Biomedicine & Pharmacotherapy 153 (2022) 113421

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Can aloin develop to medicines or healthcare products?

Yu Yang [a], Jiao-jiao Wu [a], Jia Xia [a], Yan Wan [a], Jin-Feng Xu [a], Li Zhang [a], Dong Liu [a], Lu Chen [a], Fei Tang [a], Hui Ao [a,b,*], Cheng Peng [a,**]

[a] Key Laboratory of Southwestern Chinese Medicine Resources, Chengdu University of Traditional Chinese Medicine, Chengdu, China
[b] Innovative Institute of Chinese Medicine and Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, China

ARTICLE INFO

Keywords:
Aloin
Pharmacological effects
Medicines and healthcare products

ABSTRACT

In folk medicine, Aloe, a genus of Aloaceae, is constantly developed into laxative drugs or products and skin remedies with tremendous popularity worldwide. However, almost all products of Aloe are in roughly processed form. Therefore, developing related products of the active ingredients derived from Aloe is of great medical value. Aloin is a quality standard compound based on the Chinese Pharmacopoeia (CHP). It has a wide range of pharmacological activities, including anti-tumor, anti-inflammatory, anti-osteoporotic, organ-protective, anti-viral, anti-microbial, anti-parasitic, and laxative potentials. Moreover, it regulates blood lipids and glucose and improves neuropathic pain effects, depicting potential to be transformed into promising medicines and healthcare products. In addition to the functional cosmetics and health products of Aloe, the availability, pharmacological activities, pharmacokinetics, formulation studies, and toxicity of aloin were summarized after investigating the literature from PubMed, Google, and other databases. Moreover, significant attention had been paid to the development of aloin-derived medicines and healthcare products. Thus, the present review clarified the possibility of aloin as medicines and healthcare products to develop and utilize Aloe resources.

Abbreviations: 8-OH-dG, oxidative DNA damage marker- 8-hydroxy-2′-deoxyguanosine; AKT, protein kinase B; ALT, alanine aminotransferase; AMPK, AMP-activated protein kinase; ARE, antioxidant response element; AST, aspartate aminotransferase; ATF4, transcription factors activation 4; BALF, bronchoalveolar lavage fluid; Bcl-2, B-cell lymphoma 2; BMP-2, bone morphogenetic protein 2; BUN, blood urea nitrogen; CAT, catalase; CCI, chronic constriction injury; CDAAH, choline-deficient, L-amino acid defined, high-fat; CHOP, C/EBP-homologous protein; CHP, Chinese Pharmacopoeia; CLP, cecum ligation and puncture; c-Myc, cellular-myelocytomatosis viral oncogene; CNPY2, protein canopy homolog 2; COX-2, cyclooxygenase-2; CREB, cAMP response element binding protein; DAI, disease activity index; D-gal, D-galactose; DN, diabetic nephropathy; DSS, dextran sulfate sodium salt; DUB, deubiquitination; EACC, ehrlich as cite carcinoma cell; ERK, extracellular signal-regulated kinase; ERS, endoplasmic reticulum stress; GDM, gestational diabetes mellitus; GFAP, glial fibrillary acidic protein; GSH, glutathione; GSH-Px, glutathione peroxidase; H1N1, oseltamivir-resistant influenza A pdm09; HBV, hepatitis B virus; HBVpol, polymerase/reverse- transcriptase; HMGB1, High mobility group box 1; HO-1, heme oxygenase 1; HUVECs, human umbilical vein endothelial cells; I/R, ischemia/reperfusion; ICAM-1, intercellular adhesion molecule-1; IL-1β, interleukin-1β; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; JAK, janus kinase; JNK, c-Jun N-terminal kinase; LbL, Layer-by-layer membrane; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MI/R, myocardial ischemia/reperfusion; MIC, minimum inhibitory concentration; miR-21, microRNA 21; MMP, matrix metalloproteinase; MPO, myeloperoxidase; MSK1, mitogen and stress-activated protein kinase 1; mTOR, mammalian target of rapamycin; MyD88, myeloid differentiation factor 88; NA, neuraminidase; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor κ-light-chain-enhancer of activated B; NLRP3, NOD-like receptor family pyrin domain containing 3; NO, nitric oxide; NOX, nitrogen oxide; Nrf2, nuclear factor E2-related factor 2; NSCLC, non-small cell lung cancer; PARP, poly-ADP-ribose polymerases; PBS, phosphate solubilizing bacteria; PCNA, proliferating cell nuclear antigen; PEG-2, prostaglandin E2; PERK, PKR endoplasmic reticulum kinase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K, phosphatidylinositol 3-kinase; PLGANPs, poly lacticco-glycolic acid nanoparticles; PLpro, papain like proteases; PolyP, polyphosphate; RANKL, nuclear factor κ B ligand; ROS, reactive oxygen species; Runx2, runt-related transcription factor 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SIRT1, sirtuin 1; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; SW620 CRC, human SW620 colorectal cancer; TAA, thioacetamide; TBARS, thio-barbituric acid-reactive substances; TBI, traumatic brain injury; TCP, tricalcium phosphate; TNF-α, tumor necrosis factor-α; TopoIIα, topoisomerase II- alpha; TRAF6, TNF receptor associated factor 6; TRAP, tartrate resistant acid phosphatase; TRL4, toll-like receptor 4; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

* Corresponding author at: Key Laboratory of Southwestern Chinese Medicine Resources, Chengdu University of Traditional Chinese Medicine, Chengdu, China.
** Corresponding author.
E-mail addresses: 2020ks252@stu.cdutcm.edu.cn (Y. Yang), 2020KS265@stu.cdutcm.edu.cn (J.-j. Wu), 2020KS257@stu.cdutcm.edu.cn (J. Xia), 15592038985@163.com (Y. Wan), xu-jinfeng@126.com (J.-F. Xu), zhangli2@stu.cdutcm.edu.cn (L. Zhang), liudong@stu.cdutcm.edu.cn (D. Liu), chenlu@cdutcm.edu.cn (L. Chen), tangfei0227@163.com (F. Tang), aohui2005@126.com (H. Ao), pengcheng@cdutcm.edu.cn (C. Peng).

https://doi.org/10.1016/j.biopha.2022.113421
Received 10 June 2022; Received in revised form 13 July 2022; Accepted 13 July 2022
Available online 6 August 2022

1. Introduction

Aloe, a genus of Aloaceae, is abundant and widely distributed. Aloe is a laxative and skin remedy in folk medicine [1]. Due to its extensive pharmacological effects, Aloe has newly developed into appreciable products such as laxative capsules [2] and whitening creams [3]. In 2018, the global market for Aloe was between $600 million and $1.6 billion. It is expected to grow at a 7.6–8.5% compound annual growth rate [4]. However, most Aloe products are in the roughly processed form of Aloe or Aloe gel, and only a few pharmacological activities are utilized for product development. Therefore, developing related products of the active ingredients derived from Aloe is of great medical value (Fig. 1). However, to the best of our knowledge, no such products exist in the market, hindering their development and utilization.

According to the CHP, aloin, also called barbaloin, is a quality standard compound, making it an active compound of Aloe. This compound primarily exists in Aloe latex, a yellow bitter-tasting component of Aloe leaf [5,6]. It is composed of two diastereoisomers, aloin A and B (Fig. 2). Nowadays, Aloin has anti-tumor, anti-inflammatory, anti-osteoporotic, organ-protective, antiviral, antimicrobial, and anti-parasitic activities along with the regulation of blood lipids and glucose effects [7]. These indicate that aloin has remarkable medical and healthcare benefits and the potential to develop into promising healthcare products.

In this paper, morphology, resources, pharmacological activities, functional cosmetics, and health products of Aloe, the availability, the pharmacological activity, pharmacokinetics, formulation studies, and toxicity of aloin were summarized from PubMed, Google, and other databases. Thus, we aimed to clarify the possibility of aloin as a healthcare product and provide a guideline to develop and utilize Aloe resources fully.

2. A brief introduction of Aloe

Aloe, a family of Aloaceae, is a perennial succulent medicinal plant and lives mainly in arid climates, extensively scattered in Africa, India, and other arid regions [8]. Most species of Aloe possess large, spear-shaped leaves having serrated edges and extend from a few centimeters to 2–3 m or more in height. More than 360 species of Aloe have been identified to date, possessing a longstanding history of medicinal use with health benefits.

In basic pharmacology, Aloe has exhibited a broad spectrum of biological effects such as hepatoprotection, skin protection, metabolic regulation, blood glucose reduction, wound healing promotion, and anti-tumor activity [9–12]. For example, Aloe has been registered in China as one of the 10 most commonly treated herbs for constipation [13]. Moreover, during the ancient times of the Greeks, Romans, and Babylonians, Aloe was applied as a skin ointment [14]. In addition, the extract of Aloe has been added to shaving creams and lotions in the United States to promote wound healing [15]. Moreover, Aloe products have appeared in daily lives, including Colon Cleanse® capsules, developed by By-Health®, and 92% Aloe vera Soothing Gel from Natural Republic® [16], "Golden Aloe Sunscreen SPF 20" with a sunscreen effect [17], "Yisu Whitening Aloe vera Gel" with a whitening effect [3], and "Yuan Sheng Tang Brand Aloe vera Soft Capsules" with a laxative effect [18]. Moreover, several well-known prescriptions of traditional Chinese patents appeared, such as " Geng Yi tablets " prepared from Aloe and cinnabar, having a laxative effect on the bowels [19].

Therefore, Aloe possesses a wide range of pharmacological effects and is explored for various products, including the daily chemicals with whitening, sunscreen effects, medicines, and healthcare products depicting bowel-moistening and laxative effects. It would be interesting to observe if more active ingredients from Aloe, including aloin, could be used in product development.

3. Availability of aloin

Aloin is considered one of the main bioactive compounds of Aloe. It is mainly found in Aloe leaves, and isomers of aloin are also present within the leaves. The content of aloin varies among species (e.g., *Aloe arborescens*, *Aloe barbadensis*). In a survey of 380 Aloe species, leaf exudates of 36 species of Aloe possessed aloin A and B anthrone isomers [20].

In addition, aloin contents in Aloe plants varied with the sample, light, soil, and other conditions. For instance, Coran et al. observed that the contents of aloin were different in the dried extracts of *Aloe barbadensis*, *Aloe ferox* (A), and *Aloe ferox* (B) [21]. Likewise, Machado et al. demonstrated the content of aloin in fresh and dry latex of *A. barbadensis* plant using high-performance liquid chromatography with a diode array detector (HPLC-DAD). The results revealed that the average aloin content in the fresh latex was 199.76 ± 0.74 mg/g, much higher than that in the dry latex. Furthermore, aloin content in different sections of leaves from *A. barbadensis* was measured, and the higher contents of 7.66 and 5.12 μg/g were in the upper leaf and branch of Aloe, respectively [22]. Moreover, after UV-A treatment, the aloin content in latex from initial levels was within 220 ± 22–800 mg/100 g [23]. However, Paez et al. observed that aloin content did not differ between sun and shade plants indicating that the aloin content was not elevated by light enhancement [24]. Moreover, Gupta et al. demonstrated that aloin

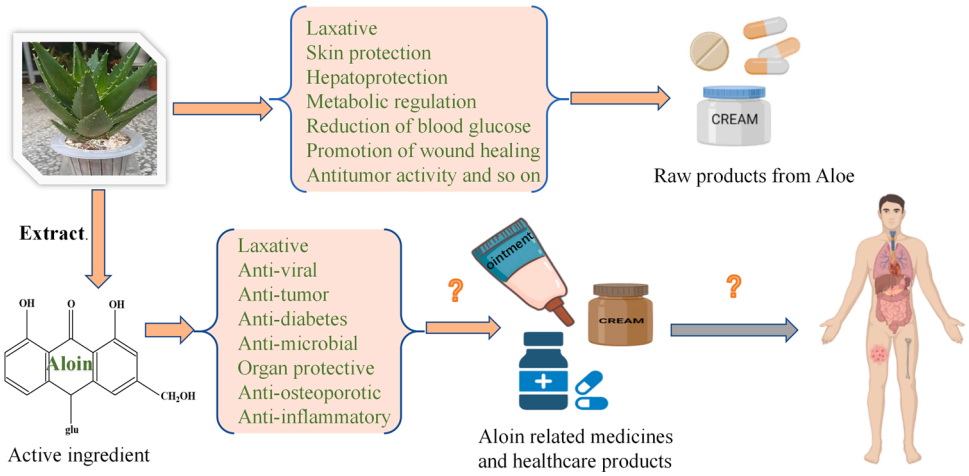

Fig. 1. Speculation on the possible development of aloin as a medicine and healthcare product for the prevention and treatment of diseases. Aloe related products have been developed, but most of its products are in the raw processed form of Aloe or Aloe gel and only a few pharmacological activities are utilized for product development. Therefore, it is of great medical value to develop related products of the active ingredients (aloin) derived from Aloe.

content was higher in soil containing tricalcium phosphate (TCP) than in soil without TCP. Furthermore, the addition of four phosphate solubilizing bacteria (PBS) such as *P. synxantha, S. marcescens, B. gladioli*, and *E. hormaechei*, and a PBS consortium to the amended TCP soil elevated the aloin content by 294%, 276%, 119%, 108%, and 673%, respectively [25].

4. Pharmacology of aloin

Many studies have confirmed that aloin has various pharmacological activities, including anti-tumor, anti-inflammatory, anti-osteoporotic, organ-protective, antiviral, antimicrobial and antiparasitic, and laxative activities, blood lipids and glucose regulation, and neuropathic pain improvement.

4.1. Anticancer activity

Aloin has inhibitory effects on various tumors in vivo or in vitro (Fig. 3, Table 1). The underlying mechanism could be attributed to its antiproliferative, pro-apoptotic, and pro-autophagic activities.

4.1.1. Inhibiting proliferation

Aloin exhibits antiproliferative potential by reducing the growth of non-small cell lung cancer (NSCLC), human SW620 colorectal cancer (SW620 CRC), Ehrlich ascites carcinoma cell (EACC), HOS and HepG2 xenograft nude mice [26–30]. Moreover, inhibiting the cell cycle development among cancer cells is an effective way to block cancer progression. Aloin induces cell arrest and regulates the expressions of cell cycle proteins in various cancer cells, including lung, liver, gastric cancer cells, and so on, thereby exerting antiproliferative effects. This agent-induced cell cycle arrest at the G2/M phase in A549 cells [26] and the S phase in HeLaS3 cells [31]. Furthermore, aloin treatment in breast and ovarian tumor cells line ($T_{47}D$) failed to alter DNA ploidy. A dose-dependent increase in the percentages of S phase fraction maintained higher ploidy levels, indicating that cancer cells exposed to aloin could undergo a full DNA replication through a difficult M phase [32]. Moreover, after aloin treatment, the expressions of Ki67 and proliferating cell nuclear antigen (PCNA) were downregulated in HepG2, Bel-7402, and KESY70 cells [30,33]. In contrast, cyclin D1 rather than cyclin E1 were reduced in HGC-27 and BGC-823 cells [34]. Moreover, aloin reversed the enhancement of lactate-mediated proliferation markers (cyclin D1, cyclin E1, and PCNA) in lactate-induced BGC-823 gastric cancer cells [35]. Furthermore, the cellular-myelocytomatosis viral oncogene (c-Myc) gene expression is related to the development and progression of various tumors [36]. Pan et al. observed that aloin down-regulated c-Myc expression in colon cancer SW620 cells [27]. In addition, topoisomerase II- alpha (TopoIIα), an essential eukaryotic DNA replication enzyme, is produced primarily in late S and during the G2M phase of the cell cycle and plays a critical role in cell cycle progression [37,38]. Esmat et al. revealed that aloin decreased the percentage of cells at the G1 phase and, in contrast, increased the percentage of cells cycling in the S and G2M phases of MCF-7 (without erbB-2-topoIIα co-amplification) and SKBR-3 (with erbB-2-topoIIα co-amplification) cells. This efficiency was due to the inhibition of topoIIα protein expression and downregulation of the cyclin B1 protein expression [39].

4.1.2. Induction of apoptosis and autophagy

The mechanisms of two programmed cell death pathways, including autophagy and apoptosis, are the two forms of cancer cell elimination, including apoptosis. There are numerous reports on the pro-apoptosis effect of aloin in various cancers. Aloin could induce apoptosis by increasing the activities of caspase-3 and − 9 in KESY70, HepG2, Bel-7402, and NSCLC cells [26,30,33]. Similarly, aloin induced apoptosis in MKN-28 and HGC-27 and MNNG/HOS cells by elevating the cleavage of poly-ADP-ribose polymerases (PARP) and reducing the pro-caspase expression levels [29,40]. Similarly, aloin induced apoptosis in the p53-proficient A549 cells by downregulating the mitochondrial membrane potential. Moreover, it enhances cytosolic Ca^{2+} level, activates B-cell lymphoma 2 (Bcl-2) homologous antagonist killer and Bcl-2 X-associated protein, and elevates p53 phosphorylation, depicting that aloin induced apoptosis through the intrinsic pathway linking with p53 phosphorylation [41]. Furthermore, cell viability, signal transducer expression and activator of transcription 3 (STAT3) protein and Bcl-xL were inhibited in SW620 cells after exposure to aloin [27]. In addition, the pro-apoptotic activities of aloin were attributed to its antioxidant power. Nićiforović et al. observed that aloin inhibited cell growth and induced cell apoptosis without impacting the catalase (CAT) activity and the nuclear factor κ-light-chain-enhancer of activated B (NF-κB) expression in HeLaS3 cells. Meanwhile, the activities of CuZnSOD and inducible nitric oxide synthase (iNOS) were decreased after aloin treatment, and that of MnSOD was enhanced. Moreover, the activity of purified CuZnSOD from bovine erythrocytes was inhibited through aloin [31].

Several molecular pathways were responsible for the anticancer properties of aloin, especially its pro-apoptotic activities. High mobility group box 1 (HMGB1) is a highly conserved nuclear DNA binding protein significantly associated with cell survival, proliferation, and metastasis in various cancers. It is also an early biological target of malignant tumors [42,43]. Li et al. demonstrated that aloin stimulated apoptosis in human melanoma A375 cells by activating the HMGB1toll-like receptor 4 (TRL4)-extracellular signal-regulated kinase (ERK) signaling pathway. Similarly, aloin inhibited HMGB1 release, reduced Bcl-2 expression, elevated cleavage-PARP, cleaved-caspase-3 expression, and suppressed HMGB1-related receptor expression (TLR4 and ERK phosphorylation levels) [44]. Analogously, rhHMGB1 revitalized the protein kinase B (AKT)-mammalian target of rapamycin (mTOR)-P70S6K and ERK-P90RSK-cAMP response element-binding protein (CREB) signaling pathways. Aloin restrained these in HGC-27cells, associated with HMGB1 expression inhibition and release and suppression of AKT, mTOR, and ERK activation by aloin [45].

Drugs targeting the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR signaling pathway can induce apoptosis and autophagy within cancer cells [46]. Previous studies have demonstrated that aloin inhibited the PI3K/mTOR/AKT signaling pathway, representing a

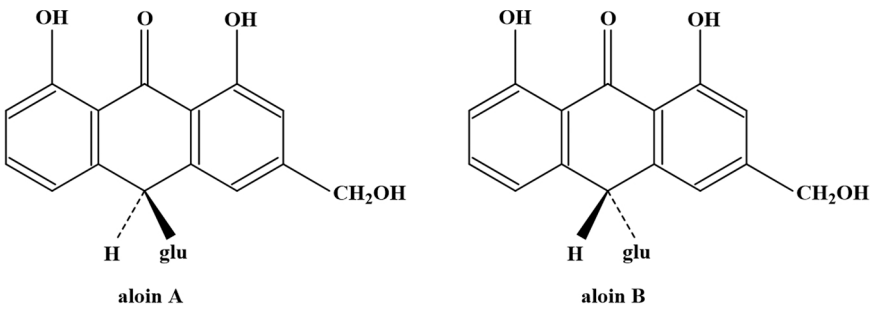

Fig. 2. Chemical structures of aloin A and B.

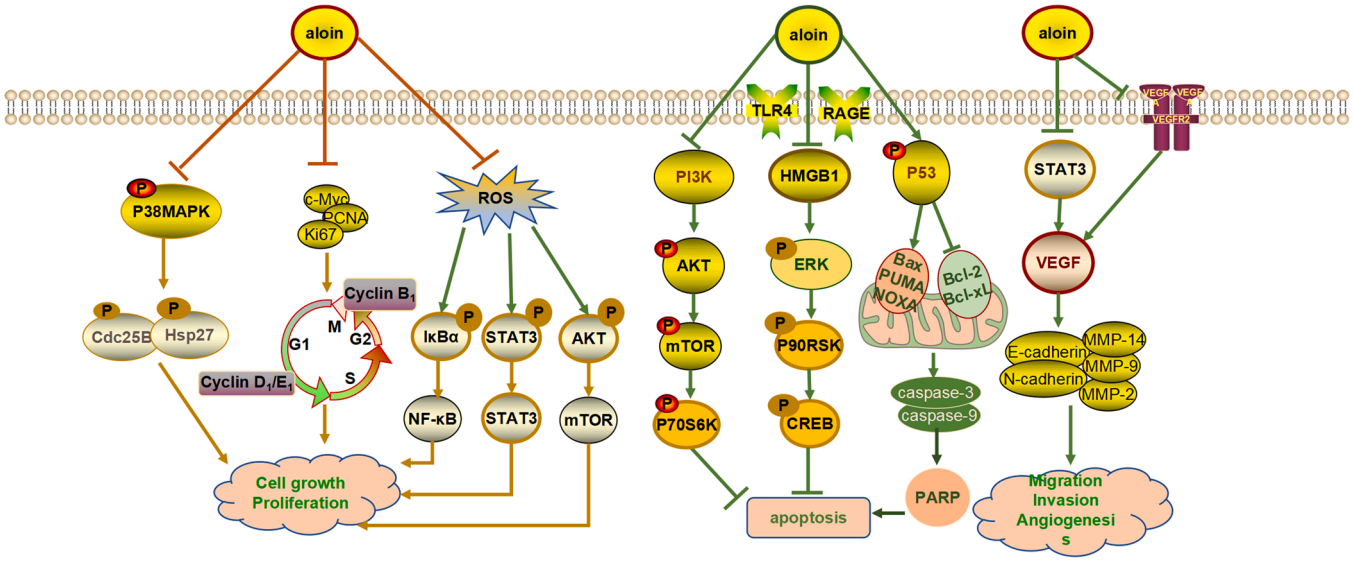

Fig. 3. Schematic diagram of the anticancer mechanism of aloin.

Table 1
The anti-tumor effects of aloin reported in previous studies.

Cancer type	Cell lines	Animal model	Effect	Pathway	References
Non-small cell lung cancer	A549 cell	NSCLC xenograft	↓Ki-67, PCNA, cyclin A, MMP-2/− 9/− 14, VEGF, p-p38MAPK, p-Cdc25B, p-Hsp27 ↑caspase-3/− 8/− 9	p38MAPK/Cdc25B/Hsp27 pathway	[26]
Colorectal cancer	HUVECs	SW620 CRC xenograft	↓tumor volume, CD31-positive vessels, c-Myc, cell viability, p-STAT3, Bcl-xL, VEGF1	–	[27]
Ehrlich ascites carcinoma	–	EACC xenograft	↓LDH, SOD, GST	–	[28]
Cervical carcinoma	HeLaS3 cells	–	↓cell viability, CuZnSOD, iNOS ↑S and G0/G percentage, MnSOD	–	[31]
Breast and ovarian cancer	$T_{47}D$	–	↑the percentages of S phase fraction	–	[32]
Breast cancer	MCF-7, SKBR-3 cell	–	↓cell growth, topoIIα, cyclin B1	–	[39]
Hepatocellular carcinoma	HepG2, Bel-7402 cells	HepG2 xenograft	↓tumor volume, Ki67, PCNA, caspase-3/− 9, Beclin-1, LC3II, ATG8, MMP, VEGF, p-PI3K, p-AKT, p- mTOR	–	[30]
Esophageal cancer	KESY70 cells	–	↓Ki67, PCNA, caspase-3/− 9, MMP, VEGF	–	[33]
Gastric cancer	BGC-823, HGC-27 cells	–	↓cyclin D1, MMP-2/− 9, N-cadherin, p-Src, p-STAT3, p-IκBα, ROS, p22Phox, p47phox ↑E-cadherin	AKT/mTOR, STAT3, and NF-κB pathways	[34]
Gastric cancer	BGC-823 cell	–	↓HMGB1, cyclin D1, cyclin E1, PCNA, MMP-2/− 9, N-cadherin ↑E-cadherin	–	[35]
Gastric cancer	MKN-28, HGC-27 cells	–	↓pro-caspase, p-ERK ↑RARP, p-JNK, p-P38	MAPKs pathway	[40]
Gastric cancer	HGC-27cell	–	↓pro-caspases3, HMGB1, RAGE, p-AKT, p-mTOR,p-ERK, p-P70S6K, p-P90RSK, p-CREB	AKT-mTOR-P70S6K, ERK-P90RSK-CREB pathways	[45]
Melanoma	A357 cell	–	↓Bcl-2, HMGB1, TLR4, p-ERK ↑caspase-3/− 9, PARA	HMGB1-TRL4-ERK pathway	[44]
Lung cancer	A549 cell	–	↑BAK, Bax, PUMA, NOXA, caspase-3/− 9, Ca^{2+}, Bcl-2, p-p53, p-c-jun, p-p38, ROS	–	[41]

significant decrease of PI3K, AKT, and mTOR and the expressions of pro-autophagic proteins including Beclin-1, LC3II, and ATG8 in HepG2 and Bel-7402 cells [30]. Furthermore, He et al. revealed that aloin induced cell autophagy-related apoptosis in osteosarcoma by elevating the ATG5 and Beclin-1 levels, the LC3BII/LC3BI ratio, and autophagosome and autophagic lysosome formation in HOS and MG-63 cells. Thus, aloin depicted this effect by downregulating PI3Kα and elevating the mTOR and AKT phosphorylated levels, thereby inhibiting the PI3K/AKT/mTOR pathway [29].

In addition, aloin regulates mitogen-activated protein kinase (MAPK)-related pathways for inducing apoptosis. A finding demonstrated that aloin downregulated the expression of phosphorylated ERK within human gastric cancer cells and elevated the expression of phosphorylated the c-Jun N-terminal kinase (JNK) and p38 in MKN-28 and HGC-27 cells, thereby promoting apoptosis [40].

4.1.3. Suppression of migration, invasion, and angiogenesis of cancer cells

Tumor metastasis is a sophisticated process that includes detachment, migration, and invasion. Regulating tumor cell metastasis is vital in managing cancer disease, particularly in early detected cancers [47]. Matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) overexpression are associated with pro-oncogenic events like neo-angiogenesis and metastasis of tumor cell proliferation. In addition, vascular endothelial growth factor (VEGF) plays an essential role in tumor angiogenesis [48]. For example, aloin down-regulated the expressions of MMP and VEGF in KESY70, HepG2, and Bel-7402 cells [30,

33]. Similarly, in BGC-823 cells, aloin reversed the lactate-induced MMP-2, MMP-9, E-cadherin, and N-cadherin expression to exert an anti-invasive effect [35]. Furthermore, aloin inhibited the expression levels of proteins related to tumor metastasis (MMP-2, MMP-9, MMP-14, and VEGF) and reduced the expression levels of p38 downstream factors p-Cdc25B and p-Hsp27 within NSCLC cells. Thus, aloin exerted an anti-invasive effect by inactivating the p38MAPK/Cdc25B/Hsp27 pathway. Like the in vitro analysis, aloin inhibited tumor angiogenesis within the xenograft mouse model of NSCLC [26]. Moreover, aloin treatment downregulated VEGF receptor 2 and STAT3 phosphorylation expressions to inhibit the migration of human umbilical vein endothelial cells (HUVECs) and tube formation in vitro [27].

4.2. Anti-inflammatory activity

The inflammatory response occurs in multiple organism injury processes and engages a range of cellular signaling pathways where many immune cells and cytokines are released (Table 2). Notably, aloin exhibited anti-inflammatory activities in various inflammatory cell models, and the underlying mechanisms have been explained (Fig. 4).

Inhibiting NF-κB related pathways were involved with the anti-inflammatory activity of aloin. Luo et al. demonstrated that aloin inhibited lipopolysaccharide (LPS)-induced elevation of the tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) in RAW264.7 cells through a dose-dependent manner. It also resisted LPS-induced nitric oxide (NO) production by down-regulating the expression of iNOS without any effect on cyclooxygenase-2 (COX-2) expression. Additionally, aloin attenuated p38, mitogen, stress-activated protein kinase 1 (MSK1)-induced phosphorylation, and p300-stimulated acetylation. Consequently, it prevented p65 post-translational modifications, resulting in the latter ameliorating p65 nuclear translocation and cell apoptosis [49,50]. In addition, Jiang et al. revealed that aloin reduced the expression of proinflammatory factors and the phosphorylation levels of IκBα and NF-κB p65 along with the DNA binding activity of NF-κB p65 within LPS-induced RAW264.7 cells. Moreover, the protective effect of aloin was similar to LY294002, an inhibitor of PI3K/AKT. These results indicated that aloin exerted anti-inflammatory effects by inhibiting NF-κB activation using the reactive oxygen species (ROS)--mediated PI3K/AKT/NF-κB pathway [51]. Moreover, vascular barrier disruption, enhanced expression of vascular cell adhesion molecule-1 (VCAM-1) and the intercellular adhesion molecule-1 (ICAM-1), neutrophils adhesion and migration, activation of NF-κB/ERK, and production of IL-6 and TNF-α, were induced by polyphosphate (PolyP) in HUVECs were attenuated using aloin [52].

Nuclear factor E2-related factor 2 (Nrf2) and HMGB1 had an essential role in the anti-inflammatory activity of aloin within LPS-mediated HUVECs. Nrf2 coordinates the mobilization of inflammatory cells and moderates the expressions using the antioxidant response element (ARE) [53]. In HUVECs, aloin inhibited LPS-stimulated iNOS/NO and COX-2/prostaglandin E2 (PEG-2), NF-κB activity, and the pSTAT-1 expression. This agent also reversed the low-expression of heme oxygenase 1 (HO-1) due to LPS, inhibiting the iNOS/NO pathway. A key finding in this study was that aloin promoted Nrf2 translocation from cytoplasm to nucleus to enhance the Nrf2-ARE binding activity and attenuated interleukin-1β (IL-1β) production in LPS induced HUVECs [54]. HMGB1 is a potent proinflammatory cytokine that is closely related to sepsis [55]. Yang et al. described that aloin impaired HMGB1 release in LPS-induced HUVECs through sirtuin 1 (SIRT1)-stimulated HMGB1 deacetylation and the PI3K/Nrf2/HO-1 pathway by strengthening the expressions of HO-1, Nrf2, and PI3K. Among the HUVECs exposed to HMGB1, aloin inhibited the elevated levels of TNF-α and IL-6. Moreover, the activation of the NF-κB/ERK pathway inhibited vascular hyperpermeability and p38 activation [56].

In addition, the Janus kinase (JAK)/ STAT pathway is critical for many pivotal cytokines in the pathogenesis of the inflammatory disease. Ma et al. identified that aloin could partly elicit its anti-inflammatory activities by preventing the ROS-activated JAK1-STAT1/3 signaling pathway in RAW264.7 macrophages. Aloin inhibited the release of IL-1β, IL-6, TNF-α, ROS, NO, and iNOS expression in LPS-treated RAW264.7 cells but failed to regulate the COX-2 level. Moreover, aloin suppressed LPS-induced activation and nucleo-cytoplasmic translocation of STAT1 and STAT3 but did not affect the NF-κB and MAPK signaling pathways. Notably, JAK1, not JAK2, was down-regulated through aloin [57].

4.3. Anti-osteoporotic activity

Osteoporosis is an unbalanced disorder evidenced by inactive osteoblasts and enhanced osteoclast activity [58]. Therefore, the anti-osteoporosis drugs are applied to promote osteoblast formation, inhibit osteoclast formation, and reduce the occurrence of osteoporosis, rheumatoid arthritis, and other bone diseases. Studies have revealed that osteoblasts and osteoclasts can communicate through direct cell-cell contact, cytokine, and extracellular matrix interaction [59]. Therefore, the anti-osteoporotic activity of aloin has been proposed. On the one hand, Pengiam and his colleagues observed that aloin promoted the expression of the osteoblast differentiation genes bone morphogenetic protein 2, runt-related transcription factor 2 (Runx2), and collagen 1a. In addition, it highly induces the expression of transcription factor Runx2 through the MAPK and Wnt-dependent BMP signaling pathways, thus facilitating the MC3T3-E1 cells to differentiate into osteoblasts [60]. On the other hand, Pengiam et al. also demonstrated that the inhibitory effect of aloin on osteoclast formation was associated with inhibiting NF-κB activation. Bone pit assay revealed that aloin inhibited

Table 2
The anti-inflammatory effects of aloin reported in previous studies.

Inflammation	Cell lines	Animal model	Effects	Pathway	References
Lung injury	HUVECs	LPS-induced lung injury in C57BL/6 mice	↓iNOS, NO, COX-2, PEG-2, NF-κB, p-STAT-1, IL-1β ↑HO-1, NRF2-ARE	–	[54]
Acute lung injury	RAW246.7 cells	LPS-induced acute lung injury in C57BL/6 mice	↓total cells, neutrophils, macrophages in BALF, TNF-α, IL-1β, MPO, MDA, NF-κB, NLRP3, ↑SIRT1, GSH, SOD	–	[64]
Acute lung injury	RAW246.7 cells	LPS-induced acute lung injury in BALB/c mice	↓TNF-α, IL-1β, IL-6, TLR4, p-IκBα, p-NFκB p65, NF-κB, ROS, p-PI3K, p-AKT	PI3K/AKT/NF-κB pathway	[51]
Sepsis	HUVECs	PolyP-induced lethal model in C57BL/6 mice	↓VCAM, ICAM, TNF-α, IL-6, NF-κB, e-selectin, ERK1/2, AST, ALT, BUN, LDH	NF-κB pathway	[52]
Sepsis	HUVECs	CLP-induced sepsis model in C57BL/6	↓HMGB1, TNF-α, IL-6, NF-Kb, TLR2/4, RAGE, ERK1/2, p38, p65 NF-κB, p38, ALT, AST, BUN, LDH ↑HO-1, Nrf2, P13K	PI3K/Nrf2/HO-1 pathway	[56]
Inflammation	RAW246.7 cells	–	↓NO, TNF-α, IL-6, iNOS, COX-2, P38, MSK1, caspase-3/− 9, p-NF-κB P65	NF-κB pathway	[49]
Inflammation	RAW264.7 cells	–	↓IL-1β, IL-6, TNF-α, ROS, NO, iNOS, p-STAT1, p-STAT3, JAK1	JAK1-STAT1/3 pathway	[57]

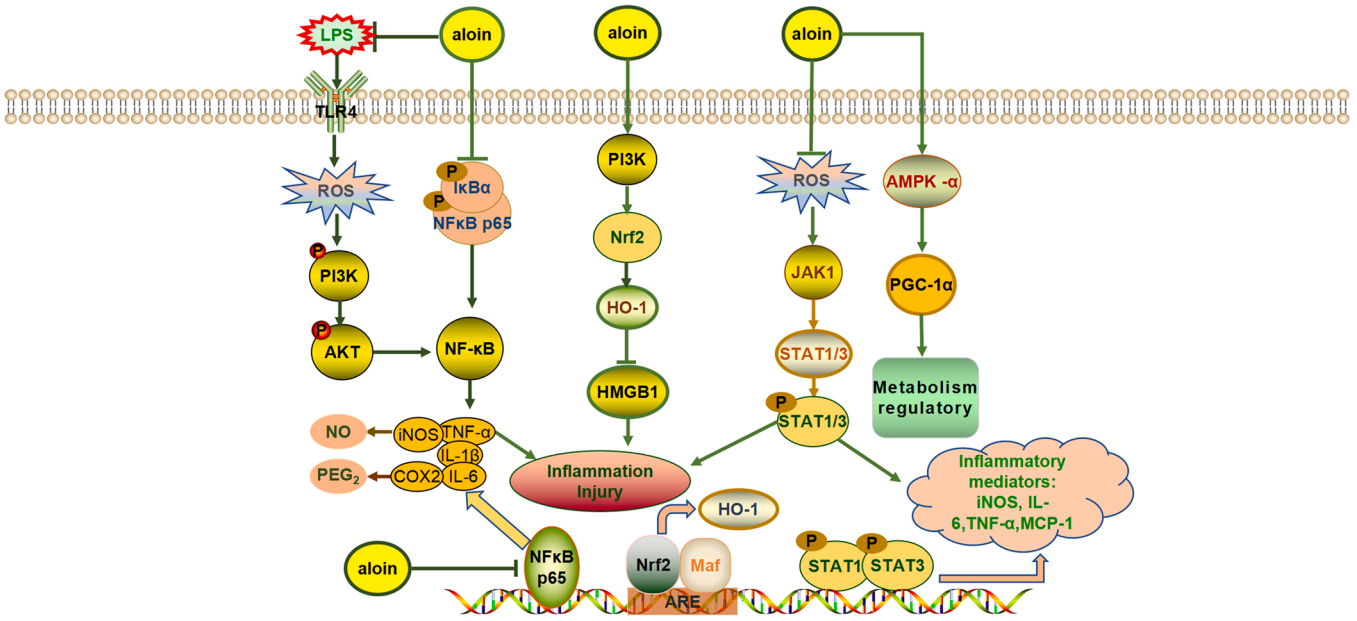

Fig. 4. Schematic summary of the major targets and signaling pathways related to organ protection and metabolic regulation modulated by aloin.

the growth of nuclear factor κ B ligand (RANKL) induced RAW264.7 macrophages, restricted bone degradation, and reduced intracellular fluorescence content. These outcomes were attributed to the inhibition of the NF-κB signaling pathway, tartrate-resistant acid phosphatase (TRAP) content, and the osteoclast-specific gene cathepsin K expression level [61]. Several studies established the crucial role of microRNA 21 (miR-21) within aloin-mediated inhibition of osteoclast formation. Aloin inhibited RANKL-induced production of miR-21 by inhibiting the NF-κB activation, leading to up-regulating programmed cell death protein 4 and down-regulating TRAP and cathepsin K [62]. In addition, aloin repressed the expression of the extracellular matrix catabolic markers, including ADAMTS-5, MMP-3, and MMP-13 and proinflammatory factors. Moreover, it improved the homeostasis of the extracellular matrix of osteoarthritic chondrocytes and attenuated the inflammatory response. Further, this efficacy was associated with reducing p-PI3K/PI3K and p-AKT/AKT ratio, thereby inhibiting the IL-1β-induced PI3K/AKT/NF-κB signaling pathway [63].

4.4. Organ protection

Due to the multiple activities of aloin, its protective effect against organ damage includes the lung, brain, liver, heart, kidney, skin, etc. (Figs. 4 and 5, Table 3).

4.4.1. Pulmonary injury

Aloin demonstrated an excellent protective effect against LPS-induced lung injury. It alleviated LPS-induced lung injury and inflammation by reducing iNOS protein and TNF-α in bronchoalveolar lavage

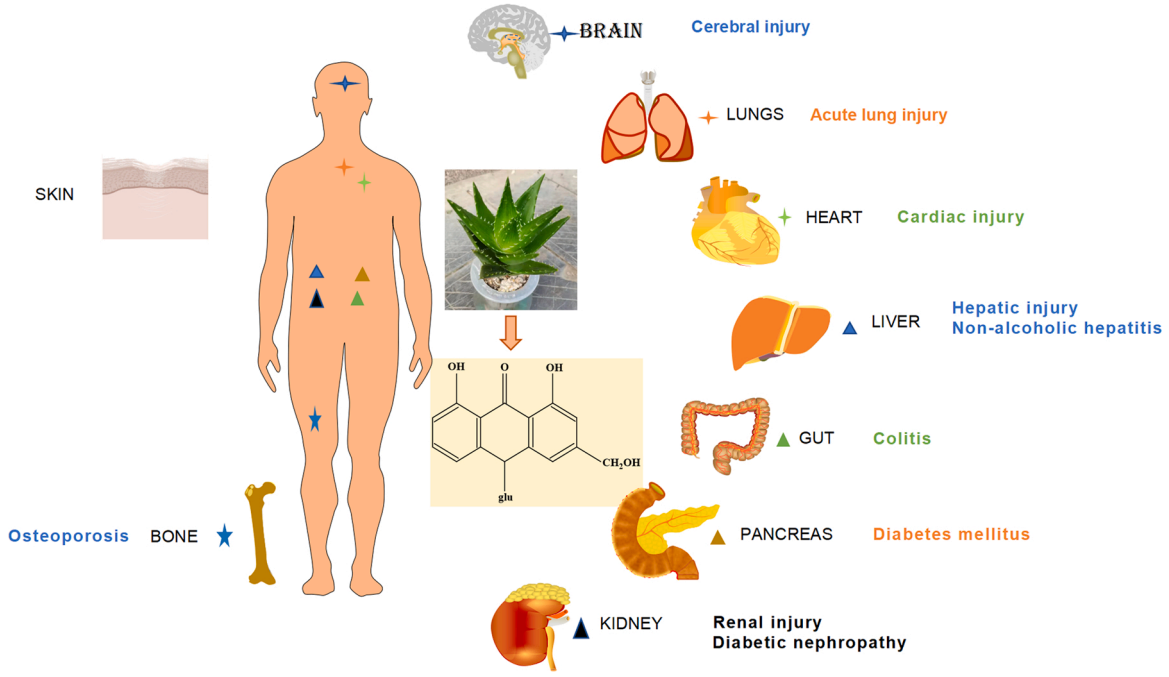

Fig. 5. Protective effects of aloin against different human general diseases related to a variety of organs.

fluid (BALF) of LPS-treated mice [54]. Similarly, aloin ameliorated LPS-induced pathological conditions in the mouse model of acute lung injury induced by LPS. It dose-dependently inhibited the elevation of total cell count, neutrophils, and macrophages in BALF induced by LPS, reduced proinflammatory cytokines production, reduced pulmonary hemorrhage and inflammatory cell accumulation, and inhibited the enhancement of lung wet-dry ratio. Moreover, aloin inhibited the myeloperoxidase (MPO) activity and malondialdehyde (MDA) content and enhanced the glutathione (GSH) and superoxide dismutase (SOD) levels [51]. Additionally, aloin activated the expression of SIRT1. It reduced the expression of phosphorylated NF-κB p65 and IκBα and NOD-like receptor family pyrin domain having three (NLRP3) inflammatory bodies, alleviating lung injury, which could be blocked through the SIRT1 inhibitor EX-527 [64].

4.4.2. Cardiac injury

A large body of evidence shows that aloin prevents the development of ischemia/reperfusion(I/R) injury and cardiac arrhythmias in the heart. Sun et al. and Zhang et al. observed that aloin protection against (myocardial ischemia/reperfusion) MI/R-induced myocardial injury was exerted by improving myocardial oxidative stress and inflammation [65] and activating the AMP-activated protein kinase (AMPK) signaling [66]. However, Sun et al. observed that this positive effect increased Nrf2 and HO-1 expression, promoting the Nrf2/ HO-1 pathway in H9c2 cells [65]. Moreover, a myocardial ischemia-reperfusion rat model (MIRI) was established by ligating the anterior descending branch of the left coronary artery in rats. Then the effect of aloin on rat cardiomyocytes apoptosis was explored. The results revealed that the apoptosis rate and TNF-α levels of the cardiomyocytes were significantly reduced. In contrast, the Ca^{2+}-ATPase activity [67] and the endoplasmic reticulum stress (ERS)-related protein expression [68]were reduced after aloin pretreatment. Furthermore, a study by Cui et al. demonstrated that aloin pretreatment alleviated MIRI by decreasing the expression of PKR endoplasmic reticulum kinase (PERK), transcription factors activation 4 (ATF4), C/EBP-homologous protein (CHOP), and p-PERK. Moreover, it cleaved the caspase-3 proteins, thus repressing the protein canopy homolog 2 (CNPY2)-PERK apoptotic pathway [68]. In addition, aloin had an inhibitory effect on aconitine-induced arrhythmia. Cao et al. described that aloin exhibited antiarrhythmic efficacy in Langendorff-perfused rabbit hearts by reducing the heart

Table 3
Aloin against different human general diseases related to variety of organs.

Organ injury	Cell lines	Animal model	Effects	Pathway	References
Pulmonary injury	HUVECs	LPS-induced lung injury in C57BL/6 mice	↓iNOS, NO, COX-2, PEG-2, NF-κB, p-STAT-1, IL-1β ↑HO-1, NRF2-ARE	–	[54]
	RAW246.7 cells	LPS-induced acute lung injury in C57BL/6 mice	↓total cells, neutrophils, macrophages in BALF, TNF-α, IL-1β, MPO, MDA, NF-κB, NLRP3, ↑SIRT1, GSH, SOD	–	[64]
	RAW246.7 cells	LPS-induced acute lung injury in BALB/c mice	↓TNF-α, IL-1β, IL-6, TLR4, p-IκBα, p-NFκB p65, NF-κB, ROS, p-PI3K, p-AKT	PI3K/AKT/NF-κB pathway	[51]
Cardiac injury	–	Doxorubicin-induced cardiotoxicity model in Wistar rats	↓IL-1β, IL-6, TNF-α, LDH, CK-MB, ALT, AST	–	[70]
	–	Langendorff-perfused rabbit hearts	↓heart rates, the incidence of VT and VF	–	[69]
	–	MIRI-induced myocardial injury in Sprague-dawley rats	↓CK, LDH, GRP78, caspase-12, CNPY2, p-PERK, PERK, ATF4, CHOP, caspase-3	cNPY2-PERK pathway	[68]
	–	IR-induced myocardial injury in Wistar rats	↓Apoptosis index, TNF-α ↑Ca^{2+}-ATPase	–	[67]
	–	MI/R-induced myocardial injury in Sprague-dawley rats	↓SOD, MDA, TNF-α, IL-6, IL-10 ↑MABP, HR, LVSP, AMPKα, GC-1α, GLU4	AMPK pathway	[66]
	H9c2 cells	–	↓Bax, ROS, LDH, MDA, SOD, TNF-α, IL-6, IL-1β ↑Bcl-2, Nrf2, HO-1	Nrf2-HO-1 pathway	[65]
Hepatic injury	–	CDAAH-induced NASH in Nrf2 knock- out mice	↓ALT, AST, MDA, TUNEL-positive hepatocytes, caspase-3, Bax, TNF-α, IL-6, IL-1β, Keap1, ROS ↑GSH, SOD, Bcl-2, IL-10, Nrf2, HO-1	Nrf2/HO-1 pathway	[71]
	Primary hepatocytes	I/R-induced liver injury in mice	↓ALT, AST, TNF-α, IL-6, Bcl-2, caspase-3 ↑SOD, GSH, IL-10, Bax, TLR4, Fadd, MyD88, TRAF6, p-IKKα/β, p-NF-κBp6	TLR4/MyD88/ NF-κB	[72]
	Müller cell	Thioacetamide-induced hepatic retinopathy in Sprague-dawley rats	↓blood ammonia, Müller cells swelling, GFAP, AQP4 ↑Kir4.1	–	[73]
Renal injury	Kidney endothelial cell	CLP-induced renal injury in C57BL/6	↓BUN, Scr, NO, TNF-α, IL-6, MOP, COX2, p38, JNK, MDA, iNOS, NF-κB p65, p-IκB, ↑GSH, CAT, SOD, Nrf2, HO-1	–	[74]
	Podocyte	STZ-induced diabetic nephropathy in rats	↓blood glucose, TNF-α, IL-6, MDA, ROS, NOX4, p-p38 MAPK ↑SOD, SOD/MDA, Nephrin, Podocin	NOX/ROS/p38 pathway	[75]
Cerebral injury	–	D-galactose induced ageing in C57BL/6 mice	↓TNF-α, IL-1β, IL-6, microglia activation, ROS, p-ERK, P-P38, NF- κB, MDA ↑SOD, GSH	ERK, p38, and NF-Kb pathways	[76]
	Oxygen and glucose deprivation-reoxygenated induced in PC12 cell	–	↓SOD, Ca^{2+}, Bax, caspase-3 ↑MDA, LDH, Bcl-2	–	[77]
	bEnd.3 cell	TBI-induced BBB disruption in C57BL/6 mice	↓ROS, p-p38, p-p65, Bax, caspase-3 ↑p-p38, p-p65, Bax, caspase-3, TJ protein, Bcl-2	–	[78]
Skin injury	Hs68 cell	–	↓ROS, 8-OH-dG, TBARS, ↑GSH, SOD	–	[83]
	–	UVB-induced paw skin in Wistar rats	↓H_2O_2, protein carbonyl, lipid peroxidation ↑non protein thiol		[82]

rates and repressing the ventricular tachycardia and ventricular fibrillation incidences [69]. Furthermore, aloin had a dose-dependent protective effect against the arsenic trioxide-induced cardiotoxicity in mice, mainly manifested by reducing ST segment and QT interval in ECG, inhibiting oxidative stress and enhancing the antioxidant defense function [70].

4.4.3. Hepatic injury

Aloin had protective effects against liver injury due to nonalcoholic hepatitis, ischemia-reperfusion, and thioacetamide (TAA). Notably, aloin-treated nonalcoholic steatohepatitis (NASH) mice that were induced by formulated choline-deficient, L-amino acid defined, high-fat (CDAAH) diet depicted a reduced proinflammatory cytokine (e.g., TNF-α, IL-6, and IL-1β) and MDA level and a significant elevation of GSH and SOD levels. Moreover, aloin reversed the Bcl-2 downregulation and the Bax upregulation and repressed the cleaved caspase-3 activity. Mechanically, aloin further enforced the activation of Nrf2/HO-1 signaling by up-regulating Nrf2, HO-1 and Bcl-2 and downregulating the abundance of Keap1, Bax, and Bax caspase-3 and protected against liver injury during NASH, which was associated with the enhanced antioxidant, anti-inflammatory, and anti-apoptotic activities [71]. Du et al. observed that aloin alleviated liver tissue damage by downregulating the alanine aminotransferase (ALT) and the aspartate aminotransferase (AST) activities. Within the liver tissues of the I/R mice, the levels of neutrophils, malondialdehyde, TNF-α, and IL-6 expression were increased, whereas the SOD, GSH, and IL-10 levels were depressed. Aloin reversed these increases and decreases, exhibiting antioxidant and anti-inflammatory properties and alleviating I/R-induced liver injury. Furthermore, aloin demonstrated anti-apoptotic activity in hypoxia/reoxygenation hepatocytes through the collagenase perfusion method by suppressing the Bcl-2 expression and up-regulating Caspase3, Bax, TLR4 FADD, myeloid differentiation factor 88 (MyD88), TNF receptor-associated factor 6 (TRAF6), p-IKKα/β and p-NF-κBp65 [72]. Moreover, the protective effect of aloin on Müller cell swelling in rats due to TAA was explored. The results revealed that aloin could improve liver injury by alleviating Müller cell swelling, reversing the overexpression of glial fibrillary acidic protein (GFAP), and normalizing the Kir4.1 and Aquaporin-4 channels [73].

4.4.4. Renal injury

Aloin depicted better protection against cecum ligation and puncture (CLP) or oxidative stress-induced kidney injury. In the CLP-induced mouse model, aloin ameliorated renal tissue injury. It increased the survival rate by reversing the increased levels of blood urea nitrogen (BUN), creatinine, urine level, and lactate dehydrogenase (LDH). The anti-inflammatory effect of aloin was associated with the down-regulation of TNF-α, IL-6, and MPO levels, the reduction of nitric oxide synthase induction, and nitric acid products. Additionally, aloin post-treatment causes a significant enhancement in the antioxidant defense system, evidenced by the elevated levels of LPO, GSH, GPO, CAT, SOD, and the NF-kB pathway inactivation [74]. Studies have demonstrated that the increase of nitrogen oxide (NOX) in renal tissue accelerates the inflammatory reaction and promotes pathological changes within the renal tissue. Ma et al. explored the effects of aloin on podocyte function through a rat model of diabetic nephropathy (DN). The result indicated that aloin reduced blood glucose and IL-1β and TNF-α levels, improved the inflammatory infiltration, reversed the abnormal levels of SOD, MDA, and ROS, and inhibited NOX4 and p38MAPK activities within renal tissues. Therefore, aloin could inhibit the NOX4/-ROS/p38 MAPK signaling pathways, contributing to renal tissue and podocyte protection in DN rats [75].

4.4.5. Cerebral injury

Aloin improved cognitive dysfunction, blood-brain barrier, and neuroinflammation associated with brain injury. A D-galactose (D-gal) induced aging mice was established to investigate the neuroprotective effect of aloin. The results showed that aloin-treated ameliorated neuroinflammation in mice by reducing hippocampal histopathological damage, impairment of microglial activation, and downregulation of inflammatory factors expressions such as TNF-α, IL-1β, and IL-6. In addition, aloin attenuated D-galactose-mediated oxidative damage in aging mice by reversing ROS accumulation and enhancing the antioxidant enzyme activity, indicating that aloin resisted damages from oxidative stress and neuroinflammation. It inhibited ERK and p38 phosphorylation levels and NF-κB activity, thus improving D-galactose-induced cognitive and memory impairment within mice [76]. Additionally, aloin protected against the OGD-reoxygenated PC12 cell damage and the blood-brain barrier after traumatic brain injury (TBI) through its antioxidative stress and the anti-apoptotic effects. *In vitro*, aloin enhanced cell viability and MDA level, declined the LDH leakage, reversed the SOD activity reduction, and repressed the increase in calcium concentration in OGD-reoxygenated induced PC12 cells. Furthermore, aloin maintained the damaged cells by regulating mitochondria-mediated apoptotic pathways. This outcome was reflected by enhancing Bcl-2 mRNA expression, down-regulating Bax mRNA expression, and activating the caspase-3 mRNA expression [77]. Moreover, Jing et al. observed that aloin protected against TBI-induced blood-brain barrier disruption in mice. Further, aloin could facilitate bEnd.3 cell survival, hinders the intracellular ROS levels and changes in mitochondrial membrane potential after the retraction injury in vitro. Consequently, aloin protected the integrity of TJ protein and reduced the p-p38/p38 expression in the MAPK pathway and p-p65/p65 in the NF-κB pathway. Moreover, it down-regulated the Bax/Bcl-2 and cleaved caspase-3/caspase-3 ratios in the mitochondrial apoptotic pathway through in vivo and in vitro experiments [78]. Thus, aloin exhibited antioxidative and anti-apoptotic activities against the OGD-reoxygenated PC12 cell damage and the blood-brain barrier post-TBI.

4.4.6. Skin injury

Aloin exhibited UV radiation protection, whitening, and anti-wrinkle functions. UV radiation plays an essential role in damaging human skin [79], and aloin could be a UV absorber to prevent damage from UV radiation. UV radiation impeded the proliferation and reduced the SOD and glutathione peroxidase (GSH Px) activity and collagen synthesis among fibroblasts cells. A specific concentration range of aloin reversed these damages within fibroblasts cells [80]. In addition, oxidative stress or UVB-induced skin damage was attributed to the oxidant/antioxidant balance disruption in affected tissues, contributing to increased cellular ROS levels [81]. Silva et al. found that aloin could decrease oxidative stress by reducing H2O2, protein carbonyl levels, lipid peroxidation, and increasing non-protein thiol content in UVB-induced paw skin and alleviating skin injury [82]. Likewise, Liu et al. demonstrated that ROS accumulation enhanced the thiobarbituric acid-reactive substances (TBARS) activity and oxidative DNA damage marker 8-hydroxy-2′-deoxyguanosine (8-OH-dG) levels in Hs68 cells. It further resulted in oxidative damage of lipids and DNA, aggravating skin damage. However, aloin reversed these oxidative indicators and enhanced the antioxidant defense system for protecting the skin from oxidative stress damage within hs68 cells [83].

Furthermore, aloin possesses the potential to treat hyperpigmentation. Skin exposure to UV rays stimulated histamine and kinin release, thus promoting melanin production and skin blackening [84]. Aloin was a new endogenous adrenergic releaser and could affect melanin aggregation within the isolated tail melanophores of tadpoles *B. melanostictus*, thereby lightening the skin [85]. Meanwhile, Tan et al. explored the whitening effect of aloin and observed that aloin was a potent tyrosinase inhibitor of melanin formation [86]. Moreover, Li et al. confirmed that low concentrations of aloin could restrain tyrosinase activity and melanin synthesis without impacting melanocyte proliferation [87]. Thus, aloin could be applied as a melanin dissolving agent in treating hyperpigmentation. In addition, Ro et al. revealed that aloin depicted an

anti-wrinkle effect due to collagen production and the inhibition of MMP-1 synthesis among human fibroblasts [88].

4.4.7. Other injuries

Aloin demonstrated beneficial effects against *Staphylococcus aureus*-induced mastitis, dextran sulfate sodium salt (DSS)-induced colitis, and CLP-induced sepsis. In the DSS-induced rat model of colitis, dietary aloin could reverse the colonic shortening and tissue malformation caused by DSS. Moreover, it represses MPO activity and the expression of leukotriene B4, down-regulates the levels of TNF-α, IL-1β, and PEG-2, and decrease the DAI score [89]. Additionally, aloin-mediated silver nanoparticle technology, AAgNPs, synthesized by silver nitrate and aloin, could reduce breast weight and decrease the bacterial breast load. It also inhibits the increase of C-reactive protein levels and CAT activity in *Staphylococcus aureus*-induced murine mastitis in adult female albino mice [90]. Furthermore, the anti-septic effect of aloin and its underlying mechanism was also investigated in a CLP-induced sepsis mice model. Based on the result in vitro, aloin strengthened the expressions of SIRT1 and HO-1 via the Nrf2 and PI3K pathways and alleviated tissue injuries within lung, kidney, and heart and sepsis-related mortality [56].

4.5. Antivirus, antimicrobial, and antiparasitic activities

Aloin demonstrated inhibitory effects on various influenza viruses, including hepatitis B virus (HBV), oseltamivir-resistant influenza A pdm09 (H1N1), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The inhibition of polymerase/reverse-transcriptase (HBVpol) activity is the core of viral inhibition. A study by Parvez et al. found that aloin B had anti-HBV activity in Hepatoma cells for the first time. Thus, aloin B could constitute a very steady and high free energy complex with HBVpol, covering the active site of HBVpol, and repressing the HBV antigens (HBsAg and HBeAg) expression in a time-dependent manner [91]. In addition, Huang et al. established that aloin reduced the infection of the H1N1 strain in vitro. Moreover, it enhanced host immune function by clearing viral load from the lungs, maintaining body weight, and improving the survival in mice infected with the H1N1 influenza virus. Mechanistic studies have suggested that the aloin efficacy was attributed to an activity-dependent inhibition of neuraminidase (NA)-mediated transforming growth factor-β activation and the enhancement of HA-specific T cell effector functions [92]. Furthermore, Devin et al. described that aloin isomers A and B could restrain the hydrolytic activity of the viral gene-encoded protein papain-like proteases (PLpro) and repress the deubiquitination activity of SARS-CoV-2PLpro in vitro. Thus, aloin isomers A and B could inhibit SARS-CoV-2 virus replication, which led to a pandemic of coronavirus disease 19 and robbed millions of lives worldwide [93].

Aloin had many antibacterial effects against common pathogenic bacteria and fungi such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, *Staphylococcus aureus*, *Cryptococcus neoformans*, *Salmonella*, etc. Firstly, Asamenew et al., Donkor et al., and Megeressa et al. observed that aloin depicted antibacterial activity against *C. albicans* [94,95]. The latter observed that the minimum inhibitory concentration (MIC) of aloin against the *C. albicans* was 400 μg/ml [96]. Secondly, a study by Wang et al. and Donkor et al. revealed that aloin had an in vitro inhibitory effect on *S. aureus* through a concentration-dependent manner. The inhibition zone diameter and MIC were 21.5 mm and 12.5 mg/ml, respectively. When exploring the impact of aloin on clinical strains, the inhibition circle diameter and MIC were 17 mm, and 15 mg/ml for clinical strain SA1.5, respectively. In addition, aloin demonstrated an inhibitory effect on the hemolytic viability of the standard strain ATCC 25923 under different concentrations to reduce organismal damage [97]. Moreover, Donkor et al. also showed that the growth of *Klebsiella pneumoniae*, *E. coli*, *Aspergillus flavus* and *P. aeruginosa* was inhibited by aloin A in a dose-dependent manner MICs were 2.5–5.0 mg/ml [95]. Furthermore, Oumer et al. revealed that aloin A/B depicted a general antibacterial activity against *E. coli* and Salmonella, with MICs ranging between 10 and 400 μg/ml [98]. Finally, Brilhante et al. described that aloin showed in vitro inhibition of *C. neoformans*, an antifungal resistant fungus, with a MIC of 64–128 μg/ml. Notably, aloin had synergistic or additive effects when combined with amphotericin B and itraconazole [99].

In addition, aloin depicted inhibitory activity against certain infectious parasitic diseases, such as *Leishmaniasis*. Tewabe et al. evaluated that aloin A/B had potent in vitro antileishmanial activities against the *L. aethiopica* and *L. donovani* promastigotes and axenically cultured amastigotes [100]. In addition, Kumar et al. indicated that aloin had a specific inhibitory effect on *Plasmodium*, and its EC_{50} was 67 μg/ml [101]. Furthermore, aloin A/B showed insecticidal activity against the *Amblyomma varigatum* larvae, and its LC_{50} was 257.69 ± 6.31 mg/ml [102]. Moreover, aloin (4 mg/ml) restrained the activity of *Trypanosoma congolense* during the incubation period between 15 and 40 min [103].

4.6. Other effects

Aloin had regulatory roles in metabolic diseases, including gestational diabetes mellitus (GDM). Diabetes is a chronic disease with high glucose levels due to insulin resistance or deficiency. Wang et al. described that aloin treatment could restore the rebalance of blood glucose and lipids within mice. More, inflammatory responses and ROS levels in the liver were reduced, and insulin levels were enhanced by aloin in the GDM mice. Furthermore, aloin enhanced AMPK and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) levels inside the liver of GDM mice. It indicated that this regulatory effect could be associated with activating the AMPK/PGC-1α signaling pathway (Fig. 4) [104]. In addition, aloin showed a laxative effect in the constipation model rats, which was reflected in the increase of fece number, fece weight, and small intestinal propulsion percentage of the rats [105]. Moreover, aloin was protective against chronic constriction injury (CCI)-induced neuropathic pain in rats by decreasing the CCI-induced mechanical and thermal allodynia. It also regulated the motor nerve conduction velocity and reduced MDA, TNF-α, IL-6, and IL-1β levels, elevating GSH levels, indicating that the aloin effect could be related to its antioxidant and anti-inflammatory activities [106].

5. Pharmacokinetics of aloin

Although aloin possesses multiple biological activities, studies have revealed that the oral bioavailability of aloin was poor [107]. Currently, the absorption rate of aloin is being investigated in several models. Shim et al. observed that 50% of aloin was recovered in an in vitro digestion model associated with Caco-2 cells [108]. Similarly, Park et al. described the intestinal absorption rates of aloin within two intestinal absorption models. They observed that a 5.51–6.60% absorption rate of aloin was detected among the Everted intestinal capsule model, and similar data were obtained in the Caco-2 monolayer model [109]. Additionally, the pharmacokinetic characteristics of different routes of administration in rats were analyzed using the Ultra-high-performance liquid chromatography-tandem mass spectrometry method. Aloin had a half-life of 3.96 h after oral administration (10 mg/kg) and 2.43 h after intravenous administration (2 mg/kg). The peak plasma concentration was achieved at 0.25 h after oral administration of aloin, whereas the maximum plasma concentration (Cmax) was 412.89 ng/ml. Moreover, the apparent volume of aloin-A distribution in rats was 5.32 L/Kg. Therefore, aloin-A had the characteristics of fast elimination and wide distribution within the blood circulatory system. The oral bioavailability of aloin-A was confirmed to be 5.79% [107].

Studies have demonstrated that aloin, an anthraquinone glycoside, was hydrolyzed into anthraquinone aglycone by the intestinal bacteria after entering the intestinal tract. Hattori et al. believed that intestinal bacteria metabolized aloin into aloe-emodin anthrone. Further research by Hattori et al. and their colleagues found that this was because of intestinal bacteria, such as *Eubacterium sp*. BAR, an anaerobic bacteria,

could cleave the C-glucosyl group of aloin and then transform it into aloe-emodin anthrone [110–112].

6. Formulation of aloin

Developing a drug delivery system is an effective strategy for improving the low permeability, poor targeting, and variable release rate of aloin. Novel drug delivery systems of aloin, including oral films, patches, copolymers, etc., have been developed. Di et al. revealed information about aloin films (Eudradit® Rs100) targeting oral diseases, a mixture of aloin, Eudradit, propylene glycol, acrylic, sorbitol, PVP K90, and sodium saccharin. It had appropriate weight, thickness, drug content, suitable surface pH value (6.32–6.79), good mucoid cohesiveness, and low swelling. Moreover, it had a drug release rate of up to 89% and 10 times higher accumulation than after administration of aloin solution in the porcine buccal mucosa [113,114]. Furthermore, in a study by Xavier et al., aloin immobilized in Layer-by-layer membrane (LbL) films incorporated inside palmitoyl oleoyl phosphatidylglycerol or dipalmitoyl phosphatidyl glycerol liposomes to control the release of aloin at a slower release rate for patches. The data indicated that the release rates in the LbL films were lower than that in solution, and aloin was nearly fully released within 30 h from this optimized system [115]. In addition, Wang et al. developed a novel aloin-loaded galactosamine (Gal)-conjugated polydopamine (pD) modified copolymer (Gal-pD-PLA-TPGS/NPs), with a particle size distribution of 204.8 nm. It could accurately target gastric cancer cells and demonstrate a higher rate of cellular uptake in SGC-7901 cells and gastric cancer xenografts mice, administrating through the tail vein [116]. In addition, there was an aloin-mediated silver nanoparticle technology, viz., AAgNPs, with cluster sizes between 287.5 and 293.2 nm and an average particle size of 70 nm for individual particles. These particles had satisfactory antibacterial and anti-inflammatory effects than cefepime in the mice after drug injection [7].

7. Toxicity of aloin

Aloe has certain safety issues as a dietary supplement. For example, Guo et al. found that Aloe depicted intestinal and reproductive toxicity, causing intestinal lymph node hyperplasia, sperm damage, and hematological changes [117]. Furthermore, anthraquinones could cause safety concerns [118]. Thus, aloin, as the main anthraquinone component of Aloe, has essential research value in toxicity evaluation. Buenz et al. confirmed an accepted model for in vitro toxicity in Jurkat cells, aloin dose-dependently impaired cell volume, induced cell cycle arrest, and apoptosis [119]. In addition, male F344/N Nctr rats were treated with different concentrations of aloin (0, 6.95, 13.9, 27.8, 55.7, 111, 223, and 446 mg/kg) drinking water for 13 weeks. Thus, the counts of white blood cells and neutrophils and total cholesterol levels were abnormal within the high-dose groups. Moreover, the incidences and severity of the intestinal mucosa and cupped cell hyperplasia were significantly increased with the enhancement of the aloin dose [120].

8. Discussion

The widespread species presence, pharmacological effects, and medicinal value of Aloe is a hot source of medicines and healthcare products. Aloin, the main component of Aloe latex, has various pharmacological effects. Thus, aloin faces new challenges in developing drugs and healthcare products. Therefore, reviewing the availability, the pharmacological activities, pharmacokinetics, formulation studies, and toxicity of aloin provides a basis for development and application.

Aloin possesses a wide range of biological activities, including antitumor, anti-inflammatory, anti-osteoporotic, organ-protective, antiviral, antimicrobial, and antiparasitic activities, and the regulation of blood lipids and glucose, laxative and improving neuropathic pain. In addition, in-depth studies uncovered the potential mechanism behind aloin facilitating these effects. The underlying mechanism of the pharmacological action of aloin primarily involves the modulation of MAPKs, NF-κB, Stat3, HMGB1-TRL4-ERK, p38MAPK/Cdc25B/Hsp27, AKT-mTOR-P70S6K, ERK-P90RSK-CREB, AMPK/PGC-1α, Nrf2, PI3K/Nrf2/HO-1, and JAK1-STAT1/3. It also includes crucial cellular processes, such as mitochondrial fusion, apoptosis, autophagy, and migration. Thus, aloin has multi-functional and multi-targeted properties in treating cancer, organ injuries, osteoporosis, and other diseases.

Researchers have investigated aloin regarding its sources, pharmacokinetics, and pharmaceutics. Aloe is widely available, and aloin can be obtained from various species of Aloe, ensuring an adequate supply of aloin. Pharmacokinetic studies revealed that although the oral bioavailability of aloin was low, aloin exhibited excellent blood absorption after intravenous administration. Moreover, the development of copolymer and liposome formulations improved the poor oral bioavailability of aloin in recent years.

Aloe has developed into related products due to its extensive pharmacological activity. Aloin extracted from Aloe has a wide range of pharmacological properties. However, whether aloin can be developed into medicines and healthcare products remains unclear. The current paper puts forward a conjecture. Firstly, creating aloin into functional skincare products is noteworthy because of its whitening and UV radiation protection effects. Sunscreen and whitening products associated with beauty-damaging diseases, including pigmentation and acne, could be developed. This agent can also be exploited as a coating, cream, or ointment with a whitening property. Secondly, it is possible to build aloin into capsules or pills for the daily treatment of constipation due to its laxative effect. In addition, aloin has various significant pharmacological effects, such as anticancer, anti-inflammatory, anti-osteoporosis, antiviral, antibacterial activities, and so on. These effects enable aloin to be developed into healthcare products.

Many issues need to be addressed before the better development and application of aloin. Firstly, certain essential pharmacological effects of aloin have not been discussed, including the prevention and treatment of oral diseases, wound healing characteristics, etc. The lack of these pharmacological studies could restrict the development of aloin products. Secondly, although aloin is widely obtained from the leaves of different species of Aloe, there are fewer reports on the isolation, purification, and synthesis of aloin. Moreover, it is not a suitable method to enhance the extraction efficiency of aloin. Thirdly, the most frequent administration route of aloin was gavage. New modes of administration should be explored due to the low bioavailability of aloin after oral administration. Furthermore, the bioavailability of aloin could be improved by effective delivery systems like polymeric micelles, phospholipid complexes, liposomes, nanoparticle encapsulation techniques, and altering the delivery mode. These techniques have been proved to improve the bioavailability of monomer components of traditional Chinese medicine. For example, polylactic acid-glycolic acid nanoparticles (PLGANPS) nanotechnology can be applied to improve the bioavailability of nuciferine in rats after oral administration [121]. In addition, clinical research on aloin in cancer, organ injuries, and other diseases is severely lacking. Hence, clinical studies should be undertaken in the future. Only a very few toxicity studies on aloin have been reported. Additional studies could explore the acute toxicity, long-term toxicity, and neurotoxicity of aloin.

Therefore, we have comprehensively summarized the therapeutic potentials of aloin in vivo and in vitro to alleviate cancer, inflammation, diabetes, osteoporosis, organ injuries, viruses, bacteria, and parasites and explained the underlying mechanisms of action. Based on the products developed by Aloe, it is speculated that aloin could be transformed into medicines and healthcare products.

Author contributions

Yu Yang contributed to the drafting of the manuscript. Jiao-jiao Wu, Jia Xia,Yan Wan, Hui Ao and Cheng Peng obtained funding, designed,

conceived and supervised process, and revised the manuscript. Others were involved in searching, screening the search results, translation, and data collection. All the authors have read and approved the final manuscript.

Declaration of Competing Interest

All authors declare no conflict of interest regarding the present work and they have no involvements that might raise the question of bias in the work reported or in the conclusions, implications or opinions stated.

Acknowledgments

We acknowledge the funding supports from the National Natural Science Foundation of China (81503272, 81630101, 81891012, U19A2010), Application Foundation Research Project of Sichuan Provincial Department of Science and Technology (2017JY0187), Xinglin Scholar Research Premotion Project of Chengdu University of TCM (2018016), National Interdisciplinary Innovation Team of Traditional Chinese Medicine: Multi-dimensional evaluation and multi-disciplinary cross-innovation team of traditional Chinese medicine resources with Southwest characteristics (ZYYCXTD-D-202209), Sichuan Traditional Chinese Medicine Technology Industry Innovation Team: Multidimensional Evaluation of Characteristic Traditional Chinese Medicine Resources and Product Development Innovation Team (2022C001), and Sichuan Provincial Traditional Chinese Medicine Administration Project (2020JC0031).

References

[1] T. Reynolds, A.C. Dweck, Aloe vera leaf gel: a review update, J. Ethnopharmacol. 68 (1–3) (1999) 3–37, https://doi.org/10.1016/s0378-8741(99)00085-9.
[2] ⟨https://db.yaozh.com/jinkoubaojian/7025615970000033.html⟩.
[3] ⟨https://db.yaozh.com/huazhuang/6800.html⟩.
[4] A.W. Hayes, R.A. Clemens, P. Pressman, The absence of genotoxicity of a mixture of aloin A and B and a commercial aloe gel beverage, Toxicol. Mech. Methods (2022) 1–10, https://doi.org/10.1080/15376516.2021.2023828.
[5] A. Sanches-Silva, J. LÃ3pez-Cervantes, R. SendÃ3n, Aloe vera: Ancient knowledge with new frontiers, Trends Food Sci. Technol. 61 (2017) 94–102, https://doi.org/10.1016/j.tifs.2016.12.005.
[6] R. Majumder, C.K. Das, M. Mandal, Lead bioactive compounds of Aloe vera as potential anticancer agent, Pharm. Res. 148 (2019), 104416, https://doi.org/10.1016/j.phrs.2019.104416.
[7] J. Xiao, S. Chen, Y. Chen, J. Su, The potential health benefits of aloin from genus Aloe, Phytother. Res. 36 (2) (2022) 873–890, https://doi.org/10.1002/ptr.7371.
[8] R.R. Klopper, G.F. Smith, The genus Aloe (Asphodelaceae: Alooideae) in Namaqualand, South Afr. Haseltonia 2007 (13) (2007) 38–51, https://doi.org/10.2985/1070-0048(2007)13[38:TGAAAI]2.0.CO;2.
[9] R.H. Davis, K.Y. Rosenthal, L.R. Cesario, G.A. Rouw, Processed Aloe vera administered topically inhibits inflammation, J. Am. Podiatr. Med Assoc. 79 (8) (1989) 395–397, https://doi.org/10.7547/87507315-79-8-395.
[10] A.R. Pradeep, V. Garg, A. Raju, P. Singh, Adjunctive Local Delivery of Aloe vera Gel in Patients With Type 2 Diabetes and Chronic Periodontitis: A Randomized, Controlled Clinical Trial, J. Periodontol. 87 3 (2016) 268–274, https://doi.org/10.1902/jop.2015.150161.
[11] J. Liang, L. Cui, J. Li, S. Guan, K. Zhang, J. Li, *Aloe vera*: A Medicinal Plant Used in Skin Wound Healing, Tissue Eng. Part B, Rev. 27 (5) (2021) 455–474, https://doi.org/10.1089/ten.TEB.2020.0236.
[12] B.K. Chandan, A.K. Saxena, S. Shukla, N. Sharma, D.K. Gupta, K.A. Suri, J. Suri, M. Bhadauria, B. Singh, Hepatoprotective potential of Aloe barbadensis Mill. against carbon tetrachloride induced hepatotoxicity, J. Ethnopharmacol. 111 (3) (2007) 560–566, https://doi.org/10.1016/j.jep.2007.01.008.
[13] L. Zhong, G. Zheng, L. Da Ge, C.Y. Lin, T. Huang, L. Zhao, C. Lu, A.P. Lu, Z. X. Bian, Chinese herbal medicine for constipation: zheng-based associations among herbs, formulae, proprietary medicines, and herb-drug interactions, Chin. Med. 11 (2016) 28, https://doi.org/10.1186/s13020-016-0099-4.
[14] Z.J. BAYATI, K.N. MORADI, Component and application Aloe vera plant in medicine, Int. J. Adv. Biol. Biomed. Res. 2 (5) (2014) 1876–1882.
[15] K. Eshun, Q. He, Aloe vera: a valuable ingredient for the food, pharmaceutical and cosmetic industries–a review, Crit. Rev. Food Sci. Nutr. 44 (2) (2004) 91–96, https://doi.org/10.1080/10408690490424694.
[16] Y. Gao, K.I. Kuok, Y. Jin, R. Wang, Biomedical applications of *Aloe vera*, Cri Rev. Food Sci. Nutr. 59 (sup1) (2019) S244–S256, https://doi.org/10.1080/10408398.2018.1496320.
[17] ⟨https://db.yaozh.com/huazhuang/9341.html⟩.
[18] ⟨https://db.yaozh.com/baojian/6927028420000009.html⟩.
[19] ⟨https://db.yaozh.com/chufang/117138.html⟩.
[20] A.M. Viljoen, B.V. Wyk, L.E. Newton, The occurrence and taxonomic distribution of the anthrones aloin, aloinoside and microdontin in Aloe, Biochem Syst. Ecol. 29 (1) (2001) 53–67, https://doi.org/10.1016/s0305-1978(00)00024-7.
[21] S.A. Coran, G. Bartolucci, M. Bambagiotti-Alberti, Selective determination of aloin in different matrices by HPTLC densitometry in fluorescence mode, J. Pharm. Biomed. Anal. 54 (2) (2011) 422–425, https://doi.org/10.1016/j.jpba.2010.09.019.
[22] D.I. Sánchez-Machado, J. López-Cervantes, M.F. Mariscal-Domínguez, P. Cruz-Flores, O.N. Campas-Baypoli, E.U. Cantú-Soto, A. Sanches-Silva, An HPLC Procedure for the Quantification of Aloin in Latex and Gel from Aloe barbadensis Leaves, J. Chromatogr. Sci. 55 (3) (2017) 251–257, https://doi.org/10.1093/chromsci/bmw179.
[23] D. Martínez-Romero, F. Guillén, H. Pérez-Aguilar, S. Castillo, M. Serrano, P. J. Zapata, D. Valero, Is it possible to increase the aloin content of Aloe vera by the use of ultraviolet light? J. Agric. Food Chem. 61 (9) (2013) 2165–2170, https://doi.org/10.1021/jf304930q.
[24] A. Paez, G. Michael Gebre, M.E. Gonzalez, T.J. Tschaplinski, Growth, soluble carbohydrates, and aloin concentration of Aloe vera plants exposed to three irradiance levels, Environ. Exp. Bot. 44 (2) (2000) 133–139, https://doi.org/10.1016/s0098-8472(00)00062-9.
[25] Y. Guo, R. Ji, X. Lü, Y.F. Wan, X. Jiang, The protective effects of sodium selenite and aloin against ultraviolet A radiation, J. Sichuan Univ. Med. Sci. Ed. 42 (1) (2011) 61–118.
[26] Z. Zhang, W. Rui, Z.C. Wang, D.X. Liu, L. Du, Anti-proliferation and anti-metastasis effect of barbaloin in non-small cell lung cancer via inactivating p38MAPK/Cdc25B/Hsp27 pathway, Oncol. Rep. 38 (2) (2017) 1172–1180, https://doi.org/10.3892/or.2017.5760.
[27] Q. Pan, H. Pan, H. Lou, Y. Xu, L. Tian, Inhibition of the angiogenesis and growth of Aloin in human colorectal cancer in vitro and in vivo, Cancer Cell Int 13 (1) (2013) 69, https://doi.org/10.1186/1475-2867-13-69.
[28] H.A. El-Shemy, M.A. Aboul-Soud, A.A. Nassr-Allah, K.M. Aboul-Enein, A. Kabash, A. Yagi, Antitumor properties and modulation of antioxidant enzymes' activity by Aloe vera leaf active principles isolated via supercritical carbon dioxide extraction, Curr. Med Che 17 (2) (2010) 129–138, https://doi.org/10.2174/092986710790112620.
[29] J. He, W. Zhang, X. Zhou, W. Yan, Z. Wang, Aloin induced apoptosis by enhancing autophagic flux through the PI3K/AKT axis in osteosarcoma, Chin. Med. 16 (1) (2021) 123, https://doi.org/10.1186/s13020-021-00520-4.
[30] R. Sun, R. Zhai, C. Ma, W. Miao, Combination of aloin and metformin enhances the antitumor effect by inhibiting the growth and invasion and inducing apoptosis and autophagy in hepatocellular carcinoma through PI3K/AKT/mTOR pathway, Cancer Med. 9 (3) (2020) 1141–1151, https://doi.org/10.1002/cam4.2723.
[31] A. Nićiforović, M. Adzić, S.D. Spasić, M.B. Radojcić, Antitumor effects of a natural anthracycline analog (Aloin) involve altered activity of antioxidant enzymes in HeLaS3 cells, Cancer Biol. Ther. 6 (8) (2007) 1200–1205, https://doi.org/10.4161/cbt.6.8.4383.
[32] A.Y. Esmat, S.M. El-Gerzawy, A. Rafaat, DNA ploidy and S phase fraction of breast and ovarian tumor cells treated with a natural anthracycline analog (aloin), Cancer Biol. Ther. 4 (1) (2005) 108–112, https://doi.org/10.4161/cbt.4.1.1445.
[33] H. Cai, Z. Wang, Y. Jiang, Effects of Aloin on Proliferation, Apoptosis and Invasion of Esophageal Cancer KESY70 Cell Line, Cancer Reserch Prev. Treament 45 (7) (2018) 5.
[34] Z. Wang, T. Tang, S. Wang, T. Cai, H. Tao, Q. Zhang, S. Qi, Z. Qi, Aloin Inhibits the Proliferation and Migration of Gastric Cancer Cells by Regulating NOX2-ROS-Mediated Pro-Survival Signal Pathways, Drug De. Devel Ther. 14 (2020) 145–155, https://doi.org/10.2147/DDDT.S219247.
[35] T. Cai, X. Chen, J. Cheng, Z. Cheng, X. Wu, S. Qi, Z. Qi, Aloin inhibits lactate-induced proliferation and migration of gastric cancer cells by downregulating HMGB1 expression, Nan Fang. yi ke da xue xue bao = J. South. Med. Univ. 41 (11) (2021) 1700–1706, https://doi.org/10.12122/j.issn.1673-4254.2021.11.15.
[36] W. Ung, S. Vivarelli, L. Falzone, M. Libra, B. Bonavida, Regulation of the c-myc Oncogene by the Circadian Clock and Oncogenesis, Crit. Rev. Oncog. 26 (4) (2021) 55–66, https://doi.org/10.1615/CritRevOncog.2022042689.
[37] L.Y. Lu, H. Kuang, G. Korakavi, X. Yu, Topoisomerase II regulates the maintenance of DNA methylation, J. Biol. Chem. 290 (2) (2015) 851–860, https://doi.org/10.1074/jbc.M114.611509.
[38] J.L. Delgado, C.M. Hsieh, N.L. Chan, H. Hiasa, Topoisomerases as anticancer targets, Biochem J. 475 (2) (2018) 373–398, https://doi.org/10.1042/BCJ20160583.
[39] A.Y. Esmat, C. Tomasetto, M.C. Rio, Cytotoxicity of a natural anthraquinone (Aloin) against human breast cancer cell lines with and without ErbB-2: topoisomerase IIalpha coamplification, Cancer Bio Ther. 5 (1) (2006) 97–103, https://doi.org/10.4161/cbt.5.1.2347.
[40] Z. Wang, H. Tao, Y. Ma, T. Tang, Q. Zhang, Q. Jiang, S. Qi, J. Li, Z. Qi, Aloin induces apoptosis via regulating the activation of MAPKs signaling pathway in human gastric cancer cells in vitro. J. South. Med. Univ. 38 (9) (2018) 1025–1031, https://doi.org/10.12122/j.issn.1673-4254.2018.09.01.
[41] L. Wan, L. Zhang, K. Fan, J. Wang, Aloin promotes A549 cell apoptosis via the reactive oxygen species-mitogen activated protein kinase signaling pathway and p53 phosphorylation, Mol. Med Rep. 16 (5) (2017) 5759–5768, https://doi.org/10.3892/mmr.2017.7379.
[42] K.D. Dyer, H.F. Rosenberg, Physiologic concentrations of HMGB1 have no impact on cytokine-mediated eosinophil survival or chemotaxis in response to Eotaxin-2 (CCL24), PloS One 10 (3) (2015), e0118887, https://doi.org/10.1371/journal.pone.0118887.

[43] W. Lee, O. Yuseok, S. Yang, B.S. Lee, J.H. Lee, E.K. Park, M.C. Baek, G.Y. Song, J. S. Bae, JH-4 reduces HMGB1-mediated septic responses and improves survival rate in septic mice, J. Cell Biochem 120 (4) (2019) 6277–6289, https://doi.org/10.1002/jcb.27914.
[44] P. Li, K. Ren, Y.Y. Liang, J.K. Liu, Z.W. Liang, Y.F. Zhang, Aloin promotes cell apoptosis by targeting HMGB1-TLR4-ERK axis in human melanoma cells, EXCLI J. 19 (2020) 641–651. PMCID: PMC7290104.
[45] H. Tao, T. Tang, S. Wang, Z. Wang, Y. Ma, T. Cai, X. Cheng, S. Qi, Y. Zhang, Z. Qi, The molecular mechanisms of Aloin induce gastric cancer cells apoptosis by targeting High Mobility Group Box 1, Drug Des. Dev. Ther. 13 (2019) 1221–1231, https://doi.org/10.2147/DDDT.S201818.
[46] A.C. Tan, Targeting the PI3K/AKT/mTOR pathway in non-small cell lung cancer (NSCLC), Thorac. Cancer 11 (3) (2020) 511–518, https://doi.org/10.1111/1759-7714.13328.
[47] K.C. Tay, L.T. Tan, C.K. Chan, S.L. Hong, K.G. Chan, W.H. Yap, P. Pusparajah, L. H. Lee, B.H. Goh, Formononetin: a review of its anticancer potentials and mechanisms, Front Pharmacol. 10 (2019) 820, https://doi.org/10.3389/fphar.2019.00820.
[48] F. Mohammadi, H. Javid, A.R. Afshari, B. Mashkani, S.I. Hashemy, Substance P accelerates the progression of human esophageal squamous cell carcinoma via MMP-2, MMP-9, VEGF-A, and VEGFR1 overexpression, Mol. Biol. Rep. 47 (6) (2020) 4263–4272, https://doi.org/10.1007/s11033-020-05532-1.
[49] X. Luo, H. Zhang, X. Wei, M. Shi, P. Fan, W. Xie, Y. Zhang, N. Xu, Aloin suppresses lipopolysaccharide-induced inflammatory response and apoptosis by inhibiting the activation of NF-κB, Molecules 23 (3) (2018) 517, https://doi.org/10.3390/molecules23030517.
[50] M.Y. Park, H.J. Kwon, M.K. Sung, Evaluation of aloin and aloe-emodin as anti-inflammatory agents in aloe by using murine macrophages, Biosci. Biotechnol. Biochem 73 (4) (2009) 828–832, https://doi.org/10.1271/bbb.80714.
[51] K. Jiang, S. Guo, C. Yang, J. Yang, Y. Chen, A. Shaukat, G. Zhao, H. Wu, G. Deng, Barbaloin protects against lipopolysaccharide (LPS)-induced acute lung injury by inhibiting the ROS-mediated PI3K/AKT/NF-κB pathway, Int Immunopharmacol. 64 (2018) 140–150, https://doi.org/10.1016/j.intimp.2018.08.023.
[52] I.C. Lee, J.S. Bae, Suppressive effects of aloin on polyphosphate-mediated vascular inflammatory responses, J. Asian Nat. Prod. Res 23 (1) (2021) 89–99, https://doi.org/10.1080/10286020.2020.1724969.
[53] S.M. Ahmed, L. Luo, A. Namani, X.J. Wang, X. Tang, Nrf2 signaling pathway: Pivotal roles in inflammation, Biochim Biophys. Acta Mol. Basis Dis. Biochim Biophys. Acta Mol. Basis Dis. 1863 (2) (2017) 585–597, https://doi.org/10.1016/j.bbadis.2016.11.005.
[54] W. Lee, S. Yang, C. Lee, E.K. Park, K.M. Kim, S.K. Ku, J.S. Bae, Aloin reduces inflammatory gene iNOS via inhibition activity and p-STAT-1 and NF-κB, Food Chem. Toxicol. 126 (2019) 67–71, https://doi.org/10.1016/j.fct.2019.02.025.
[55] J.S. Bae, Role of high mobility group box 1 in inflammatory disease: focus on sepsis, Arch. Pharm. Res 35 (9) (2012) 1511–1523, https://doi.org/10.1007/s12272-012-0901-5.
[56] S. Yang, W. Lee, B.S. Lee, C. Lee, E.K. Park, S.K. Ku, J.S. Bae, Aloin Reduces HMGB1-Mediated Septic Responses and Improves Survival in Septic Mice by Activation of the SIRT1 and PI3K/Nrf2/HO-1 Signaling Axis, Am. J. Chin. Med 47 (3) (2019) 613–633, https://doi.org/10.1142/S0192415×19500320.
[57] Y. Ma, T. Tang, L. Sheng, Z. Wang, H. Tao, Q. Zhang, Y. Zhang, Z. Qi, Aloin suppresses lipopolysaccharide-induced inflammation by inhibiting JAK1-STAT1/3 activation and ROS production in RAW264.7 cells, Int J. Mol. Med 42 (4) (2018) 1925–1934, https://doi.org/10.3892/ijmm.2018.3796.
[58] I. Kim, J.H. Kim, K. Kim, S. Seong, N. Kim, The IRF2BP2-KLF2 axis regulates osteoclast and osteoblast differentiation, BMB Rep. 52 7 (2019) 469–474, https://doi.org/10.5483/BMBRep.2019.52.7.104.
[59] X. Chen, Z. Wang, N. Duan, G. Zhu, E.M. Schwarz, C. Xie, Osteoblast-osteoclast interactions, Connect Tissue Res 59 (2) (2018) 99–107, https://doi.org/10.1080/03008207.2017.1290085.
[60] Y. Pengjam, H. Madhyastha, R. Madhyastha, Y. Yamaguchi, Y. Nakajima, M. Maruyama, Anthraquinone glycoside aloin induces osteogenic initiation of MC3T3-E1 cells: involvement of MAPK mediated wnt and bmp signaling, Biomol. Ther. 24 (2) (2016) 123–131, https://doi.org/10.4062/biomolther.2015.106.
[61] Y. Pengjam, H. Madhyastha, R. Madhyastha, Y. Yamaguchi, Y. Nakajima, M. Maruyama, NF-κB pathway inhibition by anthrocyclic glycoside aloin is key event in preventing osteoclastogenesis in RAW264.7 cells, Phytomedicine 23 (4) (2016) 417–428, https://doi.org/10.1016/j.phymed.2016.01.006.
[62] R. Madhyastha, H. Madhyastha, Y. Pengjam, Q.I. Nurrahmah, Y. Nakajima, M. Maruyama, The pivotal role of microRNA-21 in osteoclastogenesis inhibition by anthracycline glycoside aloin, J. Nat. Med 73 (1) (2019) 59–66, https://doi.org/10.1007/s11418-018-1237-3.
[63] C. Zhang, Z. Shao, X. Hu, Z. Chen, B. Li, R. Jiang, N. Bsoul, J. Chen, C. Xu, W. Gao, Inhibition of PI3K/AKT/NF-κB signaling by Aloin for ameliorating the progression of osteoarthritis: In vitro and in vivo studies, Int Immunopharmacol. 89 (Pt B) (2020), 107079, https://doi.org/10.1016/j.intimp.2020.107079.
[64] J. Lei, Y. Shen, G. Xv, Z. Di, Y. Li, G. Li, Aloin suppresses lipopolysaccharide-induced acute lung injury by inhibiting NLRP3/NF-κB via activation of SIRT1 in mice, Immunopharmacol. Immunotoxicol. 42 (4) (2020) 306–313, https://doi.org/10.1080/08923973.2020.1765373.
[65] W. Sun, Z. Wang, M. Sun, W. Huang, Y. Wang, Y. Wang, Aloin antagonizes stimulated ischemia/reperfusion-induced damage and inflammatory response in cardiomyocytes by activating the Nrf2/HO-1 defense pathway, Cell Tissue Res 384 (3) (2021) 735–744, https://doi.org/10.1007/s00441-020-03345-z.
[66] P. Zhang, X. Liu, G. Huang, C. Bai, Z. Zhang, H. Li, Barbaloin pretreatment attenuates myocardial ischemia-reperfusion injury via activation of AMPK, Biochem Biophys. Res Commun. 490 (4) (2017) 1215–1220, https://doi.org/10.1016/j.bbrc.2017.06.188.
[67] C. Huang, Effects of barbaloin pretreatment on myocardial cell apoptosis, the contents of Tnf-α And Activity Of Ca 2-atpase In Rats With Ischemia Reperfusion, Chin. J. Mod. Appl. Pharm. (2009).
[68] Y. Cui, Y. Wang, G. Liu, Protective effect of Barbaloin in a rat model of myocardial ischemia reperfusion injury through the regulation of the CNPY2-PERK pathway, Int J. Mol. Med 43 (5) (2019) 2015–2023, https://doi.org/10.3892/ijmm.2019.4123.
[69] Z.Z. Cao, Y.J. Tian, J. Hao, P.H. Zhang, Z.P. Liu, W.Z. Jiang, M.L. Zeng, P. P. Zhang, J.H. Ma, Barbaloin inhibits ventricular arrhythmias in rabbits by modulating voltage-gated ion channels, Acta Pharm. Sin. 39 (3) (2018) 357–370, https://doi.org/10.1038/aps.2017.93.
[70] L.A. Birari, U.B. Mahajan, K.R. Patil, D.D. Patil, N.A. Bagul, S. Belemkar, S. N. Goyal, S. Ojha, C.R. Patil, Aloin protects against arsenic trioxide-induced myocardial membrane damage and release of inflammatory cytokines, Naunyn Schmiede Arch. Pharm. 393 (8) (2020) 1365–1372, https://doi.org/10.1007/s00210-020-01833-1.
[71] Q. Xu, Y. Fan, J.J. Loor, Y. Liang, H. Lv, X. Sun, H. Jia, C. Xu, Aloin protects mice from diet-induced non-alcoholic steatohepatitis via activation of Nrf2/HO-1 signaling, Food Funct. 12 (2) (2021) 696–705, https://doi.org/10.1039/d0fo02684k.
[72] Y. Du, B. Qian, L. Gao, P. Tan, H. Chen, A. Wang, T. Zheng, S. Pu, X. Xia, W. Fu, Aloin preconditioning attenuates hepatic ischemia/reperfusion injury via inhibiting TLR4/MyD88/NF-κB signal pathway *In Vivo* and *In Vitro*, Oxid. Med Cell Longev. 2019 (2019) 3765898, https://doi.org/10.1155/2019/3765898.
[73] E. Jung, J. Kim, Aloin Inhibits Müller cells swelling in a rat model of thioacetamide-induced hepatic retinopathy, Molecules 23 (11) (2018) 2806, https://doi.org/10.3390/molecules23112806.
[74] W. Lee, G.S. Jeong, M.C. Baek, S.K. Ku, J.S. Bae, Renal protective effects of aloin in a mouse model of sepsis, Food Chem. Toxicol. 132 (2019), 110651, https://doi.org/10.1016/j.fct.2019.110651.
[75] B. Ma, W. Qian, Z. Luo, W, L, Effect of barbaloin on the NOX4 /ROS /p38 MAPK signaling pathway and podocyte function in rats with diabetic nephropathy, Chin. J. Comp. Med. 30 (9) (2020) 1–7, doi: 10.3969 /j.issn.1671-7856.2020. 09. 001.
[76] J. Zhong, F. Wang, Z. Wang, C. Shen, Y. Zheng, F. Ma, T. Zhu, L. Chen, Q. Tang, J. Zhu, Aloin attenuates cognitive impairment and inflammation induced by d-galactose via down-regulating ERK, p38 and NF-κB signaling pathway, Int Immunopharmacol. 72 (2019) 48–54, https://doi.org/10.1016/j.intimp.2019.03.050.
[77] R. Chang, R. Zhou, X. Qi, J. Wang, F. Wu, W. Yang, W. Zhang, T. Sun, Y. Li, J. Yu, Protective effects of aloin on oxygen and glucose deprivation-induced injury in PC12 cells, Brain Res Bull. 121 (2016) 75–83, https://doi.org/10.1016/j.brainresbull.2016.01.001.
[78] Y. Jing, D.X. Yang, W. Wang, F. Yuan, H. Chen, J. Ding, Z. Geng, H.L. Tian, Aloin protects against blood-brain barrier damage after traumatic brain injury in mice, Neurosci. Bull. 36 6 (2020) 625–638, https://doi.org/10.1007/s12264-020-00471-0.
[79] N. Pustisek, M. Situm, UV-radiation, apoptosis and skin, Coll. Antropol. 35 (Suppl 2) (2011) 339–341.
[80] Y. Guo, R. Ji, X. Lü, Y.F. Wan, X. Jiang, The protective effects of sodium selenite and aloin against ultraviolet A radiation, J. Sichuan Univ. Med. Sci. Ed. 42 (1) (2011) 61–118.
[81] S. Kawashima, T. Funakoshi, Y. Sato, N. Saito, H. Ohsawa, K. Kurita, K. Nagata, M. Yoshida, A. Ishigami, Protective effect of pre- and post-vitamin C treatments on UVB-irradiation-induced skin damage, Sci. Rep. 8 1 (2018) 16199, https://doi.org/10.1038/s41598-018-34530-4.
[82] M.A. Silva, G. Trevisan, C. Hoffmeister, M.F. Rossato, A.A. Boligon, C.I. Walker, J. Z. Klafke, S.M. Oliveira, C.R. Silva, M.L. Athayde, J. Ferreira, Anti-inflammatory and antioxidant effects of Aloe saponaria Haw in a model of UVB-induced paw sunburn in rats, J. Photochem. Photobio. B 133 (2014) 47–54, https://doi.org/10.1016/j.jphotobiol.2014.02.019.
[83] F.W. Liu, F.C. Liu, Y.R. Wang, H.I. Tsai, H.P. Yu, Aloin protects skin fibroblasts from heat stress-induced oxidative stress damage by regulating the oxidative defense system, PloS One 10 (12) (2015), e0143528, https://doi.org/10.1371/journal.pone.0143528.
[84] M. Brenner, V.J. Hearing, The protective role of melanin against UV damage in human skin, Photochem. Photobiol. 84 (3) (2008) 539–549, https://doi.org/10.1111/j.1751-1097.2007.00226.x.
[85] S.A. Ali, J.M. Galgut, R.K. Choudhary, On the novel action of melanolysis by a leaf extract of Aloe vera and its active ingredient aloin, potent skin depigmenting agents, Planta Med. 78 (8) (2012) 767–771, https://doi.org/10.1055/s-0031-1298406.
[86] C. Tan, W. Zhu, Y. Lu, Aloin, cinnamic acid and sophorcarpidine are potent inhibitors of tyrosinase, Chin. Med J. 115 (12) (2002) 1859–1862.
[87] C. Li, W. Zhu, D. Wang, X. YUE, The optimum concentration of aloesin to inhibit tyrosinase activity of human epidermal melanocytes, J. Clin. DERMATOLOGY-NANJING 35 (8) (2006) 506.
[88] H.S. Ro, H.J. Jang, G.R. Kim, S.J. Park, H.Y. Lee, Enhancement of the anti-skin wrinkling effects of aloe arborescens miller extracts associated with lactic acid fermentation, Evid. Based Complement Altern. Med 2020 (2020) 2743594, https://doi.org/10.1155/2020/2743594.
[89] M.Y. Park, H.J. Kwon, M.K. Sung, Dietary aloin, aloesin, or aloe-gel exerts anti-inflammatory activity in a rat colitis model, Life Sci. 88 (11–12) (2011) 486–492, https://doi.org/10.1016/j.lfs.2011.01.010.

[90] T.V. Chaitanya Kumar, Y. Muralidhar, P.E. Prasad, T.N. Prasad, M. Alpha Raj, Evaluation of therapeutic potential of nanosilver particles synthesised using aloin in experimental murine mastitis model, IET Nanobiotechnol. 7 (3) (2013) 78–82, https://doi.org/10.1049/iet-nbt.2012.0045.
[91] M.K. Parvez, M.S. Al-Dosari, P. Alam, M. Rehman, M.F. Alajmi, A.S. Alqahtani, The anti-hepatitis B virus therapeutic potential of anthraquinones derived from Aloe vera, Phytother. Res. P TR 33 (11) (2019) 2960–2970, https://doi.org/10.1002/ptr.6471.
[92] C.T. Huang, C.Y. Hung, Y.C. Hseih, C.S. Chang, A.B. Velu, Y.C. He, Y.L. Huang, T. A. Chen, T.C. Chen, C.Y. Lin, Y.C. Lin, S.R. Shih, A. Dutta, Effect of aloin on viral neuraminidase and hemagglutinin-specific T cell immunity in acute influenza, Phytomedicine 64 (2019), 152904, https://doi.org/10.1016/j.phymed.2019.152904.
[93] D. Lewis, J. Ho, S. Wills, A. Kawall, A. Sharma, K. Chavada, M. Ebert, S. Evoli, A. Singh, S. Rayalam, V. Mody, S. Taval, Aloin isoforms (A and B) selectively inhibits proteolytic and deubiquitinating activity of papain like protease (PLpro) of SARS-CoV-2 in vitro, Sci. Rep. 12 (1) (2022) 2145, https://doi.org/10.1038/s41598-022-06104-y.
[94] G. Asamenew, D. Bisrat, A. Mazumder, K. Asres, In vitro antimicrobial and antioxidant activities of anthrone and chromone from the latex of Aloe harlana Reynolds, Phytother. Res. P TR 25 (12) (2011) 1756–1760, https://doi.org/10.1002/ptr.3482.
[95] A.M. Donkor, M.N. Donkor, N. Kuubabongnaa, Evaluation of anti-infective potencies of formulated aloin A ointment and aloin A isolated from *Aloe barbadensis* Miller, BMC Chem. 14 (1) (2020) 8, https://doi.org/10.1186/s13065-020-0659-7.
[96] M. Megeressa, D. Bisrat, A. Mazumder, K. Asres, Structural elucidation of some antimicrobial constituents from the leaf latex of Aloe trigonantha L.C. Leach, BMC Complement Alter. Med 15 (2015) 270, https://doi.org/10.1186/s12906-015-0803-4.
[97] Y. Wang, Y. DI, L. Zhu, S. Shao, Inhibitory effects of aloin on growth activity and hemolytic toxin expression of Staphylococcus aureus, Chin. J. Clin. Lab. Sci. 259–262 (2018). ID: wpr-694832.
[98] A. Oumer, D. Bisrat, A. Mazumder, K. Asres, A new antimicrobial anthrone from the leaf latex of Aloe trichosantha, Nat. Prod. Commun. 9 (7) (2014) 949–952, https://doi.org/10.1177/1934578×1400900717.
[99] R. Brilhante, G. Araújo, X. Fonseca, G. Guedes, L. Aguiar, D. Castelo-Branco, R. A. Cordeiro, J. Sidrim, W.A. Pereira Neto, M. Rocha, Antifungal effect of anthraquinones against Cryptococcus neoformans: detection of synergism with amphotericin B, Med Mycol. (2020) myaa081, https://doi.org/10.1093/mmy/myaa081.
[100] Y. Tewabe, B. Kefarge, H. Belay, D. Bisrat, A. Hailu, K. Asres, Antileishmanial Evaluation of the Leaf Latex of *Aloe macrocarpa*, Aloin A/B, and Its Semisynthetic Derivatives against Two *Leishmania* Species, Evid. Based Complement Altern. Med 2019 (2019) 4736181, https://doi.org/10.1155/2019/4736181.
[101] S. Kumar, M. Yadav, A. Yadav, P. Rohilla, J.P. Yadav, Antiplasmodial potential and quantification of aloin and aloe-emodin in Aloe vera collected from different climatic regions of India, BMC Complement Alter. Med 17 (1) (2017) 369, https://doi.org/10.1186/s12906-017-1883-0.
[102] T. Hailesillassie, D. Bisrat, K. Asres, Larvicidal effect of the leaf latex of Aloe yavellana Reynolds and its major compounds against Amblyomma variegatum (Ixodidae), Vet. Parasitol. 263 (2018) 23–26, https://doi.org/10.1016/j.vetpar.2018.09.015.
[103] Y. Tewabe, D. Bisrat, G. Terefe, K. Asres, Antitrypanosomal activity of aloin and its derivatives against Trypanosoma congolense field isolate, BMC Vet. Res 10 (2014) 61, https://doi.org/10.1186/1746-6148-10-61.
[104] Y. Wang, H. Wang, F. Yang, Barbaloin treatment contributes to the rebalance of glucose and lipid homeostasis of gestational diabetes mellitus mice, 1559325820984910, Dose Response 18 (4) (2020), https://doi.org/10.1177/1559325820984910.
[105] P. Sun, X. Zhang, H. Li, A. ANSARI, Individual and combined laxative effects of aloin and fructooligosaccharide in constipation model rat. Shandong Chem. Ind. 50 (18) (2021) 199–200+203, https://doi.org/10.19319/j.cnki.issn.1008-021x.2021.18.072.
[106] A.S. Kale, A.R. Wadkar, U.B. Mahajan, L.A. Birari, S. Belemkar, S.N. Goyal, K. R. Patil, Aloin attenuates chronic constriction injury-induced neuropathic pain in rats by inhibiting inflammatory cytokines and oxidative stress, Asian Pac. J. Trop. Biomed. 11 (5) (2021) 205, https://doi.org/10.4103/2221-1691.311768.
[107] C. Niu, W. Ye, X. Cui, J. Sun, S. Xiao, G. Chen, S. Bao, R. Chen, UHPLC-MS/MS method for the quantification of aloin-A in rat plasma and its application to a pharmacokinetic study, J. Pharm. Biomed. Anal. 178 (2020), 112928, https://doi.org/10.1016/j.jpba.2019.112928.
[108] S.M. SHIM, H. Kwon, Assessing absorbability of bioactive components in aloe using in vitro digestion model with human intestinal cell, J. Food Biochem 34 (2) (2010) 425–438, https://doi.org/10.1111/j.1745-4514.2009.00289.x.
[109] M.Y. Park, H.J. Kwon, M.K. Sung, Intestinal absorption of aloin, aloe-emodin, and aloesin; A comparative study using two in vitro absorption models, Nutr. Res Pr. 3 (1) (2009) 9–14, https://doi.org/10.4162/nrp.2009.3.1.9.
[110] M. Hattori, T. Akao, K. Kobashi, T. Namba, Cleavages of the O- and C-glucosyl bonds of anthrone and 10,10'-bianthrone derivatives by human intestinal bacteria, Pharmacology 47 (Suppl 1) (1993) 125–133, https://doi.org/10.1159/000139851.
[111] Q.M. Che, T. Akao, M. Hattori, K. Kobashi, T. Namba, Isolation of a human intestinal bacterium capable of transforming barbaloin to aloe-emodin anthrone, Planta Med. 57 (1) (1991) 15–19, https://doi.org/10.1055/s-2006-960007.
[112] Q.M. Che, T. Akao, M. Hattori, Y. Tsuda, T. Namba, K. Kobashi, Barbaloin stimulates growth of Eubacterium sp. strain BAR, a barbaloin-metabolizing bacterium from human feces, Chem. Pharm. Bull. 39 (3) (1991) 757–760, https://doi.org/10.1248/cpb.39.757.
[113] G. Di Prima, A. Conigliaro, V. De Caro, Mucoadhesive polymeric films to enhance barbaloin penetration into buccal mucosa: a novel approach to chemoprevention, AAPS PharmSciTech. 20 (1) (2019) 18, https://doi.org/10.1208/s12249-018-1202-1.
[114] V. De Caro, A.L. Scaturro, G. Di Prima, G. Avellone, F.M. Sutera, O. Di Fede, G. Campisi, L.I. Giannola, Aloin delivery on buccal mucosa: ex vivo studies and design of a new locoregional dosing system, Drug Dev. Ind. Pharm. 41 (9) (2015) 1541–1547, https://doi.org/10.3109/03639045.2014.971030.
[115] A.C. Xavier, M.L. de Moraes, M. Ferreira, Immobilization of aloin encapsulated into liposomes in layer-by-layer films for transdermal drug delivery, Mater. Sci. Eng. C. Mater. Biol. Appl. 33 (3) (2013) 1193–1196, https://doi.org/10.1016/j.msec.2012.12.021.
[116] Y.R. Wang, S.Y. Yang, G.X. Chen, P. Wei, Barbaloin loaded polydopamine-polylactide-TPGS (PLA-TPGS) nanoparticles against gastric cancer as a targeted drug delivery system: studies in vitro and in vivo, Biochem Biophys. Res Commun. 499 (1) (2018) 8–16, https://doi.org/10.1016/j.bbrc.2018.03.069.
[117] X. Guo, N. Mei, Aloe vera: A review of toxicity and adverse clinical effects, J. Environ. Sci. Health Part C., Environ. Carcinog. Ecotoxicol. Rev. 34 (2) (2016) 77–96, https://doi.org/10.1080/10590501.2016.1166826.
[118] E.M. Malik, C.E. Müller, Anthraquinones as pharmacological tools and drugs, Med Res Rev. 36 (4) (2016) 705–748, https://doi.org/10.1002/med.21391.
[119] E.J. Buenz, Aloin induces apoptosis in Jurkat cells, Toxicol. Vitr. 22 (2) (2008) 422–429, https://doi.org/10.1016/j.tiv.2007.10.013.
[120] M.D. Boudreau, G.R. Olson, V.P. Tryndyak, M.S. Bryant, R.P. Felton, F.A. Beland, From the cover: aloin, a component of the aloe vera plant leaf, induces pathological changes and modulates the composition of microbiota in the large intestines of F344/N Male Rats, Toxicol. Sci. 158 (2) (2017) 302–318, https://doi.org/10.1093/toxsci/kfx105.
[121] Y. Wan, J. Xia, J.F. Xu, L. Chen, Y. Yang, J.J. Wu, F. Tang, H. Ao, C. Peng, Nuciferine, an active ingredient derived from lotus leaf, lights up the way for the potential treatment of obesity and obesity-related diseases, Pharm. Res 175 (2022), 106002, https://doi.org/10.1016/j.phrs.2021.106002.