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Literature review of *Aloe vera* cytotoxicity

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Abstract

Aloe vera juice enables the body to heal from cancer and from the damage caused by radio and chemotherapy that destroys healthy immune cells crucial for recovery. *Aloe vera* emodin, an anthraquinone, can suppress or inhibit the growth of cancer cells making it have antineoplastic properties. The role of *Aloe* in carcinogenicity has not been evaluated well. The chronic abuse of Anthracoid-containing laxatives has been hypothesized to play a role in colorectal cancer. *Aloe vera* tincture and melatonin administration were studied as standard therapy against metastatic solid tumors. (c, 2016 For thousands of years, plants are an important source of medicine in pharmaceutical biology. As per WHO, 80% of the population today relies on traditional medicine.

Keywords: *Aloe vera*; Cell-line; Cancer; Extracts

1. Introduction

The genus *Aloe* is widespread in eastern and southern Africa extending north to Sudan, but in Asia is only known from southwest Arabia. Here there is considerable diversity which is reflected in a large number of described species, one of the difficulties of studying *Aloe* has been the shortage of herbarium material. Most collectors avoid *Aloe* because of the succulent leaves, and many of those who have tried to make specimens have only collected inflorescences. (Wood, 2016) The role of *Aloe* in carcinogenicity has not been evaluated well. The chronic abuse of anthracoid-containing laxatives has been hypothesized to play a role in colorectal cancer, however, no causal relationship between anthracoid laxative abuse and colorectal cancer has been demonstrated. *Aloe vera* juice enables the body to heal from cancer and from the damage caused by radio and chemotherapy that destroys healthy immune cells crucial for recovery. *Aloe vera* emodin, an anthraquinone, can suppress or inhibit the growth of cancer cells making it have antineoplastic properties. (Sahu et al., 2013).

2. Literature review

Aloe is referred to as the 'Miracle Plant' and 'Healing Plant'. The Egyptians called *Aloe* "the plant of immortality." The genus *Aloe* is widespread in eastern and southern Africa extending north to Sudan, but in Asia is only known from southwest Arabia, for thousands of years, plants are an important source of medicine in pharmaceutical biology. As per WHO, 80% of the population today relies on traditional medicine.

Majumder et al (2020) In this study, they had found that the IC50 of *Aloe vera* leaf extract against breast cancer cell line (MCF-7) is 23 µg/mL which is much lower than the IC50 (332 µg/mL) of *Aloe vera* leaf extract against non-cancerous cell line (NIH-3T3). Also calculate the total concentration of phenolic acid (385.662 µg/mL), flavonoids (160.402

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μg/mL), and alkaloids (276.754 μg/mL) in *Aloe vera* leaf extract. The free radical scavenging activity of *Aloe vera* leaf extract is 67% to 89% (at 50 to 300 μg/ml). His virtual molecular docking study suggests that bioactive compounds like *Aloe*-emodin (−8.8 Kcal/mol), 7-hydroxy-2,5 dimethylchromone (−7.5 Kcal/mol), Beta-sitosterol (−7.3 Kcal/mol), etc. have a greater binding affinity toward estrogen alpha receptor as compared to standard drug Tamoxifen (−6.4 Kcal/mol).

AKEV, et al (2020) in this study the Fresh leaf skin aqueous and methanolic extracts, as well as shade-dried leaf skin methanolic extracts prepared separately from the leaves of *Aloe vera* and *Aloe*-emodin (AE), were assayed on human gastric (AGS), colon (HT-29, HCT116) and hepatocellular (HEPG2) cancer cell lines relative to human umbilical vein endothelial cells (HUVEC). AE, 5-fluorouracil (5-FU), and imatinib (IM) were tested as positive controls. Among the four extracts studied, *Aloe vera* gel extract (AVG) had the highest cytotoxic effect on cancer cells, with the highest effect on HCT116 cells, while no cytotoxic effect on HUVEC cells was detected. AE has also selective cytotoxic and apoptotic effects on the cancer cells and was ineffective on normal cells.AVG treatment in HCT116 cells induced apoptosis by the activation of caspase-9 and caspase According to the results, AVG and AE could be proposed as promising cytotoxic drugs of natural origin.

Bista, et al (2020) in this studied Fresh *Aloe vera* leaves collected from Itahari, Sunsari district Nepal and were well washed with distilled water and subjected to cabinet drying at 50°C until the constant weight of the sample was obtained. Thus, obtained dry powder was extracted using Soxhlet apparatus in two different solvents i.e., methanol and ethanol, and further concentrated using a rotatory vacuum evaporator that was used for Total Phenol Content (TPC), Total Flavonoid Content (TFC), and tannin content determination.

The mean values of methanolic and ethanolic extract were then statistically analyzed at a 5% level of significance by paired t-test. Fresh *Aloe vera* leaves were extracted in 96% methanol to determine chlorophyll-a, chlorophyll- b, and total carotene content. Similarly, 99% methanol was used to determine Total Antioxidant Capacity (TOAC), DPPH radical scavenging activity, and reducing power assay of fresh *Aloe vera* leaves.

The preliminary phytochemical analysis of the aqueous extract of *Aloe vera* showed the presence of protein, carbohydrates, phenols, tannin, steroids, terpenoids, and glycosides.

Total Phenol Content (mg GAE/g), Total Flavonoid Content (mg QE/g), and Tannin Content (mg GAE/g) of methanolic extract of *Aloe vera* were respectively 30.53±0.30, 14.29±0.44, 73.26±2.4, and that of ethanolic extract was 54.95±2.46, 1.13±0.19, 0.844±0.04 respectively. The methanol and ethanol extracts showed a significant difference in the phytochemical contents (p-value<0.05). Fresh leaves showed chlorophyll-a, chlorophyll-b, and total carotene content to be 0.088±0.007mg/100, 0.017±0.006 mg/100g, and 35±0.23μg/100g respectively. Similarly, Total Antioxidant Capacity (TOAC), DPPH radical scavenging assay, and reducing the power of fresh *Aloe vera* leaves were found to be 103.49±0.24%, 81.91±0.04%, and 67.08±0.85% of dry mass respectively. The study showed *Aloe vera* is a good source of antioxidants and phytochemicals and can be used as a medicinal herb but the toxicological properties are yet to be studied.

Lima, et al (2020) studied the Different types of extraction that were tested and specific bioactive compounds were quantified. Cancer cell invasion inhibitory activities were measured in vitro using the wound healing assay in human colon cancer cells (HT29). Effects on gelatinase activities were further assessed by dye-quenched gelatin and gelatin zymography. The results showed Different types of extraction yielded significantly different levels of bioactivities and of bioactive compounds, which might be due to a greater amount of extractable bioactive compounds such as anthraquinones. Both *Aloe* arborescent and *Aloe vera* have potential as inhibitory agents in cancer cell proliferation via MMP-9 and MMP-2 enzymatic activity inhibition, being able to reduce colon cancer cell proliferation and migration but *Aloe arborescens* has shown to be a more effective inhibitor of cancer cell migration than *Aloe vera*. This work opens novel perspectives on the mode of action of *Aloe* species in cancer cell migration and may provide clues as to why there are so many conflicting results on *Aloe*'s activities.

Martínez, et al (2020) in this study showed the flowers of *Aloe vera* are a byproduct providing a valuable source of bioactive compounds with different functions for health benefits. The characterization in amino acids, organic acids, sugars, trigonelline, volatiles compounds, fatty acids, total phenolic, carotenoids, vitamin C content, and antioxidant capacity of *Aloe* flowers (*Aloe* barbadensis Miller) has been studied at three maturity stages (I: immature; II: mature; III: mature, with flowers buds opened). Immature flowers presented the highest content of phenylalanine, tyrosine, citric acid, trigonelline, carotenoids, retinol activity equivalent, vitamin C, and total phenolic and antioxidant capacity. As the flower develops, the content of these compounds decreases. *Aloe vera* flowers presented an important content of fatty acids, and the principal concentration was identified in polyunsaturated unsaturated fatty acids (PUFAs) as α-linolenic

acid, and linoleic acid, with a ratio close to one. The main saturated fatty acid was palmitic acid, followed by stearic acid. Maturity stage III showed the lowest fatty acid content. The bioactive compounds found in *Aloe vera* flowers have potential applications in the cosmetic, pharmaceutical, nutraceutical, and food industries. Depending on the compound of interest, harvesting flowers at the maturity stage could be worthwhile, thereby reducing the energy consumption of flowers from the plant and thus favoring plant development. This is an example of a circular economy for *Aloe vera* producers, generating economic and business opportunities and thus providing environmental and social benefits.

Kurizaki, et al (2019) showed the (3R)-3,4-Dihydro-6,8-dihydroxy-3-(2'-acetyl-3'-O-β-d- glucopyranosyl-5'-hydroxyphenyl) methyl-2(1H)-benzopyran-1-one (feralolide-3'-O-β-d- glucopyranoside, 1), feralolide (2), *Aloe*-emodin (3), peroxide (4), and chlorogenic acid (5) were isolated from the 70% EtOH extract of flowers of *Aloe arborescens*. The structures of these compounds were elucidated based on physical and spectral data. The absolute structure of 1 was determined based on circular dichroism spectra for the first time.

Karpagam, et al (2019) studied human adipose-derived stem cells (hASCs) after harvesting adipose tissues from abdominal subcutaneous adipose tissue and isolation, were cultured in four groups of Control, Collagen gel, *Aloe vera* gel, and *Aloe vera*/Collagen blended in vitro environment at 24h and then cell viability was assessed by MTT assay. The results of MTT showed that the combination of *Aloe vera* /Collagen retained the cell viability at the normal range and improved it. In real-time RT-PCR results, integrin α1β1 and PECAM-1 gene expression were increased in the *Aloe vera*/Collagen blended group compared to the control group.

Froldi et al (2019) identified and quantified *Aloe*-emodin and aloin in the methanolic and the hydroalcoholic extract of *Aloe* arborescent leaves, and the investigation of free radical scavenging capacities and antiglycation properties of the isolated compound and *Aloe* leave extract. Lastly, the cytotoxicity and the capacity of aloin and *Aloe*-emodin to cross the HT29 cellular membranes were assessed. this assessment indicated that *Aloe*-emodin can substantially pass through the cell membrane (~20%), whereas aloin did not permeate to HT29 cells. overall, the data show that both the methanolic and the hydroalcoholic *Aloe arborescens* extracts determine significant inhibition of glycation and free radical persistence without any cytotoxic activity.

Karpagam, et al (2019), In the present study, anticancer and cytotoxicity of *Aloe vera* ethanolic leaves extract were evaluated as the leaves of *Aloe vera* are reported to have great medicinal value with potential therapeutic applications. The anticancer activities of the ethanolic leaves extract of *Aloe vera* were investigated using 3-(4,5-dimethylthiazole-2yl)-2,5- diphenyl tetrazolium bromide assay on three human cancer cell lines HepG2 (liver cancer), HeLa (human cervical carcinoma cell line), and A549 (human lung adenocarcinoma epithelial cell line). In anticancer studies, *Aloe vera* ethanolic leaves extract showed potent proliferation inhibitory activity against HepG2, HeLa, and A549 cell lines. The results have shown that the *Aloe vera* ethanolic leaves extract contains some active ingredients with potential anticancer agents. *Aloe vera* ethanolic leaves extract has the potential to fight against cancer cells. Further work should be carried out on the characterization of specific anticancer components of *Aloe vera*.

Benzidine, et al (2019) This study aims at the characterization of tannins extract of *Aloe vera* (TAV) by gas chromatography coupled to mass spectrometry (GC/MS), phytochemical screening, morphological and histological identification of the species, and extraction (tannins extract) from its green rind. The antioxidant activity of the tannin extract was tested using the 1.1-diphenyl-2-Picrylhydrazyl-Hydrate (DPPH) method. The results of the main constituents found were Palmitic acid (11.91%), E-Phytol (14.40%), Linolenic acid (16.59%), and Diisooctylphtalate (11.84%). The tannins extract was also fractionated over a silica gel dry column. Three main fractions were isolated. The first fraction contains 25.99% of Palmitic acid, the second comprised Dibutyl phthalate (30.93%), and the third fraction showed an amount of 54.13% Diisooctylphtalate. The phytochemical screening showed the alkaloid, tannins, flavonoids, sterols, triterpenes, mucilages, oses, holosides, and their reducing compounds metabolites, As for the coumarins and saponins, they were absent. The tannin extract showed antiradical activity with a percentage inhibition of about 74.17% at 6 mg/ml

Carvalho, et al (2018) this study aimed to evaluate, in vitro, the effect of *Aloe vera* associated with endodontic medication, with or without laser photo biomodulation (FTL) irradiation in FP6 human pulp fibroblasts. The materials were divided into eight groups: CTR- control; CL - FTL alone; AA - *Aloe vera* with distilled water; *Aloe vera* with distilled water and FTL; HA - calcium hydroxide P.A. with distilled water; HL - calcium hydroxide P.A. with distilled water and FTL; HAA - calcium hydroxide P.A. with *Aloe vera* and distilled water; HAL - calcium hydroxide P.A. with *Aloe vera*, distilled water, and FTL. The cytotoxicity was evaluated by MTT assay at 24, 48, and 72 h, and the genotoxicity by micronucleus test assay. This study was performed in triplicate. Data obtained in both tests were statistically analyzed by ANOVA and Tukey's tests ($p \leq 0.05$). Group AA presented high genotoxicity and low cytotoxicity. After 24, 48, and 72 h, the group HAA significantly reduced the cell viability. Interaction with FTL showed a slight increase in cell viability

after 24 and 48 h in groups CL and HL ($p < 0.001$), despite the high genotoxicity in group CL and low genotoxicity in group HL. Group AL showed a higher cell survival rate at 72 h ($p < 0.05$) and high genotoxicity ($p < 0.001$). It was concluded that *Aloe vera* allowed higher cell viability in human pulp fibroblasts in the presence of calcium hydroxide or with FTL separately, but genotoxicity increased in these associations

Quispe, et al (2018). In this study, the chemical characterization was performed using liquid chromatography (UHPLC) coupled to PDA and high-resolution mass spectrometry (HESI- QOrbitrap®-MS) in four different plant parts of *Aloe* (peel, flowers, gel, and roots). Twenty-five phenolic compounds were identified, including cinnamic acids and other derivatives (e.g., caffeic and chlorogenic acids), chromones (e.g., *Aloe*sin and iso*Aloe*resin D), anthracene compounds and derivatives (e.g., aloin A/B and emodin), and several C-flavonoids (e.g., orientin and isovitexin), among others. The total antioxidant activity of the ethanolic extracts of the peels, flowers, gel, and roots was measured as the capturing of the DPPH• and ABTS •+ radicals, while the iron-reducing antioxidant power (FRAP) was measured by spectroscopic methods. *e peel had the highest antioxidant activity with values of 2.43 mM ET/g MF (DPPH•), 34.32 mM ET/g MF (ABTS •+), and 3.82 mM ET/g MF (FRAP). According to our results, the peel is the best part of the plant for the production of nutraceuticals or cosmetics products for its greatest number of bioactive compounds. * is a new and innovative finding since the only part used in traditional medicine is the gel of *Aloe*, and the peel is generally considered waste and discarded.

Debnath, et al (2018) This research highlights the phenolic constituents' profile and antioxidant activity of 70% ethanol extracts of *Aloe vera* flower for the first time. The ethanol-based extracts showed inhibition for linoleic acid oxidation and free radical-induced DNA damage. Among about 11 phenolic constituents of the extract, identified by using high-performance liquid chromatography (HPLC), the content of vanillic acid was highest, corresponding to the strong antioxidant activities of the extract. The extracts elevated superoxide dismutase, catalase, and glutathione peroxidase enzymes activities in the liver tissue of hydrogen peroxide-treated BALB/c mice. The radical-scavenging activities of the extracts were well-correlated to the total phenolic content. Therefore, the *Aloe bardadensis* flower might be an effective source of natural antioxidants.

Rehman, et al (2017) Bioassay-guided fractionation of *Aloe vera* resulted in the isolation and characterization of one new C-glucosyl chromone, 7-methoxy6′-O-coumaroyl*Aloe*sin (1), along with the known dihydroisocoumarin feralolide (2). The structure of 1 was elucidated based on 1D, 2D-NMR, and mass spectrometry. Both compounds 1 and 2 were tested for their effects on the growth of cancer cells in culture and it was observed that unlike compound 1, compound 2 displayed concentration-dependent antiproliferative effects on breast cancer cells (MDA-MB-231) and ovarian cancer cells (SKOV-3). Additionally, only feralolide (2) demonstrated good urease, weak α-glucosidase enzyme inhibition, and weak antioxidant effects.

Fox, et al (2017) The present study aimed at determining the wound healing properties of the gel and whole-leaf materials of *Aloe vera*, *Aloe* ferox, and *Aloe marlothii*, as well as their cytotoxic effects on normal human keratinocyte cells (HaCaT). Materials and Methods: Nuclear magnetic resonance spectroscopy was used to chemically fingerprint the *Aloe* gel and whole-leaf materials by identifying characteristic marker molecules of *Aloe* gel and whole-leaf materials. An MTT assay was performed to determine the cytotoxicity of the various *Aloe* whole leaf and gel materials on HaCaT cells. Wound healing and in vitro cell migration were investigated with HaCaT cells using the CytoSelect™ assay kit. Results: The in vitro wound healing assay suggested that all the *Aloe* gel and whole-leaf materials examined, exhibited faster-wound healing activity than the untreated control group. After 48 h, all the *Aloe* gel and whole-leaf materials almost completely caused full wound closure, displaying 98.07% (*Aloe marlothii* whole-leaf), 98.00% (*Aloe vera* gel), 97.20% (*Aloe marlothii* gel), 96.00% (*Aloe vera* whole-leaf), 94.00% (*Aloe* ferox gel) and 81.30% (*Aloe* Ferox whole-leaf) wound closure, respectively. It was noteworthy that the gel materials of all three *Aloe* species exhibited significantly faster ($p < 0.05$) wound healing actions when compared to their respective whole-leaf materials at 32 h. Conclusion: The gel and whole-leaf materials of *Aloe vera*, *Aloe* forex, and *Aloe marlothii* have shown the ability to heal wounds at a faster rate and to a larger extent than untreated keratinocytes. The MTT assay results suggested that the gel and whole-leaf materials of all the selected *Aloe* species showed negligible toxicity toward the HaCaT cells.

Çandöken, et al (2017), this study was conducted to demonstrate the cytotoxic effects of several leaf extracts and *Aloe*-emodin (AE) on a type of skin cancer. *Aloe vera* aqueous and methanolic extracts from fresh leaves, methanolic extract from dried leaves, and leaf gel extract (AVG) were prepared separately. Cytotoxicity was assessed using the MTT test. Apoptosis and necrosis were detected by flow cytometry using Annexin V/PI. All the extracts exhibited a selective cytotoxic effect on the cells. The mechanism of AVG cytotoxicity on B16F10 murine melanoma cells was found to be apoptosis, whereas that of AE was necrosis. The observation that treatment with AVG delayed the apoptosis in NIH3T3 cells, while it exerted an apoptotic activity on B16F10 cells, provides some scientific evidence for the folkloric and

alternative uses of *Aloe vera* gel as a protective and skin healer. Therefore, *Aloe vera* gel and *Aloe*-emodin can be used as potential targets for anticancer drug research.

Shahbandeh (2017), the present study was designed to evaluate the anti-proliferative and apoptotic effects of *Aloe vera* extract on HL60 h-AML and MCF-7 breast cancer cell lines by cell viability assay, changes in cell morphology, and apoptosis analysis, according to the results, the treated cells with *Aloe vera* extract in comparison to the untreated cells exhibited a significant decline in viability in a time and dose-dependent manner. MTT assay showed that the IC50 value of *Aloe vera* extract on MCF-7 cells was 0.5 mg/ml during the first 24 hours, while at this time IC50 of the extract on HL 60 cells was 1 mg/ml. Also.

Alrumman, (2017), this study aimed to evaluate the antimicrobial activities of various extracts of fresh and dry leaf gel of *Aloe vacillans* against eight clinical isolates of human pathogens. The chemical compounds present in the gel extract were identified and quantified by gas chromatography-mass spectrometry. Solvent extracts inhibited 62.5% of the examined microbes, whereas the fresh leaf extract was more potent and active against *Staphylococcus aureus*, *Micrococcus luteus, Klebsiella oxytocin, Proteus mirabilis, and Candida albicans* compared to the dry leaf extract. No antimicrobial activities were observed against *Klebsiella pneumonia, Shigella flexneri,* and *Pseudomonas aeruginosa*. *Candida albicans* was the most susceptible pathogen based on its zone of inhibition. The maximum inhibitory activities were shown by the fresh gel of the chloroform extract against M. luteus, the methanol extract against

S. aureus, the petroleum ether extract against *P. mirabilis, C. Albicans, and K. pneumonia*, and hot water extracts against *K. oxytocin.* Gram-positive bacteria and *C. Albicans* were more susceptible than gram-negative bacteria. Compounds were identified and quantified; the major constituents of the gel.

Basak, et al (2017) ware showed that the *Aloe vera* leaf extract is effective on various cancers like colon cancer, and neuroectodermal cancer but there is very little sufficient data on breast cancer. Therefore, they evaluated the effect of *Aloe* leaf extract on breast cancer cells. A phytochemical test of the extract confirms the presence of Alkaloids, Phenolic compounds. The antioxidant activity of such phytochemicals is very useful to inhibit cancer. MTT Assay was performed on PBMC and MCF-7 cell lines with *Aloe vera* extract. Experimental data suggest that *Aloe vera* whole leaf extract significantly increases the cytotoxic effect on human breast cancer cells compared to normal cells (PBMC). This study evaluated the specific cytotoxic effect of *Aloe vera* extract on human breast cancer cells and further study is required to develop an *Aloe vera* extract base drug for the treatment of breast cancer.

ÜNLÜ, et al (2016), *Aloe vera*, a succulent plant species, has a long history in folk medicine. It's clear, viscous liquid has been used to treat skin problems and other disorders since ancient times. In the last century, oral consumption and the injection of *Aloe* have also come to popular attention. Its topical use is effective in the treatment of burns and abrasions, and oral use is effective in the treatment of constipation. However, it is not superior to standard treatments. Most recently, claims of anti-cancer properties are prevalent. It has been found to inhibit proliferation and angiogenesis and induce apoptosis in cancer cells. Yet other clinical studies indicate that *Aloe vera* did not prevent or reduce the number of radiotherapy-related lesions; it merely delayed onset. Furthermore, many instances of toxicity and mortality have been reported in the literature. Today, it is better to avoid it, especially in forms taken orally or by injection.

HĘŚ, et al (2016). They evaluate the results of the antioxidant properties of the aqueous extract of *Aloe* in model systems. Analyses were conducted on true *Aloe* (*Aloe vera* L.). Extraction was run using water at a temperature of 80–90°C. The level of phenolics was determined spectrophotometrically with the Folin-Ciocalteu reagent, using gallic acid as a standard. The antioxidant activity of the extract was analyzed about linoleic acid, running incubation for 19 h, by scavenging of stable radical DPPH (2,2-diphenyl-1-picrylhydrazyl) and cation radical ABTS (2,2'-azino-bis[3- -ethylbenzothiazoline-6-sulfonic acid]) and based on metal chelating ability. Recorded results were compared with the activity of BHT (butylated hydroxytoluene). The results of the total phenolic content of the water extract of *Aloe* were 17.85 mg/g d.m. The extract exhibited concentration-dependent DPPH and ABTS radical scavenging activity. The ability was in the range of 4.32–8.87 and 0.58–0.87 mg of Trolox per 1 g d.m., respectively. The lower chelating ability of the *Aloe* extract was 1.23 mg EDTA per 1 g d.m. at 20 mg/ml concentration and the higher was 8.76 mg EDTA per 1 g d.m. at 10 mg/ml concentration. The *Aloe* extract reduced levels of the conjugated dienes in the emulsion system. The samples with additions of 0.1–0.5 mg/ml extract contain over 90% fewer dienes than the control sample. The addition of 0.05 mg/ml and 0.06 mg/ml results in significantly lower (40% and 57%, respectively) activities of the *Aloe* extract.

Shalabi, et al (2015), investigated the in vitro anticancer effect of *Aloe vera (A. vera)* and *Calligonum comosum (C. comosum)* extracts against hepatocellular carcinoma (HepG2) cells. HepG2 cells were tested against different doses of *A. vera and C. comosum*. The viability of the cells was assessed by MTT assay. The annexin V apoptosis detection kit evaluated apoptosis and DNA damage in HepG2 cells. The expression of p53 and anti-apoptotic (Bcl-2) were tested by

real-time-PCR and flow cytometer analyzer. Hematoxylin and eosin-stained sections from untreated and treated HepG2 cells were observed using light microscopy. According to the results, the IC50 values of *A. vera and C. comosum* extracts were (10.45 ± 0.31) and (9.60 ± 0.01) µg/mL respectively. The extracts separately increased cytotoxicity against HepG2 cells in a time and dose-dependent manner. Also, it induced apoptosis through increased P53 and decrease Bcl-2 gene expressions. Conclusions The results indicated that the extracts could have an anti-hepatocarcinogenic effect, at least in part, through modulation of apoptosis.

YONEHARA, et al (2015), showed that Neuroblastoma is a pediatric solid tumor refractory to eradication by chemotherapy. To determine whether *Aloe vera* (AV), a potential anticancer reagent, could be useful in neuroblastoma therapy, they investigated the antiproliferative effects of an AV protein extract. Materials and Methods: Human neuroblastoma cell lines (IMR-32, TGW, CHP-126, and NBL-S) were cultured with AV protein extract and proliferation status was assessed by cell counting, Ki-67 staining, and gene expression. Results: Among tested lines, the number of viable, AV-treated IMR-32 cells significantly decreased 1.98-fold by day 2 and 1.33-fold by day 5 of culture relative to untreated controls ($p<0.05$). Treatment also decreased the number of Ki-67(+) IMR-32 cells by 13% by day 5 ($p<0.05$) and, unlike untreated controls, CCND2 mRNA expression levels became undetectable by day 1. Conclusion: AV-protein extract suppresses human IMR-32 neuroblastoma cell proliferation, possibly by suppressing CCND2 transcript levels in vitro.

Hussain (2015), many of the anti-cancer agents currently used have an origin in natural sources including plants. *Aloe vera* is one such plant being studied extensively for its diverse health benefits, including cancer prevention. In this study, the cytotoxic potential of *Aloe vera* crude extract (ACE) alone or in combination with cisplatin in human breast (MCF-7) and cervical (HeLa) cancer cells was studied by cell viability assay, nuclear morphological examination, and cell cycle analysis. Effects were correlated with the modulation of expression of genes involved in cell cycle regulation, apoptosis, and drug metabolism by RT-PCR. Exposure of cells to ACE resulted in considerable loss of cell viability in a dose- and time-dependent fashion, which was found to be mediated through the apoptotic pathway as evidenced by changes in the nuclear morphology and the distribution of cells in the different phases of the cell cycle. Interestingly, ACE did not have any significant cytotoxicity towards normal cells, thus placing it in the category of a safe chemopreventive agent. Further, the effects were correlated with the downregulation of cyclin D1, CYP 1A1, and CYP 1A2, and increased expression of Bax and p21 in MCF-7 and HeLa cells. In addition, a low-dose combination of ACE and cisplatin showed a combination index of less than 1, indicating synergistic growth inhibition compared to the agents applied individually. In conclusion, these results signify that *Aloe vera* may be an effective anti-neoplastic agent to inhibit cancer cell growth and increase the therapeutic efficacy of conventional drugs like cisplatin. Thus promoting the development of plant-derived therapeutic agents appears warranted for novel cancer treatment strategies.

Qasem et al. (2013), tested ethanolic extracts of the *Aloe vacillans* leaves juice for antihepatotoxic activity in albino rats intoxicated with CCl4, liver weight, and biochemical parameters were studied. They indicated that ethanolic extracts decrease the liver enzyme levels of ALT, and AST, when compared with the CCl4- the treated group, and increased the T.P and albumin levels when compared with CCl4 –the treated group. The data suggested that oral administration of an ethanolic extract from the leaves of *Aloe vacillans* significantly decreases the intensity of hepatic damage induced by CCl4 in rats.

López, et al (2013). In this study, the methanol extracts of leaf skins and flowers of *Aloe vera* from the Canary Islands were analyzed for their phenolic profiles and screened for their antioxidant and anti-mycoplasmic activities. The use of reversed-phase high-performance liquid chromatography (RP-HPLC) allowed the identification of 18 phenolic constituents. Leaf skin extracts were characterized by the abundance of catechin, sinapic acid, and quercitrin. Gentisic acid, epicatechin, and quercitrin were the most prominent phenolic compounds of the flowers. The in vitro antioxidant activities determined by using the 1,1-diphenyl-2- picrylhydrazyl (DPPH) and ferric antioxidant reducing power (FRAP) assays revealed that both extracts exhibited antioxidant activity, being the leaf skin extract being the most active fraction. The leaf skin extract was also found to be active against the microbial strains tested. Therefore, A. vera extracts from leaf skin and flowers can be considered good natural antioxidant sources.

Moniruzzaman, et al (2012) In this study, the total phenolic and flavonoid contents, the 2,2-diphenyl-1-picryl hydroxyl (DPPH) radical scavenging ability, and the ferric reducing power (FRAP) of *Aloe vera* were measured to determine the antioxidant activity of this species. The in vivo antidiabetic effects of the plant were also investigated using streptozotocin-induced type 2 diabetic model rats that were divided into five groups based on the treatment received: (1) water (WC); (2) glibenclamide; (3) concentrated gel extract (Gel-C); (4) ethanol (80%) gel extract (Gel-Et); and (5) ethanol (80%) skin extract of *Aloe vera* (Skin-Et). Skin-Et, which contained the highest level of total phenolics (62.37 ± 1.34 mg gallic acid/kg) and flavonoids (20.83 ±0.77 mg/kg), exhibited the highest scavenging activity (85.01 ± 0.52%) and the greatest reducing power (185.98 ± 0.41 µM), indicating that the skin contained the highest level of antioxidants.

The oral consumption of Gel-Et for 4 weeks a caused significant reduction in the fasting serum glucose levels of the rats. The rats in the Gel-C-, Gel-Et- and Skin-Et-treated groups experienced a reduction in their total cholesterol levels by 11%, 17%, and 25%, respectively, and a reduction in their LDL cholesterol levels by 45%, 3%, and 69%, respectively. The in vivo experimental antioxidant parameter MDA is strongly correlated with the in vitro antioxidant parameters of flavonoids and polyphenols, namely the DPPH and FRAP values (r = 0.94, 0.92, 0.93, 0.90), thus confirming the antioxidant potential of the *Aloe vera* extracts.

Ozsoy, et al (2012) in this study A new and rapid affinity chromatography method based on cyanogen bromide (CNBr)-activated Sepharose 4B bound-ovalbumin was presented for the purification of the main lectin present in *Aloe vera* (L.) Burm. fil. The lectin was purified 60- fold to apparent homogeneity in native polyacrylamide disc gel electrophoresis (PAGE) showing an apparent molecular weight of 45000 kDa. The fact that sodium dodecyl sulfate (SDS)-PAGE gave a subunit molecular weight of 14 400 kDa tends to propose that the lectin is composed of three subunits and thus is in agreement with Aloctin I previously partially purified and characterized by us. The lectin did not exhibit an antioxidant effect as assessed by the DPPH· radical-scavenging assay

Harlev, et al (2012) This review looks at *Aloe*, both the genus and the folk medicine, often being called informally "*Aloe*s", and delineates their chemistry and anticancer pharmacognosy. Structures of key compounds are provided, and their pharmacological activities are reviewed. Particular attention is given to their free radical scavenging, antiproliferative, and immunostimulatory properties. This review highlights major research directions on *Aloe*s, reflecting the enormous potential of natural sources, and the genus *Aloe* in particular, in preventing and treating cancer.

3. Conclusion

Cancer is one of the deadly diseases which are characterized by irregular cell proliferation the most common reason behind cancer is lifestyle changes and therefore an urgent need to find a bitter treatment for the disease is required. According to the World Health Organization (Roy et al., 2017). Cancer as a major public health problem is responsible for 13% (7.6 million deaths) of all deaths in the world. According to the latest reports provided by the Ministry of Health and Medical Education (MOHME) (Shahbandeh, Eghdami, 2017). Treatments such as chemotherapy can put patients under a lot of strain and further damage their health. Therefore, there is a focus on using alternative treatments and therapies against cancer. For many years herbal medicines have been used and are still used in developing countries as the primary source of medical treatment (Padmaharish, et al., 2017).

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no competing interests.

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