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Review

Lead bioactive compounds of *Aloe vera as* potential anticancer agent

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ABSTRACT

Aloe vera (*Aloe barbadensis Miller)* is a perennial succulent medicinal plant. It has been used as a traditional or folk medicine for thousands of years and claimed that it possesses wound and burn healing activities, and anti-inflammatory as well as immunomodulatory effects. In recent years, the use of *Aloe vera* has been growing as a dietary supplement. The pre-clinical studies over the last couple of decades uncover the potential therapeutic activities of *Aloe vera* and its bioactive compounds, especially against neoplastic disease. Such investigations indicate the possible preventive as well as therapeutic effects of *Aloe vera* against cancer. Here, we discuss the crucial bioactive compounds of *Aloe vera* that have been harnessed against cancer and also address several mechanisms of action of these lead bioactive compounds compared to other standard drugs involved in cancer prevention and treatment.

1. Introduction

Medicinal plants are essential sources of drug discovery. Over the last few decades, new drugs and bioactive compounds are being searched from different plants. Their safety and useful applications in the treatment of various diseases have been extensively studied [1]. Phytochemicals (phyto = plant in Greek) are the plant-based bioactive non-nutrient chemicals/compounds which can interact with one or more components of the living system and exert a broad range of probable effects [2]. Cumulating studies have indicated that many substances originated from natural products exert anticancer effects [2–5]. For example, the bitter melon extract has shown anticancer activity against breast, head, and neck cancer [6–8]. Bitter melon extract inhibits breast cancer development (*in vitro/in vivo*) effectively by inducing autophagy and also suppresses head and neck squamous cell carcinoma (HNSCC) by manipulating immunomodulatory action. In fact, it can be observed that 47.1% of the 155 clinically approved anticancer drugs from 1981 to 2006 were untailored natural products or their semi-synthetic by-products or even synthesized chemical molecules based on the natural models [9]. The primary advantage of using phytochemicals as anticancer agents is that they appear to have lower adverse effects, and have more cost-benefit ratio compared to the commercially available drugs. According to the World Health Organization, medicinal plants would be the best sources for obtaining a variety of drugs and between 65% to 80% of the human population in the developing countries are currently using medicinal plants as a source of phytochemicals for remedies [10,11]. It has been figured out that around 300,000 plant species are present in the earth, and only 15% of that has been investigated to elucidate their pharmacological activities [12]. Therefore, it is worth searching for new biologically active phytochemicals to fight against cancer [13].

Aloe vera is an evergreen, cactus-like perennial succulent xerophyte belongs to the genus Aloe [14]. Xerophyte plants have versatility and adaptiveness to survive in hot-dry areas, and particularly, the succulence property of these plants is one of the important xerophytic adaptations [15]. In hot-dry areas, they are forced to collect and store water for their long-run survival. Such kind of adaptation makes it a rich source of diverse phytochemicals. Therefore, *Aloe vera* is a native plant of sub-Sahara Africa, Saudi Arabian Peninsula, and several Indian Ocean islands [15]. The term “aloe” originates from the Arabic word *alloeh*, implies “bitter and shiny substance” and “vera” means for truth in Latin [16]. It has a long history of medicinal use and providing health benefits. Ancient cultures like Indian and Chinese recorded it as a medicinal plant, and Greeks, Romans, and Babylonians used *Aloe vera* leaves as an ointment for the skin [17]. Traditionally, *Aloe* latex has been used as a laxative to treat constipation, and the *Aloe vera* gel has

Abbreviation: EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinases; ERα, estrogen receptor α; PI3K, phosphoinositide 3-kinases; mTOR, mammalian target of rapamycin; APO1, apoptosis antigen 1; HER-2, human epidermal growth factor receptor 2; JNK, cJun NH2-terminal kinase; VEGFR, vascular endothelial growth factor; STAT3, signal transducer and activator of transcription 3; LDH, lactate dehydrogenase; ROS, reactive oxygen species; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK, mitogen-activated protein kinase

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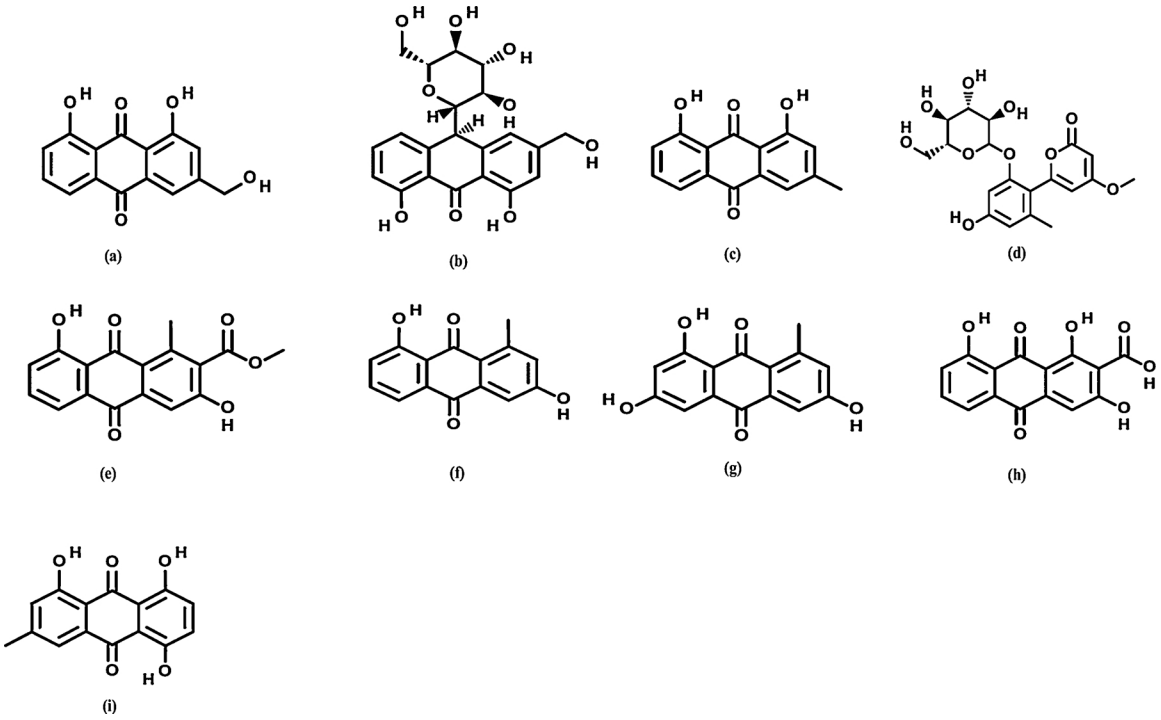

Fig. 1. Chemical structures of anthraquinones: aloe-emodin (a), aloin (b), chrysophanol (c), aloenin (d), aloesaponarin I (e), aloesaponarin II (f), deoxyerythro –laccin (g), laccaic acid D-methylester (h), and helminthosporin (i).

been used for anti-inflammatory effect, skin related problem, and wound healing purpose [14]. In modern time, the application of *Aloe vera* has been observed in pharmaceutical products, functional foods, and cosmetics [18]. Several research studies have shown antibacterial, anti-cancer, and anti-viral activities of *Aloe vera* [19]. Especially, anticancer effects of *Aloe vera* and its phytochemicals have been reported in numerous studies [19–24]. It is claimed that the anticancer properties of *Aloe vera* are mainly due to the two separate mechanisms: antiproliferative and immuno-stimulatory activities [20]. The anti-proliferative activity is exhibited due to the presence of aloe latex, a yellow bitter-tasting component in *Aloe vera*, while the immuno-stimulatory effect is due to aloe polysaccharides [20]. Aloe latex is produced in the thin middle layer of *Aloe vera* leaf, composed of chlorenchyma and vascular bundles. This latex contains the major secondary metabolites, such as glycosylated anthraquinones (aloin A and aloin B), glycosylated chromones (aloesin and aloeresin), and polyphenols as well as the free anthraquinones such as aloe-emodin as the minor components [25,15]. Latex also contains several secondary metabolites, even more than Aloe gel. Aloe latex is used as a laxative due to the presence of C_8 – hydroxyl substituted anthranoids [26] and various reports suggest that bioactive components of Aloe latex are responsible for inducing apoptosis in several cancer cell lines such as HL60, HeLa, Jurkat, and MCF-7 [27–30]. However, it is the matter of concern that some *in vitro/in vivo* studies have also found the potential mutagenic and carcinogenic activities of aloe latex (aloe-emodin, aloin, aloesaponarin) [16,31], as a result, the International Aloe Science Council (IASC) suggested that the limit of aloin content should be less than 10 ppm in aloe product for oral consumption [32]. *In vitro* studies have revealed that the *Aloe vera* gel exhibits proliferative activity, and the latex component possesses cytotoxic effects [33]. Therefore, further study is urgently essential to validate the efficacy and the safety profile of *Aloe vera* and its bioactive compounds for the cancer treatment as well as for the preventive purpose. Here, we try to discuss the current research status of *Aloe vera* and its lead bioactive compounds compared to standard drugs regarding cancer treatment and prevention.

2. Drug development from phytochemicals

Phytochemicals are rising as a rich source of diverse bioactive agents which are effective as well as safer against many chronic diseases. In spite of having all the technological advancements in conventional cancer therapies still, cancer remains one of the prominent causes of death just after cardiovascular diseases worldwide [34]. Although synthetic drugs have been developed for cancer chemotherapy, they possess serious off-target toxicity toward tumor-adjacent non-cancerous cells and tissues. Apart from that, drug resistance has evolved as a major obstacle for their application after a prolonged period. For a long time, phytochemicals or bioactive compounds from natural sources have been investigated to develop anticancer agents with minimum or no adverse effects. For example, the well known anticancer drugs vincristine and vinblastine are derived from vinca alkaloids, which have been isolated from *Catharanthus roseus* (C. roseus) (Apocynaceae) plant [35]. The main advantages of drug development from plant-derived products are, most of the selected medicinal plant species have a long history of human utilization (ethnomedicine). Therefore, it is assumed that the isolated bioactive compounds from medicinal plants are safer than compounds derived from plants with no record of human use. On the other hand, developing drugs from natural resources also have some disadvantages. Most of the time, a drug derived from natural products leads to unsuitable environmental concerns due to the commercialization pressure of that drug. Though synthesis of the bioactive molecules may be the alternative, every time it could not be possible due to the complex structure of the molecules. Anticancer agents like paclitaxel, docetaxel, etoposide, topotecan, and irinotecan are highly dependent on plant resources for the beginning materials as the complete synthesis is not possible till now [35]. Therefore, it is necessary to focus on ethno-plants, which can be found abundantly for drug development and met commercial demand to avoid further environmental concerns.

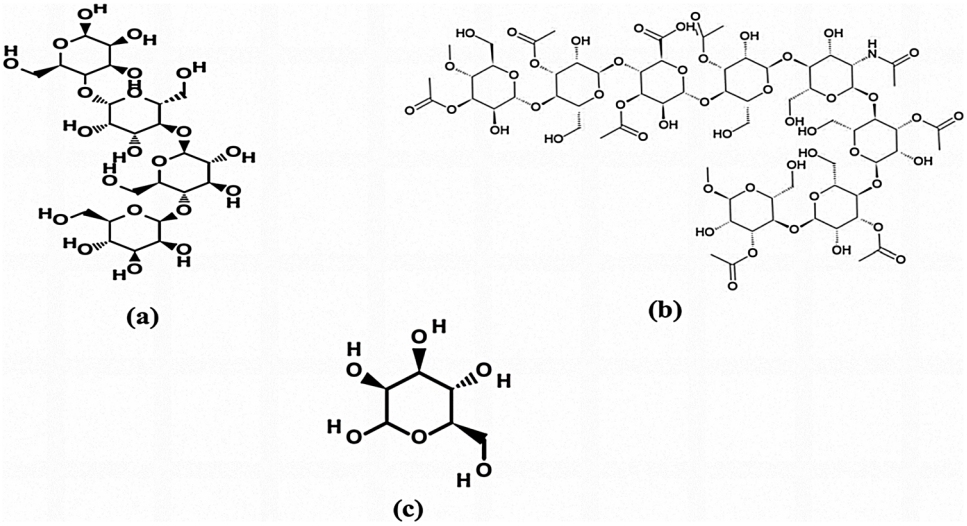

Fig. 2. Chemical structures of aloe polysaccharides: glucomannan (a), acemannan (b), mannose (c).

3. Major phytochemicals in *Aloe vera*

Aloe vera is one of the oldest known medicinal plants. According to the World Health Organization (WHO), *Aloe vera* is the most bioactive plant among all the 420 *Aloe* species [14]. Several studies related to isolation and characterization, have been reported that phytochemicals from *Aloe vera* possess various pharmacological activities [36]. It contains 75 potential bioactive phytochemicals [37]. The main phytoconstituents are anthraquinones, naphthalenones, polysaccharides, proteins, enzymes, and organic acid, etc [38]. Among these, anthraquinones (Fig. 1) [25,15,36] are the major bioactive compounds present in the bitter yellow latex of *Aloe vera* leaf. The main ingredient of *Aloe vera* gel is aloe polysaccharide with water (99%), and the most found aloe polysaccharide (Fig. 2) is glucose-mannose polysaccharide [39]. Moreover, there are other bioactive phytochemicals also present in *Aloe vera*, such as aloe lectin (protein), chromones (aloesin, umbelliferone, and esculetin) (Fig. 3), cellulase, catalase, and superoxide dismutase [40,41].

4. Molecular targets of bioactive phytochemicals present in *Aloe vera* against cancer: pre-clinical studies

In the laboratory experiments (*in vitro/in vivo)*, different phytochemicals from *Aloe vera* have shown promising anticancer activities: anti-proliferation, cell cycle inhibition, induce apoptosis, anti-inflammation, upregulation of tumor suppressor genes, down-regulation of oncogenes, regulation of hormonal levels, growth factor regulation, and suppression of invasion and metastasis. We have discussed the detailed mechanisms of action of all the lead bioactive compounds of *Aloe vera* and compared side by side their efficacy to other standard anti-cancer drugs below and in Table 1. We have also depicted the mechanisms of action of the lead bioactive compounds of *Aloe vera* in Fig. 4.

4.1. Aloe-emodin

Aloe-emodin (1,8-dihydroxy-3-(hydroxymethyl)anthraquinone) (Fig. 1a), an anthraquinone bioactive compound found in the *Aloe vera* leaf. A recent study has reported that aloe-emodin promotes cell cycle arrest in S phase, generates ROS, induces DNA damage, and mitochondrial-dependent apoptosis in sensitive and resistance lymphoblastic leukemia cells [42]. In this study, it has been revealed that the efficacy of aloe-emodin against resistance lymphoblastic leukemia cells has shown notable efficacy as compared to standard drug doxorubicin. Aloe-emodin also promotes mitotic death and inhibits the cell cycle by interfering the G_2/M phase, thus activates the lysosome dependent apoptotic pathway in the cervical cancer cells, whereas standard drug doxorubicin induces apoptosis by elevating pro-apoptotic genes (A20, BCL6, TNF) [43–45]. Cytotoxicity study of aloe-emodin on non-cancerous human peripheral mononuclear cells (PBMCs) has revealed that aloe-emodin has no significant amount of toxic effect towards non-cancerous cells as compared to anticancer drug doxorubicin [46] though aloe-emodin possesses cytotoxicity against cancer cells [42]. Such results indicate selective toxicity of aloe-emodin towards cancer cells only. Chemotherapeutic drugs, such as doxorubicin, cis-platinol, and 5-fluorouracil have an anti-proliferative effect against Merkel cell carcinoma (MCC) [47]. It has been reported that combinational use of aloe-emodin with each of these anticancer drugs enhance the inhibitory action against MCC, especially when a low concentration of these drugs are used [47]. In an *in vitro* study, it has been observed that combinational use of aloe-emodin and radiation have suppressed the proliferation of human cervical cancer cells (HeLa) significantly as compared to

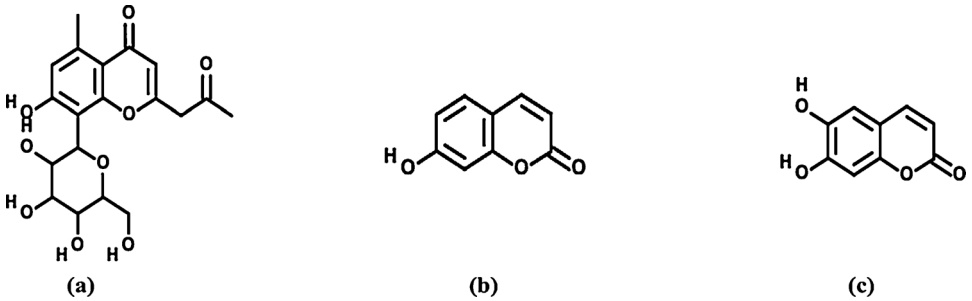

Fig. 3. Chemical structures of chromones: aloesin (a), umbelliferone (b), esculetin (c).

Table 1
Bioactive compounds of *Aloe vera* and their anticancer effects compared to other standard drugs.

Compounds from *Aloe vera* (PubChem CID)	Standard drugs (PubChem CID)	Cell lines	Type of human cell	IC_{50} of Aloe com-pound (μM)	IC_{50} of Standard drug (μM)	Mechanism of Action	Ref.
Aloe-emodin# (10207)	5- Fluoro-uracil* (3385)	HepG2	Hepatomacarcinoma	43.55	49.60	↑ Apoptosis by ↑ p53#, ↑ Bax#*, ↓ Bcl-2#*, ↑ Bad*,	[53] [54] [113]
		Hep3B		57.99	48.68		[114]
	Doxorubicin* (31703)	HeLa	Cervical cancer	66.40	11.65	↑ Multinucleate cells#, ↑ Cell cycle arrest in G_2/M phase#, ↑Apoptosis* by ↑BCL6*, ↑ TNF*, ↑ A20*	[43] [115] [45]
	Tamoxifen* (2733526)	MCF-7	Breast cancer	80	27	↓ Cell Growth by ↓ Ras#*, ↓ MEK1/2#*, ↓ ERK1/2#*, ↓ Er α#*, ↓ IGF-1R#*	[50] [52] [51]
		MCF-10A	Breast normal	–	38		[116]
	Doxorubicin* (31703)	CCRF- CEM	Acute lymphoblastic leukemia	9.872	0.0007	↑Apoptosis#*,↑ ROS#*, ↑ Cell cycle arrest in S#* and G_2/M* phase, ↓ Mitochondrial membrane potential#*,	[42]
		CEM/ ADR5000	Childhood T acute lymphoblastic leukemia	12.85	10.98		
Aloin# (313325)	Tamoxifen* (2733526)	MCF-7	Breast cancer	143.40	27	↓ Growth by Er α*, IGF-1R*, ↓ Topo IIα#, ↓ Cyclin B1#, ↑ p53#, ↑ Cell cycle arrest in G_2/M phase#	[116] [51] [67] [117] [118]
	Doxorubicin* (31703)	SKBR-3		358.51	0.072	↓ Topo IIα#, ↑ Caspase 3,7 and 9*, ↑ Procaspase 3*, ↑ PARP*	
	Doxorubicin* (31703)	A549	Non-small-cell lung carcinoma	150	3.10	↑ ROS#*, ↑ MAPK#*, ↑p53, ↑ Mitotic catastrophe#, ↑ Apoptosis#* by ↑ Bax#*, ↑ Bak#, ↑ Bad*, ↑ Cytochrome c*, ↑ Caspase-3 and 9#, ↑ Caspase-8 and 9* ↓ Autophagy# by ↓ LC3-II#,	[73] [119] [120] [121] [122]
		H1299		200	0.23		
	5- Fluoro-uracil* (3385)	SW-620	Colorectal cancer	200	227.40	↑ Apoptosis# by ↓ Bcl-xL#, ↓ c-Myc#, ↓ Angiogenesis# by ↓ VEGF#, ↑ Apoptosis* by ↑ Bax*, ↑ Cytochrome c*, ↓ Bcl-2*, ↑ Caspase 3,8,9*	[123] [124] [125] [126]
		HCT-116		240	5		
Chrysophanol# (10208)	Camptothecin* (24360)	MCF-7	Breast cancer	1.27	3.33	↑ Apoptosis# by ↓ Bcl-2#*, ↓ NF-κB#, ↑ Cell cycle arrest at (G_1-S)# (G_2/M)* point by ↑ Cyclin D1/E#, ↑p21#*, ↑ Cyclin A/B1*	[77] [78] [79]
	Doxorubicin* (31703)	A549	Non-small-cell lung carcinoma	50	3.10	↑ Cell death by ↑ ROS#*, ↑ Ca^{2+} #, ↓ ATP#, ↑ Cytochrome c#*	[127] [80] [122]
	Amphotericin B * (5280965)	J5	Hepatocellular carcinoma	120	18.65	↑ Cell death by ↑ ROS#*, ↑ LC3*, ↓ Mitochondria membrane potential#, ↓ ATP#, ↑ LDH#,	[127] [81] [128] [82]
	Finasteride* (57363)	–	Benign prostatic hyperplasia	–	–	↓ Tumor growth by ↓ 5α- reductase#*,	[84]
	Axitinib* (6450551)	Caki-2	Renal Cell Carcinoma	20	36	↑ Cell death by ↑ ROS#*	[83] [129]
Aloesaponarin I# (11098986)	Griseofulvin* (441140)	KB-3-1	Cervical cancer	16.0	19.00	–	[86]
Aloesaponarin II# (3085033)				0.98			
Aloesin# (160190)	Cisplatin* (84691)	SKOV3	Ovarian cancer	5	51.73	↓ Cell growth, ↑ Cell cycle arrest in S-G_2/M#, G_1-G_2/M* ↑ Apoptosis#* by ↑ Caspase-3#, ↑ Caspase-9#, ↑ PARP1, ↑ Bax#*, and ↓ Bcl-2#* ↓ Cell migration and invasion#	[92] [130]
Umbelliferone# (5281426)	Pingyangmycin* (84046)	KB	Oral carcinoma	200	347.08	Depolarization of mitochondria by ↑ ROS#, ↑ DNA damage#*, ↑ Cell cycle arrest in G_0/G_1#, G_2-M* phase	[101] [102]
	5- Fluoro-uracil* (3385)	HepG2	Hepatocellular carcinoma	5	49.60	↑ Apoptosis#*, ↑ Cell cycle arrest in S# phase, ↑ DNA fragmentation#*	[98] [99] [100] [54]

(*continued on next page*)

Table 1 (*continued*)

Compounds from *Aloe vera* (PubChem CID)	Standard drugs (PubChem CID)	Cell lines	Type of human cell	IC_{50} of Aloe com-pound (μM)	IC_{50} of Standard drug (μM)	Mechanism of Action	Ref.
Esculetin# (5281416)	Doxorubicin* (31703)	PANC-1	Pancreatic cancer	200	1.7	↑ Cell cycle arrest in G1#,* phase ↑ Apoptosis by ↑ Caspase-3#, 8#,* and 9#, ↑ Cytochrome c#, ↓ ROS#, ↓ p65-NF- κB by ↑ Nrf2# and ↓ KEAP1#, ↑ p53*, ↑ p21*, ↓ Bcl-2*	[108] [131] [132] [133]
	5- Fluoro-uracil* (3385)	MIA PaCa-2		100	4.63	↑ Cell cycle arrest in G1# phase ↑ Apoptosis by ↑ Caspase-3#, 8# and 9#, ↑ Cytochrome c#, ↓ ROS#, ↓ p65-NF- κB# by ↑ Nrf2# and ↓ KEAP1#, ↑ Bak*, ↓ Bcl-xL*, ↓ Bcl-2*, ↓ Mcl-1*	[108] [134]
	LY294002* (3973)	AsPC-1		100	40	↑ Cell cycle arrest in G1# phase ↑ Apoptosis by ↑ Caspase-3, 8 and 9#, ↑ Cytochrome c#, ↓ ROS, ↓ p65-NF- κB by ↑ Nrf2 and ↓ KEAP1 ↓ PI3K/Akt*, ↓ Bcl-2*, ↓ XIAP*,	[108] [135]
	Docetaxel* (148124)	SMMC-7721	Hepatocellular carcinoma	300	0.0005	↑ Apoptosis by ↓ c- Myc#, ↓ cyclin D1#, ↓ Wnt/β-catenin #, ↑ ROS*, ↓ GSH*, ↑ Cell cycle arrest in G_2/M phase	[107] [136]
	Etoposide* (36462)	HCT116	Colorectal cancer	32.9	1.6	↓ Cell growth and metastasis by ↓ c-Myc#, ↓ Cyclin D1#, ↓ Survivin#, ↑ E-cadherin#, ↓ Axin2#, ↑ p53*	[111] [137]
		SW480		32.8	1.1		
		LS174T		44.0	1.7		
		HCT15		37.1	2.2		

Note: # = lead bioactive compound of *Aloe vera*, * = standard drug.

aloe-emodin or radiation alone by inducing apoptosis, increasing cyclin B and γ-H2AX expression [48]. Other studies reveal that aloe-emodin increases cytotoxicity of tamoxifen by downregulating EGFR, Ras/ERK, c-Myc, ERα, MEK1/2, and PI3K/mTOR pathways which regulate cell survival and growth in breast cancer cells [49,50]. Aloe-emodin has exhibited cytotoxicity towards ER^+ breast cancer cells by inhibiting estrogen alpha receptor without any cytotoxic effect on normal breast cells, where tamoxifen has shown cytotoxicity on both normal and cancerous breast cells [51,52]. It shows selective cytotoxicity of aloe-emodin on breast cancer cells. Aloe-emodin has shown anti-proliferative activity against human hepatoma cell lines [53]. In that study, it has been reported that aloe-emodin suppresses cell growth and promotes apoptosis in both HepG2 and Hep3B cell lines. But the mechanisms of action are different, such as in HepG2 cell line aloe-emodin elevates the cell cycle arrest in G1 phase by upregulating p53 as well as p21 expression and above that aloe-emodin also increases the level of Fas/APO1 receptor and Bax expression, leading to induce apoptosis. On the other hand, in the p53 deficient Hep3B cell lines, aloe-emodin induces apoptosis by enhancing Bax expression. Similar kind of mechanism of action can be observed when hepatocarcinoma cells (HepG2 and Hep3B) were treated with standard drug 5-fluorouracil [54]. Aloe-emodin also suppresses tumor initiation, cell migration, and cell invasion in HER-2- positive breast cancer cells (*in vitro/ in vivo*) through the downregulation of YB-1 expression, integrin-linked kinase (ILK), and protein kinase B (Akt /mTOR) signaling pathway [55]. According to Chang et al., aloe-emodin inhibits the proliferation of esophageal cancer cell TE1 by suppressing AKT and ERK phosphorylation [56]. The nano-formulation of aloe-emodin has enhanced apoptosis and suppressed proliferation in the human lung squamous carcinoma by generating reactive oxygen species (ROS) [57]. Here, it has been reported that nano-formulation of aloe-emodin elevates cleavage of Caspase-3, PARP, Caspase-8, and Caspase-9. It also activates Mitogen-activated protein kinases (MAPKs) and inactivates PI3K/AKT. Photoactivated aloe-emodin has shown the inhibition of cell proliferation through blocking G1 phase, inducing apoptosis and autophagy in human oral mucosa carcinoma and human osteosarcoma cells [58,59]. Autophagy plays a dual role at the junction of cell death and survival in response to various therapeutic regimens [60–62]. However, the above studies reveal the pro-death role of autophagy in response to aloe-emodin. The effects are exerted due to the huge reactive oxygen species (ROS), produced by photoactivated aloe-emodin. It increases the expression of pro-apoptotic proteins, like Caspase-3, Bax, and p-JNK and suppresses the expression of anti-apoptotic protein Bcl-2. Similarly, it also enhances the expression of key autophagic proteins, like LC3-II and Beclin-1.

4.2. Aloin

Aloin (Fig. 1b) is one of the major anthraquinone compounds present in *Aloe vera* extract and gel. It is also known as barbaloin [63] and has been distinguished as the C-glycoside of aloe-emodin [25,63]. Aloin has chemo-preventive activity against chemically induced colon toxicity through increasing antioxidant level and exerting anti-inflammatory as well as anti-proliferative activities [64]. Here, it is important to mention that aloin possesses a good amount of antioxidant activity (*in vitro/in vivo*) [65]. It has also been observed that aloin possesses anti-proliferative activity against various cancer cell lines, but it does not produce any oxidative stress-induced cardiotoxicity as compared to anticancer drug doxorubicin [65–67]. In a study against cervical cancer cell line, aloin has shown a significant level of inhibition of cell proliferation, induction of apoptosis, S phase cell cycle arrest and besides that, the noticeable elevation of antioxidant enzyme MnSOD activity can be observed [66]. Anticancer drug doxorubicin has cytotoxic effects against cervical cancer cell line by regulating the notch signaling pathway, but doxorubicin has strong side effects like low white blood cell number and cardiac problems [68,65]. On the other

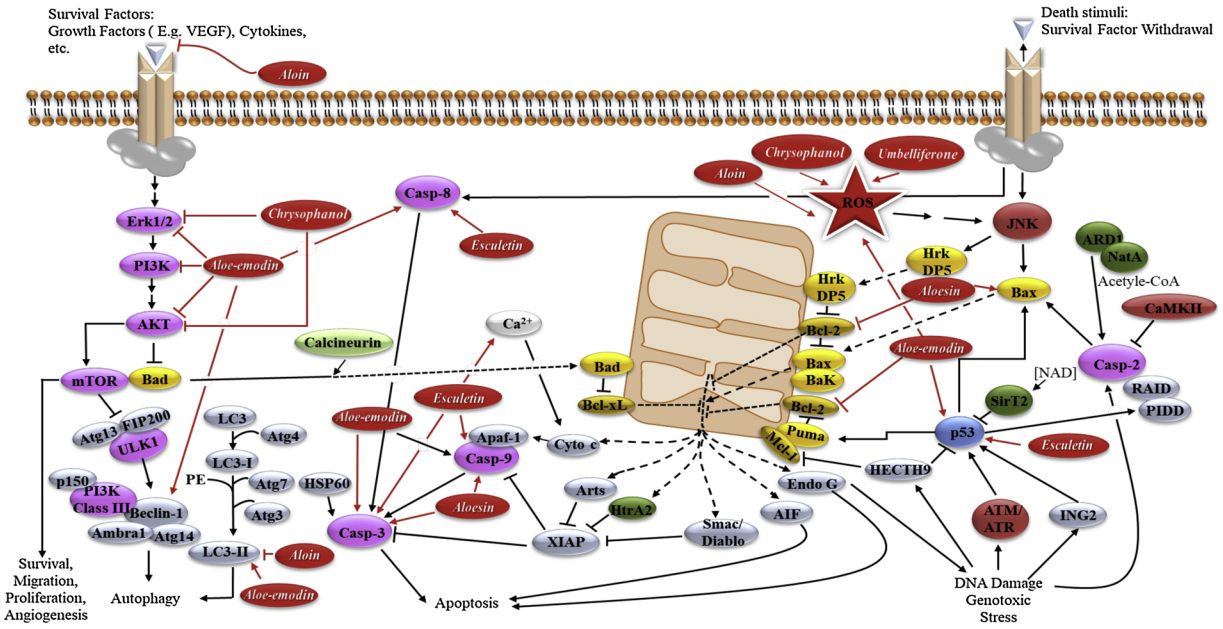

Fig. 4. Molecular targets of lead bioactive compounds of *Aloe vera* in cancer cell.

hand, aloin has not been reported to exhibit such kind of adverse effects [65]. It has been claimed that aloin has more potency as a pro-apoptotic compound than a 2 Gy fractional dose of ionizing radiation [66]. At high concentration, aloin suppresses cell mitosis via inducing apoptosis, downregulates topo II α, and cyclin B1 protein level in the breast cancer cells [67]. While on the contrary, breast cancer drug tamoxifen has been reported to cause endothelial dysfunctions by regulating NO-sGC-cGMP pathway, which leads vascular dysfunctions [69], but such type of side effects are not reported with aloin [65]. Loss of mitochondrial membrane potential has been observed after the treatment of aloin, indicating the induction of apoptosis by the mitochondrial-dependent pathway [27]. Combination of low dose cisplatin and aloin enhances the anti-proliferative activity of aloin [70]. Aloin can also suppress angiogenesis, migration, tube formation, and growth of tumor through inhibiting VEGF receptor-2 (VEGFR-2) and STAT3 activation in human umbilical vascular endothelial cells *in vitro* and as well as in xenografts *in vivo* mouse models without significant toxicity [71], whereas VEGFR inhibitors such as aflibercept, cabozantinib have been shown severe cardiotoxicity [72]. Activated STAT3 protein expression regulates anti-apoptotic (Bcl-xL), proliferative (c-Myc), and angiogenic (VEGF) proteins. These proteins are also downregulated by aloin treatment in human colorectal cancer cells [71]. It can also effectively suppress the growth of human non-small cell lung carcinoma (NSCLC) through inducing apoptosis, manipulating autophagy via altering LC3-II expression level and inducing giant multinucleated cells, leading to the mitotic catastrophe [73].

4.3. Chrysophanol

Chrysophanol (1,8-dihydroxy-3-methylanthraquinone) (Fig. 1c), also known as chrysophanic acid, belongs to the anthraquinone family. It has been reported that chrysophanol inhibits cell viability in colon cancer through anti-inflammatory activity by suppressing the NF-κB and caspase activation (*in vitro/ in vivo)* [74]. Chrysophanol also reduces cell viability by inducing apoptosis in human choriocarcinoma cells. It increases oxidative stress. Thus the elevating ROS generation further induces apoptosis in a mitochondrial-dependent pathway, though it has not exhibited any cytotoxic effect on non-cancerous cell line JAR [75]. It has shown a significant amount of growth inhibition against human choriocarcinoma cells compared to standard drug paclitaxel and cisplatin. Chrysophanol may also vitiate mitochondrial ATP synthesis in human liver cancer cells [76]. A recent study has shown that chrysophanol effectively induces cell death in breast cancer cell lines by regulating cell cycle progression and inducing apoptosis as compared to positive control camptothecin [77–79]. Chrysophanol induces necrosis in lung cancer cells as similar to the anticancer drug doxorubicin, through generating ROS and Ca^{2+} which lead to the release of cytochrome c from mitochondria due to the significant decrease of mitochondria membrane potential [80]. It induces necrosis in human liver cancer cells by increasing ROS production, losing mitochondrial membrane potential, reducing ATP levels, and increasing LDH activity in contrast amphotericin B induces necrosis in human liver cancer cells through elevating ROS and LC3-II [81,82]. Chrysophanol also induces necrosis in human renal cell carcinoma Cells (Caki-2) significantly as compared to anticancer drug axitinib by increasing intracellular ROS generation [83]. Chrysophanol is also reported to reduce testosterone-induced benign prostatic hyperplasia in rats effectively through down-regulating 5α- reductase and ERK phosphorylation as compared to positive control finasteride without any significant level of cytotoxicity on normal prostate epithelial cell-line RWPE-1 cells [84]. Gold nanoparticles of chrysophanol inhibit histone deacetylases (HDACs) and reduce cell proliferation as well as induce apoptosis through arresting the cell cycle in sub-G1 phase in human prostate cancer cells with minimal toxicity on normal human prostate cells and normal human liver cells [85]. It also regulates cell cycle-related proteins such as p27, CHK1, cyclin D1, CDK1, p-AMP-activated protein kinase (AMPK), and p-protein kinase B (AKT). Such kind of protein regulation helps to prevent the proliferation of human prostate cancer cells. Pharmacokinetics study suggests that application of chrysophanol gold nanoparticles increase bioavailability and efficacy of chrysophanol in mice model without any significant toxic effect on liver, renal, and lung [85].

4.4. Aloesaponarin I & II

Aloesaponarin I (Fig. 1e) and aloesaponarin II (Fig. 1f) are the two important anthraquinone compounds have been found in *Aloe vera*

[36]. Only a few investigative studies are there on the biological activity of aloesaponarin I & II. A recent study has reported that aloesaponarin I (IC_{50} = 16μM) and aloesaponarin II (IC_{50} = 0.98μM) have cytotoxic activity against human cervix carcinoma cell line [86]. Here, these two bioactive compounds of *Aloe vera* have effectively inhibited human cervix carcinoma cells as compared to control Griseofulvin. The cytotoxic effect of aloesaponarin II is sixteen times higher as compared to aloesaponarin I. Though these two compounds have almost similar chemical structure except an electron-withdrawing methyl ester group in aloesaponarin I, such kind of chemical difference may alter the cytotoxic activity of these two compounds [86].

4.5. Acemannan

Acemannan (Fig. 2b) is a major carbohydrate fraction, a polysaccharide present in *Aloe vera* leaf gel. It has various bioactivities, such as immunomodulatory and antitumor effects [87]. The antitumor activity of acemannan may be due to the pluripotent effector cells, such as macrophages. It induces macrophage cytokine production, nitric oxide (NO) release, surface molecular expression, and cell morphological alteration in mouse macrophage cell line [88]. The yielding of cytokine interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α) increases with acemannan in a dose-responds manner. The main objective of chemoprevention is to decrease the occurrence of human cancer by preventing the process of carcinogenesis. Acemannan has shown antigenotoxic and chemopreventive activities on benzo[*a*]-pryrene (B[a]P)-DNA adducts [89]. Acemannan has also shown to reduce the γ-radiation-induced oxidative damage by participating in free radical scavenging due to the presence of hydroxyl groups, and it possesses a stronger immunomodulatory effect on mice [90].

4.6. Aloesin

Aloesin (Fig. 3a) is a bioactive compound of *Aloe vera* plant [91]. *In vitro* and *in vivo* experiments suggest that aloesin inhibits the ovarian cancer cell growth [92]. It increases cell cycle arrest in S-G2/M phase by downregulating cyclin A, CDK2, and cyclin D1 proteins. It upregulates apoptosis through activating cleavage of caspase-3, caspase-9, PARP1 and elevates the level of pro-apoptotic protein Bax and downregulates anti-apoptotic protein Bcl-2. Aloesin also inhibits cell migration and invasion in the ovarian cancer cells without any significant toxicity on normal cells [93]. While on the contrary, anticancer drug cisplatin inhibits ovarian cancer cell growth by inducing apoptosis through DNA fragmentation, upregulating pro-apoptotic protein Bax, and down-regulating anti-apoptotic protein Bcl-2. It also elevates the cell cycle arrest in G1-G2/M phase with adverse side effects like hepatotoxicity, nephrotoxicity, cardiotoxicity, and gastrotoxicity [94,95].

4.7. Umbelliferone

Umbelliferone (7-hydroxycoumarin) (Fig. 3b) is a biologically active agent present in the *Aloe vera* plant [91]. It has shown anti-carcinogenic effects alone or in combination with 5-fluorouracil against 1,2-dimethylhydrazine-induced colon cancer [96]. Here umbelliferone reduces the side effects of 5-fluorouracil. It indicates that umbelliferone is a potential chemopreventive agent. It exhibits anticancer effect against laryngeal cancer cells by inhibiting cell viability and migration [97]. It has shown significant cytotoxic activity against hepatocellular carcinoma cells as compared to anticancer drug 5-fluorouracil through inducing DNA damage, apoptosis, and cell cycle arrest in S phase [98–100]. It has been reported that umbelliferone reduces cell viability and growth effectively as compared to standard drug pingyangmycin against oral carcinoma cell line via increasing intracellular ROS, oxidative stress-mediated depolarization of mitochondria, DNA damage, and cell cycle arrest in G_0/G_1 phase [101,102].

4.8. Esculetin

Esculetin (6,7- dihydroxy coumarin) (Fig. 3c) is a coumarin derived compound, found in *Aloe vera* plant [103]. It has a pyron and benzene ring conjugated structure. The toxic effect of esculetin due to the presence of electron and charge transport properties with minimum adverse side effects [104]. Esculetin has efficient bioavailability, and the half-life in plasma is 45 min [105]. It has been reported that esculetin inhibits the growth of murine Lewis lung cancer (LLC) (*in vitro and in vivo*) through suppressing c-myc, cyclin D1, and NF-κB [106]. It exhibits anti-proliferative effects on human hepatocellular carcinoma cells by downregulating the mRNA and protein expression of c-Myc, cyclin D1, and β-catenin as well as inhibiting Wnt/ β-catenin signaling pathway which controls cell growth, migration, and differentiation [107]. In a study, it has been found that esculetin inhibits the proliferation of pancreatic cancer cell lines through G_1 Phase cell cycle arrest and inducing mitochondrial-dependent apoptosis via activation of caspase-3, 8 and 9 [108]. It has also been observed that intracellular ROS and protein expression of p65-NF-κB are significantly decreased after 8–12 h of esculetin exposure in the pancreatic cancer cells. ROS mediated NF- κB is required for tumorigenesis, inflammation, cancer, cell survival, growth, and metastasis [109]. Esculetin binds with Nrf2 inhibitor KEAP1 and elevation of Nrf2 leads to inhibition of NF- κB pathway [108]. In breast cancer cell line (ZR-75-1), esculetin exhibits Ca^{2+}-mediated mitochondrial apoptotic pathway by releasing cytochrome c from mitochondria due to the reduction of membrane potential and activation of caspases-3, 9 [110]. Such activities also lead to an increase of cell cycle arrest in the G_2/M phase by manipulating the expressions of p53, p21, CDK1, and cyclin B1. Esculetin shows anti-proliferative and anti-invasive activities in colorectal cell lines by inhibiting Axin2 and stimulating E-cadherin, which lead to inhibition of the Wnt signaling pathway [111]. Esculetin shows very low potency against different cancer cell line as compared to available standard drugs (Table 1) but it exhibits protective effects against doxorubicin-induced cardiotoxicity in non-cancerous cells (H9c2) by suppressing ROS production and mitochondria DNA damage [112]. It suggests that esculectin may be used as an adjuvant therapy with doxorubicin to reduce side effects.

5. Clinical studies

Efficacy of *Aloe vera* treatment in oral sub-mucous fibrosis has been clinically studied [138]. Oral sub-mucous fibrosis is an oral cavity related potential malignant disorder, mainly occurs due to areca nut which is predominant in South Asia. Seventy-four patients (63 male and 11 female) of oral sub-mucous fibrosis have been randomly divided into 2 groups. One group has been treated with aloe juice and tropical *Aloe vera* (gel) for 3 months and another group has received an intralesional injection of hydrocortisone and hyaluronidase for 6 weeks with antioxidant supplements for 3 months. It has been observed that *Aloe vera* showed significant clinical response compared to the combination of intralesional injections of hydrocortisone, hyaluronidase, and antioxidant supplements. No adverse effects of *Aloe vera* have been reported in this study [138]. In another study, 64 patients with acute myeloid leukemia and acute lymphocytic leukemia, who have been receiving chemotherapy, randomly divided into control and an intervention group [139]. The purpose of the study was to observe the preventive action of *Aloe vera* against stomatitis, an inflammatory response due to chemo and radiation therapy in the oral cavity which can be lead to swelling, redness, and pain. Intervention group patients have been

asked to wash their mouths with 5 ml of *Aloe vera* solution for two minutes three times a day for 14 days. On the other hand, control group patients have used only the ordinary mouth wash recommended in the hematologic centres. It has been observed that *Aloe vera* mouth wash has significantly suppressed the intensity of stomatitis and its inflammation in the intervention group as compared to the control group. A similar type of clinical trial has been conducted in 60 cancer patients (mostly breast, pelvic, and head cancer) who have been undergoing through prescribed radiotherapy (minimum dose of 40 Gy) to observe the preventive effect of *Aloe vera* lotion on radiation-induced dermatitis [140]. The irradiated area has been divided into two symmetrical halves, and patients have been asked to use *Aloe vera* lotion on the one half of the irradiated area and no medication for the other half. It has been reported that the preventive use of *Aloe vera* reduces the impact of radiation-induced dermatitis. Such clinical trials suggest that *Aloe vera* may contain some anticancer bioactive molecules and it can be used to prevent the side effects of conventional chemo and radiotherapy.

6. Adverse effects of *Aloe vera*

Aloe vera has long been regarded as a safe for oral and topical use [141], but in many cases, the contradiction has been found. Several research studies have reported that *Aloe vera* possesses some compounds which are responsible for the cytotoxicity, genotoxicity, and carcinogenicity [16,142]. *Aloe vera* extract can be obtained majorly from three parts of the plant: the whole leaf extract, inner gel, and latex [143]. The toxic effects of *Aloe vera* are mostly due to the anthraquinones and phenolics compounds (mainly aloin and its derivatives) present in *Aloe vera* latex [144]. The National Toxicology Program (NTP) has reported that *Aloe vera* whole leaf extract shows potential carcinogenic effects: F344/N rats were treated with 1% (non-decolourized) whole leaf extract in drinking water for 2 years, and the treated rats developed intestinal adenomas or carcinomas; while the same treatment did not show any neoplasms in B6C3F1 mice [145]. This study was highly criticized, especially by International Aloe Science Council (IASC), as the aloin content in treated aloe samples were approximately 6500 ppm, which was 650 times higher than the industry standard [146]. Moreover, no negative effects were found on F344 rats when treated with charcoal decolourized whole leaf extract for 13 weeks even when the rats were administrated with 5 to 6 times higher dose of *Aloe* extract which is suggested for human [147]. Due to such contradictory results, a greater extent of study is required to investigate the possible adverse effects of *Aloe vera* and its bioactive compounds to ensure the safety and efficacy of its application.

7. Summary and future perspectives

Aloe vera has a long history of ethnomedicinal use. In the last few decades, pre-clinical and clinical studies have revealed that *Aloe vera* possesses anticancer as well as chemopreventive properties due to the presence of some lead bioactive compounds such as anthraquinones, polysaccharides, and chromones. It has been observed that these bioactive compounds inhibit the proliferation, migration, and invasion of cancer cell by interfering various cell signaling pathways. As these promising bioactive agents are in their early stages of research and a long way to go to be approved for cancer therapy, thus further preclinical and clinical investigations are necessary to decipher the in detailed molecular mechanisms of these lead bioactive compounds. Also, the pharmacokinetics and pharmacodynamics properties of these bioactive compounds should be explored properly to determine the bioavailability and the safety profile. Moreover, there is a huge possibility to develop the lead bioactive molecules of *Aloe vera* as the anticancer drugs, but before that, it must go through proper scientific screening and validation. In our literature review, we have found that standard anticancer drugs such as tamoxifen, doxorubicin, cisplatin, and others possess many severe toxic effects on non-cancerous cells, where phytochemicals from *Aloe vera* have not shown any significant level of cytotoxicity on non-cancerous cells [51,118]. Therefore, these lead bioactive molecules can be modulated for cancer cell-targeted drug delivery. To this end, the virtual molecular docking and dynamics simulation study may be fruitful to predict affinity and stability between the lead bioactive compounds of *Aloe vera* and the targeted receptor proteins involved in cancer development. In such a way, off targeted delivery of lead molecules may be avoided. Computational chemistry can be used to predict the toxicity, bioavailability, drug-likeness, and synthetic accessibility of these lead candidates by evaluating their physicochemical properties [148]. As *Aloe vera* plant contains a large number of bioactive compounds [15,37], it may possible that novel molecules from *Aloe vera* can be isolated and purified by utilizing chromatography and spectroscopy techniques, such as thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC), UV/visible detection, nuclear magnetic resonance (NMR). Later on, these novel molecules can be investigated for anticancer properties by high throughput screening exploring *in silico*, *in vitro,* and *in vivo* techniques. Utilizing such screening techniques, cancer-treating and preventive agents may be developed from an ethno-plant like *Aloe vera.*

Declaration of Competing Interest

The authors declare that they do not have any conflict of interest.

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