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Bulletin of the National Research Centre (2022) 46:259
https://doi.org/10.1186/s42269-022-00943-5

Bulletin of the National Research Centre

REVIEW

Open Access

Mechanisms involved in the anticancer effects of sinapic acid

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Abstract

Background: Cancer refers to a group of diseases characterized by the development of abnormal cells that divide uncontrollably and have the ability to infiltrate and destroy normal body tissue. Worldwide, it is the second most leading cause of death. Dietary intake of bioactive compounds from plant sources has been documented for their protective effect against different types of human ailments including cancer.

Main body: Sinapic acid (3,5-dimethoxy-4-hydroxycinnamic acid) (SA) is a promising phytochemical, available in oil seeds, berries, spices, vegetables and cereals. SA has been well documented for its antibacterial, anti-peroxidative, anti-hyperglycemic, anticancer, hepatoprotective, reno-protective, anti-inflammatory, neuroprotective, immunomodulatory and anticancer effects. Nevertheless, the anticancer activity of SA has remained a challenge with regard to understanding its mechanism in health and diseases.

Short conclusion: This review is an effort to summarize the updated literature available about the mechanisms involved in the anticancer effects of SA in order to recommend this compound for further future investigations.

Keywords: Sinapic acid, Antioxidant, Anti-inflammatory, Anticancer, Cardioprotective, Neuroprotective

Background

Cancer is a deadly disease caused by abnormal cell growth with aggressive potentials (Hausman 2019). Several reports have shown that cancer incidence and deaths are due to various environmental and genetic factors such as heredity, decreased intake of plant-based products, excessive body mass index, absence of physical activity, increased tobacco use, alcohol addiction, severe radiation exposure and uncontrolled infections (Iranda-Galvis et al. 2021; Willenbrink et al. 2020). Application of dietary phytochemicals has been considered to be a novel and therapeutic approach to treat variety of tumors on the basis of their mechanism of action (Al-Ishaq et al. 2020; Mao et al. 2020).

In recent years, many studies have reported that foods enriched with polyphenols have the potential to protect against various disorders like, diabetes mellitus, hepatic disorders, cardiovascular disease, cancer, arthritis, Alzheimer's disease and many more (Bungau et al. 2019; Fraga et al. 2019). Findings from various studies have proved that plant-derived compounds are found to be non-toxic when taken in smaller quantities and they possess exceptional therapeutic effects (de Lima Cherubim et al. 2020; Bracci et al. 2021). Sinapic acid (SA) is one such polyphenol that is reported to show several health promoting activities.

Sinapic acid (SA), a cinnamic acid derivative is predominantly found in the plant kingdom. It is chemically 3,5-dimethoxy-4-hydroxycinnamic acid and is present in rye, fruits and vegetables (Niciforovic and Abramovic 2014; Russell et al. 2009) (Fig. 1). SA is seen as a yellow–brown crystalline powder. It has a molecular weight of 224.21 g/mol. The melting point of SA is 203–205 °C, and it is found to be incompatible with strong oxidizing agents and strong bases. Studies have shown that SA is poorly soluble in water, but soluble in carbitol and freely soluble in DMSO (Hosny et al. 2018).

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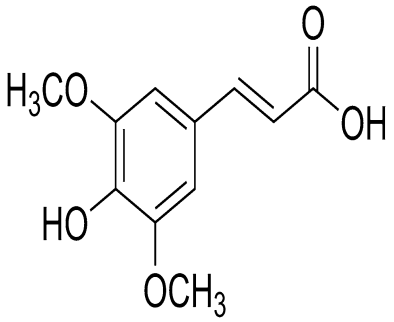

Fig. 1 Structure of sinapic acid

Importance of SA

SA has been reported to possess various beneficial activities. SA is demonstrated to be a vital chain-breaking antioxidant that efficiently functions as radical scavenger (Gaspar et al. 2010). SA is also reported to show potent hepatoprotective activity against several toxic agents (Shin et al. 2013a, b). Studies have reported the beneficial effect of SA on cisplatin-induced nephrotoxicity (Ansari 2017). The neuroprotective function of SA in Alzheimer's disease is also investigated (Lee et al. 2012). Many studies have reported the effective anti-hyperglycemic and antidiabetic role of SA against experimental diabetes (Cherng et al. 2013). Other than this, anti-inflammatory (Lee 2018), anticancer (Huang et al. 2021), cardioprotective (Bin Jardan et al. 2020) and anxiolytic effects (Yoon et al. 2007) of SA are also reported.

The pharmacological effects of SA have been extensively documented over the past few decades. In this review, we discuss the molecular mechanisms involved in the anticancer effect of SA.

Main text

Bioavailability and metabolism

Studies have shown that the bioavailability of SA has been potentially significant and it is dependent on its solubility in different medium. Reports on SA metabolism indicated the presence of SA and their conjugates in urine (Shirley and Chapple 2003). SA can be efficiently stored and transported in blood by albumin; this was confirmed by UV absorption spectrometry and fluorescence quenching method (Markovic et al. 2005). Various pre-clinical studies have shown that SA is well tolerated and oral tolerance of SA was appreciable (Alaofi 2020; Shin et al. 2013a, b; Roy and Maizen Prince 2013).

Mechanisms involved in the anticancer activity of SA

Anti-tumorigenic and chemopreventive effects of SA

Balaji et al. reported the anticancer role of SA on 1,2 dimethyl hydrazine (DMH) in Wistar rats (Balaji et al. 2014). DMH was given at a dose of 20 mg/kg body weight subcutaneously to induce colon cancer in rats. SA was supplemented through oral gavage route at different doses (20, 40, 60 and 80 mg/kg body weight) for 16 weeks to study its effect. SA treatment reduced the incidence of polyp up to 66.66% and prevented the DMH-induced histological abnormalities such as dysplasia, enlarged nuclei and densely packed inflammatory cell infiltrates and lymphoid aggregates in colon. In another study (Balaji et al. 2015) on colon cancer, oral administration of SA up to 80 mg/kg body weight reduced the number of aberrant crypt foci up to 34.55% compared to the DMH-induced colon cancer-induced group (58.83%). Anti-tumor effect of SA on dimethyl benz(a)anthracene (DMBA)-induced experimental oral cancer was reported in Syrian hamsters (Kalaimathi and Suresh 2015a). SA was administered orally (50 mg/kg body weight) for 16 weeks. The incidence of oral cancer was 100% in DMBA-induced group that was reduced to 20% in SA-supplemented animals. SA treatment also reduced tumor volume and ameliorated the histological changes such as hyperkeratosis, hyperplasia, thickened epithelial layer and keratin pearl formation induced by DMBA. All these findings support the anti-tumorigenic and chemopreventive effects of SA.

SA modulates cellular redox homeostasis

Free radical and non-radical oxidizing species (reactive oxygen species) (ROS) are commonly elevated in cancerous conditions and reports suggest that these free radicals and electrophiles mediated oxidative stress have an important role in all stages of chemical carcinogenesis and tumorigenesis (Anandakumar et al. 2008). These toxic radicals are involved in inducing cellular lipid peroxidation (LPO) that disturb the cellular redox homeostasis. SA has the ability to reduce carcinogenic burden by its potent anti-peroxidative efficacy by strengthening the cellular antioxidant defense system. Balaji et al. (2015) have reported that the levels of serum thiobarbituric acid substances (TBARS) and conjugated dienes (CDs) were increased (1.5-fold and 0.5-fold) in the DMBA-induced colon cancer in rats; the levels/activities of antioxidants like SOD, CAT, GPX, GST, GR, GSH, vitamin C and vitamin E were also decreased in colon cancer-bearing rats. Supplementation of SA was found to be effective in improving the abnormalities induced by DMBA. Another study also reported the ability of SA to improve cellular antioxidants against lung cancer (Hu et al. 2021). Tungalag et al. (2021) showed that the expression of antioxidant proteins such as SOD1, SOD2 and CAT were significantly increased upon SA treatment in SH-SY5Y human neuroblastoma cells. Other than its potent antioxidant function, SA also possesses pro-oxidant effect

that has been identified to affect the redox state of tumor cells (Martin-Cordero et al. 2012). Due to increased alterations in their metabolism and signaling pathways, cancer cells produce high amount of ROS that results in a state of increased basal oxidative stress (Shah and Rogoff 2021). At this state, cancer cells become highly susceptible to pro-oxidant agents that enhance the production of ROS to a level where they become cytotoxic. SA at higher concentrations acts as a potent pro-oxidant agent, resulting in increased generation of free radicals. Janakiraman et al. (2014) reported this effect of SA in human laryngeal carcinoma cell line (HEp-2). SA-treated cells showed increased ROS levels in the treated cells (108.32 ± 7.32) compared to untreated cells (76.41 ± 7.09) (Janakiraman et al. 2014). Hu et al. (2021) reported that in human lung A549 cells, SA (50 and 75 μM) increased ROS accumulation in the treated cells compared to the untreated cells. Similar results were reported by Badr et al. (2019) in A549 and Caco-2 cancer cell lines.

Effect of SA on liver biotransformation enzymes and intestinal bacterial enzyme activity

The activity of biotransformation enzymes plays a critical role in the activation as well as elimination of carcinogens. While phase I enzymes are responsible for the activation of pro-carcinogen to its active carcinogen, phase II enzymes are involved in the conjugation of such compounds, making them more water soluble and excretable. Balaji et al. (2014) studied the modulatory effect of SA on biotransformation enzymes in rat colon cancer, and Kalaimathi and Suresh (2015a, b) also reported the modifying effect of SA on phase I and II enzymes in rat buccal carcinogenesis. In all these studies, the activities of liver phase I biotransformation enzymes like CYP450 and CYP2E1 were markedly increased and the activities of phase II biotransformation enzymes such as glutathione-S-transferase (GST), DT-diaphorase (DTD) and UDP-glucuronyl transferase (UDP-GT) were markedly decreased in cancer-bearing animals on SA treatment. The activities of biotransformation enzymes were reinstated to near normal levels in both the studies.

The intestinal bacterial enzymes play a significant part in the pathogenesis of several cancers (Jackson and Theiss 2020). These enzymes are responsible for activating the metabolism of carcinogens and tumor promoters in the colon. Additionally, the toxic and genotoxic metabolites produced by the intestinal microflora may bind to the particular intestinal cell surface receptors and regulate intracellular signal transduction. Balaji et al. (2015) have reported the influence of SA on regulating the intestinal bacterial enzyme activity in a rat colon cancer model. The activities of fecal bacterial enzymes such as β-glucuronidase, β-glucosidase, β-galactosidase, nitro-reductase, sulfatase and mucinase were modulated in SA-treated animals.

Effect of SA on serum marker enzymes

LPO-induced tissue damage is the sensitive feature in the cancerous conditions and any damage to membrane may result in the leakage of these enzymes from the tissues (Scandolara et al. 2022). Cancer chemoprevention and therapy depends on the investigation of these marker enzymes. Hu et al. (2021) have studied the effect of SA on changes in the levels of serum marker enzymes in benzo(a)pyrene (B(a)P) induced lung cancer in mice. The levels of serum CEA, AHH, LDH, GGT, and 5'NT were abnormally raised in the B(a)P-induced lung cancer-bearing mice. These changes in the serum enzymes were reinstated in the SA (30 mg/kg body weight)-treated mice.

Effect of SA on hematology and immunoglobulins

Hematological abnormalities are commonly found in cancer. The most common one being anemia because of acute or chronic blood loss, marrow involvement by the malignancy, marrow suppressive effects of chemotherapy or radiation therapy (Yoshida et al. 2022). Hu et al. studied the effect of SA on hematological alterations in experimental lung cancer (Hu et al. 2021). Changes in the levels of hematological parameters such as leucocytes, neutrophils, lymphocytes, absolute lymphocyte count and absolute neutrophil count were observed in lung cancer-bearing animals. SA treatment effectively improved all the abnormalities in hematological parameters.

The level of immunoglobulin (IgG and IgM) production is diminished in patients with cancer, an indicative of compromised humoral immunity and immune reaction (Gasser et al. 2021). Modulation of immunoglobulin production during cancer can be considered as an alternate approach for the prevention of the disease. The effect of SA on modulating immunoglobulin levels in lung cancer in rats has been reported (Hu et al. 2021). SA administration markedly improved the levels of IgG and IgA in the treated animals compared to the untreated animals. It can be understood that SA has the capability to modulate immune response during cancer.

Effect of SA on inflammation

Chronic inflammation signifies an important pathologic basis for the majority of human cancers (Michels et al. 2021). There is copious evidence from animal and human studies that persistent inflammation works as a major driving force in the path to cancer (Blanchard and Girard 2021). It is reported that about 26% of all cancers are somehow related to chronic infection and inflammation and chronic inflammation is associated in all stages of carcinogenesis, i.e., initiation, promotion and progression

(Missiroli et al. 2020). Even though inflammation functions as an adaptive host defense against infection or injury and is commonly a self-limiting process, abnormal regulation of inflammatory responses may result in several chronic ailments including cancer (Piotrowski et al. 2020). The regulatory role of SA on inflammation in B(a)P-induced lung cancer in Swiss albino mice was demonstrated (Hu et al. 2021). Lung cancer animals showed increase in the levels of pro inflammatory cytokines such as TNF-α (150 times) IL-6 (100 times) and IL-1β (140 times) suggesting inflammation. SA treatment was found to markedly reduce the levels of TNF-α, IL-6 and IL-1β levels. The anti-inflammatory effect of SA reported in this study is its ability to regulate NF-kB pathway. However, the exact molecular mechanism on which SA exerts its effect is not clear.

Effect of SA on cell cycle arrest

The cell cycle is central to keep continuity in cell proliferation and to ascertain the protection of proliferating cells from DNA damage. The key regulators of cell cycle are cyclin-dependent kinases (CDKs), cyclins, and CDK inhibitors (CKIs). Cancer development is often associated with loss/dysregulation of cell cycle (Feitelson et al. 2015). Many anticancer compounds are found to regulate cell cycle progression as a part of their chemopreventive/chemotherapeutic mechanism (Meeran and Katiyar 2008). Studies have reported that SA has the potential in arresting cancer cells at different phases of cell cycle progression through stimulation and inhibition of different protein regulators and checkpoints. For instance, Janakiraman et al. (2014) reported the effect of SA on cell cycle regulation in Hep-2, laryngeal carcinoma cell line. The findings of the study showed that SA induced an early G0/G1 phase arrest in Hep-2 cells in a dose-dependent manner. Zhao et al. (2021) found that SA induced G2/M phase cell cycle arrest in Hep G2 and SMMC-7721 cell lines. The percentage of apoptotic cells of HepG2 cells and SMMC-7721 cells in G2/M phase treatment increased from 12.79 ± 0.89% in control to 22.60 ± 2.26% and 26.00 ± 1.30% after SA along with cisplatin treatment. Similarly, Kampa et al. (2004) showed that SA significantly reduced the number of cells in the G2/M phase and enhanced the S phase in T47D breast cancer cells compared to the untreated cells.

Effect of SA on autophagy

Autophagy also known as type II programmed cell death plays a critical role in cancer. Autophagy has an active tumor-suppressive or tumor-stimulating function in various process and stages of cancer development (Bai et al. 2022). In the early stage of cancer, autophagy acts as a survival pathway and quality-control mechanism inhibits tumor initiation and suppresses cancer progression. During the later stages of tumor, autophagy functions as a dynamic degradation and recycling system, leading to the survival and growth of the tumors and induces aggressiveness of the cancers by helping in metastasis. This indicates that regulation of autophagy can be used as effective interventional strategies for cancer therapy (Russell and Guan 2022).

The autophagy inducing effect of SA has been reported by Zhao et al. (2021) in HepG2 and SMMC-7721 cells. MDC staining for autophagy showed increased number of green granular structures in cytoplasm and nucleus area of both SA along with cisplatin treated HepG2 and SMMC-7721 cells compared to the untreated cells. The protein expression of Beclin, Atg 5 increased and expression of p62 decreased in SA along with cisplatin treated HepG2 and SMMC-7721 cells. mRNA expressions of protein involved in autophagy, LC3-II also increased considerably in SA along with cisplatin treated HepG2 and SMMC-7721 cells.

Effect of SA on angiogenesis, cell invasion and metastasis

Angiogenesis is a complex physiological process through which the new blood vessels form from the existing vasculature. Angiogenesis plays a foremost function in the tumor growth and metastasis (Poto et al. 2022). Cancer cells are highly dependent on the vascularization for further growth of cells beyond 1–2 mm^3 (Ozel et al. 2022). SA has been demonstrated to inhibit angiogenesis, cell invasion and metastasis in cancer cells through different mechanisms (Huang e t al. 2021; Eroglu et al. 2018).

Effect of SA on epithelial-to-mesenchymal transition (EMT)

Huang et al. (2021) reported the effect of SA on angiogenesis, cell invasion and metastasis in pancreatic cancer cell lines (PANC-1 and SW1990). SA (10 mM) treated cells showed decreased protein expression of EMT related proteins such as vimentin, MMP-9, MMP-2, and Snail and increased expression of E-cadherin in PANC-1 and SW1990 cell lines. Furthermore, with the increasing concentration of SA, the expression of MMP-9 and MMP-2 gradually decreased. This showed that SA can effectively regulate EMT.

Effect of SA on downregulation of AKT/Gsk-3β signal pathway

The AKT/Gsk-3β signal pathway regulates proliferation, invasion, apoptosis, and metabolism, and plays a prominent role in the progression of cancer. The regulatory

role of SA on AKT/Gsk-3β signal pathway in prostate cancer cell lines has been reported (Huang et al. 2021). SA treatment downregulated phosphorylated AKT and Gsk-3β in PANC-1 and SW1990 prostate cancer cell lines. The results of the study showed that SA inhibited prostate cancer by the downregulation of AKT/ Gsk-3β signal pathway. Eroglu et al. (2018) have also reported the anticancer property of SA (1000 μM) on human prostate cancer cell lines (PC-3 and LNCaP) through a similar mechanism. Further experimentation in a wider range of cell lines is required to confirm the effect of SA.

Effect of SA on cell proliferation and apoptosis

Cell proliferation is thought to play an important role in several steps of the carcinogenic process. Apoptosis has now established its significance in various areas of biology, and it recently received outstanding attention as a vital area related to the development and treatment of cancer (Wong Kaewkhiaw 2022). Apoptosis is a distinct form of cell death explicated by characteristic morphological and biochemical features. Numerous studies have revealed that imbalance in the homeostatic mechanisms, which control cell proliferation and cell death (apoptosis), can add to the development and growth rate of a tumor (Shen et al. 2022). In fact, apoptosis has a central role in restricting the population expansion of tumor cells early in the process of carcinogenesis, and inhibition of apoptosis has been shown to play a significant part in the genesis of tumor (Kang et al. 2022). If DNA damaged cells no longer respond to apoptosis, mutations may be acquired and fixed through further proliferation, which may lead to malignant neoplasia. Therefore, it is important that apoptosis-inducing and proliferation-inhibiting activity may be considered as a primary aspect in determining the effectiveness of chemopreventive agents.

A number of studies have demonstrated that SA can inhibit cell proliferation in prostate cancer (Eroglu et al. 2017), liver cancer (Zhao et al. 2021), breast cancer (Raj Preeth et al. 2019), pancreatic cancer (Huang et al. 2021) and myeloid leukemia (Rajendran et al. 2017) and induce apoptosis in cell line models. Badr et al. (2019) studied the effect of free and nano-capsulated SA on human lung (A549) and colon cancer (Caco-2) cell lines. The protein expression of Bax and p53 was increased; Bcl-2 was decreased in SA (free and capsulated)-treated cells. Janakiraman et al. (2014) studied the apoptotic effect of SA on human laryngeal carcinoma cell line (HEp-2). SA-treated cells showed significant membrane blebbing, chromatic condensation, and innumerable micronuclei in cells indicating apoptosis. The apoptotic inducing effect of cisplatin combined with SA on the hepatic cancer cells (HCC) HepG2 and SMMC-7721 were investigated by Zhao et al. (2021). SA dose dependently induced apoptotis in both HepG2 and SMMC-7721 cell lines. It is reported that the percentage of apoptotic cells of HepG2 cells and SMMC-7721 cells in G2/M phase treatment increased from 12.79 ± 0.89% in control to 22.60 ± 2.26% and 26.00 ± 1.30% after SA along with cisplatin treatment. The apoptotic inducing function of SA on human hepatocellular carcinoma cell lines (Hep 3B and Hep G2) was studied (Eroglu et al. 2017). Results of qPCR analysis showed that the mRNA expressions of CASP3 and FAS were significantly increased to 23.37-fold and 27.47-fold in SA-treated Hep 3B cells. Similarly, the mRNA expression of CASP3 was increased to 1.53-fold; CASP8 to 1.77-fold; CASP9 to 1.21-fold; BAX to 1.47-fold and FAS to 1.39-fold. Other studies have also reported the apoptosis-inducing nature of SA in neuroblastoma (Tungalag and Yang 2021), breast cancer (Kampa et al. 2004) and oral cancer (Kalaimathi and Suresh 2015b).

Effect of SA as a co-adjuvant in anticancer therapy

SA acts in collaboration with other chemotherapeutic agents to improve treatment sensitivity. A study investigated the anticancer effects of cisplatin combined with SA against hepatic cancer cells (Zhao et al. 2021). SA in combination with cisplatin was found to effectively induce apoptosis, autophagy and prevented cell proliferation. This study showed that SA along with cisplatin treatment exhibited a better anti-tumorigenic effect compared to only cisplatin treatment in hepatocellular carcinoma.

Toxicity of SA

SA is found to be generally non-toxic, but few studies have reported its toxicity. One study reported that SA showed slightly increased cytotoxic activity than its ester derivate (Fan et al. 2009). The cytotoxic profiles of SA in V79 Chinese Hamster lung fibroblasts were reported. The study showed that SA up to 2000 μM concentration did not show any appreciable effects on the viability of V79 cells and at a very high concentration of above 5000 μM resulted in cytotoxic effects (Zheng et al. 2008). The genotoxic effect of SA on adenocarcinoma colon cells was reported by Lee-Manion et al. (2009). Results using Comet assay revealed that SA did not induce appreciable genotoxicity in human adenocarcinoma cells.

Future applications of SA

It is interesting to know that SA is principally involved in regulating oxidative stress, cellular antioxidants, cell proliferation, xenobiotic metabolism, metastasis, apoptosis, cell cycle, DNA damage, angiogenesis, inflammation and autophagy. Some studies on SA consistently explore that SA improves the effect of pro-apoptotic chemotherapeutic agents like cisplatin, especially in the human cell line models. In the future, further studies of SA are to be undertaken to explore its potential implication in treating different human carcinomas.

Conclusions

This review has summarized the plausible mechanisms involved in the anticancer effect of SA against different types of cancer in cell lines and animal models (Table 1; Fig. 2). Therefore, the bioavailability, toxicity and route of administration of SA requires further research and development. Moreover, since most of the investigations mentioned in the current work are based on in vitro studies, more findings on animal models and human subjects are highly recommended in the future in order to implement SA as a potential anticancer drug.

Table 1 Summary of the anticancer effects of Sinapic acid

S. No.	References	Cancer type	Model used	Major mechanism/effect	References
1	Balaji et al. (2014)	Colon cancer	Wistar Albino rats	Reduction of tumor incidence, altering lipid peroxides, enhancing cellular antioxidants and modulating the activities of biotransformation enzymes	27
2	Balaji et al. (2015)	Colon cancer	Wistar Albino rats	Decreasing pre-neoplastic lesions, curbing LPO, improving cellular antioxidants, modulating the activities of bacterial enzymes	28
3	Hu et al. (2021)	Lung cancer	Swiss albino mice and A549 cell line	Reduction of tumor burden, oxidative damage and inflammation	31
4	Badr et al. (2019)	Lung and Colon cancer	A549 and Caco-2 cell lines	Regulation of apoptotic pathway and cell cycle arrest	36
5	Janakiraman et al. (2014)	Laryngeal carcinoma	Hep-2 cell line	Regulation of apoptotic pathway and cell cycle arrest	35
6	Eruglu et al. (2018)	Prostate cancer	PC-3 and LNCaP cell lines	Prevention of cell proliferation, cell invasion and induction of apoptosis	53
7	Zhao et al. (2021)	Liver cancer	Hep G2 and SMMC-7721 cell lines	Prevention of cell proliferation, induction of autophagy and apoptosis	47
8	Eruglu et al. (2017)	Liver cancer	Hep 3B and HepG2 cell lines	Regulation of apoptotic pathway	57
9	Tungalag et al. (2021)	Neuroblastoma	SH-SY5Y cell line	Regulation of oxidative stress, ER stress, antioxidants and apoptosis pathway	32
10	Kampa et al. (2004)	Breast cancer	T47D cell line	Regulation of apoptosis and cell cycle arrest	48
11	Raj Preeth et al. (2019)	Breast cancer	MCF7 and MDA-MB23 cell lines	Reduction of cell proliferation and regulation of angiogenesis	58
12	Rajendran et al. (2017)	Myeloid leukemia	K562 cell line	Reduction of cell proliferation and regulation of ROS production	59
13	Kalaimathi and Suresh (2015a)	Buccal pouch carcinoma	Syrian Hamsters	Modulation of antioxidant defense system and regulating the activities of biotransformation enzymes	29
14	Kalaimathi and Suresh (2015b)	Buccal pouch carcinoma	Syrian Hamsters	Modulation of proteins involved in apoptosis pathway	60
15	Huang et al. (2021)	Pancreatic cancer	In vivo and in vitro studies	Regulation of cell proliferation, migration and invasion by down-regulating AKT/Gsk-3β signal pathway	19

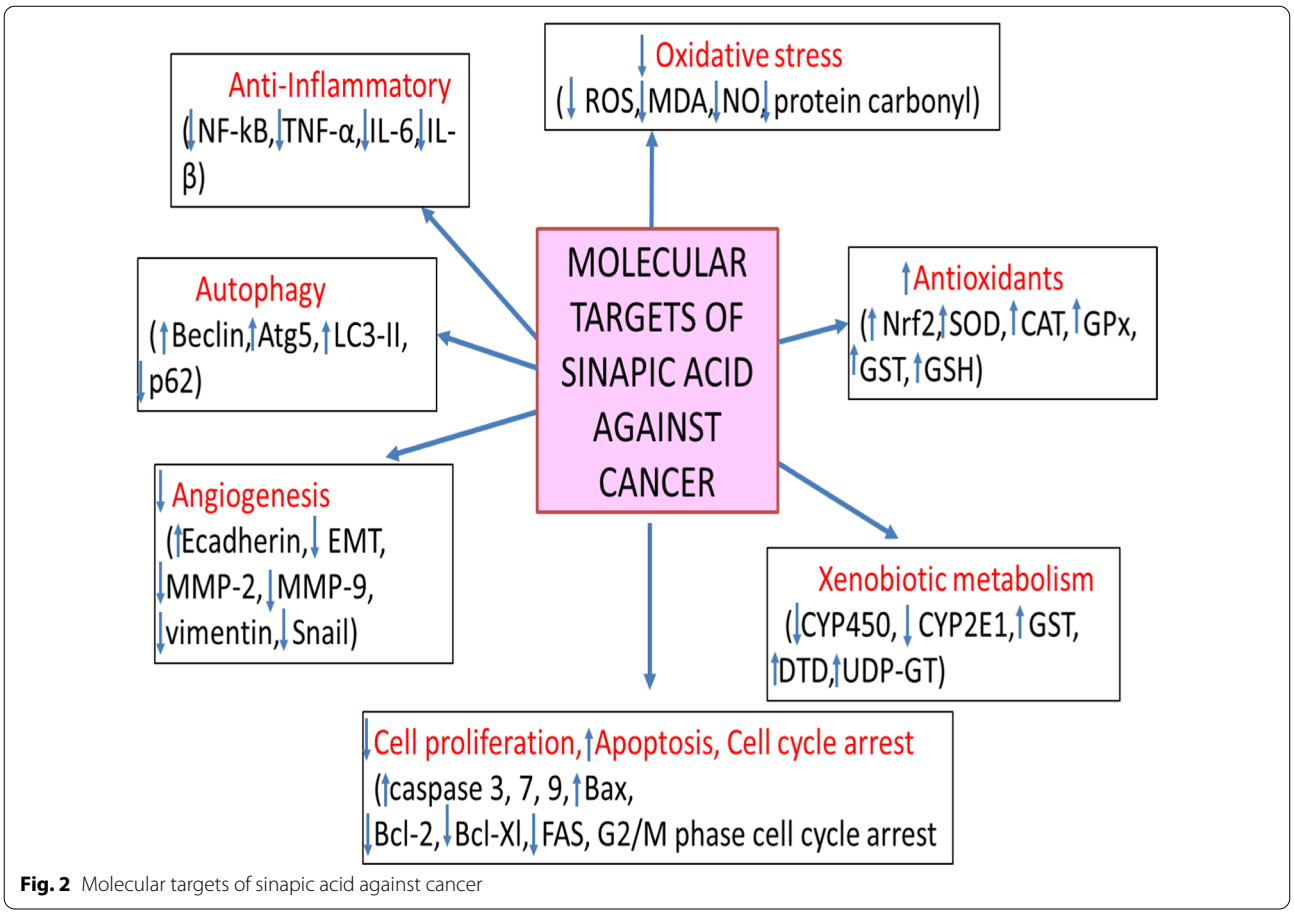

Fig. 2 Molecular targets of sinapic acid against cancer

Abbreviations
SA: Sinapic acid; HCC: Hepatic cancer cells; Ig: Immunoglobulin; CEA: Carcinoembryonic antigen; AHH: Aryl hydrocarbon hydroxylase; LDH: Lactate dehydrogenase; GGT: Gamma glutamyl transpeptidase; NT: Nucleotidase; GST: Glutathione-S-transferase; DTD: DT diapharose; SOD: Superoxide dismutase; CAT: Catalase; GR: Glutathione reductase; GSH: Reduced glutathione; LPO: Lipid peroxidation; ROS: Reactive oxygen species; DMBA: Dimethyl benza(a)nthracene; TNF: Tumor necrosis factor; IL: Interleukins; CDK: Cyclin-dependent kinase; CKI: CDK inhibitors; MMP: Matrix metalloproteinase; EMT: Epithelial-to-mesenchymal transition.

Acknowledgements
Not applicable.

Author contributions
All authors have read and approved the manuscript. AP planned and written the manuscript, VMK helped in preparing the tables and figures. All authors read and approved the final manuscript.

Funding
No funding was obtained for this study.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
Authors declare that there are no competing interests.

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Received: 16 July 2022 Accepted: 6 October 2022
Published online: 15 October 2022

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