqueous leaf extract of *A. ferox* using Wistar rats.

1.5.4 *Phytochemical and antioxidant activity of the plant*

There is clear evidence that oxidative stress is related to several aspects of constipation. For example, constipation can adversely affect health, with disorders of host intestinal immunity, thus enhancing oxidative stress (Li et al., 2011). Kilciler et al., (2011) showed that constipation increased oxidative stress with hypoxic attack, compressing and increasing the intra abdominal pressure. Antioxidants are reducing agents that limit oxidative damage to biological structures. Plants are natural antioxidants because they are a source of metabolites responsible for the prevention of free radicals related diseases (Veerapur et al., 2009). Several studies revealed that some phytochemicals are responsible for the antioxidant activities of plants in scavenging free radicals by inhibiting the upshot of reactive oxygen species (Rice-Evans et al., 1995; Ripa et al., 2009). Phytochemicals, such as the phenolics are believed to help in the quenching of the catalytic reaction of the free radicals. Hence, the use of medicinal plants as natural antioxidants with few or no side effects is proposed for the cure of oxidative stress generated diseases. Few scientific investigations have evaluated the antioxidant activities of *A. ferox* using only the leaf pulp or the gel (Loots et al., 2007; Botes et al., 2008). One of the objectives of this study therefore, was to evaluate the leaf of *A. ferox* for antioxidant activity.
1.5.5 **Isolation and identification of compounds**

Medicinal plants are sources of bioactive compounds which have been a foundation for the development of new drugs (Palombo, 2006). The use of synthetic laxatives with subsequent side effects makes it imperative to use medicinal plants which are cheap, fast acting and readily available to the rural community. It thus, becomes essential to isolate and identify the active laxative compound(s) in the leaf extract of *A. ferox* and compare with the over-the-counter laxative drugs. This will assist not only the academia, but the medical practitioners and the traditional healers. For example, identification of the bioactive ingredients responsible for therapeutic activity of the plant would partially justify the traditional use of the plant by the healers. Such knowledge would further boost the confidence of the healers in their ethnomedicinal practice. The long term objective of this project is to stimulate future research in the field of new drug development and exploration of medicinal compounds from plants.

1.6 **Objectives of the study**

The overall objective of this study was to conduct ethnobotanical and phytomedicinal research on the plants used by the herbalists, rural dwellers and traditional healers for the treatment of constipation in the Eastern Cape Province, South Africa, with the view to identifying the most efficacious species.

The specific objectives were:

1. To collect information, by means of interviews and questionnaires, on the plants used by the traditional healers for the treatment of constipation, the part used method of preparation, possible dosage administered to patients and the efficacy of the herbs;
2. To investigate the laxative activity of the aqueous leaf extract of the plant in loperamide-induced constipated rats;

3. To evaluate the toxicological effect of the aqueous leaf extract of the species in loperamide-induced constipated rats; and

4. Having identified *A. ferox* as the most common plant species used for the treatment of constipation, other specific objectives were to determine the phytochemical and antioxidant activity;

5. To isolate and identify the compounds responsible for the laxative effect of the plant and by comparing this with the over-the-counter laxative drugs.

1.7 The study Area

Nkonkobe Municipality in the Eastern Cape of South Africa is located within 32° 47' 0" South, 26° 50' 0" East. The area is bounded by the sea in the east and drier Karroo in the west (Fig.4). The altitude is approximately 1300 m above sea level and the vegetation is veld type 7 (Masika and Afolayan, 2003). The major ethnic group in the area is *Xhosa*, with farming as their main occupation. The low socio-economic standing of the predominantly rural Eastern Cape populations suggests that the majority of the people in this area use herbal medications either alone or in combination with orthodox medicines for the treatment of several diseases, including constipation.
Figure 4: Map of Amatole District in Nkonkobe Municipality of the Eastern Cape Province.
1.8 Structure of the thesis

This thesis consists of discrete chapters that have been published, accepted or under review in various accredited Journals. The ethnobotanical study of plants used for the treatment of constipation in Nkonkobe Municipality of the Eastern Cape Province is presented in Chapter 2. It is the analysis of the questionnaires administered to the rural dwellers and the traditional healers in an ethnobotanical survey. Chapter 3 is the report on the effect of the aqueous leaf extract of A. ferox in loperamide-induced constipation in rats. The effect of A. ferox aqueous leaf extract on the biochemical parameters in loperamide-induced constipated rats is in Chapter 4. Chapter 5 is the report on the phytochemical and antioxidant activity of the leaf of A. ferox using different solvents, while Chapter 6, reports the process of isolation of the laxative compound in A. ferox relative to two of the commonly used over-the-counter laxative drugs. Chapter 7 focuses on the general discussion and conclusions of the entire study, in an attempt to provide a clear insight of the investigation.
1.9 References


Chiarelli, P., Brown, W., McElduff, P., 2000. Constipation in Australian women: prevalence and


