A SYSTEMATIC REVIEW ON THE ROLE OF ARTOCARPUS HETEROPHYLLUS (JACKFRUIT) IN CANCER RESEARCH

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Abstract

Introduction: *Artocarpus heterophyllus*, otherwise known as jackfruit, has been proven to possess several pharmacological properties. However, many remain unaware of its potential to exhibit chemopreventive effects against the development and growth of various types of cancer. Therefore, this study aimed to review present literature on the role of *Artocarpus heterophyllus* and its derivatives in preventing and suppressing cancer growth. **Methods:** Studies were identified through seven electronic databases based on six keywords and were included if they met the following criteria: described the interventions towards *in vitro* samples, specifically human cancer cells, compared the growth of cancer cells between treated and untreated control groups, were peer reviewed articles, and published in English in the year 2010 onwards. **Results:** In total, 755 relevant abstracts were screened, and 32 full-text articles were evaluated. The final ten included studies showed positive results whereby *Artocarpus heterophyllus* demonstrated significant cytotoxic activity, acting in a dose dependent manner. The most valuable part of the plant exhibiting the strongest anticancer properties was the seeds, in which jacalin, artocarpin and artinM were the major compounds associated with anticancer activity. Breast, lung, and colon cancer cells were most commonly used to investigate the chemopreventive properties of *Artocarpus heterophyllus.* **Conclusion:** This review compiles evidence of the potential chemopreventive properties of *Artocarpus heterophyllus* and the outcome of this review is expected to be beneficial in promoting the utilization of *Artocarpus heterophyllus* in alternative treatments for cancer.

Keywords: *Artocarpus heterophyllus,* anticancer, chemoprevention, jackfruit, cancers

Introduction

As one of the most fatal diseases in the world, cancer remains a global health threat due to the aggressive nature of the disease and poor prognosis. Morbidity and mortality remain at all-time highs despite advances in diagnosis and treatment methods (Mazalovska & Kouokam, 2020). Statistics illustrate the gravity of the disease, with cancer-related deaths estimated to be about 10 million in 2020 alone (Sung et al., 2021). Being a preventable disease, current cancer prevention techniques involve the use of early detection through screening or the avoidance of risk factors such as physical inactivity, tobacco use, excessive consumption of alcohol and unhealthy diets.

Beyond prevention, several types of cancer treatments exist to cure cancer or considerably prolong a patient's life. Unfortunately, existing cancer treatments such as chemotherapy, radiation therapy, pharmacological therapies, and surgery often cause adverse side effects. These side effects, which include nausea, vomiting, and asthenia, strongly diminish a patient's quality of life (Sibeoni et al., 2018). Chemotherapy, for instance, may be able to suppress malignant cells but it is non-specific in that it also exerts equally harmful effects on noncancerous cells, severely threatening disease prognosis and patient wellbeing. With such poor outcomes, the need for alternative treatments with selective targeting options that can distinguish malignant cells, with ability for cancer treatment and prevention are highly necessary (Mazalovska & Kouokam, 2020).

Naturally derived products are receiving increased interest for being relatively inexpensive, easily accessible, and are notably less toxic in comparison to existing treatments such as chemotherapy (Kooti et al., 2017). Research has been conducted to investigate and identify the anticancer properties of natural compounds to be used as alternative treatments for cancer. One such natural product that has shown potential in cancer prevention is *Artocarpus heterophyllus*, otherwise known as jackfruit. Studies have shown that *Artocarpus heterophyllus* is highly effective against cancerous cells due to its active medicinal properties and the presence of dormant qualities that may be exerted as therapeutic promoters to obstruct tumor growth and development. The plant is known to produce various phytochemical compounds such as stilbenes, sterols, and prenylflavanoids, some of which have expressed many pharmacological properties such as antioxidative activity, cytotoxicity, anti-inflammatory activity, and so on (Di et al., 2013). Therefore, this paper aims to review the studies that have investigated the bioactive compounds of *Artocarpus heterophyllus* that demonstrate medicinal and therapeutic effects against cancer development.

Methods

Systematic review process

This study has been done through systematic review for which the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) were used as the guidelines.

Search Strategy

Seven databases were searched in this study: Science Direct, Semantic Scholar, Google Scholar, Scopus, PubMed, SAGE Journal and Jstor. A manual search through a reference list of obtained articles was also done to obtain additional records. Moreover, the PICOS elements, Population (P), Intervention (I), Comparison (C), Outcome (O) and Study (S) design, were used as the search strategy to obtain as many relevant studies as possible regarding the topic. Boolean operators (AND, OR, NOT) were used to find the relationship between search terms by inserting the appropriate keywords in the search engine. The keywords were *Artocarpus heterophyllus,* anticancer, chemoprevention, jackfruit, and cancers.

Eligibility Criteria

Studies were selected if they carried out intervention towards *in vitro* samples, specifically human cancer cells, compared the growth of cancer cells between treated and untreated control groups, and were peer reviewed articles published in English in the year of 2010 and onwards. Studies that did not evaluate anticancer properties of *Artocarpus heterophyllus* were excluded.

Study Selection

The titles and abstracts of selected studies were reviewed if the inclusion criteria were fulfilled while the full-text articles that did not meet the inclusion criteria and failed to address the research question were excluded from this review to avoid bias in results. The screening process was repeated three times.

Quality of Assessment

The Cochrane's guidelines were used to assess the risk of bias in the studies, focusing on seven domains to be assessed for judgement (high, low, or unclear) for individual elements of each domain. Another risk of bias tool, the National Toxicology Program Tool, was also used as a reference to assess the risk of bias for *in vitro* studies.

Collating, Summarizing, and Reporting Results

After a complete process of data charting, the gathered information from all included studies were summarized through descriptive and numerical analysis. Tables were used to present the collected information such as the number of studies included, publication years, types of study design, number of participants, level of evidence, parts of *Artocarpus heterophyllus* used, active compounds, and the outcomes.

Results

Database screening and article selection

A total of 928 articles managed to be identified from the initial search and duplications were removed using the Mendeley Software, resulting in 755 articles left to be screened. After scanning the titles and analyzing the abstracts of the studies, 32 articles were chosen for further analysis according to the exclusion and inclusion criteria. Finally, ten intervention studies were selected to be included in the review after all the full text articles were evaluated and examined. The article selection process is outlined in the PRISMA diagram (Figure. 1). Common reasons for articles to be excluded included cases where the articles did not evaluate the therapeutic effect of *Artocarpus heterophyllus* towards cancer cell development, animals such as rats and mice were used as experiment subjects, and different species of jackfruit (not *Artocarpus heterophyllus*) were used in the studies.

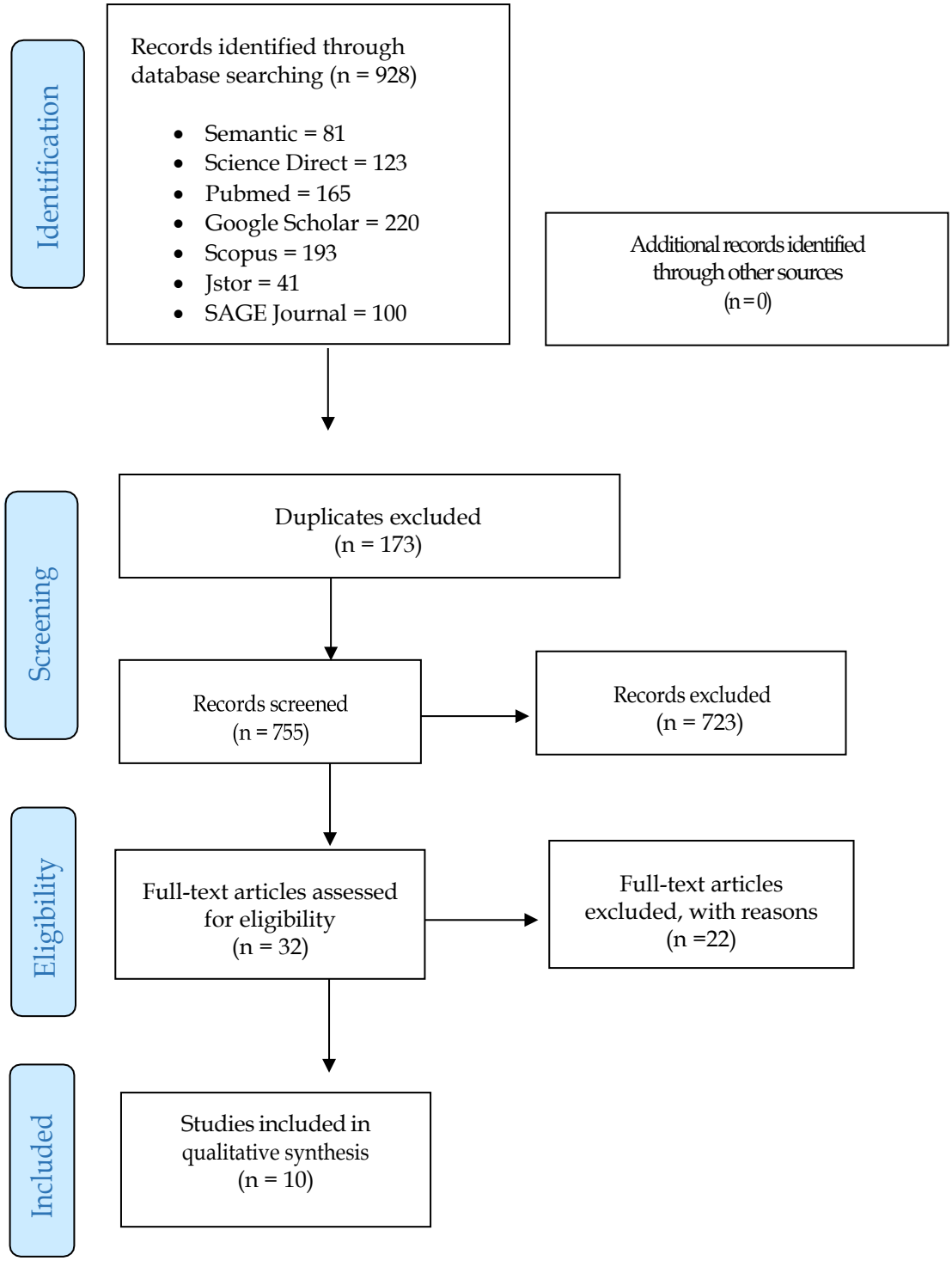
Of the 32 full text articles, there were two articles and one thesis excluded as they were not applicable to this study and lacked explanation regarding the results and discussion. An additional three studies were excluded for using animals as the sample while another 26 articles either showed no relation between *Artocarpus heterophyllus* and cancer development or were simply unrelated to the purpose of this study.

Description of the studies

Ten articles on the potency and efficacy of *Artocarpus heterophyllus* were reviewed. The details of the *in vitro* studies that investigated anticancer properties of *Artocarpus heterophyllus* are summarized in Table 1. Among the ten studies, five studies (Studies 1, 2, 4, 7, 9) targeted breast cancer cells, three studies (Studies 1, 4, 5) targeted lung cancer cells, four studies (Studies 3, 6, 7, 10) targeted colon cancer cells, one study (Study 5) targeted prostate cancer cells, one study (Study 8) targeted leukemia cells, one study (Study 4) targeted cervical cancer cells, and one study (Study 7) targeted low wall melanoma. All ten studies were of experimental research design with the presence of different concentrations of *Artocarpus heterophyllus* as interventions and the absence of *Artocarpus heterophyllus* as a control.

Moreover, four studies (Studies 2, 3, 5, 9) examined the artocarpin compound, two studies (Studies 1, 6) examined the jacalin compound, one study (Study 8) examined the artinM compound, one study (Study 10) examined water-soluble polysaccharides, and two studies (Studies 4 & 8) examined the crude methanolic and ethanolic extract of *Artocarpus heterophyllus* for its therapeutic potential against cancer development.

Figure I PRISMA 2009 Flow Guideline



Discussion

This review aims to investigate the anticancer properties and therapeutic potential of *Artocarpus heterophyllus* against cancer development. The review showed that the application of compounds derived from *Artocarpus heterophyllus* has the potential to reduce the growth of cancer cells due to their ability to exhibit cytotoxic activity, induce apoptosis, and inhibit cell proliferation. Based on the MTT assay tests, nearly all the studies proved that the viability of cancer cells decreased with increasing concentration of *Artocarpus heterophyllus*-derived compounds. From all ten included papers, the review also gathered three general findings.

Firstly, the review recognizes jacalin, artinM, and artocarpin as the specific compounds that reduce cancer development. Of the studies reviewed, two studies (Studies 1, 6) reported that jacalin inhibited the cell proliferation of certain types of cancer cells such as breast cancer cells (MCF7), non-small lung carcinoma cells (H1299), and colorectal adenocarcinoma cells (HCT-15). This is due to the ability of jacalin to recognize an antigen identified as Thomsen-Friedenreich (TF-Galβ1- 3GalNAc), which is expressed in more than 85% of human carcinomas and also reduces the growth of human colon cancer cells (Geraldino et al., 2017). The second compound, artinM, demonstrated its ability to suppress the growth of cancer cells and trigger the process of apoptosis via autophagic-associated pathways as well as the identification of Man a1-3(Man a1-6) Man b1 in the context of b1,6-GlcNAc-branched N-glycans that are needed to activate antigen-presenting cells (Carvalho et al., 2011). Furthermore, as demonstrated in four studies (Studies 2, 3, 5, 9), the final compound artocarpin was shown to be effective in preventing three types of cancers such as lung, colon, and breast cancer. The studies show that artocarpin introduces cell death to cancer cells via the activation of two apical caspases (caspase 8 and 10) and triggers the production of ROS.

Secondly, the review found that the part of the *Artocarpus heterophyllus* plant that exhibits the strongest anticancer properties through the derivation of specific compounds and extracts were the plant seeds. Five of the reviewed studies (Studies 1, 4, 6, 7, 8) have shown that jacalin, artocarpin, and artinM can be found in the seeds. *Artocarpus heterophyllus* seeds are highly rich in trypsin, chrymotrypsin, the lectin family of glycoprotein, and elastase inhibitors and also contain secondary metabolites that display anticancer effects, especially anti-angiogenesis (Mohd Ali et al., 2014). In addition, the effects of the combination of *Artocarpus heterophyllus* and cancer drugs were investigated in two studies (Studies 6, 9). In Study 6, among the tested nanoformulations (IP6, IP-GNP, and IJP-GNP), IJP-GNP, which is IP6 loaded jacalin-pectin-gold nanoparticles, was found to be the most effective formulation against colon cancer cells by demonstrating critical cytotoxicity with the least IC_{50} and triggering apoptosis through the generation of ROS. In Study 9, artocarpin enhanced the anticancer activity of a cancer drug, cisplatin, against non-small lung cancer cells (H460) and breast cancer cells (MCF7) with a combination index (CI) value of 0.2 and 0.18, respectively, and caused morphological changes which led to apoptosis.

Lastly, the review showed that the types of cancer cells most commonly investigated

were breast cancer cells (T47D and MCF7) in five studies (Studies 1, 2, 4, 7, 9), lung cancer cells (H1299, NCI-H460, A549, H460) in four studies (Studies 1, 4, 5, 9) and colon cancer cells (HCT-15, DLD1, HT29, SW480) in four studies (Studies 3, 6, 7, 10). However, further research is required to reliably identify and confirm the mechanism behind the therapeutic potential of *Artocarpus heterophyllus* towards these three types of cancer cells.

These collective findings point towards the relevance of *Artocarpus heterophyllus* in the prevention and treatment of various cancers. Due to their recognition properties, lectins such as jacalin have been used to differentiate between normal and malignant cells, and act as carriers that specifically target malignant cells (Mishra et al., 2019). Artocarpin has been found to demonstrate selective cytoxicity against human colon cancer cells through the specific targeting of Akt kinase (Sun et al., 2017). The ability of jacalin, artocarpin, and artinM to demonstrate cell recognition and specificity in cell targeting would serve to overcome the limitations of current cancer therapies, which lack this trademark.

It would be worth noting that the seeds of *Artocarpus* heterophyllus, where these compounds are primarily found, account for between 10 to 15% of the entire weight of the fruit (Hossain, 2014). Despite their high nutritional value and health benefits, the seeds are often unutilized and discarded as waste. However, the abundance of *Artocarpus heterophyllus* trees in many South and Southeast Asian regions make it a sustainable source material for the extraction of these anti-cancer components (Sy Mohamad et al., 2019; Weintraub et al., 2022). Reliable plant yield, stability, and the ease of compound extraction and purification make *Artocarpus heterophyllus* a cost-effective component in chemopreventive treatment and an attractive option for the development of alternative cancer treatments.

Conclusion

In conclusion, the part of the *Artocarpus heterophyllus* plant found to exhibit the strongest anticancer properties was the plant seeds. Many of the included studies supported the notion that the major compounds demonstrating anticancer activity are jacalin, artocarpin and artinM. Moreover, based on the reviewed studies, breast, lung, and colon cancer cells were most commonly used to investigate the chemopreventive properties of *Artocarpus heterophyllus.* This review displays promising baseline fundamentals for the potential use of *Artocarpus heterophyllus* and its derivatives as chemopreventive agents, encouraging further research and evaluation before the application of these findings in clinical settings.

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Table 1: Summary of findings on anticancer properties of *Artocarpus heterophyllus*

Author (Year)	Level of Evidence/ Study Design/ Sample	Part of *A. heterophyllus*/ Active Compound	Intervention/ Control Groups	Results
STUDY 1 Zuraidah, Mimi & Wan Sulaiman (2014	LEVEL II Experimental Design Sample: 1) Human breast cancer cell (MCF7) 2) Non-small lung carcinoma (H1299)	Seeds Plant lectin (Jacalin)	*Intervention* Cancer cells incubated with (0-10µL/ml) crude protein and jacalin. *Control* Cancer cells incubated with (0-10µL/ml) jacalin standard.	MTT Assays - At highest concentration (10 µL), jacalin was more effective against MCF7 than H1299 whereby the percentage of viable cells were 64.73% and 67.72%, respectively.
STUDY 2 Arung et al., (2010)	LEVEL II Experimental Design Sample: Human breast cancer cells (T47D)	Wood Prenylated flavonoid (Artocarpin)	*Intervention* T47D cells incubated with (5.7, 11.5, 20, and 28.7 µM) artocarpin. *Control* T47D cells incubated with media only.	Cell Viability Assay - The number of viable cells decreased as artocarpin concentration increased. - The IC_{50} value of artocarpin on T47D cells was 12.6µM. Immunoblotting Test - As the concentration of artocarpin increased at 5.7, 12.6, and 20 µM, the expression of cleaved-caspase 3 and 8 gradually increased.
STUDY 3 Sun et al., (2017)	LEVEL II Experimental Design Sample:	Not mentioned Prenylated flavonoid (Artocarpin)	*Intervention* DLD1, HCT15, HCT116, HT29, and SW480 cells treated with artocarpin.	MTS Assay - Artocarpin only showed potent cytotoxicity against human colon cancer cells with IC_{50} values at around

	Human colon adenocarcinoma cells (DLD1, HCT15, HCT116, HT29, and SW480)		*Control* Human normal colon fibroblast cells (CCD- 18Co) treated with artocarpin.	15µmol/L. Non-malignant human colon fibroblast cells (CCD-18Co) were less sensitive to the cytotoxic effects.
STUDY 4 Patel & Patel (2011)	LEVEL II Experimental Design Sample: 1) Breast cancer (MCF7) 2) Cervic cancer cells (HeLa) 3) Embryonic kidney cancer cells (HEK293T)	Seeds Not mentioned	*Intervention* HEK 293T, A549, HeLa and MCF-7 cells incubated with (0-6 gm/mol) methanolic extract of *Artocarpus heterophyllus.* *Control* Cancer cells incubated with (0-6 gm/mol) of methotrexate.	MTT Assay - Lower cytotoxic activity was shown in HEK293 and MCF7 having IC_{50}, 45.42 and 49.42 µgm/ml, respectively. - The cytotoxic activity of methanolic extract of *Artocarpus heterophyllus* only showed against A549 cell line with IC_{50}: 35.26 µgm/ml while other cell lines showed no activity. SRB Assay - Lower cytotoxic activity was shown in HEK293 and MCF7 (IC_{50}: 16.531 and 45.671 µgm／ml). - Cytotoxic activity of methanolic extract of *Artocarpus heterophyllus* only showed against A549 cell line IC_{50}: 35.27 µgm/ml while other cell lines showed no activity.

STUDY 5 Wang et al., (2016)	LEVEL II Experimental Design Sample: 1) Human prostate cancer cell (PC-3) 2) Human lung cancer cell (NCI-H460) 3) Human lung adenocarcinoma epithelial cell (A549)	Leaves 1) Artocarstilbene B. 2) Benzal- 197-dehyde 3) Artocarmitin B 4) Artocarpin 5) Cudraflavone C 6) Albanin A 7) Cudraflavone 8) Brosimone I 9) Norartocarpanone 10) Euchrenone a7 11) Moracin M 12) Moracin C 13) Albafuran B 14) Artoindonesianin B-1 15) Demethylmoracin I 16) Moracin D 17) Artocarbene 18) Griffithine A	*Intervention* The cancer cells were cultured in standard conditions and test compounds were added before the cells were incubated for 72 hours. *Control* Test compounds were not added.	MTT Assay - Moderate to weak cytotoxic activity against PC-3, A549 cells and NCI-H460 cells was found for compounds 3-5. - Compounds 10, 14, and 16 showed weak inhibitory activity (IC_{50} < 20 mmol/L) on some or all of the three cancer cell lines while remaining compounds were inactive in the study (IC50 > 20 mmol/L).
STUDY 6 Arya et al., (2019)	LEVEL II Experimental Design Sample: 1) Human colorectal adenocarcinoma cell lines (HCT -15) 2) Human normal colon epithelial cell lines (NCM460)	Seeds Plant lectin (Jacalin)	*Intervention* Cells were treated with different concentrations of P-GNP, IP-GNP and IJP-GNP at 24, 48, and 72 hours. *Control* Cells were treated with different concentrations of pure IP6 at 24, 48, and 72 hours.	Cytotoxicity Evaluation - IP6 loaded jacalin-pectin-gold nanoparticles (IJP-GNP) showed the least IC_{50} against colon cancer cells. - The treatment of HCT-15 cells with IJP-GNP (10 and 15 µM/ml) indicated apoptotic cells with nuclear chromatin condensation and the formation of nuclear

				fragments and apoptotic bodies. - When compared with untreated cells (control), production of ROS was raised by 160.53% ($p< 0.05$) at 15 µM/ml of IJP -GNP when compared with untreated cells (control).
STUDY 7 Burci et al. (2019)	LEVEL II Experimental Design Sample: 1) Breast cancer (T47D) 2) Colon cancer (HT29) 3) Low wall melanoma (B16F10) 4) Normal cell lines (L929)	Seeds Not mentioned	*Intervention* T47D, HT29 and B16F10 were incubated with 1, 10, 100 and 1000 µg/ml of extracts and fractions of *Artocarpus heterophyllus*. *Control* L929 cells were incubated with 1, 10, 100 and 1000µg/ml of extracts and fractions of *Artocarpus heterophyllus*.	MTT Assay - Extraction of *Artocarpus heterophyllus* seeds showed cytotoxic effect against T47D, HT29 and B16F10 but no effect on L929, a normal cell line. - IC_{50} determination showed the lowest value was obtained for ethanolic extract (against HT-29), chloroform extract (against T47D) and ethyl acetate extract (against B16F10). - These three extracts presented IC_{50} values less than 80 µg/ml (23.42, 46.67, and 74.31 µg/ml respectively).
STUDY 8 Carvalho, Soares, Tamarozzi, Rego, &	LEVEL II Experimental Design Sample: Leukemia cell lines	Seeds ArtinM	*Intervention* Leukemia cells were cultured in 0 to 100mg/mL of ArtinM for 48 hours. *Control*	MTT Assay - ArtinM was more effective against NB4 and K562 cells, displaying IC_{50} of 10 (±1) and 14 (±1) mg/mL respectively, while U937 cells exhibited an

Roque-Barreira (2011)	(K562, NB4, and U937)		Leukemia cells were cultured in the presence of 0 to 100 mg/mL of L-PHA (Phaseolus vulgaris leukophytohemagglutinin) for 48 hours.	IC_{50} of 84 (±1,5) mg/mL. - In NB4 cells, ArtinM supported the caspase-independent cell death.
STUDY 9 Daud, Septama, Simbak, Bakar & Rahmi (2019)	LEVEL II Experimental Design Sample: 1) Human breast cancer cell lines (MCF-7) 2) Non-small lung cancer cell line (H460)	Heartwoods Artocarpanone, artocarpin, cycloartocarpin, and cyanomaclurin	*Intervention* 31.25, 15.63, 7.81, 3.91, and 1.95 µg/mL of the compound were added to the plate and incubated for 72 hours. *Control* Cells were untreated (negative control) and cisplatin drug was used as positive control.	MTT Assay - Artocarpin showed the highest cytotoxic activity against MCF-7 and H460 cell line with IC_{50} values of 12.53 µg/mL (28.73µM) and 9.77 µg/mL (22.40 µM), respectively. Isobologram Analysis - Artocarpin when combined with cisplatin exhibited a synergistic effect in H460 cells and MCF-7 cells with CI values of 0.2 and 0.18, respectively.
STUDY 10 Wiater et al., (2020)	LEVEL II Experimental Design Sample: Human colon tumor	Fruits Water-soluble polysaccharide (WSP)	*Intervention* Cells were grown in 100 µL of culture medium and (25–250 µg/mL) of WSP *Artocarpus heterophyllus* for 24 and 48 hours.	Neutral Red (NR) Uptake Assay - Both HT29 and SW620 cells did not show signs of viability loss after cultured with *Artocarpus heterophyllus* WSP at concentration values up to

	cell line (HT29 and SW620)		250 µg/mL. ELISA Assay - IL-6 levels increased in a WSP concentration- dependent manner only in the HT29 cell culture. Properties of *Artocarpus heterophyllus* towards Anticancer Development - *Artocarpus heterophyllus* compounds exerted immunomodulatory activity and significant anti- oxidative effects but did not show any strong toxicity towards human colon tumor cells.
		Control Cells were not treated with *Artocarpus heterophyllus* WSP.	