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REVIEW

A Systemic Review on *Aloe arborescens* Pharmacological Profile: Biological Activities and Pilot Clinical Trials

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Since ancient times, plants and herbal preparations have been used as medicine. Research carried out in the last few decades has verified several such claims. *Aloe arborescens* Miller, belonging to the *Aloe* genus (Family Asphodelaceae), is one of the main varieties of Aloe used worldwide. The popularity of the plant in traditional medicine for several ailments (antitumor, immunomodulatory, antiinflammatory, antiulcer, antimicrobial and antifungal activity) focused the investigator's interest on this plant. Most importantly, the reported studies have shown the plant effectiveness on various cancer types such as liver, colon, duodenal, skin, pancreatic, intestinal, lung and kidney types. These multiple biological actions make Aloe an important resource for developing new natural therapies. However, the biological activities of isolated compounds such as glycoprotein, polysaccharides, enzyme and phenolics were insufficient. Considering all these, this contribution provides a systematic review outlining the evidence on the biological efficacy of the plant including the pharmacology and the related mechanisms of action, with specific attention to the various safety precautions, and preclinical and clinical studies, indicating the future research prospects of this plant.

Keywords: Aloe arborescens; biological activity; glycoprotein; polysaccharides; clinical use; safety.

Abbreviations: 5-FU, 5-fluorouracil; AOM, azoxymethane; CPase, carboxypeptidase; DMH, dimethylhydrazine; ENNG, ethyl-*N*′-nitro-*N*-nitrosoguanidine; Hb, hemoglobin; IL-2, interleukin 2; IL-10, interleukin 10; IL-12, interleukin 12; IL-6, interleukin 6; O6-MeG, O6-methylguanine; Sz, streptozotocin; TEARS, thiobarbituric acid reactive substances; TGF-β, transforming growth factor beta; WHO, World Health Organization.

INTRODUCTION

The use of natural products with therapeutic properties is as ancient as human civilization. For a long time, plants and animal products were the main sources of drugs (De Pasquale, 1984). According to the World Health Organization, medicinal plants would be the best source for obtaining a variety of drugs (Rates, 2001). The public interest in Aloe species has quickly grown, and now a considerable amount of research about the various components of Aloe is being conducted to find out more about their properties (Li, 2009).

Basic research over the last two decades has begun to reveal the extent of Aloe's pharmaceutical potential, particularly against neoplastic disease (Harlev *et al.*, 2012). Medicinally, the gel and dried leaf exudates of Aloe species have been used since ancient civilizations of the Egyptians, Greeks and Mediterranean peoples and also for its cosmetic uses (Evans, 2009). Worldwide attention was drawn to the possible value of gel prepared from *Aloe arborescens* after the Second World War, when skin burns of victims of the nuclear bombs on Japan were successfully treated with its gel (Reynolds, 2004).

Several folk uses of *A. arborescens* were investigated; the split or crushed fresh leaves are widely used to treat burns and wounds. In South Africa, a leaf decoction is given to women to ease childbirth. In Japan, the leaves are used as a vegetable and to ease constipation. Preparations are sold as over-the-counter drugs for acceleration of gastric secretion, as a purgative and for dermatological use (Stewart, 2007).

Although a vast majority of researchers have studied the pharmacological activities of different *A. arborescens* extracts, there is no detailed literature available concerning the biological activity of the individual components. This systematic review therefore aims to provide an overview of the ethnomedicinal use, pharmacological activities and clinical applications of *A. arborescens*, as well as providing a base for further research, enabling to develop new formulations with higher therapeutic value.

VERNACULAR NAMES

Krantz aloe, Kidachi aloe, mountain bush aloe, candelabra aloe, octopus plant, torch plant (En). Aloès arborescent (Fr).

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ORIGIN AND GEOGRAPHIC DISTRIBUTION

Aloe arborescens is native to South Africa and has been exported to countries in the tropics and subtropics, as an ornamental and medicinal plant. In Italy, it is grown for both medicinal and cosmetic uses, whereas in Japan, it was cultivated for both medicine and food. Also, commercial growing of the plant began recently in Israel and China (Smith *et al.*, 2012).

METHOD

The present review covers the literature available from 1976 to 2015. The information was gathered from books, journals and electronic searches (PubMed, Google Scholar, Springerlink, ScienceDirect, www.jstor.org, *isiknowledge.com*, *biomedcentral.com*, *swetswise.com* and Web of Science). The references are collected from 54 articles covering the different biological activities of *A. arborescens* (Fig. 1); literature abstracts and full-text articles were analyzed and included in the review. Several such activities have been investigated in this matrix, most of the studies being devoted to the screening of antitumor activity against liver and colon (Fig. 2).

BIOLOGICAL CHARACTERIZATION

Anticancer activity

Liver cancer. The inhibitory effects of freeze-dried powdered leaf on the induction of preneoplastic glutathione *S*-transferase positive hepatocyte foci GST-P$^+$ were studied in animal models. The results indicated that 30% Aloe extract inhibited the promotion and possibly the initiation stage of hepatocarcinogenesis (Tsuda *et al.*, 1993). Zago (1954) claimed that Aloe preparation (*A. arborescens*, honey of bees and distillate) gave positive results in several diseases including cancer (skin, bladder, prostate, liver and others). The folk used preparation showed a great health improvement, when used by several people, who suffered from two types of cancer: melanoma and bladder cancer. On the light of this background, Anwar *et al.* (2009) directed to further evaluation of the beneficial health effects of oral intake of this preparation on liver health, aiming to understand the mechanisms of such activity. The author investigated the effect of the supplement on the splenic and hepatic cellular immune functions using dimethylnitrosamine-induced liver fibrosis in rats. The preparation showed fibrosuppressive effects with increases in the total proportion of CD4$^+$ cells among splenic T cells and the interferon-γ production after 21 days of treatment. On the other hand, the cytotoxicity of methanol extract and its fractions was assessed using a modified tetrazolium-based colorimetric assay on a human hepatoma cell line; the result revealed no cytotoxic effects after 72 h of treatment (Bisi-Johnson *et al.*, 2011).

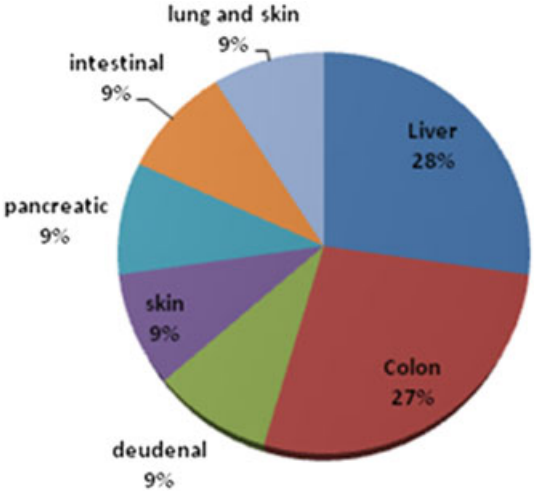

Figure 2. Summary of the antitumor activity analyzed of *A. arborescens* in the last 41 years. This figure is available in colour online at wileyonlinelibrary.com/journal/ptr

Colon cancer. Aloe extract decreased the development of azoxymethane (AOM) that caused aberrant crypt foci in the rat colon with an observed increase in cytosolic

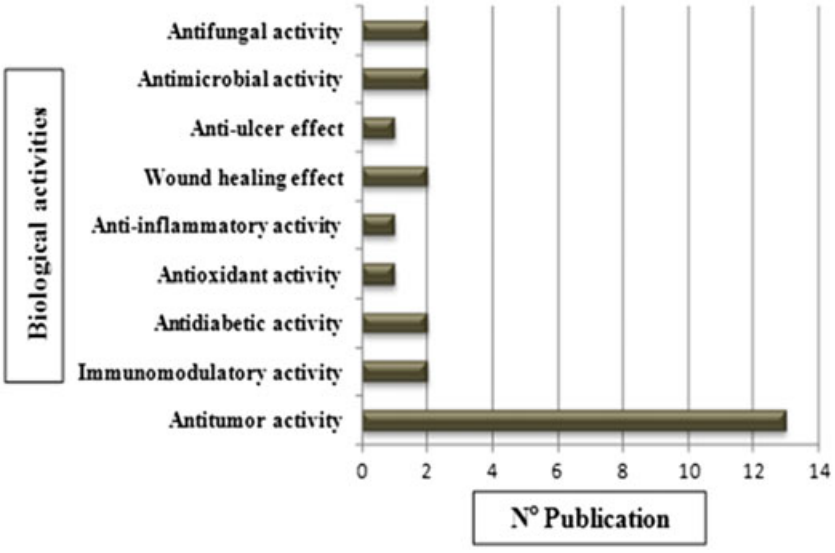

Figure 1. Evolution of the published works related to the biological activity determination of *Aloe arborescens* (data up to 2015). This figure is available in colour online at wileyonlinelibrary.com/journal/ptr

quinone reductase activity of the liver; therefore, Aloe leaf extract was suggested to have a chemopreventive effect against colon carcinogenesis in the initiation stage (Shimpo *et al.*, 2001). The same author in 2003 attempted to clarify the possible mechanism of inhibition of freeze-dried whole leaves extract and commercial crude aloin on the rat colorectum through studying the sample effect on the formation of AOM-induced DNA adducts [O6-methylguanine (O6-MeG)]. The results showed significant inhibition of O6-MeG levels by Aloe extract (50% reduction) and Aloin (30% reduction). Furthermore, Shimpo *et al.* (2003a, 2003b) examined the modifying effects of freeze-dried whole leaf on 1,2-dimethylhydrazine (DMH)-induced colorectal tumorigenesis in ICR (Imprinting Control Region) mice, and the results indicated that Aloe reduced the incidence and multiplicity of DMH-induced colorectal proliferative lesions, especially adenomatous hyperplasia.

Duodenal cancer. Chihara *et al.* (2000) examined the modifying effects of freeze-dried whole leaf on *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine (ENNG)-induced duodenal tumorigenesis in C57BL/6 mice. The results revealed that Aloe, particularly at 10% in the diet, inhibits ENNG-induced duodenal tumorigenesis.

Skin cancer. The acetone-soluble fraction of ethyl acetate extract inhibited 12-*O*-tetradecanoylphorbol-13-acetate-induced ear oedema (Shimpo *et al.*, 2002).

Pancreatic cancer. The modifying activity of freeze-dried powdered leaf during the initiation phase of carcinogenesis was evaluated in hamsters treated with *N*-nitrosobis (2-oxopropyl) amine and the results assessed histopathologically. Furukawa *et al.* (2002) reported that aloe prevents pancreatic neoplasia in relation to decreased DNA adduct formation in the target tissue.

Intestinal cancer. Shimpo *et al.* (2006) examined the modifying effect of freeze-dried leaf extract on AOM-induced intestinal carcinogenesis in animal model; the result showed that Aloe ingestion in low doses might have a mild suppressive effect on growth with no side effects.

Lung and kidney cancer. Skopi'nski *et al.* (2013) reported that Aloe behaves as tumor angiogenesis inhibitors through *in vivo* study after intradermal injection of syngeneic sarcoma or xenogeneic (human) lung and kidney cancer cells.

Studies concerned with the antitumor action mechanism. There are very few studies that have addressed the biological effects of Aloe at the molecular level. Di Luccia *et al.* (2013) proved the antiproliferative properties of the leaf extract using an integrated proteomic and cellular biological approach on a panel of human cell lines and has prodifferentiative activity on both primary and immortalized human keratinocyte. Proteomic analysis of whole cell extracts indicated the presence of proteins with a strong antiproliferative specifically induced in human keratinocytes and this finding verifying its application as a therapeutic agent. Ceccarelli *et al.* (2012) described the significant cytotoxic activities on murine myeloma cells at the cytological level by immunofluorescence techniques and both scanning electron microscopy and transmission electron microscopy for both *A. arborescens* epidermis leaf extract and its fraction. Chromatographic and spectroscopic methods revealed that the main components of the active fraction consisted of two constituents: a phenylpyrone derivative and three *C*-glucosylanthrones: aloenin A, aloin A and aloin B. The results revealed that leaf extract treatment affected the microtubular cytoskeleton of P3X cells inducing (i) modification of the organization and distribution of microtubules, (ii) disruption of the center of origin of microtubules and (iii) the presence of diffuse fluorescent staining in the cytoplasm that suggested its probable relation to the presence of free unpolymerized tubulin molecules. These findings could provide a clue about the possible molecular mechanisms of antiproliferative activity through the loss of cell membrane integrity that was preceded by a loss of mitochondrial membrane potential and proposing a mitochondrial-dependent pathway for inducing apoptosis.

Immunomodulatory activity

Immunochemical distinction reaction by Yagi *et al.* (1998) was established in order to distinguish between nondialysable fractions of *A. arborescens*, *A. chinensis* and *A. vera* as an immunoprecipitated agent using verectin antiserum raised in white rabbits. During an Ouchterlony double immunodiffusion and immunoblotting test, immunopositive band was detected against the fraction of *A. vera* but not against those of *A. arborescens* and *A. chinensis* gel. However, Picchietti *et al.* (2013) provided a new perspective for the use of *A. arborescens* to prevent or oppose bacterial and viral fish diseases, focusing on its possible usage as therapeutic alternative to antibiotics. The study tested the immune modulatory effects of the extract on the *Sparus aurata* fibroblast cell line SAF-1; the extract exhibited a powerful immunostimulant effect in lipopolysaccharides and polyinosinic–polycytidylic acid potassium salt that activated SAF-1 cells, and it also caused a synergic effect on interconnected genes expected to be involved in different aspects of the immune responses.

Antidiabetic activity

Beppu *et al.* (1993) indicated that *A. arborescens* improves the diabetic condition by direct hypoglyceration and also activated β-cells. Two different components were separated by cold acetone precipitation: one was isolated from the succulent layer of the *Aloe* leaf (leaf pulp) and the other one from the superficial layer of the Aloe leaf (leaf skin). The effect of Aloe differed between the leaf skin components and the leaf pulp components in mice with streptozotocin (Sz)-induced diabetes. The leaf skin one suppressed the increase in the blood glucose level seemingly by potentiating islet cells, while the leaf pulp one only caused a rapid hypoglycemic action by decreasing the blood glucose level for approximately 24 h. The results confirmed by microscopical examination of the tissue section showed less denaturation and necrosis of islet β-cells, so these results indicated that Aloe contains at least two antidiabetic active components. More evidence for the antidiabetic activity of high molecular weight components was reported based on a study on ICR mice by Beppu *et al.* (2006a, 2006b).

After using 2% whole-leaf extract and 10 KDa fraction powder derived from leaf skin juice *A. arborescens* in the experimental model using Sz-induced diabetes, the incidence of insulitis was markedly decreased to 51% and 38%, respectively. Moreover, the phenolic constituents showed an antioxidant activity in the pancreas and blood, which could protect islets of Langerhans from destruction, and systemic absorption dynamics of components were observed. The result has proved the possibility of using the 10 KDa fraction powder to alleviate the burden of insulin secretion through an inhibitory action on glucose absorption. Mogale *et al.* (2011) investigated the antidiabetic activity and the possible mechanisms of action of aqueous extract of *A. arborescens* leaf gel in normal and alloxan-induced diabetic rats. The results elucidated that extract ameliorates physiological parameters altered by the diabetic state, where these effects may be mediated through the protection mechanism of pancreatic β-cells.

Antioxidant activity

Beppu *et al.* (2003) evaluated the scavenging effects of different extracts on free radicals generated by Sz, alloxan and hypoxanthine–xanthine oxidase. Finding indicated that the action mechanism of boiled leaf skin components involved free radical inhibition, and it may be associated to a thermostable low molecular component. According to the study, the author expected that the Kidachi aloe-derived components 2′-*O*-p-coumaroylaloesin, 2′-*O*-feruloylaloesin and aloin existence resulted in the potentiating of free radical-scavenging effect.

Antiinflammatory

Kodym *et al.* (2002) applied a biopharmaceutical assessment for eye drops made of aloe water extract and neomycin sulphate to assess the permeability of biologically active aloe component identified as aloenin, through lipophilic and hydrophilic synthetic membranes in a standard perfusion apparatus and *in vitro* verification of the transport possibilities of the substances through the isolated cornea of pig's eye. Estimated quotas of permeability rated constant as the chemical constituents of aloe that diffused through the applied membranes. On the basis of the result, the formula should be particularly useful in the treatment of inflammations and infections of external parts of the eye, such as conjunctiva, eyelid edges, lachrymal sac and cornea.

Wound healing activity

Numerous studies on *A. arborescens* species dealt with the protective effects on mouse skin injury induced by soft X-irradiation by measuring scavenging activity of activated oxygen, protective effects of nucleic acid, induction of antioxidative protein and metallothionein in the skin and liver compared to normal mice according to Sato *et al.* (1990). Jia *et al.* (2008) provided the positive evidence for *A. arborescens* supporting their therapeutic properties for topical treatment of skin wounds. The study monitored the wound closure rate in animal model showing that the whole-leaf juice facilitated the healing process and selectively inhibited the microbial growth with no visible side effects. This suggested that aloe species have beneficial effects for skin medicinal applications.

Antiulcer activity

The antigastric effects of *A. arborescens* extract with high molecular weight components [(A) MW over 5000 and (B) MW over 50,000] were evaluated by changes of ulcer index. The suppressive effects were evaluated with three different experimental models; under stress, ligation of pylorus and the healing effects were examined with the acetic acid test. Results showed that both fractions have a slight suppressive effect on the stressed animals. In addition, the model with pylorus ligation and extract (A) significantly disclosed suppressive effects with a significant healing effect. However, the fraction (B) produced only a slight positive effect as reported by Teradaira *et al.* (1993). The study indicated that the high molecular weight components are responsible for protection against peptic ulcers.

Antimicrobial activity

Studies of the physicochemical–microbiological properties and the stability of ointments containing aloe extract or aloe extract associated with neomycin sulphate were analyzed by Kodym and Bujak (2002), considering the physicochemical and microbiological stability of the freshly prepared formula. After 2 years of storage, the ointment was in accordance to the requirements of the *Polish Pharmacopoeia* mentioned in the monograph *Guttae ophthalmicae.* The effects of *A. arborescens* dermal and inner gel leaf fractions were tested on the growth of five microorganisms (*Escherichia coli*, *Bacillus cereus*, *Bacillus licheniformis*, *Staphylococcus epidermidis* and *Saccharomices boulardii*) by Pellizzoni *et al.* (2012). Both water extract of the gel and methanol/ethyl acetate extracts of leave skin possessed the higher antimicrobial effects, and the results indicated that *Gram positive* microorganisms were more susceptible than *Gram negative* microorganisms.

Antifungal activity

The antifungal activity was investigated for a lyophilized powder containing aloe leaf homogenate against *Trichophyton mentagrophytes*, and the minimal inhibitory concentration was 25 mg/mL using the agar dilution method. Fresh whole leaves homogenates higher than 10,000 Da showed minimal inhibitory concentrations against three strains of *T. mentagrophytes* (10 mg/mL). Experiment supposed that the high molecular weight component of aloe had a fungicidal activity (Fujita *et al.*, 1978). *In vivo* investigations of Aloe on experimental tinea pedis in guinea-pig feet were carried out, and the antifungal effects were evaluated in comparison with lanoconazole. Culture studies after application of 30% freeze-dried Kidachi aloe for 10 days showed a 70% growth inhibition. On the other hand, *in vitro* experiment showed that the fraction with molecular

weights less than 10 KDa and a bioactive compound of barbaloin inhibited the growth of *Trichophyton* at a minimum concentration of 75 mg/mL and 200 μg/mL, respectively, according to Kawai *et al.* (1998).

Biological activity of isolated compounds

Glycoprotein (lectins). Lectins are proteins that bind to carbohydrates and sugar containing substances in a specific and reversible way or precipitate glycoconjugates (Liener, 2012). These heterogeneous classes of carbohydrate-binding proteins or glycoproteins of non-immune origin are capable of reversibly binding to carbohydrates without altering their covalent structure. Generally, lectins manifest a diversity of general activities including anti-insect activities, antitumor, immunomodulatory, antimicrobial and HIV-1 reverse transcriptase inhibitor, which may find applications in many therapeutic areas (Hamid *et al.*, 2013). Two lectins have been isolated from leaves of *A. arborescens* by Suzuki *et al.* (1979): one lectin (P-2) has a molecular weight of approximately 18,000, consisting of two subunits (α and β) and containing more than 18% by weight of neutral carbohydrate, and the other lectin (S-1) has a molecular weight of approximately 24,000, consisting of two subunits (γ_2) with a molecular weight of approximately 12,000 and containing more than 50% by weight of neutral carbohydrate. S-1 possesses a strong hemagglutinating activity. On the other hand, P-2 has not only hemagglutinating activity but also the mitogenic activity of lymphocytes, precipitate-forming reactivity with serum proteins, one of which is α_2-macroglobulin and complement C3. Furthermore, Imanishi *et al.* (1981) isolated a glycoprotein that markedly inhibited the growth of a syngeneic transplantable fibrosarcoma of mice in ascites form, which revealed that the inhibition mechanism is host mediated and not a direct toxic effect on the tumor cell. Saito *et al.* (1982) separated a glycoprotein, Aloctin A, from *A. arborescens*, which markedly inhibits adjuvant arthritis in rats and carrageenan-induced edema in rats. Yagi *et al.* (1985) found that isolated Aloe lectin (a homogeneous glycoprotein, molecular weight 40,000 Da) contains 34% carbohydrate capable of inducing blastmitogenesis, and it might be responsible for the therapeutic effect of aloe on burns. This activity reported at a concentration of 5 micrograms/mL, as the glycoprotein was shown to stimulate DNA synthesis in baby hamster kidney cells and to have the properties of a lectin, which reacts with sheep blood cells. Yagi *et al.* (1986) demonstrated the phagocytic activity of glycoprotein A in a dose-dependent manner; the assay revealed that heat treatment destroyed the activity, suggesting that the native structure of the protein moiety in glycoprotein A is essential for the activity. Saito *et al.* (1989) studied the effect of aloctin A, a glycoprotein separated from leaves of *A. arborescens* on gastric secretion and acute gastric lesions in animal models. The results revealed that aloctin A when given intravenously showed a significant inhibition of the development of Shay ulcers. In addition, it also inhibited water-immersion stress lesions induced in pylorus-ligated rats.

Saito (1993) purified the previously separated aloctin A and described its biological and pharmacological activities. It showed many activities as follows: hemagglutinating, cytoagglutinating, mitogenic effect of lymphocytes, precipitate-forming reactivity with macroglobulin, complement C3-activating activity, inhibition of heat-induced haemolysis of rat erythrocytes, antitumor, antiinflammatory, inhibition of gastric secretion and gastric lesions.

Imanishi (1993) considered that aloctin A showed inhibitory effects on the growth of tumor cell lines examined. However, it was a promising candidate as an immunomodulator with host-mediated mechanisms of antitumor activity through elevation of natural killer cell activity, augmentation of cytotoxicity of peritoneal exudates cells and the generation of lymphokine-activated killer cells. This result was analyzed after implantation of methylcholanthrene-induced nurine fibrosarcoma (Meth A2) and lymphocytic leukemia (P388) in a BALB/c mice system. Moreover, according to Koike *et al.* (1995), another lectin was separated from the leaf skin by sequential chromatographic techniques; it exhibited a molecular mass of about 35 kDa and exhibited hemagglutinating activity toward rabbit but not human and sheep erythrocytes.

Polysaccharides. Polysaccharides are a structurally diverse class of macro-molecules of relatively widespread occurrence in nature. They play major roles in the growth and development of living organisms. In the last few decades, the biological activities of polysaccharides acquired increasing importance in medicine (Ooi and Liu, 2000).

Two different reports described the polysaccharides previously isolated from *A. arborescens* plant:

Arborans [(1–4) linked glucomannans]. Bioassay-guided fractionation of the *A. arborescens* polysaccharide fraction afforded two glycans, arborans A and B, which exhibited marked hypoglycemic effects in normal and alloxan-induced hyperglycemic mice (Hikino *et al.*, 1986).

Polysaccharide (A, B and C). (**A**: a linear (1–6)-*O*-α-glucan, **B**: a branching (1–2)-*O*-L-arabinose with (1–2)-*O*-D-galactose linkages and **C**: (1–4)-*O*-β-mannan with 18% acetyl group)

As different types of biologically active polysaccharides have been separated from various sources, some have antitumor activity. Yagi *et al.* (1986) postulated the possibility that activity of polysaccharides is due to its host-mediated action, where it may activate the depressed functions of phagocytes in tumor-bearing hosts. To confirm this hypothesis, the author applied an assay for phagocytosis and nitroblue tetrazolium chloride reduction test using neutrophils from asthmatic patients, who are not receiving corticosteroid. Screening activity of polysaccharides A, B and C showed that polysaccharide C demonstrated the most potent phagocytosis-enhancing effect in a dose-dependent manner. The results suggested that the phagocytic activity of polysaccharide C may provide biomedical evidence for *A. arborescens* as an antiinflammatory.

Peptides. A novel endophytic actinomycete, designated strain NEAU-LZS-5^T, was separated by He *et al.* (2014) from the leaf, and it was characterized using a polyphasic approach. Analysis of the 16S rRNA gene sequence showed that strain NEAU-LZS-5^T belongs to the genus *Streptomyces* and exhibited 99.51% and 97.37% similarity to *Streptomyces sedi* YIM 65188^T and *Streptomyces specialis* GW41-1564^T, respectively. A comparative study between strain NEAU-LZS-5^T and the type strains of related species of the genus *Streptomyces*

showed differences in morphological, physiological and biochemical characters. Therefore, strain NEAU-LZS-5^{T}represents a novel species of the genus *Streptomyces*, for which the name *Streptomyces zhaozhouensis* sp. nov. is proposed; the type strain is NEAU-LZS-5^T (=CGMCC 4.7095^T = DSM 42101^T). The study requires further investigation for detailed identification of the biological activity of isolated actinomycete as it may be a potential novel source of antibiotics or cytotoxic drugs.

Enzyme. Mechanism of antiinflammatory and antithermal burn action of carboxypeptidase (CPase) from *A. arborescens* was estimated in an animal model by Obata *et al.* (1993) as CPase was partially purified and administered intravenously to female ICR mice with inflammation. The enzyme preparation had significant analgesic effects and inhibited vascular permeability in the abdominal region. The result indicated an antithermal burn action on the hind paw and suggested that the mechanism may be due to the following: (i) Aloe CPase hydrolyzes bradykinin *in vivo*, thus reducing pain; (ii) it may inhibit the acceleration of vascular permeability in the abdominal region; and (iii) action may be due to its vasopressor activity as hydrolysis of angiotensin I and the production of angiotensin II occurred. Beppu *et al.* (2006a, 2006b) investigated the protective actions of components separated from *A. arborescens* on Sz-induced necrosis of β-cells in the pancreatic islets of the mouse, in order to clarify the mechanism of action for antidiabetic activity. Aloe CPase fraction and glycoprotein components were tested; the result suggested that CPase is an aloe-derived protease that inhibited the acetic acid-related enhancement of intraperitoneal vascular permeability.

Phenolics. Aloenin was proved to inhibit the activity on gastric juice secretion, bioassay evaluation of volume and pH of gastric juice secreted in experimental animals after 4 h of oral administration; the activity was investigated by Hirata and Suga (1976). The antiinflammatory action of Aloe extract, fractions and isolated active constituents (aloenin, barbaloin, aloe-emodin and a mixture of straight-chain higher alcohols) were examined toward carrageenan-induced edema in animal models. The methanol extract significantly reduced edema. The activity was observed mainly in the *n*-butanol partially purified fraction. Furthermore, the isolated active compounds exhibited the same inhibitory activity as that of aspirin, which proved the important role of these compounds in the antiinflammatory action (Yamamoto *et al.*, 1991).

Lucini *et al.* (2015) suggested that several components might contribute to the scavenging activity; the stable radical DPPH test and the oxygen-radical absorbing capacity assay were evaluated. The result indicated that the outer green rind was the most active, while the inner parenchyma was less effective; furthermore, 5-methylchromones aloesin, aloeresin A and aloesone were the most active pure secondary metabolites.

TOXICITY AND SAFETY STUDIES

Matsuda *et al.* (2008) assessed the chronic toxicity of *A. arborescens* in the diet at doses 4.0%, 0.8% and 0.16% to male and female Wistar rats. No deaths occurred at any dose level throughout the treatment period. In rat groups receiving 4.0% and 0.8% extracts, Hb decreased, and relative heart and brain weights were decreased. Both sexes receiving 4.0% extract showed the following: diarrhea, reduced body weight gain, increase of white blood cells, decrease of calcium and alanine transferase, relative kidney weight showed increases, severe sinus dilatation and yellowish pigmentation of ileocecal lymph nodes and renal tubules. The study showed no observed adverse effect level for Aloe in a dose 0.16% in diet, which is equivalent to 87.7 and 109.7 mg/kg/day in males and females, respectively.

According to Yokohira *et al.* (2009), a study was conducted to assess toxicity and carcinogenic potential of *A. arborescens* in the diet at doses of 4% and 0.8% in groups of male and female Wistar rats. The results indicated that Aloe, used as a food additive, exerted equivocal carcinogenic potential at 4% high-dose level on colon in the 2-year carcinogenicity study in rats. Aloe is not carcinogenic at nontoxic-dose levels, and the carcinogenic potential at 4% high-dose level on colon is probably due to irritation of the intestinal tract by diarrhea.

CLINICAL TRIALS

Bioaron C *product*—assay of antiviral activity

Bioaron C® syrup is a popular herbal medicament used as immunostimulant. It has been used in Poland in cases of upper respiratory tract infections and in the prevention of recurrent bacterial and viral infections. The formula includes *A. arborescens* aqueous leaf extract, chokeberry fruit juice (*Aronia melanocarpa* Elliot.) and vitamin C. A post-marketing surveillance study of the tolerance and efficacy of the drug was carried out by Pampura *et al.* (2007). The treated group included 21 children (3 to 6 years) and 39 children (6 to 12 years); the disease duration was within 6 months after intake of the product. The investigated T cell immunity test was increased in the relative and total T cell counts ($CD3^+$, $CD4^+$ and CD8). A significant reduction in the relative number of $CD16^+$ cells was detected. The results revealed an immunomodulatory effect of a Bioaron C® syrup, where phagocytic activity of neutrophils was noticed. Moreover, in the safety tests, no biochemical abnormalities in blood parameters have been noticed. The product showed a potent activity in children with recurrent upper respiratory tract infections and reduction of infection incidence in the treated children.

According to Bastian *et al.* (2013), a clinical study of 572 children between age 3 and 14 years has been included in prospective, open trials with or without control groups conducted mostly with the same finished product (Bioaron C). Together with a large retrospective study conducted by the same group comprising 3069 patients from age 3 to 14 years receiving Bioaron C, these data showed that *A. arborescens* can be safely used also as a concomitant treatment.

Biostimine product—assay of antioxidant and cytokine synthesis

Basta *et al.* (2013) concluded that Biostimine supplementation reduces the post-exercise level of thiobarbituric

acid reactive substances (TEARS) by increasing the antioxidant activity of plasma but has no action on inflammatory markers. The study examined the effect of Biostimine supplementation, on the levels of pro-oxidant–antioxidant equilibrium markers, and antiinflammatory and proinflammatory cytokines in a double-blind study in athletes. Superoxide dismutase and glutathione peroxidase activity and the concentration of TEARS were evaluated in erythrocytes. Additionally, total antioxidant capacity and creatine kinase activity were measured in plasma samples, and cytokine (IL-6 and IL-10) concentrations were assayed in the serum. The results showed that post-exercise and recovery levels of TEARS were significantly lower in athletes receiving Biostimine than in control groups.

Chemo-biochemotherapeutic regimen assessment of a formula against cancer (*Aloe fresh leaves + honey + 40% alcohol*)

The formulation of chemo-biochemotherapeutic regimens could represent a promising strategy in the treatment of human neoplasms (Cerea *et al.*, 2002, Lissoni *et al.*, 2003). A randomized study was conducted by Lissoni *et al.* (2009) to compare the effect chemotherapy versus biochemotherapy with chemotherapy plus *A. arborescens* in metastatic cancer patients. The experiment was designed to include 240 patients given oral dose (10 mL three times daily) of the mixture either during or after chemotherapy, until the progression of disease.

The clinical response and toxicity were evaluated according to WHO criteria in relation to tumor histotype and clinical status. Lung cancer patients were treated with cisplatin and etoposide or weekly vinorelbine, while colorectal cancer patients received oxaliplatin plus 5-fluorouracil (5-FU), gastric cancer patients were treated with weekly 5-FU and pancreatic cancer patients received weekly gemcitabine. The results showed that the percentages of both objective tumor regressions and disease control were significantly higher in patients concomitantly treated with Aloe than with chemotherapy alone. The clinical study suggested that Aloe is effective if associated with chemotherapy by increasing its efficacy in terms of both tumor regression rate and survival time.

CONCLUSION

In this review, it is well established that extracts and fractions of *A. arborescens* possess various therapeutic effects, and consequently, it seemed to be good candidates for possible medicinal applications such as anticancer, immunomodulator, antidiabetic, antiinflammatory, antioxidant, antiulcer, antimicrobial, antifungal and wound healing. However, it is not clarified whether the bioactivities exhibited by the plant extract are due to single components or the consequence of synergistic effect of many components. It is not only important to identify the constituents of the extracts but also relate them to the suggested therapeutic value.

The different biological activities of extracts have been reported previously, as shown in (Fig. 1). Interestingly, the antitumor activity was the most widely investigated

Table 1. *In vivo* experimental models of antitumor effect *A. arborescens* plant

Cancer type	Plant part	Animal model	Induction of cancer	Route of administration	Dose	Duration of treatment	References
Liver cancer	Freeze-dried whole leaf	Wister rats	2-Amino-3-methylimidazo(4,5,f) quinoline	Basal diet	30% aloe extract	8 days	Tsuda *et al.* (1993)
			Diethylnitrosamine			3–8 weeks	
	Preparation (*A. arborescens*, honey and distillate)	C57BL/6 mice Wister rats	Dimethylnitrosamine	Intragastrically	0.1 mL per day	21 days	Anwar *et al.* (2009)
Colon cancer	Freeze-dried whole leaves and commercial crude aloin	F344	Azoxymethane	Basal diet	5% aloe in diet	4 weeks	Shimpo *et al.* (2001, 2003)
	Freeze-dried whole leaf	ICR mice	1,2-dimethylhydrazine	Basal diet	1%, 0.5% or 0.1% in diet	32 weeks	K. Shimpo *et al.* (2003)
Duodenal cancer	Freeze-dried whole leaf	C57BL/6 mice	*N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine	Basal diet	10% in the diet	15 weeks	Chihara *et al.* (2000)
Skin cancer	The ethyl acetate extract of the acetone-soluble fraction		12-*O*-tetradecanoylphorbol-13-acetate	To both ears with a micropipette	20 μL of extract	5 h	Shimpo *et al.* (2002)
Pancreatic cancer	Freeze-dried whole leaf powder	Hamsters	*N*-nitrosobis (2-oxopropyl)amine	Basal diet	1% and 5% in the diet	5 weeks	Furukawa *et al.* (2002)
Intestinal cancer	Freeze-dried whole-leaf extract	F344	Azoxymethane	Basal diet	1% in the diet	28–35 weeks	Shimpo *et al.* (2006)
Lung and kidney cancer	Bioaron C® syrup Biostymina ampoules	Balb/c mice	L-1 sarcoma cells	Intragastrically	As product dose	3 days	Skopi'nski *et al.* (2013)

Bioaron C® syrup (100 mL contains the following: extracted *A. arborescentis recens* fluidum—38.4 g, Vitaminum C—1.02 g and *Aroniae melanocarpae* succus—23.3 g). Biostymina ampoules. 1 mL. Each ampoule contains an aqueous extract (1:4) from fresh leaves.

one against different cancer types as elicited in Table 1, such as liver cancer, colon, duodenal, skin, pancreatic, intestine, lung and kidney cancer. Nonetheless, even with the limited reports on mechanism of active components responsible for these activities, it has become obvious that numerous mechanisms would have been involved in different activities of a given medicine. Furthermore, together with all these findings, our observations that all previous studies focused only on carcinoma's cancer type suggest additional investigations on possible cellular target(s) in sarcoma, lymphomas and leukemia bioassay models. In addition, as it found, the conflict in the results about the antitumor activity of the plant against liver cancer might be due to (i) the different duration of treatment, (ii) mechanism of action that can relate to immunomodulation rather than direct cytotoxic effect, (iii) use of plants from different locations with variations in their chemical composition and (iv) the different extraction techniques.

Several recent studies were addressed to clarify the mechanism of anticancer activity. However, the exact mechanism of its immunomodulatory therapy in cancer has still to be established in detail. In our opinion, further studies measuring the most important immune biomarkers such as IL-2, IL-12, IL-6, IL-10, TGF-β and T regulator lymphocytes will be necessary to clarify the effect of aloe on the anticancer cytokine network.

From our point of view, it seems reasonable to include the clinical trials of humoral and cellular immunity among the objectives of further research and to determine the parameters that are directly associated with the immunochemical status of the body (such as the levels of immunoglobulin and prostaglandins, the components of complement system and total leukocyte count, differential analysis of granulocyte, and B and T cell subpopulations).

In the light of previous studies of aloe extracts against different tumors, it seems that the plant extract has a direct oncostatic effect and also improves the efficacy of chemotherapy in terms of both tumor regression rate and survival time. However, there are critical points in these studies such as (i) the lack of use a high number of patients to allow definitive conclusions on impact of a concomitant aloe therapy on the life of chemotherapy-treated patients and (ii) double-blind randomized studies were also absent.

Phase zero studies are also recommended to benefit as an early identification of the promising anticancer agent, reducing cost and expediting their drug development. Phase zero clinical trials will overcome stagnation of anticancer drug development (Bergström *et al.*, 2003).

It is also noticed that there is a conflicting point of cross-bioactivity of this aloe species as it has an antioxidant activity; hence, this effect may hamper the effectiveness of chemotherapy by its free radical-scavenging activity. There is also a possibility that antioxidants alleviate unwanted chemotherapy toxicity, allowing the increase of chemotherapy doses (Kwee, 2014). Thus, it is recommended to detect glutathione and its enzyme-linked system, which are considered as relevant parameters for chemotherapy response. In addition, they can be utilized as useful biomarkers for selecting tumors potentially responsive to chemotherapeutic regiments.

It is obvious that there are only very few reports concerning immunomodulator activity of *A. arborescens*, although it was claimed that some of the biological activities of this plant can be attributed to the polysaccharides found in the leaf gel. It is a daunting task to link individual polysaccharides to specific therapeutic properties. However, Tzianabos (2000) illustrated the possible mechanism of polysaccharides for immunomodulation efficacy as their study considered the immunotropic and antiinflammatory properties resulting from polysaccharides activating the synthesis and release of IL-1 and IL-6. That initiates the entire cascade of cellular reactions and is associated direct or indirect to antiinflammatory, antiviral, antidiabetic and antineoplastic effects.

Practice Points

- No observed adverse effects of plant at dosages of 87.7 and 109.7 mg/kg/day. However, it exerted equivocal carcinogenic potential at 4% high-dose level on colon in 2-year carcinogenicity study in rats.

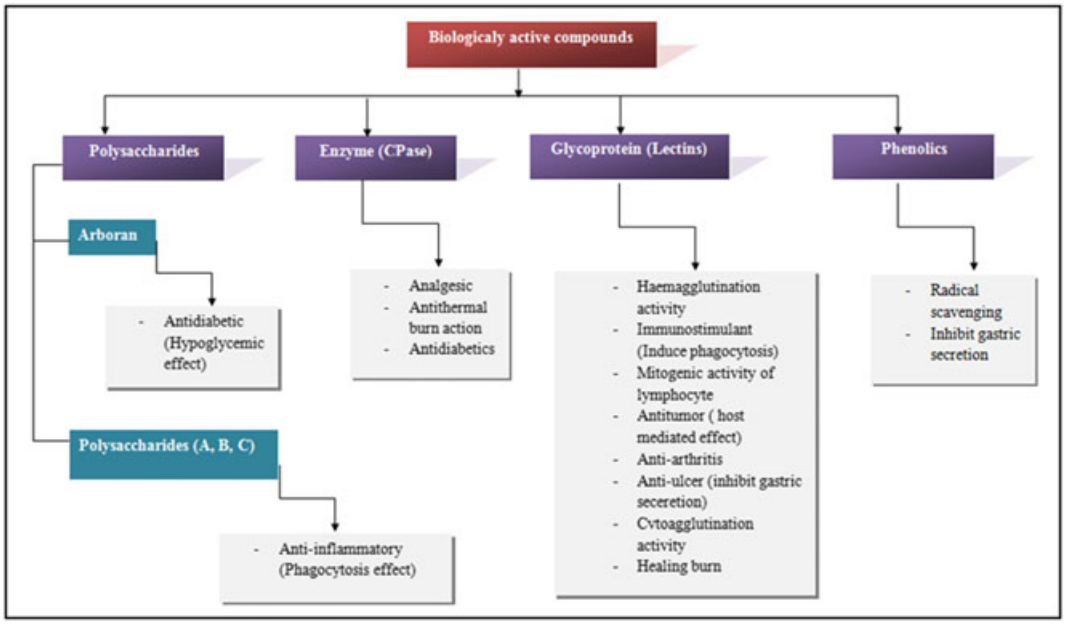

Figure 3. Pharmacological profile of isolated active compounds from *A. arborescens*. This figure is available in colour online at wileyonlinelibrary.com/journal/ptr

- Biological activity of lectin was the most component researchers assessed (Fig. 3).
- Carboxypeptidase and actinomycetes are new unique phytochemical components isolated from *A. arborescens* with little or null pharmacological studies.
- Reports showed developing evidence about the antitumor effect of *A. arborescens* extract and fractions, although there are two common types of carcinoma not investigated (breast and prostate cancer type).
- From the current review of the literature, it was concluded that the plant has high medicinal value.

Proposed Research Agenda

- Investigations on possible cellular target(s) in sarcoma, lymphomas and leukemia bioassay models should be taken in consideration.
- Biological studies on polysaccharides and phenolics were limited; thus, researchers should esteem their activity in the future search.
- Although the antitumor activity of anthraquinones from other Aloe species was investigated, that of *A. arborescens* was not studied.
- Immunomodulating and antiproliferative clinical studies with single aloe molecules could allow further benefits in the treatment of human neoplasms.
- Lack of actinomycete identification evidence introduced a preferred investigation by the researcher to its biological activity, thus providing new information on its cytotoxic or antimicrobial effects.
- *A. arborescens* has been shown to be a safe product and is supposed unlikely to cause harm in the majority of patients during clinical trials. Evidence on colon carcinogenesis in 4% dose is lacking and requires more future study; particularly, there are reports recommending the use of the extract in the case of colon and intestinal cancer.
- In the future, the research level of *A. arborescens* on anticancer and immunomodulatory fields should be further improved, to establish the hypothesis considering the possible use of the plant as an immunotherapy in case of cancer using a pharmacodynamic and pharmacokinetics background.
- Future studies should focus not only on the relationship between chemical structure and bioactivities, but also on interactions among chemical components and their synergistic effect with the help of systems biology.

Conflict of Interest

The authors have declared that there are no conflicts of interest.

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