Chapter 18
Aloe Species as Valuable Sources of Functional Bioactives

Chukwuebuka Egbuna, Ena Gupta, Shahira M. Ezzat, Jaison Jeevanandam, Neha Mishra, Muhammad Akram, N. Sudharani, Charles Oluwaseun Adetunji, Priyanka Singh, Jonathan C. Ifemeje, S. Deepak, A. Bhavana, Angelo Mark P. Walag, Rumaisa Ansari, Juliana Bunmi Adetunji, Umme Laila, Michael Chinedu Olisah, and Peculiar Feenna Onyekere

18.1 Introduction

Herbal medicines occupy distinct position right from the primitive period to present day. In every ethnic group, there exists a traditional health care system, which is culturally patterned. In rural communities, health care seems to be the first and fore-

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C. Egbuna (✉)
Department of Biochemistry, Faculty of Natural Sciences, Chukwuemeka Odumegwu Ojukwu University, Uli, Anambra State, Nigeria

Nutritional Biochemistry and Toxicology Unit, World Bank Africa Centre of Excellence, Centre for Public Health and Toxicological Research (ACE-PUTOR), University of Port-Harcourt, Port Harcourt, Rivers State, Nigeria
e-mail: egbuna.cg@coou.edu.ng

E. Gupta
Department of Home Science, University of Allahabad, Allahabad, Uttar Pradesh, India

S. M. Ezzat
Department of Pharmacognosy, Faculty of Pharmacy, Cairo University, Cairo, Egypt

Department of Pharmacognosy, Faculty of Pharmacy, October University for Modern Sciences and Arts (MSA), 6th of October, Egypt

J. Jeevanandam
Department of Chemical Engineering, Faculty of Engineering and Science, Curtin University, Miri, Sarawak, Malaysia

N. Mishra
Sam Higginbottom University of Agriculture, Technology and Sciences, Allahabad, Uttar Pradesh, India

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most line of defence. The WHO has already recognized the contribution of traditional health care in tribal communities. These medicines have fewer side effects and are easily accessible to mankind in the nature. It has been a source of medicinal agents for thousands of years and an impressive number of modern drugs have been formulated out of it. Therapeutically, interesting and important drugs have been developed from plant sources which are being used in traditional system of medicines. The use of plants as a therapeutic material due to their chemical substances of medicinal value is very common all over the world from ancient period of time.

The Genus Aloe belongs to the family Xanthorrhoeaceae which is also previously known as Asphodelaceae, Aloaceae or Liliaceae (Chen et al. 2012). The genus contains over 500 species of Aloe which vary greatly in their heights and sizes ranging from very small shrub-like plants to very large trees (Grace 2011). Out of these 500, about 160 are indigenous to South Africa and some species are found in Jordan, Madagascar, Arabian Peninsula and Indian Ocean Islands contributing to regional bio-cultural diversity (Cottam and Curtis 1956; Cock 2015). The genus is thought to have originated from the highlands of Southeast Africa and almost 82% of the rec-

M. Akram · R. Ansari · U. Laila
Department of Eastern Medicines, Government College University, Faisalabad, Pakistan

N. Sudharani
Department of Food Science & Nutrition, College of Horticulture,
Mudigere, Karnataka, India

C. O. Adetunji
Applied Microbiology, Biotechnology and Nanotechnology Laboratory, Department of Microbiology, Edo University Iyamho, Auchi, Edo State, Nigeria

P. Singh
Centre of Food Technology, University of Allahabad, Allahabad, Uttar Pradesh, India

J. C. Ifemeje
Department of Biochemistry, Faculty of Natural Sciences, Chukwuemeka Odumegwu Ojukwu University, Uli, Anambra State, Nigeria

S. Deepak · A. Bhavana
Department of Food Science & Nutrition, University of Agricultural Sciences, Gandhi Krishi, Vignana Kendra (GKVK), Bangalore, Karnataka, India

A. M. P. Walag
Department of Science Education, University of Science and Technology of Southern Philippines, Cagayan de Oro City, Philippines

J. B. Adetunji
Nutritional and toxicological Research Laboratory, Department of Biochemistry Sciences, Osun State University, Osogbo, Nigeria

M. C. Olisah
Deparment of Medical Biochemistry, Chukwuemeka Odumegwu Ojukwu University, Uli, Anambra State, Nigeria

P. F. Onyekere
Department of Pharmacognosy & Environmental Medicine, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria

ognized species are found to be present in High Africa (Holland 1978). There is a presence of rosette of leaves at the base except stem in many members of the genus Aloe. Its name is derived from the Arabic word "Alloeh", which basically means "shining bitter substance". In many cultures for long time its name is used as a remedy. The well-investigated Aloe species includes *Aloe vera*, *Aloe barbadensis*, *Aloe arborescens* and *Aloe ferox.* There is a cultivation of different evergreen species of Aloe as ornamentals due to its spiny sharp-pointed sword-shaped leaves terminating at the trunk and clusters of colourful red and yellow flowers. The plants of the genus Aloe have been used worldwide for their medical and cosmetic benefits and their effectiveness has been accepted internationally. Despite their common use, internationally scientific studies and experimental data on the pharmacological uses and the toxicology of these Africa species is seriously lacking (Srikanth et al. 2014).

Aloe vera is considered as the most potent and popular plant of the genus (Eshun and Qian 2004). *Aloe vera* has been used in folk medicine for over 2000 years, and has remained an important component in the traditional medicine of many contemporary cultures, such as in China, India, West Indies and Japan (Foster et al. 2011). *Aloe vera* has been used for many centuries for its curative and therapeutic properties. *Aloe vera* is a perennial succulent xerophyte, which develops water storage tissue in the leaves to survive in dry areas of low or erratic rainfall. The aloe leaf can be divided into two major parts, namely the outer green rind, including the vascular bundles, and the inner colourless parenchyma containing the aloe gel. Main chemical constituents of *Aloe vera* include (Table 18.1): amino acids, anthraquinones, enzymes, minerals, vitamins, lignins, monosaccharide, polysaccharides, salicylic acid, saponins, and phytosterols (Surjushe et al. 2008).

Apart from *Aloe vera*, *Aloe ferox* also known as Cape aloe or bitter aloe is the second most studied member and has been shown to exhibit wound healing, laxative properties, antioxidant, anti-inflammatory, antimicrobial, anticancer, antimalarial and anthelmintic activities (Chen et al. 2012). The plant is also used as an ornamental plant as it shows flowering of red, yellow, orange and a rare white color. The plant is native to the Cape coastal region of South Africa and hence the name Cape aloe. The botanical name ferox is attributed to the presence of thorns and sharp spines of reddish color giving the plant its ferocious appearance (Chen et al. 2012).

Aloe vera exhibits many pharmacological activities due to the phytochemical such antioxidant, antimicrobial, immune boosting, antitumor, hypolipidemic, wound healing, and antidiabetic (Cosmetic Ingredient Review Expert Panel 2007). It is also reported that *Aloe vera* helps in reducing serum cholesterol and triglycerides and increasing level of high density lipoprotein cholesterol. Many traditional uses are also reported such as in burn injury, eczema, cosmetics, inflammation, and fever, which continue to be studied, although further research still has to be done. Thus, it is quite promising as a multipurpose medicinal agent so further experiments are needed to elucidate and to find out the mechanism of the bioactive chemicals using modern instruments, such as high-performance liquid chromatography, high-performance thin layer chromatography, and clinical trials has to be done to generate novel drugs. The US Food and Drug Administration have already approved the developmental study of *Aloe vera* in the treatment of cancer and AIDS. In future, controlled studies are required to prove the effectiveness of *Aloe vera* under various conditions.

Table 18.1 Active components of *Aloe vera*

Class	Active components
Anthraquinones	Aloe-emodin, aloetic-acid, anthranol, aloin A and B (or collectively known as barbaloin), isobarbaloin, emodin, ester of cinnamic acid
Carbohydrates	Pure mannan, acetylated mannan, acetylated glucomannan, glucogalactomannan, galactan, galactogalacturan, arabinogalactan, galactoglucoarabinomannan, pectic substance, xylan, cellulose
Chromones	8-C-glucosyl-(2′-O-cinnamoyl)-7-O-methylaloediol A, 8-C-glucosyl-(S)- aloesol, 8-C-glucosyl-7-O-methyl-(S)-aloesol, 8-C-glucosyl-7-O-methylaloediol, 8-C-glucosyl-noreugenin, isoaloeresin D, isorabaichromone, neoaloesin A
Enzymes	Alkaline phosphatase, amylase, carboxypeptidase, catalase, cyclooxidase, cyclooxygenase, lipase, oxidase, phosphoenolpyruvate carboxylase, superoxide dismutase
Inorganic compounds	Calcium, chlorine, chromium, copper, iron, magnesium, manganese, potassium, phosphorous, sodium, zinc
Miscellaneous including organic compounds and lipids	Arachidonic acid, γ-linolenic acid, steroids (campestrol, cholesterol, βsitosterol), triglicerides, triterpenoid, gibberillin, lignins, potassium sorbate, salicylic acid, uric acid
Non-essential and essential amino acids	Alanine, arginine, aspartic acid, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, threonine, tyrosine, valine
Proteins	Lectins, lectin-like substance
Saccharides	Mannose, glucose, L-rhamnose, aldopentose
Vitamins	B1, B2, B6, C, β-carotene, choline, folic acid, α-tocopherol

Ni and Tizard (2004), Dagne et al. (2000), Femenia et al. (1999), and Choi and Chung (2003)

For centuries, Aloe plants have been widely used as therapeutic and topical agents due its medicinal and pharmacological properties, where it participate in the treatment of different types of diseases through molecular and biochemical pathway modulation (Surjushe et al. 2008; Rahmani et al. 2015). Research studies demonstrate that there is a presence of wide variety of phytochemicals and nutrients in the different Aloe species (Table 18.1) which includes simple and complex polysaccharides (notably glucomannans), fatty acids, vitamins, minerals, enzymes and many interesting secondary metabolites like phenolic compounds, flavonoids, phytosterols, glycoproteins, coumarins, alkaloids, pyrones, anthrones, naphthalenes, indoles, anthraquinones (aloe-emodin, aloins, aloectic and barbaloin), alkanes, aldehydes, ketones and dicarboxylic acids with potential toxicological and biological activities, however presence of the active components elude definition. (Nejatzadeh-Barandozi 2013; Boudreau et al. 2013a). It has been reported that due to presence of these secondary metabolites Aloe plants have been shown to possess numerous biological properties such as antimicrobial, antibacterial, antifungal, antiviral, anti-inflammatory, antitumor, anticancer, antidiabetic, anti-rheumatoid, anti-arthritic, detoxification, laxative, treating constipation, promoting digestion, wound or burn healing and enhancing immune system (Boudreau et al. 2013a). Conversely, ingestion of some toxic variety of Aloe plants produces adverse symptoms like kidney failure, hypersensitive reactions, diarrhoea, pseudomelanosis coli, phototoxicity and hypokalemia (Guo and Mei 2016). The different parts of Aloe plants like fleshy

leaves, latex and gel have been used commercially in food, cosmetics and pharmaceutical industries. This review article summarizes the phytochemistry, pharmacotherapy and toxicological profile of the Aloe genus plants.

18.2 Botany

Aloe genus (see classification below) is a succulent, monoecious, perennial species with shallow roots. Aloe species are widely spread throughout the warmer regions mainly in arid areas like Africa, India, etc. Although they can also be grown in subtropical winter rainfall and summer rainfall regions. There are some key factors which limit the genus distribution such as temperature, rainfall, fire tolerance and soil moisture. A wide diversity of habitats is occupied by Aloe species ranging from altitudes of 2700 m to sea level. Some Aloe species are particularly restricted to some geographical area although distribution of Aloe species is effected by specificity and seed pollinator morphology (Jordan 1996). In a broad range of soils Aloe species can be cultivated and mainly loamy mixture is preferred with temperature and pH ranging from 4 to 21 °C and 7.0 to 8.6. Conversely, some cold tolerant species can grow below 4 °C. Generally, grass Aloe species like *Aloe plicatilis*, *Aloe commixta* and *Aloe haemanthifolia* desires to grow in acidic soils (Giddy 1973). Most of the Aloe species under optimal environmental conditions can reach heights of up to 61–99 cm and flowering period is between the months of May to June. Entire Aloe species are evergreen with majority of species are with separate rosettes of fleshy, sword-shaped and thick leaves terminating at the trunk or branches in case of branched species. In individual species the leaves differ in colour, size and prickles distributed on the faces and margins of leaves. Usually flowers are of different shades (red, orange or yellow) with narrow to tubular shaped usually clustered at the apex of long stemmed spikes. Subsequently, up to 5 cm long oval fruits are formed after fertilization. The most commonly used part of Aloe plants is leaf which can be divide into three major parts as shown in Fig. 18.1. Outer green rind consisting of structural components containing glycosides and anthraquinones (Reynolds 2004), below the rind is outer pulp region with sap or latex and vascular bundles. Principally most phenolic compounds (Flavonoids, anthraquinones, anthrones, preanthraquinones, pyrones, chromones and coumarins) are present in the latex region (Gutterman and Chauser-Volfson 2000).

Kingdom:	Plantae- Plants
Subkingdom:	Tracheobionta- Vascular plants
Superdivision:	Spermatophyta- Seed plants
Division:	Magnoliophyta- Flowering plants
Class:	Liliopsida- Monocotyledons,
Subclass:	Liliidae
Order:	Liliales
Family:	Aloaceae (Aloe family)
Genus:	*Aloe L.- Aloe*

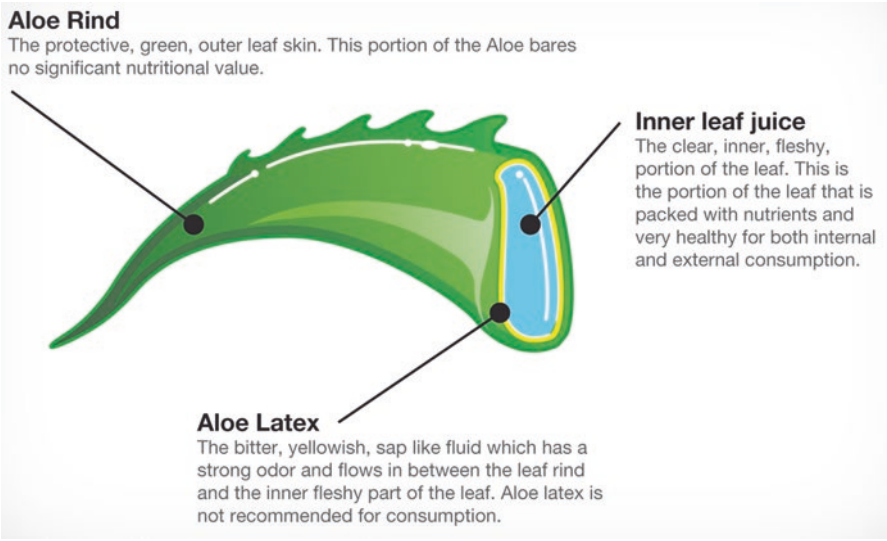

Fig. 18.1 A schematic illustration of Aloe leaf morphology showing a leaf cross section

The parenchyma cells are present in the inner leaf pulp of Aloe gel. In all aloe species the pulp consists of high acemannan polysaccharide and water content (approximately 99% for *Aloe vera*). There is a presence of numerous proteins, minerals, vitamins, enzymes, phytochemicals or secondary metabolites in the inner leaf pulp which includes flavonoids, alkaloids, coumarins, chromones, anthrones and anthraquinones (Reynolds 2004; Dagne et al. 2000; Boudreau and Beland 2006).

18.3 Phytochemistry

Aloe vera is a succulent plant meaning that the plant can bear droughts of water and can survive in areas of less water availability, due to possessing large water storage inside it. Though the studies are lacking, the plant's pulp is said to be associated with the storage of water (Ni et al. 2004). Succulents also use a different photosynthetic metabolism called as crassulacean acid metabolism (CAM) that involves malic acid (Denius and Homann 1972; Kluge et al. 1979).

In diverse Aloe genus plants, a variety of biologically active substances are present which shows interesting pharmacological activities. The potential bioactive compounds are present in different parts of Aloe plant such as leaves, outer pulp, inner leaf pulp (gel) or latex. The phytoconstituents present in Aloe genus includes enzymes, amino acids, saccharides, lignin, salicylic acids, alkaloids, flavonoids, sterols, saponins, coumarins, pyrans, pyrones, anthrones, benzene, anthroquinones, naphthalene, chromones, and furan derivatives (Cock 2015). In leaf gels of unspecified Aloe species various vitamins are present namely vitamin E (α-tocopherol), vitamin C (ascorbic acid), vitamin B_1 (thiamine), vitamin B_2 (riboflavin), vitamin B_6

(pyridoxal phosphate) and vitamin B_{12} (cyanocobalamin) along with presence of various inorganic minerals (copper, calcium, phosphorus, magnesium, potassium, zinc, iron, copper, manganese, molybdenum and sodium). According to researches, the diverse biological activities of different Aloe species is due to synergistic action between numerous compounds instead of single chemical compound. The various phytoconstituents present in different parts of Aloe species are presented in Table 18.2.

Many beneficial activities of the plant have been reported and attributed especially to the plant's polysaccharides. The activities may include, anti-bacterial, anti-viral, anti-inflammatory property, laxative, immunomodulation, and protection against radiations.

The various polysaccharides isolated from the plant include galactan, mannan, arabinanarabinorhamnogalactan, glucuronic acid-containing polysaccharide, and pectic substance. Mannan and pectic substance have been found to be the primary polysaccharides with some studies suggesting mannan to be the main polysaccharide while still others suggesting pectic substance to be the main one (Ovodova et al. 1975; Mandal and Das 1980). These controversies have been attributed to the plant's different geographical occurrences (Mandal and Das 1980; Grindlay and Reynolds 1986).

The leaves of the *Aloe vera* plant have shown strong antioxidant activities. One study showed that the plant is more antioxidant than some of the standards like butylated hydroxytoluene (BHT) and α-tocopherol. The study was conducted using plants of different age such as 2–4 year old plants. It was determined that the 3 years old plant contained a significantly higher number of flavonoids and polysaccharides than the 2 and 4 years old plants. Also the extract of the 3 year old plant showed a higher antioxidant potential than the extracts of 2 years old plants in the first 10 min of the experiment. When the different plant's extracts were ranked in terms of their antioxidant activity along with butylated hydroxytoluene (BHT) and α-tocopherol, it was found that in first 10 min α-tocopherol had the highest antioxidant potential while the 3 years old plant was at the second highest rank. However when their antioxidant potential was observed for 110 min it was observed that radical scavenging potential of α-tocopherol had decreased significantly ranking the 3 years old plant's extract at the highest point in terms of showing antioxidant potential. The study also concluded that the 2 years old plant showed the lowest antioxidant activity (Hu et al. 2003).

The plant contains very high amounts of the phenolic compounds such as anthrones, anthraquinones, chromones, saponins, coumarins, and polysaccharides in the leaf gel. The phenolic compounds have been attributed to showing antioxidant activities of the plant (Rice-Evans et al. 1997).

18.3.1 Anthraquinones

Several anthraquinones occur in roots and leaves of the species of aloe genus. Aloe emodin is found widely in the species of aloe and is found mostly in leaves of the plant. The roots of aloe contain two types of anthraquinones such as aloe saponarin

Table 18.2 Phytoconstituents present in various parts of Aloe species

Phytoconstituents	Description	Source	Plant part used	Molecular Formula	References
Alkaloids	O,N dimethyltyramine,	*Aloe* spp.	Leaves	$C_{10}H_{15}NO.HCl$	Nash (1992)
	N-methyltyramine	*Aloe* spp.	Leaves	$C_9H_{13}NO$	Nash (1992)
	γ-coniceine	*A. gillilandii*	Leaves	$C8H_{15}N$	Cock (2015)
	coniine	*A. viguleri*	Leaves	$C_8H_{17}N$	Cock (2015)
Flavonoids	Dihydro-isorhamnetin	*Aloe* spp.	Leaves	$C_{16}H_{14}O_7$	Cock (2015)
	Naringenin	*Aloe* spp.	Leaves	$C_{15}H_{12}O_5$	Cock (2015)
	Isovitexin	*Aloe* spp.	Leaves	$C_{21}H_{20}O_{10}$	Cock (2015)
	Apigenin	*Aloe* spp.	Leaves	$C_{15}H_{10}O_5$	Cock (2015)
Sterols	Lupeol	*A. barbadensis*	Leaves	$C_{30}H_{50}O$	Cock (2015)
	Cholesterol	*A. barbadensis*	Leaves	$C_{27}H_{46}O$	Cock (2015)
	β-sitosterol	*A. arborescens*	Leaves	$C_{29}H_{50}O$	Cock (2015)
	Campesterol	*A. barbadensis*	Leaves	$C_{28}H_{48}O$	Cock (2015)
Coumarins	Dihydroisocoumarin	*A. hildebrandtii*	Leaves	$C_{15}H_{12}O_4$	Wintola and Afolayan (2011)
	Feralolide	*A. ferox, Cape Aloe*	Leaves	$C_{23}H_{26}O_{13}$	Veitch et al. (1994)
Pyrans and pyrones	Bisbenzopyran	*A. barbadensis*	Root	$C_{22}H_{26}O_8$	Saleem et al. (1997)
	Aloenin (Aloecarbonoside)	*Aloe nyeriensis*	Leaves	$C_{19}H_{22}O_{10}$	Conner et al. (1987)
	Aloenin B	*Kenya aloe*	Leaves	$C_{34}H_{38}O_{17}$	Speranza et al. (1986)
	Aloenin acetal	*A. arborescens*	Leaves	NS	Woo et al. (1994)
	Aloenin aglycone	*A. nyeriensis*	Leaves	$C_{13}H_{12}O_5$	Conner et al. (1987)
	Aloe-2″-p-O-coumaroyl ester	*A. nyeriensis*	Leaves	NS	Conner et al. (1987)

	10-O-β-D-glucopyranosyl aloenin	*A. arborescens*	Leaves	NS	Duri et al. (2004)
Benzene	Pluridone	*A. pluridens*	Leaves	$C_{12}H_{12}O_3S$	Confalone et al. (1983)
	Protocatechuic acid	*A. berhana*	Leaves	$C_7H_6O_4$	Dagne and Alemu (1991)
	Fluridone	*A. pluridens Haw*	Leaves	$C_{19}H_{14}F_3NO$	Cock (2015)
	Methyl-p-coumarate	*A. ferox*	Leaves	$C_{12}H_{12}O_4$	Graf and Alexa (1982)
Naphthalene	Plicataloside	*A. plicatilis*	Leaves	$C_{23}H_{30}O_{13}$	Wessels et al. (1996)
	Feroxidin,	*A. ferox*	Leaves	$C_{11}H_{14}O_3$	Speranza et al. (1990)
	Feroxidin A	Cape aloe	Leaves	$C_{11}H_{14}O_3$	Rainsford et al. (2015)
	Feroxidin B	Cape aloe	Leaves	$C_{11}H_{14}O_3$	Rainsford et al. (2015)
	Aglycone isoeleutherol	Aloe spp.	Roots and leaves	$C_{14}H_{12}O_4$	Salehi et al. (2018)
	Isoeleutherol-5-O-glucoside	*A. saponaria*	Roots and leaves	NS	Salehi et al. (2018)
Furan derivatives	3-methylnaphto[2,3-c]furan-4,9-dione	*A. ferox*	Leaves	NS	Cock (2015)
	3-methylnaphto[2,3-c]furan-4(9H)-one,	*A. ferox*	Leaves	NS	Cock (2015)
	5-OH-3-methylnaphto[2,3-c]furan-4(1H)-one	*A. ferox*	Leaves	NS	Cock (2015)
Chromones	Aloeresin A	*Aloe* spp.	Leaves	$C_{28}H_{28}O_{11}$	Dell'Agli et al. (2014)
	Aloesin (Aloeresin B)	*Aloe* spp.	Leaves	$C_{19}H_{22}O_9$	Manitto et al. (1990)
	Aloeresin C	Cape aloe	Leaves	$C_{38}H_{38}O_{16}$	Cock (2015)

(continued)

Table 18.2 (continued)

Phytoconstituents	Description	Source	Plant part used	Molecular Formula	References
	Aloeresin D	*Aloe* spp.	Leaves	$C_{29}H_{32}O_{11}$	Cock (2015)
	Aloeresin E	*A. peglerae*	Leaves	$C_{34}H_{38}O_{15}$	Van Heerden et al. (1996)
	Aloeresin F	*A. peglerae*	Leaves	$C_{28}H_{28}O_{10}$	Van Heerden et al. (1996)
	Aloesol	*Aloe* spp.	Leaves	$C_{13}H_{14}O_4$	Cock (2015)
	Iso-aloesin	*A. vera var. chinensis*	Leaves	$C_{19}H_{22}O_9$	Cock (2015)
	Iso-aloeresin A	Cape aloe	Leaves	$C_{28}H_{28}O_{11}$	Speranza et al. (1988)
	Iso-aloeresin D	*A. vera*	Leaves	$C_{29}H_{32}O_{11}$	Okamura et al. (1996)
	7-O-methylaloesin	*A. rupestris*	Leaves	$C_{20}H_{24}O_9$	Bisrat (2000)
	7-O-methylaloesinol	*A. capensis*	Leaves	NS	Park et al. (1997)
	7-O-methylaloeresin A	*A. marlothii*	Leaves	NS	Bisrat (2000)
	8-[C-β-D-[2-O-(E)-cinnamoyl] glucopyranosyl]-2-[(R)-2-hydroxypropyl]-7-methoxy-5-methylchromone	*A. barbadensis*	Leaves	NS	Hutter (1996)
	8-C-glycosyl-7-O-methylaloediol	*A. vera*	Leaves	NS	Okamura et al. (1997)
	8-C-glycosyl-7-O-methyl-(S)-aloesol	*A. vera*	Leaves	NS	Okamura et al. (1996)
	2-acetonyl-7-hydroxy-8-(2-furanonyl)-7-hydroxy-5-methylchromone	Cape aloe	Leaves	NS	Speranza (1997)
	7-hydroxy-2,5-dimethylchromone	Cape aloe	Leaves	$C_{11}H_{10}O_3$	Speranza et al. (1993)
	8-*C*-glucosyl-(2'-*O*-cinnamoyl)-7-*O*-methyl-aloediol	*A. vera*	Leaves	NS	Okamura et al. (1998)

	8,2-acetonyl-8-(2′,6′-di-*O*,*O*-coumaroyl)-glucopyranosyl-7-hydroxy-5-methylchromone	*A. speciosa*	Leaves	NS	Holzapfel (1997)
	2-acetonyl-8-(2′, cinnamoyl)-glucopyranosyl-7-hydroxy-5-methylchromone	*A. broomii*	Leaves	NS	Cock (2015)
	6'-*O*-coumaroylaloesin	*A. castanea*	Leaves	$C_{28}H_{28}O_{11}$	Van Heerden et al. (2000)
	2′-p-*O*- methylcoumaroylaloesin	*A. excelsa*	Leaves	NS	Cock (2015)
Anthrones	Barbaloin	*A. vera*	Leaves	$C_{21}H_{22}O_9$	Patel et al. (2012a)
	Nataloin	*A. ellenbeckii*	Leaves	NS	Grace et al. (2008)
	Homonataloin	*A. marlothii* Berger, *A. jacksonii*	Leaves	$C_{22}H_{24}O_9$	Conner et al. (1990)
	Homonataloside	*A. lutescens*	Leaves	NS	Van Heerden et al. (2000)
	Aloe barbendol	*A. barbadensis*	Roots	$C_{15}H_{14}O_4$	Saleem et al. (1997)
	Aloinoside A/B	*Aloe* spp.	Leaves	$C_{27}H_{32}O_{13}$	Cock (2015)
	Aloe-emodin anthrone	*Aloe* spp.	Leaves	$C_{15}H_{12}O_4$	Sigler and Rauwald (1994)
	Aloe emodin-10-C-rhamnoside	*A. rabaiensis*	Leaves	NS	Cock (2015)
	Chrysophanolanthrone	*Aloe* spp.	Leaves	$C_{15}H_{12}O_3$	Sigler and Rauwald (1994)
	8-*O*-methyl-7-hydroxyaloin A/B	*A. barbadensis*	Leaves	$C_{22}H_{24}O_{10}$	Rauwald (1990)
	6′-*O*-*p*-coumaroyl-7-hydroxyaloin	*A. barbadensis*	Leaves	NS	Rauwald (1990)
	6′-*O*-cinnamoyl-8-*O*-methyl-7-hydroxyaloin	*A. barbadensis*	Leaves	NS	Rauwald (1990)
	6′-*O*-cinnamoyl-5-hydroxyaloin A	*A. broomii*	Leaves	NS	Koroch (2009)
	7-hydroxyaloin-4′,6′-*O*-diacetate	*A. succotrina*	Leaves	NS	Sigler and Rauwald (1994)
	6′-*O*-diacetate				
	Deacetyllittoraloin	*A. littoralis*	Leaves	$C_{26}H_{30}O_{12}$	Koroch (2009)

(continued)

Table 18.2 (continued)

Phytoconstituents	Description	Source	Plant part used	Molecular Formula	References
	Microstigmin A	*A. microstigma*	Leaves	$C_{30}H_{28}O_{13}$	Koroch (2009)
	Littoraloside	*A. littoralis*	Leaves	$C_{32}H_{40}O_{17}$	Dagne et al. (1997)
	Littoraloin	*A. littoralis*	Leaves	$C_{28}H_{32}O_{13}$	Koroch (2009)
	Microdontin	*A. microdonta*	Leaves	$C_{30}H_{28}O_{11}$	Koroch (2009)
Anthraquinones	Aloesaponarin	*A. saponaria*	Roots	$C_{15}H_{10}O_4$	Cock (2015)
	Aloechrysone	*A. berhana*	Roots	$C_{15}H_{16}O_4$	Koroch (2009)
	Aloesaponol	*A. saponaria*	Roots	$C_{15}H_{14}O_4$	Cock (2015)
	Desoxyerythrolaccin	*A. saponaria*	Roots	$C_{15}H_{10}O_5$	Cock (2015)
	Chrysophanol	*A. saponaria*	Roots	$C_{15}H_{10}O_4$	Cock (2015)
	Prechrysophanol	*A. graminicola*	Roots	$C_{15}H_{14}O_4$	Yenesew et al. (1993)
	Helminthosporin	*A. saponaria*	Roots	$C_{15}H_{10}O_5$	Cock (2015)
	1,5-dihydroxy-3-hydroxy Methylanthraquinone	*A. excelsa*	Leaves	NS	Koroch (2009)
	7-hydroxyaloe emodin	*A. succotrina*	Leaves	NS	Sigler and Rauwald (1994)
	Nataloe emodin	*A. nyeriensis*	Leaves	$C_{15}H_{10}O_5$	Koroch (2009)
	Nataloe emodin-8-methyl ester	*A. specrosa*	Leaves	NS	Cock (2015)
	Isoxanthorin	*A. saponaria*	Roots	$C_6H_5N_5O_2$	Cock (2015)
	Laccaic acid-d-methyl ester	*A. saponaria*	Roots	NS	Cock (2015)
	Aloe emodin-11-*O*-rhamnoside	*A. rabaiensis*	Leaves	NS	Koroch (2009)
	Aloesaponol-*O*-methyl-4-*O*-glucoside	*A. barbadensis*	Leaves	NS	Yagi et al. (1998)
	Aloesaponol-6-*O*-glucoside	*A. saponaria*	Roots	NS	Cock (2015)
	Aloesaponol-8-*O*-glucoside	*A. saponaria*	Roots	NS	Cock (2015)
	Nataloe emodin-2-*O*-glucoside	*A. nyeriensis*	Leaves	NS	Cock (2015)
	Asphodelin A	*A. saponaria*	Roots	$C_{15}H_{10}O_6$	Cock (2015)

	Bianthracene	*A. saponaria*	Roots	$C_{28}H_{18}$	Cock (2015)
	Elgonicardine	*A. elgonica*	Leaves		Conner et al. (1990)
	5-hydroxyaloin A	*A. khamiensis Pillans*	Leaves	$C_{21}H_{22}O_{10}$	Rauwald and Beil (1993)
	7-hydroxyaloin A/B	*A. succotrina* Lam	Leaves	$C_{21}H_{22}O_{10}$	Sigler and Rauwald (1994)
	10-hydroxyaloin A	*A. arborescens; A. barbadensis*	Leaves	$C_{21}H_{22}O_{10}$	Park et al. (1998)
	5-hydroxyaloin A 6′-*O*-acetate	*A. marlothii* and *A. rupestris*	Leaves	$C_{23}H_{24}O_{11}$	Bisrat et al. (2000)
	7-hydroxyaloin-6′-*O*-monoacetate	*Aloe* spp.	Leaves	NS	Cock (2015)
	10-hydroxyaloin-6-*O*-acetate	*Aloe* spp.	Leaves	NS	Cock (2015)

NS Not Specified

I-type and chrysophanol-type while chrysophanol-type is also found in the leaces of aloe (Dagne et al. 2000). Anthraquinones such as aloe emodin and aloin exhibit strong anti oxidant activities probably due to their ability to scavenge free radicals and also inhibit peroxidation of lipids.

In the study, the antioxidant activity of anthraquinones, anthrones, aloe emodin, rhein amodin have been studied using a linoleic acid system. Thiocyanate method was used to determine the degree of peroxidation inhibition of the linoleic acid system at 37 °C. Anthrones and alzirin were identified to show the strongest antioxidant potential with no significant difference between them. Their scavenging power was found to be even stronger than α-tocopherol and BHT while anthraquinone had antioxidant potential stronger than rhein emodin but lesser than α-tocopherol. It was also determined that anthrone and alzinrin's antioxidant activity is due to their strong reducing powers and their reducing potential increases with their concentrations. The other anthraquinones did not show any reducing activity in the experiment. Similarly in the same study the scavenging activity of anthrones and anthraquinones was determined on the hydroxyl radicals with the result that emodin exhibits strong scavenging potential at a concentration of 0.25 mg/ml while chrysophanol, anthraquinone, rhein and alizarin at the same dose increase the formation of such radicals. Anthrone and aloe emodin also exhibit scavenging potential but their capacity is lesser than that of emodin at the same concentration (Yen et al. 2000).

In another study, aloin and aloe emodin were studied for their pro-oxidant and antioxidant activities at different doses. Radicals scavenging properties were determined using Chemiluminescence assay. Epigallocatechin-3-gallate (EGCG) was used as a comparative antioxidant agent. The experiment established that both aloin and aloe emodin showed antioxidant potential which increased by increasing their dose however it was less than that of EGCG at all concentrations and aloe emodin showed scavenging activity lesser than that of both aloin and EGCG at all concentrations. It was also found that aloin had a greater reducing tendency than aloe emodin at all concentrations attributing it's antioxidant potential to its reducing capacity. Also at high doses of 1.25–2.5 mM aloin prevented DNA breakage due to OH radicals by 5–30% over the control value but increases DNA damage at lower concentrations of 300–8 μM. Both aloe emodin and EGCG at high concentrations show pro-oxidant effects. The experiments established that the different effects of both aloin and aloe emodin on DNA may be attributed to the difference in their structures and concentration dependencies (Tian and Hua 2005). Studies have established that several antioxidant agents can become pro-oxidants at different concentrations and therefore their right doses should be established before their clinical use (Lee and Park 2003).

18.3.2 Bianthraquinoids

Genus does not contain many dimers however elgonica-dimers A and B (Elgonicardine) are found in *Aloe elgonica* while *Aloe saponaria* contains Asphodelin, Bianthracene II, III and IV in the plant's rhizomes and roots.

18.3.3 Anthrones

Anthrones has been reduced from anthraquinones and are a class of compounds mainly responsible for producing laxation and purgation effects. Alloin A and B are collectively called as barbaloin or alloin are C-glycosyl anthrones and are the first anthrones to be discovered in aloe. Anthrones have been found not only in *Aloe vera* but in amost a hundred species of genus Aloe in high concentrations of 10–20% (Dagne et al. 2000). Aloe ferox has almost a 30 percentage of such anthrones (Van Wyk et al. 1995).

Alloin however is not only confined to the genus Aloe but several other plant species belonging to different genus also contain alloin. Nataloin and homonataloin have been detected to be present in a species of aloe called *Aloe marlothii* Berger. The anthrone 10-Hydroxyaloin B is found in abundance in *Aloe llittoralis*. Anthrones are mostly present in the leaves and have not yet been discovered to present in the roots of the species (Dagne et al. 2000).

Anthrons such as alloin have been reported to act as strong antioxidants and protective of the DNA breakage at high concentrations (Yen et al. 2000; Tian and Hua 2005), but at lower concentrations, they act as prooxidants.

18.3.4 Chromones

It is one of the most abundant phenolic compound present in the aloe species including aloesin and aloeresin. These have been found and identified in most of the aloe species. Aloesin has been identified to occur in at least 30% of the examined species of the genus aloe (Dagne et al. 2000). Chromines such as aloesin and 7-O-methylaloesin are the major components found in Aloe rupestris Bak (Dagne et al. 2000).

18.3.5 Coumarins, Pyrans and Pyrones

Aloe ferox has been reported to contain coumarins a such as dihydroisocoumarin glycoside and feralolide (Speranza et al. 1993). Apart from his species *A. hildebrandtii* has also been reported to contain the said two coumarines (Veitch et al. 1994). Coumarin such as aloenin is a very bitter tasting component found in the leaf exudant of aloe and has been derived from phenylpyrone. These constituents of the aloe plants have been reported to suppress hunger (Costa et al. 2016). A double blind placebo controlled study, in an attempt to treat lymphedema of arms and legs with 5,6-Benzo- α -pyrone was carried out with the findings that the said pyrone stimulates macrophagaes to cause degradation of the albumins present outside the cells ultimately resulting in a rapid reabsorption of the fluid and thus lowering of the edematous swellings at a dose of 400 mg for a duration of 6 months. After the first

month of therapy, the side effects were reported to have diminished as well (Casley-Smith et al. 1993).

18.3.6 Flavonoids

The studies on the presence of flavonoids had been seriously lacking as the focus was mainly on the presence of anthraquinones, anthrones and coumarines in aloe species. Out of three hundreds of the species flavonoids have been reported to occur in only thirty one species of the genus exhibiting their rare occurance. The major flavonoids found in these species are identified to include apigenin, naringenin, dihydroisorhamnetin, and isovitexin. Flavonoids have a strong antioxidant potential as they have been observed in inhibiting the lipid peroxidation in several trials. Due to the antioxidant properties of flavonoids they have been reported to prevent coronary heart diseases (Martikainen et al. 2007).

18.3.7 Alkaloids

O, N-dimethyltryamine and N-methyltryamine have been reported as the most common alkaloids found in aloe species. Gama-coniceine has been reported to occur in 6 species including *Aloe gillilandii* while coniine is found to occur only in one aloe species namely *Aloe viguieri* (Dagne et al. 2000). Alkaloids have been reported to exhibit toxic properties and aloe's toxicology may be attributed to their presence as exudates of the plant have been reported to be used as arrow poisons. It has been identified in a study that the alkaloids cause muscle paralysis. The mechanism underlying is observed to be their ability to block the nicotinic receptors of the post-synaptic neurons (Reynolds 2005).

18.3.8 Sterols

A number of important sterols have been found in the leaves of the aloe species including campesterol, cholesterol, lupeol, β-sitosterol and their glucosides (Dagne et al. 2000). These sterols present in plants have been reported to exert healing properties thus justifying the uses of aloe for healing purposes. The sterols are identified to increase production of the cells of endothelial walls of arteries as they increase the production of proteins important in keeping the integrity of vessels intact (Moon et al. 1999). The sterols found in the plant may also play a role attributing to the plant's anti-inflammatory properties as the sterols suppress the pain associated with inflammation and may provide analgesic properties (Sahu et al. 2013).

18.3.9 Other Compounds

Other compounds reported to be present in aloe include benzene, furan and naphthalene derivatives. Protocatechuic acid a benzene derivative found in aloe have been identified to exhibit antioxidant activities as it gets rid of free radicles as reported in a study (Lodovici et al. 2001). The aloe species also contain a number of important minerals such as magnesium, calcium, zinc, copper, and iron etc. The plants also contain sugars such as glucose, arabinose, mannose, galactose, and xylose apart from containing important dietary vitamins like vitamins B1, B2, B6, B12 and also vitamin C. The plant is also a source of amino acids and folic acid. An important polysaccharide acemannan is also present in *Aloe vera* gel and is thought to be the major reason behind the various benefits of the plant (Dagne et al. 2000).

18.4 Acceptable Daily Intake (ADI)

In India, Caribbean, China, and Japan Aloe plants are considered as traditional medicine for more than 2000 years. Researchers reported that various parts of Aloe plant especially gel and latex possesses wide range of pharmaceutical activities due to presence of numerous beneficial bioactive compounds. It has been reported that 8.5–13.8% of people of Hispanic populations in the southern USA frequently use *Aloe vera* in alternative and complementary medicine. According to surveys, it is also used regularly by 7.6%, 10.8% and 10.3% of adults in Jamaica, Australia, and Italy respectively (Ngo et al. 2010). A single-strength leaf gel of fluid ounces (59–237 mL) of *Aloe vera* was recommended for total daily consumption by the International Aloe Science Council (IASC 2013). Pure *Aloe vera* gel can be used generously as topical cream for skin. *Psoriasis vulgaris* and genital herpes can be treated by using hydrophilic cream, three times per day for five consecutive days per week made with 0.5% (by weight) of a 50% ethanol extract of *Aloe vera* (Ulbricht et al. 2007).

The gel/latex of Aloe plant can be used as medicinal laxative. The European Medicines Agency (EMA 2006) suggested that consumption of a correct individual dose of 30 mg of hydroxyanthracene glycosides per day produce soft-formed stool. The recommended dose for children and adults above 10 years of age is 10–30 mg of hydroxyanthraquinones/day, 40–110 mg of the dried latex or 100 mg as a single dose in the evening (WHO 1999). In adults oral dose of 4.5:1 *Aloe vera* gel concentrate of 25–100 mL per day was suggested for therapeutic applications (Morgan et al. 2005).

Recent research evidences on *Aloe vera* by the Natural Standard Research Collaboration reported that *Aloe vera* extract, gel or latex is safe if used as topical application for the treatment of mild to moderate skin conditions like inflammation, burn or wound (Ulbricht et al. 2008), its oral use has shown potential benefits like hypoglycaemic property, regulation of blood pressure, treatment of ulcerative coli-

tis, stabilization of metastatic cancer and laxative effect (Ulbricht et al. 2008). Conversely, long term consumption of the latex or gel is unsafe as it can lead to allergic reactions, electrolyte imbalance, dehydration and diarrhoea. Individuals should follow the recommended dosing mentioned on package labelling before using the Aloe products. There is a need to understand in detail optimal dosage and of Aloe plant's preparations in the treatment of definite disorders.

18.5 Pharmacotherapy

Worldwide, traditional healers from a wide variety of cultural and ethnic group use members of genus Aloe for a broad range of medicinal purposes. In different parts of the world mostly in Asia (India and Nepal) and Africa maximum Aloe plants are used. The different parts of Aloe plants are used traditionally in the treatment of various ailments.

18.5.1 Antimicrobial Activity

Recent researches reported that different Aloe species possess antibacterial, antifungal and antiviral activities. The leaf extract of four different Aloe species *A. barbadensis*, *A. rupestris, A. juvenna* and *A. maculata* var. pulchra showed varied levels of antimicrobial activity against pathogenic bacteria *Bacillus cereus* (Sonam and Tiwari 2015). Water, petroleum ether and dichloromethane extracts of leaves, young bark, roots and upper stem of South African species *A. barberae* exhibit antimicrobial activity against Gram-negative (*Klebsiella pneumonia, Escherichia coli)* and Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) bacteria (Ndhlala et al. 2009). In vitro studies have shown that acetone extract of *A. vera* shows strong activity against *E. coli*, *S. aureus, Pseudomonas aeruginosa and Streptococcus pyogenes* compared to ethanol and aqueous extracts. Antibacterial activity of leaf extract from *Calotropis procera, Pongamia pinnata, Aloe vera, Lantona camara, Datura stromonium* were studied by Johnson et al. (2011). In a separate studies, Adetunji et al. (2011) evaluated the effect of aqueous extracts and ethanolic extract obtained from *Aloe vera* leave extracts against some pathogenic microorganism of clinical origin. The result obtained shows that the ethanolic extract exhibited a higher antibacterial activity against all the tested isolates. The high antimicrobial activity might be linked to the presence of phytochemical constituents available in the *Aloe vera* plant such as phenolics, tannins, alkaloids and saponin and cardiac glycosides. The antimycobacterial potential of *Aloe vera* were *Aloe vera* by Chandran et al. (2017) against *Mycobacterium smegmatis*. The result shows that

1000 mg/mL exhibited the highest antimycobacterial of 31 mm against the tested pathogen while the purified fraction exhibited a zone of inhibition of 40 mm. The antimicrobial activity exhibited by the purified compound were linked to the availability of acemannan or aloverose.

Kedarnath et al. (2012) evaluated the biologically active compound present in *Aloe vera and* the effect of these extract obtained from the leave was against some clinical isolates. The clinical isolates includes *Neurospora crassa, Aspergillus niger, and Aspergillus fumigates.* The antifungal activity was observed from ethanol and petroleum ether having 22 mm.

Aloe vera gel has been identified to show antibacterial activities against *Pseudomonas aeruginosa*. The polysaccharide acemannan was found to hinder its attachment to the epithelial cells of the human lungs (Azghani et al. 1995). Apart from *Streptoccocus pyogenes* and *Streptococcus faecalis* have also been found to be inhibited by *Aloe vera* gel (Heggers et al. 1995). *Aloe vera* gel also has properties to stimulate the immune system against foreign bodies. The plant has also exhibited antifungal activities against *Candida albicans* as reported in a study (Heggers et al. 1995). *Aloe vera* administration in rats showed that the plant has wound healing properties as it rids of the bacteria that may enhance the inflammation associated with wounds (Heggers et al. 1995).

Numerous research studies demonstrate that *A. vera* shows antiviral activity by preventing virus entry, adsorption, and attachment into host cells. According to Zandi et al. (2007) *A. vera* gel shows antiviral activity against herpes simplex virus (HSV) type 2 strains. Derivatives of anthraquinone (chrysophanol, aloe-emodin and emodin) present in Aloe exhibits antiviral activity by inhibiting virus-induced cytopathic effect and influenza A virus replication (Li et al. 2014).

18.5.2 Anti-dental Caries Activities

Studies has shown that Aloe vera possesses ant-dental caries activities. For instance, Fani and Kohante (2012) evaluated the effect of *Aloe vera* gel against periodontopathic (*Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis*), opportunistic periodontopathogen (*Bacteroides fragilis*) and cariogenic (*Streptococcus mutans*) infected by patients suffering from dental caries and periodontal diseases. The authors tested the *Aloe vera* gel against 20 isolates which were bacteria using microdilution methods and disk diffusion. The highest antimicrobial activity was exhibited against *S. mutans* at the minimum inhibitory concentration of 12.5 µg/ml while *B. fragilis, A. actinomycetemcomitans*, and *P. gingivalis* show less sensitivity with minimum inhibitory concentration of 25–50 µg/ml. Their study shows that *Aloe vera* gel could be utilized for the prevention of periodontal diseases and dental caries.

18.5.3 Anti-urinary Tract Infection

Urinary tract infection (UTI) is a serious medical condition capable of affecting any part of the urinary system including the kidneys, ureters, bladder and urethra. Bukhari et al. (2017), tested *Aloe dera* gel against some UTI causing microorganisms, *Pseudomonas aeruginosa, Staphylococcus aureus,* and *E. coli.* The result observed shows that *Aloe vera* gel exhibited antimicrobial activity against all the selected uropathogens. The level of inhibition observed against the tested selected uropathogens were *E. coli* (76.9%), *Staphylococcus aureus* (75%) and *Pseudomonas aeruginosa* (40%). Their study shows that *Aloe vera gel* could be used for the management of UTI.

Begum et al. (2016) evaluated the antimicrobial efficacy of *Aloe vera* against *Streptococcus pneumonia, Staphylococcus saprophyticus*, *Klebsiella pneumonia, Staphylococcus aureus*, *Staphylococcus pyogenes*, *Pseudomonas aeruginosa*, *Escherichia coli*. The level of antimicrobial activity was assessed using zones of inhibition during antimicrobial susceptibility testing. The result obtained shows that *Aloe vera* gel exhibited an inhibitory effect against all the tested isolates most especially the ethanolic extract.

18.5.4 Antioxidant Activity

Overproduction of free radicals or reactive oxygen species (ROS) results in oxidative stress, which subsequently damages the DNA, protein and lipids of the body resulting in the development of numerous diseases. Antioxidants are those substances which at low concentration inhibits the oxidizable substrate oxidation. In vitro antioxidant potential was reported by the methanol extracts of leaf epidermis and flower of *A. vera* (López et al. 2013). The radical scavenging activity of most Aloe species is due to presence of chromone glycosides. 70% ethanol extracts of *A. vera* flower inhibit the free radical induced DNA damage and linolenic acid oxidation. High performance liquid chromatography (HPLC) was used to identify the 11 phenolic constituents present in the extract; vanillic acid content was found to be high in the extract which corresponds to high antioxidant activity. The extracts raise the antioxidant enzymes (glutathione peroxidise, superoxide dismutase and catalase) in the liver tissue of hydrogen peroxide-treated BALB/c mice. Presence of total phenolic content in the extracts promotes radical-scavenging activities. Thus, flowers of *A. bardadensis* are a valuable source of natural antioxidant (Debnath et al. 2018).

Free radical scavenging activity of Aloe gel was showed on nitric oxide radicals, 2,2-diphenyl-1-picrylhydrazyl(DPPH)and2,20-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) + (Saini and Saini 2011). Antioxidant capacity of *A. ferox* was determined using ferric reducing antioxidant power (FRAP) analyses and oxygen radical absorbance capacity (ORAC). Results showed that it prevents or allevi-

ates the symptoms of oxidative stress-related diseases due to presence of phytochemicals like aloeresins and 7-hydroxychromones in *A. ferox* shows strong antioxidant activity by suppressing the generation of reactive oxygen species and free radicals (Jones et al. 2002; Jia and Farrow 2005). In literature in vitro antioxidant activity of various Aloe species (*A. melanacantha*, *A. arborescens*, *A. harlana*, *A. ferox, A. saponaria, A. greatheadii* var. *davyana* and *A. marlothii*) leaf extracts have been reported (Asamenew et al. 2011; Yoo et al. 2008; Cardarelli et al. 2017).

18.5.5 Anti-ulcer Activity

Worldwide, one of the most common problem which impairs the quality of life is a chronic disease known as peptic ulcer which is linked to increased mortality and morbidity. Imbalance between aggressive factors (*Helicobacter pylori*, bile salts, chemicals, free radicals, acid, pepsin and pancreatic enzymes) and defensive factors (mucosa, adherent mucin, prostaglandins and bicarbonate) leads to ulcer formation.

In both humans and animals, *A. vera* gel has the ability to minimize the gastric ulcers (Suvitayavat et al. 2004). To promote digestion and in the treatment of peptic ulcer, extract of *A. vera* leaf have been generally recommended due to its efficient antibacterial activity and cytoprotective action. *A. vera* gel acts as a promising natural antibiotics which inhibit the growth of resistant *H. pylori* strains (Radha and Laxmipriya 2015).

A. vera gel extract shows gastro-protective nature as it acts against the aggressive factors and protects the gastric mucusa from ulceration by increasing the levels of glycoproteins and resist the attack of proteolytic enzymes. Presence of flavonoids in *A. vera* gel ameliorate the glycoprotein abnormalities and stabilize the antioxidant status of the gastric mucosa (Subramanian et al. 2007).

In pylorus ligated and lumen perfuse rats, hydrochloric acid induced-gastric mucosa damage and gastric acid secretion was studied after application of varying doses of ethanol extract of *A. vera* (Liliaceae) results demonstrate that extract possess gastroprotective activity and gastric acid inhibitory properties at lower concentration (Yusuf et al. 2004). Another study established that a mixed treatment with sucralfate and *A. vera* reduced ulcer sizes, gastric inflammation, elongate gastric glands and enhance epithelial cell proliferation (Eamlamnam et al. 2006).

18.5.6 Anticancer Activity

In the human population one of the most common and lethal malignancies is hepatocellular carcinoma with approximately 550,000 new cases. Aloe species are considered as a source of medicine in rural areas. Shalabi et al. (2015) evaluated the in vitro anticancer effect of different doses of *A. vera* and *C. comosum* extracts against hepatocellular carcinoma (HepG2) cells. Results signify that both the

extracts induce genotoxic and cytotoxic effect on human hepatocellular carcinoma (HepG2) cells in a time and dose dependent manners through induction of apoptotic pathway by increasing P53 and decreasing Bcl-2 genes expressions.

Aloin[10-glucopyranosyl-1,8-dihydroxy-3-hydroxymethyl-9(10H)-anthracenone, l] or barbaloin is an anthraquinone glycoside, a natural phytochemical present in *A. vera* and many other plants of Aloe genus are shown to exhibit cytotoxic and chemoprotective effects against 1,2-dimethylhydrazine-induced colon preneoplastic lesions in Wistar rats (Hamiza et al. 2014). The antiproliferative nature of anthracycline aloin isolated from *A. vera* was tested against human uterine carcinoma HeLaS3 cells. Results indicate that aloin shows anti-metastatic potential by causing cell cycle arrest in the S phase and markedly increasing HeLaS3 cell apoptosis (Niciforovic et al. 2007). The polysaccharide mannan isolated from *A. saponaria* was evaluated for its anti-proliferative effects using normal human cells (PBMC), murine cells (SpMC) and many tumor cell lines. It was found that proliferation of both normal and tumor or cancer cells were inhibited by mannan and it affected the expression of CD3+ SpMC, signifying inhibition of mostly T-lymphocyte proliferative response (Sampedro et al. 2004). Aloin obtained from Aloe plant was tested for cytotoxicity against two human breast cancer cell lines with (SKBR-3) erbB-2-topolla coamplification and without (MCF-7). It was reported that SKBR-3 was less sensitive to aloin than MCF-7 cell line, as established by the clonogenic and MTT assays (Esmat et al. 2006).

An anthracenedione derivative aloe-emodin (1,8-dihydroxy-3-hydroxymethyl-9,10-anthracenedione) is also derived from *A. vera* leaves are shown to possess antiproliferative effects in few cancer cell types like neuroectodermal, lung, glioma and squamous cancer cells by inhibiting gene expression and N-acetyl transferase activity (Masaldan and Iyer 2014). The bioactive component obtained from *A. ferox* is used as potential anticancer agent. It has been reported that Aloe-emodin does not affect normal cells and active against neuroectodermal tumors. It promotes cell death through uptake of specific drug by neuroectodermal tumors (Pecere et al. 2000).

In leaves of Aloe plants, sugar-binding proteins present are commonly known as lectins which have many immunological activities. In vivo studies report that plant lectin act as protein carrier which activate T cells and increase antitumor immunity (Yoshimoto et al. 1987).

Anthraquinones and anthrones at specific safe doses get rid of free radicals such as hydroxyl radicals and prevent DNA damage. In a study, aloin and aloe emodin were studied for their prooxidant and antioxidant activities at different doses. Radical scavenging properties were determined using Chemiluminescence assay. Epigallocatechin-3-gallate (EGCG) was used as a comparative antioxidant agent. The experiment established that both aloin and aloe emodin showed antioxidant potential which increased by increasing their dose however it was less than that of EGCG at all concentrations and aloe emodin showed scavenging activity lesser than that of both aloin and EGCG at all concentrations. It was also found that aloin had a greater reducing tendency than aloe emodin at all concentrations attributing its

antioxidant potential to its reducing capacity. Also at high doses of 1.25–2.5 mM aloin prevented DNA breakage due to OH radicles by 5–30% over the control value but increases DNA damage at lower concentrations of 300–8 μM. Both aloe emodin and EGCG at high concentrations show prooxidant effects. The experiments established that the different effects of both aloin and aloe emodin on DNA may be attributed to the difference in their structures and concentration dependencies (Tian and Hua 2005). Studies have established that several antioxidant agents can become prooxidants at different concentrations and therefore their right doses should be established before their clinical use (Lee and Park 2003).

18.5.7 Anti-inflammatory Activity

During inflammatory process, highly active pro-inflammatory mediators (prostaglandins) are produced from arachidonic acid in the presence of cyclooxygenase (COX) enzymes (prostaglandin-H_2-synthases) which act as catalysts (Steinmeyer 2000). Inhibiting COX enzymes, particularly the COX-2 enzyme inhibit production of prostaglandin to resolve inflammation. Fifty-one different Aloe species were reported to show different activity levels against COX-1 enzymes (Amoo et al. 2014). Administration of Aloe has been resulted in proliferative and phagocytic activity by reducing prostaglandin E2 production and inhibiting COX pathways (Park et al. 2009). Methanol extract of *A. ferox* inhibit the COX-1 effects as reported by Lindsey et al. (2002). In the early phase of acute inflammatory response tumor necrosis factor (TNF)-α genes and albumin transcription levels are involved. Elimination of albumin gene transcription was observed in rats treated with aloe-emodin. After administration of aloe- emodin, decreased level of TNF-α was detected in livers. Rats treated with aloe-emodin showed a reduced inflammatory infiltration of the Kupffer cells and lymphocytes (Arosio et al. 2000). The presence of chromones and anthraquinones in the inner Aloe gel acquire strong anti-inflammatory effects in murine macrophages (Park et al. 2009).

Studies report that *A. vera* gel had strong NLRP3 (NACHT, LRR, and PYD domains-containing protein 3) inflammasome expression, immunomodulatory activity and downregulating lipopolysaccharide-induced inflammatory cytokine production in human macrophage (Budai et al. 2013). In severe traumatic–hemorrhagic rats pre-treatment of Aloe polysaccharide can attenuate reperfusion injury and cerebral ischemia by inhibiting lipid peroxidation, systemic inflammatory response and leukocyte aggregation (Liu et al. 2012).

Bradykinin is an inflammatory substance that is associated to cause pain during inflammation. Bradykinase is an enzyme that causes the breakdown of bradykinin has been discovered and isolated from aloe that cause breakdown of bradykinin thus attributing to the plant's anti-inflammatory properties. Furthermore, sterols present in the plants are natural analgesics and help suppress pain (Sahu et al. 2013).

18.5.8 Immunomodulatory Activity

Aloe has been used for its immunomodulatory properties as the plant has been studied to enhance immune responses and strengthening the immune system. In a study, rats were administered with cancerous agents before administering with aloe. It was observed that there was an increase in production and release of interleukin 1 and tumor necrosis factor which caused the necrosis of the cancerous cells. Acemannan a polysaccharide was found to cause such immune mediated response (Sahu et al. 2013).

18.5.9 Antidiabetic Activity of Phytochemicals from Genus *Aloe*

Medicinal plants or natural products are source of bioactive compounds which minimise adverse effects and offer promising efficient drugs with low cost. The plants that belong to genus *Aloe* contains numerous phytochemicals that can be extracted via aqueous, alcohol (Nejatzadeh-Barandozi 2013) and chloroform as solvent (Raphael 2012). Tannin, saponin, flavonoids, and terpenoids are the most significant phytochemicals that are present almost in all the plants of genus *Aloe*, irrespective of their species (Arunkumar and Muthuselvam 2009). Other than these phytochemicals, these plants contain lectins, fatty acids, chromones, anthraquinones, cholesterol, mono and polysaccharides, sterols, choline, aloetinic acid, sapogenins, choline salicylate and complex mucopolysaccharides. In addition, they also possess amino acids such as serine, aspartic acid, arginine, glutamic acid and arparagine, as well as vitamins, namely folic acid, β-carotene, B1, B2, B6, C, α-tocopherol and mannose 6-phosphate as predominant sugar component (Joseph and Justin Raj 2010). Several literatures reported that the phytochemicals extracted from genus *Aloe* are highly beneficial as an antidiabetic agent to reduce serum glucose, cholesterol level and enhance wound healing process in diabetic patients. However, their antidiabetic effect is based on the plant part where the phytochemicals are extracted, which directly correlates with the quantity of extracted phytochemicals and solvent used in the extraction process (Singh et al. 2010).

Research findings indicate that leaf latex extract of *A. megalacantha* exhibit significant antihyperglycemic activities in STZ-induced diabetic mice. This plant ameliorates diabetes and its related complications. *A. megalacantha* is showed to improve parameters like body weight, hypoglycemic activity, oral glucose tolerance, antioxidant potential and lipid profile (Hammeso et al. 2019). In vitro and in vivo studies established that the water soluble fraction of *Aloe* species possesses some components that can modulate glucose transporter-4 mRNA expression along with glucose-lowering activities (Kumar et al. 2011).

High priority research includes plant derived various naturally active ingredients used in the treatment of diabetes viz. *A. vera* is considered as an antidiabetic agent.

Research studies shown that polysaccharide present in the plant protects β-cells of islets of langerhans from oxidative damage by alloxan monohydrate and also enhance the insulin levels showing hypoglycaemic effect (Das et al. 2011). The major plant derived phytosterols like 24-methylene cycloartanol, lophenol, cycloartanol, 24-methyl-lophenol, and 24-methyl-lophenol were reported to show beneficial effects in obesity and diabetes (Misawa et al. 2012). In another study a phytoconstituent (aloe-emodin-8-*O*-glycoside) isolated from *A. vera* gel were reported to enhance transport of glucose through proximal and distal marker modulation concerned with better uptake of glucose and its transformation into glycogen (Anand et al. 2010). Aloe species shows positive effect in the treatment of diabetes over short intervention periods. Through pilot study, improvements were observed in serum insulin, end-point glucose, TC:HDL-C and HDL-C using leaf gel extracts of *A. greatheadii* var. davyana, in a STZ-induced diabetic rodent model. Another Aloe species *A. ferox* intervention showed similar positive effects but to a lesser extent (Loots et al. 2011).

Jain et al. (2010) reported that *A. vera* gel shows significant cardioprotective and antidiabetic effects, as it significantly enhance antioxidant status and reduce oxidative stress in streptozotocin-induced diabetic rats.

18.5.9.1 Leaf Extract

The leaf of genus *Aloe* is different from the normal leaves, which contains a latex and gel. In most of the literatures, the latex is referred to as leaves and gel as a separate entity from the plant (Bozzi et al. 2007). In an experiment, *Aloe vera* juice was prepared with the aloe gel, sorbitol as sweeting agent and certain preservatives are given to 50- and 22-women diabetic subjects for 42 days. The result of the study revealed that the *Aloe vera* gel has antidiabetic activity by reducing total cholesterol, post-prandial and fasting blood sugar, total lipids, triglycerides and increase high density lipoproteins (Yongchaiyudha et al. 1996). Similarly, alcoholic extract of *Aloe vera* leaf gel was orally administered to diabetic rats to evaluate their antidiabetic effect. The result confirmed that the phytochemicals present in alcoholic extract decrease blood glucose level, glycosylated hemoglobin and increases the hemoglobin level. Further, the extract brings down the level of lipid peroxidation and hydroperoxides in diabetes rat tissues, and increases superoxide dismutase, catalase, reduced glutathione, glutathione peroxidase and glutathione-S-transferase in diabetic kidney and liver of rats (Noor et al. 2008). Also, the leaf pulp and gel extract of *A. vera* was subjected to non-diabetic, type 1 and type 2 diabetic rats to evaluate their antidiabetic activity. The result emphasized that the extracts do not reduce blood sugar level in non-diabetic subjects, whereas the pulp extract reduces glucose levels in type 1 and 2 diabetes rats, compared to glibenclamide diabetic drug. However, the gel extract enhances hyperglycemic activity in type 2 diabetic rats, which showed that the pulp extracts of *A. vera* leaves are highly beneficial in the treatment of non-insulin dependent diabetes patients (Okyar et al. 2001).

In recent times, the pulp of the *A. vera*, that are free from the peel, were lyophilized and ethanolic extract was obtained via the Soxhlet method. The result emphasized that the extract significantly decreases blood glucose level and improves body weight, which is attributed to the phytochemical combinations present in the *A. vera* pulp extract (Sacan et al. 2017). Likewise, the *A. vera* leaf powder including dried latex and gel were macerated at room temperature with ethanol for 72 h to obtain the phytochemical extract. The result showed that the presence of phenol, saponins and anthraquinones in the extract were beneficial in enhancing the wound vascularity to remove dead tissue and increase wound healing ability (Negahdari et al. 2017). Moreover, the oral administration of *A. vera* leaf powder extracts proved to be useful in improving the insulin secretion and the function of pancreatic β-cell in streptozotocin-induced diabetic rates (Noor et al. 2017). Furthermore, the leaf extracts of *A. arborescens* has been reported to reduce the blood sugar, where the phenol compounds present in the extract possess antioxidant activity in the pancreas and blood to protect islets of Langerhans from the methyl radical from streptozotocin (Beppu et al. 2006). Additionally, the combined leaf (latex and pulp) extract of plants that belong to genus *Aloe* such as *A. chaboudii*, *A. inyangensis*, *A. zebrina*, *A. barbadensis*, *A. pruinosa* and *A. arborescens* × *A. barbadensis* hybrid is widely reported to contain phytochemicals that are useful as enhanced antidiabetic agents (Grčić et al. 2016). Recently, the phytochemical constitution, hypoglycemic potential, antioxidant activity and toxicity of leaf extract of *A. lateritia*, *A. secundiflora* and *A. buettneri* is investigated. The results emphasized that the extracts are nontoxic to alloxan-induced diabetic mice and the phytochemicals such as phenols, flavonoids, tannins, steroids, saponins, alkaloids, anthraquinones and carbohydrates present in the extracts possess hypoglycemic activity (Mbithi et al. 2018; Guessan and Kouakou 2017).

18.5.9.2 Root Extract

Similar to leaves, root extract of the plants that belong to genus *Aloe* also possesses phytochemicals that can act as potential antidiabetic agent. The root extract of *Aloe ferox* contains large quantities of phenols and saponins, along with small portions of flavonoids, flavonols, tannins and alkaloids (Arowosegbe et al. 2012). The presence of these phytochemicals is already proved to be beneficial in exhibiting antidiabetic activity via several literatures. The root extract of *A. vera* and *A. barbadensis* are proven to be helpful in stimulating the synthesis and release of insulin, exhibits insulin secretagogues activity via secretion of pseudoprototinosaponin AIII and prototinosaponins AIII and initiates glucose uptake through enhanced hepatic gluconeogenesis or glycogenolysis (Patel et al. 2012b; Bnouham et al. 2006). In addition, the ethanol extract of *A. barbadensis* root has been proven to increase testosterone and cholesterol concentration depending on the dosage increase, which elevates their aphrodisiac property and eventually contributes to their antidiabetic property (Erhabor and Idu 2017). Likewise, the acetone extract of *A. pulcherrima* roots were reported to contain three unique phytocompounds such as aloesaponarin I, II and

chrysophanol with antioxidant properties. Thus, these extracts can be beneficial in reducing blood sugar and other diabetes related complications (Abdissa et al. 2017). Moreover, the root extract of *A. vera* is reported to contain two unique anthraquinones namely aloesaponarin-I and II, and six of their derivatives were obtained by acetylation, O-glycosyl reactions and methylation along with a novel tetra-O-acetyl-β-D-glucopyranosyl derivative. All these novel derivatives and phytocompounds will be beneficial in triggering insulin secretion, reduce blood glucose level and reverse diabetes complications (Borges-Argáez et al. 2019). However, there are a smaller number of literatures that are available on the root extracts of plants that belong to genus *Aloe*, as these plants are mostly succulent, and they contain less concentration of phytochemicals that can be extracted. Even though, they contain less concentration, the phytochemicals present in root extracts are similar to leaf extracts and thus they exhibited antidiabetic activity.

18.5.9.3 Flower Extracts

Flowers are another exclusive part in the plants of the genus *Aloe* from where the phytochemicals can be extracted. It has been reported that the phytochemicals extracted from the flowers of A. barbadensis contain anthraquinone such as aloe-emodin and aloin are proposed to be beneficial for their antidiabetic effects (2007). Likewise, the dried flower extracts were obtained from *A. barbadensis* which was analysed and identified to contain caffeic, caffeoylshikimic, chlorogenic, 5-p-coumaroylquinic, 5-p-cis-coumaroylquinic, 5-feruloylquinic, ferulic acid, p-coumarin, apigenin, luteolin, isoorientin, saponarin, kaelpferol, 7-O-glucosides and lutonarin. In addition, they also contain anthranoids such as aloe-emodin, glycosylchromone aloeresin B, Aloin A and B along with polyphenols and flavonoids. The combination of all these phytocompounds in synergistic effect can lead to a reduction in the blood glucose level, elevates the production of insulin and reverses insulin resistance to exhibit improved antidiabetic activity (Keyhanian and Stahl-Biskup 2007). Moreover, the skin and flower of *A. vera* was used to extract phytochemicals via methanol as solvent. It is noteworthy that the flower extract contains phenolic compounds such as gentisic acid, quercitrin and epicatechin. These phytocompounds are proved to highly significant as an antioxidant agent which will eventually help in the inhibition of diabetic cells and proliferation of normal cells (López et al. 2013). Furthermore, the flower extract of *A. vera* has been reported to possess anti-inflammatory effects due to the combination of extracted phytochemicals, which will also be beneficial in their antidiabetic effects (Vazquez et al. 1996, Nejatzadeh-Barandozi and Enferadi 2012). Polysaccharides from *A. arborescens* are extracted from the skin juice, gel juice and flowers via ethanol precipitation, where the polysaccharides from the flowers are reported to be weakly acidic in nature. The result also showed that the extracted polysaccharides contain glucose, galactose, glucuronic acid, mannose and xylose. Thus, these sugar molecules can be beneficial for diabetic patients, which will be an easily soluble sugar that can be converted into ATP with less concentration of insulin (Chang et al. 2011). In recent

times, the flower extract of *A. barbadensis* and *A. vera* is highly significant as antioxidant agents which will eventually lead to enhanced antidiabetic effects (Debnath et al. 2018, Haroon et al. 2018). However, it is necessary to carry out several studies to prove the exact antidiabetic mechanism of phytochemicals that are present in the flower extract of plants under genus *Aloe*.

18.5.9.4 Other Extracts

Other than the extraction of phytochemicals from the leaf, root and flower of *Aloe* genus, the whole plant extracts are widely used for antidiabetic activity, as they contain large quantities of significant phytochemicals that are responsible for antidiabetic effects. *Aloe vera* (Arunkumar and Muthuselvam 2009), *A. barbadensis* (Boudreau et al. 2013b), *A. arborescens* (Jia et al. 2008), *A. ferox* (Wintola and Afolayan 2011) and *A. schweinfurthii* (Salawu et al. 2017) are the plants that belong to genus *Aloe* which are used to extract the phytochemicals from the whole plant. These whole plant extracts with a wide variety of phytochemicals are highly useful in exhibiting antidiabetic activity via synergistic effects (Cock 2015). However, it is difficult to evaluate the antidiabetic effect of individual phytocompounds from the whole plant extract which will be a major drawback in using these type of extracts.

18.5.9.5 Antidiabetic Nanoparticles from Genus *Aloe*

The phytochemicals extracted from the genus *Aloe* are recently employed in the formation of nanoparticles as reducing and stabilizing agent. These green synthesized nanoparticles are revealed to possess potential in reducing blood glucose, increase insulin secretion and exhibit antidiabetic effects. Zinc oxide nanoparticles are synthesized via aqueous extracts of *A. vera* gel proves to contain antioxidant property which eventually helps in reducing serum glucose. The phytochemicals present in the extract namely saponins, tannins, alkaloids, flavonoids, carbohydrates, terpenoids, gums, mucilages and phenolic compounds help as reducing and stabilizing agent for nanoparticle formation and also their antioxidant activity (Mahendiran et al. 2017). Likewise, the phytochemicals present in the flower extract of *A. vera* was also used to fabricate copper nanoparticles (Karimi and Mohsenzadeh 2015). These nanoparticles are proved to be highly significant as a potential nanomedicine to cure diabetes-related complications (Bhagwat et al. 2018). Similarly, silver (Dinesh et al. 2015), gold (Altaf and Jaganyi 2016), iron oxide (Ali et al. 2018), copper oxide (Kumar et al. 2015), carbon-based nanoparticles (Devi et al. 2018) was also synthesized by using extracts obtained from genus *Aloe*. However, extensive study has to be carried out in the future to evaluate the exact antidiabetic mechanism of *Aloe* phytochemical coated nanoparticles in reducing the complications of diabetes.

18.5.10 Antihyperlipidemic Activity

Recent studies show the antihyperlipidemic activity of *A. vera* and its positive effect in the prevention of fatty streak and development of atherosclerosis. Due to less insulin secretion or its action in the body, the increase in circulatory glucose levels is responsible for an increase in the free fatty acids (FFA's) by the action of hormone sensitive lipase from adipose tissue in the blood. The excess FFAs in circulation enter into the liver for the synthesis of Tri glycerides (TG) and further lipoprotein biosynthesis. Liver plays a vital role in glucose and lipid metabolism. In diabetes, its function is affected and results in liver steatosis (accumulation of lipids) (Seifter and England 1982). The supplementation of ethanolic extract of *Aloe vera* leaf gel (300 mg/kg body weight) in diabetic rats showed an increase in the plasma insulin levels from remnant or regenerated pancreatic β-cells, whereas blood glucose levels were brought to normal. In addition, *Aloe vera* extract administration also showed a decrease in the plasma lipids, liver cholesterol, and kidney TG levels (Rajasekaran et al. 2006). Authors concluded that, phenolic and saponin compounds present in the *Aloe vera* extract might be responsible for hypoglycemic and hypolipidemic effects.

In a randomized double-blind placebo-controlled clinical trial, efficacy of *A. vera* leaf gel was checked in hyperlipidemic type 2 diabetic patients, results showed the reduction in low-density lipoprotein (LDL) and total cholesterol levels (Huseini et al. 2012). In Zucker diabetic fatty rats administration of phytosterols isolated from gel of *A.vera* improve hyperglycemia and reduce visceral fat mass (Dana et al. 2012). Medicinal herbs like *Aloe barbadensis* Mill. or *A. vera* has shown to possess anti-hyperlipidemic and hypoglycaemic potential. Letrozole-induced polycystic ovarian syndrome rat model treated with *A. vera* gel shows increase in HDL cholesterol along with reduction in LDL and triglyceride levels. The phytoconstituents present in *A. vera* gel manage metabolic complications by improving lipid metabolizing enzyme activities, abnormal estrous cyclicity and glucose intolerance (Desai et al. 2012). A remarkable antihyperlipidemic effect was shown by a dried pulp extracted from leaf of *A. succotrina* in high-fat diet and fructose-induced hyperlipidemic Wistar albino rats. *A. succotrina* normalize serum lipid profile and ameliorate oxidative stress in liver without affecting relative heart weight (Dhingra et al. 2014). The selenium (Se) polysaccharide (Se-AVP) from *A. vera* was shown to have cardioprotective effect against myocardial I/R injured in rats, it was noted that (Se-AVP) act as endogenous antioxidant which protect rat hearts from oxidative stress-induced myocardial apoptosis (Yang et al. 2017).

The antioxidative and hypocholestrol effects of *Aloe vera* was assessed in randomly selected liver of male specific pathogen-free (SPF) Fischer 344 rats to 17 of four groups: Group A (control) was fed test chow without aloe supplementation; Group B was fed a diet containing a 1% (per weight basis) freeze-dried aloe filet; Group C was fed a diet containing a 1% (per weight basis) charcoal-processed,

freeze-dried aloe filet; and group D was fed a diet containing a charcoal processed freeze-dried, whole leaf aloe (0.02% per weight basis) in the drinking water. Results show that a life-long intake of aloe had superior anti-oxidative action against lipid peroxidation in vivo, as indicated by reduced levels of hepatic phosphatidyl choline hydroperoxide. Additional anti-oxidative action was evidenced by enhanced superoxide dismutase (SOD) and catalase activity in groups B and C. furthermore, study revealed that hepatic cholesterol significantly increased in the control group in contest to the aloe-supplemented groups, which showed approximately 30% lower cholesterol levels, thereby an effective hypocholestermic efficacy (Lim et al. 2003). The effect on man triglyceride level was estimated which is due to inhibition of the hepatic production of chylomicron (Boban et al. 2006). Saponin and phenolic components of *Aloe vera* extract also exerted the antihyperlipidemic effect by decreasing the levels of total cholesterol, triglyceride and lipoprotein. High blood cholesterol is a major risk factor for heart disease and stroke.

A study was conducted on the effect of *Aloe vera* extract on the serum cholesterol level on male Calote sversicolor Daudin. The calotes versicolor Daudin were made hypercholesterolemic by oral administration of cholesterol (100 mg/kg body weight/day) suspended in ground nut oil using dropper. In 1 month cholesterol feeding experiment, the serum cholesterol level in normal controls (not given cholesterol) was 321.333 ± 16.621 mg/dl and in cholesterol fed animals 437.333 ± 8.066 mg/dl. To such animals when different doses of raw extracts of *Aloe vera* leaves were given along with cholesterol, there was significant decrease in serum cholesterol level. Four groups of Calotes were administered Aloe vera (L) extract in four different doses (3 mg/kg, 4 mg/kg, 5 mg/kg and 6 mg/kg/day) for 21 days. There was a significant increase in serum cholesterol levels at 1% level after feeding with high cholesterol diet. There was a significant decrease in serum cholesterol levels in all the *Aloe vera* (L) treated groups. Significance level is 5% for a dose of 6 mg/kg and other doses i.e. of 3 mg/kg, of 4 mg/kg and of 5 mg/kg show significant decrease at 0.1%, 0.5% and 0.2% level, respectively (Chandrakar et al. 2008).

18.5.11 Antiaging Effects of Aloes

Photochemoprotection has recently become valuable way to prevent aging. Although there are many active synthetic antiaging drugs that have been used for years, these drugs may exert safety risk on human health. Therefore, present era of treating an aged skin has been diverted towards natural biomaterials (Rajashree and Rose 2018). The plant Aloe has also been studied to protect the skin again UV rays (Surjushe et al. 2008).

Aloe vera gel was reported to improve skin hydration and to possess moisturizing effect for stratum corneum at different tested concentrations (0.1%, 0.25%, and 0.5%) (Chandan et al. 2007). Mucopolysaccharides (MPS) present in Aloe gel is responsible for the water-holding capacity exerted by the gel to the skin. *Aloe vera* can improve the elasticity of the skin through activation of the fibroblasts which

responsible for the production of collagen and elastin fibers reducing skin wrinkles. In addition, amino acids in Aloe soften dry skin cells and increase its zinc content, and decrease pores sizes through its astringent effect (West and Zhu 2003).

Topical application of *Aloe vera* gel on the skin, yield to the production of the antioxidant protein metallothionein which scavenges hydroxyl radicals (OH•), inhibits superoxide dismutase (SOD) suppression and glutathione peroxidase (GSHx) in skin with subsequent reduction in interleukin-10 (IL-10) production (Byeon et al. 1988). Accordingly, *Aloe vera* gel can also prevent the UV and gamma rays-induced skin damages (Roberts and Travis 1995). Aloesin can act as a potential as a pigmentation-altering component for cosmetic uses through inhibition of the tyrosinase enzyme (Yagi et al. 2003).

Cho et al. 2009 studied the effect of 90 days dietary intake of *Aloe vera* gel supplementation at 2 different doses (1200 and 3600 mg/day) on thirty healthy female subjects over the age of 45. Their facial wrinkles measured using a skin replica were improved significantly in at the two doses, and facial elasticity determined by an in vivo suction skin elasticity meter were improved in the lower-dose group compared to their baseline status which was used as a control. In the photoprotected skin, the type I procollagen mRNA levels were insignificantly, increased at the two dose levels, the matrix metalloproteinase 1 (MMP-1) mRNA levels expression determined using real-time RT-PCR was significantly decreased in the higher-dose group. Type I procollagen immunostaining was substantially increased throughout the dermis in both groups. So, the gel significantly improved wrinkles and elasticity in photoaged human skin, with an increase in collagen production in the photoprotected skin and a decrease in the collagen- degrading MMP-1 gene expression. However, no dose- response relationship was found between the low-dose and high-dose groups.

Tanaka et al. (2015) investigated the capability of *Aloe* sterols (cycloartenol and lophenol) to stimulate human dermal fibroblasts in vitro. After 48-h co-culture with Aloe sterols, the production of collagen and hyaluronic acid increased in a concentration-dependent manner. Treatment of the human dermal fibroblasts with 2 μM Aloe sterols increased collagen and hyaluronic acid production by approximately twofold and 1.5-fold The gene expression levels of the enzymes responsible for the synthesis of collagen (COL1A1 and COL3A1) and hyaluronic acid (HAS2 and HAS3) was associated with a dose-dependent increase in their mRNA level after A 6-h incubation period with 0.02–2.0 μM cycloartenol and lophenol in human dermal fibroblasts.

The authors also investigated the effect of intake of *A. vera* gel powder containing 40 μg *Aloe* sterols on the skin conditions in 54 Japanese women with dry skin in a randomized, double-blind, placebo-controlled trial. An increase in arm skin hydration was observed at 8 weeks in the *A. vera* gel powder treated group, whereas a slight decrease in arm skin hydration was noted in the placebo group. However, there was no statistical difference between *A. vera* gel powder and placebo groups in skin moisture. In subgroup analysis, the change in the mean wrinkle depth was significantly lower in the *A. vera* gel powder group than in the control group. No observed harmful phenomenon during the treatment period. The study confirmed

that daily oral *Aloe* sterol-containing *A. vera* gel powder significantly reduced facial wrinkles in women aged more than or equal to 40 years, and Aloe sterols stimulate collagen and hyaluronic acid production by human dermal fibroblasts.

Tanaka et al. (2016) performed a randomized, double-blind, placebo-controlled study for 12-weeks to evaluate the effects of oral Aloe sterol-supplemented yogurt on skin elasticity, hydration, and the collagen score in 64 healthy women (age range 30–59 years; average 44.3 years). The treated group revealed statistical differences in skin moisture, trans-epidermal water loss, skin elasticity, and collagen score between the from placebo groups. The gross elasticity (R2), net elasticity (R5), and biological elasticity (R7) scores of the Aloe sterol group significantly increased with time. In addition, skin fatigue area F3, which is known to decrease with age and fatigue, also increased with Aloe sterol intake. Ultrasound echogenicity revealed that the collagen content in the dermis increased with Aloe sterol intake. The results suggest that continued Aloe sterol ingestion contributes to maintaining healthy skin.

Rajashree and Rose (2018) reported an anti-aging gel formulated by blending three biopolymers which were Collagen (3%w/v), Chitosan (1.5% w/v) and *A. vera* gel (0.21% w/v). The prepared gel was characterized by good spreadability and high hydrophyllicity. Cell culture studies on the mouse fibroblasts cells (NIH3T3) were carried out using senescence-associated-β-gal as a biomarker. A. vera blended gel stimulated proliferation rate of the fibroblasts cells (NIH3T3) reversing of the process of senesce. The prepared gel helps in regeneration and rejuvenation of the skin and is considered as a promising anti-aging gel.

18.5.12 Wound Healing Activity

The sterols present in plants have been reported to exert healing properties thus justifying the uses of aloe for healing purposes. The sterols are identified to increase production of the cells of endothelial walls of arteries as they increase the production of proteins important in keeping the integrity of vessels intact (Moon et al. 1999). Furthermore, *Aloe vera* administration in rats showed that the plant has wound healing properties as it rids of the bacteria that may enhance the inflammation associated with wounds (Heggers et al. 1995). Also glucomannan and gibberellins cause increase production of collagen by causing increase activity of fibroblasts when aloe is applied topically or administered orally (Sahu et al. 2013).

Adhikari et al. (2018) validated the antibacterial influence of gel extract of *Aloe barbadensis* against multiple antibiotic resistant *Pseudomonas aeruginosa* that is responsible for wound development from affected patients. The result obtained from their study shows that *Aloe vera* gel could be used for the treatment of multiple antibiotic resistant *Pseudomonas aeruginosa* isolated from wound specimen.

Escobar-Sierra and Perea-Mesa (2017) evaluated the capability of chitosan and polyvinyl alcohol to absorb *Aloe vera* gel for effective control release in order to facilitate the rate of healing infected wounds and their effectual healing. The fabrication of the membrane involves different composition which involve Chitosan and

Polyvinyl Alcohol (PVA/CH) at 5 and 10% w/v and employing different PVA/CH relations of 30/70, 50/50 and 70/30 (v/v) and embed them in a 2% (v/v) *Aloe vera* solution to create hydrogels. The crosslinking matrix developed from PVA/CH led to the formation of good mechanical properties, enhance absorption capacity, and control the release of the active compounds present in the *Aloe vera* gel.

18.5.13 Laxative Effects

Anthrones in aloe are a class of compounds mainly responsible for producing laxation and purgation effects (Cock 2015). Also anthraquinones have been reported to have laxative and purgative abilities as they have been found to increases intestinal motility, mucus secretion while also enhancing intestinal water content. Alloin A and B have been observed to increase intestinal motility as they are reduced by colonic flora into active compounds which irritate the GIT wall and increase motility (Sahu et al. 2013).

18.5.14 Antiseptic Activity

Presence of salicylic acid, lupeol, urea nitrogen, phenols, cinnamonic acid, and sulphur attributes to the plant's antiseptic properties (Sahu et al. 2013).

18.5.15 Analgesic Activity

Aloe rupestris Baker's root has been used in making decoctions that are used to get relief from painful menstruation in infertile women. The decoctions are either administered orally or are injected in womb (Amoo et al. 2014).

18.5.16 Antiosteoporosis Activity of the Aloe vera

Osteoporosis is a skeletal condition caused by low bone density and disorganized bone architecture (Sun et al. 2017). This is a result of excessive rate of bone resorption activity of the osteoclast compared to the rate of bone formation of the osteoblast (Jahanian et al. 2016). Excessive research has noted that antioxidants and levels of ROS are significantly correlated to osteoporosis (Jia et al. 2012; Mody et al. 2001; Zhao et al. 2015). In one study, the antioxidant and antiosteoporotic activities of 25 compounds isolated from *Aloe* exudates based on TRAP's contribution on bone resorption of osteoclasts by producing ROS (Sun et al. 2017). It was

noted that four anthraquinones, one phenolic derivative, seven chromones, and six pyrones possess significant suppression activity against TRAP at 10.0 μm. Other compounds isolated showed weak to inactive suppression activity against TRAP.

Aloe vera, together with cancellous bovine xenograft (XCB), was noted to stimulate alveolar bone growth (Kresnoadi et al. 2017). The combination of *A. vera* and XCB prevented bone resorption activity of the osteoclast and stimulated the growth of osteoblasts. Moreover, similar results were noted in an earlier study that combination of *A. vera* and XCB enable growth of bone cells increasing osteoblast activity and inhibiting osteoclast activity in alveolar bone (Kresnoadi and Rahayu 2011). It was also suggested that the role of *A. vera* is to prevent inflammation of osteoclastogenesis, thus preventing bone resorption. Furthermore, it was also noted that the antraguinon present in *A. vera* possess an anti-inflammatory which reduces osteoclast activity.

Aloin, an anthraquinone glycoside from *A. vera*, was also noted to stimulate osteoblast induction by increasing alkaline phosphatase (ALP) activity and mineralization (Pengjam et al. 2016a). It is believed that the initial osteogenic activity derived from aloin is brought about by the structure-activity of methoxyl group in anthraquinone derivatives (Lee et al. 2008). Aloin was also noted to promote osteogenesis in bone marrow-derived mesenchymal stem cells as evidenced by the increased ALP activity, enhanced mineralization, and expression of osteogenesis-related genes (Li et al. 2019). Moreover, it was noted that this compound exerts is a potent inhibition of bone resorption activity and osteoclastogenesis as shown in in vitro test bone pit assay (Pengjam et al. 2016b). Regulation of osteoclastogenesis by aloin was also noted through its unfavorable effects towards NFκB repression of miR-21 (Madhyastha et al. 2019).

18.6 Plant Disease Management

Luiz et al. (2017) found that Aloe polysaccharides and essential oils are considered as potential agents in controlling plant diseases by working as anti-microbial agents or by activating plants' defence mechanism, for example combinations of aloe polysaccharides and palmarosa essential oil is effective against *Xanthomonas fragariae* (bacterial angular leaf spot disease). Antibacterial activity of *A. barbadensis* leaf extract was evaluated against *Serratia marcescens, E. coli*, *B. cereus* and *P. aeruginosa,* results showed that maximum inhibitory activities was through hexane and methanol extract against *S. marcescens* and *B. cereus*. Broadly it was noticed that methanol extract inhibit the growth of all tested pathogenic bacteria while no inhibitory activities was shown by ethyl acetate extract (Dharajiya et al. 2017). An anti-adhesive effect was shown by polysaccharides present in Aloe gel by inhibiting the growth of *H. pylori* bacteria (Cellini et al. 2014). Isolated compounds (aloin, aloe emodin and chrysophanol) of *A. ferox* were studied by Kambizi et al. (2005) and noticed that alonin A and aloe emodin shows inhibitory activities against *Shigella sonnei, B. subtilis, Staphylococcus epidermidis, E. coli, B. cereus* and *S. aureus*.

The potential role of *Aloe* species' with respect to bioactivity, availability and safety makes it an interesting alternative as control agent especially used in preharvest and postharvest fungal diseases of vegetables and fruits. Ali et al. (1999) reported that fresh leaves extracts of *A. arborescens* and *A. barbadensis* have antifungal potential against *Fusarium moniliforme, Aspergillus niger* and *Cladosporium herbarum*. Research studies have shown that up to 20% of *Alternaria, Penicillium and Botrytis* spores survival was reduced by *A. vera* and it also inhibits up to 38% of *Colleotrichum, Fusarium and Rhizoctonia* mycelium growth (De Rodrýguez et al. 2005; Castillo et al. 2010).

Ortega-Toro (2017) analyzed anti-fungal potential of *A. vera* gel against six fungi causing plant diseases- *Botryotinia fuckeliana, Fusarium oxysporum, Colletotrichum gloeosporioides, Curvularia hawaiiensis, Alternaria alternate* and *Bipolaris spicifera*. Results showed that was most effective against *F. oxysporum*. RP-HPLC fractionated methanolic extracts of inner leaf gel of *A. barbadensis* were tested against nystatin resistant strain of the fungus *Aspergillus niger* and it was found that *A. barbadensis* was capable of inhibiting the growth of this resistant strain (Cock 2007). Research studies shows that fungal contamination were effectively controlled with highest *A. vera* ratio, treatment of *A. vera* gel with nectarine alone or with thymol addition inhibits fungal growth of *Penicillium digitatum, Rhizopus stolonifer* and *Botrytis cinerea*. Hence, application of Aloe significantly lowers two to threefold fungal infection than in non-treated nectarines. It was noticed that efficiency of Aloe gel to reduce infection was not improved by addition of thymol (Navarro et al. 2011).

Eight Aloe species gels (*A. vera* L., *A. arborescens* Mill., *A. claviflora* Strydenburg., *A. mitriformis* Mill., *A. aristata* Haw., *A. ferox* Mill., *A. striata* Haw. and *A. saponaria* A.) were evaluated for anti-fungal activity against *P. italicum*, *P. italicum*, *P. expansum* and *P. digitatum*. Results concluded that higher antifungal activity was observed for *A. saponaria*, *A. ferox* and *A. mitriformis* than *A. vera* which can be correlated with aloin content (Zapata et al. 2013).

18.7 Toxicological Profiling

It was observed that *aloe vera* gel or extract usually does not possess any toxicity although different cases of people are found having sensitivity towards them and suffered from liver problems. On using externally, many individuals have also experienced many skin problems like itching and swelling etc.

The adverse effects of aloe leaf and latex are:

- Oral ingestion of aloe spp. could be potentially toxic, and may cause abdominal cramps and diarrhea .
- Ingestion of non-decolorized liquid aloe vera is a possible carcinogen, Under the guidelines of California Proposition 65, orally ingested non-decolorized aloe vera leaf extract has been listed by the OEHHA, along with goldenseal, among

"chemicals known to the state to cause cancer or reproductive toxicity" (OEHHA 2015).

- They act as abortifacients, hence should not be taken by pregnant women. The compounds also pass to baby with the milk.
- In case of hemorrhoids aloe vera should be avoided.

Number of investigation has been carried out to check the toxicological properties of Aloe gel and leaf extracts on the basis of toxicity causing ability in humans and animals.

Side effects have been reported with the use of aloe in humans which present themselves as severe form of watery diarrhea associated with colicky abdominal pain and spasms may occur. Mild side effects occur with even a small dose of aloe but the overuse can lead to severe symptoms.

It has been reported that the overuse of anthraquinones can cause hepatitis as well as metabolic acidosis, albuminuria, malabsorption, weight loss and hematuria. Dehydration and hypotension associated with overuse of the plant follows the watery diarrhea due to the plant's laxative effects.

Hypoglycemia may occur as a result of overuse of the plant for a longer duration as the plant increase the insulin level in the body which although beneficial for diabetes can lead to serious side effects in healthy individuals by depleting of glucose levels inside the body and may cause symptoms of weakness and lethargy and excessive sleep and drowsiness.

Hypokalemia that may result due to electrolytes imbalances attributed to excessive diarrhea can lead to serious complications ranging from hypoalbuminemia and hematuria to neuromuscular and cardiac dysfunction which can ultimately lead to mortality especially along with the use of cardiac glycosides.

Ininflammatory conditions of the GIT aloe usage should not be encouraged. Aloe should also be avoided during pregnancy and in GIT symptoms such as nausea and vomiting that have not yet been diagnosed.

Experimentally, Aloe and their preparations have been reported to cause allergic conditions and hypersensitivity (Ernst 2000). Emodin exposure to rats have shown an increased incidence of renal tubule pigmentation and introduced nephropathy in mice (National Toxicology Program 2001).

On applying various forms of aloe extracts, various plant derived components and commercially available gels, by intraperitoneal or intravenous injections to mice, rats and dogs for single or eight repeated interval of 4 days the dogs has observed emesis and diarrhoea (Fogleman et al. 1992). Repeated administration of the material had led to increase in accumulation of macrophages and monocytes in the lungs of intravenously-treated animals and in the liver and spleen of intraperitoneally-treated. Intoxication approved with a clinical sign of a decrease in activity, abnormal gait and stance, piloerection, flaccid body tone, and tremors in mice. For dogs it included emesis, abdominal discomfort, decreased activity, and diarrhoea. The high (80 mg/kg per dose) and middle (40 mg/kg per dose) doses of intravenously treated mice and doses of 100 mg/kg to 200 mg/kg of intraperitoneally treated mice have resulted into early death problem.

Reduction in food efficiency and body weight as well as increase in kidney weight and testis weights was observed in a subchronic toxicity study of 88 Sprague Dawley rats when they were fed with Aloe whole leaf powder at doses of 2, 4, and 8 g/kg body weight (2.5%, 5%, and 10% Aloe in diet) for 90 days. Additionally, the introduction of pigmentation in renal tubular, increase in mesenteric lymph nodes, and lamina propria of the colonic mucosa were also observed compared to the controls (Zhou et al. 2003).

Examination was done on the growth, metabolic reactions and dietary intake of rats after ingestion of crude and decolorized Aloe gel for 1.5 and 5.5 month studies (Herlihy et al. 1998a, b) Marked changes in serum parathyroid hormone and calcitonin concentrations were observed, concluding that Aloe gel may alter calcium metabolism (Herlihy et al. 1998b).

18.7.1 Reproductive Toxicity

It was observed after a chronic oral ingestion of 100 mg/kg *Aloe vera* extract per day, for a period of 3 months have led to various reproductive losses (Shah et al. 1989). This was resulted into significant sperm losses, hematological damages, inflammation, and increased mortality in the study animals.

Similarly in a study by Nath et al. (1992), pregnant rats were given a dose with aqueous or 90% ethanol extract preparations of the plant orally for 10 days. The abortifacient activity of the plant was found to be at a high percentage in the studied animal in comparison to the controls.

It was advised not to take Aloe latex for pregnant women because of its cathartic effect, which may be a cause of severe uterine contractions and in turn increase the risk of miscarriage. Nursing mothers should also not ingest it because of the probability of inducing severe cramps and diarrhoea in the infant (Brinker 1998).

18.7.2 Genotoxicity

In a study genotoxicity of Aloe spp. whole extract-and decolorized extract were evaluated using the mouse lymphoma assay (MLA) (Guo et al. 2014). The results indicate deletions and/or mitotic recombination type of chromosomal mutations from both the treatments.

The genotoxicity of three components present in *A. vera* latex ie. emodin, danthron, and aloe-emodin was checked using the MLA, micronucleus test, and the Comet assay (Muller et al. 1996) all three compounds have shown increases in micronuclei and moderate increases in mutant frequency in L5178Ycells, at micromolar concentrations. Emodin also found to cause DNA damage in human lung carcinoma cells through the production of ROS, (Lee et al. 2006) induction of micronuclei in TK6 human lymphoblastoid cells, (Nesslany et al. 2009) and increase

aberration of chromosomes in Chinese hamster ovary cells (Lee et al. 2006). Danthron also found potent carcinogen and induced DNA damage and apoptosis in SNU-1 human gastric cancer cells with the help of mitochondrial permeability transition pores and Bax-triaggered pathways (Chiang et al. 2011).

18.7.3 Carcinogenicity

F344/N rats were administered *Aloe vera* whole leaf extract in drinking water orally for 2 years and observed clear evidence of carcinogenic activity (NTP 2015). NTP Report 577 reported that the 13-week exposure resulted into. The 2-year study described significant related increases in the incidences of adenomas or carcinomas of the ileocecal and cecal-colic junction, cecum, and the ascending and transverse colon in male and female rats in the high-dose groups.

Hydroxyanthraquinones (HA) like danthron, aloe-emodin, and emodin were investigated for tumor promotion activities, like induction of cell proliferation and initiation of malignant transformation, in mice (Wolfle et al. 1990). A two or three-fold increase in DNA synthesis was observed in primary rat hepatocytes on exposure to danthron and aloe-emodin. Danthron also found to enhance malignant transformation of C3H/M2 mouse fibroblasts concluding that HA present in Aloe latex with hydroxy groups in the 1,8 positions may exhibit tumor-promoting activity.

18.7.4 Adverse Clinical Effects on Human

Dioscorides, a Greek physician of the first century A.D have first medically recorded the therapeutic use of Aloe (Fantus 1922). Afterwards, Aloe latex was widely utilized in herbal laxative preparations in many countries. Hence ingestion of latex in high doses and prolonged time resulted into a number of adverse effects and has been reported in clinical studies. Prolonged use manifested with electrolyte imbalance due to diarrhoea, vomiting, abdominal pain, hypokalemia and the development of a cathartic colon (the colon becomes atonic and dilated) with the risk of developing colon cancer (Van Gorkom et al. 1999).

There are various single clinical cases for different types of adverse effect has been reported however there are no published controlled toxicology studies in vivo reports are available. A female patient 1-week history of progressive jaundice, pruritus, alcoholic bowel movements, and abdominal discomfort, have resulted into severe acute hepatitis with portal and acinar infiltrates of lymphocytes, plasma cells, granulocytes along with bridging necrosis and bilirubinostasis when she began ingesting tablets of an unspecified extract of Aloe barbadensis Miller (500 mg/tablet) 4 weeks prior to inspection (Rabe et al. 2005).

A. vera also found to potentially interact with the drugs prescribed to the patients for medication. It was also found that the compound present in *A. vera* can cause a

reduction in prostaglandin synthesis, which may hinder secondary aggregation of platelets. In a study Vazquez et al. (1996) showed that Aloe gel caused a 48% reduction in prostaglandin synthesis compared with a 63% reduction by indomethacin. It is evident by a case of a female patient in which she lost 5 litres of blood during surgery due to a possible herb-drug interaction between orally ingested *A. vera* tablets and sevoflurane, an inhibitor of thromboxane A_2 (Rabe et al. 2005). Interactions of Aloe gel have also been observed for hydrocortisone, antidiabetic agents, and UV radiation.

A case of acute oliguric renal failure and liver dysfunction occurred when a 47-year-old man ingested Cape Aloes (Luyckx et al. 2002). Hepatotoxicity is considered one of the most reported adverse effects caused by herbal dietary supplements (Guo et al. 2010). The first case of acute hepatitis due to the ingestion of *A. vera* compound was reported in 2005 in Germany (Rabe et al. 2005). Afterward, cases of Aloe-induced toxic hepatitis were reported in Turkey, (Kanat et al. 2006) United States, (Bottenberg et al. 2007) Argentina, (Curciarello et al. 2008), and Korea (Yang et al. 2010). A total of six females and two males were admitted to hospital for acute hepatitis after taking Aloe preparation over 3–260 weeks (Lee et al. 2014). Their clinical manifestation, liver biopsy, and laboratory findings supported the diagnosis of toxic hepatitis. All eight patients showed improved condition after discontinuing this medication. These cases emphasize the importance of considering phytopharmaceutical over-the-counter drugs as causative agents in hepatotoxicity. Adverse effects of Aloe whole-leaf powder have been reported at concentrations of 2 g/kg BW, and the LOAEL for aloin is estimated at 11.8 g/kg BW (Zhou et al. 2003).

18.8 Conclusion

Aloe is a genus with a number of beneficial and medically important species that have been used traditionally in several parts of the world especially Africa and India. Aloe species are one of the best studied medicinal plants with therapeutic properties due to presence of wide range of novel bioactive compounds with synergistic actions. The presence of the several pharmacologically important chemicals in the plants supports the clinical importance of the plants' usage within the specific doses that have been confirmed by the scientific data and are approved to be within the safety limits. This review article focuses on the present research advancement on Aloe species especially highlighting its mechanism of action in combating multiple diseases. The plants especially *Aloe vera* has been identified to exhibit a number of useful properties such as anti-inflammatory, anti-cancerous, anti-microbial, wound healing, immunomodulation, antiseptic and cosmetics use attributing to the presence of several importance constituents. Although, there are issues related to safety concerns much needs to be done for evaluateing the toxicological evaluation of Aloe species. Thus, implementation of some biotechnological techniques is required to cover a wide spectrum of scientific applications and to better understand the possible benefits offered by the significant Aloe plant.

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