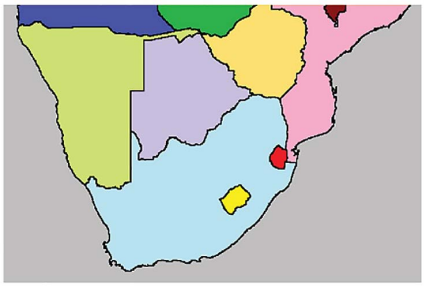
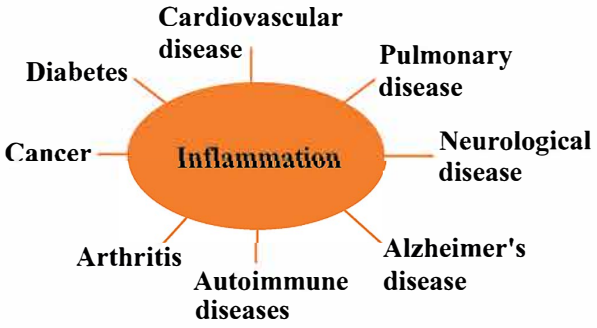
# A review of the traditional use of southern African medicinal plants for the treatment of inflammation and inflammatory pain

## Author contribution

G. Khumalo and I. Cock conceptualised the study and wrote the initial draft. Y. Feng, B-E. Van Wyk and I. Cock edited the manuscript. Y. Feng assisted with chemistry aspects. B-E. Van Wyk provided expertise with taxonomy and ethnobotany. All authors edited and approved the manuscript.

**Southern African medicinal plants**






**555 plant species**
identified as traditional therapies for inflammation

**200 plant species**
Scientific evaluations of southern African plants against inflammation

**A review of the traditional use of southern African medicinal plants for the treatment of inflammation and inflammatory pain**

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**Abstract**

*Ethnopharmacological relevance*: Inflammation is a serious global concern due to its debilitating symptoms, resulting in considerable suffering and lost productivity. Chronic and auto-immune inflammatory diseases are of particular concern. Several pharmaceutical therapies are already available. However, the use of non-steroidal anti-inflammatory drugs (NSAID's) is accompanied by harmful and toxic side effects. Hence, the search for safer alternative therapeutics with limited side effects is imperative. The use of medicinal plants is common practice amongst the southern African population and may provide targets for drug development.

*Aim of the study*: This study aims to review and document the medicinal uses and pharmacological properties of southern African medicinal plants used for inflammation and pain-related ailments.

*Material and methods*: An extensive literature review was undertaken to identify southern African plants used traditionally to treat inflammation. A variety of ethnobotanical books and grey literature, as well as ScienceDirect, Google Scholar and Scopus search engines were used as sources of information.

*Results*: This review identified 555 medicinal plants from 118 families which were traditionally used in southern Africa to treat inflammation and pain. Fabaceae was the most prominent family with 63 species, followed by Asteraceae (54 species) and Apocynaceae (33 species). The top category of ailments indicated include non-specific inflammation with 150 species, followed by inflammatory pain (148 species), headache (114 species) and toothache (114 species).

*Conclusion*: Despite a large number of southern African medicinal plants used to treat inflammation and pain, relatively few have been screened for their anti-inflammatory properties. Furthermore, biologically active plant extracts have been tested against relatively few inflammatory markers and considerable further work is required.

**Keywords**: Cyclooxygenase; Lipoxygenase; Biological activity; Ethnobotany; Chronic pain

**Contents**



*Abbreviations:* CDC, Centre for Disease Control; COX, cyclooxygenase; IL, interleukin; LOX, lipoxygenase; LPS, lipopolysaccharide; LT, leukotriene; NF$\kappa$B, nuclear factor kappa B; NSAID, non-steroidal anti-inflammatory drug; PG, prostaglandin; TNF-α, tumour necrosis factor α; WHO, World Health Organisation.

## 1. Introduction

Inflammation is a protective defence mechanism of the body's immune system against tissue injury or unwanted foreign substances or pathogens that invade tissue cells (Ribaldone

et al., 2018). Acute inflammation involves the repair and removal of damaged cells at the sites of infection over a short period of time. There are various pathways in which inflammation is resolved, depending on the type of tissue and stimulus (Fullerton and Gilroy, 2016). Invasion of foreign pathogens stimulate resident tissue cells to produce a variety of inflammatory mediators, which activate various signalling pathways resulting in the release and recruitment of leukocytes (Chen et al., 2018). Resolution of acute inflammation involves phagocytosis of injurious stimuli by neutrophils and macrophages, termination of pro-inflammatory mediators and apoptosis of immune cells (Fullerton and Gilroy, 2016; Chen et al., 2018). However, when inflammation becomes unregulated, it may develop into chronic inflammation (Feghali and Wright, 1997). Chronic inflammation plays a pivotal role in the development of various pathological disorders including Alzheimer's disease, cancer, rheumatoid arthritis, type 2 diabetes and obesity, as well as cardiovascular and pulmonary diseases (Nishimura et al., 2009; Saltiel et al., 2017; Pahwa et al., 2019). Chronic disorders are regarded as a leading cause of death globally (WHO, 2005), with 60% of these deaths due to chronic inflammatory diseases (Pahwa et al., 2019). Inflammatory and pain-related disorders remain serious global concerns that affect all individuals globally. Furthermore, pain is the leading cause of disability worldwide (Uritu et al., 2018), with lower back pain and headache being the most common categories (Turk, 2002; Tsang et al., 2008). Whilst several classes of drugs are currently available to treat these conditions, non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently used. However, the clinical use of non-steroidal anti-inflammatory drugs is often accompanied with harmful and toxic side effects (Vane and Botting, 1998; Pahwa et al., 2019). Hence, the search for alternative herbal therapeutics is imperative.

Medicinal plants have been used for millennia by all populations globally. They also form the foundation of many modern medicines, nutraceuticals, food supplements and pharmaceutical products (Mahesh and Satish, 2008; Dias et al., 2012). Medicinal plants are a rich source of secondary metabolites (Evert, 2006), which are bioactive constituents that play a major role in promoting the healing effect of various diseases (Hamburger and Hostettmann, 1991; Van Wyk and Wink, 2015). Medicinal plants may act as natural stimulators of the immune system (Taylor et al., 2001). There has been increased recent interest in the therapeutic properties of traditional medicines due to increasing problems associated with allopathic medicines, including the development of bacterial resistance (Cheeseman et al., 2018; Van Vuuren and Muhlarhi, 2017), decreasing efficacy of some drugs and harmful side effects that are associated with many synthetic drugs (Ong et al., 2007; Rao and Knaus, 2008). Notably,

over 50% of drugs used globally in modern pharmaceuticals are derived from natural products (Balandrin and Kinghorn, 1993). The importance of medicinal plants as potential sources of drugs is evident from the global commercialisation of well-known effective drugs derived from various plant species. Quinine for example, is an anti-malarial alkaloid isolated from the bark of *Cinchona officinalis* L. (Misra et al., 2008). The compound chloroquine, which is derived from quinine has also been shown to regulate inflammatory autoimmune responses (Park et al., 2019) and was recently found to be useful in antitumor medication (Goel and Gerriets, 2019). Notably, the chloroquine derivative hydroxychloroquine has recently been touted as a potential treatment for covid-19 due to its immune-regulatory properties, although there is little scientific evidence to support this usage. Indeed, several recent reports have stated that its use may actually be detrimental in individuals with covid-19. Another well-known example is the synthesis of an anti-inflammatory agent, acetylsalicyclic acid (aspirin), derived from the natural product, salicin (Vane and Botting, 1998). It is generally considered to have been first isolated from the bark of the willow tree, *Salix alba* L. (Dias et al., 2012). The glycoside of methyl salicylate (called spiraein) was actually isolated from *Spiraea ulmaria* L. (now known as *Filipendula ulmaria* (L.) Maxim.), for which Aspirin™ was indeed named (Van Wyk and Wink, 2017). Plant materials containing acetylsalicyclic acid has been traditionally used since 400 BC for treatment of pain and fever (Rao and Knaus, 2008).

## 2. Overview of inflammation and pain

Pain is a psychological, physical and emotional sensation that may be associated with tissue damage (Verhaak et al., 1998). Pain has a negative impact that greatly affects the daily lives of individuals worldwide (Turk, 2000; Louw et al., 2007; Tsang et al., 2008). These include functional activities, frequent use of medication, health care expenses, disability and unemployment burden (Turk, 2000). Musculoskeletal disorders are the major cause of disability in developed countries, with lower back pain and joint pain being the most prevalent (Woolf and Pfleger, 2003; Tsang et al., 2008). In the United Kingdom, an estimated 2.5 million people experience back pain on a daily basis (Turk, 2002). A survey carried out in 1999, revealed that 15% (37.9 million) of the United States population suffers from arthritis (Lawrence et al., 1998). The authors estimated a further increase of 57% (59.4 million) by 2020 (Lawrence et al., 1998; Bhatt et al., 2008). Moreover, about 350 million people suffer from arthritis and other joint diseases globally (Pahwa et al., 2019). In developed countries, cases of back pain were frequently reported among manual workers, especially in those aged between 25–64 years (Woolf and Pfleger, 2003). Vulnerability to chronic pain increases with age

(Verhaak et al., 1998; Woolf and Pfleger, 2003; Tsang et al., 2008). Back pain and headache were also reported as the most prevalent form of chronic pain in developing countries (Tsang et al., 2008). In southern Africa, lower back pain is common amongst manual workers due to the nature of their work, as well as poor rehabilitation methods and lack of legislation to protect employees. In addition, lower back pain cases were also noted in young pupils of South Africa, mainly because of technological advancements in schools such as learning over computers, without teaching the learners good spinal health practices (Louw et al., 2007). Information on chronic pain and associated risk factors in developing countries is limited (Kamerman et al., 2020). Indeed, of the southern African countries, studies of chronic pain occurrence were only found in South Africa (Louw et al., 2007; Tsang et al., 2008; Kamerman et al., 2020). In contrast to many other countries, where lower back pain is most reported, limb and back pain are the most common forms of chronic pain reported in South Africa (Kamerman et al., 2020).

Interestingly, pain is a necessary phenomenon as it may act as the main diagnostic symptom of various disorders **(**Almeida et al., 2001). Literature data extracted from various patients revealed that symptoms associated with chronic pain often could not be traced to an identifiable pain such as headache or backache (Turk, 2000), making it difficult to provide accurate prescription for treating pain. However, therapies are necessary to allow people to manage the pain. Available outcomes on clinical trials for assessment of chronic pain are inadequate and non-comparable, as results on pain perception depends on the verbal report of patients (Farrar et al., 2000). Furthermore, the way in which different individuals experience and interpret pain varies, making it difficult to conclude on the safety and efficacy of the treatment options (Dworkin et al., 2005, 2008). Drugs that are currently used for the management of pain have not been effective enough and are associated with unwanted side effects and often have cumulative effects (Almeida et al., 2001). There has been an increased recent interest from pharmaceutical and scientific sectors in the use of medicinal plants as analgesics (Almeida et al., 2001; Uritu et al., 2018).

About 80% of the global population utilises medicinal plants as analgesic or antinociceptive agents (Uritu et al., 2018). The search for alternative anti-inflammatory therapeutics from medicinal plants is not restricted to southern African (Shale et al., 1999; Iwalewa et al., 2007; Adebayo and Amoo, 2019; Du Preez et al., 2020). Tunon et al. (1995), screened 52 Swedish medicinal plants for prostaglandin synthase inhibitors. In Asia, a wide number of medicinal plants with potent anti-inflammatory properties were reported (Cuellar et al., 2001; Shah et al., 2011). Kupeli et al. (2007) reported the anti-inflammatory and

antinociceptive activities of eleven medicinal plants used in Turkish folk medicine. Akhtar et al. (2016), investigated the anti-inflammatory activity 17 Australian medicinal plants from the genus *Eucalyptus* that are used by Dharawal indigenous people. Ribeiro et al. (2018) documented 70 Brazilian medicinal plants with anti-inflammatory properties. A recent review by Uritu et al. (2018), recorded various species with potent analgesic and antinociceptive activity belonging to the Lamiaceae family. In Africa, relatively little is known about the anti-inflammatory properties of medicinal plants (Oguntibeju, 2018; Elgorashi and McGaw, 2019), although 25% of higher plants globally occur in sub-Saharan Africa (Van Wyk, 2008). A global increase in the interest of alternative herbal therapeutics is also evident in developed countries, especially in Europe and North America (Lazarou and Heinrich, 2019).

## 3. Commercialisation of natural products used for inflammation

Out of 85,000 medicinal plants that are used globally, 35% are commercialised in the United States, followed by Europe (33%), and Japan (18%), while African countries contributes less than 1% of the formal commercial plant trade (US$ 520 million) (Makunga et al., 2008). Despite the rich floral diversity of the southern African region, only 38 indigenous plant species were recorded to have been partially or fully commercialised in Africa and other parts of the world (Van Wyk, 2008). This is largely attributed to limited ethnopharmacological and clinical studies reporting the scientific validation of African medicinal plants (Van Wyk, 2008).

*Harpagophytum procumbens* (Burch.) DC. ex Meisn. and *Harpagophytum zeyheri* Decne. subsp. *zeyheri* are popular southern African medicinal plants used traditionally for chronic inflammation, rheumatoid arthritis, and as analgesics (Stewart and Cole, 2005; Mncwangi et al., 2012; Engels and Brinckman, 2018). Isolated compounds including iridoid glycoside harpagoside from the roots have been commercially used for degenerative rheumatoid arthritis, osteoarthritis, tendonitis, kidney inflammation and cardiovascular diseases (Stewart and Cole, 2005). *Harpagophytum procumbens* was listed among the top 15 commercially important southern African medicinal plants (Van Wyk, 2008; Makunga et al., 2008). The plant has been registered as a herbal medicine in France and Germany, and as a food supplement in the United Kingdom, the Netherlands, the United States, as well as in the Far East (Stewart and Cole, 2005). In 2001, *H. procumbens* sales reached 30 million euros, accounting for 74% of the prescriptions for rheumatism in Germany (Stewart and Cole, 2005).

The genus *Aloe* has been widely reported for its potent anti-inflammatory and anti-arthritic properties (Lindsey et al., 2002; Cock, 2015). *Aloe ferox* Mill., has been exported to European countries for commercialisation since 1761 (Van Wyk, 2008). Pharmacological and phytochemical properties of *A. ferox* have been well studied (Chen et al., 2012). *Aloe ferox* is also used in the cosmetic industry and provides a significant source of income for rural harvesters in South Africa (up to R12–15 million per year) (Street and Prinsloo, 2013). Anti-inflammatory properties of other *Aloe* species have also been reported, particularly for *Aloe vera* (L.) Burm.f. Extracts from this plant decrease levels of $PGF_2\alpha$ in aloe-treated wounds, while showing an increase in $PGE_2$ levels compared to the controls (Heggers et al., 1980). In addition, Lindsey et al. (2002), investigated the anti-inflammatory properties of 53 South African *Aloe* species. Notably, the anti-inflammatory activity against COX-1 was influenced by the phytochemical differences of *Aloe* species. Plant extracts accumulating high content of flavonoids and flavones were more active compared to other chemotypes (Lindsey et al., 2002).

The long-term use of medicinal plants makes them valuable potential sources for drug development (Hamburger and Hostettmann, 1991; Taylor et al., 2001). Unlike standard combinatorial chemistry, natural products provide a unique chemical structural diversity (Mahesh and Satish, 2008). Hence, the pharmaceutical sector has recently become interested in medicinal plants for anti-inflammatory therapeutics (Iwalewa et al., 2007; Adebayo and Amoo, 2019). Of the more than 5000 plant species that are used medicinally in Africa (Neuwinger, 2000; Taylor et al., 2001), very few have been scientifically explored. In 2012, less than 10% of the world's biodiversity had been subjected to biological screening (Dias et al., 2012). Considering the complexity of a medicinal plant mixture (Yao et al., 2018), data analysis and processing of these constituents remains a critical challenge (Liggi et al., 2018), requiring analytical tools of high sensitivity, accurate detection and quantification (Hegeman, 2010).

There is an urgent need for new anti-inflammatory drugs, especially those derived from natural products (Fürst and Zündorf, 2014). Although there are many studies reporting the biological activities of isolated compounds from medicinal plants used to treat pain and inflammation (De Sousa et al., 2011), a major challenge exists to validate the safety and efficacy in human trials (Fürst and Zündorf, 2014). Some examples of plant-derived anti-inflammatory agents that have been extensively explored and that have made it to clinical trials include curcumin (and turmeric extract), resveratrol and quercetin.

Curcumin is a major component of turmeric spice derived from *Curcuma longa* L. The plant has been used in Ayurvedic medicine for treating a wide variety of ailments including inflammation. Curcumin is reported to be a potent inhibitor of pro-inflammatory signalling pathways, including the NF$\kappa$B, MAPK, COX, and LOX pathways, to downregulate secretion of cytokines, and to inhibit the expression of cell adhesion molecules (Gupta et al., 2013). Although human trails of this compound have been undertaken, the recorded data is insufficient to satisfy the safety and efficacy regulatory requirements for commercialisation (Fürst and Zündorf, 2014). Resveratrol is a stilbene that is found in a wide variety of plant sources. Anti-inflammatory properties of this compound have been extensively studied and it has been reported to block the NF$\kappa$B-, AP-1 and COX-2 pathways, as well as activating PPAR, eNOS, and SIRT1 pathways (Fürst and Zündorf, 2014). Despite the available literature on the mechanism of actions, clinical studies of this compound are lacking (Fürst and Zündorf, 2014).

The flavonoid quercetin is found in various plant species and is widely used as a dietary supplement. It is well-known for its anti-cancer, anti-inflammatory, antioxidant, antiviral and neuroprotective properties (Li et al., 2016). Quercetin modulates prominent pro-inflammatory signalling pathways including STAT1, NF$\kappa$B, and MAPK pathways (Fürst and Zündorf, 2014). During an inflammatory response, quercetin has been reported to inhibit LOX and COX enzymes, regulate the production of prostanoids and cytokines, suppress the activation and accumulation of leukocytes and NF$\kappa$B activity, as well as inhibiting the activation and apoptosis of dendritic cell (Li et al., 2016). Despite the available literature on the bioactivity of quercetin, well-structured clinical trials of inflammatory disorders are limited, and it is yet to be approved by the FDA for clinical use (Fürst and Zündorf, 2014**;** Li et al., 2016).

## 4. Inflammatory pathways

Tissue invasion of injurious stimulus activate a cascade of intracellular signalling pathways via the cell surface receptors of resident cells (Chen et al., 2018). This process is followed by the release of inflammatory mediators including histamine, prostaglandins, cytokines and growth factors for recruitment of immune cells from the blood vessels (Fullerton and Gilroy, 2016). Thereafter, leukocytes (including neutrophils and monocytes) mature into inflammatory macrophages, exit the blood vessel and are attracted to the site of injury by chemokines to initiate tissue repair (Fullerton and Gilroy, 2016). However, when inflammation becomes unregulated, it can result in the formation of various immunopathological disorders (Ricciotti and FitzGerald, 2011). The early stages of an inflammatory response include the

release of arachidonic acid from membrane phospholipids of tissue cells by phospholipase $A_2$. Arachidonic acid is then metabolised to produce various signalling molecules such as prostanoids via the cyclooxygenases and to leukotrienes via the lipoxygenases (Haeggström and Funk, 2011).

Two isoforms of cyclooxygenases that are known to exist as homodimers are COX-1 and COX-2 (Dannhardt and Kiefer, 2001; Simmons and Botting, 2004). However, some authors have also postulated the possible existence of a COX-3 isoform (Chandrasekharan et al., 2002; Warner and Mitchell, 2002). COX-1 is mainly responsible for homeostatic functions, such as maintaining the gastrointestinal mucosa, facilitating platelet aggregation, as well as regulating renal blood flow, while COX-2 is only induced during an inflammatory response (Bjorkman, 1998; Simmons and Botting, 2004). Moreover, Ricciotti and FitzGerald, (2011) argue that both COX-1 and 2 are involved during an inflammatory response, with COX-1 being expressed during the initial phase of acute inflammation in some tissue cells. Detailed studies on the cyclooxygenase enzymes and mechanism of action are elaborated in the following reviews and will not be described here in detail (Dannhardt and Kiefer, 2001; Warner and Mitchell, 2002; Simmons and Botting, 2004; Ong et al., 2007; Rao and Knaus, 2008).

Prostaglandins are lipid autacoids that function in autocrine and paracrine signalling pathways (Park et al., 2006; Reid et al., 2003). In cells where they are produced, they exit through passive diffusion or via transporter proteins and function by binding with specific G-coupled receptor proteins (Reid et al., 2003). The four principal prostaglandins include prostaglandin $E_2$ ($PGE_2$), prostacyclin ($PGI_2$), prostaglandin $D_2$ ($PGD_2$) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), which are produced from prostaglandin $H_2$ ($PGH_2$) by various specific synthases (Reid et al., 2003; Wang et al., 2007; Ricciotti and FitzGerald, 2011).

Prostaglandins play a pivotal role during inflammation, including regulation of the immune response, increased sensitivity to stimuli, production of cytokines and chemokines, as well as activation of leukocytes (Park et al., 2006; Wang et al., 2007; Ricciotti and FitzGerald, 2011; Kalinski, 2012). Prostaglandins have been implicated in the formation of chronic inflammatory diseases. High levels of $PGD_2$ have been detected in the bronchoalveolar lavage fluid in allergy-induced asthma (Ricciotti and FitzGerald, 2011). Increased expression of $PGF_{2\alpha}$ has been detected in patients suffering from rheumatoid arthritis, psoriatic arthritis, reactive arthritis and osteoarthritis (Ricciotti and FitzGerald, 2011). The most abundant prostanoid ($PGE_2$) is involved in various immunopathological disorders including cancer,

hyperalgesia, rheumatoid arthritis and osteoarthritis (Park et al., 2006, Kalinski, 2012). Furthermore, $PGE_2$ is also implicated in the initial stages of atherosclerosis by regulating the production of the cytokines IL-1β, IL-6 and monocyte chemotactic protein-1 (Tedgui and Mallat, 2006).

Six lipoxygenase enzymes (5-LOX, 12-LOX, 12/15-LOX, 15-LOX type 2, 12(R)-LOX, and epidermal LOX) are known to occur in humans, with 5-LOX being implicated in the induction of various human diseases (Rådmark et al., 2015). During the LOX pathway, leukotriene $A_4$ ($LTA_4$), an unstable intermediate of the 5-LOX catalysed reaction from arachidonic acid, is synthesised. Thereafter, $LTA_4$ is converted into other leukotrienes including $LTB_4$ or $LTC_4$, $LTD_4$ and $LTE_4$ through the action of various other enzymes (Lewis et al., 1990). Leukotrienes are primarily produced by leukocytes and function by binding to specific receptors located in target tissue cells (Rådmark et al., 2015). Leukotriene $B_4$ plays a crucial role during inflammation as a potent chemotactic agent, while $LTC_4$, $LTD_4$ and $LTE_4$ are primarily involved in bronchoconstriction (Lewis et al., 1990) and increased vasopermeability (Rådmark et al., 2015). This ability of leukotrienes implicates their involvement in the pathophysiology of rheumatoid arthritis, psoriasis, dermatitis, nephritis, atherosclerosis, cancer, as well as cardiovascular and pulmonary disorders (Haeggström and Funk, 2011). Further studies are needed to better understand the mechanisms involved in the lipoxygenase pathway and their implication in the initiation and regulation of chronic inflammatory diseases (Haeggström and Funk, 2011).

## 5. Available treatment options

Non-steroidal anti-inflammatory drugs are the most frequently used therapeutics worldwide for the management of pain and inflammation (Bjorkman, 1998; Vane and Botting, 1998). In the United States alone, more than 30 billion over-the-counter pills are sold annually (Wolfe et al., 1999). In 2004, there were more than 111 million recorded NSAIDs prescriptions from both the public and private health sectors in the United States (Bhatt et al., 2008). This is perhaps not surprising considering their effective use in patients suffering from chronic inflammatory diseases such as rheumatoid arthritis, osteoarthritis, Alzheimer's disease, colon cancer and cardiovascular disorders (Lim et al., 2000; Yudkin et al., 2000; Tuppo and Arias, 2005; Ong et al., 2007; Bhatt et al., 2008; Trelle et al., 2011). Aspirin is a universal anti-inflammatory drug that is generally preferred and widely used by many patients (Szczeklik et al., 1977). In the United States, 60% of people over the age of 65 years use aspirin at least once

a week (Bhatt et al., 2008). Low doses of aspirin are useful for reducing cerebrovascular and cardiovascular risks (Yudkin et al. 2000; Bhatt et al., 2008). Furthermore, aspirin, ibuprofen and indomethacin administration induce exponential declines in the risk of colon, breast, lung, and prostate cancers (Dihlmann et al., 2001; Harris et al., 2005). Low doses of ibuprofen were also reported to have more rapid analgesic effects compared with a high dose of acetaminophen (Ong et al., 2007). An in-depth comparison of the analgesic efficacies and toxic side effects of over 30 traditional NSAID's and selective COX-2 inhibitors as reflected in the Oxford League Table (http://www.jr2.ox.ac.uk/bandolier/index.html) can be found in a review by Ong et al. (2007). However, prolonged use of non-steroidal anti-inflammatory drugs is associated with harmful side effects, including asthmatic attacks (Szczeklik et al., 1977), upper gastrointestinal bleeding and perforation (Garcia and Jick, 1994; Wolfe et al., 1999), increased cardiovascular risk (Howard and Delafontaine, 2004; Bresalier et al., 2005) and high blood pressure (Johnson et al., 1994).

Non-steroidal anti-inflammatory drugs function via their ability to inhibit the synthesis of prostaglandins by blocking the active sites on cyclooxygenase enzymes (Szczeklik, 1977). Some NSAIDs such as indomethacin are also effective in blocking prostaglandin transporter proteins (Reid et al., 2003). Inhibition of prostaglandins derived from COX-1 such as $PGI_2$ and $PGE_2$ by NSAIDs was found to be associated with gastrointestinal toxicity with prolonged use (Warner and Mitchell, 2002). Further attempts to develop selective COX-2 inhibitors resulted in undesirable cardiovascular risks (Bresalier et al., 2005). Prostaglandins $I_2$ is an important prostanoid that regulates cardiovascular homeostasis (Ricciotti and FitzGerald, 2011). The selective COX-2 inhibitor rofecoxib was withdrawn from the market after it was found to increase the risk of cardiovascular events (Bresalier et al., 2005; Trelle et al., 2011). In addition, patients under rofecoxib treatment also had increased thrombotic events (Bresalier et al., 2005). Prostaglandin synthetase inhibitors including indomethatin, fenamates, fenoprofen, ibuprofen, diclofenac, naproxen, noramidopyrine, and phenylbutazone are further associated with asthmatic attacks in some people (Szczeklik, 1977). A study by Trelle et al. (2011) showed that patients suffering from cardiovascular disorders expressed various side effects including stroke, myocardial infarction and death upon administration of NSAID's including naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib and lumiracoxib when compared with placebos (Trelle et al., 2011). There are few synthetic drugs that have been developed against the lipoxygenase pathway. Zileuton is a commercialised drug which inhibits the activity of 5-LOX enzyme (Haeggström and Funk, 2011). Furthermore, clinical trials of zileuton have

shown beneficial effects in rheumatoid arthritis, inflammatory bowel disease, psoriasis, allergic rhinitis and asthma (Drazen et al., 1999; Haeggström and Funk, 2011). Notably, zafirlukast, montelukast and pranlukast have passed clinical trials as selective inhibitors of $LTC_4$, $LTD_4$ and $LTE_4$ receptors (Drazen et al., 1999).

## 6. An overview of inflammation and pain in southern Africa

In southern Africa, medicinal plants play an important role as a primary source of healthcare for many individuals, particularly rural residents (Amusan et al., 2002; Maroyi, 2011; Bruschi et al., 2011; De Wet et al., 2013; Seleteng-Kose et al., 2015; Hulley and Van Wyk, 2019). The indigenous knowledge of plant use is typically restricted to a group of people with shared values and cultural beliefs and is transmitted orally across generations (Stafford, 2004). Unlike random plant selection, ethnobotanical studies have remained a major tool in the discovery of medicinal plants and their application (Mabogo, 1990, Pujol, 1990, Hutchings et al., 1996, Van Wyk and Gericke, 2000; Von Koenen, 2001; Magwede et al., 2019). However, according to Van Wyk and Gericke (2018), ethnobotanical studies are still relatively underdeveloped in the southern African region and urgent documentation is required as this knowledge is being lost to modern generations (Zobolo and Mkabela, 2006). The use of medicinal plants is not only limited to their availability and affordability (Mander, 1998), but is also culturally driven, as these plant products are also found in urban settlements (Mander, 2004; Williams, 2004, Williams et al., 2013). The holistic healing approach of traditional medicine is one of the major factors that contributes to their preferred use (Mander et al., 2007).

The limitation of natural harvesting sites in urban areas further encourages the trade of indigenous medicinal plants, which in turn forms an integral part in supplying and sustaining large numbers of consumers. In 2001, a survey conducted at the Johannesburg '*muthi'* markets revealed that approximately 12 – 15 million consumers of medicinal plant products are in urban settlements (Williams, 2004). Another survey in Durban, KwaZulu-Natal, reported that 84% of the black population is dependent on both western and traditional medicine (Mander, 2004). In South Africa alone, there are an estimated 27 million consumers of these plant products (Mander, 2007). The Faraday traditional medicine market in Johannesburg is known to be the biggest in southern Africa and also serves customers from other parts of the southern African region (Williams and Whiting 2016). In addition, many traders at the street markets of Durban and Johannesburg were reported to have come from Mozambique and Eswatini (Swaziland) due to the active plant trade from these countries to South Africa (Mander et al., 2007).

Previous reviews on anti-inflammatory properties of southern African medicinal plants have mainly focused on a specific region, particularly South Africa and these reviews included non-specific ailments of inflammation (Iwalewa et al., 2007; Adebayo and Amoo (2019). There is little information available about the southern African medicinal plants used specifically to relieve pain and inflammation. Hutchings and Van Staden (1994) recorded 96 medicinal plants used to treat headaches by the Zulu, Xhosa and Sotho ethnic groups of southern Africa. In addition, 67% of recorded medicinal plants had potential analgesic effects, and 22% display potential anti-inflammatory properties (Hutchings and Van Staden, 1994). The prevalence of chronic pain in South Africa was reported to be as high as 11.3% in young people between the ages of 15 and 24 years and 34.4% for elderly people over 65 years (Kamerman et al., 2020). Kamerman et al. (2020) interviewed 10336 people in both rural and urban settlements as part of the South African National Demographic Survey. Surprisingly, their data revealed that chronic pain prevalence in South Africa was not related to the sociodemographic status of the population groups, nor on their education, residence, employment, wealth and access to private health insurance (Kamerman et al., 2020). In contrast, in western countries, the prevalence of chronic pain varied based on the sociodemographic factors, with the highest incidences in lower income groups (Verhaak et al., 1998).

The present review focuses on ethnopharmacological properties of 555 medicinal plants belonging to 118 families that are used traditionally for inflammation and pain-related ailments in the southern African region, including Zimbabwe and Mozambique, which have generally not been mentioned in previous reviews. This study reviewed the use of plants to treat disorders including inflammation, pain, toothache, headache, backache, rheumatism, oedema or swellings, general body pains, earache, abdominal pains, arthritis, chest pains, internal body pains, haemorrhoids, labour pains and rheumatic fever. Despite popularity of their use in traditional medicine, most of these plant species still lack pharmacological and phytochemical investigation and much more work is required.

## 7. Materials and methods

The aim of this study was to document southern African medicinal plants that are used traditionally for inflammation and pain-related ailments. Several ethnobotanical books (Watt and Breyer-Brandwijk, 1962; Pujol, 1990; Hutchings et al., 1996; Van Wyk and Gericke 2000, 2018; Von Koenen, 2001; Van Wyk et al., 2009; Van Wyk et al., 2011) and grey literature in the form of thesis publications, as well as multiple peer reviewed journal articles were

consulted. Google-Scholar, PubMed, Scopus and Science-Direct electronic databases were used to identify original scientific research papers. The following terms were used as filters and were searched both alone and as combinations: “Southern Africa”, ‘’South African’’, “Namibia” ‘’Lesotho’’ “Swaziland”, “Botswana“ “Zimbabwe”, “Mozambique”, “medicinal plant”, “ethnobotany”, “pain”, “inflammation” “anti-inflammatory”, “cyclooxygenases”. All terms were searched both alone and in combinations. The initial aim was to document medicinal uses of all plant species applied therapeutically for pain and inflammatory disorders in southern Africa. A thorough literature search identified 555 plant species belonging to 118 families. This represents a substantial increase on the number of species identified in previous studies. Most of these species are native southern African plants. A further literature review was undertaken on the recorded plant species to identify those reported for their anti-inflammatory properties.

*7.1. Eligibility criteria*

Peer reviewed journal articles and grey literature were searched using specific key words, based on their relevance to the study. Abstract reading was performed to obtain the full content of publications. The cited publications included in this study were all full text manuscripts and were thoroughly read to ensure that eligibility criteria were met.

*7.2. Inclusion criteria*

The following inclusion criteria for eligibility of the study were considered:

• Publications written in English and prior to August 2020 were used in this review.
• This review study is non-biased and without any taxonomic preference.
• In terms of ethnobotanical literature surveys to be included in this review, the plant species must be recorded to be used specifically for pain and inflammatory disorders, instead of just being recorded to treat individual non-specific symptoms.
• In terms of biological activity, only plant species that are used traditionally for pain and inflammation were included, rather than random plant selection or taxonomically related species.
• Ethnobotanical studies on the flora of southern African region included Botswana, Lesotho, Mozambique, Namibia, South Africa, Eswatini (Swaziland) and Zimbabwe.

*7.3. Exclusion criteria*

The following criteria were used to exclude some studies:

• Where name changes and families of plant species were encountered, particularly in older publications, websites such as The Plant List (http://www.theplantlist.org/) and South African National Biodiversity Institute (SANBI) (http://www.sanbi.org) were used to confirm the correct or current nomenclature of the species.

• Plant species that are used to treat symptoms of inflammation such as fever, colds and coughs as well as allergies without specifically stating that they are used to treat inflammation were excluded from this study.

• Introduced and exotic species were excluded, unless they were extensively used as part of southern African traditional medicine.

*7.4. Data collection*

A thorough literature search of publications on the southern African medicinal plants used therapeutically for pain and inflammation were obtained and included in this study. Also, *in vivo* and *in vitro* biological screening of southern African medicinal plants specifically to treat pain and inflammatory disorders were included, regardless of the study origin.

The following data was collected:

• Plant name and families for each species recorded in the individual publications. Plant names, genera and families were all updated using The Plant List (http://www.theplantlist.org/) and SANBI (http://www.sanbi.org) website.

• Vernacular names of different ethnic groups were collected from publications and SANBI red list website.

• The plant part used, method of preparation and mode of administration were collected (where available).

Microsoft Excel was used for statistical data analysis.

**8. Results**

*8.1 Southern African medicinal plants used traditionally to treat inflammation and associated symptoms*

A thorough literature search including peer reviewed journal articles, grey literature as well as ethnobotanical books was conducted. The present review identified 555 medicinal plants (Appendix 1) that are used traditionally for the treatment of pain and inflammatory disorders in southern Africa. The list includes native southern African plant species and naturalised exotics (indicated by a single asterisk in Appendix 1). Disorders treated include

inflammation and pain associated with inflammation, including toothache, headache, backache, rheumatism, oedema or swellings, general body pains, earache, abdominal pains, arthritis, chest pains, internal body pains, haemorrhoids, labour pains and rheumatic fever. Our study identified 118 plant families with at least one species traditionally used to treat these conditions. The majority of medicinal plants recorded in this study were used to treat more than one ailment. Similar results have also been reported by various authors across the southern African region (Mabona and Van Vuuren, 2013; Maroyi, 2011, Bruschi et al., 2011; Hulley and Van Wyk, 2019; Magwede et al., 2019; Mhlongo, 2019; Cock and Van Vuuren, 2020). There were very few species that are used in combination for treating the same ailment. This indicates that southern African medicinal plants used for pain and inflammation are commonly taken as individual plant species. In contrast, plant combinations are common in medicinal plants used as tonics, blood cleansers and aphrodisiacs, where multiple plants are incorporated as ingredients to prepare plant mixtures known as *imbiza* in Zulu (Mhlongo, 2019), or *tshinza* in Venda (Magwede, 2018). New information from recent ethnobotanical surveys identified a number of species reported for the first time for pain and inflammatory disorders. For example, one such study by Mhlongo and Van Wyk (2019), focusing on the Zulu medicinal ethnobotany from the Amandawe area of KwaZulu-Natal, reported more than 40 species as new uses for inflammation, although they are also popularly used for various other ailments.

Figure 1 shows the 15 plant families with the greatest representation as anti-inflammatory remedies (based on the number of species represented). Fabaceae is the leading family with 63 species, followed by Asteraceae (54 species) and Apocynaceae (33 species). These findings are similar to a recent review by Elgorashi and McGaw (2019) on African medicinal plants that are used to treat inflammation. In their study, the top three commonly studied families with in vitro anti-inflammatory properties were Asphodelaceae (14.4%), followed by Fabaceae (7.3%) and Asteraceae (6.3%). Other ethnobotanical studies in the southern African region including Mozambique, Zimbabwe and Namibia have also reported Fabaceae as the predominant family for medicinal plant use to treat a variety of illnesses (Bruschi et al., 2011; Maroyi, 2011; Cheikhyoussef et al., 2011). Fabaceae and Asteraceae are also the most frequently reported families recorded for medicinal plant use by the South African Zulu, Venda and Sotho ethnic groups (Hutchings et al., 1996; Seleteng-Kose et al., 2015; Mhlongo and Van Wyk, 2019; Magwede et al., 2019). Although Asteraceae is the predominant family in southern Africa (Koekemoer et al., 2013), previous ethnobotanical studies of different ethnic groups highlight a high preference of medicinal plant use for the

Fabaceae family. Furthermore, a review by Almeida et al. (2001), recorded 166 plant species with noteworthy analgesic activity from 40 countries including South Africa. In their review, Fabaceae, followed by Asteraceae and Lamiaceae, are the predominant families globally with a high number of species exhibiting analgesic properties. A recent family-level review and analysis of African medicinal plants by Van Wyk (2020), also concluded that the Fabaceae are the dominant family in terms of species numbers. In a regression analysis, the Fabaceae were found to be significantly ($p$<0.05%) over-represented, followed by the Apocynaceae, Rutaceae and Apiaceae.

The most frequently recorded genera for the treatment of inflammation and pain include *Solanum* (9 species), *Aloe* (7 species), *Helichrysum* (7 species), *Ficus* (7 species) and *Vachellia* (7 species). The genus *Solanum* is commonly used for the treatment of toothache by multiple ethnic groups in South Africa and Mozambique. Species of the same genus with the same Zulu vernacular name were recorded for *Helichrysum (impepho)* and *Aloe (inhlaba)*. These species also had shared traditional medicinal uses and mode of administration. *Helichrysum* species are popularly used to relieve pain, while *Aloe* species are commonly used for inflammation and arthritis. Several studies have reported the anti-inflammatory properties of species from the genus *Helichrysum* (Jäger et al., 1996; Lourens et al., 2004; 2008) and *Aloe* (Lindsey et al., 2002; Chen et al., 2012; Cock, 2015).

An overview of medicinal plant uses related to pain and inflammation is shown in Figure 2. The most frequently cited categories of ailments include inflammation with 150 species, general pain (148 species), headache (114 species), toothache (114 species) and backache (102 species). Headache, associated with depression-anxiety disorders was found to be the most common chronic pain in southern Africa (Tsang et al., 2008). Other than musculoskeletal disorders, headache and abdominal pain were the most frequently reported ailments in western countries (Verhaak et al., 1998). The effectiveness of medicinal plants used to relieve headache associated with anxiety may be attributed to their sedative properties (Hutchings and Van Staden, 1994). Medicinal plants used for toothache are also popular in developed countries. Fakir et al. (2016), recorded 87 medicinal plants used for pain in Turkey, toothache was also the third most frequently reported pain-related ailment. The present study found that back pain is the fifth most common category of chronic pain, represented by a number of medicinal plants in southern Africa. These finding are quite similar to those reported by Louw et al. (2007), who observed an increase in the prevalence of lower back pain in Africa, particularly in southern Africa.

The most common methods of preparation of southern African plants to be used as anti-inflammatory and analgesic therapies are decoctions (111 species) and infusions (103 species). These plant extracts are frequently administered orally as mouthwashes to relieve toothache and other internal ailments, applied externally as a wash, taken as aqueous lotions or eyedrops to treat inflamed eyes and also used as eardrops to relieve earache. These findings are in accordance with previously published studies, which have also cited decoctions and infusions as the most frequently used method of preparations in southern Africa (Mabona and Van Vuuren, 2013; Maroyi, 2011, Bruschi et al., 2011; Magwede et al., 2019; Cock and Van Vuuren, 2020). Powdered plant preparations were also frequently used (100 species). Plant powders are usually administered as a snuff or taken orally by licking to relieve headaches and body pains. Similar observations were also recorded by various authors (Hutchings and Van Staden, 1994; Jäger et al., 1996; Khumalo, 2018), who found that most plant powders used to treat headaches are taken as inhalations, either as a snuff or smoked. Poultices (21 species) and pastes (11 species) were less frequently used methods of preparation for anti-inflammatory and analgesic therapies from southern African plants.

Figure 3 represents the frequency that individual southern African plant parts are used as anti-inflammatory and analgesic therapies. The use of leaves was most frequently recorded (201 species), followed by the roots with 177 species and bark with 111 species. Leaves were also found to be the predominant plant part used for pain related ailments in other parts of the world (Fakir et al., 2016). Various authors prefer using leaves for conducting biological assays because of their sustainability and minimal harm to the plant. However, bark and roots are the predominant plant parts sold at informal traditional *muthi* markets in southern Africa due to their long shelf life (Grace et al., 2003; Van Wyk et al., 2011; Khumalo, 2018). These markets supply millions of consumers and contribute an annual value of R2.9 billion to the South African economy. This represents approximately 5.6% of the annual National Health budget in South Africa (Mander et al., 2007). Notably, a recent study by Khumalo (2018), revealed that 82% of the 70 most popularly sold medicinal barks at the Johannesburg *muthi* markets are of least concern according to the SANBI database. It is an important consideration that different plant parts contain different secondary metabolites and cytotoxic properties. For example, bark often contains higher levels of bioactive polyphenols than other plant parts from the same species (Jablonsky et al., 2017, Mukherjee et al., 2018). Unlike underground plant parts, tree bark is a regenerative material if sustainable harvesting procedures are followed (Geldenhuys,

2004; Twine, 2004; Van Wyk et al., 2011; Khumalo, 2018). However, where bark and leaves of the same species are used for a similar purpose, it is preferable to use the leaves.

*8.2 Scientific studies into the anti-inflammatory and analgesic properties of southern African plants*

Previous studies have examined the anti-inflammatory activity of southern African medicinal plants (Table 1). Out of 555 recoded medicinal plants that are specifically used for pain and inflammation, only 200 were screened for their anti-inflammatory and analgesic properties. The recorded biological activities in this review, included medicinal plants that were screened on the basis of traditional use. Hence, it is important to note that plant species with anti-inflammatory and analgesic properties reported may not reflect a full representation of the overall southern African medicinal plants screened. However, such studies are necessary to highlight the extent of work done in the field and to identify possible species that require attention. For example, a review by Cock and Van Vuuren (2020), focusing on southern African medicinal plants used to treat fungal skin infections, reported that only 19 out of 140 species to be screened on the basis of traditional use, while, the remaining 121 plant species were screened based on availability and taxonomic similarities other than ethnobotanical uses (Cock and Van Vuuren, 2020). Such low correlation between the species screened and traditional medicinal plants used could be misleading in terms of identifying plants that have been scientifically explored for their relevant ethnopharmacological uses.

Different solvent extracts influence the outcome of biological activities of traditional medicinal plants. Figure 4 shows different solvent extracts that are commonly used for performing anti-inflammatory and analgesic assays of southern African medicinal plants. The results indicate a high preference of ethanol as a solvent extract with 59% of medicinal plants screened, followed by acetone with (38%) and methanol with (34%). There were relatively few studies whereby medicinal plants were extracted with water for anti-inflammatory assays, although this mechanism is the common practice used by lay people and traditional healers. Interesting results were noted from aqueous extract of *Melianthus comosus* which exhibited noteworthy 5-lipoxygenase inhibitory activity with an $IC_{50}$ value of 13.84 μg/mL (Frum and Viljoen, 2006). The leaf decoction of *M. cosmosus* is widely used as a wash for body pains, backache, rheumatoid arthritis, inflammation and also taken as a mouthwash to relieve toothache. Furthermore, infusion of the roots has been used traditionally in the treatment of cancer (Hutchings et al., 1994; Van Wyk et al., 2009; Hulley and Van Wyk, 2019). Other biological properties of *M. cosmosus* include antibacterial, antifungal and antioxidant activities

(Maroyi, 2019). Only 2% of the biological screening studies tested essential oils. De Sousa et al. (2011), in a review focusing on analgesic-like activity of essential oils constituents, also highlighted a lack of available studies on the essential oils of medicinal plants used as analgesics. In addition, the review documented 43 compounds with noteworthy analgesic activity extracted from essential oils of different plant species. Among these, monoterpenes (62.8%) and sesquiterpenes (18.6%) were the most frequently reported classes of secondary metabolites with analgesic properties (De Sousa et al., 2011). Multiple classes of compounds extracted from essential oils have been shown to be effective in pain models (De Sousa et al., 2011). Essential oils from the leaves of *Cinnamomum osmophloeum* Kaneh., a popular Taiwanese plant, greatly decreased IL-1β and IL-6 productions in LPS-stimulated macrophages (Chao et al., 2005). In addition, essential oils of the twigs significantly reduced $PGE_2$ production by up to 65% in LPS-induced RAW 264.7 cells (Tung et al., 2008).

Several studies have examined the anti-inflammatory and analgesic activity of southern African medicinal plants (Jager et al., 1996; Shale et al., 1999; Iwalewa et al., 2007; Akula and Odhav, 2008; Fawole et al., 2010; Chinsamy et al., 2014; Dzoyem and Eloff, 2015; Elisha et al., 2016; Adebayo and Amoo, 2019; Du Preez et al., 2020). The leaves were most frequently investigated with 118 species, followed by the bark (35 species) and roots (23 species). The fruits and bulbs were the least used plant parts for biological assays. Interestingly, fruits and bulbs were also the least preferred plant parts used traditionally for treatment of pain and inflammation. The leaves (53%), followed by roots (15%) and bark (10%), were also the most investigated plant part of African medicinal plants screened for *in vitro* anti-inflammatory activity (Elgorashi and McGaw, 2019). The majority of these biological assays have screened plant extracts against COX and LOX enzymes. Lipoxygenase inhibition assays (5-LOX and 15-LOX) were used to screen 97 species, making them the preferred technique for evaluating the anti-inflammatory activity of southern African medicinal plants. This is followed by cyclooxygenase inhibition assays (COX-1 and COX-2), with 92 species screened, and the nitric oxide inhibition assay with 41 species. While the inhibition of inflammatory enzymes has some beneficial effects in the management of pain and chronic inflammatory disorders (Adebayo and Amoo, 2019), inhibition of pro-inflammatory cytokines, chemokines and prostanoids is considered a more effective strategy to resolve inflammation (Chen et al., 2018). Notably, there are very few studies (11 plant species) that have investigated the cytokine inhibitory activity of medicinal plants using *in vivo* techniques. In addition, over 90% of these biological assays were conducted in South Africa. A recent review on African medicinal plants also reported that

most of the biologically active plant species were found in the sub-Saharan region, with 72% from South Africa (Elgorashi and McGaw, 2019).

## 9. Discussion

Inflammation and pain remain serious global concerns that have a negative impact on the well-being of many individuals worldwide. Furthermore, various treatment options (pharmacological treatments, conservative care, surgery, spinal cord stimulators, implantable drug delivery systems, and pain rehabilitation programs) for chronic pain create a huge financial burden as these pain inhibitors are very expensive (Turk, 2002). Multiple limitations exist for successful treatment of chronic pain and none was found to eliminate pain for most patients surveyed (Turk, 2002). Available current drugs to treat inflammation and pain include NSAIDs and antinociceptive drugs. However, these therapeutics are often associated with multiple harmful and toxic side effects. When acute inflammation is unresolved, various health complications that could alter the normal functioning of the body's immune system emerge. These include chronic inflammatory diseases such as rheumatoid arthritis, osteoarthritis, Alzheimer's disease, as well as cardiovascular and pulmonary disorders (Pahwa et al., 2019). Chronic inflammatory disorders are predicted to drastically increase in the next 30 years (Pahwa et al., 2019). Thus, there is an urgent need for new anti-inflammatory and analgesic drugs, especially those derived from natural products (De Sousa et al., 2011; Fürst and Zündorf, 2014). Hence, pharmaceutical industries and academic researchers have gained interest in medicinal plants in search for alternative therapeutics to treat inflammation and pain (Iwalewa et al., 2007).

Considering the rich flora and unique cultural diversity of southern Africa (Russell, 1984; Van Wyk and Gericke 2018), scientific investigation of medicinal plants with anti-inflammatory properties is imperative. The lack of infrastructure and poor health care services in developing countries could result in severe health complications, particularly those affecting the immune system (Du Preez et al., 2020). In southern Africa, skin disorders appear to be the most prevalent cause of an inflammatory response, especially those associated with sores and delayed wound healing (Mabona and Van Vuuren, 2013; Chingwaru et al., 2019; Du Preez, et al, 2020). Chronic wounds are regarded as one of the major causes of medical consultations and hospital admissions worldwide (Chingwaru et al., 2019), with 20% of cases reported from the rural areas of developing countries (Ryan, 1992; Frum and Viljoen, 2006). Hence, a large number of southern African medicinal plants associated with skin ailments are used for sores

and wound healing (Lindsey et al., 2002; De Wet et al., 2013; Mabona and Van Vuuren, 2013; Khumalo, 2018; Chingwaru et al., 2019). In contrast to modern pharmaceuticals, medicinal plants are cost effective, readily available and have limited side effects (Mander et al., 2007; Makunga et al., 2008).

Studies of southern African medicinal plants focusing specifically on pain and inflammatory disorders have received some attention. Iwalewa et al. (2007) reviewed and documented 123 South African medicinal plants used for inflammation and pain. The field has substantially advanced since then and recent updates by Adebayo and Amoo, (2019) have expanded on the knowledge by recording a further 214 plant species. Whilst this provides good basis for future studies, the available reviews only focused on a limited region (South Africa) and also included medicinal plants used for non-specific symptoms of inflammation such as asthma, fever, infections, malaria, colds and coughs. In addition, the earlier review by Iwalewa et al. (2007) was limited in not accommodating the ethnobotany of many ethnic groups in the region, as it only reported traditional uses documented in Watt and Breyer-Brandwijk, (1962) and Hutchings et al., (1996). Therefore, a large contribution of the species in that study are focused on the Zulu ethnic group. This perhaps not surprising, since Zulu ethnobotany is the most popular and most extensively documented of the southern African ethnic groups. Furthermore, the previous reviews did not describe the method and mode of administration. This is a critical aspect, especially when the motive for scientific evaluation of medicinal plants is to be used in search for alternative therapeutics. The mode of administration provides useful and important information, especially since most of the recorded medicinal plants used for inflammation and pain are for external application and may be poisonous when administered orally. Such limited information of plant use limits the potential of medicinal plants as anti-inflammatory and analgesic agents.

This review has examined the ethnobotany of a wider range of ethnic groups from the southern African region, including the Nama and Khoisan. A rather unexpected finding was the differences in ethnic groups in terms of mode of administration for plants used for headaches. In the Karroo region (Nortje and Van Wyk, 2015; Hulley and Van Wyk, 2019), the plants parts are normally placed at the forehead to relieve headaches, while the Zulu, Xhosa and Sotho ethnic groups usually smoke or inhale powdered plant material (Hutchings and Staden, 1994; Mhlongo, 2019). Most of the plants that are used for swellings and body pains are taken as raw plant material or heated over a fire and directly applied on the inflamed area of the skin. This form of administration was noted across the different ethnic groups of southern

African. In contrast with South Africa, there is little knowledge available about the medicinal plants used for pain and inflammation from other regions of southern Africa. Medicinal plants used traditionally in Botswana were the least documented across the southern African region. Not sure if this is correct. The classical source of information on Botswana medicinal plants is Hedberg and Staugård (1989) "Traditional Medicine in Botswana. Traditional Medicinal Plants." (Ipelegeng Publishers). Their Appendix 3 has a list of medicinal plants arranged by use-category. According to Motlhanka and Nthoiwa, (2013) there are relatively few ethnobotanical surveys of medicinal plant use in Botswana although more studies have focused on food plants.

*9.1 Anti-inflammatory activity of southern African medicinal plants*

This review has identified 355 out of the total 555 medicinal plants that have not been scientifically evaluated with regards to their traditional use as pain and anti-inflammatory agents. Surprisingly, there were more studies on LOX compared to COX inhibition, although this difference was not substantial. Considering that cyclooxygenases are associated with the induction of various chronic inflammatory diseases, decreasing the activity of COX enzymes may have greater effects in reducing the overall symptoms associated with inflammation. Therefore, more work focusing on screening plant extracts against the COX pathway is required. Moreover, the majority of plant extracts that have been screened against COX enzymes lack $IC_{50}$ values, which makes the biological activities non-comparable.

Medicinal plant extracts that can hinder both COX and LOX enzymes, particularly with selective COX-2 inhibition, could be considered as potential targets for the development of anti-inflammatory therapeutics (Adebayo and Amoo, 2019). Some records of popular southern African medicinal plants with significant anti-inflammatory properties against the LOX pathway include *Acokanthera oppositifolia, Burkea africana, Bidens pilosa, Bulbine natalensis, Carpobrotus dimidiatus, Carpobrotus edulis, Clausena anisata, Datura stramonium, Eucomis autumnalis, Melianthus comosus, Plantago lanceolata, Tetradenia riparia* and *Tecomaria capensis* (Frum and Viljoen, 2006; Lall and Kishore, 2014; Adebayo et al., 2015, Elisha et al., 2016; Ondua et al. 2016, 2019; Ghuman et al., 2019). Interesting results were noted for the hexane leaf extract of *T. capensis*, which displayed potent 15-LOX inhibition ($IC_{50}$ of 4.65 μg/mL) that was significantly more active than the positive control quercetin ($IC_{50}$ of 24.60 μg/mL) (Ondua et al., 2019). *Typha capensis* is a popular and important southern Africa medicinal plant used for the treatment of multiple disorders including sexually transmitted diseases, gastrointestinal ailments, male infertility and to facilitate childbirth during

pregnancy (Van Wyk et al., 2009). Further studies of the anti-inflammatory properties of this plant, including phytochemical profiling and mechanism of action studies are lacking. Furthermore, most of these medicinal plant extracts have been tested against a single biotarget, which is insufficient to validate its anti-inflammatory or analgesic properties. For example, a 50% aqueous: 50% methanol stem extract of *Zantedeschia aethiopica* displayed noteworthy 15-LOX inhibition with $IC_{50}$ of 9.05 μg/mL, while exhibiting moderate NO inhibition at $IC_{50}$ of 46.22 μg/mL (Ghuman et al., 2019). In some cases, chemical variations may influence the activity of plant extracts. The methanol leaf extract of *Carpobrotus edulis* displayed noteworthy 5-LOX inhibition at $IC_{50}$ of >100 μg/mL (Frum and Viljoen, 2006), while demonstrating good 15-LOX inhibition at $IC_{50}$ of 9.84 μg/mL (Ghuman et al., 2019). The lipoxygenase pathway catalyses the formation of leukotrienes from arachidonic acid, which are important inflammatory mediators in the recruitment of leukocytes from the blood vessels to the site of injury (Rådmark et al., 2015). Furthermore, leukotrienes have also been implicated in the formation of other chronic inflammatory diseases such as asthma, allergies and cardiovascular disorders (Lewis et al., 1990).

Southern African medicinal plants with anti-inflammatory properties against the COX pathway include *Abrus precatorius, Antidesma venosum, Bulbophyllum scaberulum, Clerodendrum myricoides, Combretum kraussii, Colocasia antiquorum, Senecio serratuloides, Synadenium cupulare* and *Vachellia sieberiana* (Jäger et al., 1996; McGaw et al., 1997; Shale et al., 1999; Eldeen et al., 2005; Fawole et al., 2009, 2010; Aremu et al., 2010; Mulaudzi et al., 2013; Chinsamy et al., 2014; Madikizela et al., 2014). The ethanol root extract of *B. scaberulum* displayed potent selective COX-2 inhibition with $EC_{50}$ of 0.44 ± 0.32 mg/mL (Chinsamy et al., 2014). Although *B. scaberulum* roots are used to treat inflammation (Adebayo and Amoo, 2019), very little is known about the phytochemical and pharmacological properties of this plant. Phytochemical analysis of the stem and roots revealed the presence of flavonoids (Chinsamy, 2012). The induction of COX-2 during an inflammatory response has also been associated with the initiation of various types of cancers (Coussens and Werb, 2002). Whilst reported to have good anti-inflammatory activity, most extracts have been screened at a single concentration and therefore cannot be benchmarked against other studies. Furthermore, many of the biological assays reported from various authors lack cytotoxicity studies. Although some of the tested medicinal plants have previously been evaluated in other studies, several others have never been screened for cytotoxicity. Considering the toxic and harmful side effects associated with NSAIDs, it is noteworthy to include toxicity assays when screening for the

anti-inflammatory and analgesic properties of medicinal plants. This is of particular interest when determining the safety and therapeutic indices of medicinal plant extracts. In addition, over 80% of studies reporting biological activities did not examine the phytochemical properties of plant extracts. Extensive work is needed to examine the phytochemical constituents of these medicinal plants used for pain and inflammation.

The nuclear factor-κB is a dimeric transcription factor, which when it is activated, regulates the production of pro-inflammatory cytokines, adhesion molecules, chemokines, growth factors and inducible enzymes such as COX-2 and inducible nitric oxide synthase (Tedgui and Mallat, 2006). Cytokines including TNF-α, IL-1, and IL-18, as well as microbial pathogen stimulation of Toll-like receptors, activate the NF-κB pathway (Tedgui and Mallat, 2006; Chen et al., 2018). Cytokines, chemokines and growth factors also act as regulators in the activation and functioning of various mechanisms involved in chronic inflammatory disorders (Feghali and Wright, 1997). Interleukin-6 for example plays a critical role in the initiation of clinical coronary diseases, obesity and type-2 diabetes through the production and regulation of the acute phase reactant, C-reactive protein in the liver (Yudikin et al., 2000). High concentrations of circulating C reactive proteins have also been reported as a major cause of cardiovascular mortality (Yudikin et al., 2000). An upregulation of IL-1β, IL-6, TNF-α, IL-8 and transforming growth factor-β, coupled with an accumulation of amyloid β peptide, neurofibrillary tangles, and neuronal degeneration in the central nervous system, act as potent inducers of Alzheimer's disease (Lim et al., 2000; Takeda et al., 2013). Weng et al., (2020) described a mechanism by which chemokines function in the invasion of neutrophils around the airways, causing severe chronic asthma. In rheumatoid arthritis, high concentrations of TNF-$\alpha$ and interleukin-1 found in the synovial and serum stimulate mesenchymal cells that release tissue-destroying matrix metalloproteinases, thus causing bone and cartilage damage (Choy and Panayi, 2001). Non-steroidal anti-inflammatory drugs have been shown to reduce the risk of chronic diseases in patients (Yudikin et al., 2000).

Very little is known about the effects of southern African medicinal plants in cytokine assays. Cytokines may exhibit physiological, pathophysiological and therapeutic functions (Tedgui and Mallat, 2006). Aqueous leaf extracts of *Adansonia digitata* induce a significant decrease of IL-6 and IL-8 *in vitro* (Selvarani and Hudson, 2009). The methanol leaf extract of *X. caffra* inhibits mRNA expression of pro-inflammatory genes (IL-6, iNOS, and TNF-$\alpha$) using RT-qPCR *in vitro*. The extract significantly decreased the NF-$\kappa$B transcription activity in a dose-dependent manner, by approximately 60% compared to the control (Zhen et al., 2015).

Furthermore, a significant decline was observed in the expression of IL-6, up to almost 100-fold compared to untreated LPS induced cells (Zhen et al., 2015). *Aspalathus linearis* (commonly known as rooibos tea) was able to significantly decrease TNF-α and IL-6 levels in the liver of mice (Oguntibeju, 2018). A recent study by Du Preez et al. (2020), reported the antiproliferation activity of popular Namibian medicinal plants that are used traditionally for inflammatory disorders. All the tested medicinal plants (*Acanthosicyos naudininus, Gomphocarpus fruticosus*, and *Cryptolepis decidua*) substantially inhibit T-lymphocyte activation by suppressing CD25 and CD69 surface receptor expression and the extracts also suppressed effector functions by decreasing the production of IFN-γ and IL-2 (Du Preez et al., 2020).

## 10. Conclusions

While southern African medicinal plants used for inflammation and pain have received some attention, substantially more work is required. Previous reviews into this topic were limited in their scope of study in terms of geographic region and the ethnobotanical knowledge of many ethnic groups was overlooked. Furthermore, information about the method of preparation and mode of administration was not reported. Whilst there was some level of contribution on the ethnobotany of other groups of southern Africa, Botswana was the least studied region. The majority of biological assays have focused on COX or LOX pathways which have only been screened on one aspect. More work is required to scientifically evaluate plant extracts against cytokine assays and *in vivo* studies.

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## Author contribution

G. Khumalo and I. Cock conceptualised the study and wrote the initial draft. Y. Feng, B-E. Van Wyk and I. Cock edited the manuscript. Y. Feng assisted with chemistry aspects. B-E. Van Wyk provided expertise with taxonomy and ethnobotany. All authors edited and approved the manuscript.

## Figures

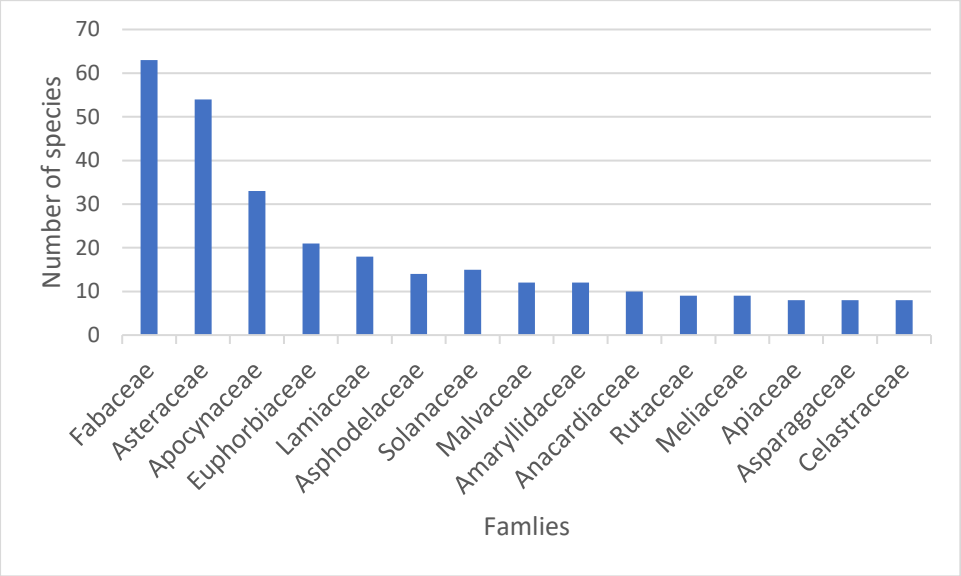


Fig. 1. Southern African plant families of medicinal plants used to treat inflammation and pain, as recorded in the literature.

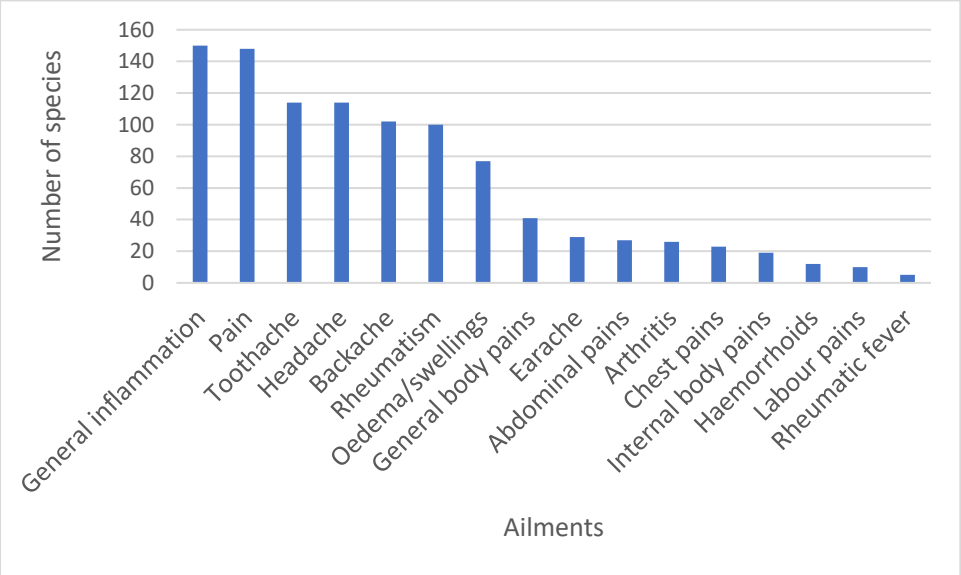


Fig. 2. The most frequently cited categories of disorders for southern African medicinal plants used to treat inflammation and pain

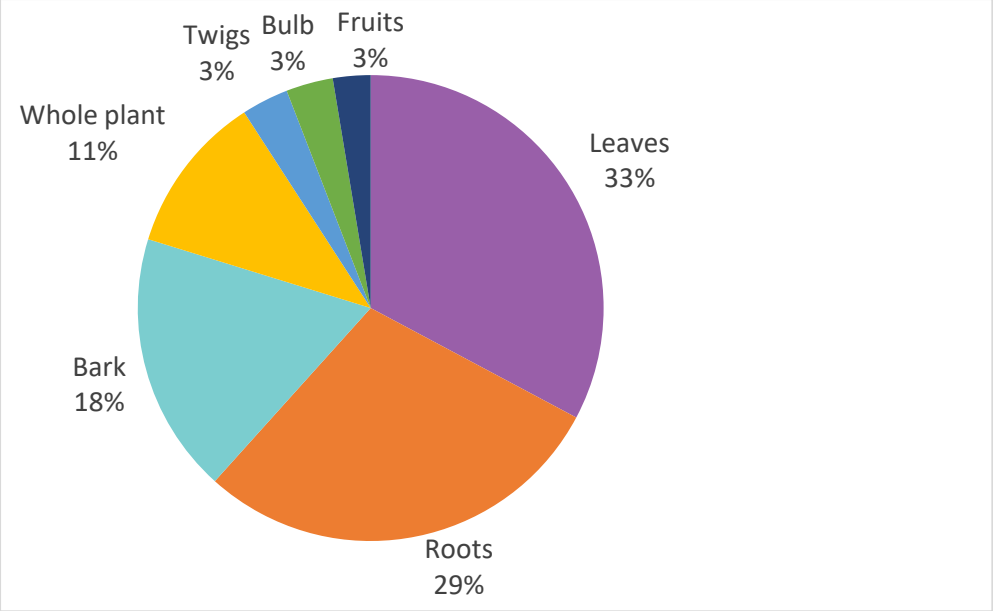


Fig. 3. The relative frequently of use of plant parts, as reported in the literature, that wereused in southern Africa to treat inflammation and pain

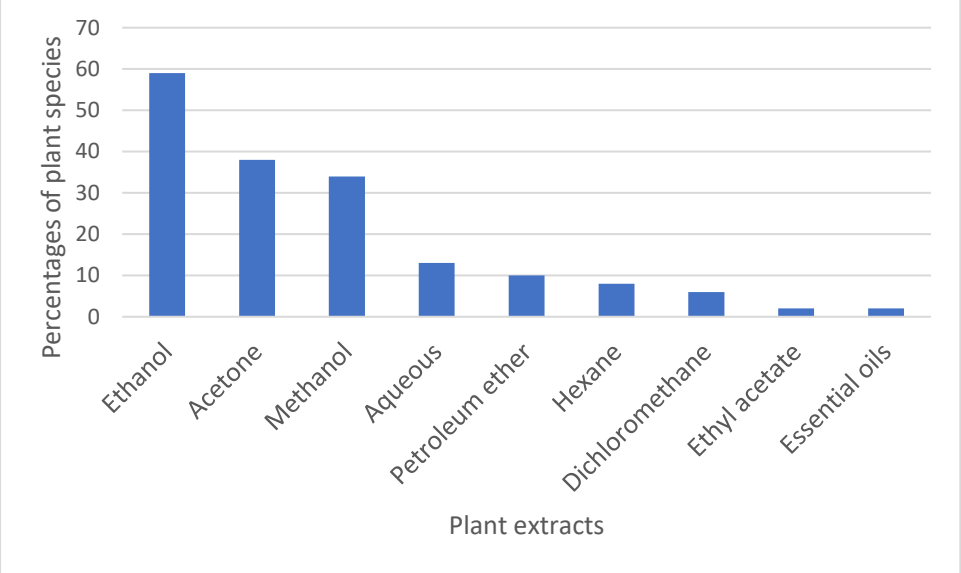


Fig. 4. The relative frequently of use of various types of plant extracts, as reported in the literature, that were used for biological screening assays in southern Africa

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Table 1 Anti-inflammatory and analgesic activities of southern African medicinal plants used traditionally to treat inflammation and pain

| **Species (Family)** | **Extracts and Pant parts** | **Assay used / method** | **Anti-inflammatory activity** | **References** |
|---|---|---|---|---|
| *Abrus precatorius* L. subsp. *africanus* Verdc. (Fabaceae) | Dichloromethane extract of the leaves | Cyclooxygenase assay | 77% COX-2 inhibition at 250 µg/mL | Madikizela et al. (2014) |
| *Acokanthera oppositifolia* (Lam.) Codd (Apocynaceae) | Ethanol extract of the roots | Cyclooxygenase assay | 78% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| | Dichloromethane extract of the leaves | Cyclooxygenase assay | 99% COX-1 inhibition at 250 µg/mL<br>81% COX-2 inhibition at 250 µg/mL | Aremu et al. (2010) |
| | Hexane extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of 7.73 µg/mL) | Ondua et al. (2016) |
| *Adansonia digitata* L. (Malvaceae) | Petroleum ether extract of the bark | Cyclooxygenase assay | >70% COX-2 inhibition at 250 µg/mL | Mulaudzi et al. (2013) |
| | Aqueous extract of the fruit pulp | Cytokine assay | Decrease of cytokine IL-8 at 70 µg/mL | Lall and Kishore (2014) |
| *Agathosma betulina* (P.J.Bergius) Pillans (Rutaceae) | Unspecified plant extracts | 5-Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of 50.37 µg/mL | Lall and Kishore (2014) |

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| *Albizia adianthifolia* (Schumach.) W.Wight (Fabaceae) | Ethyl acetate extract of the bark | Cyclooxygenase assay | 87% COX-1 inhibition at 250 µg/mL<br>87% COX-2 inhibition at 250 µg/mL | Eldeen et al. (2005) |
| *Aloe arborescens* Mill. (Asphodelaceae) | 50% Aqueous: 50% methanol extract of the leaves | Nitric oxide inhibition assay<br>15-lipoxygenase assay | NO inhibition ($IC_{50}$ of >100 µg/mL)<br>15-LOX inhibition ($IC_{50}$ of >100 µg/mL) | Ghuman et al. (2019) |
| *Aloe ferox* Mill. (Asphodelaceae) | Methanol and aqueous extract of the leaves | 5-Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of >100 µg/mL) | Frum and Viljoen (2006) |
| | Dichloromethane extract of the leaves | Cyclooxygenase assay | 96% COX-1 inhibition at 250 µg/mL<br>68% COX-2 inhibition at 250 µg/mL | Fawole et al. (2010) |
| | 50% Aqueous: 50% methanol extract of the leaves | Nitric oxide inhibition assay<br>15-lipoxygenase assay | NO inhibition at ($IC_{50}$ of >100 µg/mL)<br>15-LOX inhibition ($IC_{50}$ of >100 µg/mL) | Ghuman et al. (2019) |
| **Amaranthus hybridus* L. subsp. *cruentus* (L.) Thell (Amaranthaceae) | Methanol extract of leaves | 5- Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of 77.20 µg/mL) | Akula and Odhav (2008) |
| | Hexane extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition at ($IC_{50}$ of 59.29 µg/mL) | Ondua et al. (2019) |
| *Antidesma venosum* E.Mey. ex Tul. (Phyllanthaceae) | The ethanol extract of the leaves | Cyclooxygenase assay | 84% COX-1 inhibition at 250 µg/mL<br>41% COX-2 inhibition at 250 µg/mL | Fawole et al. (2009) |

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| *Asparagus falcatus* L. (Asparagaceae) | Methanol extract of the roots | Rat paw oedema test | 22% inhibition at a dose of 250 mg/kg (44% at 500 mg/kg) | Lall and Kishore (2014) |
| *Asparagus microraphis* (Kunth) Baker (Asparagaceae) | Methanol extract of the leaves | Cyclooxygenase assay | 97% COX-1 inhibition at 200 µg/mL | Shale et al. (1999) |
| *Asystasia gangetica (*L.) T. Anderson (Acanthaceae) | Methanol extract of the leaves | 5- Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of 55.00 µg/mL) | Akula and Odhav (2008) |
| *Ballota africana* (L.) Benth. (Lamiaceae) | Essential oils of aerial parts | 5-Lipoxygenase assays | 5-LOX inhibition ($IC_{50}$ of 29.99 µg/mL) | Frum and Viljoen (2006) |
| **Bidens pilosa* L. (Asteraceae) | Ethanol extract of the leaves | Cyclooxygenase assay | 90% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| | Methanol extract of the leaves | 5-Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of 21.80 µg/mL) | Akula and Odhav (2008) |
| *Bolusanthus speciosus* (Bolus) Harms (Fabaceae) | Ethanol extract of the stem | Cyclooxygenase assay | 95% COX-2 inhibition at 250 µg/mL | Mulaudzi et al. (2013) |
| | Acetone extract of the leaves | Nitric oxide inhibition assay<br>15-lipoxygenase assay | 61% NO inhibition at 30 µg/mL<br>15-LOX inhibition ($IC_{50}$ of < 50 µg/mL) | Elisha et al. (2016) |
| *Bridelia micrantha* (Hochst.) Baill. (Phyllanthaceae) | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of >60.00 µg/mL) | Adebayo et al. (2015) |

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| *Bulbine* sp (Liliaceae) | Methanol and aqueous extract of leaves | 5-Lipoxygenase assays | 5-LOX inhibition ($IC_{50}$ of >100 µg/mL) | Frum and Viljoen (2006) |
| *Bulbine frutescens* (L.) Willd. (Asphodelaceae) | 50% Aqueous: 50% methanol extract of the leaves and roots | Nitric oxide inhibition assay<br>15-lipoxygenase assay | NO inhibition ($IC_{50}$ of 26.32 µg/mL)<br>15-LOX inhibition ($IC_{50}$ of >100 µg/mL) | Ghuman et al. (2019) |
| *Bulbine latifolia* (L.f.) Roem. et Schult. [= *Bulbine natalensis* Baker] (Asphodelaceae) | Ethanol extract of the aerial parts | Cyclooxygenase assay | 88% COX-1 inhibition at 5.7 mg/mL | Jager et al. (1996) |
| | 50% Aqueous: 50% methanol extract of the leaves and roots | 15-Lipoxygenase assay<br>nitric oxide inhibition assay | 15-LOX inhibition ($IC_{50}$ of 6.93 µg/mL)<br>NO inhibition ($IC_{50}$ of 28.64 µg/mL) | Ghuman et al. (2019) |
| *Bulbophyllum scaberulum* (Rolfe) Bolus (Orchidaceae) | Dichloromethane extract of the roots | Cyclooxygenase assay | 17% COX-1 inhibition at 250 µg/mL<br>100% COX-2 inhibition at 250 µg/mL | Chinsamy et al. (2014) |
| *Burkea africana* Hook. (Fabaceae) | Acetone extract of the leaves | Nitric oxide inhibition assay<br>15-lipoxygenase assay | 91.33% NO inhibition at 25 µg/mL<br>15-LOX inhibition of 86% at 100 µg/mL | Dzoyem and Eloff (2015) |
| *Calpurnia aurea* (Aiton) Benth. subsp. *aurea* (Fabaceae) | Acetone extract of the leaves | Nitric oxide inhibition assay<br>15-lipoxygenase assay | 22% NO inhibition at 30 µg/mL<br>15-LOX inhibition ($IC_{50}$ of 34.70 µg/mL) | Elisha et al. (2016) |
| | 70% acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of 22.3 ± 4.11 µg/mL) | Mulaudzi et al. (2019) |

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| *Carpobrotus dimidiatus* (Haw.) L.Bolus (Aizoaceae) | | | | |
| | Methanol extract of the leaves | Cyclooxygenase assay | 28% COX-1 inhibition at 250 µg/mL<br>65% COX-2 inhibition at 250 µg/mL | Fawole et al. (2010) |
| *Carpobrotus edulis* (L.) L.Bolus subsp. *edulis* (Aizoaceae) | Methanol extract of the leaves | 5-Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of >100 µg/mL) | Frum and Viljoen (2006) |
| | Methanol extract of the leaves<br>Acetone extract of the leaves | 15-Lipoxygenase assay<br>nitric oxide inhibition assay | 15-LOX inhibition ($IC_{50}$ of 9.84 µg/mL)<br>83% NO inhibition at 50 µg/mL | Ondua et al. (2019) |
| | Acetone extract of the leaves | 15-Lipoxygenase | 15-LOX inhibition ($IC_{50}$ of 52.87 ± 2.08 µg/mL) | Mulaudzi et al. (2019) |
| *Centella asiatica* (L.) Urb. (Apiaceae) | Methanol extract of the leaves | 5-Lipoxygenase assay | 5-LOX inhibition at ($IC_{50}$ of 38.60 µg/mL) | Akula and Odhav (2008) |
| | Aqueous extract of the aerial parts | Rat paw oedema test in mice | 46% inhibition at 100 mg/kg | Lall and Kishore (2014) |

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| *Chenopodium album* L. (Amaranthaceae) | Methanol extract of the leaves | 5-Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of 33.20 µg/mL) | Akula and Odhav (2008) |
| *Clausena anisata* (Willd.) Hook.f. ex Benth. (Rutaceae) | Ethanol extract of the leaves | Paw oedema assay in mice | 71% inhibition at 450 mg/kg | Lall and Kishore (2014) |
| | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of ≥ 25.00 µg/mL) | Adebayo et al. (2015) |
| *Clematis brachiata* Thunb. (Ranunculaceae) | Ethanol extract of the stem | Cyclooxygenase assay | 73% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| *Clerodendrum glabrum* E.Mey. (Lamiaceae) | Ethanol extract of the root | Cyclooxygenase assay | 88% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| *Cleome monophylla* L. (Cleomaceae) | Methanol extract of the leaves | 5-Lipoxygenase assay | 5-LOX inhibition at ($IC_{50}$ of 32.00 µg/mL) | Akula and Odhav (2008) |
| *Clerodendrum myricoides* (Hochst.) R.Br. ex Vatke (Lamiaceae) | Dichloromethane extract of the stem | Cyclooxygenase assay | 84% COX-1 inhibition at 250 µg/mL<br>71%COX-2 inhibition at 250 µg/mL | Aremu et al. (2010) |
| **Colocasia antiquorum* Schott (Araceae) | Dichloromethane extract of the tubers | Cyclooxygenase assay | 100% COX-1 inhibition at 250 µg/mL<br>77% COX-2 inhibition at 250 µg/mL | Fawole et al. (2010) |

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| *Combretum kraussii* Hochst. (Combretaceae) | Ethyl acetate extract of the bark | Cyclooxygenase assay | 97% COX-1 inhibition at 250 µg/mL<br>90% COX-2 inhibition at 250 µg/mL | Eldeen et al. (2005) |
| *Combretum molle* R.Br. ex G.Don (Combretaceae) | Methanol extract of the bark | Paw oedema assay in mice | 62% inhibition at 300 mg/kg dose after 1 hour | Ponou et al. (2008). |
| *Combretum zeyheri* Sond. (Combretaceae) | Acetone extract of the leaves | Nitric oxide inhibition assay<br>15-lipoxygenase assay | 96% NO inhibition at 25 µg/mL<br>15-LOX inhibition of >70% at 100 µg/mL | Dzoyem and Eloff (2015) |
| **Conyza canadensis* (L.) Cronquist (Asteraceae) | Hexane extract of the leaves | Cyclooxygenase assay | COX-1 inhibition ($IC_{50}$ of 42 µg/mL)<br>COX-2 inhibition ($IC_{50}$ of 50 µg/mL) | Ondua et al. (2016) |
| *Cotyledon orbiculata* L. (Crassulaceae) | Dichloromethane extract of leaves | Cyclooxygenase assay | 93% COX-1 inhibition at 250 µg/mL<br>80% COX-2 inhibition at 250 µg/mL | Aremu et al. (2010) |
| | Acetone extract of the leaves | 15-Lipoxygenase assay<br>nitric oxide inhibition assay | 15-LOX inhibition ($IC_{50}$ of 18.10 µg/mL)<br>84% NO inhibition at 50 µg/mL | Ondua et al. (2019) |
| *Cremaspora triflora* (Thonn.) K. Schum. subsp. *triflora* (Rubiaceae) | Acetone extract of the leaves | Nitric oxide inhibition assay<br>15-lipoxygenase assay | 32% NO inhibition at 30 µg/mL)<br>15-LOX inhibition ($IC_{50}$ of < 50 µg/mL) | Elisha et al. (2016) |
| *Crinum moorei* Hook. f. (Amaryllidaceae) | Methanol extract of bulbs | Cyclooxygenase assay | 99% COX-1 inhibition at 250 µg/mL<br>76% COX-2 inhibition at 250 µg/mL | Fawole et al. (2010) |
| *Croton gratissimus* Burch. (Euphorbiaceae) | Methanol and aqueous extracts of the bark | 5-Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of >100 µg/mL) | Frum and Viljoen (2006) |

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| *Croton sylvaticus* Hochst. (Euphorbiaceae) | Ethanol extract of the bark | Cyclooxygenase assay | 59% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| | Methanol extract of roots | 5-Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of 25.64 µg/mL) | Frum and Viljoen (2006) |
| *Cryptocarya latifolia* Sond. (Lauraceae) | Hexane extract of the bark | Cyclooxygenase assay | COX-1 inhibition ($IC_{50}$ of 52 µg/mL)<br>COX-2 inhibition ($IC_{50}$ of 43 µg/mL) | Zschocke and Van Staden (2000) |
| *Cucumis hirsutus* Sond. (Cucurbitaceae) | Petroleum ether extract of leaves | Cyclooxygenase assay | 92% COX-1 inhibition at 250 µg/mL<br>80% COX-2 inhibition at 250 µg/mL | Fawole et al. (2009) |
| *Cyrtorchis arcuata* (Lindl.) Schltr. (Orchidaceae) | Ethanol extract of the leaves | Cyclooxygenase assay | 81% COX-1 inhibition at 250 µg/mL<br>77% COX-2 inhibition at 250 µg/mL | Chinsamy et al. (2014) |
| *Datura stramonium* L. (Solanaceae) | Methanol and aqueous extracts of leaves and fruits | 5-Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of > 100 µg/mL) | Lall and Kishore (2014) |
| | Acetone extract of the leaves | 15-Lipoxygenase and | 15-LOX inhibition at ($IC_{50}$ of 8.66 µg/mL) | Ondua et al. (2019) |
| *Dichrostachys cinerea* (L.) Wight & Arn. (Fabaceae) | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of >45.00 µg/mL) | Adebayo et al. (2015) |

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| *Diospyros lycioides* Desf. (Ebenaceae) | Petroleum ether extract of the leaves | Cyclooxygenase assay | 93% COX-1 inhibition at 250 µg/mL<br>92% COX-2 inhibition at 250 µg/mL | Fawole et al. (2009) |
| *Diospyros mespiliformis* Hochst. ex A.DC. (Ebenaceae) | Acetone extract of the root bark | 15-Lipoxygenase assay<br>xanthine oxidase<br>nitric oxide inhibition assay | 15-LOX inhibition ($IC_{50}$ of 78 ± 5 µg/mL)<br>XO inhibition ($IC_{50}$ of 142 ± 8 µg/mL)<br>NO inhibition ($IC_{50}$ of 79.8 ± 2.7 µg/mL) | Lawal et al. (2019) |
| *Dombeya rotundifolia* (Hochst.) Planch. (Malvaceae) | Dichloromethane extract of the bark<br>Dichloromethane extract of the leaves | Cyclooxygenase assay | 93% COX-1 inhibition<br>95% COX-1 inhibition<br>(dosage not specified) | Reid et al. (2001) |
| *Ehretia rigida* (Thunb.) Druce (Boraginaceae) | Acetone extract of the leaves | Nitric oxide inhibition assay<br>15-lipoxygenase assay | 93% NO inhibition at 25 µg/mL<br>15-LOX inhibition of >50% at 100 µg/mL | Dzoyem and Eloff (2015) |
| *Ekebergia capensis* Sparrm. (Meliaceae) | Water extract of the bark | Cyclooxygenase assay | COX-1 and-2 inhibition >70% at 250 µg/mL | Mulaudzi et al. (2013) |
| | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of ≥45.00 µg/mL) | Adebayo et al. (2015) |

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| *Elaeodendron croceum* (Thunb.) DC. (Celastraceae) | Acetone extract of the leaves | Nitric oxide inhibition assay<br>15-lipoxygenase assay | 71% NO inhibition at 30 µg/mL<br>15-LOX inhibition ($IC_{50}$ of 26.23 µg/mL) | Elisha et al. (2016) |
| *Elephantorrhiza elephantina* (Burch.) Skeels (Fabaceae) | Aqueous extract of the roots | Rat oedema assay | 94% inhibition at 50mg/kg | Lall and Kishore (2014) |
| *Emex australis* Steinh. (Polygonaceae) | Methanol extract of the leaves | 5- Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of 81.40 µg/mL) | Akula and Odhav (2008) |
| *Englerophytum magalismontanum* (Sond.) T.D.Penn. (Sapotaceae) | Acetone extract of the leaves | Nitric oxide inhibition assay<br>15-lipoxygenase assay | 96% NO inhibition at 25 µg/mL<br>15-LOX inhibition of >50% at 100 µg/mL | Dzoyem and Eloff (2015) |
| *Eriocephalus africanus* L. (Asteraceae) | Acetone extract of the leaves | 5-Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of 32.80 µg/mL) | Njenga and Viljoen (2006) |
| *Eriocephalus ericoides* (L.f.) Druce (Asteraceae) | Acetone extract of the leaves | 5-Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of 43.10 µg/mL) | Njenga and Viljoen (2006) |
| *Erythrina caffra* Thunb. (Fabaceae) | Ethanol extract of the bark | Cyclooxygenase assay | 95% COX-1 inhibition at 50 µg/mL | Pillay et al. (2001) |
| *Erythrina lysistemon* Hutch. (Fabaceae) | Ethanol extract of the bark | Cyclooxygenase assay | 96% COX-1 inhibition at 50 µg/mL | Pillay et al. (2001) |
| *Erythrina zeyheri* Harv. (Fabaceae) | Ethanol extract of the leaves | Cyclooxygenase assay | 65% COX-1 inhibition at 50 µg/mL | Pillay et al. (2001) |

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| *Erythrophleum lasianthum* Corbishley (Fabaceae) | Ethanol extract of the bark | Cyclooxygenase assay | 94% COX-1 inhibition at 50 µg/mL | McGaw et al. (1997) |
| | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of >100 µg/mL) | Adebayo et al. (2015) |
| *Euclea undulata* Thunb. (Ebenaceae) | Acetone extract of the leaves | Nitric oxide inhibition assay<br>15-lipoxygenase assay | 93% NO inhibition at 25 µg/mL<br>15-LOX inhibition of >30% at 100 µg/mL | Dzoyem and Eloff (2015) |
| *Eucomis autumnalis* (Mill.) Chitt (Hyacinthaceae) | Ethanol extract of the bulb | Cyclooxygenase assay | 90% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| | 50% Aqueous: 50% methanol extract of the leaves | Nitric oxide inhibition assay<br>15-lipoxygenase assay | NO inhibition ($IC_{50}$ of 38.09 µg/mL)<br>15-LOX inhibition ($IC_{50}$ of 6.73 µg/mL) | Ghuman et al. (2019) |
| *Eulophia petersii* (Rchb.f.) Rchb.f. (Orchidaceae) | Petroleum ether extract of roots | Cyclooxygenase assay | 100% COX-1 inhibition at 250 µg/mL<br>77% COX-2 inhibition at 250 µg/mL | Chinsamy et al. (2014) |
| *Felicia muricata* (Thunb.) Nees subsp. *muricate* (Asteraceae) | Ethanol extract of the leaves | Cyclooxygenase assay | 92% COX-1 inhibition at 50 µg/mL | McGaw et al. (1997) |
| **Ficus elastica* Roxb. ex Hornem. (Moraceae) | Acetone and methanol extract of leaves | Nitric oxide inhibition assay<br>15-lipoxygenase assay | 93% NO inhibition at 50 µg/mL<br>15-LOX inhibition ($IC_{50}$ of 3.47 µg/mL) | Ondua et al. (2019) |

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| *Ficus sur* Forssk. (Moraceae) | Dichloromethane extract of bark | Cyclooxygenase assay | 74% COX-2 inhibition at 250 µg/mL | Madikizela et al. (2014) |
| *Gomphocarpus fruticosus* (L.) Aiton f. subsp. *fruticosus* (Apocynaceae) | Hexane extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of 59.34 µg/mL) | Ondua et al. (2019) |
| *Gunnera perpensa* L. (Gunneraceae) | Aqueous extract of the rhizome | Paw-oedema test | 59% inhibition at 150 mg/kg | Nkomo et al. (2010) |
| *Gymnosporia senegalensis* (Lam.) Loes. (Celastraceae) | Petroleum ether extract of the roots | Cyclooxygenase assay | >80% COX-1 inhibition and >50% COX-2 inhibition (dosage not specified) | Mulaudzi et al. (2012) |
| *Halleria lucida* L. (Scrophulariaceae) | Methanol and aqueous extracts of leaves and roots | 5-Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of >100 µg/mL) | Frum and Viljoen (2006) |
| *Harpagophytum procumbens* (Burch.) DC ex Meisn. (Pedaliaceae) | Methanol and aqueous extracts of the roots | 5-Lipoxygenase assays | 5-LOX inhibition ($IC_{50}$ of >100 µg/mL) | Frum and Viljoen (2006) |
| | Aqueous extracts of the roots | Paw oedema assay in mice | A 3 days decrease from 7.6 mm to 6.6 mm at 800 mg/kg | Lall and Kishore (2014) |
| *Harpephyllum caffrum* Bernh. (Anacardiaceae) | Ethanol extract of the bark | Cyclooxygenase assay | 93% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |

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| | Petroleum ether extract of the bark | Cyclooxygenase assay | 60% COX-1 inhibition at 125µg/mL<br>>60% COX-2 inhibition at 125 µg/mL | Moyo et al. (2011) |
| | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of ≥40.00 µg/mL) | Adebayo et al. (2015) |
| *Helichrysum nudifolium* (L.) Less. var. *pilosellum* (L.f.) Beentje (Asteraceae) | Ethanol extract of the leaves | Cyclooxygenase assay | 96% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| *Helichrysum subglomeratum* Less. (Asteraceae) | Ethanol extract of the aerial parts | Cyclooxygenase assay | 69% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| *Heteromorpha arborescens* (Spreng.) Cham. & Schltdl. (Apiaceae) | Ethanol extract of the leaves | Cyclooxygenase assay | 88% COX-1 inhibition at 50 µg/mL | McGaw et al. (1997) |
| | Petroleum ether extracts of the roots and bark | Cyclooxygenase assay | >80% COX-1 inhibition at 250 µg/mL | Lundgaard et al. (2008) |
| | Acetone extract of the leaves | Nitric oxide inhibition assay | 90% NO inhibition at 30 µg/mL | Elisha et al. (2016) |
| *Hypericum roeperianum* G.W.Schimp. ex A.Rich. (Hypericaceae) | Acetone extract of the leaves | Nitric oxide inhibition assay | 81% NO inhibition at 30 µg/mL | Elisha et al. (2016) |
| | Ethanol extract of the corm | Cyclooxygenase assay | 48% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |

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| *Hypoxis hemerocallidea* Fisch., C.A.Mey. & Avé-Lall. (Hypoxidaceae) | Petroleum ether extract of corms | Cyclooxygenase assay | 97% COX-1 inhibition at 250 µg/mL<br>74%COX-2 inhibition at 250 µg/mL | Aremu et al. (2010) |
| *Jatropha curcas* L. (Euphorbiaceae) | Acetone extract of the leaves | Nitric oxide inhibition assay<br>15-lipoxygenase assay | 96% NO inhibition at 25 µg/mL<br>15-LOX inhibition ($IC_{50}$ of 41.50±1.24 µg/mL) | Dzoyem and Eloff (2015) |
| *Kigelia africana* (Lam.) Benth. (Bignoniaceae) | Ethanol extract of the bark | Paw-oedema test | 90% inhibition at 200 mg/ kg dose after 6 h | Lall and Kishore (2014) |
| | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of >40.00 µg/mL) | Adebayo et al. (2015) |
| *Lannea schweinfurthii* Engl. (Anacardiaceae) | A mixture of DCM and MeOH (1:1) of the roots | Inhibition of carrageenan-induced paw oedema | Reduction (1.25 ± 0.09 mL) at 200 mg/kg | Yaouba et al. (2018) |
| | Acetone extract of the root bark | 15-Lipoxygenase assay<br>xanthine oxidase<br>nitric oxide assay | 15-LOX inhibition ($IC_{50}$ of 40±3 µg/mL)<br>XO inhibition ($IC_{50}$ of 71 ± 3 µg/mL)<br>NO inhibition ($IC_{50}$ of 49.4 ± 8.0 µg/mL) | Lawal et al. (2019) |
| *Lasiosiphon capitatus* (L.f.) Burtt Davy (Thymelaeceae) | Ethanol extract of aerial parts | Cyclooxygenase assay | 87% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |

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| *Leonotis intermedia* Lindl. (Lamiaceae) | Ethanol extract of the leaves | Cyclooxygenase assay | 97% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| | Ethanol extract of leaves | Cyclooxygenase assay | 41% COX-2 inhibition at 250 µg/mL | Madikizela et al. (2014) |
| *Leonotis leonurus* (L.) R.Br. (Lamiaceae) | Ethanol extract of the leaves | Cyclooxygenase assay | 90% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| | Methanol and aqueous extract of the leaves | 5-Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of >100 µg/mL) | Frum and Viljoen (2006) |
| *Leucaena leucocephala* (Lam) DeWit (Fabaceae) | Acetone extract of the leaves | Nitric oxide inhibition assay<br>15-lipoxygenase assay | 98% NO inhibition at 25 µg/mL<br>15-LOX inhibition of >70% at 100 µg/mL | Dzoyem and Eloff (2015) |
| *Lippia javanica* (Burm.f.) Spreng (Verbenaceae) | Ethanol extract of the leaves | Cyclooxygenase assay | 53% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| | Methanol extract of leaves and stems | 5-Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of >100 µg/mL) | Frum and Viljoen (2006) |
| | Acetone extract of the leaves | Nitric oxide inhibition assay<br>15-lipoxygenase assay | 97% NO inhibition at 25 µg/mL<br>15-LOX inhibition of >70% at 100 µg/mL | Dzoyem and Eloff (2015) |

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| *Maesa lanceolata* Forssk. (Maesaceae) | Acetone extract of the leaves | Nitric oxide inhibition assay<br>15-lipoxygenase assay | 99% NO inhibition at 30 µg/mL<br>15-LOX inhibition ($IC_{50}$ of 91.77 µg/mL) | Elisha et al. (2016) |
| *Melianthus comosus* Vahl (Melianthaceae) | Aqueous extract of the leaves | 5-Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of 13.84 µg/mL) | Frum and Viljoen (2006) |
| | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of ≥ 30.00 µg/mL) | Adebayo et al. (2015) |
| *Mentha longifolia* (L.) Huds. (Lamiaceae) | Ethanol extract of the leaves | Cyclooxygenase assay | 85% COX-1 inhibition at 50 µg/mL | McGaw et al. (1997) |
| *Mesembryanthemum cordifolium* L.f. (Aizoaceae) | Ethanol extract of the aerial parts | Cyclooxygenase assay | 73% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| *Morus mesozygia* Stapf ex A.Chev. (Moraceae) | Acetone extract of the leaves | Nitric oxide assay<br>15-lipoxygenase assay | 92.69% NO inhibition at 25 µg/mL<br>15-LOX inhibition >50% at 100 µg/mL | Dzoyem and Eloff (2015) |
| | Acetone extract of the leaves | Nitric oxide assay<br>15-lipoxygenase assay | 53% NO inhibition at 30 µg/mL<br>15-LOX inhibition ($IC_{50}$ of >80 µg/mL) | Elisha et al. (2016) |
| *Ocimum obovatum* E. Mey.ex Benth. (Lamiaceae) | Petroleum ether extract of the roots | Cyclooxygenase assay | 78% COX-1 inhibition at 250 µg/mL<br>76% COX-2 inhibition at 250 µg/mL | Fawole et al. (2009) |

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| *Ocotea bullata* (Burch.) E. Mey. in Drége (Lauraceae) | Ethanol extract of the bark | Cyclooxygenase assay | 97% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| | Methanol extract of the leaves<br>Essential oils from the bark | Cyclooxygenase assay<br>5-lipoxygenase assay | 70% COX-1 inhibition at 100 µg/mL<br>5-LOX inhibition of 83±3.5% at 10 µg/mL | Zschocke et al. (2000) |
| *Olea europaea* L. subsp. *africana* (Mill.) P.S.Green (Oleaceae) | Ethanol extract of the leaves | Cyclooxygenase assay | 81% COX-1 inhibition at 100 µg/mL | McGaw et al. (1997) |
| *Oxalis pes-caprae* L. (Oxalidaceae) | Hexane extract of leaves | 15-Lipoxygenase and | 15-LOX inhibition ($IC_{50}$ of 70.53 µg/mL) | Ondua et al. (2019) |
| *Pachycarpus rigidus* E.Mey. (Apocynaceae) | Methanol extract of the leaves | Cyclooxygenase assay | 91% COX-1 inhibition at 200 µg/mL | Shale et al. (1999) |
| *Peltophorum africanum* Sond. (Fabaceae) | Petroleum ether extract of the bark | Cyclooxygenase assay | >70% COX-2 inhibition at 250 µg/mL | Mulaudzi et al. (2013) |
| | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of 12.42 µg/mL) | Adebayo et al. (2015) |
| *Pentanisia prunelloides* (Klotzsch ex Eckl. & Zeyh.) Walp. (Rubiaceae) | Methanol extract of the roots | 5-Lipoxygenase assays | 5-LOX inhibition ($IC_{50}$ of 32.71 µg/mL | Frum and Viljoen (2006) |

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| | Petroleum ether extract of the roots | Cyclooxygenase assay | 87% COX-2 inhibition at 250 µg/mL | Madikizela et al. (2014) |
| *Physalis viscosa* L. (Solanaceae) | Methanol extract of the leaves | 5- Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of 29.50 µg/mL) | Akula and Odhav (2008) |
| *Pittosporum viridiflorum* Sims (Pittosporaceae) | Ethanol extract of the bark | Cyclooxygenase assay | 86% COX inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of ≥ 30.00 µg/mL) | Adebayo et al. (2015) |
| | Acetone extract of the leaves | Nitric oxide inhibition assay<br>15-lipoxygenase assay | 81% NO inhibition at 30 µg/mL<br>15-LOX inhibition ($IC_{50}$ of > 50 µg/mL) | Elisha et al. (2016) |
| *Plantago lanceolata* L. (Plantaginaceae) | Hexane extract of the leaves | 15-Lipoxygenase assay<br>Cyclooxygenase assay | 15-LOX inhibition ($IC_{50}$ of 7.73 µg/mL)<br>COX-1 inhibition ($IC_{50}$ of 69 µg/mL)<br>COX-2 inhibition ($IC_{50}$ of 1.96 µg/mL) | Ondua et al. (2016) |
| *Plumbago auriculata* Lam. (Plumbaginaceae) | Ethanol extract of the leaves | Cyclooxygenase assay | 45% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of >30.00 µg/mL) | Adebayo et al. (2015) |

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| *Portulaca oleracea* L. (Portulacaceae) | Methanol extract of the leaves | 5- Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of 37.90 µg/mL) | Akula and Odhav (2008) |
| *Protea simplex* E. Phillips (Proteaceae) | Petroleum ether extract of the leaves | Cyclooxygenase assay | 100% COX-1 inhibition at 250 µg/mL<br>72% COX-2 inhibition at 250 µg/mL | (Fawole et al. 2009) |
| *Prunus africana* (Hook.f.) Kalkman (Rosaceae) | Ethanol extract of the bark | Cyclooxygenase assay | 96% COX-1 inhibition at 250 µg/mL<br>88% COX-2 inhibition at 250 µg/mL | Eldeen et al. (2005) |
| *Pseudolachnostylis maprouneifolia* Pax (Phyllanthaceae) | Acetone extract of the bark | Xanthine oxidase<br>nitric oxide inhibition assay | XO inhibition ($IC_{50}$ of 110 ± 15 µg/mL)<br>NO inhibition ($IC_{50}$ of 68.8 ± 4.5 µg/mL) | Lawal et al. (2019) |
| *Ptaeroxylon obliquum* (Thunb.) Radlk. (Rutaceae) | Ethanol extract of the wood | Cyclooxygenase assay | 73% COX-1 inhibition at 50 µg/mL | McGaw et al. (1997) |
| | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of >50.00 µg/mL) | Adebayo et al. (2015) |
| *Pterocarpus angolensis* DC. (Fabaceae) | Petroleum ether extract of the bark | Cyclooxygenase assay | >70% COX-2 inhibition at 250 µg/mL | Mulaudzi et al. (2013) |
| *Pycnostachys reticulata* (E. Mey.) Benth (Lamiaceae) | Methanol extract of the leaves | Cyclooxygenase assay | 30% COX-1 inhibition at 250 µg/mL<br>69% COX-2 inhibition at 250 µg/mL | Fawole et al. (2010) |
| *Rhynchosia adenodes* Eckl. & Zeyh. (Fabaceae) | Hexane extract of the leaves | Cyclooxygenase assay | 95% COX-1 inhibition at 200 µg/mL | Shale et al. (1999) |

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| **Ricinus communis* L. (Euphorbiaceae) | Acetone extract of leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of 15.40 µg/mL) | Ondua et al. (2019) |
| **Rumex crispus* L. (Polygonaceae) | Hexane extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of 2.17 µg/mL) | Ondua et al. (2019) |
| *Rumex sagittatus* Thunb. (Polygonaceae) | Ethanol extract of the roots | Cyclooxygenase assay | 95% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| *Salix mucronata* Thunb. (Salicaceae) | Ethyl acetate extract of the bark | Cyclooxygenase assay | 78% COX-1 inhibition at 250 µg/mL<br>82% COX-2 inhibition at 250 µg/mL | Eldeen et al. (2005) |
| *Merwilla plumbea* (Lindl.) Speta [=*Scilla natalensis* Planch. (Hyacinthaceae) | Ethanol extract of the bulb | Cyclooxygenase assay | 81% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| *Senecio serratuloides* DC. (Asteraceae) | Methanol extract of leaves | Cyclooxygenase assay | 39% COX-1 inhibition at 250 µg/mL<br>71.% COX-2 inhibition at 250 µg/mL | Fawole et al. (2010) |
| *Senegalia burkei* (Benth.) Kyal. & Boatwr. (Fabaceae) | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of ≥35.00 µg/mL) | Adebayo et al. (2015) |
| *Senna italica* Mill. subsp. *arachoides* (Burch.) Lock (Fabaceae) | Acetone extract of leaves | 15-Lipoxygenase assay nitric oxide inhibition assay | 15-LOX inhibition ($IC_{50}$ of 46.93 µg/mL) | Ondua et al. (2019) |
| **Senna occidentalis* (L.) Link (Leguminosae) | Methanol extract of the leaves | 5- Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of 43.50 µg/mL) | Akula and Odhav (2008) |
| *Senna petersiana* (Bolle) Lock (Fabaceae) | Dichloromethane extract of leaves | Cyclooxygenase assay | 86% COX-1 inhibition at 250 µg/mL | Aremu et al. (2010) |

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| | | | 78% COX-2 inhibition at 250 µg/mL | |
| **Solanum mauritianum* Scop. (Solanaceae) | Ethanol extract of the leaves | Cyclooxygenase assay | 97% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| *Sclerocarya birrea* (A. Rich.) Hochst. (Anacardiaceae) | Petroleum ether extract of the bark | Cyclooxygenase assay | >80% COX-2 inhibition at 125 µg/mL<br>>60% COX-2 inhibition at 125 µg/mL | Moyo et al. (2011) |
| | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of >30.00 µg/mL) | Adebayo et al. (2015) |
| *Searsia chirindensis* (Baker f.) Moffett (Anacardiaceae) | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of >25.00 µg/mL) | Adebayo et al. (2015) |
| *Solanum panduriforme* E. Mey. (Solanaceae) | Acetone extract of the rootbark | 15-Lipoxygenase assay<br>xanthine oxidase<br>nitric oxide inhibition assay | 15-LOX inhibition ($IC_{50}$ of >83.30 µg/mL)<br>XO inhibition ($IC_{50}$ of >167 µg/mL)<br>NO inhibition ($IC_{50}$ of 40.3 ± 6.2 µg/mL) | Lawal et al. (2019) |
| **Solanum nigrum* L. (Solanaceae) | Hexane extract of the leaves | Cyclooxygenase assay | 92% COX-1 inhibition at 200 µg/mL | Shale et al. (1999) |
| *Spirostachys africana* Sond. (Euphorbiaceae) | Dichloromethane extract of the | Cyclooxygenase assay | >80 COX-1 and -2 inhibition (dosage not specified) | Mulaudzi et al. (2012) |
| *Stangeria eriopus* (Kunze) Baill. (Zamiaceae) | Ethanol extract of the roots | Cyclooxygenase assay | 75% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |

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| *Stapelia gigantea* N.E.Br. (Asteraceae) | Ethanol extract of the aerial parts | Cyclooxygenase assay | 75% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| *Sutherlandia frutescens* (L.) R. Br. (Fabaceae) | Aqueous extracts of the leaves | Paw oedema assay in mice | Substantial oedema reduction at 800 mg/kg | Lall and Kishore (2014) |
| *Synadenium cupulare* (Boiss.) L.C. Wheeler (Euphorbiaceae) | Ethanol extract of the leaves | Cyclooxygenase assay | 93% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| *Syzygium cordatum* Hochst. ex Krauss (Myrtaceae) | Petroleum ether extract of the leaves | Cyclooxygenase assay | >80 COX-1 and -2 inhibition (dosage not specified) | Mulaudzi et al. (2012) |
| *Tecomaria capensis* (Thunb.) Spach (Bignoniaceae) | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of >80.00 µg/mL) | Adebayo et al. (2015) |
| *Terminalia prunioides* M.A. Lawson (Combretaceae) | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of >35. 00 µg/mL) | Adebayo et al. (2015) |
| | Acetone extract of the stembark | 15-Lipoxygenase assay<br>xanthine oxidase assay<br>nitric oxide inhibition assay | 15-LOX inhibition ($IC_{50}$ of 55.00 µg/mL)<br>XO inhibition ($IC_{50}$ of 69 ± 2 µg/mL)<br>NO inhibition ($IC_{50}$ of 44.9 ± 1.40 µg/mL) | Lawal et al. (2019) |
| | Ethanol extract of the leaves | Cyclooxygenase assay | 86% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |

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| *Tetradenia riparia (*Hochst.) Codd (Lamiaceae) | 50% Aqueous: 50% methanol extract of the stem | Nitric oxide inhibition assays<br>15-Lipoxygenase assay | NO inhibition ($IC_{50}$ of 2.05 µg/mL)<br>15-LOX inhibition ($IC_{50}$ of 3.55 µg/mL) | Ghuman et al. (2019) |
| *Trichilia dregeana* Sond (Meliaceae) | Ethanol extract of the bark | Cyclooxygenase assay | 100% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| | Ethyl acetate extract of the bark | Cyclooxygenase assay | 78% COX-1 inhibition at 250 µg/mL<br>19% COX-2 inhibition at 250 µg/mL | Eldeen et al. (2005) |
| | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of >25.00 µg/mL) | Adebayo et al. (2015) |
| *Trichilia emetica* Vahl (Meliaceae) | Ethanol extract of the leaves | Cyclooxygenase assay | 90% COX-1 inhibition at 50 µg/mL | McGaw et al. (1997) |
| | Methanol and aqueous extract of the leaves | 5-Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of >100 µg/mL) | Frum and Viljoen (2006) |
| *Tulbaghia violacea* Harv. (Alliaceae) | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition at ($IC_{50}$ of >50.00 µg/mL) | Adebayo et al. (2015) |
| *Turraea floribunda* Hochst. (Meliaceae) | Methanol extract of leaves | Cyclooxygenase assay | 56% COX-1 inhibition at 250 µg/mL<br>87% COX-2 inhibition at 250 µg/mL | Fawole et al. (2010) |
| *Typha capensis* (Rohrb.) N.E.Br. (Typhaceae) | Acetone and hexane extracts of the leaves | Nitric oxide inhibition assays<br>15-lipoxygenase assay | 79% of NO inhibition at 50 µg/mL<br>15-LOX inhibition ($IC_{50}$ of 4.65 µg/mL) | Ondua et al. (2019) |

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| *Vachellia nilotica* (DC.) Kyal. & Boatwr. subsp. *kraussiana* (Benth.) Kyal. & Boatwr. (Fabaceae) | Ethanol extract of the bark | Cyclooxygenase assay | 96% COX-1 inhibition at 250 µg/mL<br>96% COX-2 inhibition at 250 µg/mL | Eldeen et al. (2005) |
| *Vachellia sieberiana* (DC.) Kyal. & Boatwr. var. *woodii* (Burtt Davy) Kyal. & Boatwr. (Fabaceae) | Ethanol extract of the bark | Cyclooxygenase assay | 88% COX-1 inhibition at 250 µg/mL<br>76% COX-2 inhibition at 250 µg/mL | Eldeen et al. (2005) |
| | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of > 100 µg/mL) | Adebayo et al. (2015) |
| *Vernonia natalensis* Sch. Bip. ex Walp (Asteraceae) | Petroleum ether extract of the leaves | Cyclooxygenase assay | 89% COX-1 inhibition at 250 µg/mL<br>87% COX-2 inhibition at 250 µg/mL | Fawole et al. (2009) |
| *Vitex obovata* E. Mey. (Verbenaceae) | Essential oils from aerial parts | 5-Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of 42.00 µg/mL) | Nyiligira et al. (2004) |
| *Warburgia salutaris* (G. Bertol.) Chiov. (Canellaceae) | Ethanol extract of the bark | Cyclooxygenase assay | 11% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| | Methanol extract of leaves | 5-Lipoxygenase assay | 5-LOX inhibition ($IC_{50}$ of 32.11 µg/mL) | Frum and Viljoen (2006) |
| | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of > 25.00 µg/mL) | Adebayo et al. (2015) |
| *Xysmalobium undulatum* (L.) W.T.Aiton (Apocynaceae) | Ethanol extract of the roots | Cyclooxygenase assay | 72% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |

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| *Zantedeschia aethiopica* (L.) Spreng. (Araceae) | 50% Aqueous: 50% methanol extract of the stem | Nitric oxide inhibition assay<br>15-lipoxygenase assay | NO inhibition ($IC_{50}$ of 46.22 µg/mL)<br>15-LOX inhibition ($IC_{50}$ of 9.05 µg/mL) | Ghuman et al. (2019) |
| *Zanthoxylum capense* (Thunb.) Harv. (Rutaceae) | Acetone extract of the leaves | 15-Lipoxygenase assay | 15-LOX inhibition ($IC_{50}$ of 14.92 µg/mL) | Adebayo et al. (2015) |
| | Acetone extract of stembark | 15-Lipoxygenase assay<br>xanthine oxidase assay<br>nitric oxide inhibition assay | 15-LOX inhibition ($IC_{50}$ of 69.00 µg/mL)<br>XO inhibition ($IC_{50}$ of 125 ± 2 µg/mL)<br>NO inhibition ($IC_{50}$ of 29.9 ± 1.90 µg/mL) | Lawal et al. (2019) |
| *Ziziphus mucronata* Willd. (Rhamnaceae) | Ethanol extract of the leaves | Cyclooxygenase assay | 89% COX-1 inhibition at 5.7 mg/mL | Jäger et al. (1996) |
| *Ziziphus rivularis* Codd (Rhamnaceae) | Acetone extract of the leaves | 15-Lipoxygenase assay<br>nitric oxide inhibition assay | 15-LOX inhibition of >40% at 100 µg/mL<br>92% NO inhibition at 25 µg/mL | Dzoyem and Eloff (2015) |