Fruit seed extracts: A class of natural anticancer candidate resources (Review)

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Abstract. The present review aimed to explore the anticancer potential of fruit seeds, focusing on their bioactive components and mechanisms of action to evaluate the application of these natural by-products in cancer intervention. In the present article, fruits are categorized into four major groups, namely berries, stone fruits (drupes), pepo fruits (melons) and aggregate fruits. The review summarizes the active components in seeds of different families and also explains the anticancer mechanisms of polyphenols, terpenoids and other compounds. Fruit seeds from different plant families contain distinct sets of active compounds. These chemical differences lead to varied anticancer potentials. However, the extraction process needs to be standardized and clinical translation research should be accelerated.

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1. Introduction

Natural products have attracted attention in antitumor research due to their advantages of diverse structures, high safety and rich targets (1). First-line chemotherapy drugs such as paclitaxel, vincristine and camptothecin all originate from secondary metabolites of natural plants. Among the antitumor drugs approved in recent decades, >40% are related to natural products and their derivatives (2,3). Plant secondary metabolites possess advantages such as diverse structures, novel skeletons, good biocompatibility and multi-target effects (4,5). They are an important source for discovering anticancer lead compounds, overcoming drug resistance and developing low-toxicity and highly efficient preparations.

As a by-product of the fruit processing industry, fruit seeds have a huge annual output and have been abandoned or used at low value for a long time, resulting in a waste of resources and environmental pollution (6). Development of the anticancer resources of fruit seeds is in line with the green and low-carbon concepts, as well as a circular economy; it has numerous benefits, including environmental protection, and economic and societal benefits, through the conversion of processing residues into marketable products and the reduction of waste-disposal costs. It is an important direction for the high-value utilization of natural product resources. Compared to the fruit flesh and peel, fruit seeds have a higher content of active components, improved stability and are easier to store. A large number of studies have shown that the content of active substances such as polyphenols, terpenoids, flavonoids, unsaturated fatty acids, polysaccharides and protein peptides in fruit seeds is generally higher than that in the flesh, peel, leaves and stems (7,8). In addition, as the reproductive organ of plants, seeds have a more complex and diverse composition of secondary metabolites, and possess multiple activities such as antioxidant, anti-inflammatory, antitumor and immune regulation activities (6,8). Seeds also have a low water content, hard texture and strong component stability. They are easy to store at room temperature and do not easily deteriorate. The extraction process is simple and the cost is low, making it convenient for industrial-scale development and a good industrialization prospect.

At present, research on the anticancer effects of fruit seeds mainly focuses on scattered reports of a single variety or a single component, lacking systematic organization (9,10). The present review focuses on the representative fruit seeds of four major groups: Berries, stone fruits (drupes), pepo fruits (melons) and aggregate fruits. The review systematically summarizes the family and genus origins and the distribution

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characteristics of active components of representative fruit seeds in various groups, and clarifies their anticancer molecular mechanisms according to the types of chemical components. To the best of our knowledge, this is one of the first reviews to systematically link plant taxonomic origin with chemical class and anticancer mechanism for fruit seeds, with the aim of providing references for the high-value utilization of fruit seed resources and anticancer strategies based on natural products. The comprehensive overview of anticancer properties of fruit seed bioactive compounds is summarized in Fig. 1.

2. Anticancer activities of seeds from different fruit groups

Berry fruit seeds. Berries mainly include plants from families such as Vitaceae, Myrtaceae and Rosaceae. Their fruits are juicy and soft, with small and numerous seeds. The seeds contain mainly active components such as polyphenols, flavonoids, proanthocyanidins, anthocyanins, unsaturated fatty acids and polysaccharides, and have particularly prominent antioxidant and anti-inflammatory activities (11).

Grape seeds of *Vitis vinifera* L. are the most systematically and deeply studied resource among the berry types. The seeds of grapes are rich in proanthocyanidins, which belong to the flavanol type of phenolic compounds (12). The oligomers and polymers of proanthocyanidins in grape seeds possess extensive pharmacological activities and medicinal value (13). At present, the extraction and purification of grape seed extract (GSE) has been achieved and it is commonly used as a dietary supplement (12). Numerous studies have shown that GSE can exert antitumor activity through multiple mechanisms both *in vitro* and *in vivo*. GSE not only inhibits the kinase activity of purified VEGFR2 but also blocks the signal pathways regulated by mitogen-activated protein kinases (MAPK) in endothelial cells. It achieves anticancer effects by inhibiting the proliferation and migration of endothelial cells induced by VEGF and the process of vascular regeneration in the aorta, where the water-soluble polyphenol components in grape seeds are the key substances mediating this anti-angiogenic activity (14,15). In terms of promoting apoptosis, grape seed proanthocyanidins can activate caspase-3 to induce tumor cell apoptosis (16-18). In addition, GSE can interfere with the metabolism of purines and pyrimidines by inosine monophosphate dehydrogenase 1/2 inhibition, inducing cell cycle arrest and apoptosis (18,19).

Miracle berry (*Synsepalum dulcificum*) of the Sapindaceae family is a type of berry that comes from West Africa, named for its ability to convert sourness into sweetness (20). Wagner *et al* (21) obtained the extract of miracle berry seeds through supercritical fluid extraction technology. This extract is rich in pentacyclic triterpenoids and can notably inhibit mitochondrial respiration, deplete ATP and target the inhibition of cancer-related lipid metabolism, indicating its potential as a cancer metabolic inhibitor. Lupeol, a representative pentacyclic triterpenoid of this class, has itself been shown to exert marked anti-proliferation effects on cancer cells, and this activity has been verified in hepatocellular carcinoma, osteosarcoma, colorectal cancer and other tumor models (22-24).

Blackberry seeds (*Rubus* spp. L., Rosaceae) belong to the small berries of the Rosaceae family and have a high content of anthocyanins in their fruits. Due to their diverse biological activities, these fruits have become a research hotspot (25). Numerous studies have confirmed that their extracts possess multiple pharmacological effects such as antioxidant (26), anti-inflammatory (27), antibacterial (28) and antitumor (29) properties. Choe *et al* (30) found that the extract of blackberry seed powder could inhibit the expression of IL-1β mRNA induced by lipopolysaccharide in J774A.1 mouse macrophages, and also that it had a notable inhibitory effect on the proliferation of human lymph node carcinoma of the prostate (LNCaP) cells. Further research on glioma indicated that the extract of blackberry fruits could selectively inhibit the viability and proliferation ability of rat C6 and human U87 glioma cell lines and would not interfere with the normal growth of primary astrocytes. This shows a role in tumor cell selectivity (31).

Raspberry (*Rubus idaeus* L.) is a type of berry belonging to the Rosaceae family and the *Rubus* genus. It is rich in natural polyphenolic active components, among which ellagic acid is the most typical polyphenol in its fruit (32,33). *In vitro* studies have shown that ellagitannins extracted from black raspberry seeds and their metabolites, ellagic acid and urolithins, can exert anticancer activity by inducing cell cycle arrest and promoting apoptosis of human HT-29 colon cancer cells (34). Rodriguez *et al* (35) found that supplementing a diet with 10% (weight/weight) freeze-dried black raspberries in a mouse model of colitis reduced tumor multiplicity and prolonged the length of the colon, but had no notable effect on improving colitis and protecting the mucosa.

Notably, research on the anticancer activity of berry seeds is highly concentrated on grape seeds, while studies on other berry species such as blackberry and raspberry remain relatively preliminary. Most *in vitro* studies use crude extracts with poorly defined chemical profiles, making it difficult to accurately attribute the observed bioactivities to specific compounds.

Stone fruit seeds. Stone fruits (drupes) are a type of fleshy fruit characterized by a thin epicarp, a fleshy mesocarp and a hard woody endocarp enclosing a single seed. The present review focuses on açaí and date palm, whose seeds are major by-products of fruit processing (36).

Açaí (*Euterpe oleracea Mart*.) is the drupe fruit of the açaí palm, an Arecaceae species native to the Amazon region. Its fruits are rich in polyphenols. The flesh and peel have been widely reported for their various biological activities such as antioxidant, anti-inflammatory, heart protection and anticancer properties. This is mainly attributed to its key components cyanidin-3-glucoside and cyanidin-3-rutinoside (37,38). Studies have shown that the seeds of the açaí berry account for 85% of the total weight of the fruit and are rich in polyphenolic compounds such as phenolic acids, catechins and proanthocyanidins, indicating their notable pharmacological potential (37,39). *In vitro* studies have shown that the extract of açaí berry seeds induces autophagy in the MCF-7 breast cancer cell line by altering the ultrastructure of the cells (40). da Silva *et al* (41) found that the seed oil of açaí berry can induce apoptosis in CACO-2 and HCT-116 cells and interfere with the cell cycle. The water-alcohol extract of açaí berry seeds exhibited antitumor potential in the Ehrlich mouse model of breast cancer, markedly reducing tumor size and improving inflammatory and oxidative stress indicators (42).

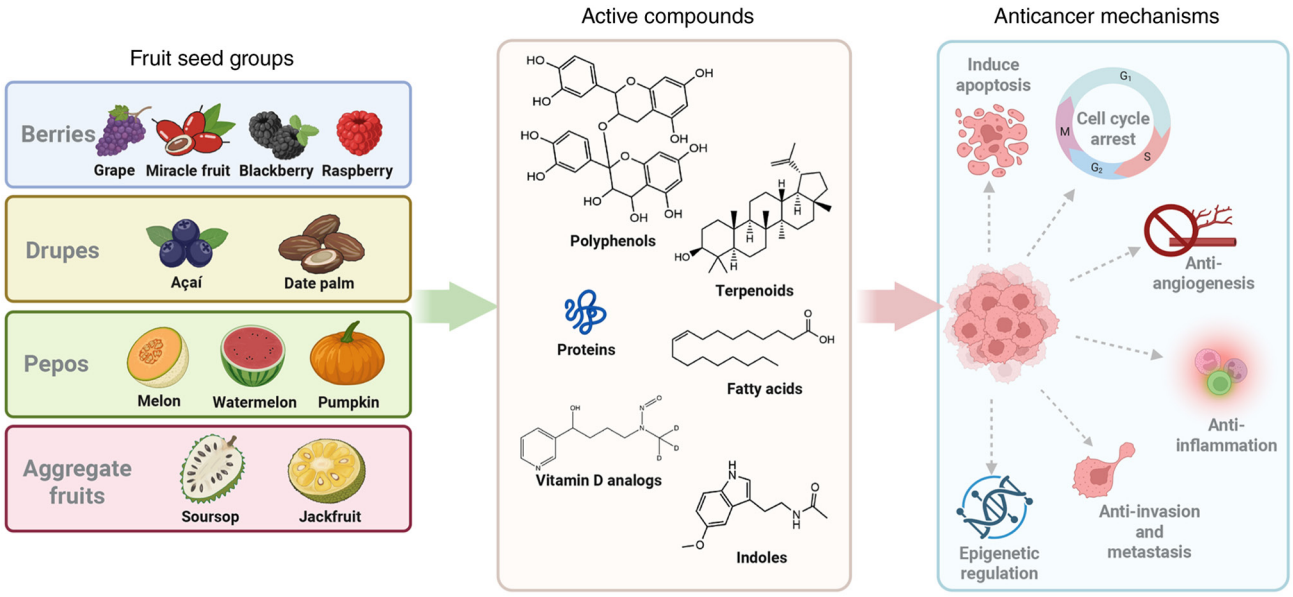


Figure 1. Graphical summary of fruit seed-derived anticancer candidates. Created using BioRender (https://biorender.com/wol3esv).

Filho *et al* (43) likewise reported that açaí seed extract exhibited cytotoxicity towards LNCaP prostate cancer cells and reduced solid Ehrlich tumor growth in mice, accompanied by antitumor and immunomodulatory effects.

Date palm (*Phoenix dactylifera* L.) is an important staple food and economic crop in regions such as the Middle East and North Africa. Its seeds are one of the main by-products of the edible pulp of date palm, and their weight usually accounts for 10-15% of the total weight of date palm (44). Studies have shown that the seeds of date palm are rich in numerous bioactive components such as phenolic acids, flavonoids, carotenoids and dietary fibers (45,46). In terms of antitumor mechanisms, date palm seed extract can inhibit the proliferation of liver, lung, colorectal and other cancer cells in a dose-dependent manner (47,48). It also induces cell apoptosis. Khan *et al* (49) demonstrated that it exerted a pro-apoptotic effect in MDA-MB-231 cells by activating caspase-3. At the mechanism level, the date seed extract downregulates the expression of peroxisome proliferator-activated receptor-γ, CCAAT/enhancer-binding protein α and adiponectin. It upregulates glucose transporter type 4 and phosphorylated AMPK. It also simultaneously upregulates p21 and p53 while inhibiting Bcl-2. This further confirms that it exerts antitumor effects through the apoptotic pathway (50).

However, numerous studies on stone fruit seeds remain at the phenotypic level of cytotoxicity screening, and in-depth mechanistic verification and *in vivo* efficacy validation are still insufficient.

Pepo fruit (melon) seeds. All pepo fruit belong to the Cucurbitaceae family, including melons, pumpkins, cucumbers and watermelons. Their fruits are large, fleshy gourd fruits, with flat seeds that are rich in oil content. Their seeds are rich in triterpenoids, cucurbitins, protease inhibitors, phenolic compounds and storage proteins (51).

Melon (*Cucumis melo* L.) is a crop of notable commercial value within the Cucurbitaceae family (52,53). The pharmacological activities of this plant have been widely confirmed, including anti-inflammatory, antioxidant, liver-protective, diuretic, anticancer, anti-ulcer and immune-regulating effects (51,54). A number of components in melons have been verified, such as cucumol A, cucumol B, phenolic compounds, trypsin inhibitors, melon trypsin inhibitor, cucurbitacin B (CuB) and cucurbitacin E (CuE) (54,55). The extract of melon seeds has shown marked anticancer activity against a number of malignant tumors such as leukemia, multiple myeloma, and breast, ovarian, colon, prostate and cervical cancer (55,56). Yuan *et al* (57) further demonstrated that CuB can increase intracellular reactive oxygen species (ROS) and Ca^{2+} levels. This increase induces Toll-like receptor 4/NOD-like receptor family pyrin domain containing 3/gasdermin D-dependent pyroptosis. As a result, CuB inhibits the progression of non-small cell lung cancer. In addition, the anticancer activity of CuB is superior to that of CuE. It can induce cell apoptosis and cell cycle arrest through the STAT3-dependent pathway (58), and can also induce the differentiation and apoptosis of human colorectal cancer RCM-1 cells in a dose-dependent manner (59). This provides a mechanism basis for the development and clinical translation of the antitumor potential of melon seed extract.

Watermelon (*Citrullus lanatus*) belongs to the Cucurbitaceae family (60). Its seeds are rich in numerous key nutrients such as protein, lipids, carbohydrates and dietary fiber (61). Watermelon seeds also possess multiple pharmacological activities, including antibacterial, antioxidant, anti-inflammatory, anti-diabetic, analgesic, preservative, anesthetic and antitumor properties (62). The core bioactive components of watermelon seeds can mostly be separated and extracted from the seed oil, and they have both high nutritional value and potential for medicinal development (63). Among them, the ethanol extract of watermelon seeds shows the most prominent activity. *In vitro* experiments have confirmed that it has notable concentration-dependent cytotoxic effects on liver cancer and cervical cancer cell lines (64).

Pumpkin (*Cucurbita moschata*) seeds are rich in a variety of phytochemicals, with palmitic acid, linoleic acid and other fatty acids as the core components. They also contain phenolic acids, flavonoid active monomers, alkaloids, steroids, terpenoids and other secondary metabolites (65). Studies have shown that these active components confer multiple pharmacological effects, such as deworming, lowering blood sugar, anti-depression, antioxidation, antitumor and cell protection effects (65,66). Among them, the antitumor effect has been verified by multiple *in vitro* experiments. For example, pumpkin seed extract can notably reduce the survival rate of melanoma cells and exhibit strong cytotoxicity (67). Alafaleq *et al* (68) found that copper-manganese bimetallic nanoparticles biogenically synthesized using pumpkin seed extract exerted a marked anti-proliferative effect on human colon adenocarcinoma HT-29 cells. Nomikos *et al* (69) further confirmed that pumpkin seed extracts prepared with different solvents, such as water, ethanol, ethyl acetate, acetone and polar lipids, all inhibited the proliferation of human androgen-independent prostate cancer PC-3 cells. Among these, the aqueous extract (200 and 400 μg/ml) and the polar lipid extract (300 μg/ml) induced autophagy, as monitored by the formation of LC3 autophagic puncta.

It should be noted that cucurbitacins, the core active components of melon seeds, have strong cytotoxicity but also potential systemic toxicity, and their therapeutic window needs to be further evaluated *in vivo* (55,57).

Aggregate fruit seeds. Aggregate fruits generally have special shapes and large seeds. They mainly include plants of the Moraceae and Annonaceae families. Representative seeds are those of the soursop and jackfruit, which are described below.

Soursop (*Annona muricata* L.) is a tropical plant from the Annonaceae family and is renowned for its various medicinal properties, including antioxidant, anti-inflammatory, antidiabetic and antitumor activities (70). The plant has been extensively explored in medicinal studies worldwide from its leaves, bark and roots to its fruits and seeds (71). In some tropical sub-Saharan countries such as Uganda and Kenya, a number of parts of the soursop are used to treat malaria, stomach pain, parasitic infections, diabetes and cancer (72). It has been reported that there are 212 bioactive compounds in soursop, among which acetogenin is the main component, as well as alkaloids and phenols (73). The seeds are also rich in oils, and the fatty acid and essential oil compositions of *Annona* seed oils have been well characterized (74). Prasad *et al* (75) discovered that the flesh of the soursop induces G_0/G_1 phase arrest and inhibits breast cancer cells. The seed extract has a stronger inhibitory effect, but its mechanism remains unclear. Kariyil *et al* (76) further revealed that the chloroform components of the seeds can induce S phase arrest and ROS-dependent mitochondrial apoptosis in triple-negative breast cancer cells. These results indicate that the extracts from different parts of the soursop can exert their effects through differentiated cell cycle checkpoints and apoptotic pathways. Among them, the active components in the seeds have notable research value in refractory breast cancer.

Jackfruit (*Artocarpus heterophyllus* Lam.) is a common economic crop in tropical regions. Its fruit pulp is widely popular, but its seeds are often overlooked. Relevant studies have shown that jackfruit seeds are rich in numerous active components such as saponins, flavonoids, lignans and alkaloids, and that they possess potential antioxidant, anti-inflammatory and anticancer activities (77-79). Jackfruit seed extract has cytotoxicity and anti-proliferative effects on tumor cells, such as liver, breast and colorectal cancer cell lines (80,81), while showing relatively lower cytotoxicity in selected experimental models. Dhani *et al* (78) further clarified that catechin, ferulic acid and other phenolic components in the fruit pit have high antioxidant capacity and multiple pharmacological properties. They reduce the risk of triple-negative breast cancer by reducing free radical production. Among them, the sugar binding protein Jacalin, found in the seeds, is one of the representative bioactive anticancer components. It shows strong antitumor activity against colon cancer, hematological malignancies and breast cancer (82).

For aggregate fruit seeds, the research on active components is mostly limited to qualitative identification, and the quantitative composition and *in vivo* anticancer efficacy data are still very scarce.

Summary of group differences in characteristics. Different groups of fruit seeds exhibit marked component specificity and enrichment patterns. Berries are mainly composed of polyphenols, proanthocyanidins anthocyanins, and their research and industrialization are the most mature. Stone fruits are rich in phenolic acids, flavonoids and anthocyanins. Pepo fruits have characteristic components such as cucurbitin, triterpenoids, phenols and oils. Aggregate fruits contain cyclic peptides, alkaloids, plant lectins and other unique substances. Except for berries, the seeds of stone fruits, cucurbitaceous fruits and aggregate fruit are mostly by-products of fruit and vegetable processing, and the mechanisms of most of their anticancer effects still need to be further clarified.

To provide a systematic overview of the current evidence base, Table I summarizes the evidence level and experimental model for each aforementioned fruit seed extract discussed (83-89). As shown, numerous findings derive from *in vitro* cell line experiments, with only a limited number of studies employing animal models. No clinical trials have been conducted for any of these fruit seed extracts in the context of cancer prevention or treatment, underscoring an important gap between preclinical observations and clinical translation.

3. Main types of chemical components in fruit seeds

Fruit seeds contain a number of bioactive substances such as polyphenols, terpenoids, fatty acids and protein peptides, as well as newly recognized indole derivatives such as phytomelatonin and plant-derived vitamin D analogs. Phytomelatonin is now considered a ubiquitous plant metabolite with antioxidant, immunomodulatory and oncostatic properties, and has been quantified in grapevine berry tissues (90) and in the seeds of date palm and other fruit species (91,92). Vitamin D-like compounds have also been identified in edible plant tissues, where they may act through the vitamin D receptor and related signaling pathways (91). Through multiple pathways and multiple targets, these components synergistically exert anticancer effects. The present review focuses on the aforementioned fruit seeds and summarizes their core

Table I. Evidence levels and experimental models for anticancer activity of individual fruit seed extracts.

Fruit seed	Major extract	Evidence level	Model system	(Refs.)
Grape seed (*V. vinifera*)	Grape seed proanthocyanidins/ proanthocyanidins	*In vitro* and *in vivo*	HL-60/ADR, MCF-7, HeLa; endothelial cells; aortic ring; zebrafish xenograft	(14,16,17, 19,83,84)
Miracle berry seed (*S. dulcificum*)	Pentacyclic triterpenoids (lupeol)	*In vitro*	Hepatocellular carcinoma, osteosarcoma, colorectal cancer cells	(21-24)
Blackberry seed (*Rubus* spp.)	Seed powder extract	*In vitro*	J774A.1 macrophages; lymph node carcinoma of the prostate; C6, U87 glioma	(29-31)
Raspberry seed (*R. idaeus*)	Ellagic acid and ellagitannins	*In vitro* and *in vivo*	HT-29 cells; mouse colitis-associated CRC model	(34,35)
Açaí seed (*E. oleracea*)	Polyphenol-rich extract; seed oil	*In vitro* and *in vivo*	MCF-7, CACO-2, HCT-116; Ehrlich mouse model	(40-42,85)
Date palm seed (*P. dactylifera*)	Polyphenol extract (date seed extract)	*In vitro*	Liver, lung, colorectal; MDA-MB-231	(47-50)
Melon seed (*C. melo*)	Cucurbitacin B, cucurbitacin E, trypsin inhibitor (melon trypsin inhibitor)	*In vitro* and *in vivo*	NSCLC; RCM-1; endothelial cells	(55-59,86)
Watermelon seed (*C. lanatus*)	Ethanol extract	*In vitro*	HepG2, HeLa	(64)
Pumpkin seed (*C. moschata*)	Multi-solvent extracts	*In vitro*	Melanoma; HCT-116; PC-3	(67-69)
Soursop seed (*A. muricata*)	Acetogenins; chloroform fraction; N-p-coumaroyl tyramine	*In vitro*	Breast cancer (triple-negative breast cancer); G_0/G_1 arrest	(73-76,87)
Jackfruit seed (*A. heterophyllus*)	Jacalin lectin; phenolic compounds	*In vitro*	MCF-7; colon; oral squamous cell carcinoma	(78,80, 88,89)

anticancer active components. The distribution and functions of the related components are detailed in Table II (93-97). The relative abundance of the six major classes of bioactive phytochemicals across the four categories of fruit seeds is visualized in the hexagonal radar chart (Fig. 2).

4. Mechanisms of anticancer actions of fruit seed extract

The principal molecular mechanisms underlying the anti-cancer activities of fruit seed extracts in tumor cell and animal models are illustrated in Fig. 3.

Induction of cell apoptosis. The dysregulation of apoptosis is an important mechanism of cancer development and drug resistance. Fruit seed extracts can induce tumor cell apoptosis through the endogenous mitochondrial pathway and exogenous death receptor pathway (83,84). In terms of endogenous pathways, grape seed proanthocyanin extract can upregulate Bax, downregulate Bcl-2, reduce mitochondrial membrane potential, promote cytochrome *c* release and activate caspase-9/3 cascade in breast cancer and colon cancer (84,98). Aglianico grape seed semi-polar extract promotes apoptosis by inhibiting the mouse double minute 2 (MDM2) pathway (99). Jackfruit and açaí seed extracts similarly activate mitochondrial pathways (43,100). Annonaceous acetogenins in soursop seeds interfere with energy metabolism and induce apoptosis or necroptosis by inhibiting complex I of the mitochondrial electron transport chain (87). In terms of the exogenous pathway, açaí seed oil induces apoptosis of colorectal cancer by upregulating the expression of annexin A2 and promoting the direct binding of its main active fatty acid components to annexin A2 (41).

Inhibition of cell proliferation and arrest of the cell cycle. Fruit seed extracts can inhibit cancer by arresting the cell cycle and inhibiting proliferation signaling pathways. GSE and melon and soursop seed extracts can induce G_1/S or G_2/M phase arrest in tumor cells, and the mechanism is related to the upregulation of cycle-inhibitory proteins and the reduction of cyclin D1, cyclin E and cyclin-dependent kinase activities (19,58,75,76). The half-maximal inhibitory concentration of the lectin extract from jackfruit seeds on MCF7 human breast cancer cells was 125 μg/ml, and this growth-inhibitory effect was associated with cell cycle arrest (80). In terms of proliferation signaling pathways, GSEs can interfere with purine and pyrimidine biosynthesis and MDM2-related pro-survival signaling (19,99), while CuE from melon seeds acts as a tyrosine kinase inhibitor of the EGFR/MAPK axis

Table II. Representative bioactive compounds, molecular targets, anticancer effects and evidence status of the fruit seeds reviewed.

A, Polyphenols

Compound class and representative	Source	Main anticancer effect	Primary molecular targets	Cancer types investigated	(Refs.)
Proanthocyanidins, catechins, gallic acid	Grape seed	Inducing apoptosis, blocking the cell cycle, inhibiting angiogenesis, and regulating epigenetics	VEGFR2, MAPK, caspase-3/9, Bax/Bcl-2, inosine monophosphate dehydrogenase 1/2	Breast, colon, bladder, leukemia, cervical	(83,84)
Anthocyanin-3-glycoside, anthocyanin-3-aceroside	Açaí seed	Activate the caspase cascade reaction, inhibit proliferation, and improve oxidative stress and inflammation	Caspase cascade, reactive oxygen species/NF-κB, cycooxygenase-2	Breast cancer, colorectal cancer, prostate cancer	(38,40,43)
Ferulic acid, lignans	Jackfruit seeds, date palm seeds	Eliminate free radicals, inhibit the NF-κB pathway, and induce apoptosis	Caspase-3, p53, NF-κB	Liver cancer, colorectal cancer, breast cancer	(49,50, 78,93)

B, Terpenoids

Compound class and representative	Source	Main anticancer effect	Primary molecular targets	Cancer types investigated	(Refs.)
Acetogenins	Soursop seeds	Inhibiting the mitochondrial electron transport chain, depleting ATP, inducing necrosis and apoptosis	Mitochondrial complex I, cyclin-dependent kinase	Triple-negative breast cancer, colon cancer	(73-76,87)
Lupeol, β-amyrin acetate	Miracle berry seeds, jackfruit seeds	Targeted inhibition of lipid metabolism, anti-proliferation, and regulation of immunity	Lipid metabolism pathways, inflammatory mediators	Hepatocellular carcinoma, osteosarcoma, colorectal cancer	(21-24)

C, Fatty acids

Compound class and representative	Source	Main anticancer effect	Primary molecular targets	Cancer types investigated	(Refs.)
Linoleic acid, oleic acid, phytosterols	Jackfruit seeds, date palm seeds	Regulate inflammatory responses, improve the tumor microenvironment, and synergistically enhance antioxidant capacity	Peroxisome proliferator-activated receptor-γ, AMPK	Liver cancer, colorectal cancer, breast cancer	(44,63, 93-95)

D, Proteins and peptides

Compound class and representative	Source	Main anticancer effect	Primary molecular targets	Cancer types investigated	(Refs.)
Trypsin inhibitor	Melon seeds	Inhibiting tumor invasion-related proteases, inhibiting angiogenesis, and reducing invasion and metastasis	MMPs, angiogenic factors	Breast cancer, colorectal cancer	(55,86)

Table II. Continued.

Compound class and representative	Source	Main anticancer effect	Primary molecular targets	Cancer types investigated	(Refs.)
Storage protein	Black-berry seeds, jackfruit seeds	Reduce DNA oxidative damage and regulate immunity	Oxidative stress pathways	Multiple tumor cell lines	(29,96)
E, Indole alkaloids					
Compound class and representative	Source	Main anticancer effect	Primary molecular targets	Cancer types investigated	(Refs.)
Melatonin, indole derivatives	Grape seeds, date palm seeds	Antioxidant, anti-inflamp matory, chemopreventive and immunomodulatory effects; epigenetic regulation	NF-κB, MAPK, epigenetic regulators	Digestive system tumors, hormone-related tumors	(90-92)
F, Vitamin D analogs					
Compound class and representative	Source	Main anticancer effect	Primary molecular targets	Cancer types investigated	(Refs.)
Plant-derived vitamin D analogs	Edible plant tissues (limited evidence in fruit seeds	Anti-proliferation, pro-differentiation	Vitamin D receptor, cell cycle regulators	Breast cancer, colorectal cancer	(91,97)

MAPK, mitogen-activated protein kinases.

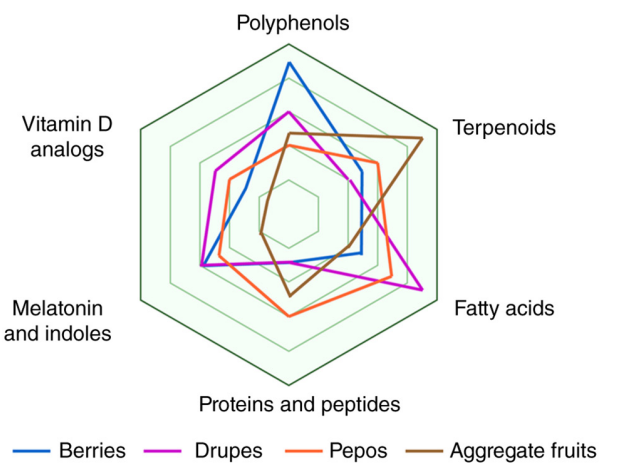


Figure 2. Visual comparison of major fruit seed categories and their characteristic bioactive compounds.

and reduces activated STAT3, thereby blocking cell division signals upstream (58).

Inhibition of tumor angiogenesis. Tumor angiogenesis and metastasis are key factors leading to recurrence and death. Grape seed proanthocyanidins have been demonstrated to downregulate the expression of VEGF and its receptor VEGFR2, and inhibit the proliferation and migration of endothelial cells (101). A trypsin inhibitor purified from melon seeds (TICMSs) has been shown to inhibit endothelial cell migration and angiogenesis, with molecular docking suggesting interactions with VEGFR1 and αVβ3 integrin (86). Jackfruit seed extracts can downregulate MMP-2 and MMP-9, further weakening vascular remodeling (88). For stone fruits, direct anti-angiogenic evidence is lacking, but açaí seed extract shows antitumor activity *in vivo* (42,43) and merits evaluation in angiogenesis models. Overall, the active ingredients derived from these plant seeds can inhibit tumor angiogenesis and metastasis through multi-target synergy, demonstrating potential as antitumor adjuvants.

Antioxidant and anti-inflammatory effects. Oxidative stress and chronic inflammation both promote cancer

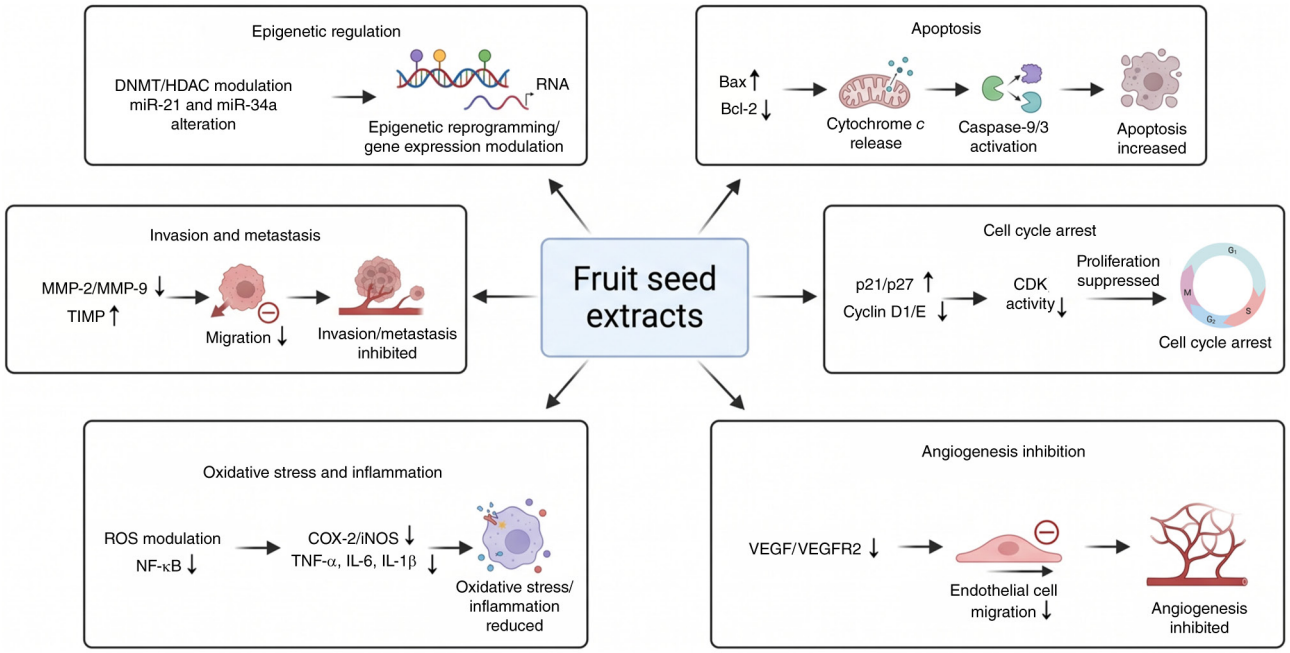


Figure 3. Principal molecular mechanisms of fruit seed extracts in cancer models. DNMT, DNA methyltransferase; HDAC, histone deacetylase; miR, microRNA; TIMP, tissue inhibitor of metalloproteinases; CDK, cyclin-dependent kinase; ROS, reactive oxygen species; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase. Created using BioRender (https://biorender.com/7o9d6a8).

progression (102). The abundant polyphenols and flavonoids in fruit seed extracts can eliminate reactive oxygen free radicals and alleviate DNA oxidative damage (103,104). They can also inhibit the activation of the NF-κB signaling pathway, reduce the levels of inflammatory factors such as TNF-α, IL-6 and IL-1β, and simultaneously downregulate inflammatory-related enzymes such as cyclooxygenase-2 and inducible nitric oxide synthase, thereby reducing the risk of cancer driven by chronic inflammation (43,103,105).

Inhibition of tumor invasion and migration. Tumor invasion and metastasis are the main causes of death in patients with cancer (106), and fruit seed extract can block this malignant process through multiple links, including the suppression of tumor cell migration and invasion and the inhibition of endothelial cell motility. Grape seed proanthocyanidins have been shown to inhibit tumor metastasis to the lungs and improve survival in mouse breast cancer models, by affecting the inhibition of tumor cell proliferation and the induction of apoptosis (84). Rizbi *et al* (89) found that jackfruit seed water extract and Jacalin lectin inhibited the migration of oral squamous cell carcinoma. TICMSs purified from melon seed water extract have been shown to inhibit endothelial cell proliferation, migration and tubulogenesis and to reduce the secretion of VEGF, MMP-2 and MMP-9 (86).

Epigenetic regulation. In previous years, studies have shown that polyphenolic natural products can exert antitumor effects through epigenetic mechanisms. Grape seed proanthocyanidins have demonstrated the ability to inhibit DNA methyltransferase and histone deacetylase (HDAC) (98,107), and their combination with resveratrol synergistically inhibits breast cancer cell proliferation and induces apoptosis by upregulating Bax and downregulating Bcl-2 (107). In addition, grape seed extract modulates microRNA (miRNA) expression profiles and the miRNA processing machinery, with downstream alterations in NF-κB, β-catenin and MAPK signaling that underlie its antiproliferative and pro-apoptotic activity (108). These epigenetic mechanisms provide new evidence for fruit seed extracts as cancer chemoprevention and adjuvant treatment preparations.

5. Current challenges and future perspectives

As a byproduct of fruit processing, fruit seeds are rich in polyphenols, terpenoids and other bioactive components, which show notable potential in the field of cancer prevention and treatment. From the perspective of their action characteristics, the selected fruit seed extracts exhibit multi-component and multi-pathway antitumor properties. They can synergistically inhibit cancer by inducing apoptosis, blocking the cell cycle, inhibiting angiogenesis and metastasis, regulating oxidative stress and by epigenetic means, which is different from traditional single-target chemotherapy drugs. This provides a new idea for overcoming tumor drug resistance. Additionally, they have the characteristics of being widely sourced, with low cost and low toxicity to non-cancer cells, making them more suitable as candidate substances for cancer prevention or adjuvant treatment than conventional cytotoxic chemotherapeutic agents, which are generally associated with higher toxicity.

The four groups of berry, stone fruit, pepo and aggregate fruits exhibit clear boundaries and notable differences in component enrichment rules. Berries are mainly composed of polyphenols, anthocyanins and pentacyclic triterpenoids, which have prominent antioxidant, anti-inflammatory and pro-apoptotic activities. Drupes are rich in flavonoids and phenolic acids, with mild components and a wide antitumor

spectrum. The core of pepos consists of triterpenoids and protease inhibitors, which have strong cytotoxicity and anti-angiogenesis activities. Aggregate fruits contain unique components such as annonaceous acetogenins and coumaroyl tyramides, which have strong cytotoxicity and unique targeted metabolic inhibitory effects. The differences among these groups directly determine the differences in activity spectra and targets, providing a scientific basis for the precise development of anticancer preparations.

Safety profile and standardization. The safety profile of fruit seed extracts remains insufficiently characterized. Extract composition can vary substantially according to species, cultivar, geographic origin, maturity, extraction solvent, extraction temperature and storage conditions. Consequently, the biological activity observed for one extract cannot necessarily be attributed to another extract prepared from the same fruit species. Standardization based on marker compounds, total phenolic content or a defined chemical fingerprint is therefore necessary before comparing efficacy or toxicity across studies. Published safety data remain scarce. A randomized, double-blind, placebo-controlled pilot trial of a jackfruit seed-based formulation reported no serious adverse events (79).

Bioavailability and pharmacokinetic considerations. A major limitation of the current literature is the frequent use of relatively high concentrations in cancer cell experiments. For example, the half-maximal inhibitory concentrations reported for seed-derived extracts and oils in the studies cited above ranged from 16 to 125 μg/ml (15,80). The effective concentrations reported *in vitro* may not be achievable in human plasma or tumor tissue after oral administration due to poor absorption, rapid metabolism, protein binding, efflux transport and elimination (3). Polyphenols, for example, may undergo extensive phase II metabolism, including glucuronidation, sulfation and methylation. Therefore, the concentrations of parent compounds used in cell culture should not be interpreted as clinically achievable systemic concentrations without supporting pharmacokinetic data.

Bioavailability may also be affected by the food matrix and by the chemical form of the active constituent. Encapsulation, lipid-based formulations, fermentation or co-administration with absorption-enhancing substances may increase exposure; however, these approaches may also alter tissue distribution and toxicity. Future studies should report pharmacokinetic parameters, including maximum plasma concentration, time to maximum concentration, area under the curve, half-life, tissue distribution and the identity of major metabolites.

Potential drug interactions. Potential interactions with anticancer drugs should be considered before fruit seed extracts are used as complementary agents. Polyphenols and other phytochemicals may affect cytochrome P450 enzymes, UDP-glucuronosyltransferases, P-glycoprotein and other drug transporters. Such interactions could theoretically modify the exposure of chemotherapeutic agents, targeted drugs or immunotherapies. In addition, antioxidant-rich preparations could interfere with therapies whose efficacy partly depends on oxidative stress, although the direction and clinical importance of this interaction remain compound- and treatment-dependent. These possibilities should be evaluated using enzyme assays, transporter studies, microsomes or hepatocytes, and well-designed animal and clinical pharmacokinetic studies.

Toxicity concerns for specific compound classes. Caution is warranted for seed-derived annonaceous acetogenins. Compounds such as annonacin have been reported to inhibit mitochondrial complex I (70,87), which may contribute to anticancer activity but may also produce mitochondrial and neurotoxic effects. Similarly, the presence of cyanogenic glycosides, allergenic proteins or other antinutritional compounds should be evaluated according to the plant species and processing method. Safety assessment should include acute and repeated-dose toxicity, genotoxicity, reproductive toxicity, hepatotoxicity, nephrotoxicity, neurotoxicity and immunotoxicity.

Limitations of dose extrapolation. The translation of experimental doses to humans requires allometric scaling and, more importantly, exposure-based pharmacology rather than simple conversion of concentrations. Finding a concentration that kills cultured cancer cells does not demonstrate that the same concentration can be safely achieved in a patient. At present, fruit seed extracts should therefore be considered investigational candidates rather than established cancer-preventive or anticancer agents. From a botanical resource perspective, all fruit-seed resources discussed in the present review are derived from commonly cultivated edible fruit species, and no protected or endangered plant species are involved.

6. Conclusions

In general, fruit seeds are a kind of natural anticancer resource with great development potential. Their high-value utilization not only conforms to the concept of green and sustainable development but also provides a new direction for the research and development of natural anticancer drugs. In the future, efforts should be focused on standardizing the preparation and quality control of extracts, systematically conducting safety evaluations, deeply analyzing the synergistic mechanism of multiple components and actively conducting clinical trials. This will promote the transition of fruit seed extracts from basic research to clinical application, making them an important supplement to the comprehensive cancer prevention and treatment system.

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Authors' contributions

JTi was responsible for review conceptualization. JTa was responsible for writing the original draft of the manuscript. CX developed graphical summaries, interpreted corresponding data and contributed to manuscript revision. PW established the literature screening framework, oversaw data extraction and refined the methodology. XZ and ZW were responsible for reviewing and editing the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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